Lupus erythematosus and the skin

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ABSTRACT

Cutaneous manifestations of patients with lupus erythematosus (LE) are very frequent, show a great variety and can occur at any stage of the disease. The most consistent environmental trigger factors so far recognized are exposure to ultraviolet light and certain drug classes known to be capable of inducing LE in otherwise healthy individuals. A classification system has been established including clinical, histologic, photobiologic, serologic, and immunogenetic findings to better define the different cutaneous subtypes of LE. During their clinical evolution, the cutaneous manifestations vary considerably, and, therefore, the diseases which should be considered in differential diagnosis are different, according to the stages of disease development.

Furthermore, 25 years of experience worldwide have revealed that individuals whose disease presentation is dominated by subacute cutaneous LE skin lesions and the presence of circulating anti-Ro/SS-A antibodies represent a rather homogeneous immunogenetic subphenotype of LE that enjoys a good prognosis over time. Treatment should be individualized according to disease severity. The majority of patients with cutaneous manifestations of LE do not require systemic immuno-suppressive/immunomodulatory therapy and the advent of recombinant biologicals has given hope to the small percentage of patients that suffer from particularly severe skin disease activity.

Cutaneous manifestations of lupus erythematosus

Cutaneous manifestations are one of the most common organ involvements in patients with lupus erythematosus (LE). The clinical expression of the skin lesions shows a great variety and consequently, this has led to the practice of identifying different subsets of the disease. In 1977, Gilliam (1) developed a classification system that divided all skin lesions that have some form of relationship to LE into those that are histologically specific for LE (LE-specific skin disease) and those that do not share this pattern of histopathologic changes (LE-non-specific skin disease). Three broad categories of LE-specific skin lesions had been suggested: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE). The adjectives "acute," "subacute," and "chronic" used in these designations conform to the classic dermatologic definitions of these terms. In contrast, LE-non-specific skin lesions, such as Raynaud's phenomenon, urticarial vasculitis, and calcinosis cutis, are those that in some way are related to the underlying autoimmune disease process but are not specific for LE and can also be encountered in other disease settings. Since the initial definition of the nomenclature system by Gilliam several attempts have been made to improve upon this system and to provide new approaches for the classification of the cutaneous manifestations of LE (2). Recent clinical, histologic and photobiologic analyses of patients with LE tumidus (LET) showed that this subtype has many specific characteristic features and that it should be considered as a separate entity (3). The prognosis in patients with LET is generally more favorable than in those with other forms of CLE and therefore, a modified classification system, including LET as the intermittent subtype of CLE (ICLE), has been introduced in 2004 (4) (Table I).

The typical clinical manifestations of ACLE are characterized by a localized erythema known as the "malar" or "butterfly" rash on the central portion of the face or by a generalized, more widespread form. Both forms usually occur in association with systemic organ manifestations preceding by weeks or months the onset of a multisystem disease (5, 6). Sun exposure is a common exogenous factor to be capable of

Table I. Düsseldorfer classification of cutaneous lupus erythematosus 2004.

Acute cutaneous lupus erythematosus (ACLE)
Subacute cutaneous lupus erythematosus (SCLE)
Chronic cutaneous lupus erythematosus (CCLE)
Discoid lupus erythematosus (DLE)
Lupus erythematosus profundus (LEP)
Chilblain lupus erythematosus (CHLE)
Intermittent cutaneous lupus erythematosus (ICLE)
Lupus erythematosus tumidus (LET

precipitating ACLE and, therefore, at the onset of disease, patients may mistake the rash for sunburn. Usually, the clinical manifestations begin with small, discrete erythematous macules and, in some patients, facial swelling may be severe; however, ACLE mostly disappears without scarring and pigmentation (7). The generalized form of ACLE is characterized by an eruption of symmetrically distributed small, confluent erythematous macules and papules with a pruritic component and may be located anywhere on the body.

Most patients with SCLE show prominent cutaneous and musculoskeletal manifestations but generally do not develop a severe systemic disease (8). The skin lesions appear on sun-exposed areas and are characterized by erythematous papules or plaque with or without adherent, pityriasiform scaling. In some patients, these lesions expand and merge, producing retiform arrays of papulosqamous plaques that can mimic those of psoriasis vulgaris. In other patients, the primary lesions evolve and produce annular plaques that may merge into polycyclic arrays (5,6). Vesicles can appear at the active margins of the lesions, and a hypopigmented central area is a characteristic sign of the annular/polycyclic form. Furthermore, several LE-non-specific skin manifestations have been described in patients with SCLE including non-scarring alopecia, painless mucous membrane lesions, livedo reticularis, periungual teleangiectasias, and Raynaud's phenomenon.

