Lúpus Eritematoso: Manifestações Cutâneas e Tratamento

Francisca Alves[1], Margarida Gonçalo[2,3]
[1]Interna de Dermatovenereologia, Serviço de Dermatologia, Centro Hospitalar de Coimbra, Coimbra, Portugal
[2]Assistente Graduada de Dermatovenereologia, Serviço de Dermatologia, Centro Hospitalar de Coimbra, Coimbra, Portugal
[3]Professora Convidada da Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal

RESUMO – Lúpus eritematoso cutâneo engloba um vasto leque de manifestações dermatológicas, que podem ou não acompanhar-se de acometimento sistémico. As lesões cutâneas específicas – definidas histologicamente pela presença de dermatite de interface – são ainda dividas em subtipos, concretamente lúpus agudo, subagudo ou crónico. O subtipo crónico inclui ainda o lúpus discóide, bem como variantes mais raras, como o lúpus profundo. As manifestações cutâneas não específicas, nomeadamente o livedo reticular ou purpura, são mais frequentes nos doentes com acometimento sistémico. A abordagem diagnóstica implica a correcta subclassificação do subtipo, através duma combinação de exame físico, estudo laboratorial, análise histológica e ocasionalmente imunofluorescência directa, sendo imperativo a exclusão de atingimento sistémico.
Do ponto de vista terapêutico, os corticosteróides tópicos e antimaláricos permanecem como a base da terapêutica; no entanto, imunossupressores, análogos da talidomida e anticorpos monoclonais são terapias sistémicas disponíveis para o tratamento da doença recalcitrante. A educação do doente acerca de medidas de fotoproteção e evicção de factores despoletantes é fulcral.
PALAVRAS-CHAVE – Lúpus Eritematoso Cutâneo/complicações; Lúpus Eritematoso Cutâneo/diagnóstico; Lúpus Eritematoso Cutâneo/tratamento.

Lupus Erythematosus: Cutaneous Manifestations and Treatment

ABSTRACT – Cutaneous lupus erythematosus (CLE) includes a broad range of dermatologic manifestations, which may or may not be associated with systemic manifestations. Specific CLE - defined by the presence of an interface dermatitis on histopathological evaluation - is divided into several sub-types, namely acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE). CCLE includes discoid lupus erythematosus (DLE), as well as other rarer forms such as LE profundus (LEP). Nonspecific skin findings, such as livedo reticularis or purpura are more frequently seen in patients with systemic disease. Diagnosis requires classification of the subtype, through a combination of physical examination, laboratory studies, histology and sometimes direct immunofluorescence, at the same time ensuring to exclude systemic disease.
Regarding the treatment of CLE, antimalarials and topical steroids continue to be the standard of care; however, immunosuppressants, thalidomide analogs and monoclonal antibodies are possible systemic therapies for recalcitrant disease. Patient education on proper sun protection and avoidance of triggers is crucial. This paper reviews the clinical manifestations of CLE, as well as the treatment.
KEY WORDS – Lupus Erythematosus, Cutaneous/complications; Lupus Erythematosus, Cutaneous/diagnosis; Lupus Erythematosus, Cutaneous/therapy.

1. INTRODUCTION

Lupus erythematosus (LE) is a complex chronic autoimmune disease. LE presents with a wide spectrum of clinical and immunological features and is characterized by pathogenic autoantibodies and immune complexes, attributed to loss of immune tolerance. Systemic lupus erythematosus (SLE) may encompass severe systemic organ involvement (kidney, blood, central nervous system, heart, etc.) in which the skin

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is also a frequently involved. However, in certain cases, LE affects only the skin.

Cutaneous lupus erythematosus (CLE) includes a broad range of dermatologic manifestations, which can be a source of significant morbidity. Cutaneous manifestations can be the single manifestation of LE, but cutaneous involvement is very common in patients with systemic manifestations. In up to 25% of cases skin lesions are the presenting sign of SLE and they are present in approximately 80% of patients during the course of the disease.[1] In fact, after articular involvement, the skin represents the second most frequently affected organ in SLE. [2]

2. EPIDEMIOLOGY

Lupus erythematosus is a common disease and its incidence in the general population is variable, depending on parameters of the studied population, such as ethnicity, age, sex, race and national origin. Most studies evaluated the incidence of SLE, and epidemiological data of the different subtypes of CLE have been more rarely investigated, but CLE appears to be two to three times more frequent than SLE.[3]

Two population-based studies reported an incidence of 4 new cases of CLE per 100 000 inhabitants per year, in Sweden and USA[4,5] with an estimated prevalence around 70 cases per 100 000 persons.[6] Highlighting the importance of skin disease in LE, there appear to be approximately as many patients who have cutaneous LE without concurrent SLE as there are patients who have SLE.[4,5] The mean age at diagnosis with CLE is around 54 years.[5]

As for risk factors, the strongest factor affecting risk for lupus is gender, with a clear female predominance. Regarding only cutaneous involvement, female patients with CLE still outnumber males, with female-to-male ratio estimated to be 3:1.[5]

Another major risk factor is ethnicity. The prevalence of SLE is fourfold higher in African-American women as compared to Caucasian American women (4 in 1000 vs 1 in 1000).[7] Moreover, African-Americans tend to develop disease at an earlier age, and are prone to more severe forms, with a higher mortality rate. SLE is also more common in Asians versus Caucasians.[8]

