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HISTOLOGY OF SKIN ALTERATIONS IN LUPUS ERYTHEMATOSUS

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Abstract. *Lupus erythematosus is an autoimmune connective tissue disorder showing a broad spectrum of clinical manifestations.* ***The aim*** *of this study was to assess the correlation of skin histology and different types of lupus erythematosus.* ***Materials and methods:*** *Fifty-one skin specimens were assessed from 39 female and 12 male patients with acute, subcutaneous and chronic lupus erythematosus, diagnosed and treated in the Department of Dermatology and Venereology, Alexandrovska University Hospital for a 4-year period.* ***Results:*** *Follicular hyperkeratosis, epidermal atrophy, vacuolar degeneration and interface dermatitis were the most frequently observed lesions in chronic cutaneous lupus erythematosus while diffuse hyperkeratosis, epidermal atrophy and indistinct interface dermatitis in the dermis were predominant in subacute cutaneous lupus erythematosus. Lupus tumidus, a rare intermittent variant of cutaneous lupus erythematosus, showed almost no epidermal involvement and mucin deposition in the dermis. However, in one of our lupus tumidus patients the disease progressed to a systemic form with histological changes of acute cutaneous lupus erythematosus including atrophy, dermal-epidermal smoothing and lymphocytic infiltration in the dermis. Of note, a few patients showed histological changes of urticarial vasculitis-like and rheumatic-like patterns.* ***Conclusion:*** *The correlation of clinical course, histopathological findings and immunological tests are of vital importance for the correct diagnosis and follow up of patients with lupus erythematodes, thus preventing complications and improving their quality of life.*

Key words: *acute, subacute and chronic cutaneous lupus erythematosus, histology, interface dermatitis*

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INTRODUCTION

Lupus erythematosus (LE) is an autoimmune connective tissue disease with a wide range of clinical manifestations and affected organs and systems. Among all others the skin lesions may have significant diagnostic importance. Cutaneous involvement clinically subdivides in chronic cutaneous lupus erythematosus (CCLE) – mainly its discoid cutaneous form (DCLE); as well as in subacute cutaneous (SCLE) and acute cutaneous lupus erythematosus (ACLE) variants [1]. CCLE manifests itself mainly with cutaneous lesions and a chronic often benign course, while SCLE affects the skin and joints. ACLE may be regarded as a cutaneous expression of systemic lupus erythematosus (SLE) and as a predictor of severe systemic disease with a serious prognosis in which the skin is only one affected organ [1, 2].

In addition to immunological tests, the most widely used diagnostic approach in CLE is the histological investigation of skin samples. The cutaneous findings are characterized by a broad spectrum of signs depending on the disease stage and the anatomical localization of the lesions [2].

The aim of this study was to address the specificity and correlation of histological changes in the epidermis and dermis typical for acute, subacute and chronic cutaneous lupus erythematosus.

MATERIALS AND METHODS

Fifty-one skin biopsies from 39 female and 12 male patients with lupus erythematosus were assessed. Patients were fully examined and skin samples were taken in the Department of Dermatology and Venereology of the Alexandrovska University Hospital – Sofia for a 4-year period (from 2017 till 2020). The diagnosis of CLE was based on the EUSCLE questionnaire [3] and according to the ACR 1997 and SLICC 2012 criteria [4]. The youngest investigated patient was 17 year-old, while the eldest one – 80 year-old (mean patients' age of 48 years).

The skin specimens were fixed in a 10% formalin solution, cut on slides and stained with hematoxylin and eosin. Twenty-nine of the samples were obtained from CCLE, 14 – from SCLE, 2 – from lupus tumidus (LT) and 6 from ACLE skin lesions.

Histological changes in CCLE and ACLE were compared using the Fisher's exact test with the PSPP software (p-value shown if significant).

RESULTS

The histological findings of the included patients are presented in Table 1, according to the clinical disease variants.

