

# Histopathology of the skin in rheumatic diseases

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## SUMMARY

Rheumatological systemic autoimmune diseases, such as connective tissue diseases, rheumatoid arthritis or spondyloarthritis, are characterized by the presence of joint involvement associated with extra-articular manifestations. Among them, cutaneous diseases are often the most relevant and representative clinical manifestation, as in psoriatic arthritis, scleroderma or systemic lupus erythematosus. In this context, it is useful for rheumatologists to understand better skin diseases and their histopathological features. Evaluation of skin biopsy specimens can be helpful not only to confirm the diagnosis in both classic and clinically atypical variants, but also to improve further our knowledge of the pathogenetic mechanisms and the close link between skin and articular diseases. In this review, we discuss the clinical features, diagnostic evaluation and the histopathological features of skin manifestation of the most relevant rheumatological autoimmune diseases.

**Key words:** Histopathology; cutaneous diseases; autoimmune diseases; skin.

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## ■ INTRODUCTION

Autoimmune rheumatological diseases are characterized by the presence of both joint and extra-articular manifestations. Among them, skin involvement is one of the most frequent signs. In a large proportion of cases, skin lesions may be the first manifestation of the disease, having a spy role for rheumatological systemic diseases such as, for example scleroderma, lupus erythematosus, dermatomyositis or psoriatic arthritis.

Histopathological evaluation of skin biopsy samples may be useful to confirm the clinical diagnosis but also to understand better and improve our knowledge of the pathogenesis of systemic autoimmune diseases. In this review, we provide an overview of the clinical features, diagnostic evaluation and the histopathological features of skin manifestation of the most relevant rheumatological autoimmune diseases (Table I).

## ■ PSORIASIS

Psoriasis is a chronic inflammatory immune-mediated skin disease, affecting 1-3% of Caucasians, characterized by excessive growth and aberrant differentiation of keratinocytes (1).

There are various clinical subtypes including chronic plaque (or psoriasis vulgaris), guttate, erythrodermic, and pustular psoriasis. Clinically, psoriatic lesions consist of erythematous-squamous patches and plaques covered by silvery scales (1). Psoriatic arthritis is a chronic inflammatory arthropathy typically associated with psoriasis.

Psoriasis is a complex multifactorial disease related to a combination of genetic, environmental and immunological factors, involving both innate and adaptive immune systems (2, 3). Keratinocytes play a key role in the recruitment and activation of T cells in psoriatic lesions and T cells are fundamental in the maintenance of the

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**Table I** - Main histological features of skin manifestations in rheumatologic diseases.

