Ref: Ro J Rheumatol. 2023;32(1)
DOI: 10.37897/RJR.2023.1.2

Skin involvement in systemic lupus erythematosus: a review article

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ABSTRACT

Cutaneous disease is one of the most frequent manifestations of systemic lupus erythematosus (SLE), being classified as LE-specific and LE-nonspecific. LE-specific skin lesions are divided into acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE) and chronic cutaneous lupus erythematosus (CCLE). The association with systemic involvement varies between each clinical subtype, with non-specific lesions being more frequent associated with active SLE than cutaneous specific lesions. The treatment consists of topical agents (glucocorticoids, topical calcineurin inhibitors) as well as systemic therapies (glucocorticoids, hydroxychloroquine, quinacrine, methotrexate, retinoids, dapsone, mycophenolate mofetil or even biologics). In the presence of strictly cutaneous involvement, periodic patient follow-up and monitoring for the progression to systemic disease remains an important mission for the dermatologist and the rheumatologist.

Keywords: cutaneous lupus erythematosus, alopecia, autoimmunity, Raynaud's phenomenon, discoid lupus, malar rash

INTRODUCTION

Systemic lupus erythematosus is one of the most heterogeneous diseases, including the aspect of cutaneous lesions. Skin involvement is present in 70%-85% of patients, making it the second manifestation in frequency after joint involvement, and it is also the first clinical manifestation in approximately 25% of patients. The presence of skin lesions as a clinical sign has been included in the American College of Rheumatology (ACR) classification criteria for SLE since 1971. Up to this day, it maintains its value as an important tool for guiding diagnosis and treatment [1]. This article presents an overview of the immunopathogenesis of cutaneous lupus erythematosus, the clinical classification of skin lesions, the association between different subtypes and systemic involvement and also the available treatment options.

PATHOGENESIS OF SKIN LESIONS

Many factors contribute to the development of skin injury in SLE, such as genetic, environmental, and immunologic pathways involving both the innate immune response and adaptive immunity.

Regarding the genetic factor, it has been proven that alleles of specific genes are associated with skin injury in SLE. For example, the ITGAM (Integrin Subunit Alpha M) gene carries a high risk for developing discoid lesions, the FCGRA2 (encoding low-affinity IgG Fc region receptor IIa) gene has been associated with a high risk of malar rash, and the presence of TREX1 (Three Prime Repair Exonuclease 1) allele has been associated with chilblain lupus. Also, the susceptibility to cutaneous lupus erythematosus is correlated with polymorphisms in the IFNK (Interferon kappa) gene that encodes for Interferon (IFN)-κ a type I IFN. In SLE, the overproduction of IFN-κ amplifies epithelia's responsiveness to IFN-α, thus increasing keratinocyte sensitivity to UV irradiation [2,3].

Concerning environmental factors, UV light exposure and smoking have been proven to contribute the most to the pathogenesis of cutaneous lupus erythematosus. UV light exposure increases the overproduction of cytokines like IFN, Tumor Necrosis Factor-

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Article History:
Received: 20 March 2023
Accepted: 27 March 2023

alpha (TNFα), Transforming growth factor beta (TGF-β), Interleukin 1α/β (IL1α/β), Interleukin 6 (IL-6), Interleukin 8(IL-8), Interleukin 10 (IL-10), Interleukin 17 (IL-17) and chemokine (CXCL9, CXCL10, CXCL11, CCL27) overproduction by keratinocytes, thus contributing to further immune cell migration to the site of aggression. Also, an interesting aspect regarding the particularities of skin immunity in lupus is the fact that plasmacytoid dendritic cells (pDC), bone marrow–derived cells that specialize in the secretion of IFN-α/β (possibly contributing to the "IFN signature" present in lupus patients), are more abundant in cutaneous lupus lesions compared to the normal tegument. This fact has been taken into consideration for the study of future dendritic cell-targeted therapies, with promising results [1,4]. Furthermore, UV radiation exposure directly causes the apoptosis of keratinocytes as well as Nucleic Acids (NA) damage at the dermis level, thus increasing autoantigen exposure to professional antigen-presenting cells (APCs). The antigen is then presented to T lymphocytes which furthermore activate the production of antibodies from B lymphocytes with the formation of immune complexes [1].