The most common form of all chronic cutaneous variants is discoid LE (DLE), which can occur only on the head or neck, referred to as "localized DLE", or can present above and below the neck, referred to as "generalized DLE". The first morphological manifestation of this subtype is a well-defined, disk-shaped erythematous patch of varying size followed by grayish-white hyperkeratosis that is extremely adherent to the skin (5, 6). The lesions slowly expand with active inflammation and hyperpigmentation at the periphery leaving depressed central scarring, teleangiectasia, and depigmentation. The central atrophic scarring is highly characteristic for this subtype. DLE lesions predominantly occur in sun-exposed areas, such as the face, ears, neck, and arms, but may also be found in inguinal folds, palmo-plantar, and the scalp. At the latter location, DLE may even be the only cutaneous manifestation and thus presents a classical differential diagnosis of scarring alopecia. Sharply marginated, erythematous patches or reticular white striae, and painful erosions or ulcerations can develop mostly on the oral mucosa, but nasal, conjunctival, genital, and anal membranes may also be affected at times. Furthermore, DLE lesions can follow in the wake of any form of trauma to the skin (Koebner's phenomenon or isomorphic response) (9).

The clinical picture of LET is characterized by erythematous, succulent, urticara-like, non-scarring plaques. The swollen appearance of the lesions and the absence of clinically visible epidermal involvement are the most important features of this subtype. The borders of the lesions are sharply limited and, in some cases, there is a tendency for the lesions to coalesce in the periphery, producing a gyrate configuration, or to swell in the periphery and flatten in the center (6). Some patients develop erythematous, annular lesions on the cheeks and upper extremities imitating the annular type of SCLE, and, recently, a patient with LET following the lines of Blaschko has been reported (10). The skin lesions of patients with LET are primarily found on sun-exposed areas, such as the face, the upper back, the V-area of the neck, and the extensor aspects of the arms. Provocative phototesting confirmed that patients with LET are more photosensitive than those with other forms of CLE, and characteristic skin lesions could experimentally be induced by UV irradiation in more than 70% of patients (22). Some skin diseases, such as polymorphous light eruption, share a variety of similar features, demanding attention to rather subtle details and appreciation of the characteristic signs of LET. However, association with systemic disease seems to be extremely rare in patients with LET, and has only been reported in very few cases.

In summary, cutaneous manifestations of patients with LE show a great variation and can result in limited patient quality of life and disability from work. Therefore, a classification system from the dermatological perspective has been developed to better evaluate the prognosis and to define specific therapeutic strategies for the different subtypes of this disease.

Subacute cutaneous lupus erythematosus: A quarter century's perspective (refs. 11-17)

In the early 1970s, James N. Gilliam and Thomas T. Provost were focusing on the idea of subsetting LE patients based upon the presence of different forms of CLE and associated immunogenetic findings. Provost chose to focus on the "ANA-negative SLE" clinical constellation in which there was an enrichment of clinical photosensitivity and Ro/SS-A assay antibody production. However, Gilliam chose to focus upon the clinical and immunogenetic significance of a widespread, symmetrical, photosensitive, non-scarring, non-indurated form of CLE for which he coined the term "subacute cutaneous lupus erythematosus (SCLE)". In retrospect, it became clear that these two investigators had been predominately focusing on the same subgroup of patients having non-scarring, photosensitive CLE skin lesions that we now recognized as SCLE.

Gilliam initially hypothesized that patients who present with a widespread, non-scarring, photosensitive/photo-inducible SCLE skin lesions might share common clinical, pathological, laboratory, and immunogenetic features and thereby represent a distinctive subset of

LE. It was not that Gilliam was the first to observe and describe SCLE skin lesions. Patients exhibiting such lesions appear to have previously been discussed under various designations in the historical literature (lupus marginatus, symmetrical erythema centrifigum, disseminated discoid LE, autoimmune annular erythema, lupus erythematosus gyratus repens, psoriasiform LE, pityriasiform LE, and maculopapular photosensitive LE).

Gilliam's subsequent work, with which one of the authors (R.D.S.) had the honor of assisting, demonstrated that SCLE skin lesions are in fact associated with a distinctive immunogenetic background including the production of anti-Ro/SS-A antibodies and the 8.1 ancestral haplotype, the common Caucasoid haplotype (HLA-A1, Cw7, B8, TNFAB* a2b3, TNFN*S, C2*C, Bf*s, C4A* Q0, C4B*1, DRB1*0301, DRB 3*0101, DQA1*0501, DQB1*0201) that is carried by most people who type for HLA-B8, DR3. This is the same genetic background upon which primary Sjögren's syndrome develops, and overlap between SCLE and Sjögren's syndrome have been observed in follow-up studies.