Rheumatological disease	Skin manifestation and histological features	
Psoriasis	S: erythematous-squamous patches and plaques covered by silvery scales H: parakeratosis of cornified layer, hypogranulosis, neutrophils within epidermis and parakeratotic foci, thinned suprapapillary plates, increased number of mitotic figures in the basal and suprabasal layers, ectatic and tortuous papillary blood vessels	
LE	S: SLE, DLE, SCLE, bullous LE, chilblain lupus, lupus tumidus, lupus panniculitis H: vacuolar degeneration of basal layer of epidermis with variable number of Civatte bodies; dermal lymphocytic infiltrate (superficial in SLE, superficial and deep and periadnexal in DLE); interstitial mucin deposition in dermis; possible dermal neutrophils with leukocytoclasia in SLE; hyperkeratosis, atrophy of spinous layer, and follicular keratotic plugging in DLE	
DM	S: erythematous, scaly lesions with a predilection for sun-exposed areas, poikiloderma, periungual erythema and telangiectases, Gottron papules, heliotrope rash H: indistinguishable from SLE; vacuolar degeneration of basal layer of epidermis with rare Civatte bodies; superficial lymphocytic infiltrate in dermis; interstitial mucin deposition in dermis; possible dermal neutrophils with leukocytoclasia	
Scleroderma	S: painless, discolored, sclerotic skin (morphea or systemic scleroderma) H: thickened dermis, broad sclerotic collagen bundles, pilosebaceous unit atrophy, dermal lymphoplasmacytic infiltrate in early lesions	
ANCA-associated vasculitides	MPA	S: purpura and petechiae, livedo reticularis, and erythema H: perivascular lymphocyte infiltration in the upper dermis and infiltration of lymphocytes, few neutrophils around small arteries in the middle to deep dermis and diffuse infiltration of histiocytes and lymphocytes in the middle dermis
	GPA	S: purpura and petechiae H: leukocytoclastic vasculitis, necrotizing granulomas
	EGPA	S: subcutaneous nodules, and purpura H: leukocytoclastic vasculitis, extravascular granulomas, eosinophils in inflammatory infiltrate
Urticarial vasculitis	S: recurrent episodes of <i>urticaria</i> (wheals causing burning pain, lasting greater than 24 h and leaving residual hyperpigmentation) H: lymphocytic infiltrate with eosinophils and red blood cell extravasation, leukocytoclastic vasculitis	
Cryoglobulinemic vasculitis	S: orthostatic palpable purpura H: eosinophilic refractile deposits within vessel lumina with extension into the intima, leukocytoclastic vasculitis	
Behçet disease	S: oral and genital ulcers, skin hyperreactivity, erythema nodosum-like lesions, papulopustular lesions, hemorrhagic blisters, infiltrated erythema, Sweet's syndrome-like eruptions and extragenital ulcerations H: dermal lymphohistiocytic infiltrate with neutrophils; at times leukocytoclastic vasculitis; septal and/or lobular panniculitis; dense perivascular neutrophil infiltrate with no fibrinoid changes in pathergic lesions	
Rheumatoid arthritis	S: rheumatoid vasculitis, rheumatoid nodules, granulomatous skin disorders, and neutrophilic dermatoses H: leukocytoclastic vasculitis; palisading necrobiotic granulomas in rheumatoid nodules	
Lyme disease	S: erythema migrans, acrodermatitis chronica atrophicans H: superficial and deep chronic inflammatory cell infiltrate in the dermis with lymphocytes and plasma cells; prominent eosinophils at the tick bite site; atrophy of the dermis and loss of elastic fibers in acrodermatitis chronica atrophicans	
Sarcoidosis	S: papular sarcoidosis, plaques, lupus pernio, erythema nodosum H: sarcoïdal granulomas (epithelioid histiocytes and giant cells surrounded by a thin rim of lymphocytes and plasma cells, <i>naked granulomas</i> )	
Pyoderma gangrenosum	S: necrotic ulcers with distinctively ragged, undermined, erythematous borders H: follicular and perifollicular inflammation with intradermal abscesses, ulceration, superficial edema at the advancing edge, tight perivascular lymphoplasmacytic infiltrate, occasionally leukocytoclastic vasculitis	

S, skin manifestations; H, histopathological features; SLE, systemic lupus erythematosus; DM, dermatomyositis; ANCA, antineutrophil cytoplasmic antibodies; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis.

disease. Inflammatory myeloid dendritic cells release interleukin (IL)-23 and IL-12 in order to activate T helper (Th) 1 cells, IL-17-producing T cells (Th17), and Th22 cells to produce cytokines such as IL-17, interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , and IL-22. These cytokines induce keratinocytes to amplify and further support the psoriatic inflammatory process (2-4).

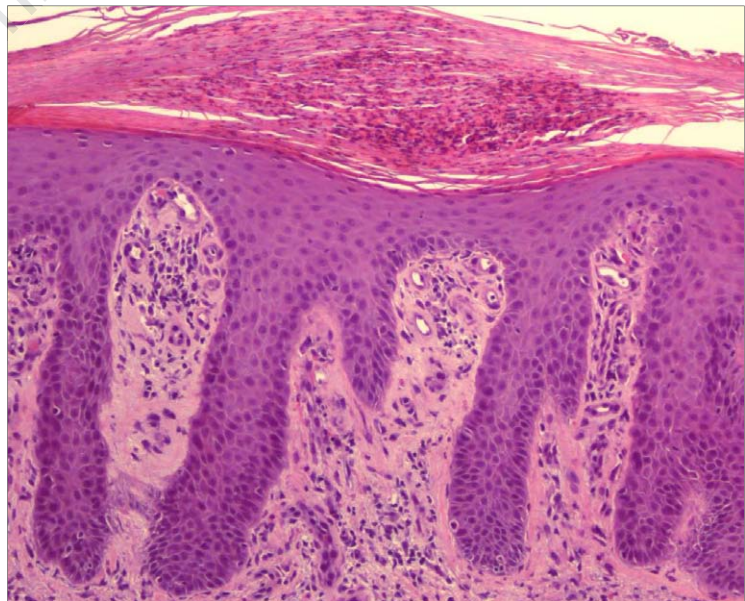
From a histopathological point of view, psoriasis is the prototype of the psoriasiform tissue reaction pattern, morphologically defined as epidermal hyperplasia with elongation of the rete ridges (5). Additional specific features are: parakeratosis of the cornified layer, hypogranulosis, the presence of neutrophils within the epidermis and parakeratotic foci, thinned suprapapillary plates, increased number of mitotic figures in the basal and suprabasal layers, ectatic and tortuous papillary blood vessels (Figure 1).

