

# Cutaneous lupus erythematosus - Clinical and laboratory aspects\*

## *Lúpus eritematoso cutâneo - Aspectos clínicos e laboratoriais\**

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**Abstract:** Lupus erythematosus is a connective tissue autoimmune disorder that demonstrates systemic, cutaneous, or both systemic and cutaneous manifestations. Cutaneous lesions are classified as specific and nonspecific. The variety of clinical manifestations of the disease is reflected in the broad spectrum of laboratory patterns. In this article we describe the distinct subsets of cutaneous lupus erythematosus, correlating them with histopathological, direct immunofluorescence and serological findings.

**Keywords:** Skin diseases; Autoimmune diseases; Collagen diseases; Connective tissue diseases; Lupus erythematosus, Cutaneous/classification; Lupus erythematosus, Cutaneous/diagnosis.

**Resumo:** O lúpus eritematoso é doença auto-imune do tecido conjuntivo que reúne manifestações exclusivamente cutâneas ou multissistêmicas, podendo apresentar exuberância de auto-anticorpos. As lesões cutâneas do lúpus eritematoso são polimorfas e podem ser específicas ou inespecíficas. A diversidade de manifestações clínicas da doença reflete-se no amplo espectro de achados laboratoriais. Este artigo descreve as variadas formas clínicas do lúpus eritematoso cutâneo correlacionando-os com achados histopatológicos, de imunofluorescência direta e sorológicos.

**Palavras-chave:** Dermatopatias; Doenças auto-imunes; Doenças do colágeno; Doenças do tecido conjuntivo; Lúpus eritematoso cutâneo/classificação; Lúpus eritematoso cutâneo/diagnóstico.

### INTRODUCTION

Lupus erythematosus (LE) is a heterogeneous, multisystem, autoimmune disease characterized by the production of auto-antibodies against several cell constituents. The skin is one of the target organs most variably affected by the disease,<sup>1</sup> cutaneous lesions making up three out of 11 criteria laid down by the American College of Rheumatology (ACR) for the diagnosis of Systemic Lupus Erythematosus: discoid lesions, malar rash and photosensitivity.<sup>2</sup>

The term cutaneous lupus erythematosus is applied to patients with cutaneous lesions produced by lupus erythematosus, whether involvement is exclusively cutaneous or part of a systemic disease.<sup>3</sup>

Several classifications for the cutaneous lesions

in lupus erythematosus have been put forward over time. Bundick, Ellis,<sup>4</sup> in 1951, underscored the need in classification to use the term "disseminated" in extensive forms of cutaneous involvement and "systemic" in those where viscera were involved. Classification into chronic discoid, disseminated (or generalized) discoid, subacute and acute forms then took shape.<sup>3</sup> Callen<sup>5</sup> added palmoplantar LE and oral LE to the subtypes of the chronic cutaneous form, and defined lupus panniculitis as nonspecific for LE; he added neonatal lupus and lupus-like syndrome with C2 deficiency to the acute form, and emphasized the frequency and importance of photosensitivity in this form of the disease. Laman, Provost<sup>6</sup> classified

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bullous lesions as nonspecific. The classification put forward by Sontheimer et al.,<sup>3</sup> based on clinical morphology, with specific histologic findings for the disease, including three forms - chronic cutaneous LE, subacute cutaneous LE and acute cutaneous LE - was interesting. Gilliam, however, expanded upon this classification on the basis of specific and nonspecific clinical and histopathologic features found in LE patients<sup>7,8</sup> (Chart 1).

### CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS

Chronic cutaneous lupus erythematosus (CCLE) is more common in women, affecting from 1.9 to 6.8 women for every man,<sup>8,9</sup> with incidence peaking in the fourth decade of life.<sup>10</sup> The commonest form of CCLE is localized discoid lupus erythematosus (LDLE), characterized by well-defined macular or papular erythematous lesions with firm scales adhering to the lesion surface.<sup>11</sup> As the disease evolves these lesions commonly become infiltrated and merge to make patches covered by thick scales and keratosis extending to the interior of the dilated hair follicle. The skin lesions in LDLLE are chronic, persistent and may regress leaving dyschromic cicatricial areas, telangiectasia and cicatricial alopecia (Figure 1). The most frequently involved sites are the scalp, pinna of the ear, anterior thoracic region and upper portion of the arms. Eyebrows, eyelids, nose, chin and cheek areas are frequently involved on the face. A symmetrical butterfly wing rash is often found in the malar and nasal dorsum regions.<sup>1</sup>

Sontheimer<sup>3</sup> stated that when discoid lesions spread beyond the region below the neck they are to be classified as disseminated discoid LE (DDLE), and will likely be the systemic form of the disease.