In addition, further studies have demonstrated that individuals who have SCLE skin lesions as a prominent component of their presenting illness represent a distinctive subset (sub-phenotype) of LE that enjoys a good prognosis with respect to life-threatening systemic manifestations of LE. It would appear that no more than 10% of such individuals experience life-threatening complications of systemic LE over their lifetime. SCLE skin lesions and anti-Ro/SS-A antibody production can be triggered by ultraviolet light (UVB and UVA) and a number of different drugs, the majority of which are capable of independently producing photosensitivity drug reactions in non-lupus patients (8).

The etiopathogenesis of SCLE skin lesions is thought to result from four sequential stages: 1) inheritance of susceptibility genes, 2) loss of tolerance/induction of autoimmunity, 3) expansion/maturation of autoimmune responses, and 4) tissue injury/disease induction resulting from various autoimmune effector mechanisms. TNF-α promoter (-308A) and C1q (*C1QA*-Gly70$_{GGG/A}$) gene polymorphisms have been suggested to represent SCLE susceptibility genes (58, 59). Dysregulated clearance of UVB-induced apoptotic keratinocytes has been implicated in the loss of tolerance to autoantigens such as Ro/SS-A. In addition, the interaction of anti-Ro/SS-A antibody with cell surface displayed Ro/SS-A antigen on keratinocytes undergoing UVB-induced apoptosis has been implicated as a potential pathogenetic factor in SCLE (60). However, this currently remains only a hypothesis.

Local therapy including sun avoidance/protection and topical immunomodulator therapy (corticosteroids, calcineurin inhibitors) are recommended as the initial therapy of SCLE. However, the majority of SCLE patients will require systemic therapy. Single agent or combination aminoquinoline antimalarial therapy will suffice for 75-80% of SCLE patients. Cigarette smoking has been shown to be associated with blunted clinical effectiveness of antimalarials in CLE patients. The remaining 20-25% will require other forms of systemic anti-inflammatory therapy (e.g. diaminodipenylsulfone (Dapsone), retinoids, thalidomide). Among these, thalidomide is most consistently associated with rapidly and complete down regulation of SCLE skin disease activity. However, the long-term use of thalidomide is limited by its toxicity (teratogenicity, sensory neuropathy, secondary ovarian failure, hypercoagulable state).

When at all possible, systemic corticosteroids should not be relied upon for the long-term management of SCLE skin disease activity because of the serious adverse actions associated with this therapeutic approach in LE patients (avascular bone necrosis, premature atherosclerosis). Methotrexate and azathioprine can be used as steroid sparing agents for severe SCLE skin disease. Several types of new recombinant biologic response modifier drugs could theoretically be of value to severely affected SCLE patients. The observations that the TNF-α inhibiting drug thalidomide is so efficacious in SCLE and that SCLE has been associated with a high responder TNF-α promoter polymorphism have suggested that other TNF-α inhibiting/blocking strategies might be of benefit in SCLE. Thus, it has been suggested that the new TNF-α inhibiting recombinant biologic drugs (etanercept, infliximab, adalimumab) that have been of value in other CLE autoimmune inflammatory disorders such as psoriasis might also be of value in SCLE. There have been anecdotal clinical observations that support this hypothesis. However, the TNF-α inhibiting biologic drugs have been associated with the induction of antinuclear antibodies and anti-double-stranded DNA antibodies in high percentages of rheumatoid arthritis patients treated with these agents. This observation has been the basis of concern about using TNF-α inhibiting biologic drugs in any type of lupus patient for fear of precipitating or exacerbating systemic LE disease activity. On rare occasions, the TNF-α inhibiting biologic drugs have been associated with precipitation of drug-induced SCLE and CLE, including SCLE.

Other classes of biologic drugs that might prove to be of value in SCLE patients would be those that interfere with the immunological synapse (alefacept, efalizumab) and those that deplete CD20 positive memory B-cells (rituximab).

Photosensitivity in lupus erythematosus (refs. 18-25)

Lupus erythematosus (LE) represents an autoimmune disease with great clinical variability in which photosensitivity is a common feature for all forms and subsets. Skin lesions of LE often arise in sun-exposed areas and it is well reported and recognized that sun exposure may also exacerbate or induce systemic manifestations of this disease. The original concept of photosensitivity in LE dates back to the first description by Cazenave in 1851 and early observations since the beginning of the 19th century, where the role of environmental factors were related to disease activity and even induction of the disease.

Pathophysiology of lupus erythematosus

Since clinical data, phototesting procedures, and experimental evidence demonstrate the detrimental effects of sun irradiation on LE patients, research on pathogenetic mecanisms of UV-induced LE has become an increasingly dynamic field in the past years, which was additionally supported by the immense progress of the disciplines of photoimmunology and genetics. Initiation and perpetuation of autoimmune responses by UV irradiation have been subjects of extensive *in vivo* and *in vitro* studies. UV irradiation is a well known trigger of apoptosis in keratinocytes, and there is growing consensus that abnormalities in the generation and clearance of apoptotic material is an important source of antigens in autoimmune diseases. Using a standardized photoprovocation protocol our group was able to detect increased numbers of apoptotic keratinocytes in CLE after UVA and UVB irradiation compared to control subjects (61).