Chronic cutaneous lupus erythematosus

The most common skin signs in our patients with CCLE were follicular hyperkeratosis, atrophy, smoothing of the dermal-epidermal junction (DEJ), vacuolar and fibrin degeneration as well as interface dermatitis and a perivascular and perifollicular lymphocytic infiltration of the dermis (Fig. 1). "Colloid" or Civatte bodies were found in 20.6% of the histological specimens. In a small group of specimens, pigmentary incontinence and solar degeneration were as well observed. When the the histopathological changes in the CLE and SLE lesions were compared follicular hyperkeratosis was significantly more frequent in discoid cutaneous lupus (Table 1).

During the follow up visits 4 of our DCLE patients fulfilled the criteria for SLE. Hyperkeratosis and atrophy in the epidermis and DEJ smoothing with very sparse infiltration in the dermis were discovered in their skin lesions (Table 2).

Table 1. Histological involvment of the skin in the different clinical variants of LE

Histological changes	DCLE n = 29	SCLE n = 14;	LT n = 2	SLE, n = 6	P (DCLE vs SLE)
Diffuse hyperkeratosis	15 (51.7%)	7 (50%)	2 (100%)	2 (33.3%)	n.s.
Follicular hyperkeratosis	15 (51.7%)	5 (35.7%)	0 (0%)	0 (0%)	$p < 0.05$
Atrophy	23 (79.3%)	8 (57.1%)	1 (50%)	5 (83.3%)	n.s.
DEJ smoothing	17 (58.6%)	6 (42.8%)	1 (50%)	4 (66.6%)	n.s.
Fibrinoid degeneration	15 (51.7%)	9 (64.2%)	1 (50%)	1 (16.6%)	n.s.
Vacuole degeneration	21 (72.4%)	7 (50%)	1 (50%)	4 (66.6%)	n.s.
Colloid bodies	6 (20.6%)	1 (7.1%)	0 (0%)	1 (16.6%)	n.s.
Interface dermatitis	13 (44.8%)	1 (7.1%)	2 (100%)	3 (50%)	n.s.
Perifollicular infiltration	13 (44.8%)	6 (42.8%)	0 (0%)	1 (16.6%)	n.s.
Perivascular infiltration	12 (41.4%)	7 (50%)	2 (100%)	3 (50%)	n.s.
Pigmentary incontinence	3 (10.3%)	0 (0%)	0 (0%)	0 (0%)	n.s.
Solar degeneration	3 (10.3%)	2 (14.2%)	0 (0%)	0 (0%)	n.s.
Mucin deposits	1 (3.4%)	0 (0%)	2 (100%)	0 (0%)	n.s.
Acanthosis	1 (3.4%)	1 (7.1%)	0 (0%)	0 (0%)	n.s.
Apoptotic keratinocytes	0 (0%)	2 (14.2%)	0 (0%)	0 (0%)	n.s.
Leukocytoclastic vasculitis	0 (0%)	2 (14.2%)	0 (0%)	1 (16.6%)	n.s.
Epidermal necrosis and bulla	0 (0%)	0 (0%)	0 (0%)	1 (16.6%)	n.s.

n.s. – not significant

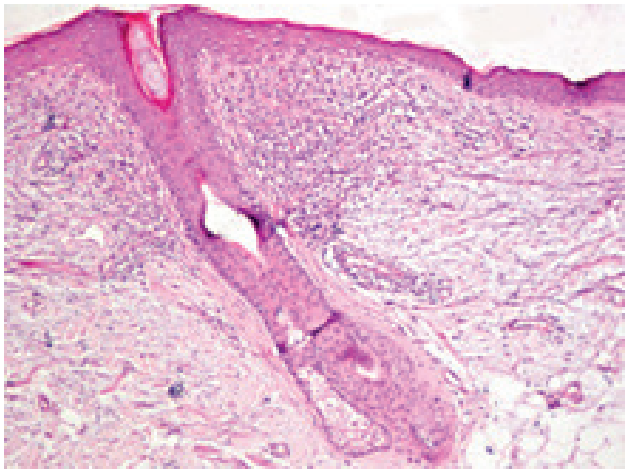


Fig. 1. Follicular plugging, atrophy and vacuolar degeneration of basal layer keratinocytes and dense perifollicular lymphocytic infiltration in the dermis in a DCLE lesion. (H&E x100)