The risk of developing SLE differs according to the type of skin involvement: it is substantially higher in patients with ACLE than in patients with localized DLE. After an initial diagnosis of CLE, the risk of developing SLE has been estimated to be between 5% and 18% within three to five years of follow-up.[4,5]

3. CUTANEOUS LESIONS IN LUPUS ERYTHEMATOSUS

Skin lesions are classically separated, according to Gilliam and Sontheimer's classification, into specific and non-specific skin manifestations, depending on the presence of an interface dermatitis on histopathological evaluation, defined by the presence of vacuolization and necrosis of basal keratinocytes and a lymphocytic infiltrate at the dermo-epidermal junction.[9,10] These specific cutaneous lesions, included under the designation of cutaneous LE (CLE), are

subdivided into acute, subacute and chronic subtypes based on clinical, histological, and serological features plus average duration of skin lesions: acute cutaneous LE (ACLE), subacute CLE (SCLE), and chronic cutaneous LE (CCLE). Chronic CLE includes discoid LE (DLE) and the less common variants of LE profundus/panniculitis and chilblain LE.[11] LE tumidus, initially included within the chronic subtype, is considered a separate form of cutaneous LE.[12,13] In a large study of more than thousand patients in Sweden, DLE was the most common subset (80%), followed by SCLE (15%), and less than 5% are other more rare types of CLE.[5]

The LE-nonspecific manifestations are more frequently seen in patients with systemic disease and may also occur in other autoimmune diseases; they include vascular changes, exanthema, alopecia and mucous membrane lesions.[14]

3.1. Acute Cutaneous Lupus Erythematosus

ACLE typically presents in the third decade of life, and is often associated with active SLE.[15,16] Acute cutaneous lesions are usually localized, but can be generalized. They tend to be sun-induced, transient and resolve without scarring, although dyspigmentation can occur, especially in patients with darker skin.

The localized form of acute CLE, classically described as "butterfly" or "malar" rash, is present in about half of SLE patients at the time of diagnosis, and can precede the onset of systemic involvement by weeks or months. The "butterfly" rash is characterized by bilateral pink-red erythematous lesions in the malar areas extending over the nasal bridge, typically sparing the nasolabial folds and the periorbital regions[11] (Fig.1a). Lesions vary from macular erythema (the most frequent) to intense edematous confluent papules and plaques, but scaling, erosions and crusting may also be present, and differential diagnosis with rosacea, seborrheic dermatitis or other facial eruptions have to be considered.

Palms and soles may also be affected and lesions on the dorsum of the hands occur between the metacarpophalangeal and interphalangeal joints typically sparing the knuckles, while the opposite occurs in dermatomyositis[1] (Fig. 1b).

Erythema and hemorrhaging patches on the hard palate and erosions or ulcerations of the oral and/or nasal mucosa are not unusual[17] (Fig. 2).

The generalized acute form is usually coincident with systemic flares of the disease. Lesions may appear after sun exposure, predominate on ultraviolet (UV)-exposed areas but progress to widespread symmetric erythematous macular and papular lesions affecting symmetrically the lateral aspect of the arms, elbows, shoulders, knees, and trunk, resembling a maculopapular drug eruption.[14] They are often associated with diffuse hair thinning, oral and nasal mucosal ulcers, which may progress to nasal septum perforation.[18,19]

Histopathology, that is seldom necessary to confirm the diagnosis, shows a very mild interface dermatitis with a dermal infiltration with predominance of neutrophils and carioclasia, and direct immunofluorescence reveals C3 and IgG

Figure 1 - Acute CLE in a patient with anti-ds-DNA and anti-Sm antibodies and severe kidney and central neural system manifestations. **(A)** Typical "butterfly rash", with erythema involving the malar area and nose and sparing the periorbital area and nasolabial folds, and **(B)** erythemato-violaceous and purpuric lesions on the palms and fingers, especially in the proximal nail folds, simulating dermatomyosisitis.

Figure 2 - Oral erosions in the hard palate in a patient with LES.

granular deposits at the dermal-epidermal junction on lesional and often also on normal skin.[14,20] A positive ANA is found in 95% of ACLE patients, as well as a high incidence of anti-double-stranded DNA (anti-dsDNA) and anti-Sm antibodies[21] and systemic involvement, particularly lupus nephritis is particularly frequent in these patients. (REF)

3.2. Subacute Cutaneous Lupus Erythematosus

SCLE occurs primarily in young to middle-aged women, although children and elderly individuals are also affected.[15,18]

Photosensitivity and anti-SSA/Ro autoantibodies occur in 70% - 90% of the patients with subacute CLE[14,22] and one-third to one-half of patients fulfill 4 or more of the classification criteria for SLE[18] but most commonly they have only mild involvement, limited to arthritis and myalgia. A minority can, nevertheless, develop severe systemic organ involvement with lupus vasculitis, nephritis and central nervous

system attainment occurring in <10%.[25,23] Since anti-SSA/Ro autoantibodies are associated with Sjögren syndrome as well as SCLE, it is not surprising that an overlap between these entities has been described.

SCLE lesions involve the face in a symmetric distribution (sparing the midfacial skin and scalp), the V-area of the neck, upper trunk, shoulders and extensor aspects of the upper arms but do not extend below the waist[18,26] (Fig. 3a,b).