Histologically, discoid lesions present: 1) hyperkeratosis with follicular plugging; 2) thinning and flattening of the stratum Malpighi's, less intense than in forms of subacute lupus erythematosus;<sup>12,13</sup> 3) hydropic degeneration of basal cells; 4) a predominantly lymphocytic infiltrate along the dermal-epidermal junction, around the hair follicles and eccrine ducts, in an interstitial pattern;<sup>14</sup> 5) edema, vasodilatation and extravasation of red blood cells in the upper dermis.<sup>6</sup>

PAS stain very often shows thickening of the basal membrane. Melanin-containing melanophages are sometimes seen in the upper dermis.<sup>4,12,13,15</sup> When present, discoid lesions are histologically similar, both in CCLE and in SLE.<sup>6</sup>

Jerdan et al.<sup>16</sup> compared the histopathologic findings of 77 biopsies from 63 cutaneous lupus erythematosus patients, and observed the following significant characteristics for a diagnosis of CCLE: hyperkeratosis, follicular plugging, thickening of the basal membrane and superficial and deep mononuclear

inflammatory infiltrate. In the present study, owing to the ease of clinical characterization, discoid lesions were used as the standard reference. Pilosebaceous atrophy and periadnexal thickening of the basal membrane showed a high predictive value for a diagnosis of CCLE, when compared to subacute cutaneous lupus erythematosus (SCLE), coming to 88% and 73%, respectively.

Bangert et al.,<sup>17</sup> stated that the presence of hyperkeratosis, thickening of the basal membrane, extensive follicular damage and dense lymphocyte infiltrate involving the deep dermis are findings that favor a diagnosis of DLE. The changes found in SCLE are quantitatively different from those found in DLE, and epidermal atrophy is an important characteristic.

In SCLE, the presence of follicular plugging, hyperkeratosis and the density and depth of the inflammatory infiltrate are less accentuated than in CCLE and less restricted to periadnexal and perivascular regions.<sup>3</sup>

Bielsa et al.<sup>18</sup> classified 92 patients based strictly on clinical characteristics, as CCLE, annular SCLE and papulosquamous SCLE. Statistical analysis (chi-squared test) of the histopathology of these cases showed that in CCLE the thickening of the basal membrane, dermal colloid bodies, pilosebaceous atrophy and periadnexal infiltrate were statistically significant. In the subacute annular form the findings were intense vacuolization of the basal layer, a large number of epidermal colloid bodies and epidermal necrosis. In conclusion, the authors state that pilosebaceous atrophy and epidermal necrosis are highly specific histopathologic features respectively for CCLE and annular SCLE. They also suggest an inter-relationship between epidermal necrosis and the presence of circulating anti-Ro antibodies.

Another variant form of cutaneous lupus erythematosus is known as verrucous or hypertrophic lupus erythematosus. In this form of the disease, verrucous papulonodular lesions that often coalesce into plaques, sometimes with a central keratotic plug, arise over pre-existing discoid lesions in sun-exposed areas, and give the lesion the appearance of keratoacanthoma (Figure 2). Pruritus may occur in some lesions.<sup>18,19</sup>

Lupus tumidus is a rare subtype of chronic cutaneous LE,<sup>20</sup> and was first described by Gougerot, Bournier<sup>21</sup> in 1930. Clinically, it presents erythema, urticariform lesions or smooth shiny red-violet plaques on the head and neck, often with a fine scale (Figure 3). The lesions may be pruritic, leave no scar when they involute, and if they recur, do so at the sites originally affected.<sup>22</sup> Histopathologically they show perivascular and periadnexal lymphohistiocytic infiltrate in the papillary and reticular dermis and intersti-

CHART 1: Classification of lupus erythematosus associated with cutaneous lesions

**Lesions that are histopathologically specific for LE**

## 1 Chronic cutaneous LE

- Localized discoid LE (head and neck)
- Generalized discoid LE (disseminated)
- Verrucous (or hypertrophic) LE
- LE tumidus
- LE profundus (lupus panniculitis)
  - with discoid LE
  - with systemic LE
- LE mucosus
- Discoid LE - lichen planus
- LE pernio
- Discoid LE with systemic involvement (relatively benign subtype)

## 2 Subacute cutaneous LE

- Papulosquamous (psoriasiform)
- Annular (polycyclical)

## 3 Acute cutaneous LE

- Facial (malar) erythema
- Maculopapulous erythema, diffuse on face, scalp, neck, thorax, shoulders, extensor surface of arms and back of hands
- Bullous LE

**Lesions that are histopathologically nonspecific for LE**

- Vascular cutaneous disease
  - Leukocytoclastic vasculitis
    - Palpable purpura
    - Urticarial vasculitis
  - Periarthritis nodosa-like
- Vasculopathy
  - Degos-like disease
  - White atrophy-like
- Periungual telangiectasia
- Livedo reticularis
- Thrombophlebitis
- Raynaud's phenomenon
- Erythromelalgia
- Alopecia (non-cicatricial)
  - Lupus hair
  - Telogen effluvium
  - Alopecia areata
- Sclerodactyly
- Rheumatoid nodules
- Calcinosis cutis
- Nonspecific bullous lesions
  - Acquired bullous epidermolysis
  - Bullous LE-like dermatitis herpetiformis
  - Erythematous pemphigus
  - Bullous pemphigoid
  - Porphyria cutanea tarda
- Urticaria
- Papulonodular mucinosis
- Anetoderma/cutis laxa
- Acanthosis nigricans
- Erythema multiforme
- Leg ulcers
- Lichen planus