Smoking is a well-known skin-damaging environmental factor, which increases the overproduction of free radicals, inflammatory cytokines, and neutrophil extracellular traps (NETs). NETs consist of DNA, chromatin and various proteins and have the potential to further activate pDCs. Cutaneous lupus subtypes such as lupus panniculitis, ACLE, DLE, and to a lesser extent, SCLE have been associated with NETs overproduction [1,5]. Smokers with cutaneous lupus erythematosus have a less-controlled disease, worse quality of life, and often require a higher dose of antimalarials or even combination therapy (hydroxychloroquine plus quinacrine) compared to non-smokers [1,6].

AN OVERVIEW OF THE CLASSIFICATION OF CUTANEOUS LUPUS ERYTHEMATOSUS

There are no universally accepted classification criteria for cutaneous lupus erythematosus. According to Gilliam and Sontheimer's classification, skin lesions are divided into LE-specific and LE-nonspecific. LE-specific skin lesions are divided into acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE); and chronic cutaneous lupus erythematosus (CCLE), with the last category including discoid lupus erythematosus (DLE), chilblain LE, tumidus LE, and lupus profundus [7]. The clinical morphology of each type is detailed in Table 1 [1,7].

ACLE is typically associated with systemic involvement, with the majority of patients having positive ANAs. The malar rash (localized ACLE) (figure 1) characterized by butterfly-shaped erythema over the cheeks and nasal bridge usually spares the nasolabial folds and must be differentiated from dermatomyositis facial erythema which tends to involve them. The generalized form of ACLE could also mimic dermatomyositis, with the appearance of maculopapular rash on the dorsum of the hands, but sparing the metacar-

TABLE 1. Lupus erythematosus-specific skin lesions

Acute cutaneous lupus erythematosus	Occurs in 30-50% of patients with SLE. Flares often parallel systemic disease activity with positive ANA, anti-dsDNA, and anti-Sm antibodies.
Localized	Raised or flat malar rash. Photosensitive, nonscarring, transient (figure 1).
Generalized	Widespread maculopapular rash above and below the neck. Dorsum of hands sparing MCP and IP joints (figure 2). Photosensitive, pruritic.
Subacute cutaneous lupus erythematosus	The recurrent course of widespread, highly photosensitive lesions that resolve without scarring, but sometimes with depigmentation. Associated sometimes with mild SLE flare. Often positive ANA, anti-Ro antibody. 1 in 3 cases are drug-induced, so is mandatory for medication reevaluation.
Annular	Scaly annular erythematous plaques often merge into polycyclic morphology (figure 3).
Papulosquamous	Resembles psoriasis or eczema.
Erythrodermic	Generalized exfoliative erythroderma
Chronic cutaneous lupus erythematosus	Chronic, recurrent disease course. Rates of SLE vary between subtypes
Discoid lupus erythematosus	Erythematous, sometimes scaly plaques exacerbated by sun exposure and trauma that progress to dyspigmentation and atrophic scarring; localized if confined to head and neck (low risk to progress to SLE) (figure 4); generalized if extends below the neck (20% risk to be associated with systemic disease).
Hypertrophic	Papular lesions on the face, extensor surfaces, palms/soles
Mucosal	Erosions and macules on mucosal surfaces.
Lupus erythematosus panniculitis	Indurated subcutaneous nodules or plaques in the face, scalp, upper torso, buttocks, and proximal extremities, associated with atrophic scars.
Chilblain lupus erythematosus	Painful violaceous plaques and nodules in cold-exposed areas may progress to erosions or ulcerations on acral surfaces.
Lupus erythematosus tumidus	Erythematous macules, papules, plaques with smooth surfaces and no scale, sharply raised borders. Very photosensitive (low risk for systemic disease).

FIGURE 1. - Acute cutaneous lupus erythematosus

pophalangeal (MCP) and interphalangeal (IP) (figure 2), as opposed to Gottron's papules [1].

SCLE lesions are highly photosensitive, involving sun-exposed areas, such as the upper chest and back