Subcutaneous lupus erythematosus

Fourteen of our LE patients were diagnosed with SCLE and the most common histological findings in their lesions were diffuse hyperkeratosis and atrophy of the epidermis together with fibrinoid degeneration as opposed to the poorly expressed interface infiltration in the dermis (Fig. 2). Perifollicular and perivascular infiltrates were found in half of the SCLE specimens.

In two SCLE patients the disease progressed to SLE, with atrophy, vacuolar degeneration, apoptotic keratinocytes and periadnexial infiltration within their skin lesions (Table 2).

Table 2. Histological changes in patients with CLE with further progression to SLE

Histological changes	DCLE n = 4	SCLE n = 2	LT n = 2
Diffuse hyperkeratosis	2 (50%)	1 (50%)	1 (100%)
Follicular hyperkeratosis	3 (75%)	1 (50%)	0 (0%)
Atrophy	4 (100%)	2 (100%)	1 (100%)
DEJ smoothing	4 (100%)	2 (100%)	1 (100%)
Fibrinoid degeneration	0 (0%)	1 (50%)	1 (100%)
Vacuole degeneration	3 (75%)	2 (100%)	1 (100%)
Colloid bodies	0 (0%)	0 (0%)	0 (0%)
Interface dermatitis	1 (25%)	0 (0%)	1 (100%)
Perifollicular infiltration	2 (50%)	2 (100%)	0 (0%)
Perivascular infiltration	2 (50%)	2 (100%)	1 (100%)
Dermal melanosis	0 (0%)	0 (0%)	0 (0%)
Solar degeneration	0 (0%)	0 (0%)	0 (0%)
Collagen fibrosis	1 (25%)	0 (0%)	0 (0%)
Apoptotic keratinocytes	0 (0%)	1 (50%)	0 (0%)

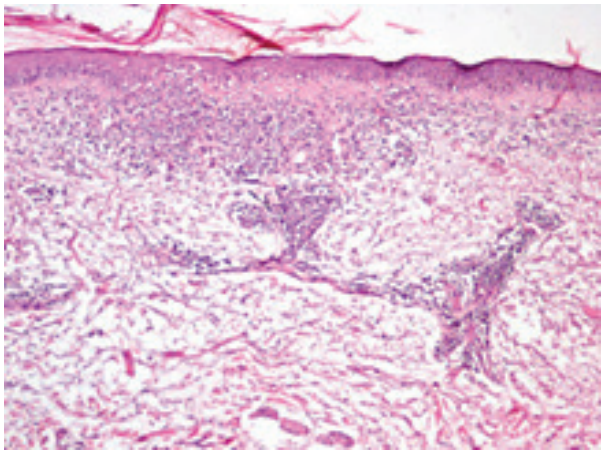


Fig. 2. Hyperkeratosis, atrophy, vacuolar degeneration of basal layer and lichenoid and perivascular lymphocytic infiltration in the dermis in a SCLE lesion. (H&E x100)

Lupus tumidus

LT is a rare variant of lupus erythematosus. Two patients were diagnosed with LT, showing diffuse hyperkeratosis, diffuse dermal and perivascular infiltrates and mucin deposits on histology. One of them developed later SLE and his skin lesions showed diffuse hyperkeratosis, atrophy, DEJ smoothing and lymphocytic infiltration in the dermis (Table 2).

Acute cutaneous lupus erythematosus

Atrophy, DEJ smoothing and vacuole degenerations are found in skin specimens of almost all patients with ACLE (Fig. 3). In one patient an infiltrate rich of neutrophils and eosinophils was found together with leukocytoclasia in the dermis and perivascular space. Such findings are typical for lekocytoclastic vasculitis and may be clinically manifested as urticarial vasculitis. One biopsy specimen showed rheumatic nodules-like changes in the deep dermis. One sample of a patient with bullous systemic lupus erythematosus (BSLE) revealed epidermal necrosis, splitting and bulla formation with debris (Fig. 4).

