REVIEWS

Clinical variants of skin and mucous membrane lesions in systemic lupus erythematosus with juvenile onset

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Skin and mucous membrane lesions are frequently seen in systemic lupus erythematosus (SLE) with the juvenile onset (juSLE), and they are extremely diverse. Skin manifestations can be the initial sign of the disease, they often respond first to adequate therapy, and recurrence or the appearance of a new type of lesions is the earliest indicator of exacerbation in many patients. In severe cases, skin lesions can lead to irreversible cosmetic defects, significantly affecting the quality of life.
The article presents the clinical manifestations of various variants of skin and mucous membrane lesions in SLE with a debut in childhood and adolescence, their recognition is important for the timely diagnosis of SLE, as well as the correction of therapy for an existing disease, which improves the long-term prognosis and quality of life of patients.

Keywords: *systemic lupus erythematosus with juvenile onset; skin lesions; mucosal involvement; acute cutaneous lupus erythematosus; subacute cutaneous lupus erythematosus; discoid lupus.*
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Systemic lupus erythematosus (SLE) is a severe life–threatening chronic disease characterized by systemic immuno-inflammatory damage to vital organs and an extreme variety of clinical manifestations [1, 2]. Different gender distribution in different age groups, a more aggressive course of SLE with juvenile onset (jSLE), as well as the presence of a monogenic variant of the disease in childhood indicate obvious differences in the pathophysiology of juvenile and adult SLE [2–4]. The authors who studied the age-related features of the pathogenesis of SLE showed a significantly greater interest in the genetic factor and innate immunity. These data are the basis for the currently proposed reclassification of variants of jSLE by the inflammatory spectrum – from auto-inflammation to autoimmunity [2, 3]. According to various estimates, 15–20% of patients with SLE develop symptoms of the disease in childhood and adolescence [2–4].

The incidence of jSLE worldwide ranges from 0.3 to 2.22 per 100 thousand per year with an estimated prevalence of 0.3 to 9.73 per 100 thousand [5–8]. Girls are more likely to have the disease (the ratio of boys and girls is from 3:4 among patients under 10 years old to 1:5 at an older age), the median age of onset, according to various studies, is 11–13 [8, 9] years.

Currently, the ACR (American College of Rheumatology) criteria of 1997 [10], the SLICC (Systematic Lupus International Collaborating Clinics) criteria of 2012 [11], as well as the EULAR (European Alliance of Associations for Rheumatology) / ACR criteria of 2019 [12] are used to verify the diagnosis of jSLE in clinical practice. All criteria are classification criteria. According to the latest data, most researchers are inclined to use for children and adolescents the 2012 SLICC criteria due to their optimal ratio of sensitivity and specificity [13, 14]. In all criteria, an important place is given to signs of damage to the skin and mucous membranes. In the ACR criteria, they occupy 4 points out of 11, including erythematous rash, discoid lupus, photosensitization and oral ulcers [10]. In the 2012 SLICC criteria, the list of types of skin and mucous lesions was expanded to include bullous rashes, toxic epidermal necrolysis, subacute cutaneous lupus erythematosus (SCLE) within the framework of acute active skin lesions. Signs of chronic cutaneous lupus erythematosus (CCLE) include hypertrophic skin lesions, panniculitis, mucosal lesions, edematous erythematous plaques on the trunk, capillaritis, discoid lupus of "overlap" type. In addition to oral ulcers, ulcerative lesions of the nasal cavity are mentioned separately, and non-pubic alopecia is included as an independent sign [11]. In the 2019 EULAR/ACR criteria, skin lesions are represented by acute cutaneous lupus erythematosus (ACLE), SCLE, discoid lupus as subtype of CCLE, oral ulcers and alopecia, ACLE being the most significant for diagnosis (6 points out of 10 required) [12]. Thus, the correct interpretation of lesions of the skin and mucous membranes is of great importance for diagnosis. In addition, it is often the skin manifestations that are the first to respond to therapy, and they can often be the initial signs of exacerbation of the disease. According to S.P. Ardoin et al. [15], a lot of attention is paid to refractory skin lesions in priority scientific studies devoted to jSLE; in these studies this area ranks 5th after nephritis, randomized clinical trials, biomarkers and neurolupus. Thus, knowledge of the features of skin lesions in jSLE is important both from the practical and scientific point of view.

Skin involvement in jSLE is present in 60–85% of patients, and occupy the 3rd place in frequency after hematological disorders (50–100%) and musculoskeletal involvement (60–90%) [5, 16, 17].

The frequency of skin manifestations of SLE with the onset before the age of 18 may depend on age and race. In the study by J.S. Massias et al. [18] at the time of diagnosis verification, the incidence of skin and mucous lesions in children under 8 years of age was 44.2%, in children aged 8 to 13 years – 32.5%, in

adolescents aged 14–18 years – 45.9%. The incidence obviously increased with the duration of the disease, reaching 76.7% in the younger age group, 65.4% in children aged 8–13 years and 66.7% in the older age group [18]. According to the authors, the index of SLE activity pBILAG2004 in patients aged 14–18 years was significantly higher, in particular, due to the domain including mucocutaneous manifestations (p=0.025) [18]. In a later work by the same authors, it was demonstrated that representatives of Asian peoples at the time of verification of the diagnosis of jSLE had dermatological manifestations significantly more often than black Africans (47% and 26% of cases, respectively) [19]. It should be noted that with an increase in the duration of the disease, the frequency of skin and mucous lesions in Africans increased significantly, but in general, in different ethnic groups it practically leveled off, amounting to 67.9% in Asians, 73.9% in black Africans and 63.4% in white race [19].

The severity of skin manifestations of SLE, as well as other systemic connective tissue diseases, according to some authors, has an inverse correlation with the severity of systemic damage: the brighter the skin rashes, the less the severity of internal organ damage and multisystem involvement [16, 20]. There is evidence that up to 31% of cases of isolated cutaneous lupus with juvenile onset subsequently evolve into a systemic disease, especially in patients with the onset at an older age and with a family history burdened by autoimmune pathology [21, 22]. At the same time, according to L.M. Arkin et al. [22], the highest risk of evolution to a systemic disease in jSLE patients who had isolated cutaneous lupus at the onset, is observed within the first year of the disease.

Classification of skin and mucous manifestations of SLE appeared in the 70s of the past century. To date, it still includes two categories of signs: specific for SLE and nonspecific [23]. This classification is used for both juvenile and adult forms of the disease, and both manifestations occur in different age groups.

Specific signs include changes pathognomonic for a certain nosology, which have a characteristic pathohistological picture. Among the specific skin-mucous manifestations of SLE, three forms are distinguished: ACLE, SCLE and CCLE [23].