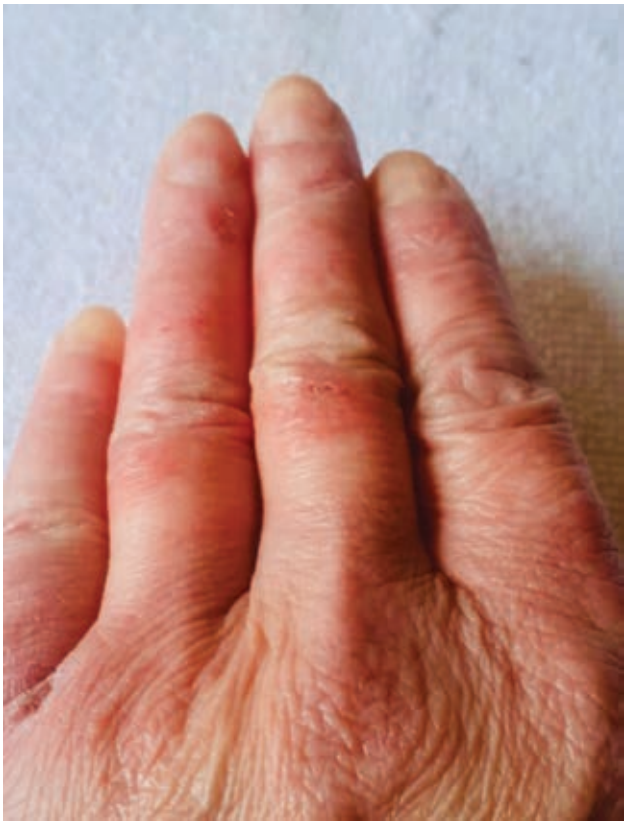

FIGURE 2. - Acute cutaneous lupus erythematosus on the dorsum of the hand, spearing IP joints

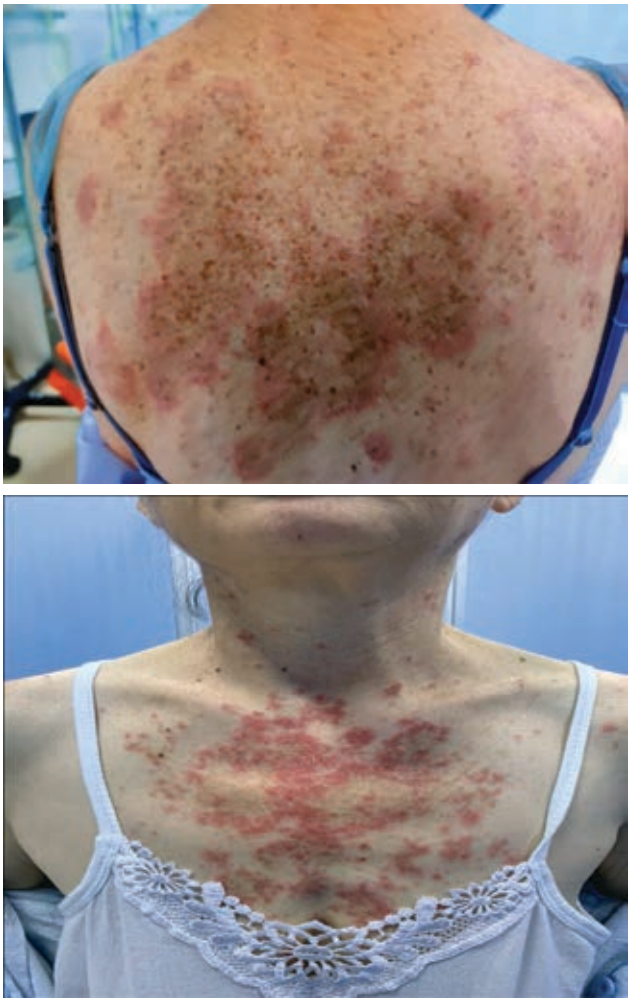

FIGURE 3. - Subacute cutaneous lupus

in a "V-shaped" distribution (figure 3), the extensor surfaces of the arms, and the sides of the face but non-scarring and are associated with mild systemic symptoms, most commonly arthritis and myalgias. The papulosquamous subtype may resemble psoriasis or eczema. Anti-SSA/Ro antibodies should be tested (even when ANAs are negative), especially in the case of young women, considering the high risk of giving birth to infants with neonatal lupus which is associated with congenital heart block in newborns. Notably, in approximately 30% of patients, the subacute cutaneous lesions are drug-induced. Some of the incriminated pharmacological agents are terbinafine, antiepileptics, interferon, chemotherapy agents, TNF-alpha antagonists, anti-IL 17 agents, anti-IL 12/23 agents, but also some medication usually prescribed for SLE patients like proton pump inhibitors, anti-hypertensive medications (calcium channel blockers, angiotensin-converting enzyme inhibitors, spironolactone), nonsteroidal anti-inflammatory drugs, antifungal agents. The possibility of a medication causing SCLE lesions should be taken into consideration when there is an apparent resistance to treatment in a patient already diagnosed with SLE. Anti-histone antibodies are present in approximately 30% of cases [1,8,9].