There are two morphologic variants of SCLE: annular and papulosquamous. A study of 58 SCLE patients found that 42% had annular SCLE and 39% exhibited papulosquamous SCLE, whereas mixed forms account for 16% of cases.[26] Other studies however have found that papulosquamous SCLE is more common.[27,28]

Annular lesions are characterized by erythematous scaly plaques with raised borders and central clearing, sometimes coalescing to produce a polycyclic array.[18] The papulosquamous variant presents with chronic psoriasiform or eczematous appearance[29] (Fig. 4a,b). Lesions often progress to hypopigmentation but with no scarring or atrophy.[30]

Histopathology is characterized by a pauci-inflammatory, vacuolar, lymphocytic interface dermatitis with hydropic degeneration of the basal keratinocytes, occasional apoptotic keratinocytes, dermal edema and superficial mucin deposition[16] (Fig. 4a,b). DIF immunoglobulin deposits at the dermoepidermal junction occur in approximately 60% of cases.[31]

3.3. Discoid Lupus Erythematosus

Discoid LE is the most common form of chronic CLE observed among dermatologists. It tends to occur in the fourth and fifth decades, and usually is not associated systemic involvement.[18] Only about 5% – 10% of patients develop SLE throughout their disease course,[32,33] the majority at the time of diagnosis or within five years, and in these cases they have the same autoantibodies found in SLE.
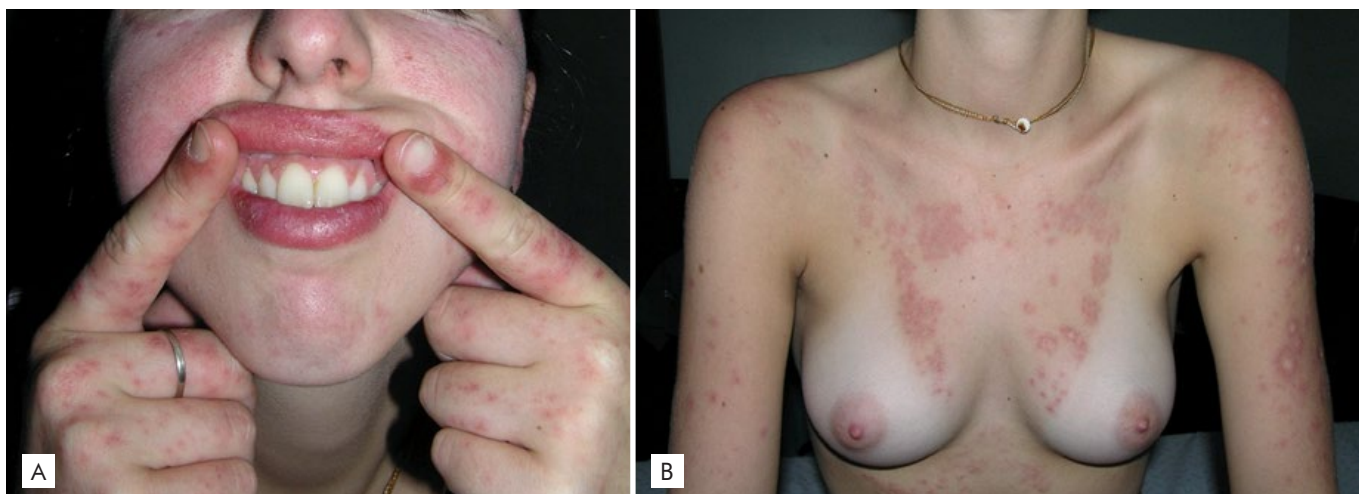
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Figure 3 – Patient with Subacute CLE in a patient with anti-Ro/SSA antibodies and photosensitivity, arthritis and leukopenia, but no other systemic involvement. **(A)** Facial lesions show with a well-demarcated malar rash sparing the nasolabial folds and eyelids, and erosions on the submucosa of the lips and dorsum on the hands. **(B)** Annular lesions in the V-of the chest, upper arms and abdomen are limited to photoexposed areas.

Figure 4 – Two patterns of subacute CLE with minor systemic symptoms, the annular pattern **(A)** and the psoriasiform pattern **(B)**.

In 80% of cases lesions are localized on the head and neck, particularly the upper lip, ears and scalp. A more widespread distribution can occur - generalized discoid LE – with a higher propensity to be associated with systemic disease when lesions extend to the trunk,[34] palms and soles[10] or the oral mucosa, where they can have a whitish lichenoid appearance at the jugal area.[35]

Discoid LE usually begins as erythematous scaly papules, with well-demarcated borders, that gradually progress to indurated coin-shaped plaques, with follicular hyperkeratosis, adherent scale, hypopigmentation in the central area and hyperpigmentation at the periphery, and later develop scarring with persistent atrophy and alopecia (Fig.s 6 and 7).In rare cases, chronic verrucous and hypertrophic lesions may also develop.[10]

