

LUPUS ERYTHEMATOSUS – A CONDITION WITH POLYMORPHIC CLINICAL ASPECTS

ALEXANDRU D. TĂTARU*

Summary

In the first part of the article, the author summarizes the basic elements in the pathogenesis of lupus erythematosus, in the second part he presents the many possible clinical aspects, according to the current classifications, of the cutaneous and systemic manifestations of lupus erythematosus and concludes with the currently validated treatment principles.

Key words: lupus erythematosus, pathogenesis, clinical aspects.

Received: 12.12.2018

Accepted: 30.01.2019

Introduction

Lupus erythematosus is perhaps the most common and frequent autoimmune disease in the area of dermatology, at the interference with general clinical immunology and rheumatology.

The clinical aspects are variable from one individual to another, from the onset, and are also variable in time as a natural progression of the disease. Without being able to give complete explanations for this variability, a few milestones are important: the gene pool involving a large number of predisposing genes whose interaction is not yet well known, the random intervention of the trigger factors in the external environment and the final response of the body affected in its entirety.

The gene pool concerns genes regulating the immune response, meaning that its self-limiting is affected by the relative depletion of suppressor T-lymphocytes (TLs) and the relative hyperfunction of effector T-lymphocytes, both type T and type B, with the appearance of autoantibodies in high amounts and, for systemic lupus, targeted to more and more antigenic targets, ultimately producing circulating immune complexes (CICs) directly responsible for renal

impairment and non-specific skin manifestations such as vasculitis, arthritis, bullous forms.

The clinical spectrum ranges from forms strictly localized to the skin to systemic forms with polyorganic affection and fatal prognosis by chronic renal failure or lupus encephalopathy. For all clinical forms, the initial pathogenetic mechanism is the same, which gives unity to all clinical variants of the disease.

Essentially, the disease appears on a genetic background predisposed to external triggering factors: mainly ultraviolet radiation (natural or artificial), sometimes drugs (triggering drug-induced lupus in predisposed patients), possibly skin surface superantigens (possibly surface microbial viruses, hypothesis without solid evidence for the time being). Feminine predominance (6:1 for systemic lupus erythematosus, 3:1 for strictly cutaneous lupus erythematosus) is explained by the effect of enhancing any immune response by the oestrogen-like hormones. The ethnic differences found - four times more common condition in African-American women than in Caucasian women in the US - are probably derived from the different genetic backgrounds.

* I. Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Dermatology.

Pathogenesis is triggered by the particular UV effect on keratinocytes: initially their activation, then keratinocyte photodestruction. Activation of keratinocytes leads to the production of chemokines CXCL5, CXCL8, CXCL20, which induce the formation of adhesion molecules on keratinocytes (ICAM-1) and more importantly on dermal endothelial cells (E-selectin, VCAM-1), preparing to initiate the immune response.

On the predisposing genetic background, UVA and intense UVB induce photodestruction of some keratinocytes by apoptosis with the release of nuclear and cytoplasmic intracellular antigens. These are processed by epidermal and dermal macrophages (Langerhans cells, non-specific dendritic cells, plasmacytoid dendritic cells) and exposed to naive T-lymphocytes residing in the dermis, with their activation and initiation of an immune response. The binding of cellular apoptosis products to Fcγ receptors of macrophages induces increased and self-sustained production of INF-α with additional recruitment of new macrophages. Naive T_H1s become T_H1 CD4⁺ and T_H1 CD8⁺ with the emergence of initial double-stranded anti-DNA autoantibodies, subsequently antiphospholipid, anti-mitochondrial auto-antibodies, etc. and direct cytotoxic effects. In the systemic LE form, different auto-antibodies occur: anti-leukocytes, anti-erythrocytes, anti-thrombocytes, anti-hepatic, anti-neuronal and others, phenomenon clinically expressed through organic co-affectation in SLE. The auto-antibodies cascade produces CIC, deposited in the synovial joint, in kidney glomeruli, rarely in teguments or other tissues, with manifestations of disseminated vasculitis type.

Pathogenetic events are reflected in the histological aspects of LE. For all LE clinical forms in haematoxylin and eosin staining, common elements are keratinocyte damage through the so-called vacuolar or hydropic degeneration and the presence of a lymphocytic infiltrate in the papillary dermis, with an approximately linear arrangement, hence the name of lichenoid infiltrate. The abundance of lymphohistiocytic cells is low in the acute form of LE, medium in the subacute form, high in the chronic discoid form where it also appears peri-

follicular with follicular hyperkeratosis, predominant lymphocytic infiltration and marked dermal mucin deposition without epidermal changes in LE tumidus and medium but only located deeply at the level of connective tissue of adipose tissue in deep LE (lupus erythematosus panniculitis).