Regarding CCLE, discoid lupus erythematosus represents approximately one-half of cases, being the most frequent form. The generalized subtype has a greater rate of progression to systemic lupus erythematosus compared to the localized discoid lesions (which appear only on the head and neck) (figure 4). In case of the progression of localized discoid lesions, the clinician should also consider reevaluation for systemic involvement. Lupus erythematosus panniculitis (lupus profundus) presents as indurated subcutaneous nodules or plaques that tend to occur in the face, scalp, upper torso, buttocks, and proximal extremities. A biopsy of the affected tissue should be performed to confirm the diagnosis because subcutaneous panniculitis-like T-cell lymphoma has a similar presentation. Lupus tumidus is characterized by extreme photosensitivity and is typically only limited to the skin, without systemic involvement [1,8].

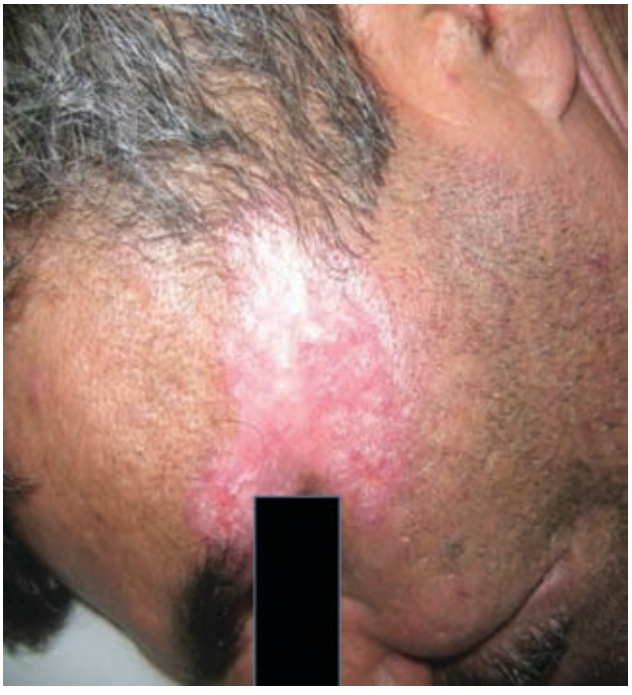

FIGURE 4. - Discoid lupus erythematosus

Lupus erythematosus non-specific lesions parallel more frequently with active systemic lupus erythematosus compared to cutaneous specific lesions and their presence in patients with an established diagnosis could be an alarm sign for a potentially underlying flare.

Cutaneous vascular disease comprises vasculitis, vasculopathy, periungual telangiectasias, livedo reticularis, thrombophlebitis, Raynaud's phenomenon, and erythromelalgia. Cutaneous vasculitis which presents as palpable purpura, urticarial vasculitis, or with a polyarteritis nodosa-like fashion with nodules or ulceration, is associated most commonly with high systemic activity and hypocomplementemia. While livedoid vasculopathy appears as an inflammatory response due to underlying hypercoagulability, livedo reticularis is caused by hypo-oxygenation, secondary to cold exposure. Raynaud's phenomenon (white, blue, and red color variation of acral skin secondary to cold exposure or stress) is one of the most frequent signs in patients with systemic lupus erythematosus being also common in other autoimmune diseases like scleroderma, dermatomyositis, and mixed connective tissue disease [1]. Some patients can be found with a scleroderma-like pattern on nail fold capillaroscopy [10].

Alopecia is a phenomenon that can be a consequence of lupus, or it can coexist separately as a clinical entity (telogen effluvium, anagen effluvium). It is crucial to establish the etiology of hair loss in the setting of lupus erythematosus taking into account that non-scarring alopecia (diffuse thinning or hair fragility with visibly broken hairs) represents a clinical criterion in both 2012 SLICC (Systemic Lupus International Collaborating Clinics) classification criteria for systemic lupus erythematosus and 2019 EULAR/ACR (European League Against Rheumatism/American College of Rheumatology) classification criteria for systemic lupus erythematosus [11-13]. Lupus erythematosus specific alopecia is represented by scalp discoid lupus erythematosus (DLE), typically scarring (figure 5), subacute cutaneous lupus erythematosus (SCLE), tumid LE, and acute LE alopecia. Lupus hair, a poorly characterized entity, falls into the lupus non-specific alopecia category, having the appearance of dry and fragile short hairs on the frontal hairline. The differential diagnoses of scarring alopecia are lichen planopilaris, frontal fibrosing alopecia, central centrifugal cicatricial alopecia, pseudopelade of Brocq, and tinea capitis (late stage). Non-scarring lupus erythematosus alopecia should be differentiated from patterned hair loss, acute diffuse and total alopecia areata, trichotillomania, syphilitic alopecia, tinea capitis (early stage). The psychological burden