Furthermore, UV irradiation may cause the formation of molecules by different epidermal and dermal cells. These molecules have the capacity to upregulate (PGE2, ROS, TNF-alfa, IL-1, ICAM1) or downregulate (IL-10, IL-1 receptor antagonist) inflammatory processes. Since genetic regulation is crucial for the induction of these molecules, a putative genetic polymorphism may play an important role in the photosensitivity of LE.

Specific pathogenetic pathways in UV-induced autoreactivity have been demonstrated experimentally. Thus, Furukawa *et al*. (18) could demonstrate in absence of apoptosis the cellular redistribution of the RO antigen upon UV radiation, which enables its presentation to the immune system as a possible first step in the autoimmune cascade.

Since there is a link between UVA-sensitivity and free radical formation, free radical scavengers may be of special value in order to prevent UV-induced LE lesions.

Plasmocytoid dendritic calls (PDC) accumulate in CLE lesions, whereas in systemic LE a decreased number of those cells are found in the peripheral blood. PDCs and their secreted products (interferon-alpha) play a crucial role in the pathogenesis of SLE. In a recent study, it the recruitment and activation pathways of skin infiltrating leukocytes in CLE has been investigated (25). This group were able to show that UV irradiation induces the release and production of a distinct set of PDC- and T-cell-attracting chemokines. In summary, these data show an amplification cycle in which UV light-induced injury induces apoptosis, necrosis, and chemokine production. These mechanisms, in turn, mediate recruitment and activation of autoimmune T cells and IFN-alfa-producing PDCs, which subsequently release more effector cytokines, thus amplifying chemokine production and leukocyte recruitment, finally leading to the development of LE lesions.

According to the present evidence it is conceivable that besides simple photoprotective measures, a further beneficial effect could be achieved by the additional use of oxygen scavengers and, i.e., nitric oxide via chemical donors. Since DNA is a primary target for UV insults, a very interesting photoprotection concept includes the addition of DNA repair enzymes into sunscreens. However, clinical data on this hypothetical treatment strategies for the prevention of UV-induced LE are still lacking.

Clinical photosensitivity and phototesting

Despite many anecdotal reports and the obvious clinical evidence showing a clear relationship between sunlight exposure and the manifestation of LE, no systematic studies existed on the photoreactivity in patients with this disease until the early 1960s.

In 1986, our group was the first to demonstrate experimental reproduction of skin lesions by UVB and UVA irradiation using a standardized test protocol on a large number of patients with the disease (24). A total of 128 patients with different forms of LE underwent phototesting with polychromatic UVB and long-wave UVA irradidation, and characteristic skin lesions clinically and histologically resembling LE were induced in 43 % of patients. Subsequent investigations confirmed UVA reactivity in LE by phototesting. In the following years, this testing regimen received much attention because the reproduction of skin lesions in patients with LE by UVB and UVA irradiation is an optimal model for clinical and experimental studies. Meanwhile, provocative phototesting in patients with LE has become routine at our department, and protocols for phototesting have become optimized by taking into account multiple factors (15). Non-lesional, non-sun-exposed areas of the upper back or extensor aspects of the arms were used for performance of the phototest reactions because other parts of the skin might not react to the same extent, probably owing to some kind of local predisposion of unknown nature other than UV irradiation, such as thickness of the stratum corneum, vascularization, presence of antigens, or distribution of antigen-presenting cells. Furthermore, it is important to use a defined test area, which should be sufficiently large to provide reactions. The initial observable response following exposure to UV irradiation is an erythema reaction that most commonly arises with the normal time course. Although the duration of the erythema was not studied in particular, a prolonged erythematous response was not a conspicuous feature. In contrast to other photodermatoses, such as PLE, the development of skin lesions in patients with LE is characterized by a latency of several days to 3 weeks or even longer, and it might persist in some cases for several months. In addition, phototesting has been crucial in further characterizing a highly photosensitive form of CLE, namely LET (22).