Histology of longstanding active DLE lesions reveals a lichenoid reaction pattern, and an intensely inflammatory superficial and deep dermal infiltrate with a significant peri-adnexal infiltrate predominantly of lymphocytes. A significant thickening of the basement membrane is frequent
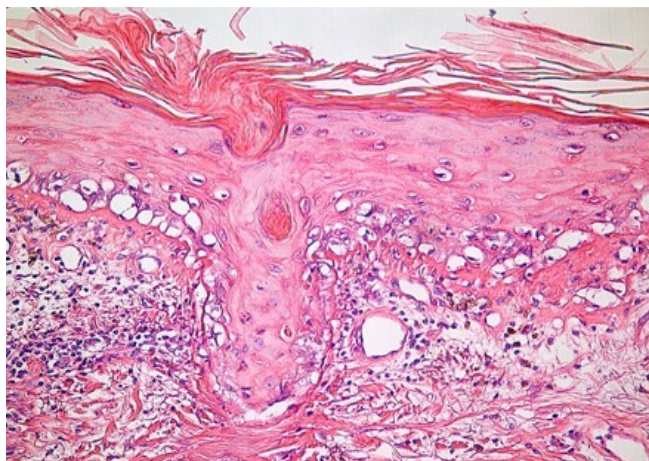
Figure 5 - Histologic aspect of subacute with intense hydropic degeneration of basal keratinocytes, occasional apoptosis, thickening of the basement membrane and superficial dermal infiltrate of lymphocytes and monocytes (HE, x40).

in long lasting lesions. Other epidermal changes include hyperkeratosis and keratotic follicular plugging. DLE patients have a lower incidence of ANA, dsDNA, Sm, and Ro/SSA antibodies, as compared to other CLE sub-types.[36]

3.4. Lupus Panniculitis

Lupus panniculitis is a rare form of CLE characterized by intense inflammation in the adipose tissue which presents as painful firm subcutaneous nodules or plaques on the upper arms, upper trunk, breasts, buttocks, thighs, face and scalp, sometimes with ulceration, and with a high propensity for disfiguring, depressed areas with prominent scarring. (Fig 8) It tends to have a chronic course, with recurrent flares, and it can present as a purely cutaneous disease, while association with SLE occurs occasionally.[16]

On histology the characteristic finding is a lobular panniculitis with prominent dense lymphocytic infiltrate, and mucin deposition between collagen bundles.[37]

Figure 6 - Discoid CLE in the face of patients with no systemic symptoms, showing erythematous lesions with thick scales, peripheral hyperpigmentation and older lesions with an atrophic white center with hypopigmentation and hair loss in the beard area.
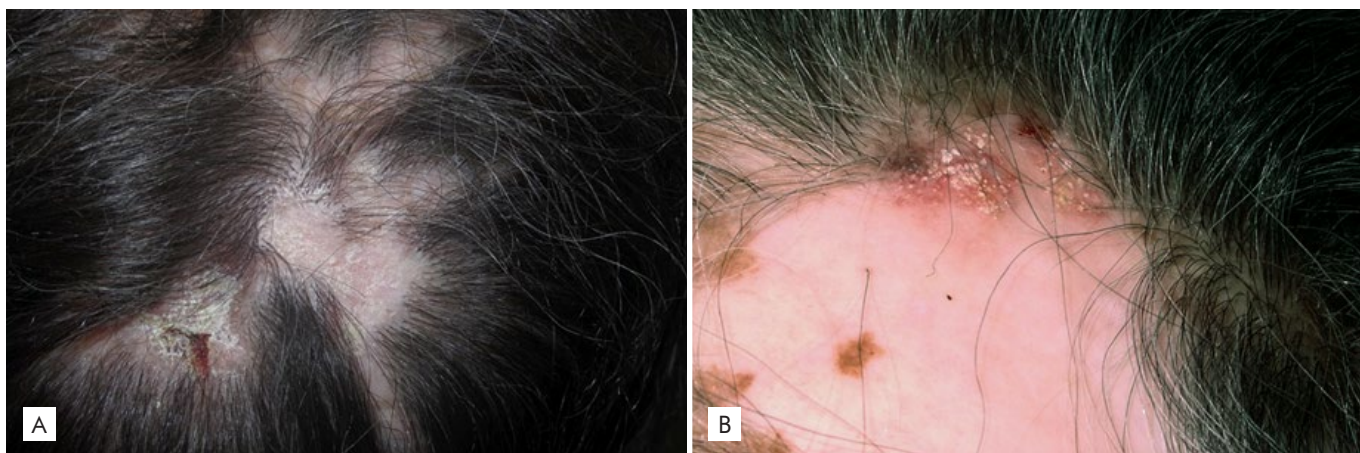

Figure 7 - Cicatricial alopecia in chronic CLE in the face of patients with no systemic symptoms, showing erythematous lesions with thick scales **(A)**, in a more advanced case with residual hypopigmentation and atrophy with no signs of hair follicles and peripheral hyperpigmentation with some active lesions with erythema and follicular keratosis **(B)**.

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3.5. Chilblain Lupus

Chilblain lupus is another form of chronic CLE resembling frostbite. It consists of pruritic, painful red to violaceous papules and plaques occurring in cold-exposed areas, such as the toes, fingers, and sometimes the nose, elbows, knees and lower legs.[36] Lesions may progress to central erosions or ulcerations and around 20% will develop systemic manifestations.[38]

A familial form of chilblain lupus with a childhood onset is caused by heterozygous mutations in *TREX1* or *SAMHD1*.[39] Affected individuals may have arthralgia and a positive ANA, but otherwise do not develop systemic disease.

