LECTURE

Skin lesions in systemic lupus erythematosus. Part 1: classification, etiology, pathogenesis

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Skin and mucous membranes lesions in systemic lupus erythematosus (SLE) significantly impair the quality of life of patients, although they are not a formidable manifestation of the disease. Skin manifestations of SLE can occur both at the onset and on the late stage of the disease. Although skin and mucous membranes lesions are clearly grouped in the latest classification criteria for SLE, verification of the diagnosis requires a multidisciplinary approach. In the etiology of SLE, environmental factors, hormonal factors, and genetic predisposition play a role. Further research will reveal differences in subtypes of cutaneous lupus erythematosus and will facilitate the development of new therapies.

Key words: *systemic lupus erythematosus; skin lesions; mucous membranes lesions; cutaneous lupus erythematosus.*
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Systemic lupus erythematosus (SLE) is a heterogeneous chronic autoimmune rheumatic disease with a vast spectrum of clinical manifestations characterized by impaired activation of cellular and humoral immunity components, uncontrolled hyperproduction of organ-specific wide-spectrum autoantibodies to nuclear antigens and the formation of immune complexes causing immuno-inflammatory damage to tissues and organs [1, 2]. There are various clinical forms of the disease – from localized skin lesions to a life-threatening variant with severe systemic manifestations.

In the course of the disease, skin involvement occurs in approximately 75% of patients with SLE [3, 4]. Cutaneous lupus erythematosus (CLE) can be accompanied by significant skin damage and discomfort with deterioration of the quality of life [5].

Avoiding such provoking factors as sun exposure inhibits the development of other signs of the disease. The combination of CLE and SLE creates difficulties in early diagnosis and can sometimes cause a delay in treatment or, conversely, lead to administration of unreasonably intensive therapy. N.K. Das et al [6] assessed the frequency of skin and mucosal lesions, which could be regarded as precursors of the transformation of CLE into SLE. Among the variety of clinical manifestations of skin and mucous lesions, statistically significant predictors of systemic development were non-scarring alopecia, photosensitization, aphthous stomatitis, malar rash. Polymorphic rashes ($p=0.0326$) were also associated with SLE, while discoid skin lesions (especially localized variants) were associated with a limited form of the disease and a low probability of SLE ($p<0,0001$). The authors did not reveal a significant association of SLE with papulo-squamous rash, Raynaud's phenomenon and scarring alopecia.

Diagnosis of SLE and CLE

The development of diagnostic criteria for SLE still remains a goal of the rheumatology community. Currently, there are only classification criteria that do not have 100% sensitivity and specificity and are used for enrollment of a homogeneous cohort of patients in clinical trials that are not aimed at the diagnosis of SLE. Over the past 40 years, five variants of classification criteria have been developed. The most widely used are the criteria of SLE, proposed by ACR (American College of Rheumatology). Their first version was published in 1971 and revised in 1982 and 1997. [7, 8]. These criteria contain 11 clinical and laboratory signs. A reliable diagnosis of SLE can be made in the presence of 4 of them. At the same time, the American Association of Dermatologists pointed out the following shortcomings of the ACR criteria: low specificity and a large number of skin signs. In particular, skin and mucous lesions, are determined by 4 criteria (malar rash, discoid lesions, photosensitization and oral ulcers), and they can potentially be used to diagnose SLE in patients with skin diseases [9, 10].

In 2012, the experts of SLICC (Systematic Lupus International Collaboration Clinics) revised the classification criteria of ACR 1997 for SLE. For greater clinical significance, classification criteria for SLE were proposed, providing for the presence of at least 4 signs, including one immunological, such as antinuclear antibodies (ANA) or antibodies to double-stranded DNA (anti-dsDNA) in the case of proven lupus nephritis as the only manifestation of SLE. The SLICC criteria allow for a greater variability of skin manifestations. The current version includes three types of skin lesions in SLE: 1) acute CLE (ACLE) – malar rash, bullous rash, skin lesions similar to toxic epidermal necrolysis, maculopapular rash, photosensitization; 2) subacute CLE (SCLE) – nonindurated psoriasiform and/or annular polycyclic lesions without scarring; 3) chronic CLE (CCLE) – discoid lupus erythematosus (DLE), hypertrophic (verrucous) lupus erythematosus, deep lupus erythematosus (lupus panniculitis), lupus erythematosus tumidus, chilblain lupus erythematosus, cross syndrome (DLE/lichen planus overlap), oral and nasal ulcers and nonscarring alopecia [11].