Psoriasis is a dynamic process, with a natural course characterized by different clinical stages (early onset, stabilization, regression, reactivation). Therefore, the histopathological findings will morphologically mirror these changes (6, 7) and may be influenced by several factors such as duration of lesions, psoriasis variant, lesion size and topography, and administered treatment (1, 6-8).

In the early phase, psoriatic lesions show non-specific histological changes such as dilatation and congestion of blood vessels in the papillary dermis and a sparse, perivascular, lymphocytic infiltrate (6-8). The following phase is characterized by the development of focal mounds of parakeratosis with loss of the underlying granular layer as well as exocytosis of neutrophils through the epidermis. Progression in the inflammatory cascade leads to the active lesion with epidermal acanthosis, regularly elongated rete-ridges and increased number of mitoses in the basal and suprabasal layers. Papillary capillaries show increased length and tortuosity, leading to the so-called *squirting papillae* (i.e. formation of a suprapapillary exudate and parakeratosis) (6-8). Neutrophils migrate into the spinous layer

and form spongiform pustules of Kogoj and extend further into the overlying stratum corneum, resulting in the development of Munro's microabscesses; parakeratosis becomes confluent. The scales can be detached, together with the extremely thin suprapapillary area, by mild scraping, causing fine bleeding points of papillary capillaries (i.e. the pathognomonic *Auspitz's sign*). Additional dermal features are papilledema and a moderately dense perivascular infiltrate predominantly composed of lymphocytes (5-8) (Figure 1). In stable psoriatic plaques the rete-ridges may exhibit some thickening at their base, and the amount of parakeratosis diminishes. With rubbing or scratching, changes of lichen simplex chronicus may be observed. Late lesions (resolving or treated plaques) show the presence of compact orthokeratosis, focal hypergranulosis and thickening of suprapapillary plates, while both psoriasiform hyperplasia and the inflammatory infiltrate are significantly less conspicuous (6-8).

As mentioned above, there are variants of psoriasis with particular clinical and histo-



**Figure 1** - Histopathological features of psoriasis. Presence of regular epidermal hyperplasia with hypogranulosis, parakeratosis and neutrophils within the stratum corneum; tortuous papillary blood vessels and lympho-monocytic dermal infiltrate (Haematoxylin & eosin stain; original magnification: x200).

logical features. In pustular psoriasis there is a remarkable increase in the number of neutrophils, with several intraepidermal spongiform pustules of Kogoj and Munro's microabscesses in the overlying parakeratotic layer. Erythrodermic psoriasis may exhibit mild parakeratosis since continuous shedding of scales and superficial dermal blood vessels tend to be more prominently dilated (1, 7, 8). Histological aspects of psoriatic lesions are also influenced by the anatomic location: *mucosal* lesions show less epidermal hyperplasia and scaling; in flexural areas (inverse psoriasis) the scaly component is generally lacking; on acral skin, spongiotic and crusted aspects are prevalent. In contrast, a significant scaling plaque formation is frequent on the scalp (6-8).

The epidermal hyperplasia observed in psoriasis reflects a profound alteration of the balance between the proliferation and differentiation of keratinocytes, as shown by up to 27 times increased mitotic activity and a greater than 7-fold increase in the epidermal turnover time. Such changes are associated with striking variations in the keratin profile expressed by keratinocytes, with overexpression of keratin 16, indicating hyperproliferation of keratinocytes (9). Immunohistochemistry studies provide evidence that psoriatic lesions contain increased numbers of T cells that are CD3+ CD2+ CD45RO+ CLA+, with a subset having activation markers CD25, HLADR, and CD27; several CD4+ T cells produce IFN-gamma, IL-17, and IL-22; some CD8+ cells and an increased number of BDCA-1 CD11c+ inflammatory dermal dendritic cells (2, 3, 10).