Source: Gilliam, Sontheimer;<sup>7</sup> Sontheimer, Provost.<sup>8</sup>



Figure 1: Localized chronic cutaneous lupus - erythematous plaque, slightly scaling, atrophic, cicatricial, dyschromic, with hyperchromic keratotic borders, located on the left hemiface

tial mucin deposition.<sup>21,23</sup> Epidermal atrophy and changes in the dermal-epidermal junction are absent.<sup>24</sup>

In lupus panniculitis (lupus profundus) the face, neck, shoulders and arms, and possibly hips and gluteal regions are affected. Hard, well-defined erythematous subcutaneous lesions are observed (Figure 4). The overlying skin may present lesions typical of DLE or even ulcerations. Focal epidermal atrophy, dilation of the follicular ostium, hyperkeratosis, vacuolar degeneration of the dermal-epidermal junction, in addition to trabecular and lobular lymphocytic panniculitis accompanied by inflammatory infiltrate of the deep dermis and the subcutaneous cellular tissue are found histologically.<sup>3,25</sup>



FIGURE 2: Hypertrophic chronic cutaneous lupus erythematosus - disseminated erythematous, scaling, hyperkeratotic nodules and plaques



FIGURE 3: Chronic cutaneous lupus tumidus - a round erythematous edematous plaque on the right malar region (Serviço de Dermatologia da UFMG)

Yell et al.,<sup>26</sup> in a study of 73 patients with systemic lupus erythematosus, found chronic discoid lesions in 17 (23%), in nine of whom (12%) the discoid lesions preceded the systemic symptoms. Tuffanelli, Dubois<sup>27</sup> reported discoid lesions in the course of SLE in 149 (28.6%) of the patients they studied; in 56 patients (10.8%) it was the initial manifestation of the disease, and in 79 patients (15.2%) the lesions were generalized. Diagnosis in these patients was based on finding LE cells, on skin biopsy, renal biopsy, and on the clinical features of the lesions. The criteria used in this study did not include the serologic tests currently used to diagnose LES.

#### SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS

Subacute cutaneous lupus erythematosus (SCLE) lies clinically and histologically between the more aggressive form of DLE with a cicatricial tendency, and the short-lived non-destructive malar erythema of acute lupus erythematosus (ALE).<sup>28</sup>

Epidemiologic data suggest that environmental factors may be responsible for some cases of SLE, SCLE and lupus-like syndrome. Among exogenous agents with a presumed role in triggering SLE and SCLE one may cite: ultraviolet light, pesticides and insecticides, heavy metals and other elements, tobacco, foodstuffs, medications (hydrochlorothiazide, anti-histamines, calcium channel blockers, naproxen, oral contraceptives, estrogens) and infections.<sup>29,30</sup> Reports showing the appearance of SCLE or exacerbation of systemic lupus in patients using terbinafine have drawn attention to the possibility of this drug helping trigger or perpetuate the clinical picture.<sup>31</sup>





FIGURE 4: Lupus panniculitis - depressed erythematous violaceous nodules on the arms

Sontheimer et al.<sup>32</sup> studied 27 SCLE patients out of a total 299 lupus patients: 70% were females; 85% were white persons, 11% were black persons and 4% were of Hispanic descent. Two varieties were observed clinically: papulosquamous and annular. The rash is often photosensitive, that is to say it is triggered or exacerbated by exposure to sunlight, and can be drug-induced. The cutaneous lesion is identical in both subgroups, presenting as a papule or small erythematous plaque that is slightly scaly.<sup>33</sup> In the papulosquamous form lesions progress and merge making psoriasiform plaques, often in a reticulated pattern; in the annular form there is peripheral progression of the lesions, with erythema and fine scale at the borders (Figure 5). Hypopigmentation and telangiectasias occasionally appear in the center of the annular lesions, as well as polycyclical or gyral patterns.<sup>32</sup>

Herrero et al.<sup>34</sup> studied 13 SCLE patients and found an 85% predominance of the annular variant, and only 15% for papulosquamous; 60% presented anti-Ro/SSA antibodies, and 82% had the HLA-DR3 phenotype. Photosensitivity was observed in 70%; joint involvement was the major systemic manifestation, with arthralgia in 46% and arthritis in 25% of cases. Vesiculobullous lesions were found on the active margins of annular lesions in 38% of this series, 46% of the patients having met four of the criteria proposed by the ACR for the diagnosis of SLE.

In neonatal lupus erythematosus (NLE) cutaneous lesions were found that were very similar to those observed in SCLE, in newborns to mothers with SLE, appearing between five and 15 months of age in approximately 50% of patients, presenting in photo-exposed areas as transitory annular or polycyclical ery-

thematos macules or papules.<sup>35</sup> Papules and scabby plaques, in addition to petechiae, mimicking Langerhans' cell histiocytosis have been reported in a four-week-old newborn that also presented hepatosplenomegaly and thrombocytopenia.<sup>36</sup> The cutaneous lesions regress spontaneously, in most cases by 12 months of age, when maternal antibodies transmitted to the child transplacentally have been metabolized.<sup>37</sup> On regression the cutaneous lesions do not present scarring, but telangiectasias may sometimes persist for several years. Complete heart block is present in approximately 50% of affected newborns, death from heart failure occurring in 10% of newborns.<sup>38,39</sup>