In 2019, at the EULAR (European Alliance of Associations for Rheumatology) conference, the criteria were revised again: now the presence of ANA is used as an inclusion criterion, and the criteria themselves are evaluated in points ranging from 2 (for delirium, non-infectious fever and antiphospholipid antibodies) to 10 (for lupus nephritis class III or IV). The criteria are grouped according to organ systems; for each system only the features with the maximum score are taken into account, and not their sum. The new criteria

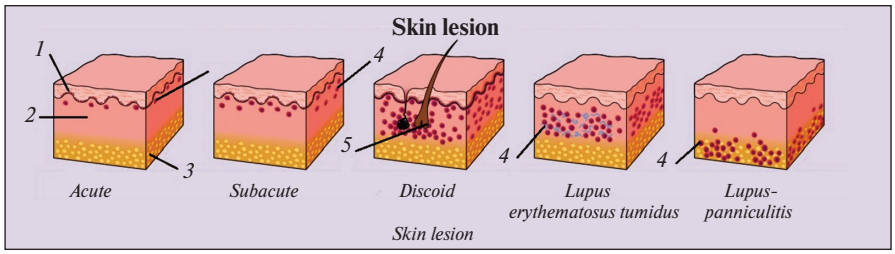

Fig. 1. *The predominant localization of inflammatory infiltrates in various types of skin lesions in patients with lupus: ACLE, SCLE, as well as DLE, lupus erythematosus tumidus and lupus panniculitis (the last three are forms of SCLE). Localization of infiltrates: superficial dermis (ACLE and SCLE); superficial, periadnexal and deep dermis (DLE); superficial and deep dermis (lupus erythematosus tumidus); subcutaneous adipose tissue (lupus panniculitis). 1 – epidermis and superficial dermis; 2 – deep dermis; 3 – subcutaneous fat infiltration; 4 – infiltrate; 5 – hair follicle [14]*

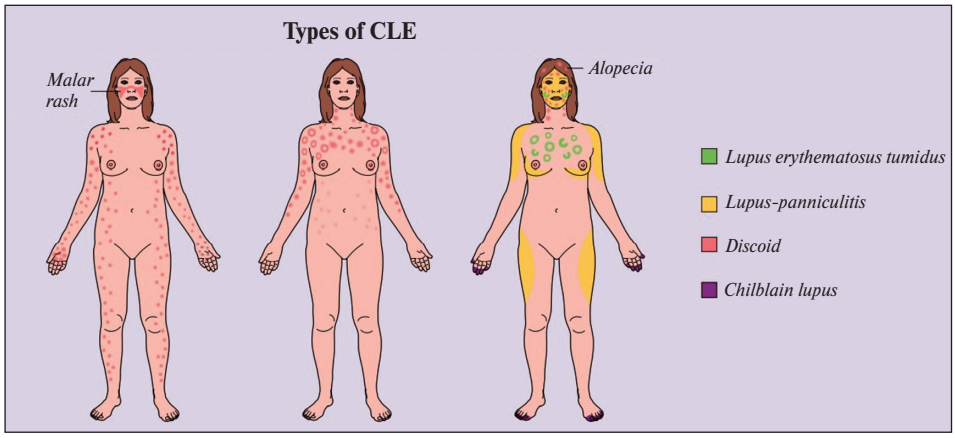

Fig. 2. *Characteristic localization of skin lesions in the main types of CLE [14]*

include the following variants of skin and mucous lesions: nonscarring alopecia (2 points), ulcers in the oral cavity (2 points), subacute cutaneous lupus or DLE (4 points), acute cutaneous lupus (6 points) [12]. Currently, all three groups of SLE classification criteria are used, the choice is ultimately based on users' preferences.