ACLE can occur in the form of a localized or generalized lesion, which is very sensitive to the effects of ultraviolet rays. Localized ACLE, or malar (butterfly) rash, is the most common lupus-specific lesion both in patients with jSLE and in adult patients [5, 16, 24]. It is characterized by a well-defined, symmetrical erythematous and edematous, non-pruritic malar rash, which can involve the bridge of the nose, tends to centrifugal spread and, as a rule, does not affect the nasolabial folds (Fig. 1, a). The lesion can also be localized in the area of the ears, chin, decollete area and the red border of the lips with the development of cheilitis (Fig. 1, b).

Less often, ACLE manifests itself as a more diffuse rash that covers areas that are not exposed to ultraviolet radiation, often with extensive erythema and edema (Fig. 1, c). If the process is severe, small hemorrhages may occur on the rash surface. In this variant of the disease, there is no tendency to scarring and atrophy, hypo- or hyperpigmentation may appear at the stage of rash resolution (Fig. 1, d).

ACLE is much more common in jSLE [25, 26], its frequency in children and adolescents ranges from 35 to 85% [16, 25, 27–29].

Both localized rash on the cheekbones and more diffuse erythema in ACLE are closely related to the activity of the systemic process and do not depend on age (Fig. 2) [5, 24, 30, 31].

SCLE is extremely rare in patients with jSLE; originally, it was described as a subtype of cutaneous lupus [32]. In a study by B.Z. Dickey et al. [33], SCLE was found in 16% of children. There are two most common variants of SCLE: annular/polycyclic rash (Fig. 3, a, b) and papulosquamous/psoriasis-like rash with scales (Fig. 3, c, d); both variants are also described in children and adolescents [32, 33]. In most cases, they are localized on the face and upper extremities and usually heal without irreversible damage [32]. Skin lesions of the lower extremities in children are more common than in adults [33]. Such rashes are photosensitive, they are characterized by pigmentation disorders and the presence of telangiectasias [34]. As a rule, they are accompanied by moderate signs of a systemic process, a lesion of the musculoskeletal system is often observed, antibodies to Ro (anti-Ro) are detected [34]. Up to 70% of anti-Ro-positive patients with SCLE may have a combination of SLE and Sjogren's syndrome [34].

In addition to ring-shaped and psoriasis-like rashes, bullous rash and toxic epidermal necrolysis-like lesions are noted in SCLE [33, 35]. The latter are described in isolated observations; in all such cases it is very difficult to differentiate lesions within the framework of SLE activity from drug-induced disorders (Fig. 4). In this regard, first of all, it is necessary to cancel all drugs that could provoke such a situation [35]. Toxic epidermal necrolysis-like lesions in SLE can be combined with lupus pancreatitis and severe neurological manifestations, which significantly affects life prognosis [36, 37].

CCLE is rare in children, but is associated with a high risk of permanent damage [23, 31]. According to N. Chottawornsak et al. [28], in adults, various variants of CCLE are observed twice as often as in children. Among the variants of CCLE, there are classical discoid rash – localized (located above the neck) and generalized (spreading above and below the neck); hypertrophic (warty) skin changes; panniculitis; mucosal lesion; edematous erythematous plaques on the trunk; chilblain lupus erythematosus (Hutchinson's lupus); tumid lupus; discoid lupus erythematosus/red lichen planus overlap.

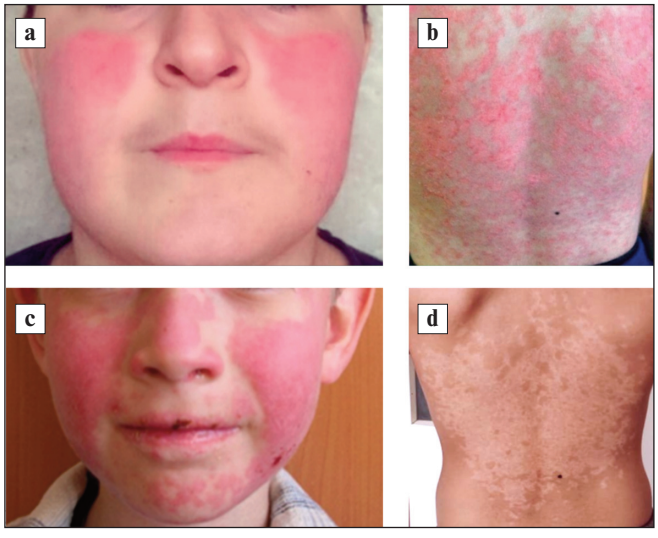

Fig. 1. *Acute cutaneous lupus erythematosus (ACLE): a – classic "lupus butterfly"; b – a common lesion with the involvement of chin area and vermilion zone of lips; c – rash on areas not exposed to ultraviolet radiation; d – hypopigmentation at resolution stage of the rash within ACLE. Here and in fig. 3–10 – photo from the authors archive*

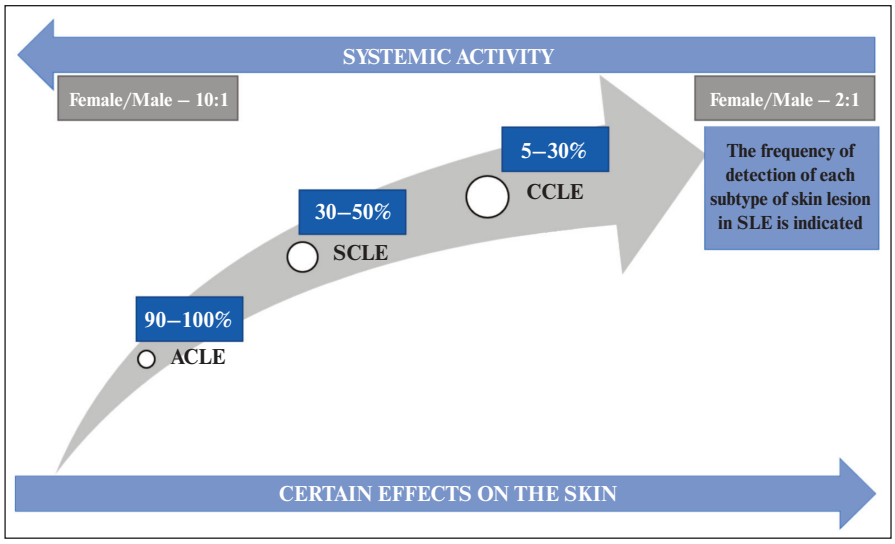

Fig. 2. *Scheme of dependence of systemic involvement and probability of damage on the form of specific skin lesions in SLE (adapted from [31]). The frequency of detection of each subtype of skin lesions in SLE is indicated*