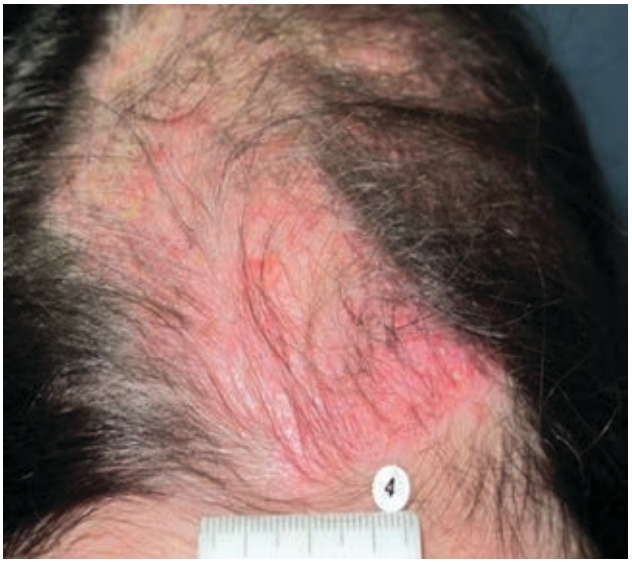

FIGURE 5. - Chronic, scarring alopecia

and the impact on the quality of life emphasize the importance of the rheumatologist-dermatologist collaboration, in diagnosing the exact etiology of alopecia in lupus patients [11].

It is known that mucocutaneous manifestations have been part of the clinical domain since the first 1972 ACR classification criteria for lupus erythematosus. It is important to note that the purpose of classification criteria is to select populations for inclusion in clinical trials, and not to establish diagnosis and treatment decisions, because some patients do not fully fulfill them at the early stages of the disease [13,14]. Regarding the impact of the mucocutaneous domain on the final score, the ACR-97 criteria included both LE-specific skin changes (malar, discoid lesions), and relatively nonspecific skin changes (oral and nasal mucosal ulcers, and photosensitivity), with the patient being classified as having systemic lupus erythematosus if any 4 of the 11 criteria where positive. Thus, many patients with isolated skin manifestations were fulfilling the required criteria for systemic disease. With a higher sensitivity, SLICC 2012 criteria include 11 clinical and 6 immunological criteria. Fulfillment of at least four of them, with at least one clinical criterion and one immunologic criterion, is required thus the impact of the skin lesions alone on the final score is relatively reduced. Nonscarring alopecia takes place of photosensitivity, next to acute cutaneous lupus, chronic cutaneous lesions, and oral ulcers, with the mention that the exact cause of hair loss should be established, as stated above [8,13]. The latest 2019 ACR/EULAR classification criteria reach a sensitivity of 96.1% (similar to 2012 SLICC criteria) and a specificity of 93.4% (similar to ACR-97 criteria), requiring antinuclear antibodies (ANA) as an entry criterion. Because it is considered that the cutaneous manifestations are not entirely independent (acute, subacute, discoid lesions, oral ulcers, and non-scarring alopecia may well be related), only the highest-scoring item in the mucocutaneous domain is being taken into account for classification. In this manner, the risk of including patients in the systemic disease category is avoided [13,15].

CUTANEOUS VERSUS SYSTEMIC INVOLVEMENT

The association between cutaneous lupus erythematosus and systemic lupus erythematosus varies among the subtypes. The following percentages represent the cross-sectional co-prevalence between cutaneous LE and SLE resulting from cross-sectional and retrospective studies, rather than a prospective incidence. Thus, ACLE has been associated in over 90% percent of cases with SLE, SCLE in approximately 50% of cases, and localized DLE in 5 to 10% compared to generalized DLE which has been associated in 15 to 28% of cases with SLE. Lupus panniculitis presents a 5 to 10% association with the systemic presentation, as opposed to lupus tumidus which has been rarely found to coexist with systemic lupus [16]. As mentioned above, non-specific skin lesions are associated with increased systemic disease activity. Although patients with cutaneous lupus erythematosus will not automatically progress to systemic disease, periodic follow-up is important for monitoring the course of the skin disease. Some of the prognostic indicators which have been reported are the presence of generalized subtypes of DLE and SCLE, LE-nonspecific lesions (Raynaud's phenomenon, nonscarring alopecia and periungual telangiectasias being some of the most frequently associated with underlying systemic activity), laboratory abnormalities such as leucopenia, thrombocytopenia, anemia, high ESR, low complement and serological abnormalities (elevated titers of ANA, anti-dsDNA antibodies and anti-Sm antibodies). Some correlations have been found between autoantibody specificities and CLE subtypes. Acute lesions are strongly associated with ANAs, and anti-dsDNA antibodies, while subacute lesions have been positively correlated with anti-Ro/SSA, anti-Smith, and anti-RNP antibodies. The identification of quantifiable molecular markers for predicting the progression from cutaneous to systemic disease remains an important future perspective [5,17,18].

