Lupus Erythematosus: a dermatologist’s perspective

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Summary

Lupus Erythematosus (LE) is an autoimmune disease with multifactorial etiology; it is characterized by dysregulation of the immune system which produces autoantibodies that, together with immune complexes and autoreactive T lymphocytes, cause disease-specific tissue lesions. Besides joint involvement, skin is the most commonly affected organ and one of the target organs most variably affected by the disease. Although the diagnosis of skin LE is mainly clinical, morphological and histopathological, support is provided by detection of antinuclear autoantibodies which are not disease-specific, but are often very important from a prognostic point of view. The differential diagnosis of chronic LE is usually easy and based on the morphologic assessment of lesions. In case of subacute CLE, the differential diagnosis is made against psoriasis, generalized LE and inflammatory annular dermatoses. The differential diagnosis against some forms of acute CLE (especially malar or butterfly erythema) is made against actinic keratosis, seborrheic or rosacea dermatitis, polymorphic light dermatitis and dermatomyositis. Differential diagnosis of generalized forms should be made against drug reactions, photodermatities, viral exanthems.

KEY WORDS: lupus erythematosus, skin manifestations; differential diagnosis; autoantibodies.

Cutaneous Lupus Erythematosus (CLE) is the polar form of a heterogeneous spectrum of diseases defined as “lupus”.

The prevalence of Systemic Lupus Erythematosus (SLE) is estimated to be approx. 17-48/100,000 in the USA, being threefold higher for cutaneous forms as compared to other clinical manifestations; in the province of Florence (during the observation period of 2010) considering a population of approx. 970,000 inhabitants – the sample studied included primary care patients – SLE incidence was 5.4/100,000 and the prevalence was 75/100,000 (1).

Cutaneous manifestations are often the first signs and symptoms of SLE and lead to the consultation of a dermatologist or inspire an internist or rheumatologist to consult a dermatologist for appropriate differential diagnosis with other types of dermatoses. Cutaneous manifestations are present in over 75% of patients with SLE and are the second most frequent presenting symptom in the systemic forms following joint involvement (Figure 1) (2, 3).

According to Sontheimer and other authors correct diagnosis of LE cutaneous manifestations requires a high level of suspicion and broad understanding of the disease (4).

Difficulties lie not only in differentiating CLE from a wide range of predominantly non-autoimmune and common inflammatory skin disorders (including rosacea or seborrheic dermatitis), but equally important appears the diagnosis of systemic disease, i.e. if CLE is associated with internal organ involvement, since cutaneous manifestations precede the clinical onset of systemic symptoms for weeks to months in about 25% of patients.

Although the serious cutaneous forms are rather rare, skin involvement significantly contributes to disease burden in terms of personal and psycho-social well-being, as well as with professional disability and healthcare and social costs.

The definition of cutaneous manifestations dates back to 1981 when Gilliam e Sontheimer (5) divided these manifestations into two groups: specific and diagnostic manifestations and non-specific and non-diagnostic manifestations. The specific ones were then divided into chronic, subacute and acute CLE, including several subtypes: discoid LE (localized and disseminated), hypertrophic LE, Lupus Erythematosus panniculitis and chilblain LE. There are also some subacute forms including annular, papulo-squamous and mixed/rare, as well as the acute form which can be localized or generalized. The intermittent or tumid LE was recently added to this classification (Figure 2).

The initial chronic forms are rather difficult to diagnose since lesions are hardly distinguishable from a number...
of common diseases. The localized forms are sometimes nuanced and so not well defined therefore very difficult to diagnose. Discoid lesions, when located on the nasal pyramid, have to be distinguished from actinic keratosis, sometimes from seborrheic keratosis, and in some cases from squamous-cell cancer (a diagnosis that the dermatologist cannot fail). Typically, some erythematous-squamous lesions can be found, with adherent white-greyish scaling resembling an extremely adherent verrucous hyperkeratosis, which in case of removal would be painful due to skin hyperalgesia showing small corneous sharp formations. Purple infiltrated lesions with a central depression are suggestive of LE clinical diagnosis, as well as the butterfly rash distribution of lesions leading to a easier diagnosis suspect. Different evolution phases may occur: the same patient can show an atrophic phase and an hypertrophic one; disseminated clinical forms can spread over the face as well as to limb extensor surfaces and have a verrucous appearance (Figure 3). In the hypertrophic subset, the lesions tend to be distributed in the periunguinal area, near proximal interphalangeal joints and may sometimes look like common manifestations, i.e. viral warts.

Panniculitic lesions leave defigurating outcomes, for example in the deltoid area (Figure 4), that may also affect the face and the gluteal region. The subacute form is characterized by the presence of erythematous lesions which tend to join in reticular forms and to expand themselves predominantly on the shoulders and décolleté. The lesions tend to become hypopigmentated – even for a long time – and common conditions including pityriasis versicolor, should be considered in the differential diagnosis. The papulo-squamous form or the psoriasiform with annular manifestations can be considered in the differential diagnosis with very different diseases (tinea, psoriasis, pityriasis, etc.), thus requiring a careful morphological assessment. Polyclinic annular forms are rather extensive, they have a erythematous and edematous centrifuge halo which may allow for better clinical definition. Acute forms are divided into localized and generalized; the localized form commonly defined as butterfly rash falls into differential diagnosis against common forms including rosacea or seborrheic dermatitis, or more severe patterns including dermatomyositis. Finally, there are some generalized forms characterized by maculopapular rash, extensively involving the face and limbs, as well as the palmar surface which can simulate drug-induced reactions.
Tumid lupus is characterized by intermittence and has no atrophic, scarring or dyschromic outcomes. However, photosensitivity is increased – much higher than that observed in the discoid pattern – even if there is a very low incidence of switching to systemic forms; histologically, it is characterized by a non-specific pattern, since interface dermatitis and hyperkeratosis are absent, while there is a considerable presence of mucin deposition. In differential diagnosis, some infiltrative forms (Jessner-Kanof syndrome) and pseudolymphomas should be taken into consideration. In some tumid forms, also the discoid pattern may be associated, resulting into considerable diagnostic difficulties leading to repeated biopsies.