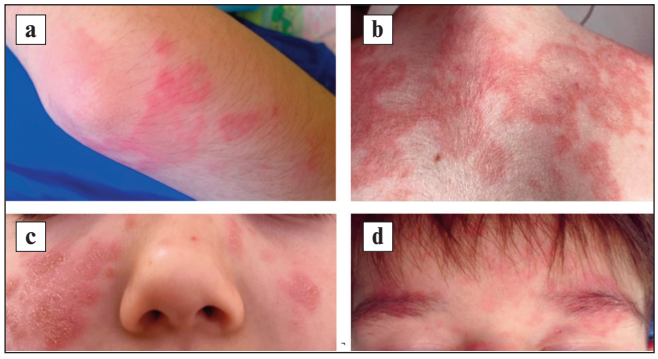

Fig. 3. *Subacute cutaneous lupus erythematosus: a – polycyclic; b – ring-shaped; c – papulosquamous rashes; d – psoriasis-like scaly rashes*

The most common variant of CCLE is discoid rash [23]. This is a much rarer manifestation in children, especially under the age of 10 [5, 16, 27], but it is associated with systemic signs much more often than in adults [22]. The incidence of discoid lupus in jSLE ranges from 6.5% to 37% [16, 25, 38, 39]. Discoid lupus has rarely been detected in children without systemic symptoms [33, 40], with the exception of the study by S.K. Lee et al. [29], in which its frequency in isolated cutaneous lupus in children was 47.1%. This type of rash in SLE most often occurs on the face (Fig. 5, a), the scalp (on the vertex; Fig. 5, b) and the auricles. Cicatricial alopecia refers to specific manifestations of SLE that develop as a result of discoid lesions of the scalp, in contrast to diffuse alopecia, which is a non-specific manifestation of SLE [41]. Discoid foci usually have the appearance of scarring hardened purple papules, expanding in the form of a coin with atrophic formation and telangiectasia. If the lesions are located on the scalp, persistent hair loss is observed. Interestingly, the risk of transformation of isolated discoid lupus into SLE is significantly higher in children than in adults (23.5–26% and 5–10%, respectively), and higher in children with a family history of autoimmune rheumatic diseases [40]. Generalized discoid lupus in children has been described in several studies and is apparently associated with a worse prognosis [33, 39, 40].

Other forms of CCLE, such as lupus panniculitis (Fig. 5, c), deep lupus erythematosus (lupus profundus), chilblain lupus erythematosus (Hutchinson's lupus; Fig. 5, d), mucosal lupus erythematosus, tumid lupus (Fig. 5, e), are extremely rare in children [33, 42–45]. According to V.R. Guissa et al. [42], the frequency of lupus panniculitis in jSLE is 0.7%. In a study by S.K. Lee et al. [29] there was a high prevalence of panniculitis (17.6%) in isolated cutaneous lupus in children. Only in one of these cases there was a subsequent evolution into jSLE. We have not found in the available literature information about the development in children of a combination of discoid lupus erythematosus and lichen planus described in adults. To date, there is evidence that such variant of CCLE as chilblain lupus erythematosus is associated with a mutation in the TREX1 gene that causes the development of Aicardi– Goutiиres syndrome with lupus-like manifestations [46]. This confirms the need to include monogenic lupus in the spectrum of differentiable conditions in children with early onset of SLE, including rare, atypical skin manifestations [2–4].

Along with specific skin manifestations in SLE, children, as well as adults, often have nonspecific variants of lesions [16, 23]. The key difference between them is that non-specific changes can manifest themselves in other inflammatory diseases, including those that are not within the competence of a rheumatologist. Most of the nonspecific changes of the skin and mucous membranes, usually observed in children and adults with SLE, are similar to each other and are associated with vascular pathology (for example, cutaneous vasculitis, livedo reticularis and Raynaud's phenomenon) [23]. Other common nonspecific changes are photosensitivity, ulcers in the oral cavity and diffuse alopecia without scars [23].

Cutaneous vasculitis usually affects small blood vessels (leukocytoclastic vasculitis) and can visually manifest as petechiae or palpable purpura. According to S.M. Gamal et al. [47], vasculitis with skin lesions occurs in SLE more often than other variants of vasculitis (59.2% in the structure of vasculitis with lesions of various organs and systems). As shown in this study, in the presence of vasculitis with damage to more than one organ, cutaneous vasculitis is the most frequent component. Rashes are usually localized on the face (Fig. 6, a), palms (Fig. 6, b) and soles. D. Chivchengchol et al. [16], examined 241 patients with SLE and detected cutaneous vasculitis in 12% of cases. In a Brazilian study involving 414 patients with SLE, including 60 patients with jSLE, the incidence of vasculitis with skin lesions in children was higher than in adults (21.6% and 15.4%, respectively) [48]. A higher probability of cutaneous vasculitis in jSLE was also indirectly confirmed by T.A. Gheita et al. [49], who demonstrated that patients with cutaneous vasculitis were significantly younger than patients who did not develop vasculitis. A number of authors indicate a connection between the presence of vasculitis with skin lesions and the activity of systemic lesions [50]. N. Chottawornsak et al. [28] revealed an association of cutaneous vasculitis with damage to the central nervous system. A special case of cutaneous