## ■ CONNECTIVE TISSUE DISEASES

Autoimmune connective tissue disorders encompass a heterogeneous group of immune-mediated diseases with a variable potential for cutaneous involvement. Skin manifestations of such diseases are changeable, with occasional clinical and histopathological overlapping, thus requiring appropriate clinicopathological correlation (11).

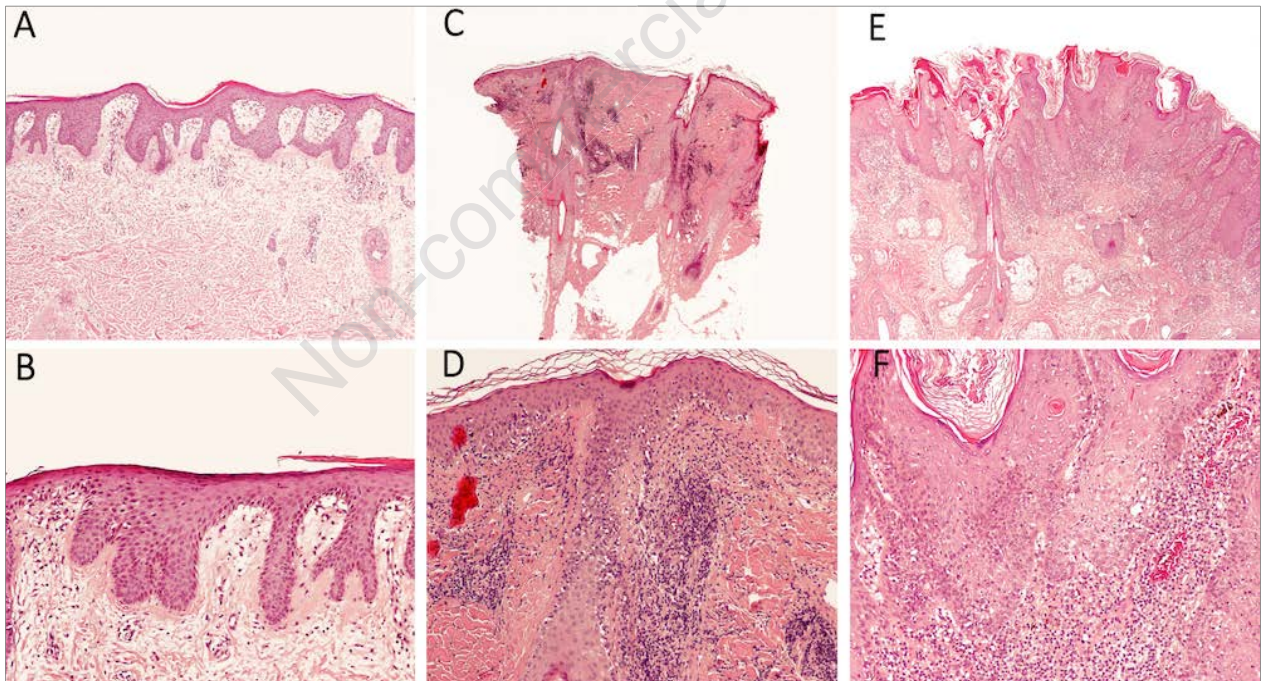
Lupus erythematosus (LE) is a chronic autoimmune disorder of unknown aetiology mainly affecting fertile young women (12). Conventionally, three clinical subtypes are recognized: systemic LE (SLE), cutaneous-limited chronic (discoid) LE (DLE), and subacute LE (SCLE), which is characterized by the association between specific skin lesions and variable, usually mild, systemic involvement (11, 12). Additionally, less common cutaneous variants of LE have been recognized including bullous LE, chilblain lupus, lupus tumidus, neonatal LE, and lupus panniculitis (12). Overlap may occur between histopathological changes observed in cutaneous lesions of the three main LE clinical variants, with the lichenoid reaction pattern (*i.e.*, interface dermatitis) being a significant feature in most of cutaneous LE biopsies (13).