The presence of anti-Ro/SSA or anti-La/SSB antibodies, or both, has been recorded in over 95% of NLE cases.<sup>40</sup> Lee et al.,<sup>41</sup> state that anti-Ro/SSA antibodies are of maternal origin and cross the placenta; their presence in the serum of affected newborns is correlated to the activity of the disease. Anti-U1RNP antibodies are found less frequently, and cardiac or systemic manifestations are reported to be absent in these cases, implying a better prognosis for the child.<sup>35,37</sup>

The SCLE and DLE lesions are qualitatively identical on histopathology, differing only in a smaller follicular dilation, degree of hyperkeratosis, intensity of the dermal inflammatory infiltrate, the presence of melanophages in the dermis and in the greater degree of epidermal atrophy in SCLE lesions.<sup>15,16,42</sup>

Magro et al.<sup>15</sup> acknowledge the current controversy as to the accuracy of histologic classifications and advance the following criteria for the histopatho-



FIGURE 5: Annular subacute lupus - annular erythematous scaling plaque in polycyclical pattern on the back. (Serviço de Dermatologia da UFMG)

logic diagnosis of SCLE:

- 1) suprabasal lymphocyte exocytosis and dyskeratosis spreading into the stratum spinosum;
- 2) prominent epidermal atrophy;
- 3) minimal or non-existent follicle plugging or thickening of the basal membrane;
- 4) mild to moderate mononuclear cell infiltrate, restricted to the superficial dermis.

#### CUTANEOUS MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Skin involvement in SLE is very common, occurring in 70-80% of patients during the evolution of the disease and constituting the initial manifestation in approximately 20% of cases. The acute form of cutaneous LE manifests in cases of SLE as malar rash, diffuse macular or papular lesions and bullous LE. These lesions are shorter-lasting than in the discoid and sub-acute forms.

#### MALAR RASH

An erythema or rash in the malar region and nasal dorsum, producing a "butterfly wing" appearance, which may be transitory or more persistent; it may also present as a more discreet scaling maculopapular eruption, or as a lesion that is frankly discoid in appearance. It may be triggered by sunlight, and local edema is frequent.<sup>42</sup>

#### PHOTOSENSITIVE LUPUS DERMATITIS

Macules, papules or erythematous plaques, sometimes violaceous, possibly with light scaling. The lesions are not pruriginous and occur mainly in sun-exposed areas such as the face, thorax, shoulders, extensor surface of the arms and backs of the hands, regressing without atrophy<sup>10</sup> (Figure 6). They occur in a range from 55% to 85% of patients.<sup>42</sup>

#### BULLOUS L.E.

Bullous lesions in patients with SLE have been a source of difficulty in diagnosis owing to the fact that several other bullous diseases such as bullous pemphigoid<sup>43-46</sup> and dermatitis herpetiformis<sup>47,48</sup> have been reported concomitantly with SLE

Bullous lesions occur due to intense hydropic degeneration of the basal layer of the epidermis.<sup>49</sup> Although they are considered by some authors to be specific to SLE, they can occur on the edges of annular SCLE lesions.<sup>34,50</sup> Clinically, they are frequently observed on the face, neck and trunk. Nephropathy has been reported in some of these patients.<sup>51,52</sup>

Camisa, Sharma<sup>53</sup> proposed the following criteria for the diagnosis of bullous LE:

- (1) Diagnosis of SLE based on criteria put forward by the ACR;



FIGURE 6: Acute cutaneous lupus - slightly raised erythematous violaceous plaques, on the face, sparing the perioral region and the nasogenian sulci. (Serviço de Dermatologia da UFMG)

- (2) Presence of vesicles or bullae in sun-exposed areas, albeit not restricted to these sites;
- (3) Histology compatible with a diagnosis of dermatitis herpetiformis;
- (4) Negative indirect immunofluorescence for circulating anti-basal membrane antibodies;
- (5) Positive direct immunofluorescence for IgG, IgM or both, and positive direct immunofluorescence for IgA in the basal membrane zone.

#### DIRECT IMMUNOFLUORESCENCE

Direct immunofluorescence (DIF) is deemed a major breakthrough in the diagnosis of connective tissue disease, particularly lupus erythematosus, and is a valuable diagnostic auxiliary to histopathology.<sup>54</sup>

Pohle, Tuffanelli,<sup>55</sup> studying 16 patients with DLE and 12 with SLE, two of which did not present cutaneous lesions, found positive DIF in 93.7% and 100% of lesions, respectively. Four out of eight cutaneous fragments, without apparent changes, obtained from patients with SLE, were found to be simultaneously positive for IgG and IgM. Although the dose was not mentioned, seven patients with SLE were using oral steroids.