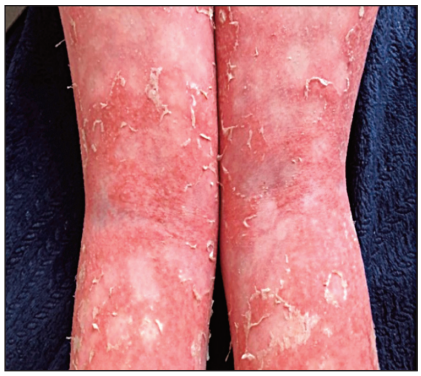

Fig. 4. *Drug-induced lesion of the toxic epidermal necrolysis type in juSLE*

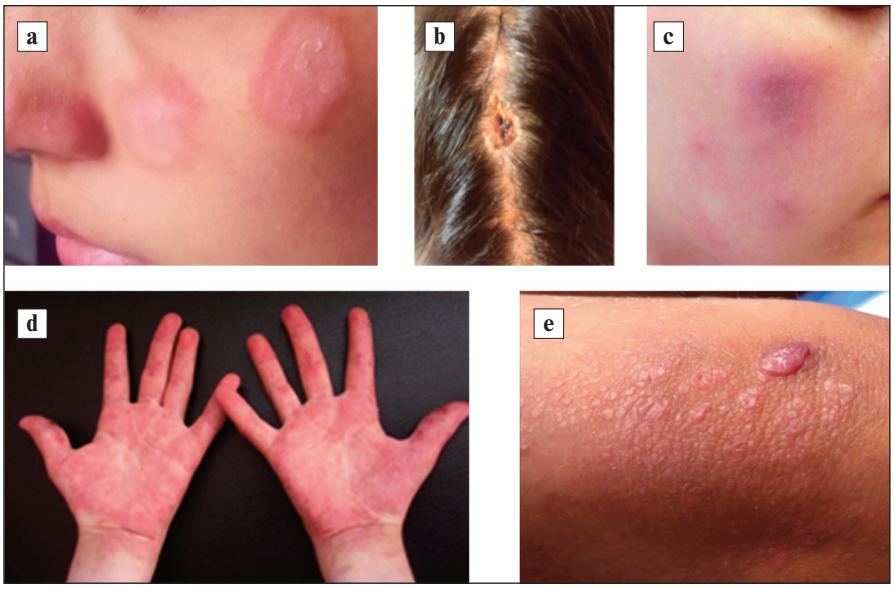

Fig. 5. *Chronic cutaneous lupus erythematosus: a – discoid lesions on the face; b – discoid focus on the scalp; c – lupus panniculitis; d – chilblain lupus erythematosus; e – lupus tumidus*

vasculitis in jSLE is digital vasculitis, which in the study of A.P. Sakamoto et al. [51] was found in 3% of patients. According to these authors, 48% of children with digital vasculitis had periarticular hemorrhages, 28% had infarctions of the nail bed and 16% had ulcers on the fingertips. The development of digital vasculitis was statistically significantly associated with acute skin lesions, discoid lupus and other manifestations of cutaneous vasculitis. A rare variant of cutaneous vasculitis in jSLE may be urticaria vasculitis (Fig. 6, c), manifested by urticaria lasting more than 24 hours, which may be completely asymptomatic or accompanied by severe itching or hyperesthesia of the skin. Usually, hyperpigmentation or purpura remains after urticaria vasculitis [52, 53]. The incidence of urticaria vasculitis associated with jSLE is unknown, because only isolated cases have been described [54–56]. The term "hypocomplementemic urticaria vasculitis" indicates hypocomplementemia in such patients, which is combined with the presence of antibodies to the complement component C1q [54].

An extremely rare variant of cutaneous vasculitis in SLE is IgA vasculitis, which develops at onset of the disease. A work of C. Murata et al. [57] described 15 children who suffered from this disease at an older age and had a lower hemoglobin level compared with children with classic IgA vasculitis.

Livedo reticularis is characterized by erythematous or cyanotic discoloration of the skin with a reticulated pattern, usually on the lower extremities. It has been described both in jSLE and in adult patients and, according to the literature, is more often associated with the development of antiphospholipid syndrome [58]. Histological examination reveals endotheliitis and obliterating endarteritis without signs of true vasculitis [59]. S.M. Gamal et al. [47] demonstrated that the frequency of livedo reticularis in jSLE is higher than in adults (5.9% and 2.1%, respectively).

The development of Raynaud's syndrome (RS) is most characteristic of systemic scleroderma; in such patients it is more persistent, more common and associated with severe trophic disorders [60]. In SLE, RS in typical cases is characterized by classic "three–phase" skin color changes, the localization of which is usually limited to the fingers: whiteness (white phase), followed by cyanosis (blue phase), then erythema (red, or reactive hyperemia). However, in real clinical practice, monophasic RS occurs more often (Fig. 7) [61]. To date, there is no convincing evidence that this syndrome correlates with the systemic nature of the process in SLE [60, 61]. According to various studies, the incidence of RS in SLE in general, regardless of age, varies from 15.3% to 49% [27, 47, 62]. In 10–14% of patients, RS may be the initial sign of SLE [27, 63]. F.E. Heimovski et al. [62] observed an association of RS with the presence of antibodies to ribonucleoprotein and Smith antigen, while in patients with kidney damage, serositis and hemolytic anemia RS was significantly less common. This study also revealed an association of RS with a later age of SLE onset in adults, whereas, according to S.M. Gamal et al. [47], with the development of SLE in childhood or adolescence the frequency of RS was higher than in adults (27.4% and 15.3%, respectively).

Photosensitivity is an excessive reaction of the skin to exposure to ultraviolet or visible radiation and can manifest itself in the form of any skin rash that occurs on exposed areas of the body (face, upper chest or limbs) tends to increase after exposure to the sun (Fig. 8). In childhood and adolescence, photosensitivity can be caused not only by the development of SLE, but also by a number of other genetically determined (for example, Rothmund–Thomson syndrome, Bloom syndrome) and acquired pathologies, as well as be idiopathic [64]. Photosensitivity with malar rash is found not only in SLE, but also in juvenile dermatomyositis, so it is necessary to take into account other signs in order to distinguish between these two diseases [64, 65]. In 60% of adult patients, the onset of SLE is associated with a hypersensitivity reaction to exposure to ultraviolet rays [66]. The frequency of photosensitivity in patients with jSLE varies, according to various sources, from 17% to 71,6% [16, 17, 25, 27, 38]. Reports on the dependence of photosensitivity in SLE on age are contradictory. B. Artim-Esen et al. [38] indicate that photosensitivity in children is more common than in adults (in 71.6% and 56.5% of cases, respectively). However, other authors have not revealed differences in its frequency depending on the age of SLE onset [17, 25]. At

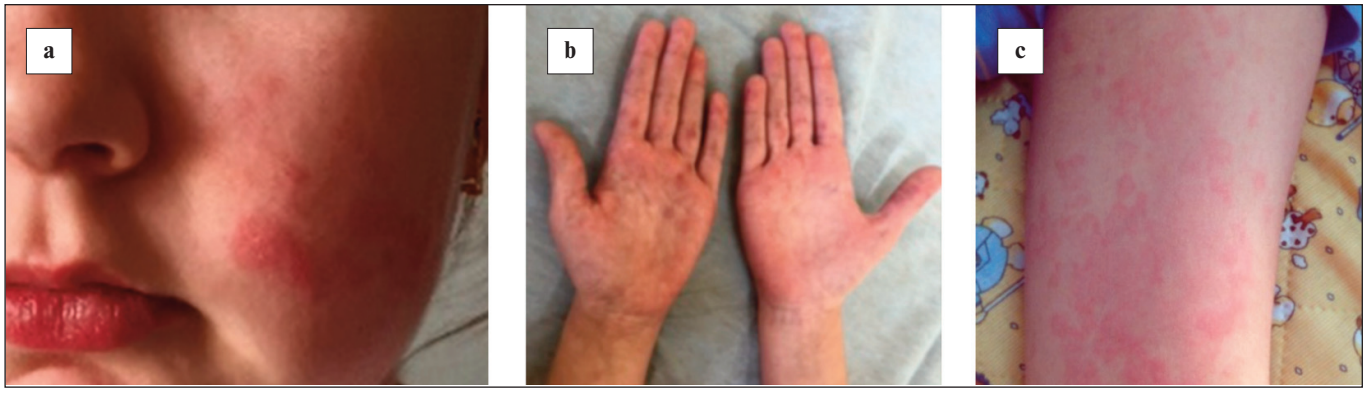

Fig. 6. *Cutaneous vasculitis in juSLE: a – localization on the face; b – localization on the palms; c – urticarial vasculitis*

