

Cutaneous lupus erythematosus

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Abstract

Lupus erythematosus (LE) is a chronic, autoimmune, inflammatory disease that presents a striking diversity of clinical patterns with variable evolution and prognosis. Skin involvement (*i.e* cutaneous lupus erythematosus (CLE)) occurs in 70-85% of all patients with LE. CLE includes a variety of specific skin lesions that are subdivided, based on clinical morphology, average duration of skin lesions and routine histopathological examination, into three categories: chronic CLE where discoid lesions are the most common skin manifestations (DLE) subacute CLE (SCLE) and acute CLE (ACLE). Etiology of LE remains to be clarified. Interactions between genetic, infective and hormonal factors trigger alterations of immunoregulation that mediate the pathogenesis of this disease. In the USA, prevalence of systemic LE is 14.6-130/100000; epidemiological studies from other countries almost overlap with such values. Effective sun screening and sun protection are considered the first rule in the management of CLE. Antimalarials are crucial in the treatment of CLE and are the first-line systemic agents. Retinoids, known as the second-line drugs for systemic therapy, are sometimes used to treat chronic forms of CLE. Systemic immunosuppressive agents are required to manage the underlying systemic LE disease activity in cases of ACLE. Oral prednisone or parenteral "pulsed" methylprednisolone are useful in case of exacerbations of disease activity. Thalidomide provides one of the most useful therapeutic alternatives for chronic refractory DLE even if, for the risks of teratogeny and polyneuropathy, its distribution is limited to few countries. Topical treatment with local corticosteroids remains the mainstay of CLE treatment, especially for DLE and SCLE. Finally, patient education regarding the disease is also important in the management of CLE, because it helps to relieve undue anxiety and to recruit the patient as an active participant in the treatment regimen.

Keywords

Autoimmune disease, subacute cutaneous lupus erythematosus, discoid lupus erythematosus, acute cutaneous lupus erythematosus, sun protection, antimalarials, retinoids, thalidomide, corticosteroids

Definition/diagnostic criteria

Lupus erythematosus (LE) is a chronic, autoimmune, inflammatory disease that presents a striking diversity of clinical patterns with

variable evolution and prognosis. Skin involvement occurs in 70-85% of all patients with LE. Cutaneous manifestations can be classified as LE specific or LE non-specific on the basis of

Careful assessment of the morphology of the cutaneous lesions and the results of routine histopathological examination (Gilliam & Sontheimer, 1981). LE-specific skin manifestations can be classified into three types: chronic cutaneous LE (CCLE), subacute CLE (SCLE) and acute CLE (ACLE). Non-specific cutaneous lesions, which are also present in other autoimmune cutaneous diseases, include vasculitis, periungual telangiectasias, Raynaud's phenomenon, livedo reticularis and non-scarring alopecia. The identification of such lesions is particularly important in LE since their presence implies systemic involvement and they are thus useful indicators of systemic disease activity.

Etiology

Etiology of LE remains to be clarified. Interactions between genetic, infective and hormonal factors trigger alterations of immunoregulation that mediate the pathogenesis of this disease. Immunogenetic studies showed that HLA-A1, -B8, -DR3, -A3, -B7, -DR2 and -C4A haplotypes are significantly associated with the risk of developing LE (Graham *et al.*, 2002). The influence of sexual hormones is underlined by the prevalence of the disease in females and in the post-pubertal period; furthermore, in about 20% of cases reactivation of LE is triggered by pregnancy and by treatment with oral contraceptives. Several viral factors have been suspected to play at least a provoking role (Osmola A *et al.*, 2004). Other provoking/aggravating factors include ultraviolet rays and drugs (e.g. procainamide, hydralazine and isoniazide) (Shapiro M *et al.*, 2004).

Clinical description

Chronic cutaneous lupus erythematosus

Discoid lupus erythematosus (DLE).

Discoid lesions are the most common skin manifestations of CCLE. DLE generally represents the benign pole of the LE spectrum. It is frequent in women (female/male ratio 3:1) especially in the fourth and fifth decades. The localized form, characterized by limited cutaneous involvement to the head and scalp, usually accounts for 70% of DLE cases, while the generalized one, characterized by the extension to more than the head-body area, for 30%. Photosensitivity or summer exacerbations are found in about 70% of DLE subjects. Typical DLE lesions may be present at the onset of systemic LE (SLE) in about 6-10% of the patients, and about 25-33% of patients may develop DLE lesions, usually of the generalized type, during the course of SLE (Burch *et al.*, 1970). The first morphological manifestation of DLE is a well-defined, disk-shaped erythematous patch of varying size (from a few mm to 15 cm).