Classification

The most commonly used classification of skin lesions is that proposed by J.N. Gilliam and R.D. Sontheimer [13]. Skin lesions in CLE are divided into specific and nonspecific on the basis of histopathological data. Specific skin lesions have a typical histological pattern with a tissue lichenoid reaction and are subdivided into ACLE, SCLE and CCLE [13]. The terminology is based on the clinical picture of skin lesions: ACLE is characterized by photosensitive malar erythema; CCLE – by long–term, slowly progressing foci leading to scarring; SCLE – by rashes occupying an intermediate position between ACLE and CCLE, localized in areas of the body exposed to solar irradiation, not prone to scarring.The category of chronic skin lesions includes not only skin manifestations of SLE, but also less common signs, such as lupus panniculitis, lupus erythematosus tumidus and chilblain lupus (рис. 1, 2).

A specific skin lesion does not exclude the presence of nonspecific changes: the patient may have more than one type of skin manifestations.

There is also an expanded alternative classification of specific and non-specific skin manifestations of CLE, presented in the Table [13].

Epidemiology, etiology and pathogenesis of skin lesions in SLE

The role of sex hormones

SLE is usually considered a "female" disease, which is due to epidemiological indicators – the ratio of morbidity among women and men of reproductive age (a population comparable in age) is 8–15:1 [2, 3, 17]. However, there are significantly more men among patients with DLE (the ratio of women to men is approaching 2–4:1) [18]. This is reflected in the work of S.K. Tedeschi et al. [19], who considered sex hormones to be the key reason for the predominance of women among SLE (but not DLE) patients: a higher level of sex hormones (in particular, estrogens) is a risk factor for SLE development when exposed to similar genetic and environmental factors. A prospective cohort study has shown that there is a higher risk of developing SLE after exogenous estrogen therapy [20]. These data confirm that estrogens can trigger the development of SLE in women [21]. Progesterone, on the contrary, rather counteracts the effects of estradiol. Similar results were obtained for testosterone, which apparently inhibits the production of pro-inflammatory cytokines and immunoglobulins [22], having a protective effect against SLE. At the same time, the activity of DLE does not change during pregnancy and does not depend on the use of estrogen-containing oral contraceptives, which indicates an estrogen-independent mechanism for the development of this disease [23].

Microbiota

Currently, the role of microbiota in the pathogenesis of autoimmune diseases is attracting increasing attention, but there is not enough direct evidence confirming the contribution of microbiota to the development of lupus. It has been shown that in SLE patients skin microbiota, in contrast to gut microbiota, is characterized by a significant increase in the number of staphylococci and corynebacteria, as well as a decrease in the number of cutibacteria. It is noteworthy that *Staphylococcus aureus* and *Staphylococcus epidermidis* are probably involved in the progression of skin lesions in SLE [24]. According to recently published data, the quantitative and specific composition of the skin microbiome at the sites of skin rashes in SLE is different from that in the control groups, which requires further study. [25].

Ultraviolet radiation

It is known that ultraviolet (UV) radiation is a provoking factor in the development of SLE in predisposed individuals. At the same time, the effect of UV radiation depends on the wavelength. According to the range of the light spectrum, three types of UV radiation are distinguished: short-wave (UV-C, with a wavelength

of 200–290 nm, that is absorbed by the ozone layer and does not reach the earth's surface), medium-wave (UV-B, with a wavelength of 290–320 nm) and long-wave (UV-A, with a wavelength of 320–400 nm). Two subtypes of UV-A are distinguished based on the differences in their properties: UV-A1 (340–400 nm), whose properties partially overlap with visible light, and UV-A2 (320–340 nm), which has some common characteristics with UV-B. It has been shown that in patients with SLE and DLE, exposure to UV-B and UV-A2 will cause or worsen skin damage, whereas low-dose UV-A1 irradiation can be used for treatment and significantly reduce the activity of the disease [26].