There is still to date considerable controversy as to the diagnostic and prognostic value of the lupus band test; however, if it is conducted with skin collected from the non-lesional area that is totally protected from the sun, such as the gluteal region or the internal surface of the upper portion of the arm, a positive result with the presence of three or more classes of immunoglobulins or complement has high specificity for SLE.<sup>1</sup>

The presence of immunoglobulins in lupus lesions and in lesion-free skin from non-sun-exposed areas has shown a range of results.<sup>9,54,56,57</sup>

Sugai et al.,<sup>10</sup> analyzed 71 patients with DLE and found 66.2% positive lesions; they raise the possibility that in earlier studies patients with SCLE or SLE had been included, which would account for a higher incidence of positive results for direct immunofluorescence. Prystowsky et al.,<sup>9</sup> in a group of 80 patients, assessed 17 DLE patients, and had positive DIF for lesioned skin in 77%, whereas in 31 patients in whom cutaneous fragments collected from normal, non-sun-exposed areas, were analyzed, no deposit of immunoglobulin was found.

Fabré et al.,<sup>58</sup> in a study of 50 healthy adults, found immunoglobulin deposits in cutaneous tissue from sun-exposed areas in 20% of the samples, compared with tissue samples obtained from photoprotected areas, which were immunoglobulin-free. They commented upon the controversies and contradictions in the literature concerning use of DIF and the confusing terminology that is sometimes used to characterize immunoglobulin deposits. In their view only DIF consisting of a continuous shiny band is to be considered diagnostic of LE.

The pattern of DIF may be useful in distinguishing lupus erythematosus from other clinically similar diseases. The specificity of IgG or complement in the dermal-epidermal zone shows negative in cases of contact dermatitis, reactions to drugs, polymorphous sunlight eruption, pseudopelade, psoriasis, vitiligo, Jessner's lymphocytic infiltration, sarcoidosis, lichen planus, localized scleroderma, seborrheic dermatitis, rheumatoid arthritis, dermatomyositis and glomerulonephritis.<sup>59</sup>

Smith et al.,<sup>60</sup> comparing DIF findings for normal skin from the deltoid region of 102 patients with SLE and 151 with a range of other rheumatic diseases, found IgM deposits at the dermal-epidermal junction (DEJ), particularly among those with other rheumatic diseases. They concluded that the nature and number of proteins found at the DEJ are important determinants for the specificity and predictive value for a diagnosis of lupus erythematosus. A finding of a single protein, especially IgM, at the DEJ, is of little diagnostic value for SLE.

Dahl<sup>56</sup> demonstrated the difficulties and uncertainties inherent in interpreting the morphology of deposits on DIF, giving examples of positive reactions in vasculitis, rosacea, necrobiosis lipoidica, annular granuloma, telangiectasias, porphyria, erythematous pemphigus, dermatomyositis, amyloidosis, psoriasis, graft-versus-host disease, pityriasis lichenoides et varioliformis acuta, facial granuloma, lichen planus, polymorphous sunlight eruption and Jessner's lymphocyt-

ic infiltration. The LE lesions are characterized by a massive deposit of immunoglobulins of several classes concomitantly, in the DEJ, while other diseases show a single class of immunoglobulin and less intense fluorescence. Lesions up to one month old are less positive to DIF (33%) than lesions of over three months' duration (60%).

Proença et al.<sup>61</sup> analyzed DIF in 69 patients with DLE; 58.33% were positive, with a predominance of C1q (41.66%), IgG (33.33%), C3 (33.33%) and IgM (21.66%). The authors suggest that IgM appears in lesions with over one year's duration. David-Bajar et al.,<sup>62</sup> analyzing 11 patients with DLE and seven with SCLE, found differences in the distribution patterns of immunoglobulin bands. Deposits of IgA, IgM, IgG and C3b were observed in particulate distribution at the dermal-epidermal junction in DLE lesions. In lesions of patients with SCLE, IgG particulate deposits were shown in the epidermis of all patients (they were anti-Ro/SSA positive); IgM was present in all seven patients, with distribution to the DEJ, the lower epidermis and upper dermis; deposits of C3b in the DEJ were shown in five out of the seven patients. The authors conclude that DIF characteristics in SCLE were decisively different from those found in DLE.

Al-Suwaid et al.,<sup>54</sup> studying 18 patients with DLE, found positive DIF in 72.7% of lesions, with a predominance of IgG (77.8%), accompanied by IgM, IgA or complement, or in isolation in 27.7%. A homogenous pattern for IgG deposit occurred in 55.5% of cases. Positive DIF in DLE lesions was superior to positive histopathology (66%), and when both techniques were used (DIF and histopathology), there was 83% positivity, with one or both methods.

Nieboer<sup>63</sup> reported that the DIF-histopathology combination proved more sensitive than either method used separately, albeit not statistically significantly. The author recommended that in cases of DLE, histopathology and DIF be used for diagnosis as well as HE and PAS stainings.