This is followed by greyish-white hyperkeratosis that is extremely adhesive to the skin and involves dilated pilosebaceous follicles whose removal is difficult and painful. Resolution of the lesions leaves more or less evident atrophy and scarring, depending on the duration and severity of the lesions during the active phase. Pigmentary changes are common especially in dark-skinned people, with white hypopigmentation in the central area and a hyperpigmented zone at the active border. Periungual telangiectasias and erythema of the proximal nailfold are significant cutaneous features that can occur in subjects prone to develop SLE.

Hypertrophic or verrucous lupus erythematosus (HLE)

HLE is a rare (2%) subset of CCLE (Sontheimer, 1997). This form consists of dull, red and indurate lesions that are covered by keratotic multilayered horny white or yellow scales. These lesions commonly affect the extensor surface of the arms and legs and the upper back. When palms and soles are involved, hypertrophic lupus produces localized or partially diffuse keratoderma. This variety usually occurs together with typical discoid lesions. Patients with HLE rarely develop systemic disease. The clinical course is characterized by chronicity and resistance to treatment (Spann, 1988).

Lupus panniculitis. LE profundus or lupus panniculitis (LP)

It generally occurs in middle-aged women (female/male ratio: 3-4:1) who usually show associated findings of DLE or SLE. Multiple firm, well-demarcated, persistent and painless subcutaneous nodules or plaques with relatively normal-appearing overlying skin are the typical lesions of this form. The arms (particularly the deltoid area), face and buttocks are the sites most frequently involved. Ulceration is rare. The course is usually chronic with exacerbations and remissions and the lesions finally resolve leaving atrophic scars.

Chilblain lupus (CL).

It is a rare manifestation of LE characterized by cold-induced lesions localized in acral areas in patients without cold agglutinins or cryoglobulins. CL consists of lesions that resemble common "frostbite", located on fingers, toes, calves, heels, knees, elbows, nose and ears, and are generally aggravated by exposure to cold. These lesions are represented by papulo-erythematous purplish, sometimes infiltrated, pruriginous or painful lesions that, in their evolution, may ulcerate or present hyperkeratosis (Doutre *et al.*, 1992).

Lupus erythematosus tumidus (LET).

This rare and neglected subset of CLE is characterized by remarkable photosensitivity, preferential involvement of males and unusual systemic involvement. The swollen appearance of the lesions and the absence of clinically visible follicular plugging are the most important features of this peculiar form that develops mainly on the face and manifests as single or multiple raised erythematous plaques with bright reddish or violaceous, smooth surface. The borders are sharply limited and often there is a tendency to swelling in the periphery and flattening in the center (Mascarò *et al.* 1997).

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) is a distinct subset of LE that identifies patients with clinically erythematous, non-scarring lesions, pronounced light sensitivity, musculoskeletal complaints, characteristic serological abnormalities and a variety of relatively mild systemic symptoms. SCLE can, therefore, be considered a relatively benign illness that is intermediate in severity between ACLE and DLE (Sontheimer *et al.*, 1979); SCLE occurs almost exclusively in caucasian females, especially in the third decade of age. SCLE is the most photosensitive subset of CLE, in which 70-90% of patients are abnormally photosensitive (Callen *et al.*, 1988). The primary lesion is an erythematous macule, papule or small plaque covered with fine scales. These lesions expand and merge in some patients, producing retiform arrays of papulo-squamous lesions that can mimic those of psoriasis vulgaris. In other patients, the primary lesions expand and clear centrally to produce annular lesions that may merge into polycyclic arrays. The papulo-squamous form is more frequent than the annular-polycyclic one (Parodi *et al.* 2000). SCLE has a characteristic distribution of lesions in sun-exposed areas, in particular on the extensor aspects of forearms, arms, deltoid aspect of the shoulders, upper anterior chest and back. In regard to evolution, SCLE lesions may result in pigmentary changes and teleangiectasias, but characteristically they do not produce dermal atrophy or scarring. Generally, SCLE lesions are trauma-induced and photo-aggravated. Furthermore, many drugs (especially hydrochlorothiazide, terbinafine, naproxen, calcium channel blockers, interferons and statins) have been associated with the onset and/or exacerbation of the disease (Srivastava *et al.*, 2003).