3.6 Lupus Erythematosus Tumidus

Lupus erythematosus tumidus (or intermittent cutaneous LE) has distint clinical and histological features, with an extreme photosensitivity and a high response to antimalarials,[40,41] and rare association with SLE.[40,42]

LE tumidus occurs preferentially in men and has a benign course, with numerous flares but no progression to scarring or atrophy.[42] Lesions are located on sun-exposed areas, most commonly the face, or upper back, neck, arms and shoulders[40] and consist of swollen erythematous papules and plaques, without scale or follicular plugging, often forming polycyclic plaques with sharp raised borders and smooth surfaces, with central clearing (Fig 9).

3.7 Bullous Lesions in LE

Bullous lesions occur mostly in SLE can occur either as a result of major basal cell vacuolization or massive keratinocyte apoptosis (acute syndrome of pan-epidermolysis)[43,44] and may have an higher association with lupus nephritis and hematological abnormalities.[45,46]

Lesions may simulate erythema multiforme with target-like lesions (Rowell syndrome)[29] but rarely, a dramatic, acute extensive eruption like toxic epidermal necrolysis (TEN) may appear *de novo* or occur in patients with a preexisting diagnosis (Fig. 10a,b).[45]

Other bullous eruptions in SLE can resemble auto-immune bullous skin diseases, namely dermatitis herpetiformis (vesicles and bullae in an arciform or figurate distribution on clinically normal-appearing skin or over an erythematous base that respond to dapsone), bullous pemphigoid or epidermolysis bullosa acquisita, or they may represent overlap between these auto-immune diseases.

3.7 Neonatal Lupus Erythematosus (NLE)

A neonatal form of SCLE may occur in infants whose mothers transfer anti-SSA/Ro autoantibodies causing cutaneous manifestations as well as systemic disease, such as congenital heart block, although only about 10% of the children have both manifestations.[5]

Lesions are clinically and histologically identical to adult SCLE. Erythematosus, non-scarring annular plaques frequently affected the face, especially in the scalp and peri-orbital
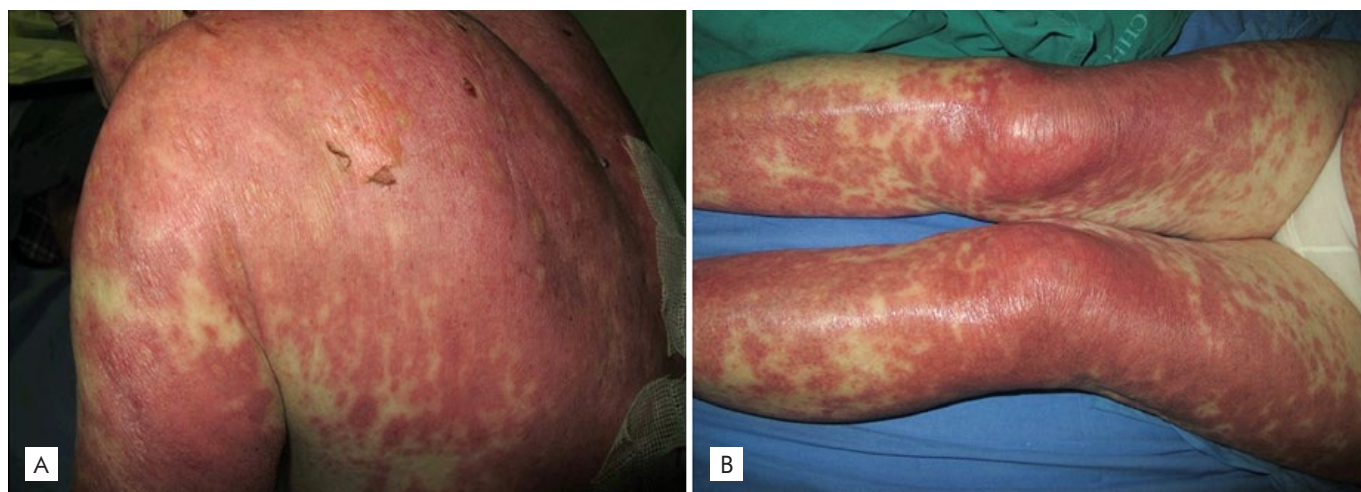
Figure 10 – "TEN-like" lupus erythematosus after sun exposure as a presenting sign in a patient who developed severe SLE. Vesicular and bullous confluent lesions in a symmetric distribution had a positive Nikolsky sign on the back **(A)**, but mucosal erosions were missing.

region ("raccoon or owl eye").[2] Photosensitivity is very common in NLE, but sun exposure is not required, as occasionally lesions are present at birth. Lesions occur shortly after birth (0-2 months) and as the titers of maternal antibodies degrade within the first 6 months[2] lesions resolve spontaneously without scarring, although dyspigmentation may persist for many months, and some children have residual telangiectasias.

3.8 Nonspecific Cutaneous Lesions in LE

Nonspecific cutaneous lesions in LE are mostly due to vasculitis/vasculopathy. They are frequent in SLE patients, particularly during flares.[47]

About 10% – 20% of SLE patients have some form of cutaneous vasculitis, either small vessel leukocytoclastic vasculitis, manifesting as palpable purpura or less frequently as urticarial vasculitis with hypocomplementemia (non-pruritic and painful long-lasting urticarial lesions that resolve after transient purpura).[14]

Splinter hemorrhages, purpura, urticarial papules, ulcerations or cutaneous infarctions resembling Degos disease or *atrophie blanche* due to vasculitis scars may occur, as well as thrombophlebitis and erythromelalgia. Nail fold telangiectasia with prominent tortuous capillaries and hemorrhage can be observed on capillaroscopy but abnormalities are more subtle than in DM and there are no avascular areas as in SSc.[48]

Thrombotic vasculopathy, often in the context of antiphospholipd syndrome encompasses a wide range of cutaneous manifestations, including *livedo reticularis*, *livedo racemosa*, Raynaud's phenomenon and palmar erythema.