Skin lesions of SLE are characterized by prominent vacuolar degeneration of the epidermal basal layer with only rare *Civatte bodies*; a sparse lymphocytic infiltrate is seen in the superficial dermis, along with edema and mild red blood cell extravasation (14). Perivascular and interstitial neutrophils may be present in the superficial dermis in early lesions of SLE as well as leukocytoclasia with no clear small vessel vasculitis (13, 15). DLE is characterized by a superficial and deep lymphohistiocytic inflammatory infiltrate with stereotypical lichenoid reaction pattern (*i.e.*, prominent vacuolar change of the epidermis and scattered *Civatte bodies*) and adnexotropism (11, 12). Additional histological features of DLE include hyperkeratosis with atrophy of the spinous layer, and keratotic plugging of hair follicles. Marked hyperkeratosis and epidermal hyperplasia are distinctive features of hypertrophic lesions of DLE (16). The histopathological features of SCLE are linked to those of DLE and SLE. Compared to DLE, typical lesions of SCLE exhibit a diminished amount of inflammatory cells and epidermal/follicular changes, with concomitant increasing dermal edema and mucin deposition (13) (Figure 2).

Bullous LE is an uncommon but distinctive manifestation of SLE with striking clinicopathological similarities to dermatitis herpetiformis such as subepidermal blisters with edema and a superficial inflammatory infiltrate composed of neutrophils and lymphocytes (17). Histopathological findings in chilblain lupus include perivascular, superficial and deep lymphocytic infiltrate with overlying vacuolar degeneration of the epidermal basal layer (18). Tumid lesions of chronic LE (*i.e.*, lupus tumidus) have an increased deposition of dermal mucin with subepidermal edema and perivascular lymphocytic infiltrate of variable density and only rare epidermal involvement (19, 20). Histological changes observed in neonatal cutaneous LE resemble those observed in SCLE (21). Lupus panniculitis (*i.e.*, LE profundus), a chronic, recurrent panniculitis, may precede, be as-

sociated with, or follow the occurrence of any cutaneous or systemic manifestation of LE. Histological hallmarks of LE profundus include a lobular panniculitis characterized by a lymphoplasmacytic infiltrate and occasional lymphoid follicles, often associated with mild epidermal and dermal changes of cutaneous LE (22).

Special stains may be useful to highlight thickening of the basement membrane zone and dermal interstitial mucin deposition in LE cutaneous lesions, irrespectively of the clinical variant (23). Clusters of CD123+ plasmacytoid dendritic cells may be observed by means of immunohistochemistry, although the sensitivity and specificity of this finding are variable and depend on the clinical presentation (24). Additionally, in LE direct immunofluorescence of involved skin (*i.e.*, lupus band test) may show IgG and IgM deposition at the base-



**Figure 2** - Histopathological features of skin manifestations during systemic lupus erythematosus. A, B) Cutaneous lesion of SLE with vacuolar degeneration of the epidermal basal layer, only rare Civatte bodies, sparse lymphocytic infiltrate in the superficial dermis, dermal edema and mild red blood cell extravasation (Haematoxylin & eosin stain; original magnification: x100). C, D) scalp lesion of DLE with superficial and deep lymphohistiocytic inflammatory infiltrate with interface dermatitis (vacuolar change of the epidermis and scattered Civatte bodies) and marked adnexotropism (Haematoxylin & eosin stain; original magnification: x100). E, F) lesion of SCLE with superficial lymphohistiocytic inflammatory infiltrate with lichenoid arrangement, vacuolar change of epidermis with scattered Civatte bodies, hyperkeratosis with intermittent atrophy of the spinous layer (Haematoxylin & eosin stain; original magnification: x100).

ment membrane in a variable percentage of cases depending on the clinical subtype, with highest rates of positivity being recorded in SLE (25).

Cutaneous manifestations of dermatomyositis (DM) include nonspecific erythematous, scaly lesions with a predilection for sun-exposed areas, poikilodermatous changes, periungual erythema and telangiectases, Gottron papules, and heliotrope rash (26). Histologically, DM skin lesions exhibit features of cutaneous SLE, namely vacuolar changes of the basal layer with scant apoptotic keratinocytes, a mild chronic infiltrate in the superficial dermis, edema and interstitial mucin deposition (14, 26). Indeed, in most cases, cutaneous lesions of DM and SLE appear to be histologically indistinguishable (14, 26). Gottron papules are distinguished by the presence of epidermal hyperkeratosis and acanthosis, while poikilodermatic skin is characterized by the combination of interface dermatitis with the triad of epidermal atrophy, melanin incontinence, and superficial vessel dilatation (26, 27).