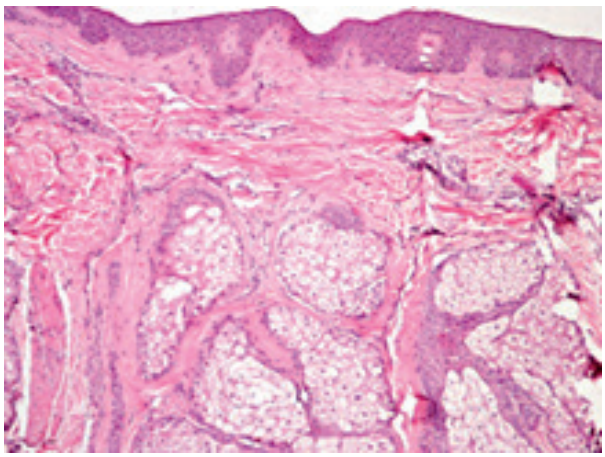


Fig. 3. Vacuolar degeneration of the basal layer and apoptotic keratinocytes in the epidermis, mucin deposition, perivascular and periadnexal mononuclear infiltrate in the dermis (H&E x100)

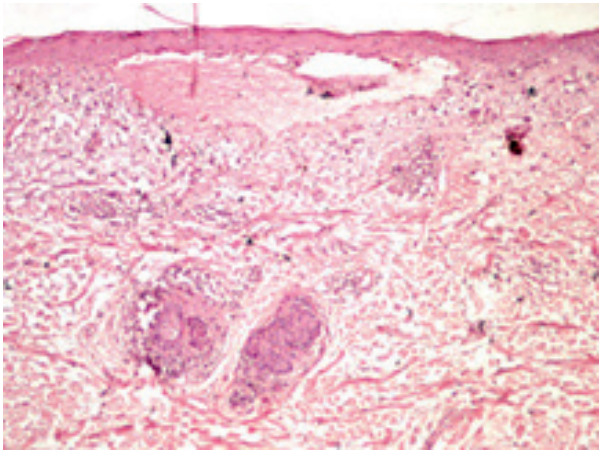


Fig. 4. Blister formation and polymorphonuclear infiltrate in the dermis in a BSLE lesion (H&E x100)

DISCUSSION

Lupus erythematosus is an autoimmune connective tissue disease showing a broad spectrum of clinical manifestations and various prognosis and severity. It could present itself as an isolated skin disease (CCLE) or as a multi-organ systemic disease (SLE), with the rare variant of SCLE in between [2].

Based on the Gilliam clinical/histologic classification [5], later revised by Werth [6] and Ting [7], the cutaneous lupus erythematosus lesions can be divided into LE-specific and LE-nonspecific ones. LE non-specific manifestations had been observed in about 30% of SLE patients and included Raynaud's phenomenon, urticaria vasculitis, alopecia, lupus pernio, palpable purpura, livedo reticularis, periungual telangiectasia, anetoderma, erythema multiforme, papulo-nodular mucinosis and others [3, 6].

CCLE is considered as three times more frequent than SLE. Its clinical manifestation is mainly described as DCLE with active or late cutaneous lesions [9, 10]. Common histological hallmarks for the active lesions are diffuse hyperkeratosis with prominent keratotic follicular plugging, epidermal atrophy with variable acanthosis [11, 12]. Colloid bodies along the DEJ are an uncommon feature and could be found in several other diseases as lichen planus, dermatomyositis, graft-versus-host disease, erythema multiforme, and cutaneous drug reactions [13]. Although the colloid bodies are nonspecific for lupus, they have important diagnostic value [14, 15]. In the dermis, superficial and deep perivascular and perifollicular infiltrates are observed in a lichenoid like distribution [16, 17]. Erythrocyte extravasation, mucin deposits and pigmentary incontinence can also be observed.