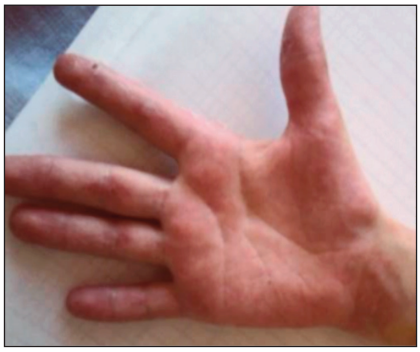

Fig. 7. *Monophasic Raynaud's syndrome in juSLE*

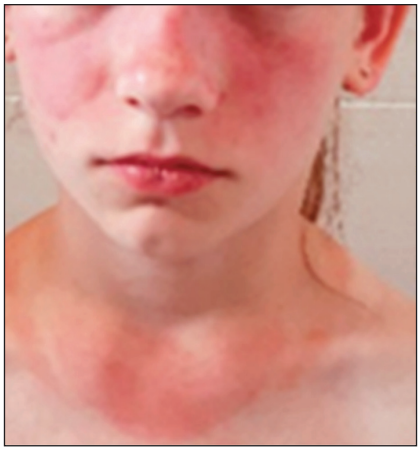

Fig. 8. *Photosensitive erythematous rash on the face and dŭcolletŭ in the onset of juSLE*

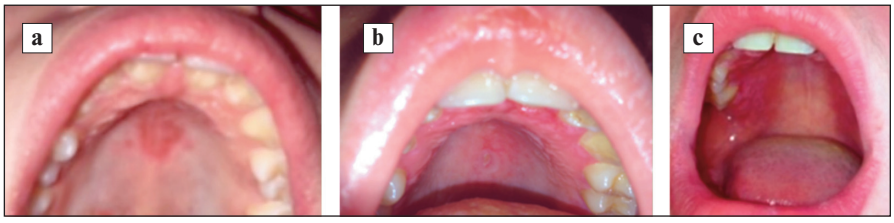

Fig. 9. *Lesions of the oral mucosa in juSLE: a – single erythema of the upper palate; b – discoid ulcer; c – nonspecific aphthous ulcers*

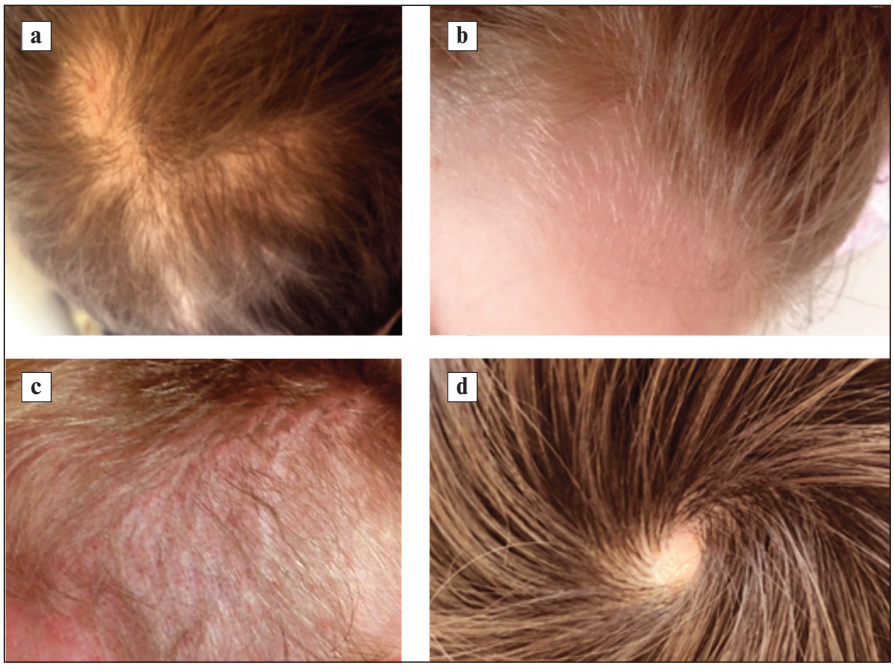

Fig. 10. *Alopecia in juSLE: a – diffuse alopecia; b – peripheral lupus alopecia; c – patchy alopecia without scars; d – alopecia areata*

the same time, there is no data on the correlation of photosensitivity with the severity of systemic manifestations.

Ulcers of the oral or nasal cavities are included in the classification criteria of SLE. There are two types of such ulcers: ulcers with classical histological changes pathognomonic for SLE (discoid elements in the oral cavity), and nonspecific ulcers [67, 68]. A mucosal lesion specific to SLE often begins with a single site of erythema and hemorrhages (Fig. 9, a), which then evolve into discoid ulcers with a mesh border (Fig. 9, b). As a rule, these changes are painless and located on the hard palate. On the contrary, nonspecific aphthous ulcers are usually painful and multiple, localized on the buccal mucosa, lips, and nasal

septum, and tend to bleed (Fig. 9, c) [68]. Oral or nasopharyngeal ulcers directly related to the disease itself, are usually detected during its active phase. During remission, they usually heal, regardless of the age of SLE development, in contrast to a visually similar lesion, but associated with ongoing therapy or with concomitant infections [68]. The frequency of mucosal ulcers in jSLE, according to various data, ranges from 10% to 51% [16, 17, 25, 27, 38]. A number of authors have identified a high frequency of mucosal involvement in jSLE [17, 38]. However, L. Wen et al. [25] did not observe significant differences in the frequency of mucosal ulcers in SLE in children and adults (19.6% and 19.3%, respectively). Ulcers of the nasal cavity are somewhat less common than ulcers of the oral cavity (in 8% of cases) [27]. N. Chottawornsak et al. [28] found an association of mucosal ulcers with leukopenia.

Diffuse alopecia without scars is also a nonspecific symptom of SLE, manifested by generalized hair loss without signs of inflammation on the scalp (Fig. 10, a) [41]. Diffuse non-scarring alopecia occurs in a wide range of childhood diseases (systemic connective tissue diseases, as well as iron deficiency anemia, thyroid pathology, type 1 diabetes mellitus) [69]. The frequency of diffuse alopecia in jSLE, according to the literature, ranges from 15% to 47% [16, 17]. In patients with SLE, regardless of age, the presence of diffuse alopecia usually implies an active disease [70]. However, it should be remembered that in SLE delayed development of telogen alopecia associated with hair development cycle impairment is also possible as a non-specific reaction to any significant systemic process or drug exposure, developing most often 2–3 months after an exacerbation of SLE [71]. Other forms of alopecia, including those described in jSLE, comprise lupus hair (thin and weakened hair at the periphery of the scalp; Fig. 10, b), patchy non-scarring alopecia (mild erythematous, scattered patchy hair loss; Fig. 10, c) and alopecia areata (Fig. 10, d) [72].