Acute cutaneous lupus erythematosus

ACLE appears almost exclusively in patients with active SLE. It is possible to distinguish a

localized form known as malar or "butterfly rash" (very common) and a generalized one. The latter form presents as a more widespread morbilliform or exanthematous eruption (maculo-papular lupus rash) and is rare.

Malar rash

Malar rash is commonly the first manifestation of SLE, preceding by weeks or months the onset of multisystem disease, or frequently it coincides with exacerbations of SLE. It generally presents as a photosensitive eruption, although sun exposure is not always required. Photosensitive SLE patients sometimes report an exacerbation of their systemic symptoms after sun exposure. The classic butterfly rash is characterized by erythema and edema, occasionally associated with fine scales that involve both the malar areas and the bridge of the nose while they spare the nasolabial folds. At the onset the patient may mistake this rash for sunburn and seek medical advice only after the lesion has persisted for a few days. Malar rash disappears without scarring and pigmentation.

Maculopapular lupus rash

Maculopapular lupus rash (MPLR) is an uncommon generalized cutaneous manifestation, whose incidence is estimated at about 5-10% of SLE patients. It may resemble a drug eruption and frequently occurs after sun exposure. The lesions are often pruritic and may be located anywhere on the body, although the preferred sites are above the waistline. Like in butterfly rash, onset of maculopapular rash usually coincides with the exacerbation of the systemic disease. This variety is characterized by a generalized eruption of symmetrically distributed small, confluent erythematous spots and papules with a purpuric component. The colour of the lesions is usually red or, less frequently, dull red or livid.

Bullous systemic lupus erythematosus (BSLE).

BSLE is recognized as a rare blistering disease with a distinctive combination of clinical, histologic and immunopathologic features that together constitute a unique bullous disease phenotype (Gammon *et al.*, 1993). The bullous lesions are predominantly on the face, neck and upper trunk but may also be more widespread. They may arise on erythematous or normal skin, tend to be tense and may rupture leaving erosions, crusts and pigmentary changes.

Diagnostic criteria

Diagnosis criteria of cutaneous lupus erythematosus are summarized in table 1

Table 1: Diagnostic criteria of cutaneous types of Lupus Erythematosus

<p>Discoid Lupus Erythematosus DLE</p> <p>1-Well-demarcated disk-shaped lesion associated with follicular plugging 2-Lesions most often located on exposed surfaces (face, ears, scalp) 3-Characteristic histologic alterations (ortho-hyperkeratosis of the epidermis, dilated follicular orifices filled with compact keratin, vacuolar degeneration of the basal keratinocytes, perivascular and perifollicular mononuclear cell infiltrate of the dermis) 4-Evolution of the lesions with atrophy, scar formation and pigmentary changes 5-Positive lupus band test on lesional and sun-exposed skin</p> <p>Hypertrophic Lupus</p> <p>1-Dull, red, indurated lesions covered by multilayered scales 2-Frequent association with typical DLE lesions 3-Characteristic histologic alterations (marked acanthosis, hyperkeratosis and hypergranulosis) 4-Good response to administration of retinoids (topical and systemic)</p> <p>Lupus Panniculitis</p> <p>1-Multiple, subcutaneous nodules on the arms, face and buttocks with female prevalence 2-Chronic-relapsing course 3-Characteristic histologic alterations (lobular lymphocytic panniculitis with hyaline necrosis of fat, lymphoid nodules and lymphocytic nuclear dust) 4-Positive lupus band test (IgG, IgM, C₃) on lesional skin in about 70%</p> <p>Chilblain Lupus</p> <p>1-Cold induced or aggravated lesions resembling "frostbite" in acral locations 2-Histopathological features of LE 3-No evidence of cryoglobulins and cold agglutinins 4-Junctional and perivascular granular deposits of immunoreactants at direct immunofluorescence technique</p> <p>Lupus Erythematosus tumidus</p> <p>1-Swollen aspect of the lesions without evidence of follicular plugging with male prevalence 2-Remarkable photosensitivity with high incidence of positive phototest reactions 3-Characteristic histological findings (minimal follicular hyperkeratosis, considerable dermal lymphocytic infiltration and interstitial mucin deposition)</p> <p>Subacute cutaneous Lupus Erythematosus</p> <p>1-Characteristic skin lesions in female patients with typical distribution on sun-exposed areas and sparing of the face 2-Extreme photosensitivity, frequent disease exacerbations in spring and summer 3-Possible induction by several drugs (thiazide, terbinafine, piroxicam, penicillamine, glyburide) 4-Anti-Ro/SSA antibodies (60 KD peptide) 5-"Dust-like particles" of IgG deposition in the epidermis 6-Strong association with the A1, B8, DR3 haplotypes 7-Mild systemic involvement (especially regarding kidney and central nervous system)</p> <p>Acute cutaneous Lupus Erythematosus</p> <p>1-Photo-distributed erythema ("malar rash") or widespread maculopapular eruption in female patients 2-Photosensitivity 3-Association with oral ulcerations (for maculopapular lupus rash) 4-Associated systemic diseases (arthralgia, anemia, leukopenia, serositis, nephritis and central nervous system disease) 5-ANA (> 80%), anti-Sm antibodies (in about 20% of SLE), anti-dsDNA, anti-Ro/SSA, anti-La/SSB antibodies 6-Positive lupus band test on sun-protected non-lesional skin</p>
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Diagnostic methods

