

# Cutaneous lupus erythematosus: An update

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## ABSTRACT

Lupus erythematosus (LE) is a chronic, autoimmune, multisystem disease that displays many diverse symptoms in which localized cutaneous LE (CLE) is on one end of the spectrum and severe systemic LE (SLE) on the other end. The underlying cause of LE is unknown but the etiology is thought to be multifactorial and polygenic. CLE is a disfiguring, chronic skin disease, with a significant impact on the patients' everyday life. CLE are further divided into three main subsets: Acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE), where classic discoid LE (DLE) is the most common form. These subsets are defined by clinical symptoms, average duration of symptoms and histological and serological findings, although, the three subtypes can have overlapping clinical features. CLE patients display well-defined skin lesions, often in sun-exposed areas. The disease often has a chronic and relapsing course that can be induced or aggravated by UV light. It is important to confirm a CLE diagnosis histopathologically by a biopsy and in that there are several differential diagnoses and because CLE is a chronic disease in which regular follow-up is important and systemic treatment is sometimes indicated.

**Key words:** Acute cutaneous lupus erythematosus, chronic cutaneous lupus erythematosus, cutaneous lupus erythematosus, cutaneous, discoid lupus erythematosus, erythematosus, lupus, subacute cutaneous lupus erythematosus

## INTRODUCTION

Lupus Erythematosus (LE) is a chronic, autoimmune disease that includes a broad spectrum of symptoms. Lupus is the Latin word for wolf and has been used to name various skin diseases at least since the 10<sup>th</sup> century. LE is included among the so called connective tissue diseases and is divided into one systemic form – SLE and one cutaneous form – CLE. They can occur both together and separately [Figure 1]. The LE disease follows a chronic course with sudden exacerbations and periods of remission. The classification of CLE can be difficult and confusing but the improved classification in 1979 by the American dermatologists (Gilliam and Sontheimer) has gained wide acceptance.<sup>[1]</sup> According to Gilliam and Sontheimer, the cutaneous manifestations of LE can be divided into LE-specific and LE-non-specific skin manifestations based on histopathological findings.<sup>[2]</sup> The LE-specific skin manifestations show a typical histopathological picture with a lichenoid tissue reaction. LE-specific skin manifestations can be further subdivided into acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE) where classic discoid LE (DLE) is the most common form [Table 1].

An alternative classification has also been suggested which includes lupus erythematosus tumidus (LET) as a separate subgroup; the intermittent subtype of CLE (ICLE).<sup>[3]</sup> The LE-non-specific skin manifestations include a wide range of symptoms with different histopathological pictures. The LE-non-specific skin manifestations are not exclusive to LE disease but are often seen in patients with active SLE but also in several other autoimmune diseases. It is important to screen a patient with CLE for LE-non-specific symptoms since their presence can imply systemic involvement and progression to SLE.<sup>[4]</sup> An overview of LE-non-specific manifestations is included in Table 2.

## EPIDEMIOLOGY

Earlier epidemiological research of CLE has been hampered by a shortage of case ascertainment and much of the knowledge is based on rather small and often retrospective studies. Recent population-based studies have shown that the incidence of CLE in Sweden and USA is 4/100,000 inhabitants;<sup>[5,6]</sup> in both studies the population majority were Caucasians. SLE is more common in Asians and African Americans