Other non-specific types of skin lesions, such as calcinosis cutis, acanthosis nigricans, are described in isolated cases, bullous rashes on the skin and mucous membranes are presented in a series of observations (with a frequency of 0.35%) [73–75].

In general, it should be noted that children and adolescents with SLE have a high incidence of mucocutaneous lesions, which tends to increase as the duration of the disease increases in the absence of adequate control of its activity and the development of exacerbations. Such manifestations of the disease are extremely diverse and require competent interpretation. Assessment of the probability of systemic disease in a child with signs of a mucocutaneous lesion, which is regarded as a manifestation of cutaneous lupus, is crucial for the subsequent prognosis of the disease and achieving its inactive status. Therefore, every child with an isolated lesion of the skin and / or mucous membrane needs a regular re-examination and observation.

REFERENCES

1. Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med*. 2008 Feb 28;358(9):929-39. doi: 10.1056/NEJMra071297.
2. Hedrich CM, Smith EMD, Beresford MW. Juvenile-onset systemic lupus erythematosus (jSLE) – Pathophysiological concepts and treatment options. *Best Pract Res Clin Rheumatol*. 2017 Aug;31(4):488-504. doi: 10.1016/j.berh.2018.02.001.
3. Alexander T, Hedrich CM. Systemic lupus erythematosus – Are children miniature adults? *Clin Immunol*. 2022 Jan;234:108907. doi: 10.1016/j.clim.2021.108907.
4. Silva CA, Avcin T, Brunner HI. Taxonomy for systemic lupus erythematosus with onset before adulthood. *Arthritis Care Res (Hoboken)*. 2012 Dec;64(12):1787-93. doi: 10.1002/acr.21757.
5. Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am*. 2012 Apr;59(2):345-64. doi: 10.1016/j.pcl.2012.03.007.
6. Huemer C, Huemer M, Dorner T, et al. Incidence of pediatric rheumatic diseases in a regional population in Austria. *J Rheumatol*. 2001 Sep;28(9):2116-9.
7. Houghton KM, Page J, Cabral DA, et al. Systemic lupus erythematosus in the pediatric North American Native population of British Columbia. *J Rheumatol*. 2006 Jan;33(1):161-3.
8. Hiraki LT, Feldman CH, Liu J, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. *Arthritis Rheum*. 2012 Aug;64(8):2669-76. doi: 10.1002/art.34472.
9. Miettunen PM, Ortiz-Alvarez O, Petty RE, et al. Gender and ethnic origin have no effect on longterm outcome of childhood-onset systemic lupus erythematosus. *J Rheumatol*. 2004 Aug;31(8):1650-4.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997 Sep;40(9):1725. doi: 10.1002/art.1780400928.
11. Petri M, Orbai AM, Alarcyn GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012 Aug;64(8):2677-86. doi: 10.1002/art.34473.
12. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2019 Sep;71(9):1400-12. doi: 10.1002/art.40930.
13. Batu ED, Akca UK, Kisaarslan AP, et al. The Performances of the ACR 1997, SLICC 2012, and EULAR/ACR 2019 Classification Criteria in Pediatric Systemic Lupus Erythematosus. *J Rheumatol*. 2021 Jun;48(6):907-14. doi: 10.3899/jrheum.200871.
14. Chang LS, Huang PY, Kuo HC, et al. Diagnostic accuracy of the American College of Rheumatology-1997, the Systemic Lupus International Collaborating Clinics-2012, and the European League Against Rheumatism-2019 criteria for juvenile systemic lupus erythematosus: A systematic review and network meta-analysis. *Autoimmun Rev*. 2022 Sep;21(9):103144. doi: 10.1016/j.autrev.2022.103144.
15. Ardoin SP, Daly RP, Merzoug L, et al. Research priorities in childhood-onset lupus: results of a multidisciplinary prioritization exercise. *Pediatr Rheumatol Online J*. 2019 Jul 1;17(1):32. doi: 10.1186/s12969-019-0327-4.
16. Chiewchengchol D, Murphy R, Morgan T, et al. Mucocutaneous manifestations in a UK national cohort of juvenile-onset systemic lupus erythematosus patients. *Rheumatology (Oxford)*. 2014 Aug;53(8):1504-12. doi: 10.1093/rheumatology/keu137.
17. Ambrose N, Morgan TA, Galloway J, et al. Differences in disease phenotype and severity in SLE across age groups. *Lupus*. 2016 Dec;25(14):1542-50. doi: 10.1177/0961203316644333.
18. Massias JS, Smith EMD, Al-Abadi E, et al. Clinical and laboratory characteristics in juvenile-onset systemic lupus erythematosus across age groups. *Lupus*. 2020 Apr;29(5):474-81. doi: 10.1177/0961203320909156.
19. Massias JS, Smith EM, Al-Abadi E, et al. Clinical and laboratory phenotypes in juvenile-onset Systemic Lupus Erythematosus across ethnicities in the UK. *Lupus*. 2021 Apr;30(4):597-607. doi: 10.1177/0961203320984251.