A history of photosensitivity in patients with LE does not necessarily predict positive reactions on phototesting, and results of reported photosensitivity often differ between various groups. This might be because skin lesions after UV irradiation do not develop rapidly after sun exposure, and, therefore, a relationship between sun exposure and exacerbation of LE does not seem obvious to the patient. The term “photosensitivity” (skin rash as a result of ununsual reaction to sunlight by patient history or

physician observation) is poorly defined, although it is listed as one of the ACR criteria for the classification of SLE. Therefore, a detailed clinical history is important to the diagnosis and assessment of photosensitivity in patients with LE. There are several key components to a history of photosensitivity, including the morphology of the rash, duration, distribution, and the relationship to sun exposure and specific symptoms (such as pain, pruritus, burning, blistering, and swelling). Each of these symptoms may provide clues to the nature of the photosensitive eruption and thus the diagnosis. Differentiating between the morphology and the time course of CLE and, for instance, PLE, according to the history alone can be difficult; clinically, PLE tends to consist of an acute eruption of tiny, pruritic plaques and vesicles that lasts several days, in contrast to SCLE, which usually involves larger, non-pruritic annular or psoriasiform lesions that persist for weeks to months after UV exposure. In contrast, LET may, in some cases, be clinically very similar to PLE. A past medical history should also include a detailed drug history, particularly in temporal relation to a suspected phototoxic eruption.

Provocative phototesting is an objective means of demonstrating whether a patient has an abnormal response to UV exposure; however, phototesting does not play a role in the routine assessment or diagnosis of a patient with CLE. Indications for phototesting in patients with LE include (a) the objective demonstration of photosensitivity where there is doubt about the history and where such demonstration would support a diagnosis of LE; (b) the exclusion of other causes of photosensitivity, such as PLE, chronic dermatitis, solar urticaria, and drug-induced phototoxicity; and (c) use of the photoprovocation test as a useful research tool with which to study the immunopathology of evolving lesions of LE-specific skin disease.

In conclusion, extensive clinical and experimental evaluation of photosensitivity and phototesting in LE has lead to significant better understanding of the pathophysiology of LE, the clinical subgroups of this complex disease, verification of treatment effectiveness of photoprotective measures, and, finally, the elaboration of responsible action spectra, which lead to the induction and/or exacerbation of LE.

Differential diagnoses of LE-specific skin lesions

Though the clinical features and the pathology of the cutaneous manifestations of LE are rather characteristic, many different diseases have to be considered in the differential diagnoses.

Acute cutaneous lupus erythematosus

The diseases which we may include in the differential diagnoses with localized ACLE are acne rosacea, contact dermatitis and photodermatitis, seborrheic dermatitis, dermatomyositis, and erysipelas. All these diseases may involve the malar area and the bridge of the nose as in localized ACLE. Nonetheless, the clinician may rely on some characteristic differentiating features.

Rosacea may involve also the central part of the forehead and the chin, is frequently associated with a diffuse network of telangiectasia, and with time it tends to develop papules and pustules.

The localization of the rash in the case of contact dermatitis and photocontact dermatitis depends on the exposure to the sensitizer and UV-light. The onset is generally acute, with blistering and oozing, and accompanied by itching or burning. Seborrheic dermatitis is sometimes localized on the malar region but it generally has a peculiar distribution, characteristically involving the nasolabial fold which are – as a rule – spared in ACLE. Moreover, a certain amount of scaling is invariably present, with greasy, yellowish scales. Erysipelas has an acute onset, with high fever, malaise, and lesions are more edematous than in ACLE.

Generalized ACLE should be differentiated from morbilliform drug reactions (26) and erythema multiforme. In both of these diseases there is no butterfly erythema and no precise photodistribution as in ACLE. The palms and soles may be frequently involved, while they are spared in ACLE patients, unless they have a concomitant vasculitic process. Erythema multiforme rapidly evolves towards the formation of characteristic “target” lesions.

Subacute cutaneous lupus erythematosus

The diseases which we may consider in the differential diagnosis with the papulosquamous pattern of SCLE are psoriasis and polymorphic light eruption. Psoriasis is a chronic disease with a very peculiar distribution, with involvement of the elbows, the knees, the scalp and no tendency to a photodistribution as in SCLE. Polymorphic light eruption follows the exposure to UV-light with a latency period of a few hours, therefore shorter than in SCLE, and is characteristically accompanied by a severe itch. The rash has a short duration and resolves within a few days after sun avoidance (27, 28).

The annular-polycyclic pattern of SCLE should be differentiated from superficial gyrate erythema and tinea corporis. Neither of these diseases presents with a characteristic photodistribution as in SCLE. Gyrate erythema frequently involves the buttocks or other sun-protected areas, whereas the annular lesions tend to enlarge more rapidly than SCLE and to resolve spontaneously in a shorter time. Tinea corporis is generally not as widespread as SCLE, it is not symmetrically distributed and can be localized on the flexor as well as on the extensor surfaces of the limbs.

Chronic cutaneous lupus erythematosus

Various diseases have to be considered in the differential diagnoses according to the different stages of the evolution of CCLE. For this reason we have separated early, fully developed and late CCLE lesions, and within early lesions we have arbitrarily identified two clinical patterns: non-scaling and scaling early CCLE.

The non-scaling pattern of early CCLE presents as an erythematous plaque, sharply demarcated, with minimal scaling, and the scaling pattern of early CCLE shows an erythematous plaque with follicular hyperkeratosis and scaling.