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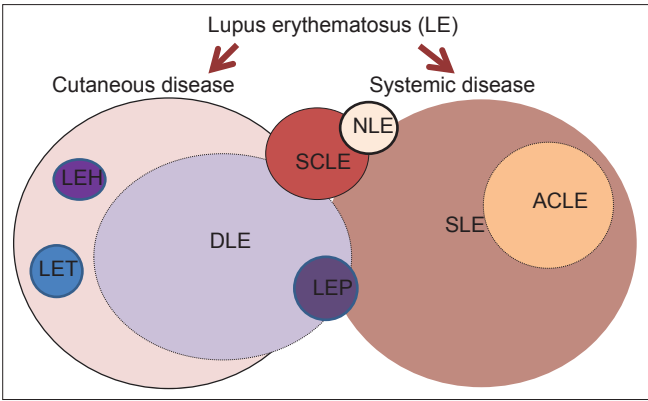
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**Figure 1:** Schematic illustration of the CLE subsets and their relation to SLE. LEH-LE hypertrophicus, LET-LE tumidus, DLE-discoid LE, SCLE-subacute LE, LEP-LE profundus, NLE-neonatal LE, ACLE-acute cutaneous LE, SLE-systemic LE



**Figure 2a:** Subacute cutaneous lupus erythematosus



**Figure 2b:** Close-up image of the SCLE lesion seen in Figure 2



**Figure 3:** Close up view of a DLE lesion

than in Caucasians;<sup>[7-9]</sup> no such studies have been made for CLE but DLE is considered more common among African Americans and SCLE is more common among Caucasians. DLE is the most common subset (80%), followed by SCLE (15%) and less than 5% are other more rare types of CLE such as lupus profundus or lupus panniculitis.<sup>[5]</sup> In a recently published study, the female to male ratio have been shown to be 3:1 for both DLE and SCLE, mean age for being diagnosed with CLE was around 54 years in that study.<sup>[5]</sup>

**PATHOGENESIS**

The pathogenesis of CLE is multifactorial and a genetic predisposition is essential.<sup>[7,10]</sup> The disease is then affected by different environmental causes. CLE is polygenic, which means that many genes are important for the disease development. Genome wide scans have been performed in SLE patients and more than 25 risk loci have been identified,<sup>[7,11-13]</sup> no such scans have been done in CLE yet. The major histocompatibility (MHC) complex and the complement pathway have been shown to be involved in both SLE and CLE and just recently the integrin alpha M (ITGAM) gene has

Table 1: A modified version of Gilliam's classification of LE-specific skin manifestations <sup>[2,4,15,21,61,74,77,78]</sup>	
Acute CLE (15%)	
Localized ACLE (malar rash, butterfly rash) (90-95%)	
Generalized ACLE (morbilliform) (5-10%)	
Toxic epidermal necrolysis-like ACLE (very rare)	
Subacute CLE (8%)	
Annular SCLE (42%)	
Papulosquamous/psoriasiform SCLE (39%)*	
Vesiculobullous annular SCLE	
Toxic epidermal necrolysis-like SCLE (very rare)	
Chronic cutaneous LE (73%)	
Discoid LE (80-85%)-Localized DLE (70%)-Generalized DLE (30%)	
Hypertrophic/verrucous LE	
LE profundus/panniculitis	
LE tumidus/papulomucinous LE	
Mucosal LE (Oral, nasal, conjunctival, genital)	
Chilblain LE	
Lichenoid DLE: LE-lichen planus overlap syndrome (lupus planus), probably represent the coexistence of two skin diseases	
*16% is a combination of the annular and the papulosquamous form.	
LE: Lupus Erythematosus	

**Table 2: A modified version of Gilliam's classification of LE-non-specific skin disease.** [15,21,46,77,78]

Cutaneous vascular disease
Vasculitis
Leukocytoclastic
Periarteritis nodosa-like
Vasculopathy
Degos disease-like lesions
Secondary atrophie blanche
Periungual telangiectasia
Livedo reticularis
Trombophlebitis
Raynaud's phenomenon
Erythromelalgia
Non-scarring alopecia
Telogen effluvium
Alopecia areata
Sclerodactyly
More associated with RA and scleroderma <sup>[45]</sup>
Rheumatoid nodules
More associated with RA and scleroderma <sup>[45]</sup>
Calcinosis cutis
LE-non-specific bullous lesions
Urticaria
Papulonodular mucinosis
Cutis laxa/anetoderma/mid-dermal elastolysis
Acanthosis nigricans
Erythema multiforme (Rowell's syndrome)
Leg ulcers
Lichen planus
Photosensitivity
Chilblain (perniosis)