20. Sontheimer RD. Skin manifestations of systemic autoimmune connective tissue disease: diagnostics and therapeutics. *Best Pract Res Clin Rheumatol.* 2004 Jun;18(3):429-62. doi: 10.1016/j.berh.2004.03.003.
21. Curtiss P, Walker AM, Chong BF. A Systematic Review of the Progression of Cutaneous Lupus to Systemic Lupus Erythematosus. *Front Immunol.* 2022 Mar 11;13:866319. doi: 10.3389/fimmu.2022.866319.
22. Arkin LM, Ansell L, Rademaker A, et al. The natural history of pediatric-onset discoid lupus erythematosus. *J Am Acad Dermatol.* 2015 Apr;72(4):628-33. doi: 10.1016/j.jaad.2014.12.028.
23. Gilliam JN, Sontheimer RD. Skin manifestations of SLE. *Clin Rheum Dis.* 1982 Apr; 8(1):207-18. doi.org/10.1016/S0307-742X(21)00208-3.
24. Papadimitraki ED, Isenberg DA. Childhood – and adult-onset lupus: an update of similarities and differences. *Expert Rev Clin Immunol.* 2009 Jul;5(4):391-403. doi: 10.1586/eci.09.29.
25. Wen L, Chen Z, Jin Z, et al. Clinical and laboratorial outcome of different age-onset systemic lupus erythematosus patients in Jiangsu, China: a multicentre retrospective study. *Sci Rep.* 2022 Jun 23;12(1):10683. doi: 10.1038/s41598-022-14840-4.
26. Ramirez Gomez LA, Uribe Uribe O, Osio Uribe O, et al. Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. *Lupus*. 2008 Jun; 17(6):596-604. doi: 10.1177/0961203307088006.
27. Hiraki LT, Benseler SM, Tyrrell PN, et al. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. *J Pediatr.* 2008 Apr;152(4):550-6. doi: 10.1016/j.jpeds.2007.09.019.
28. Chottawornsak N, Rodsaward P, Suwannachote S, et al. Skin signs in juvenile- and adult-onset systemic lupus erythematosus: clues to different systemic involvement. *Lupus*. 2018 Nov;27(13):2069-75. doi: 10.1177/0961203318805851.
29. Lee SK, Baek J, Roh JY, et al. Clinical characteristics of pediatric cutaneous lupus erythematosus: experience from a tertiary referral center in Korea. *Lupus.* 2019 Jun;28(7): 888-92. doi: 10.1177/0961203319851568.
30. Stichweh D, Arce E, Pascual V. Update on pediatric systemic lupus erythematosus. *Curr Opin Rheumatol.* 2004 Sep;16(5):577-87. doi: 10.1097/01.bor.0000137852.42270.0f.
31. Lenormand C, Lipsker D. Lupus erythematosus: Significance of dermatologic findings. *Ann Dermatol Venereol.* 2021 Mar; 148(1):6-15. doi: 10.1016/j.annder.2020.08.052.
32. Berry T, Walsh E, Berry R, et al. Subacute cutaneous lupus erythematosus presenting in childhood: a case report and review of the literature. *Pediatr Dermatol.* 2014 May-Jun;31(3): 368-72. doi: 10.1111/pde.12007.
33. Dickey BZ, Holland KE, Drolet BA, et al. Demographic and clinical characteristics of cutaneous lupus erythematosus at a paediatric dermatology referral centre. *Br J Dermatol.* 2013 Aug;169(2):428-33. doi: 10.1111/bjd.12383.
34. Rai VM, Balachandran C. Subacute cutaneous lupus erythematosus (SCLE) presenting in childhood. *Dermatol Online J.* 2005 Aug 1; 11(2):27. doi.org/10.5070/D34G28D2DX.
35. Yu J, Brandling-Bennett H, Co DO, et al. Toxic Epidermal Necrolysis-Like Cutaneous Lupus in Pediatric Patients: A Case Series and Review. *Pediatrics*. 2016 Jun;137(6):e20154497. doi: 10.1542/peds.2015-4497.
36. Stevic M, Budic I, Ristic N, et al. Toxic epidermal necrolysis in a child with lupus-associated pancreatitis. *Rheumatol Int.* 2017 Jul;37(7):1221-6. doi: 10.1007/s00296-017-3677-6.
37. Bhattarai D, Vignesh P, Chaudhary H, et al. Epidermal necrolysis as the presenting manifestation of pediatric lupus. Pediatr Dermatol. 2020 Nov;37(6):1119-24. doi: 10.1111/pde.14324.
38. Artim-Esen B, Sahin S, Cene E, et al. Comparison of Disease Characteristics, Organ Damage, and Survival in Patients with Juvenile-onset and Adult-onset Systemic Lupus Erythematosus in a Combined Cohort from 2 Tertiary Centers in Turkey. *J Rheumatol.* 2017 May;44(5):619-25. doi: 10.3899/jrheum.160340.
39. Vera-Recabarren MA, Garcia-Carrasco M, Ramos-Casals M, et al. Comparative analysis of subacute cutaneous lupus erythematosus and chronic cutaneous lupus erythematosus: clinical and immunological study of 270 patients. *Br J Dermatol.* 2010 Jan;162(1):91-101. doi: 10.1111/j.1365-2133.2009.09472.x.
40. Sampaio MC, de Oliveira ZN, Machado MC, et al. Discoid lupus erythematosus in children – a retrospective study of 34 patients. *Pediatr Dermatol.* 2008 Mar-Apr;25(2): 163-7. doi: 10.1111/j.1525-1470.2008.00625.x.
41. Concha JSS, Werth VP. Alopecias in lupus erythematosus. *Lupus Sci Med.* 2018 Oct 25;5(1):e000291. doi: 10.1136/lupus-2018-000291.
42. Guissa VR, Trudes G, Jesus AA, et al. Lupus erythematosus panniculitis in children and adolescents. Acta Reumatol Port. 2012 Jan-Mar;37(1):82-5.
43. Weingartner JS, Zedek DC, Burkhart CN, et al. Lupus erythematosus panniculitis in children: report of three cases and review of previously reported cases. *Pediatr Dermatol.* 2012 Mar-Apr;29(2):169-76. doi: 10.1111/j.1525-1470.2011.01544.x.
44. Piras D, Cottoni F. Mucosal involvement in childhood discoid lupus erythematosus. *J Eur Acad Dermatol Venereol.* 2003 Nov;17(6):731-2. doi: 10.1046/j.1468-3083.2003.00837.x.
45. Sonntag M, Lehmann P, Megahed M, et al. Lupus erythematosus tumidus in childhood. Report of 3 patients. *Dermatology*. 2003; 207(2):188-92. doi: 10.1159/000071793.
46. Yi C, Li Q, Xiao J. Familial chilblain lupus due to a novel mutation in TREX1 associated with Aicardi-Goutie'res syndrome. *Pediatr Rheumatol Online J.* 2020 Apr 15;18(1):32. doi: 10.1186/s12969-020-00423-y.
47. Gamal SM, Mohamed SS, Tantawy M, et al. Lupus-related vasculitis in a cohort of systemic lupus erythematosus patients. *Arch Rheumatol.* 2021 Oct 12;36(4):595-692. doi: 10.46497// ArchRheumatol.2021.8804. eCollection 2021 Dec.
48. Das Chagas Medeiros MM, Bezerra MC, Braga FN, et al. Clinical and immunological aspects and outcome of a Brazilian cohort of 414 patients with systemic lupus erythematosus (SLE): comparison between childhood-onset, adult-onset, and late-onset SLE. *Lupus.* 2016 Apr;25(4):355-63. doi: 10.1177/0961203315606983.
49. Gheita TA, Abaza NM, Sayed S, et al. Cutaneous vasculitis in systemic lupus erythematosus patients: potential key players and implications. *Lupus*. 2018 Apr;27(5):738-43. doi: 10.1177/0961203317739134.
50. Smith EMD, Lythgoe H, Hedrich CM. Vasculitis in Juvenile-Onset Systemic Lupus Erythematosus. *Front Pediatr.* 2019 May 9; 7:149. doi: 10.3389/fped.2019.00149.
51. Sakamoto AP, Silva CA, Silva MFCD, et al. Initial digital vasculitis in a large multicenter cohort of childhood-onset systemic lupus erythematosus. *Rev Bras Reumatol Engl Ed.* 2017 Nov-Dec;57(6):583-9. doi: 10.1016/j.rbre.2017.09.002.
52. Uva L, Miguel D, Pinheiro C, et al. Cutaneous manifestations of systemic lupus erythematosus. *Autoimmune Dis.* 2012;2012:834291. doi: 10.1155/2012/834291.
53. Jachiet M, Flageul B, Deroux A, et al. The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a French nationwide study of fifty-seven patients. *Arthritis Rheumatol.* 2015 Feb;67(2):527-34. doi: 10.1002/art.38956.
54. DeAmicis T, Mofid MZ, Cohen B, et al. Hypocomplementemic urticarial vasculitis: report of a 12-year-old girl with systemic lupus erythematosus. *J Am Acad Dermatol.* 2002 Nov;47(5 Suppl):S273-4. doi: 10.1067/mjd.2002.108586.
55. Macedo PA, Garcia CB, Schmitz MK, et al. Juvenile systemic lupus erythematosus and dermatomyositis associated with urticarial vasculitis syndrome: a unique presentation. *Rheumatol Int.* 2012 Nov;32(11):3643-6. doi: 10.1007/s00296-010-1484-4.
56. Yamazaki-Nakashimada MA, Duran-McKinster C, Ramirez-Vargas N, et al. Intravenous immunoglobulin therapy for hypocomplementemic urticarial vasculitis associated with systemic lupus erythematosus in a child. *Pediatr Dermatol.* 2009 Jul-Aug;26(4): 445-7. doi: 10.1111/j.1525-1470.2009.00950.x.
57. Murata C, Rodriguez-Lozano AL, Hernandez-Huirache HG, et al. IgA vasculitis (Henoch – Schönlein Purpura) as the first manifestation of juvenile Systemic Lupus