Fully developed CCLE presents as an annular lesion with an active border with erythema, infiltration and scaling and a central area with sclerosis, atrophy, alopecia, and telangiectasia.
Late CCLE appears as a scleroatrophic, alopecic patch with telangiectasia and only limited areas of residual inflammation within the patch and in the periphery, forming an incomplete active margin.
The diseases which we may consider in the differential diagnoses with the non-scaling pattern of early CCLE and also LET are polymorphic light eruption, Jessner's lymphocytic infiltration of the skin, lymphocytoma cutis, granuloma faciale, pernio (chilblain), and lupus pernio (sarcoidosis). All these diseases can be differentiated from CCLE on histologic examination but some peculiar clinical features may help.
Jessner's lymphocytic infiltration of the skin tends to a peripheral extension and central resolution evolving to annular or horseshoe-like configuration, and occurs mainly on the face and less often on non-exposed areas of the trunk. They may be induced or aggravated by sun exposure, but most of the patients have active lesions during wintertime (29).
Granuloma faciale can develop a reddish-brown pigmentation, due to hemosiderin deposition (30) while chilblain LE tends to a violaceous hue. Both diseases have a very slow evolution and sometimes show prominent follicular orifices but never hyperkeratosis or follicular plugging as in CCLE. Chilblain lesions are accompanied by itching and at times also soreness and pain. They are most commonly localized on the dorsal surface of the fingers and in other acral areas, and tend to persist throughout the cold season (31,32).
The scaling pattern of early CCLE has to be differentiated from actinic keratoses, seborrheic dermatitis, tinea faciei, psoriasis, and lichen planus.
Actinic keratoses may be similar to early CCLE but are slower in their evolution, rougher to the touch, and the scales are very difficult to detach, with no follicular plugging. Moreover, they are always observed within areas of photo-damaged skin in individuals older than the average CCLE patient.
Tinea faciei may take on unexpected forms, particularly in the adult or in immuno-compromized patients, thus resembling other diseases, most frequently DLE (33). It may appear as non-symmetric erythematous plaques, with variable scaling and sometimes follicular plugging and a suspicion of CCLE may arise when the nose or the malar areas are involved. For the differential diagnosis, KOH examination of cutaneous scales or the identification of the causative dermatophyte on culture media may be employed.
Fully developed CCLE lesions have a unique appearance and can hardly be confused with other diseases. According to Sontheimer's statements (1995), "Discoid-shaped skin lesions that have erythema and hyperpigmentation at their active borders, and depigmentation, telangieactasia, and atrophy at the centres are very unlikely to result from dermatological disorders other than CLE".
The diseases which can be considered in differential diagnoses with late CCLE are lupus vulgaris and other granulomatous infectious diseases. Lupus vulgaris may present with ulcerations and crusts, which are rather unusual in CCLE, and the characteristic "apple-jelly" nodules.
Finally, in the case of the scalp involvement lichen planopilaris (34) may produce a scarring alopecia that may mimic burnt out discoid lesions. It can be differentiated because it generally presents with small clustered areas of alopecia, with no telangiectasia, hyperpigmentation, or residual areas of inflammatory activity and scaling at the margins of the patch.

Response criteria for cutaneous manifestations in lupus erythematosus

Systemic lupus erythematosus (SLE) is a very complex and heterogeneous disease characterized by a variety of clinical and serological manifestations. Furthermore, each organ involvement may show a variable degree of severity. In view of the complexity of the disease, the OMERACT (Outcome Measures in Rheumatology) has suggested that the assessment of SLE patients should include measures of disease activity, disease damage, and quality of life (35).
Indices to assess disease activity have been developed and validated and are used in routine clincal practice as well as in clinical trials (36). In a recent paper, Liang *et al*. have evaluated the ability of six activity indices (British Isles Lupus Assessment Group- *BILAG*; European Consensus Lupus Activity Measurement- *ECLAM*; Systemic Lupus Activity Measure- SLAM-R; Systemic Lupus Erythematosus Disease Activity Index- *SLEDAI* and *SELENA-SLEDAI*; Responder Index for Lupus Erythematosus- *RIFLE*) in capturing response to treatment demonstrating that all of them had discriminatory properties more than sufficient for use in clinical trials (37).
Skin manifestations are very frequent in SLE; in an analysis of 1000 SLE patients from different European Centres, Cervera *et al*. have observed that cutaneous manifestations appear in most patients and are mainly represented by malar rash (58%), photosensitivity (45%), oral ulcers (24%), livedo reticularis (14%), discoid lesions (10%), subacute cutaneous lesions (6%) (38). Some authors have also suggested that skin lesions may parallel disease activity in SLE (39). Interestingly, CLE without systemic manifestations may be 2-3 times more frequent than SLE (40).
Taking into account its frequency as well as its potentially disfiguring effects, skin involvement represents an important issue for the treating physician and may represent an important target for drugs that are under development. The definition of the severity of skin manifestations and clinically significant improvement in LE is, therefore, of paramount importance, since it may be used to classify patients and to establish the effectiveness of the treatments.
As previously reported, many indices have been developed and validated for the assessment of disease activity in SLE; however, few data are available relatively to their use to measure disease activity in single organ systems. Many activity indices, in fact, may not

be adequate for assessing activity in single organ systems, since they have been developed as cumulative indices, aimed at giving an overall view of the disease activity (41). While some organ systems may be assessed more easily, for example kidney or hematological manifestations, difficulties may arise with organs such as skin or nervous system.