The direct immunofluorescence from tegument affected by cutaneous LE reveals a typical granular deposition of antibodies (IgG, IgM, rarely IgA) and complement to the dermo-epidermal junction, a phenomenon called the „lupus band“, as well as perifollicular in chronic discoid LE. The direct immunofluorescence in systemic LE constantly reveals antibody depositions in the lupus band, but on the seemingly non-injured skin, a phenomenon called lupus band test. It should be noted that positive direct immunofluorescence confirms the diagnosis of LE, while a negative one does not invalidate it.

The following clinical variants are described in strictly cutaneous lupus erythematosus: acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), LE cutaneous chronic discoid LE (CCDLE), LE tumidus, deep and intermediate LE (lupus erythematosus panniculitis, always chronic) and with an intermediate position LE pernio (chilblain lupus), initially cutaneous but with a high rate of evolution towards SLE. In addition, any of the above-described variants may evolve to systemic LE or may be present at onset or in time in any association, emphasizing the pleomorphic nature of the disease.

Systemic lupus erythematosus (SLE) typically evolves from onset as a systemic form with frequent skin manifestations occurring in about 80% of cases but also completely devoid of clinically visible skin manifestations in 20% of cases. Medical supervision is mandatory since any initially strictly cutaneous form may evolve to SLE. Particular clinical variants are SLE with pernio (chilblain), bullous SLE, SLE/ lichen planus overlap syndrome, and Rowell syndrome (SLE associated with major polymorph erythema).

Particular forms are neonatal LE by passive antibodies transfer from the mother, with manifestations of transient SLE and drug-induced LE, equivalent also to the systemic form.

Acute cutaneous lupus erythematosus (ACLE)

It is clinically expressed by bilateral malarial erythema, similar to vesperilio in SLE, usually accompanied by moderate to very marked local oedema, without sputum. It occurs frequently after an exaggerated sun exposure, persists for days-weeks, and usually reverts spontaneously without scars. It rarely occurs on the back of the hands, sometimes with telangiectasia, minimal epidermal atrophy, poikiloderma. Typically, the association of temporary oral ulcers is relatively common. Exceptionally it appears disseminated on the face and upper chest.

Subacute cutaneous lupus erythematosus (SCLE)

It is clinically expressed very characteristically by multiple annular eruptions, with elevated, erythematous and desquamative edges, with the centre in spontaneous involution and healing with hypopigmentation, without scars, persistent for months or years. The typical topography is facial, latero-facial (respecting the centre-facial area), on the upper trunk and extensors of limbs. It is always photosensitive, appearing after sun or artificial UV exposures, even moderate but repeated. It can also have a post-drug development, often involving terbinafine, griseofulvin, naproxen, and calcium channel blockers. Unlike the previous form in which serum immunological examinations are consistently negative, in about 70% of the cases of anti-Ro antibodies are positive, and the evolution towards a SLE occurs in about 15% of the cases.

Chronic discoid lupus erythematosus (CDLE)

It is clinically expressed by annular erythematous (discoid) eruptions, always hardened, only with peripheral desquamation, extremely adherent, with hyperkeratosis of the follicular aphasia, which detaches at the squeezing of the squama, conferring the aspect metaphorically described as „cat tongue squama“, with small protrusions on the internal face, constantly present central atrophy,

stationary or slowly increasing in size, with hyperchronic persistence and constant remission by vitiligo depigmentation and atrophic, depressive, sometimes mutilating (nose, ear) scars. On the scalp, the scarring process leads to definitive alopecia. Rarely linear telangiectasias develops at the centre of the eruptions. Typical topography includes face, scalp and ears, but over time the plaques can be propagated with dissemination in both photoexposed and exposure-protected areas without any stable relation with sun or artificial irradiation. In the hypertrophic CDLE variant there is an abundant deposit of adherent squama at the periphery of the lupus plaques. They rarely associate erosions on the lips, the nasal or genital mucosa. The rate of natural evolution to SLE is about 5% - 10%.

LE tumidus

Clinically, it is expressed by intense erythematous, oedematous plaques, without desquamation or follicular hyperkeratosis, frequently located on the forehead, with post-sun exposure emergence, persistent for several months, with spontaneous remissions and recurrent. They probably represent the same entity described by Jessner and Kanoff as benign lymphocytic infiltrate. The progression to SLE is very rare.

Lupus erythematosus panniculitis (deep LE)

It is manifested by extremely hardened violet plaques, with marked depressed or even ulcerated central area, preferentially located on the thighs, buttocks, rarely on the arms, breast, front. The diagnosis is given by the histological appearance.

Lupus pernio (Chilblain lupus)

Clinically, it is characterised by red-violet papules and plaques whose hint darkens when exposed to cold weather, typically located on the extremities: the tip of the nose, the fingers of the toes and legs, possibly elbows, knees. Association with SLE is common, as is the occurrence in children.