DIAGNOSIS

The diagnosis of cutaneous lupus erythematosus is clinical, especially in the context of underlying systemic manifestations. Biopsy with histopathologic examination could be used in cases of atypical clinical presentation such as lupus profundus (which should always be differentiated from subcutaneous panniculitis-like T-cell lymphoma), or lupus tumidus (which isn't associated with systemic lupus). Subacute lesions could often resemble psoriasis, but in the context of positive immunology for anti-Ro/SSA antibodies, the diagnosis can be established in the absence of histopathology [16].

Direct immunofluorescence (lupus band test) evaluates the deposition of a continuous band of immunoreactants along the dermal-epidermal junction of the lesional integument, but it can also be present in non-lesional skin. It is not routinely performed but it could bring a contribution to the diagnosis in cases of unclear histopathology. However, it has been shown that false-positive results could appear from the examination of sun-exposed skin, which makes it a non-specific test [16,19], but underlines the importance of skin and UV exposure into the pathogenesis of SLE.

MONITORING FOR SKIN DISEASE ACTIVITY

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is a standardized and validated tool conceived for the evaluation of skin disease severity and it is used in clinical trials for measuring the outcome of potential therapies. The CLASI consists of two scores summarizing the activity of the disease and the damage done by the disease. Because one patient can present more than one subtype of LE-specific lesion at the same time, CLASI is designed as a single instrument that can assess at least three clinical entities (DLE, SCLE and SLE) and in this manner, the subject subgroups can be realistically recruited to reflect clinical reality [20].

TREATMENT

Regarding the therapeutic approach to cutaneous disease, the 2019 EULAR recommendations for the management of systemic lupus erythematosus state the necessity of smoking cessation and effective UV protection with the use of broad-spectrum sunscreens as general measures. First-line treatment includes topical glucocorticoids and/or topical calcineurin inhibitors with or without the addition of systemic glucocorticoids, the starting dose of the latter depending on the severity of skin involvement. The antimalarial of choice is hydroxychloroquine and in cases of inadequate response or toxic retinopathy, quinacrine may be used as an add-on/sequential therapy when available. In case of lack of response (approximately 40% of patients), second-line therapies such as methotrexate, retinoids, dapsone, and mycophenolate mofetil can be added. However, dermatological involvement of SLE – specific or non-specific – is usually part of a SLE flare and treatment will be tailored according to other organ involvement, comorbidities, desire for pregnancy. Used in SLE, Belimumab and Rituximab (off-label) have also shown efficacy in mucocutaneous manifestations, with the latter possibly being less beneficial in chronic lesions. Thalidomide has been shown to be effective in cutaneous disease, but because of its weak safety profile it is considered a "rescue" therapy [21,22]. Anifrolumab showed in TULIP trials a favorable effect on mucocutaneous SLE, as evaluated by CLASI score [23].

CONCLUSION

The cutaneous involvement in lupus erythematosus is characterized by high heterogeneity, the rheumatologist-dermatologist collaboration being a mandatory task for optimizing patient care. In the absence of proper general measures (adequate UV-rays protection, smoking cessation) and medical treatment, subacute and chronic lesions could lead to dyspigmentation and scarring respectively, with negative psychological impact, thus, being a major contributor to the quality of life even in the absence of systemic involvement. Subacute lesions are triggered by various pharmacological agents in a large patient population. The clinician should take into account this possibility when collecting anamnesis. Preconception counseling in young women with positive anti-SSA/Ro antibodies should always be recommended. From a future perspective, the identification of quantifiable molecular markers for predicting the progression from cutaneous to systemic disease could bring an important contribution to disease management.

Conflict of interest: none declared
Financial support: none declared

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