In Table II, the cutaneous manifestations included in the most widely used indices are summarized. In 1993, Hay *et al*. in a study aimed at evaluating the between-rater reliability, the criterion validity and the construct validity if the BILAG index, have showed a high inter-rater agreement for the "mucocutaneous system" (88% of agreement at first and subsequent assessment); furthermore, a strong correlation was also observed between the mucocutaneous scores and physician assessment (42). However, no other data are available on the use of the BILAG index in assessing CLE.

In 2000, Parodi *et al*. (43) have used the mucocutaneous manifestations of the SLAM index to evaluate skin manifestations in 176 patients with CLE; their major criticisms concerned the grouping of SLAM cutaneous parameters, since manifestations such as localized and disseminated DLE, SCLE or scarring and nonscarring alopecia, are all placed in the same group, although not equivalent and probably representing different conditions. The authors, therefore, concluded that a revision of the grouping of the cutaneous parameters is advisable. Although with these limitations, the SLAM index is the only one used so far to score cutaneous manifestations *per se*.

The RIFLE index was specifically designed to assess response and worsening in SLE; partial response and resolution of various disease manifestations have been defined (44). However, some difficulties in the application of these criteria derive from the lack of specific definition of some items (e.g. malar rash).

No other data are available on the use of SLE disease activity indices in assessing cutaneous manifestations. From the analysis of the literature, it appears that the disease activity indices now available are not able to capture the complexity and severity of cutaneous manifestations observed in LE. Therefore, the development of indices aimed at assessing disease activity, severity, and meaningful changes in activity of cutaneous manifestations in LE appears necessary.

Table II. Cutaneous manifestations included in SLE disease activity indices.

Manifestation	SLEDAI	SELENA SLEDAI	SLAM-R	BILAG	ECLAM	RIFLE
Malar rash	+	+	+	+	+	+
Maculopapular eruption	+	+	+	+	+	-
Discoid lesions	+	-	+	+	+	+
Lupus profundus	-	-	+	+		-
Panniculitis	-	-	+	+	-	+
Bullous eruption	+	+	+	+	+	+
Cutaneous vasculitis	+	+	+	-	+	+
Mucosal ulceration	+	+	+	+	+	+
Photosensitivity	-	-			-	+
Alopecia	+	+	+	+	-	+
Angioedema	-	-	-	+	-	+

Where is the boundary between systemic and cutaneous LE?

Classification concerns

Criteria of the American College of Rheumatology (ACR) for SLE show high sensitivity and specificity in many clinical studies, and a sensitivity of 93% in a group of 213 SLE patients and a specificity of 88% in 212 controls affected with difficult-to-distinguish conditions, particularly connective tissue diseases, has been described (45). However, despite their high performance and very widespread use, ACR criteria have some limitations.

Patients affected with pure CLE may result false positive to ACR criteria for SLE. For example, a patients with oral ulcers, discoid lesions, photosensitivity and positive antinuclear antibody (ANA) test fulfils 4 ACR criteria and is classified as SLE. It is worth noting that SCLE is not included in the ACR criteria. However, it has been planned to also consider this skin manifestation in the future revision of ACR criteria. Fifty percent of patients with SCLE developed SLE according to the ACR classification crriteria compared with only 5% of those with CCLE (only about 10% of SCLE patients develop potentially life-threatening manifestations of SLE such as lupus nephritis and lupus cerebritis). Therefore, the inclusion of such a skin manifestation will result in an increase in the criteria sensitivity for SLE, but in a decrease in their specificity against exclusive CLE.

A further limitation of the ACR criteria is the questionable definition of some items. First, the definition of photosensitivity reported in ACR criteria is too imprecise: "skin rash as a result of unusual reaction to sunlight by patient's history or physician's observation".

We have tested (46) photosensitivity according to the ACR definition and by minimal erythemal dose measurement (MED) in 45 SLE patients and in 31 healthy subjects, as controls. Fifty-seven percent of patients and 45% of controls were photosensitive according to the ACR definition without any significant difference; whereas 79% of patients and 51% of controls were photosensitive according to MED measurement. Although in this case the difference was significant, the prevalence of photosensitivity in controls was very high. Moreover, we did not find any agreement between questionnaire and phototest.