The effect of UV radiation also depends on the content of induced nitric oxide synthase (iNOS), an enzyme responsible for the production of nitric oxide (NO) which is absent in most cells under normal conditions. There is evidence that iNOS produced by epidermal keratinocytes, after endo- and exogenous stimulation, plays an important role in the development of autoimmune diseases, in particular SLE [27]. In SLE, UV-B radiation can cause prolonged expression of iNOS in the skin, especially in the basal layer of the epidermis, whereas in the control group of patients without SLE, iNOS expression is limited to the surface layer and has a much shorter duration after exposure to UV-B, which can explain severity, duration and possible heterogeneity of skin manifestations of the disease [28].

Autoimmunity

SLE is characterized by the production of a large pool of autoantibodies to autoantigens, while antibodies targeting the protein complex of DNA cause tissue damage more often than antibodies reacting only to DNA [29]. The most important of the antigens are Ro, La and snRNP, which are structurally ribonucleoproteins [30].

When exposed to UV radiation, cell necrosis and apoptosis occur, as a result of which nucleosomes are released from the nucleus and initiate tissue damage by the formation of immune complexes. S. Koutouzov et al. [31] demonstrated that nucleosomes appear to be one of the primary antigens in the initiation of SLE, while in another study on mice with SLE it was shown that antibodies to nucleosomes occur at the onset of the disease earlier than anti-dsDNA [32].

In 77% of patients with SLE, immunological disorders (highly positive levels of autoantibodies) appeared several years before the first clinical manifestations of the disease. It is noteworthy that ANA, antibodies to Ro/SS-A (anti-Ro/SS-A) and La/SS-B (anti-La/SS-B) are detected earlier than anti-dsDNA and antiphospholipid autoantibodies; the last detected antibodies (closer to the appearance of clinical signs) are anti-Sm and anti-RNP (ribonucleoprotein) [33]. This may indicate that as the disease progresses, more and more antigens are involved in the autoimmune response, which con-

Table. Classification of skin lesions in CLE [13]

I. Specific	II. Non-specific
1. ACLE (15%): – localized (90–95%) – widespread indurated erythema (5–10%) – toxic epidermal necrolysis (TEN)	1. Lesion of skin vessels: – secondary leukocytoclastic vasculitis: • palpable purpura • urticarial vasculitis – vasculopathies • Degos-like lesions • livedo-vasculitis • telangiectasia of nail folds • livedo reticularis • thrombophlebitis • the Raynaud phenomenon • erythromelalgia
2. SCLE (8%): –annular (42%) – papulosquamous/psoriasiform (39%)* – bullous (rare) – TEN-like (very rare)	2. Nonscarring alopecia: – lupus-alopecia – telogen alopecia –alopecia areata
3. CCLE (73%): – discoid (80–85%): • localized (70%) • widespread (30%) – hypertrophic/verrucose – deep/lupus-panniculitis – tumidus /papulomucinous CLE (1%): – chilblain lupus erythematosus– CLE of the mucous membranes (oral cavity, nose, genitals, conjunctiva) – lichenoid DLE (CLE/lichen planus overlap)	3. Sclerodactyly
	4. Rheumatoid nodules
	5. Calcification of the skin
	6. Non-specific bullous lesions
	7. Urticaria
	8. Papulonodular mucinosis
	9. Anetoderma
	10. Acanthosis nigricans
	11. Erythema multiforme
	12. Lower leg ulcers
	13. Red lichen planus

Note. TEN – toxic epidermal necrolysis; * – in 16% of cases, a combination of annular and papulo-squamous forms is observed [15, 16].

tribute to the recognition of new autoantigens by lymphocytes and further expansion of the immune response. Administration of serum from a patient with active SLE to healthy mice induced skin lesions in them [34].

It is considered that an increase in the levels of anti-Ro/SSA, anti-La/SSB, anti-Sm and antibodies to ribosomal protein P (anti-P) is associated with skin damage and photosensitivity [35]. As for SCLE, patients with annular erythema more often have anti-La/SS-B and less significant systemic manifestations than patients with papulosquamous (psoriasiform) rash, which can be considered a variant of DLE. Negative anti-Ro/SS-A or their low levels are more common in DLE, which can be used to differentiate DLE from SLE and SCLE [36, 37].