Careful history and physical examination of the skin are the first step in the diagnostic. Clinical examination should be integrated by complete blood count, sedimentation rate, antinuclear antibodies (ANA) test, complement levels, urinalysis (proteinuria, hematuria, cylinders), creatinine and creatinine clearance. Then, a biopsy taken from a typical lesion in active phase is necessary for both histological examination and direct immunofluorescence technique (DIF). DIF is almost always positive, revealing deposits of immunoglobulins (Igs), particularly IgG and IgM, and complement components (such as C3 and C1q). If distributed in a granular band-like distribution at the dermal-epidermal junction, such deposits are described with the term "lupus band test" (LBT). A positive test (at least two immunoreactants, especially IgG), if performed on sun-protected non-lesional (SPNL) skin, may be useful to confirm an underlying SLE (Cardinali *et al.*, 1999). When SPNL skin is tested for prognostic purposes, the biopsy specimen is taken from the buttock area. ANA are frequently found in CLE patients. This reactivity is more common in those who have had the disease for a long time, when there is a generalized skin involvement and in older patients. Antibodies to single-stranded-DNA usually indicate widespread and progressive disease. The determination of ANA and other autoantibodies should be repeated 1-2 times per year as well as the complement levels for monitoring the disease. Diagnostic criteria of various types of CLE are reported in Table 1. Patients with CLE should be investigated in the presence of systemic disease by evaluation of symptoms (fever, malaise, arthralgias, seizures, psychosis, pleural chest pain and photosensitivity) and signs of myositis, arthritis, dyspnea, pleuritis, pericarditis, neurologic and neuropsychiatric disorders.

Differential diagnosis

Most cases of CLE do not present great difficulty in diagnosis, although sometimes histopathologic examination is required to rule out polymorphous light eruption, seborrheic dermatitis, psoriasis, tinea, sarcoidosis, basal cell epithelioma or lichen planus pilaris. Main differential diagnoses of SCLE include psoriasis and annular-polycyclic erythemas. In the typical patient with major manifestations, the diagnosis of SLE is obvious. However, at times the differentiation between SLE and other connective tissue diseases may be very difficult.

Epidemiology

In the USA, prevalence of SLE is 14.6-130/100000 (Siegel *et al.*, 1970; Uramoto *et al.*,

1999); epidemiological studies from other countries almost overlap with such values. SLE appears to be more common among Afro-Americans and Asians and among female subjects (female/male ratio = 9/1 within the age range 15-64 years, = 4/1 within the other ranges). No certain epidemiological data are available concerning cutaneous lupus erythematosus. DLE is estimated to be present in a 3-7:1 ratio to SLE (Tebbe *et al.*, 1997; Wallace *et al.*, 1992).

Management

Photoprotection, topical steroids and hydroxychloroquine are the mainstays of therapy of CLE. In severe and refractory disease, antimalarials remain the drug of choice and multipharmacological strategies can be employed in order to achieve optimal results with minimal toxicity. Retinoids, dapsone, clofazimine, and thalidomide are effective but more toxic alternatives. Their use dictates frequent and careful monitoring. Retinoids and thalidomide are teratogenic, the use of dapsone is limited by its hematologic toxicity.