Typical for the advanced DCLE lesions are hyperkeratosis and central atrophy of the lesions. The vacuolar degeneration may be more prominent together with a sparse infiltrate in the dermis further replaced by collagen fibrosis and marked follicular plugging leading to alopecia on the scalp [18, 19]. Due to the clinical presence of dyspigmentation in the advanced lesions, a distinct histological feature is pigmentary incontinence [20].

SCLE is regarded as a superficial inflammatory form of CLE [21]. From a clinical point of view it is a separate variant, although the histological signs may show an overlap with DCLE [22, 23]. Epidermal changes with patchy parakeratosis zones of weakly expressed vacuolar and lichenoid changes are often seen. However, in most specimens we observed in addition a fibrinoid degeneration. Interface dermatitis was prominent and necrotic keratinocytes were present in ~15% of the histological specimens of our SCLE patients. Dermal features were presented as a sparse perivascular lymphocytic infiltrate.

Lupus tumidus is regarded as a variant of DCLE or as a separate entity. It is characterized by minimal epidermal changes and typical prominent interface dermatitis [24]. The epidermal atrophy and hyperkeratosis are not typical. However, we found hyperkeratosis, atrophy and DEJ smoothing in one of our LT patients. The most typical sign was the mucin deposition in the dermis [25].

Compared to the remaining variants, the ACLE skin lesions were mostly non-specific and might be easily confused with those in DCLE, SCLE or other dermatoses with a lichenoid dermatitis histology. Patchy parakeratosis of the corneal layer, mild basal vacuolar degeneration with colloid bodies in the epidermis and poorly defined infiltrations in the dermis are hallmarks of the disease [26]. However, LE specific lesions show vacuolar degeneration of the basal membrane, oedema, erythrocyte extravasation and a lymphocytic infiltration in the upper dermis, while neutrophils are present at the dermal-epidermal junction in early lesions [26], a finding we also found in the specimens of one SLE patient.

Urticarial vasculitis-like and rheumatic nodules-like lesions were found in a few ACLE patients. Cutaneous vascular involvement in SLE was represented clinically by vasculitis, vasculopathy, livedo reticularis, periungual telangiectasia, thrombophlebitis, and Raynaud's phenomenon [9, 27]. A small-vessel leukocytoclastic vasculitis was the most common vasculitis in the SLE patients usually presenting clinically as a palpable purpura. It may be associated with urticarial lesions persisting for longer than 24 hours with a resolving pigmentation [28]. Some of them showed urticarial vasculitis-like lesions with neutrophil and eosinophil infiltration and leukocytoclastic dust in the dermis.

A patient with SLE who presented with erythematous papules and plaques in an annular pattern on the facial

skin and the hard palate associated with intermittent fever, anemia and arthritis showed rheumatoid nodules-like histological findings in the papules. Further immunological investigations revealed positive antinuclear antibodies, anti-ds-DNA and anti-SS/A and low complement levels with a negative rheumatoid factor. Histological signs of rheumatoid nodules could be found in several conditions except rheumatoid arthritis as deep granuloma annulare, Jaccoud's arthritis and SLE [29, 30].

A rare variant of SLE is BSLE that presents clinically with vesicles and bullae, resembling dermatitis herpetiformis or bullous pemphigoid [31, 32]. Histologically it is characterized by a pronounced neutrophilic infiltrate in the dermis, forming papillary abscesses, and resembling dermatitis herpetiformis. In some long-standing BSLE lesion bullae surrounded by mononuclear infiltrate were also observed [24].

CONCLUSION

Although typical the histological presentation of CLE with follicular hyperkeratosis, atrophy and periadnexial lymphocytic infiltration is not always enough for the correct diagnosis. The clinical-histopathological correlations and the immunological tests are important hallmarks in the correct diagnosis and follow up the patients in an attempt to prevent complications and improving their quality of life.

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