Genetic and cellular mechanisms

Polymorphism of various genes is important in the development of SLE. The fact that SLE rarely develops in both monozygote twins may be due not only to genetic susceptibility, but also to epigenetic factors. Genes that can affect overall immunoreactivity contain proteins (more than 40) involved in the activity of B and T cells [38]. The interaction of genetic and epigenetic factors triggers a complex cascade of pro-inflammatory reactions of cytokines, chemokines and inflammatory cells. It affects the epidermis, dermis, adnexal structures, activating keratinocytes, endothelial cells and dendritic skin cells, as well as the production of interferons (IFN) type I followed by recruitment and activation of cytotoxic T cells CD4+ и CD8+. Both the existing genetic background and mutations in specific genes contribute to the clinical heterogeneity of skin manifestations of SLE [38].

W. Zhang et al. [39] revealed an increase in the percentage of T cell subpopulations, especially T helper cells, C-C-chemokine receptor 6 (CCR6)+ T, CCR6+ Th22, Th17, Th17.1 and CCR6-Th2 along with an increase in the concentration of interleukin (IL) 22, IFNγ, tumor necrosis factor (TNF) α and IL17 in patients with SLE. The highest levels of CR6+ T and CR6+ Th22, as well as IL22 in plasma were detected in patients with isolated skin and/or kidney damage. There was a direct correlation of the percentage of Th22 cells with the area and severity of skin lesions, the level of IgG, and an inverse correlation with the level of the C3 component of the complement.

Significance of IFN Type 1

An increase in the level of type I IFN is important in the mechanism of skin lesions in SLE and CLE [40, 41]. Type I IFNs (in particular, IFNα and IFNЯ) are usually a component of antiviral protection in the normal immune system, but their production by plasmacytoid dendritic cells is significantly increased in CLE. Antiviral mixovirus protein (MxA) – a specific surrogate marker of type I IFN production – was detected in CLE, which confirmed the participation of type I IFN in the development of skin and mucous lesions in SLE. DLE is specifically characterized by a large number of granzymes (a family of serine proteases expressed in cytotoxic T-lymphocytes and natural killers), closely related to the impaired expression of the myxovirus resistance protein (MxA) [42]. In skin lesions, the production of type I IFN is a key factor stimulating inflammation through the formation of an infiltrate associated with T helper cells 1, which can contribute to the development of an autoimmune response [43]. Thus, cases are described when patients without autoimmune diseases develop syndromes similar to SLE after IFNα therapy. This suggests that an increase in the level of type I IFN is a pathogenetic factor in the development of SLE [44, 45]. In patients with SLE and their healthy relatives, an increase in serum IFNα levels was detected compared with healthy individuals (control groups), which may be due to a change in the IFN signature genes [46]. IFNα can stimulate production of chemokines (for example, CXCL9, CXCL10), the expression of which is significantly increased and directly correlates with the distribution of inflammatory infiltrates in skin lesions in patients with CLE [47]. In CLE, type I IFN, together with IFNλ, induces the production of ligands 9 and 10 of chemokines (CXCL9 and CXCL10), which leads to the development of an interface-dermatitis pattern (histologically manifested as the presence of hydropic dystrophy of the basal layer of the epidermis, lymphocytes in the basal layer of the epidermis, colloid bodies) at the border of the dermis and epidermis due to the recruitment of CXCR3+ [48]. It was also found that in patients with SLE, in the process of dendritic cells differentiation, monocytes (but not lymphocytes), as well as TNFα and TNF R1, but not TNF R2, are crucial in the development of skin inflammation [49]. Further study of the pathogenesis of skin lesions in various variants of CLE will expand our understanding of the differences and cross-links in the pathogenetic mechanisms of CLE and SLE, as well as their prognostic biomarkers and treatment methods [50].

Conclusion

Skin manifestations of SLE can occur both at the onset of the disease and in a later period. In the latest classification criteria of SLE, lesions of the skin and mucous membranes are clearly grouped, but despite this, verification of the diagnosis requires a multidisciplinary approach. Environmental factors, hormonal factors, genetic predisposition play a role in the etiology of SLE. Future studies will allow us to detect differences in the subtypes of CLE and determine the appropriate goals of therapy.

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