Non-scarring alopecia occurs in 40% – 70% of SLE patients, with diffuse hair thinning and hair fragility due to *telogen/anagen effluvium* and lupus hairs (diffuse thinning or a receding frontal hairline with broken hairs). In the absence of other causes, alopecia is one of the SLICC 2012 criteria for the classification of SLE.[49]

Other less-frequent non-specific lesions observed particularly in SLE include: - papulonodular mucinosis, presenting as skin-colored or slightly erythematous papules and nodules without epidermal changes especially involving the trunk, scalp and upper extremities; - a Sweet syndrome-like, also named non-bullous neutrophilic LE, and other dermatoses with striking cutaneous infiltration of neutrophils related to the activation of the innate immune response,[72] such as amicrobial pustulosis of the skin folds, neutrophilic urticarial dermatosis and pyoderma gangrenosum.[51,52]

4. DIAGNOSTIC APPROACH

To properly establish the diagnosis of CLE, systemic involvement of the disease must be excluded first. Also, the cutaneous sub-type must be correctly classified. A specific diagnostic approach should be based on the findings of patient history, clinical examination, laboratory studies as well as histology.

Laboratory studies should always include a complete blood count (CBC) to evaluate anemia, thrombocytopenia or leucopenia, screening for renal involvement with serum creatinine and urinalysis. Autoantibody testing is critical and should begin with an ANA screen, knowing that a negative ANA is helpful, as it is seldom negative in SLE but, on the other hand, a positive ANA can be seen in patients with CLE, with or without systemic manifestations, and a positive ANA is seen in up to 35% of the general population healthy individuals at a dilution of 1:40, especially in older people.[53] Further autoantibody tests revealing positive dsDNA, Sm and ribosomal P is highly specific for SLE, and these autoantibodies serve as markers for the development of systemic disease (54). Other autoantibodies occurring in SLE (although not specifically) include antibodies to Ro, La, U1RNP, histones and single-stranded DNA (ssDNA). Except anti-Ro/SSA- and anti-La/SSB-antibodies, which occur particularly in patients with SCLE, there are no other specific autoantibodies to

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differentiate the subtypes of CLE used in routine practice. One further possible target of auto-antibodies is annexin 1, which has been suggested to play an important role in the prevention of autoimmune diseases.[55] A study revealed that, compared to controls, a significantly higher level of anti-annexin 1 antibodies was observed in CLE patients.[56] A high C-RP or ESR as well as a low C3 and C4 may indicate severity of systemic involvement.

Lesional biopsy histology is often critical for the diagnosis, and histologic findings depend in large part on the subtype. DIF of lesional biopsies can supplement non-definitive histologic findings, detecting immunoglobulins and complement deposits at the dermal-epidermal junction. Deposits are typically granular in appearance, and most commonly contain IgG and IgM, and in rare cases, IgA, as well as the complement component C3.[57] Non-lesional lupus band tests are seen in SLE and have been reported in multiple other auto-immune conditions including rheumatoid arthritis, Sjogren's syndrome, dermatomyositis, scleroderma and leprosy.[1]

On another level, photoprovocation is a potential adjunct to histopathological diagnosis of the CLE sub-type. Photoprovocation according to a standardized protocol has been established to confirm the diagnosis of CLE and to evaluate the photosensitivity of the disease.[58]

The present classification criteria for SLE, both ACR (American College of Rheumatology), SLICC and EULAR (European League Against Rheumatism) consider cutaneous lesions. The more recent EULAR classification, shown to have a high sensitivity and specificity, includes positive ANA at least once as obligatory entry criterion.[59] Other additive criteria grouped in seven clinical domains (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and 3 immunologic domains (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) that are weighted individually from 2 to 10. Patients that score ≥10 points are classified as SLE.

5. TREATMENT OF CUTANEOUS LE
When managing CLE, preventing the formation of new lesions and improving skin appearance are important goals, achieved through a combination of patient education (trigger avoidance) and topical and systemic therapies.

Sun protection is a crucial part of the management because UV irradiation exacerbates both skin and also for systemic disease in SLE patients. Both UVA and UVB irradiation have been shown to induce CLE lesions.[60] Sun protection should be emphasized even in patients whose skin lesions are not induced or exacerbated by sun exposure and also to prevent skin cancer particularly in hypopigmented skin or in chronic discoid lesions and in those on immunosuppressive therapy. Based on a vehicle-controlled, randomized, double-blind trial of 25 photosensitive CLE patients, which reported 100% protection from UVA and UVB irradiation with a broad-spectrum sunscreen,[61] sunscreen with a sun protection factor (SPF) of at least 50 should be applied to exposed skin 20-30 min prior to expected exposure on a daily basis, and more often if

sun sensitivity is high or sun exposure is intense or prolonged.

Protective clothing is also very important (often, the proper protective clothing is significantly better than sunscreens) and sun avoidance is even more effective.