LE: Lupus Erythematosus, RA: Rheumatoid Arthritis

also been shown to play a role in both SLE and DLE.<sup>[7,13-18]</sup> HLA-A1-B8, DR-3 is a haplotype strongly associated with the SCLE subset.<sup>[10,17,19-22]</sup> A majority of the CLE patients are very sensitive to the sun and exposure to sunlight can cause an exacerbation.<sup>[13,23,24]</sup> Smoking is more prevalent among patients with CLE and smoking has been associated with both a more severe disease and worse response to treatment, especially antimalarial.<sup>[25-27]</sup> CLE is not associated with alcohol drinking.<sup>[27]</sup> Sex hormones are thought to play an important role in CLE as well as in several other autoimmune diseases with a female predominance. Diet, infections and stress have also been associated with CLE but this is a more uncertain association so far.<sup>[10,28,29]</sup> Drug-induced subacute CLE have been well known for several years and more than 100 case reports have been published but it is only recently that the association has been shown in a larger epidemiological study.<sup>[30]</sup> In this study about one third of the SCLE cases were associated to a previous drug exposition. The largest

relative risks were seen for terbinafine, tumor-necrosis-factor alpha (TNF- $\alpha$ ) inhibitors, antiepileptic and proton-pump inhibitors (PPIs).<sup>[30]</sup>

## CLASSIFICATION OF CLE

The most common forms of CLE all show the same histopathological lichenoid tissue reaction (interface dermatitis) but the subsets have a gradual difference between them and the histopathological picture is also highly dependent of the age of the lesion.<sup>[2,7,21,22,31,32]</sup> The interface is the junction zone between epidermis and dermis and the basal keratinocytes here are the primary focus of injury in CLE.<sup>[7,21,23,31,33]</sup> A lichenoid tissue reaction can also be seen in lichen planus, lichen sclerosis et atrophicus, dermatomyositis and erythema multiforme.<sup>[31,32]</sup> Interferon (IFN) has been shown to play an important role in the development of CLE skin lesions.<sup>[23]</sup> It is important to confirm a CLE diagnosis histopathologically by a punch biopsy since the disease is chronic and sometimes need systemic treatment and careful advice concerning triggering factors. The subsets of CLE are further classified according to different clinical symptoms, average duration of symptoms and serological findings into acute CLE, subacute CLE and chronic CLE [Table 1].

### Acute CLE

Acute CLE is almost always associated with systemic disease and the most typical patient is a fair-skinned female in her 30s.<sup>[2]</sup> The lesions can be localized (concentrated above the neck) or generalized. Malar rash or butterfly erythema is the most typical localized lesion, an erythema (and/or oedema) over the malar eminence with a tendency to spare the nasolabial folds; it often comes after sun exposure. The lesions last for hours to days. Postinflammatory hyperpigmentation is common but scarring does not occur. Differential diagnoses are erysipelas, contact/atopic/seborrheic dermatitis, dermatomyositis, rosacea, drug-induced phototoxic reactions, and viral rash.<sup>[2,31]</sup>

The generalized form of acute CLE is more uncommon but it is also associated with a previous sun exposure and preferably located to sun-exposed areas. Differential diagnoses are toxicodermatitis, viral exanthema and erythema multiforme.<sup>[7,34-36]</sup>