The term scleroderma (Sc) refers to a heterogeneous group of diseases distinguished by abnormal collagen deposition in the skin (28). Two major subtypes of Sc are recognized, namely localized Sc (*i.e.*, morphea; linear Sc) and systemic Sc (SSc). Regardless of the clinical variant, the histopathological hallmarks of Sc include a striking increase in dermal thickness with broadening of sclerotic collagen bundles, also replacing the periadnexal adipose tissue and extending into the subcutis (29). Atrophy of follicular units is a frequent finding, while eccrine coils appear at a higher level than normal in the dermis due to underlying collagen deposition and dermal sclerosis (30). Epidermal changes are nonspecific, with prevalence of epidermal atrophy. A perivascular lymphoplasmacytic infiltrate may be seen through the mid- and lower dermis and subcutis, especially at the borders of lesions. Indeed, early lesions are characterized by a more prominent degree of inflammation, while late lesions are dominated by collagen deposition and dermal sclerosis (29).

## ■ SYSTEMIC VASCULITIDES

Systemic vasculitides are a group of rare diseases characterized by inflammation of the arterial or venous vessel wall, causing stenosis or thrombosis. Clinical symptoms may be limited to the skin or other organs, or may involve multiple manifestations as systemic conditions (31). Primitive vasculitides have been recently re-classified. Among the small vessel vasculitides, the antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are granulomatosis with polyangiitis (Wegener, GPA), eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA) and Microscopic polyangiitis (MPA), while the immune complex (IC) vasculitides are IgA vasculitis (Henoch-Schönlein), cryoglobulinemic vasculitis (CV), urticarial vasculitis (UV) and anti-glomerular basement membrane (GBM) disease (32). Skin findings such as palpable purpura, nodules, urticaria, ulcers, and infarction are clues to the presence of vasculitis. Histological findings of fibrinoid necrosis, infiltration by neutrophils or lymphocytes, and deposition of complement and immunoglobulin may be helpful in reaching a specific diagnosis. However, there is considerable overlap across different conditions. The more relevant skin manifestations will be described in the next paragraphs (32).

The AAV is a group of systemic vasculitis associated with ANCA specific for myeloperoxidase (MPO) or proteinase-3 (PR3), characterized by predominant inflammation of small vessels. Three mechanisms of vascular inflammatory damage can be considered: IC deposition, ANCAs (humoral response), and T-lymphocyte response with granuloma formation (cell-mediated response) (33) leading to activation of endothelial cell, with subsequent vessel obstruction and ischemia of dependent tissue, and consequent haemorrhage in the surrounding tissues with weakening of the vessel wall, and aneurysm formation (Figure 3).

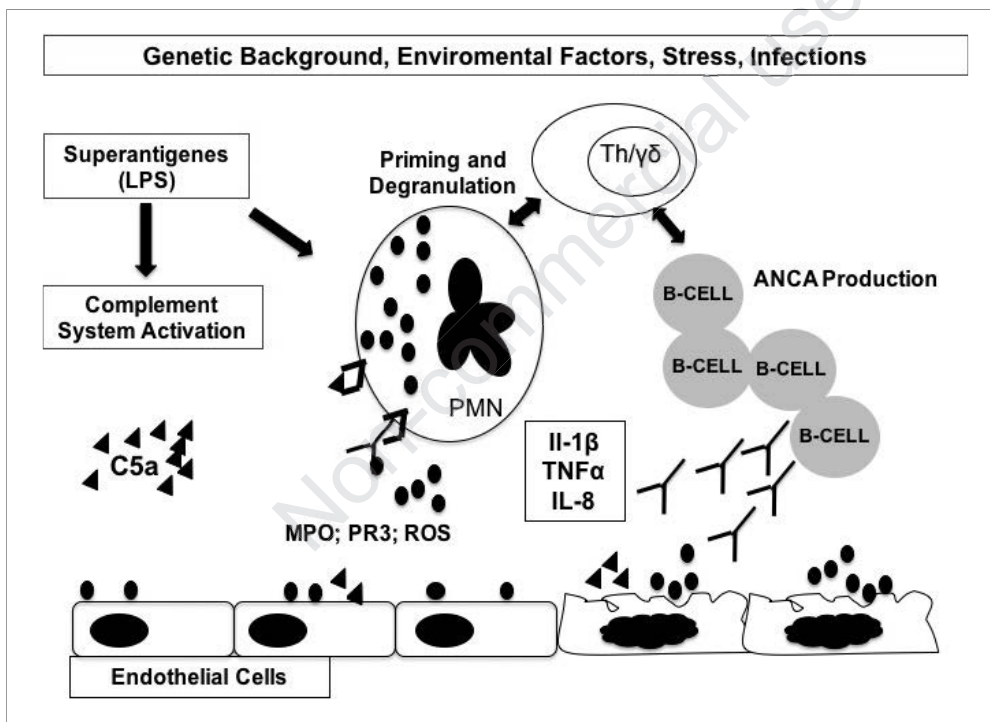
MPA is histologically characterized by small-vessel involvement. Anti-myeloperoxidase antibodies (MPO-ANCA) are of-