## SEROLOGIC TESTS

Of all available tests, the antinuclear antibody test using indirect immunofluorescence with rat liver as the substrate for nuclear antigens, yielding 90% positivity for SLE patients, has for some time been the most useful in screening for systemic lupus erythematosus. The most widely used substrate is currently human cells originating from esophagus tumor cells (HEp-2) for detecting antinuclear antibodies (ANA), with 99% positivity.<sup>64</sup> The high positivity of this test makes it the most sensitive for lupus, but it is not the most specific, since these antibodies may be detected in other autoimmune or infectious diseases or even in



the elderly.<sup>65,66</sup>

Four antinuclear fluorescence patterns are recognized:

(1) Speckled, the most frequent but least specific result. Related to the presence of nuclear antibody systems such as nuclear ribonucleoprotein (nRNP), detected in patients with mixed connective tissue disease, rheumatoid arthritis and progressive systemic sclerosis; and Sm (the initial letters of "Smith", the first patient from whom the antigen was extracted), highly specific for SLE, possibly indicating greater risk of kidney disease and Raynaud's phenomenon.<sup>67</sup> A speckled pattern may mean the presence of antibodies against so-called extractable nuclear antigens (ENA), which include antibodies against RNP, Sm, Ro and La. The presence of anti-Ro antibodies is strongly correlated with photosensitivity in 90% of these patients.<sup>68</sup>

(2) Peripheral rim, which is highly specific for SLE, but found in patients with other vascular collagen diseases. It shows antibodies against native DNA. It is associated with greater risk of kidney disease.<sup>64</sup>

(3) Homogeneous, observed in patients with antibodies against nucleoprotein, responsible for the LE phenomenon.

(4) Nucleolar, occurring in approximately 50% of progressive systemic sclerosis patients, but rare in SLE.

Complement dosage for SLE is an important indicator of disease activity. The presence of hypocomplementemia is a strong signal of kidney damage.<sup>63,66</sup>

In assessing the results of these tests it is important to bear two aspects in mind: first, some antibodies are not exclusive to patients with collagenoses and may be found in the serum of normal persons or those with other conditions; therefore, the mere presence of these antibodies does not always reveal collagenosis. Generally, however, the total quantity of antibodies against certain antigens, shown in the titer, is greater in patients with collagenosis.<sup>65</sup> Second, the specificity of each antibody varies according to the type of collagenosis, with anti-Sm and anti-nDNA antibodies being highly specific for SLE,<sup>64</sup> while other antibodies, such as anti-DNAs, are of more restricted value and found in most collagenoses. The type and the frequency of antibodies present vary according to the different types of collagenoses. Patients with mixed connective tissue disease (MCTD) have antibodies against nuclear ribonucleoproteins (also known as uridine-rich ribonucleoproteins, U1 RNP) and patients with CREST syndrome possess antibodies that are virtually limited to anticentromeres. Patients with SLE have antibodies against several cellular antigens. Significant levels of anti-nDNA antibodies con-

firm a clinical diagnosis of SLE; however, low levels may be detected in the following conditions: rheumatoid arthritis, Hashimoto's disease, Graves' disease, Waldenström's macroglobulinemia, MCTD, systemic sclerosis, autoimmune hepatic disease and Sjögren's syndrome.<sup>68</sup>

The anti-nDNA antibody should be used when SLE is suspected and a significantly positive test will confirm the diagnosis; a negative result, however, does not rule out the disease, since from 50% to 83% of patients with SLE have this antibody.<sup>68</sup>

Histones are basic proteins that attach to the DNA helix, and are characteristic of drug-induced SLE.<sup>68</sup> Drugs reportedly inducing SLE are allopurinol, captopril, chlorpromazine, clonidine, danazol, diphenylhydantoin, etosuximide, griseofulvin, hydralazine, isoniazid, lithium, lovastatin, mephenytoin, mesalazine, methyl dopa, minocycline, oral contraceptives, para-amino benzoic acid, penicillamine, penicillin, phenothiazine, phenylbutazone, piroxicam, practolol, primidone, propylthiouracil, quinidine, streptomycin, sulfasalazine, sulfonamides, tetracycline, thiamazole, trimethadione, valproate and procainamide.<sup>67</sup> Other chemicals suspected of triggering SLE or lupus-like syndromes are structurally related to hydrazines and aromatic amines. Hydrazines are found in insecticides, herbicides, preservatives, paints, plastics, rubber, foodstuffs and tobacco, while aromatic amines are present in dyes and foodstuffs. The link between triggering collagenoses (SLE, scleroderma and polymyositis) and the use of hair dyes containing aromatic amines has been put forward by some authors,<sup>69</sup> but contested by others.<sup>70</sup>

In collagenoses, autoantibodies against small ribonucleoproteins (sRNP), the smallest part of cellular RNA (<1% of total RNA), are often present, and are called sRNP molecules, for example Ro/SSA, La/SSB, U1 RNP, and Sm. The exact role that these antibodies play in disease pathogenesis is not clear; their presence, however, is valuable in the diagnosis of these diseases. Thus the Sm antibody is characteristic of SLE, while Ro/SSA has been reported in the several subtypes of lupus and in other collagen diseases.<sup>67,68</sup> These antibodies are strongly linked to photosensitivity, especially in SCLE patients, both in idiopathic and drug-induced forms; they are also associated with a high incidence of vasculitis. Anti-La/SSB antibodies are usually associated with anti-Ro/SSA antibodies. Where the anti-La/SSB antibody is positive, anti-Ro/SSA antibodies are concomitantly positive.<sup>68</sup> There seems to be a genetic predisposition toward the presence of anti-Ro/SSA antibodies; a 100% frequency of the HLA-DR3 phenotype has specifically been shown in patients with SCLE who present annular and polycyclical



lesions. The HLA-DR3 phenotype has been detected in approximately 70% of patients with SCLE and psoriasisiform lesions.<sup>71</sup>