Erythematosus: Case-control study and systematic review. *BMC Pediatr.* 2019 Nov 26;19(1):461. doi: 10.1186/s12887-019-1829-4.
58. Ravelli A, Martini A. Antiphospholipid syndrome in pediatrics. *Rheum Dis Clin North Am.* 2007 Aug;33(3):499-523. doi: 10.1016/j.rdc.2007.07.001.
59. Miyamae T, Kawabe T. Non-Criteria Manifestations of Juvenile Antiphospholipid Syndrome. *J Clin Med.* 2021 Mar 17;10(6):1240. doi: 10.3390/jcm10061240.
60. Pain CE, Constantin T, Toplak N, et al. Raynaud's syndrome in children: systematic review and development of recommendations for assessment and monitoring. *Clin Exp Rheumatol.* 2016 Sep-Oct;34 Suppl 100(5):200-6. Epub 2016 Jul 27.
61. Nigrovic PA, Fuhlbrigge RC, Sundel RP. Raynaud's phenomenon in children: a retrospective review of 123 patients. *Pediatrics.* 2003 Apr;111(4 Pt 1):715-21. doi: 10.1542/peds.111.4.715.
62. Heimovski FE, Simioni JA, Skare TL. Systemic lupus erythematosus and Raynaud's phenomenon. *An Bras Dermatol.* 2015 Nov-Dec;90(6):837-40. doi: 10.1590/abd1806-4841.20153881.
63. Jiang Q, Li RX, Hu P. Raynaud's phenomenon in childhood-onset systemic lupus erythematous. *Arch Med Sci.* 2022 Nov 7;18(6):1716-7. doi: 10.5114/aoms/153469.
64. Kumar R, Kumari S. Evaluation and management of photosensitivity in children. *Indian Pediatr.* 2008 Oct;45(10):829-37.
65. Kotrulja L, Ozanic-Buli S, Sjerobabski-Masnec I, et al. Photosensitivity skin disorders in childhood. *Coll Antropol.* 2010 Apr;34 Suppl 2:263-6.
66. Werth VP, Bashir M, Zhang W. Photosensitivity in rheumatic diseases. *J Investig Dermatol Symp Proc.* 2004 Jan;9(1):57-63. doi: 10.1111/j.1087-0024.2004.00839.x.
67. Nico MM, Vilela MA, Rivitti EA, et al. Oral lesions in lupus erythematosus: correlation with cutaneous lesions. *Eur J Dermatol.* 2008 Jul-Aug;18(4):376-81. doi: 10.1684/ejd.2008.0388.
68. Rodsaward P, Prueksrisakul T, Deekajorndech T, et al. Oral Ulcers in Juvenile-Onset Systemic Lupus Erythematosus: A Review of the Literature. *Am J Clin Dermatol.* 2017 Dec;18(6):755-62. doi: 10.1007/s40257-017-0286-9.
69. Al-Refu K. Hair loss in children: common and uncommon causes; clinical and epidemiological study in jordan. *Int J Trichology.* 2013 Oct;5(4):185-9. doi: 10.4103/0974-7753.130393.
70. Parodi A, Massone C, Cacciapuoti M, et al. Measuring the activity of the disease in patients with cutaneous lupus erythematosus. *Br J Dermatol.* 2000 Mar;142(3):457-60. doi: 10.1046/j.1365-2133.2000.03356.x.
71. Asghar F, Shamim N, Farooque U, et al. A Review of the Literature. *Cureus.* 2020 May 27;12(5):e8320. doi: 10.7759/cureus.8320.
72. Trüeb RM. Hair and nail involvement in lupus erythematosus. *Clin Dermatol.* 2004 Mar-Apr;22(2):139-47. doi: 10.1016/j.clindermatol.2003.12.021.
73. Dönmez O, Durmaz O. Calcinosis cutis universalis with pediatric systemic lupus erythematosus. *Pediatr Nephrol.* 2010 Jul;25(7):1375-6. doi: 10.1007/s00467-010-1441-1.
74. Miquel J, Hadj-Rabia S, Boddaert N, et al. Atypical presentation of neuropsychiatric lupus with acanthosis nigricans. *Pediatr Neurol.* 2012 Oct;47(4):291-4. doi: 10.1016/j.pediatrneurol.2012.06.005.
75. Panombualert S, Techasatian L, Uppala R, et al. A Rare Manifestation of Bullous Systemic Lupus Erythematosus in Children: A 10-year Retrospective Study in a Tertiary Care Hospital. *Autoimmune Dis.* 2022 Jul 19;2022:9388745. doi: 10.1155/2022/9388745.

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