The second questionable definition concerns oral ulcer, defined as "oral or nasopharingeal ulceration". It is worthy to note that oral mucositis and ulceration frequently coexist with and might be considered as a different manifestation of the same phenomenon. Therefore, the coexistence of oral mucositis with specific cutaneous manifestations may lead to an over count of the same lesion.

Genetic relationship

A genetic link between CLE and SLE is evidenced in cases of SLE and CLE occurring in families, although this is not frequent. Familial CLE is much less frequent than SLE in families and in CCLE the results of haplotype studies were heterogeneous and inconclusive. Genetic similarities and differences between pure CLE and SLE have been reported.

A very recent retrospective study has shown that in patients with CLE (both CCLE and SCLE) there is a high percentage of C2, C4A, and C4B deficiency and the authors conclude that partial deficiency of C4, C2 or C2 and C4 is a common finding in patients with CLE, like in SLE (47).

On the other hand, it has been demonstrated by cytokine promoters' genotype studies that patients with high susceptibility for CCLE are high IL10/low TNF-α producers whereas higher producers of TNF-α have a high susceptibility for SLE (48).

Immunologic features

Immune cells. CLE is a T-cell mediated disease. Immunophenotyping of the cellular components of the dermal infiltrate shows a predominance of $CD4^+$ and $CD8^+$ lymphocytes and a high CD4/CD8 ratio (49), and it is worth noting that infiltrate of $CD4^+$ and $CD8^+$ lymphocytes is described also in the kidney of patients with active glomerulonephritis (50).

In a recent study, it has been shown that patients with pure CCLE had increased numbers of circulating HLA-DR^+ $CD3^+$ T cells and HLA-DR^+ $CD4^+$ T cells, indicating systemic T-cell activation, and an expansion of $CD5^+$ $CD19^+$ B cells. In patients with SLE, immunological changes were similar but more pronounced (51). These data suggest a systemic activation of the cellular immune system in patients with pure CLE and similarities in the lymphocyte immunophenotypic profiles in patients with CCLE compared with SLE suggest that there is a common immunopathological process in these two conditions.

Autoantibodies. On the other hand it is worth noting that SLE is characterized by the production of diverse autoantibodies, some of them specific to the disease (anti-Sm, anti-dsDNA), which lead to an immune complex-formation and deposition. These immunological perturbations are not significant in patients with pure CLE. However, the detection of anti-Ro/SSA antibodies is common in both pure CLE and SLE patients. Anti-Ro/SSA antibodies were observed in over 70% of CLE patients (52) usually in a low titre. Differently from that observed in SCLE patients, no deposits of anti-Ro/SSA antibodies are found in lesional skin of CCLE patients probably due to the low titre of these antibodies. Therefore, the significance of anti-Ro/SSA antibodies in CCLE is not clear. Moreover, it is rather doubtful whether low-titre of anti-Ro/SSA antibodies could have some predictive value concerning a possible conversion of CCLE into SLE or SCLE over time. However, detection of anti-Ro/SSA antibodies in circulation of patients with CLE strongly favors a relationship between the exclusively cutaneous disease and systemic subtypes.

Cytokines. It has been shown that TNF-α is expressed in lesional skin, but not in non-lesional skin of patients with SCLE (53). Interestingly, an over-expression of TNF-α was also observed in renal biopsies from SLE patients (54). Moreover, high serum levels of TNF-α and TNF-α receptors have been reported in patients with SLE and a significant correlation between TNF-α and TNF-α receptor serum levels and disease activity was observed.

IL-6 is also expressed in lesional skin of patients with SCLE and CCLE (55). Finally, IL-6 serum levels are high in SLE patients compared with healthy controls and in SLE they are correlated with disease activity (56).

Immunopathologic features

Direct immunofluorescent (DI) technique shows immunoglobulins (mostly IgG, IgA, and IgM) and complement (mostly C1q, C3, C4, and properdin) deposition at the dermal-epidermal junction (DEJ) in lesional skin of patients with exclusive CLE and in lesional and non-lesional skin of patients with SLE (50). The pattern of immune deposits can be linear in a continuous thick or thin band or discontinuous with coarse or fine granular deposits in all subtypes of CLE (62). The exact mechanisms leading to immune deposits along the DEJ in CLE are still unknown. Interestingly, DI has also demonstrated immunoglobulins and complement deposition in the kidney of patients with SLE, specifically in the mesangium and in the peripheral capillary walls.

In conclusion, a number of clinical, genetic, immunologic, and immunopathologic findings overlap between pure CLE and SLE suggesting that these two conditions are different expressions of the same disease. Why some patients only develop cutaneous manifestations and others develop SLE remains to be clarified.

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