Figure 5 reports data collected by the Italian Group of Skin Immunopathology on approx. 300 patients, the most common clinical pattern being the chronic discoid form. Data are partially overlapping with those from the study by Sontheimer et al. published in 2010 (6) and those by our Group from Florence of Cardinali et al. published in 2000 (7). In the paper recently published by the European Society of Cutaneous Lupus Erythematosus (EUSCLE) on 1002 patients, the involvement of women was prevalent as compared to men with an age of onset generally over 40 years (8).

With regard to non-specific and non-diagnostic manifestations according to Gilliam e Sontheimer (4) classification, the most frequent ones are certainly vascular, vasculitic and vasculopathic lesions, but other relevant manifestations should be considered, including alopecia, sclerodactyly, calcinosis cutis and rheumatoid nodules. In the alternative classification proposed by Lipsker in 2010 (9), skin manifestations were grouped by the dermoepidermal infiltration depth, therefore acute, subacute and chronic subsets are characterized by a predominantly dermoepidermal infiltration, the tumid form and Jessner’s lymphocytic infiltrate of the skin by dermal infiltration, lupus panniculitis and other less common forms by a predominantly hypodermic infiltrate. Finally, skin lupus forms with predominantly neutrophilic infiltration include urticarial vasculitis of LE, bullous forms and other patterns which are more rarely observed (Figure 6).

The histopathological pattern of skin lupus erythematosus has no pathognomonic features, but only compatible features, therefore there is a group of histopathological characteristic which per se do not al-
low to obtain a definite diagnosis: this is why the relationship with the clinical presentation is crucial for diagnostic purposes.

Figure 7 reports a list of histopathological alterations characterizing chronic skin lupus. Direct immunofluorescence (IFD) can be performed on healthy skin – in presence of photoexposure or not – or on lesional skin: in this case, in 60-90% of cases, the "lupus band test" will show deposits at the dermoepidermal junction, with detection of the so-called "fluorescent bodies". Obviously, IFD on healthy skin has a higher diagnostic sensitivity.

Phototest can be useful in differential diagnosis to distinguish LE from other photosensitive diseases and to correctly interpret the photosensitivity level and identify the responsible radiation, in order to establish an appropriate photoprotection strategy.

Among the forms of lupus erythematosus, particular attention should be drawn to drug-induced LE (DILE: Drug-Induced Lupus Erythematosus): in this case skin involvement is present in 25% of cases; this syndrome is characterized by clinical and immunopathological manifestations similar to those observed in idiopathic lupus erythematosus, but related to the continued use of specific drugs; treatment discontinuation usually results into resolution of the clinical pattern, with no permanent damage (10).

Drug-induced lupus erythematosus is estimated to account for approx. 10% of all lupus forms and currently it seems that about 100 different drugs can be implied in its pathogenesis; similarly to idiopathic lupus erythematosus, it can be systemic, subacute, chronic and tumid.

Drugs which are most frequently involved include hydralazine, procainamide, carbamazepine and terbinafine. The form with systemic involvement seems to be rather rare, with latency time from drug intake ranging from months to years; resolution generally occurs after drug discontinuation. Symptoms also include leukopenia, thrombocytopenia and increased ESR.

In conclusion, we can state that there is an association between drugs and lupus, that at least one third of the cases can be attributed to drug exposure in the subacute subset, and that in a number of cases drug discontinuation results into clinical resolution, therefore a very careful patient history screening is crucial.

The mainstay of skin lupus erythematosus treatment (Figure 9) include adequate photoprotection, topical treatment, as well as calcinurin inhibitors, and systemic treatment, if deemed necessary; with regard to this, use of hydroxychloroquine or chloroquine associated with quinacrine, dapsone, thalidomide, as well as immunosuppressants including methotrexate, micophenolate or corticosteroids has been reported (11).

A paper published in 2012 by EUSCLE clearly shows that in over 80% of cases, dermatologists propose an adequate photoprotection strategy. Then, topical steroids, calcineurine inhibitors, chloroquine, hydroxychloroquine and systemic immunosuppressors follow. The use of basic topic treatment – photoprotection and steroids – seems to be able to significantly modify the clinical pattern, as well as the disease activity (12).
Photoprotection prescribed in patients with skin lupus erythematosus in 84% of cases, has shown a high level of efficacy in preventing skin manifestations in all subtypes of lupus erythematosus and seems to reduce disease activity. Topical steroids have been used in 81.5% of cases and showed an efficacy of 88.4% while calcineurin inhibitors have only been used in 16.4% of patients with a measured efficacy of 61.7%. Systemic agents – used in 84.4% of the cases – are prescribed mainly in acute forms of skin lupus and include antimalarials, systemic steroids, but also methotrexate is being increasingly included in the therapeutic management of these patients with good results (12).

References