Smoking cessation should be strongly encouraged[62,63] as it enhances toll-like receptor 9 responsiveness and IFN type 1 production in plasmacytoid dendritic cells.[64] A larger percentage of cigarette smokers are represented amongst CLE patients and smokers may have more extensive cutaneous disease and tend to be more refractory to systemic therapies.

Cutaneous lesions in SLE usually benefit from systemic treatments and can improve in parallel with the control of systemic disease, but sometimes the skin may oblige specific additional cutaneous and systemic therapies. Treatment of CLE should begin with topicals, but topical therapy is often insufficient in SCLE and LE tumidous.[65]

5.1 Topical Therapy
Topical (or intralesional) corticosteroids are a mainstay of topical therapy, as they are rapid to produce therapeutic effects. Although systemic side effects of corticosteroids are largely avoided, cutaneous side effects (atrophy, telangiectasia) are not, as there is a need to use potent topical corticosteroids often as ointments. For safety reasons, the lowest potency allowing for resolution should be used for the shortest duration possible and only on affected sites

In active discoid lesions and LE tumidus, and particularly in refractory localized lesions, monthly injections of intralesional triamcinolone (4-5 mg/mL) can be very effective.[66]

Because of the concern with cutaneous side effects of corticosteroids, topical calcineurin inhibitors have emerged as an alternative for various CLE sub-types,[67] especially for children and facial lesions A double-blind, randomized control trial treated half the face of 20 patients with tacrolimus 0.1% ointment and the other half with clobetasol propionate 0.05% ointment showed equal efficacy; nevertheless, 61% of patients developed telangiectasia on the clobetasol side as early as week 3, indicating that tacrolimus may be a safer option.[68] Most ACLE and CCLE lesions respond well to treatment,

Physical treatments available for CLE include laser therapy, cryotherapy and dermabrasion. Efficacy of pulsed-dye and argon lasers has been shown in several case reports and series. An open prospective study of 12 discoid LE patients treated with pulsed-dye laser demonstrated efficacy after 6 weeks of treatment, but purpura, pain and post-inflammatory pigmentation were the reported as side effects.[69]

5.2. Systemic Therapy
Systemic therapies are added to topical therapy in situations refractory to topical treatments, or in cases where there is widespread involvement or significant tendency to scarring. With the exception of thalidomide, drugs used for the treatment of the various CLE sub-types are generally also used for SLE treatment.

Antimalarial therapy, with response rates up to 95%, is considered the first-line systemic therapy for all CLE sub-types

and it remains the gold standard for systemic therapy. Nevertheless, response to antimalarials is relatively slow: 2 or 3 months for results to be apparent, and several more months to achieve maximal efficacy.

Hydroxychloroquine sulfate is considered the drug of choice, at 200-400 mg/day or up to 6.5 mg/kg *ideal body* weight/day. It is considered safer than its more effective counterpart, chloroquine, due to a lower incidence of retinopathy. In patients unresponsive to hydroxychloroquine, quinacrine 100 mg may be added for a synergistic effect, without an increased risk of retinopathy.[70] This combined therapy heightens efficacy, with a reported 67% improvement rate in patients who had previously failed hydroxychloroquine monotherapy.[70] If a patient fails the hydroxychloroquine plus quinacrine combination, a switch to chloroquine may be considered, but due to the unacceptable risk of retinopathy, hydroxychloroquine and chloroquine should not be used together.[71] For chloroquine, the eye toxicity-minimizing dose is < 3.5-4 mg/kg *ideal body* weight/day. Antimalarials are usually is well tolerated but besides ocular toxicity, xerosis, lichenoid drug eruptions, blue–gray skin hyperpigmentation, gastrointestinal upset, myopathy and cardiomyopathy may occur. Quinacrine in particular can cause yellow discolouration of skin, sclera and bodily fluids. Regular retinopathy screenings are recommended by the American Academy of Ophthalmology, at intervals based on the risk status.[72] Antimalarial therapy is contraindicated in patients with pre-existing retinopathy, blood disorders and myasthenia gravis.[73]

Cutaneous disease refractory to antimalarials is often refractory to other systemic treatments, but risks are deemed to be worth the potential benefits for oral retinoids, thalidomide or lenalidomide, systemic corticosteroids, immunosuppressive agents such as mycophenolate mofetil or methotrexate, or biological agents. Nevertheless, 10% of patients are intolerant or have recalcitrant lesions and there are no large studies addressing the efficacy of current therapies for refractory CLE.

Systemic corticosteroids are usually avoided, taking into consideration the well-known deleterious effects of prolonged therapy, particularly in LE patients who are at an increased risk of developing avascular necrosis. Corticosteroids can occasionally be considered as a short course option in patients with severe disease as a brigde therapy before the onset of action of other therapies. Appropriate doses of prednisone (0.5-1.0 mg/kg/day) can be tapered over 2-4 weeks.[74] In cases with moderate to severe organ involvement, corticosteroids are the primary treatment, possibly with pulse cyclophosphamide and/or pulse corticosteroids.