### Subacute CLE

Subacute CLE has been considered as a subset of its own since 1979 when it was first described by Gilliam and Sontheimer.<sup>[1]</sup> A majority of the patients (85%) are considered photosensitive and the lesions are mainly located to sun exposed areas; neck, chest, upper back, shoulders, dorsal parts of the arms and hands but surprisingly the face and scalp are seldom involved.<sup>[4,21,37]</sup> Subacute CLE is more common among Caucasians. The lesions start as erythematosus plaques or papules and then become widespread annular, polycyclic lesions that clear



centrally or papulosquamous (psoriasiform) lesions or a combination of these two forms [Figure 2a and 2b].<sup>[2,38,39]</sup> The lesions are non-scarring but often heal with pigmentary changes that are long-lasting.<sup>[7,21]</sup> Subacute CLE is strongly associated with the anti-Ro/SSA antibody, about 70% display the antibody, 60-80% display positive anti-nuclear antibody (ANA) and 30-50% display the anti-La/SSB antibody which is almost always seen together with the anti-Ro/SSA antibody.<sup>[21,40-42]</sup> About 15-20% of SCLE patients also have other types of CLE lesions (e.g. DLE or ACLE) and about 50% of SCLE patients fulfill the American College of Rheumatology (ACR) criteria for SLE but seldom develop severe systemic disease. Arthritis and arthralgia are the most common symptoms.<sup>[4,7,17,22,43,44]</sup> There are many possible differential diagnoses, for example psoriasis vulgaris, lichen planus, pityriasis rubra pilaris, mycosis fungoides, tinea corporis, nummular eczema, polymorphic light eruption, drug rash, and dermatomyositis.<sup>[13,39,42,45,46]</sup>

### Drug-induced SCLE

Over 125 case reports of drug-induced SCLE have been published and more than 40 drugs with diverse latencies have been involved but large observational studies have been lacking.<sup>[47]</sup> Just recently a population-based matched case-control study that included all individuals registered with a SCLE diagnosis for the first time during 2006-9 in Sweden were published.<sup>[30]</sup> The aim of that study was to examine the association between exposure to certain suspected drugs (previously reported as possible triggers) and the subsequent development of SCLE in a large group of incident SCLE cases. A total of 234 SCLE patients were enrolled together with 2311 matched controls. They were then linked to the Prescribed Drug Register to determine information on drug exposure of the *a priori* suspected drugs 0-6 months before SCLE diagnosis. Exposure to terbinafine and TNF- $\alpha$  inhibitors 0-6 months before SCLE diagnosis showed the greatest increase in risk (OR 52.9 (95% CI 6.6- $\infty$ ) and OR 8.0 (95% CI 1.6-37.2), respectively) for a subsequent diagnosis of SCLE. No increased risks were found when other systemic antimycotics were investigated. Exposure to antiepileptic and PPIs 0-6 months before SCLE diagnosis showed about threefold elevated risk estimates and twofold elevated risks were seen for thrombocyte inhibitors, angiotensin-converting enzyme (ACE)-inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs). The analysis was repeated after excluding SCLE cases previously diagnosed with SLE. However, no significant changes in the estimates were found. This study concludes that about one third of all SCLE cases can be attributed to previous drug exposure.<sup>[30]</sup>

### NEONATAL LE

Neonatal LE is a rare disease which develops in fetuses whose mothers have anti-Ro/SSA and/or anti-La/SSB antibodies and more rarely Ribonucleoprotein (RNP) antibodies.<sup>[10,21,48,49]</sup> There is a transmission of antibodies over the placenta which can cause congenital heart block and cutaneous manifestations.

The heart block can occur already during the pregnancy but the cutaneous manifestations occur shortly after birth (0-2 months) and resolve spontaneously as the titers of maternal antibodies degrade within the first 6 months.<sup>[31]</sup> Avoiding breastfeeding does not seem to reduce the cutaneous manifestations.<sup>[48]</sup>

About one-half of the NLE patients are thought to have skin manifestations and the other half to congenital heart block. In addition, about 10% of the children have both manifestations.<sup>[13]</sup> The children can also suffer from photosensitivity, hepatobiliary disease, hemolytic anemia and thrombocytopenia or leucopenia, all of which also resolve spontaneously.<sup>[13,39]</sup> In contrast, heart block is persistent and often starts in fetal life. About two-third of the children with cardiac NLE require pacemaker implantation and the mortality is about 15-20%.<sup>[13]</sup> Children not having heart block have a good prognosis, often healing without sequel.<sup>[13]</sup>

The cutaneous symptoms include a SCLE-like rash, erythematosus, non-scarring annular plaques most typical occurrence in the face and especially peri-orbital ("raccoon or owl eye").<sup>[31]</sup> Differential diagnoses are atopic or seborrheic dermatitis.