Anti-U1RNP antibodies are present in the serum of patients with MCTD and SLE. These antibodies are detected in 100% of patients with MCTD and in approximately 30% of patients with SLE, but may also occur in neonatal lupus and, very rarely, in systemic sclerosis. The presence of anti-U1RNP antibodies is usually associated with sclerodactyly, esophageal dysmotility, a low incidence of kidney disease, pulmonary dysfunction, arthritis, myositis and Raynaud's phenomenon.<sup>72</sup>

Although anti-Sm antibodies are detected in only from 15% to 40% of patients with SLE, using immunodiffusion, a positive result is diagnostic for LE. This antibody has not been reported to be positive in patients with other collagenoses, and is deemed by some authors to be pathognomonic for systemic lupus

erythematosus.<sup>65,66</sup>

## CONCLUSIONS

Persons with collagenoses have an autoimmune phenomenon that leads to the production of antibodies against several antigens found in all cell components (nucleus, cytoplasm and cell membrane molecules). The accuracy of the diagnosis of LE depends on the assessment of four parameters: the clinical and histopathological parameters, DIF and serologic reactions. Although extremely useful in themselves, the use of serologic tests alone will not substitute for other parameters.

Constant growth in knowledge of the pathogenesis of lupus has opened up a new range of opportunities for new concepts and approaches, undertaken in the diagnosis and classification of the disease, allowing greater uniformity in therapeutic strategies. □

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1. Assinale a alternativa incorreta:
  - a) O lúpus eritematoso cutâneo crônico (LECC) é mais comum em mulheres, apresentando pico de incidência na quarta década.
  - b) A forma de LECC mais comum é o lúpus cutâneo discóide localizado (LCDL).
  - c) As lesões cutâneas do LCDL são crônicas, persistentes e podem regredir deixando áreas cicatríciais discrômicas, telangiectasias e alopecia cicatricial.
  - d) As localizações preferenciais do LCDL são pescoço e dorso.
2. No exame histopatológico das lesões discóides do LECC não se observa:
  - a) Adelgaçamento e achatamento do estrato de Malpighi.
  - b) Degeneração hidrópica das células basais.
  - c) Infiltrado predominantemente eosinofílico, com tendência a circundar anexos.
  - d) Espessamento da membrana basal.
3. São características histopatológicas altamente específicas para o LECC e para o lúpus eritematoso subagudo (LESA) anular, respectivamente:
  - a) Hiperqueratose e infiltrado inflamatório perianexial.
  - b) Atrofia pilosebácea e necrose epidérmica.
  - c) Tampão folicular e corpos colóides dérmicos.
  - d) Necrose epidérmica e hiperqueratose.
4. Assinale a alternativa correta:
  - a) Na paniculite lúpica são geralmente acometidos face, pescoço, ombros e braços.
  - b) As lesões do lúpus tímido geralmente envolvem com cicatriz.
  - c) No LECC, clinicamente observam-se duas variedades: papuloescamosa e anular.
  - d) No lúpus eritematoso neonatal (LEN) não costuma haver regressão espontânea das lesões cutâneas.
5. No LEN encontram-se, em mais de 95% dos casos, os seguintes anticorpos:
  - a) Anti-U1RNP.
  - b) Anti-Sm.
  - c) Anti-DNAn.
  - d) Anti-La/SSB, anti Ro/SSA ou ambos.
6. O diagnóstico histopatológico do LESA inclui os seguintes critérios, exceto:
  - a) Atrofia epidérmica acentuada.
  - b) Tampão folicular ou espessamento da zona da membrana basal mínimo ou ausente.
  - c) Infiltrado mononuclear leve a moderado, limitado à derme superficial.
  - d) Espessamento da membrana basal.
7. Assinale a alternativa incorreta. A forma aguda do LE cutâneo manifesta-se nos casos de LES como:
  - a) Eritema malar.
  - b) LE bolhoso.
  - c) Lesões maculosas ou papulosas difusas.
  - d) Lesões atrófico-cicatríciais.
8. De todos os testes disponíveis, o de maior valor na triagem para o LES é:
  - a) Determinação de anticorpos antinucleares (Hep-2).
  - b) Imunofluorescência direta da pele lesada.
  - c) A presença de banda lúpica em fragmento de pele lesada não exposta ao sol.
  - d) Anticorpos anticardiolipina.
9. Dos padrões de fluorescência antinuclear, o mais comum e inespecífico é:
  - a) Nucleolar.
  - b) Homogêneo.
  - c) Salpicado.
  - d) Periférico.
10. O padrão de fluorescência antinuclear considerado altamente específico para LES e cuja presença está associada a um maior risco de doença renal é:
  - a) Homogêneo.
  - b) Periférico.
  - c) Salpicado.
  - d) Nucleolar.
11. A especificidade de cada anticorpo varia conforme o tipo de colagenose. São altamente específicos para o LES:
  - a) Anti-Sm e anti-DNAn.
  - b) Anti-DNAs.
  - c) Anti-Ro/SSA e anti-La/SSB.
  - d) Anti-U1RNP.
12. Assinale a alternativa incorreta:
  - a) Um resultado negativo na detecção do anti-DNAn não exclui LES.
  - b) Anticorpos anti-histona são positivos em 90% dos pacientes em LES induzido por drogas.
  - c) Anticorpos anti-DNAs têm grande valor para o diagnóstico de LES.
  - d) Anticorpos anti-Ro/SSA são muito relacionados à fotossensibilidade, especialmente em pacientes com LESA.
13. Assinale a alternativa incorreta em relação aos anticorpos anti-U1RNP:
  - a) Ocorrem em 30% dos pacientes com LES.
  - b) Geralmente sua presença associa-se ao fenômeno de Raynaud, à esclerodactilia, à artrite,