Methotrexate (7.5-25 mg orally or subcutaneously once a week) is advised in antimalarial-refractory cases as a second line therapy, especially in ACLE and CCLE, and also as a corticosteroid-sparing agent.[74] A retrospective analysis of 43 treatment-refractory CLE patients found improvement in 98% of cases.[75]

Oral retinoids have been especially useful in hypertrophic CLE and discoid lupus.[76] Multiple case reports attest

isotretinoin's efficacy[66] and in a randomized controlled trial, acitretin was demonstrated to be effective in half of CLE patients. Recommended dosages of acitretin and isotretinoin are 0.2-1.0 mg/kg/day. Since retinoids are highly teratogenic, it is critical to ensure effective contraception in women of childbearing potential, both during and after treatment.[73]

Dapsone has been used effectively in bullous LE, lupus panniculitis, oral ulceration, as well as vasculitic and urticarial lesions. Hyperkeratotic lesions do not respond to dapsone,[77] but the bullous form responds very well.[78] Combined results of three case series of 55 CLE patients treated with dapsone demonstrated a 55% improvement rate.[66] Dapsone is started at 50 mg daily, with 25 mg week increments, until a maximum of 200 mg/day. Regular monitoring for haematologic and hepatic toxicities is crucial. Dapsone is contra-indicated in patients with glucose-6-phosphate dehydrogenase deficiency.

Mycophenolate mofetil (MMF) has been shown to be effective in all CLE sub-types in small studies and multiple case reports. In an open pilot trial with patients with SLE treated with MMF, improvements in skin manifestations were noticed.[79] MMF is usually dosed at 1.0 to 3.0 g/day and needs renal dosage adjustment. Adverse effects that are commonly seen with MMF include leukopenia, vomiting and abdominal cramping.

Azathioprine, was also shown to successfully treat DLE in several small case series.[80-82]

Multiple case series validate the use of *thalidomide* in CCLE, SCLE and LE tumidus.[83,84] The initial recommended dose (400 mg/day) can be tapered down to 50-100 mg/day. Lenalidomide (5-10 mg/day) is a thalidomide analogue more recently used in a case series of refractory CLE and two small open-label trials.[85-87] Both drugs are very and rapidly effective in severe-treatment resistant cases,[88] and both are used in severe CLE, especially in deep-seated and discoid lesions.[89] They are mostly used as remission-inducing agents in combination with antimalarials. Thalidomide is a potent teratogen, and a frequent side effect is peripheral neuropathy (25% - 30%), which can be irreversible and whose frequency is maximal during the first year of treatment.[90,91] Lenalidomide may have a lower risk of developing peripheral neuropathy. Additional potential side effects are drowsiness, amenorrhea, and thrombotic events.

Intravenous immunoglobulin (IVIG) has proven effective as a remission-inducing agent, especially for SCLE, but positive results are generally short lived. It should be reserved to gain rapid control of severe disease, while initiating other long-term therapies.

Rituximab is a chimeric monoclonal antibody specific for human CD20, with a poor efficacy in DLE and variable efficacy for SCLE, implying that the underlying pathogenesis is not mainly dependent on B cells.[92]

Belimumab is another monoclonal antibody used in SLE that reduces B cell survival, but efficacy in CLE has not been well studied. Nevertheless, in a case series of five patients with ACLE, SCLE, and/or DLE, with the addition of intravenous

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belimumab all had significant improvement in disease activity evaluated by the CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index).[93]

Additional therapies that have been used in the treatment of CLE include ustekinumab, phenytoin, sulfasalazine, danazol and extracorporeal photophoresis. Agents currently under investigation for their efficacy and safety in CLE include topical R-salbutamol oral apremilast and intravenous sirukumab (a human anti-IL-6 monoclonal antibody). Additional information is necessary to establish their efficacy and safety, although early findings suggest that these agents may constitute valid treatment alternatives.

CONCLUSION

LE can present with an extremely broad spectrum of cutaneous manifestations, and cutaneous lesions occur in 80% of patients with SLE and often as the initial manifestation of the disease; thus, their early recognition is of major importance, in order to provide an adequate management of affected patients.

Due to their different prognosis, the diagnosis of CLE requires further classification into the different sub-types, which is accomplished by evaluating clinical and histologic findings. Appropriate laboratory studies should be individually requested in order to exclude extra-cutaneous involvement.

Further research will identify and refine the physiopathological mechanisms that lead to the disease, and facilitate development of specific therapies, which go beyond general immunosuppressive approaches, especially for recalcitrant disease.

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VERIFIQUE O QUE APRENDEU

1. **Regarding CLE treatment, choose the right sentence:**
   a) Talidomide frequently causes peripheral neuropathy, which is always reversible with its discontinuation.
   b) In refractory cases, hydroxychloroquine and chloroquine can be used together, without significant risk of retinopathy.
   c) Hyperkeratotic lesions respond very well to dapsone.
   d) Bullous lesions respond very well to dapsone.

2. **Choose the false sentence:**
   a) LE tumidus, initially included within the chronic subtype, is considered a separate form of cutaneous LE.
   b) The LE-nonspecific manifestations are more frequently seen in patients with systemic disease.

   c) The great majority of patients with discoid LE eventually develop SLE throughout their disease course.
   d) The more recent EULAR classification for includes positive ANA at least once as obligatory entry criterion.

3. **Choose the right sentence:**
   a) In neonatal lupus, lesions are clinically and histologically identical to adult ACLE, and systemic disease may occur.
   b) Concerning lupus panniculitis, on histology, the characteristic finding is a septal panniculitis with prominent dense lymphocytic infiltrate.
   c) ACLE lesions tend to be sun-induced and usually resolve with proeminent scarring.
   d) Lupus erythematosus tumidus lesions characteristically have extreme photosensitivity.

Correct answers: 1-d); 2-c); 3-d).