### Chronic CLE

Discoid LE is the most common subtype of CLE, 60-80% is localized above the neck and 20-40% is generalized (lesions both above and below the neck).<sup>[4,38,43]</sup> 70-90% of the patients suffer from photosensitivity and sun exposed areas such as the scalp, ears and cheeks, which are most commonly involved areas.<sup>[4,7,12,13]</sup> The lesions start as erythematosus maculae or papules with a scaly surface and then grow peripherally into larger discoid plaques that heal with atrophic scar and pigmentary changes [Figure 3]. A typical clinical sign is when the keratin accumulates in the hair follicle and when peeled back a follicle-sized keratotic spike can be seen protruding from the under surface of the scale (carpet-tack sign).<sup>[7,38]</sup> Mutilation with tissue loss can be seen when the lesions affect the ears and tip of the nose.<sup>[13]</sup>

Mucosal involvement is very usual in CLE patients, at least 25% of CLE patients have mucosal lesions but this is probably an underestimation since many patients have asymptomatic involvement.<sup>[13,31,50]</sup> Most often the buccal mucosa is involved. In DLE the involvement of autoantibodies is less clear but about 50% display low titers of ANA.<sup>[17,51-53]</sup> Differential diagnoses are basal cell carcinoma, actinic keratosis, lichen planus, superficial fungal infection, secondary syphilis, sarcoidosis, cutaneous tuberculosis, leprosy, scars.<sup>[31]</sup>

A recent study has shown that about 25% of the DLE patients already are diagnosed with SLE when they get their DLE diagnosis and the probability of receiving an additional diagnosis of SLE during the following three years is about 17%.<sup>[5]</sup>

### Less common forms of chronic CLE

#### *LE hypertrophicus*

Only about 2% of CLE patients show this form where the skin lesions often are solitary, red, verrucous and hyperkeratotic.<sup>[13]</sup> The patients very often also have DLE lesions which facilitate the diagnosis.<sup>[52]</sup> These patients rarely develop systemic symptoms but the skin manifestations are often chronic and refractory to therapy. Possible treatment is local cryotherapy, topical corticosteroids, intralesional triamcinolone acetonide and systemic antimalarial therapy.<sup>[52]</sup> Topical tretinoin and systemic isotretinoin have also been tried and shown to be effective.<sup>[13]</sup>

#### *LE profundus*

This is a rare panniculitis where the inflammation is primarily located in the lower dermis and subcutaneous adipose tissue. This subset does not show the typical interface dermatitis. The lesions are mainly located to areas with increased fat deposition and UV exposure seems to be of minor importance in this subset.<sup>[52,54,55]</sup> Determined and quick treatment may prevent chronic deep scarring. The most commonly described treatments include antimalarial agents (approximately 70% of patients respond to these drugs) and corticosteroids.<sup>[56]</sup>

### Association with SLE

Cutaneous manifestations are very common in SLE patients (over 80% display skin symptoms sometime during the course of the disease and in 20–25% of patients cutaneous manifestations are the first symptom of SLE disease).<sup>[35,57-60]</sup> The Systemic Lupus International Collaborating Clinics (SLICC) group recently revised and validated the ACR-SLE classification criteria to improve clinical relevance. In the new classification criteria four of the eleven criteria used for SLE classification are mucocutaneous and include ACLE (also including SCLE), CCLE, oral ulcers and non-scarring alopecia.<sup>[61,62]</sup> A recent study in 260 SLE patients showed that LE-non-specific cutaneous manifestations were present in 43% of the SLE patients and LE-specific in 23% of the patients.<sup>[63]</sup> Of the LE-specific, DLE (11%) was the most common followed by SCLE (8%) and ACLE (4%). Of the LE-non-specific skin manifestations Raynaud's phenomenon was the most common (25%), followed by non-scarring alopecia (9%) and vasculitis (8%).<sup>[63]</sup>