Systemic lupus erythematosus (SLE)

SLE frequently debuts with prolonged febrile syndrome, muscle asthenia, weather-sensitive arthralgia and weight loss.

Skin manifestations occur in 80% of cases and in 20% are completely absent. The typical appearance is that of infiltrated and violet plaque, without squama or atrophy, disposed „as a butterfly“ on the nose and cheeks. The atypical aspect may be one of the chronic LE forms described, as well as: livedo racemosa, Raynaud syndrome, persistent palmar erythema, periungual telangiectasia and rarely mouth erosions or ulcers.

Visceral manifestations are polymorphic and consist of: lupus glomerulonephritis by deposition of immune complexes in the glomerular capillary wall, which may lead to chronic renal failure and death, glomerulonephritis being the leading cause of death in SLE; lupus myopathy with diffuse loss of muscle strength and constantly various painful and weather-sensitive inflammatory arthritis; lupus hepatitis, manifested by alteration of liver biochemical samples; diffuse interstitial pulmonary fibrosis with effort dyspnoea and sometimes serum fibrous pleurisy; cardiovascular myocarditis, pericarditis and possibly Liebmann-Sachs lupus endocarditis, very rarely; lupus encephalopathy manifested by epileptic seizures, cranial nerve palsies, strokes and various psychoses, also very rare, but being the second major cause of death in untreated SLE.

Rare manifestations: Bullous SLE (anti-collagen VII antibodies emerge from anchoring fibrils), antiphospholipid syndrome (recurrent thrombophlebitis, false positive VDRL, negative TPHA), various leukocytoclastic vasculitis associated by CIC endothelial deposition, SLE overlap syndrome plus systemic scleroderma, SLE overlap syndrome associated with disseminated lichen planus, Rowell's syndrome by SLE associated with major and recurrent polymorph erythema.

Constantly present laboratory changes are: double-stranded anti-DNA (AAN) antibodies in serum, specific for SLE, very high circulating immune complexes (CICs), very high HCV. The following appear inconstantly: hypergammaglobulinemia, decreased serum complement (namely C3), leukocytopenia, thrombocytopenia and/or haemolytic anaemia (by autoantibodies),

false positive RBW (VDRL) reactions (by antiphospholipid antibodies). Single-stranded anti-DNA antibodies are not strictly specific and may occur in a variety of autoimmune diseases and even in healthy people.

Neonatal lupus

Clinically, it typically has the appearance of a subacute LE, with typical disseminated annular eruptions, and the mothers present at least intensely positive anti-Ro antibodies during pregnancy. Since we are talking about a passive transplacental transfer of antibodies, complete remission occurs within a few months.

Drug-induced lupus erythematosus

Clinically, it is manifested as a LES with fever, myalgia, arthralgia, pleurisy, various typical and/or atypical skin aspects, but always without CNS and renal impairment. Immunology may be identical to SLE. More commonly involved medication includes hydralazine, minocycline, procainamide, quinidine and hydralazide.

Principles of treatment

For all SLE forms, general corticotherapy between 0.5 - 1 mg/kg body weight/day is the indication of choice, to which in the case of renal and/or CNS pulseco-affectation - cyclophosphamide therapy (600 mg daily, three days per month) or continuous therapy with azathioprine 100-200 mg daily is added. After the disappearance of the clinical symptoms, the patient continues with synthetic antiplatelet agents (SAA) for several years, under ophthalmic trimester control. Residual medication consists for the time being in the Rituximab biological therapy.

The indications for treatment with retinoids, dapsone, thalidomide are more anecdotal.

For all cutaneous LE forms, the indication of choice is SAA: hydroxychloroquine 200 - 400 mg daily for several years. SAAs may be associated with each other (hydroxychloroquine with chloroquine or mepacrine, if available). One should note that ocular toxic dose only occurs from over 400 mg daily (or over 6.5 mg/kg body weight).

Potential corticosteroids without marked atrophic effects and mandatorily permanent photoprotection are recommended for topical treatment.

Bibliography

1. Bologna J, Jorizzo J, Rapini RP : Dermatology, 2nd ed, Ed.Mosby Elevier, 2008.
2. Burgdorf WHC,Plewig G,Wolff HH,Landthaler M : Dermatology and Cosmetic Surgery, 3rd ed., Ed.Springer Verlag, 2009.
3. Goldsmith LA et all : Fitzpatrick's Dermatology in General Medicine, 8th ed., Ed.McGrawHill Professional, 2012
4. Elder PE : Lever's histopathology of the skin, 7th ed., Ed.Philadelphia : Walters Kluwer, 2015.

Conflict of interest
NONE DECLARED

Correspondance address: Alexandru Tătaru
Faculty of Medicine, „Iuliu Hațieganu University of Medicine and Pharmacy
Cluj-Napoca, Romania
e-mail: dr.tataru@yahoo.com