miosite e disfunção pulmonar.

- c) Não ocorrem no lúpus neonatal.
- d) Raramente são detectados na esclerose sistêmica.

14. Ao exame histopatológico o encontro de hiperqueratose, espessamento da membrana basal, dano folicular extenso e infiltrado linfocitário denso, com envolvimento da derme profunda, são achados que favorecem o diagnóstico de:

- a) LESA
- b) Lúpus tímido
- c) Paniculite lúpica
- d) Lúpus eritematoso cutâneo crônico localizado.

15. Entre os agentes exógenos provocadores do LES estão:

- a) Raios infravermelhos, hidroclorotiazida, griseofulvina.
- b) Naproxen, contraceptivos orais e anti-histamínicos.
- c) Fluconazol, cetoprofeno e lítio.
- d) Sulfato ferroso, bloqueadores do canal de cálcio e dipirona.

16. Assinale a alternativa correta:

- a) No lúpus subagudo, ocorre predomínio do subtipo anular com 85%, contra apenas 15% do subtipo papuloescamoso.
- b) No lúpus subagudo, ocorre predomínio do subtipo papuloescamoso com 85%, contra apenas 15% do subtipo anular.
- c) No lúpus subagudo, ocorre predomínio do subtipo anular com 60%, contra apenas 40% do subtipo papuloescamoso.
- d) No lúpus subagudo, os subtipos anular e papuloescamoso têm igual frequência.

17. Com relação ao LE bolhoso, entre os critérios propostos por Camisa & Sharma encontramos, exceto:

- a) Presença de vesículas e/ou bolhas exclusivamente em áreas expostas ao sol.
- b) Histologia compatível com dermatite herpetiforme.
- c) Imunofluorescência direta positiva para IgM e/ou IgG na zona da membrana basal.
- d) Imunofluorescência indireta para anticorpos circulantes antimembrana basal negativa.

18. Com relação à imunofluorescência direta (lupus band test), assinale a alternativa incorreta:

- a) O padrão da imunofluorescência direta pode ser útil na diferenciação do lúpus de outras doenças clinicamente similares.
- b) O depósito de imunocomplexos na pele livre de lesões, em pacientes portadores de LES, está correlacionado, possivelmente, à alta incidência

de doença renal, podendo ser auxiliar no prognóstico.

c) Pode-se encontrar bandas positivas à imunofluorescência direta na rosácea, erupção polimorfa à luz solar e pêfigo eritematoso.

d) As lesões de LE caracterizam-se por leve depósito de apenas uma classe de imunoglobulina, na junção dermoepidérmica.

19) Assinale a alternativa correta:

a) Estima-se que entre 5 e 10% dos pacientes que preencham os critérios da ARA (American Rheumatism Association) para LES tenham anticorpos antinucleares negativos.

b) A dosagem de complemento no LES não auxilia na identificação da atividade da doença.

c) O padrão periférico de fluorescência nuclear é forte indicador de esclerose sistêmica progressiva.

d) O padrão homogêneo de fluorescência nuclear sugere a possibilidade de doença renal.

20) Assinale a alternativa incorreta:

a) A acurácia do diagnóstico do lúpus eritematoso depende da avaliação de quatro parâmetros: clínica, histopatologia, imunofluorescência direta e reações sorológicas.

b) Os anticorpos anti-histona estão presentes em cerca de 90% dos pacientes com LES induzido por drogas e em aproximadamente 30% dos pacientes com LES idiopático; entretanto a maioria desses doentes também apresenta outros anticorpos antinucleares.

c) A presença de anticorpos anti-U1 RNP é geralmente associada à esclerodactilia, dismotilidade esofágica, baixa incidência de doença renal, disfunção pulmonar, artrite, miosite e ao fenômeno de Raynaud.

d) Os anticorpos anti-La/SSB raramente estão associados aos anti-Ro/SSA.

#### GABARITO

Primeiro atendimento em queimaduras: a abordagem do dermatologista. 2005;80(1):9-19

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|-------|-------|
| 1- d  | 11- b |
| 2- c  | 12- b |
| 3- c  | 13- a |
| 4- a  | 14- c |
| 5- b  | 15- a |
| 6- d  | 16- d |
| 7- c  | 17- b |
| 8- a  | 18- c |
| 9- c  | 19- a |
| 10- c | 20- d |