Of newly diagnosed CLE patients almost a quarter (24%) had a previous known SLE diagnosis. The probability of receiving an additional diagnosis of SLE was 18.1% (95% CI 14.1–22.1%) during the first three years after being diagnosed with CLE.<sup>[6]</sup>

### CO-MORBIDITY

Previous epidemiologic studies have shown that patients with SLE and other autoimmune diseases, such as rheumatoid

arthritis have increased morbidity and mortality in cancer.<sup>[64,65]</sup> There are more than 100 published case reports of DLE and squamous cell carcinoma in lesional skin and SCLE has been associated with various internal cancers.<sup>[13,66-68]</sup> It has recently been shown that patients with CLE have a significantly increased cancer risk (HR 1.8; 95% CI 1.5–2.2).<sup>[69]</sup> The most increased risk estimates were found for buccal cancer (HR 5.4; 95% CI 1.8–16.1), accompanied by an approximately four times increased risk for lymphomas (HR 4.4; 95% CI 1.8–10.7), respiratory cancer (HR 3.8; 95% CI 2.2–6.4), and non-melanoma skin cancer (NMSC) (HR 3.6; 95% CI 1.8–7.2). The increased risk estimates were not influenced by a concomitant diagnose of SLE.<sup>[69]</sup> Although no causal relationship between potential risk factors and cancer development in CLE patients could be established in this study, smoking is probably a substantial confounder in the CLE patients who have been shown to smoke more than the general population. Other possible explanations could be that CLE patients are more sensitive to UV-light and certain virus infections (for example HPV).

### TREATMENT

CLE can be managed but so far not cured. Avoidance of trigger factors is of utmost importance such as cessation of smoking and avoidance of sun exposure. The treatment is about the same for the different CLE subsets where first-line of treatment is sun-protection and local therapy with corticosteroids or calcineurin inhibitors. There are very few randomized controlled trials for the treatment of CLE (so far only two trials for systemic therapy and neither of these were randomized placebo-controlled trials).<sup>[70]</sup> The treatment is about the same for the different CLE subsets where first-line of treatment is sun-protection and local therapy with potent corticosteroids or calcineurin inhibitors.<sup>[71]</sup> Antimalarial are the first choice of systemic treatment. With local therapy and antimalarial treatment about 75% of the CLE patients responds.<sup>[15]</sup> For the refractory cases, a number of different treatments can be tried such as retinoids, methotrexate, thalidomide, mycophenolate, azathioprine and dapsone. The latest Cochrane review concluded that hydroxychloroquine and acitretin had the same clinical effect but acitretin had numerous and severe adverse effects.<sup>[71]</sup> Methotrexate has been shown to be effective for recalcitrant CLE in a retrospective study.<sup>[72]</sup>

It is important to avoid both natural and artificial UV light and use both clothes and broad-spectrum sunscreen. There is often a latency period of several weeks between UV exposure and disease symptoms so it is important to repeatedly inform the patients about this association.

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), was developed as a clinical instrument to quantify the activity of CLE.<sup>[73]</sup> CLASI is a clinical tool to follow disease progression in an individual patient, classify

patients into severity groups, determine responsiveness after treatment, and compare new therapies.<sup>[21,74,75]</sup> A revised version of CLASI (RCLASI) has also been developed as an alternative instrument to assess disease severity.<sup>[76]</sup>

Newer epidemiological studies based on population-based registries and ongoing CLE quality registers as well will improve the knowledge and treatment of CLE. Hopefully, in the future more specific treatments will be available when pathogenesis and genetics have been more clarified.

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