Cytotoxic agents are generally restricted to the patients with concomitant organ-threatening systemic disease as well as systemic corticosteroids that are given for the treatment of active SLE with heart, kidney, hematologic or central nervous system involvement. New therapeutic agents for SLE include mycophenolate mofetil (Buratti *et al.*, 2001), intravenous immunoglobulins (Rutter *et al.*, 2002) and both α - and γ -interferon (Stanislav *et al.*, 1992).

CCLE Treatment

General measures play a large part in the management of DLE patients, who should be warned against excessive exposure to sunlight, and a physical sun block (containing titanium dioxide and zinc oxide) should be prescribed. Local treatment with various types of steroids is generally prescribed for isolated DLE lesions; these drugs should be applied two or three times daily, but only on the lesions. Recently, tazarotene has been reported to be helpful in the treatment of localized DLE (Kimberly *et al.*, 1999). In the event of cutaneous lesions that are refractory to local treatment, systemic aminoquinoline antimalarials should be instituted; chloroquine (3.5 mg/kg daily) and hydroxychloroquine (5-6.5 mg/kg daily) are the most commonly prescribed, with a preference for the latter because it appears to produce less retinal toxicity. In our experience, antimalarials should be used for 6-8 months, especially in the summertime, with a short suspension in winter. Periodical tests as well as ophthalmologic

controls are recommended to evaluate hematologic, hepatic and retinal toxicity while patients are taking these drugs. Systemic corticosteroid therapy (e.g. prednisone 0.5-1 mg/kg daily) is useful to control the active phase of the disease or in cases where antimalarials fail to clear the skin lesions. In our experience, the association of prednisone (0.5 mg/kg daily), for 2 or 3 weeks, and antimalarials can achieve a faster resolution of the lesions at the beginning of treatment. Thalidomide, administered at a median dose of 100 mg daily, is another referential drug for DLE, but because of the serious side effects, including teratogeny and neuropathy, its clinical use is limited to refractory cases. In non-responders or in case of contraindications some alternative drug, such as sulfasalazine (2 g daily), should be considered. Gold as well as retinoids are considered second-line systemic drugs in the treatment of DLE (Drake *et al.*, 1996). Gold has been reported to be effective in chronic DLE although complete remission is not always obtained. Retinoids are especially useful in hypertrophic LE. The dosages administered are 1mg/kg daily for isotretinoin and 0,5-1 mg/kg daily for etretinate. Other additional therapies for DLE are represented by argon and ND-Yag laser therapy that has proven successful in vascular lesions such as telangiectasias of the face that are common in DLE (Kuhn *et al.*, 2000). A warm environment and suitable clothes for protection from cold are important in CL management. Combined therapy with systemic corticosteroids (0.5 mg/kg daily) and antimalarial drugs (hydroxychloroquine: 5-6.5 mg/Kg/day; chloroquine: 3.5 mg/kg daily) is usually adopted in LP. The steroids are gradually tapered as the lesions subside and hydroxychloroquine is continued for 6 to 12 months to maintain suppression.

SCLE Treatment

Local treatment of SCLE lesions with topical corticosteroids is usually not completely effective. Although a brief course (3-4 weeks) of systemic corticosteroids (20-40 mg/day) can be administered initially to attain rapid control in cases of diffuse cutaneous manifestations in mild systemic disease, every effort should be made to avoid the use of long-term systemic corticosteroids to treat skin lesions. Antimalarials represent the first line agents in systemic treatment of SCLE. The use of hydroxychloroquine sulfate (at the initial daily dose of 400 mg for two to four weeks followed by 200 mg) controls about 80% of SCLE cases. This treatment should be continued for many months, especially during summer, and with the knowledge that, as for DLE, the therapeutic effects are seen only after 6 weeks of treatment.

Other therapies, including thalidomide, retinoids, oral gold, or clofazimine are helpful for patients with resistant disease (Versapuech *et al.*, 2000). Some SCLÉ patients respond favourably to dapsone (100 to 200 mg/day), and this drug can be administered in case of failure with antimalarials. Oral cyclophosphamide (50 mg/day) has been employed with moderate improvement of skin lesions after two months of therapy (Callen *et al.*, 1988).

ACLE Treatment

Since malar rash occurs together with the involvement of internal organs, treatment should depend on the activity and severity of the disease. SLE is usually kept under control only by the combination of corticosteroids with other immunosuppressive drugs. Dapsone (100 mg daily) alone or in combination with prednisone, is the treatment of choice for BSLE. Glucose-6-phosphate dehydrogenase enzyme levels should be obtained before therapy is initiated.

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