ten positive in serum. The skin is affected in 20-70% of patients with purpuric lesions, petechiae, livedo reticularis, and erythema. Histological findings showed perivascular lymphocyte infiltration in the upper dermis and infiltration of lymphocytes and a few neutrophils around small arteries in the mid to deep dermis and diffuse infiltration of histiocytes and lymphocytes in the mid dermis (34).

While no cutaneous lesion is specific for *GPA*, several histopathological entities can be observed, including, in decreasing order: leukocytoclastic vasculitis, granulomatous inflammation, nonspecific ulceration, superficial dermal and epidermal necrosis without inflammation, erythema

nodosum, granuloma annulare, chronic inflammation, and acute inflammatory lesions without vasculitis (35).

EGPA is a multisystemic disorder defined as an eosinophil-rich and granulomatous inflammation. Among the most frequent skin manifestations, subcutaneous nodules and purpura (especially involving the legs) represent a clinical hallmark of the vasculitic phase. A skin biopsy of purpuric lesions generally shows a leukocytoclastic vasculitis. Extravascular granulomas, small and medium-sized vessels vasculitis, and the eosinophilic infiltrates are the typical features. Interstitial and vascular granulomas are composed of eosinophilic necrotic matrix surrounded by giant cells and pali-



**Figure 3** - ANCA-associated vasculitis. Pathogenetic mechanisms proposed for anti-neutrophil cytoplasmic auto-antibody (ANCA)-mediated vascular inflammation. Neutrophils are primed by cytokines to express ANCA antigens (myeloperoxidase and proteinase-3) at the cell surface and then adhere to susceptible endothelium and ANCA antibodies interact with the ANCA antigens, resulting in neutrophil activation. The ANCA-activated neutrophils release factors (e.g. properdin, factor B, proteases, ROS and MPO) cause damage to vascular endothelium and activate the alternative complement pathway with the generation of the powerful neutrophil chemoattractant C5a. This causes an amplification of neutrophil influx and activation with severe necrotizing inflammation of the vessel wall. B, B cells; Th, T helper; IL-1 $\beta$ , interleukin 1 beta; TNF $\alpha$ , tumour necrosis factor alpha; PMN, polymorphonuclear cells; MPO, myeloperoxidase; PR3, proteinase 3; ROS, oxygen radicals.

sading lymphocytes. The vasculitic process mainly affects small and medium vessels (especially small arteries) and is characterized by fibrinoid necrosis of the vessel wall associated or not with granuloma or eosinophilic infiltrates (36).

Urticarial vasculitis (UV) is characterized by a cutaneous presentation resembling urticaria; skin biopsy often shows a predominantly lymphocytic infiltrate with eosinophils and red blood cell extravasation. Occasionally, a true leukocytoclastic vasculitis, mainly involving capillaries and venules, is encountered (37). Peculiar characteristics of the lesions associated with laboratory findings, such as low levels of C3, C4 and C1q, presence of anti-C1q antibodies, high erythrocyte sedimentation rate, suggest diagnosis of UV, although a skin biopsy is required for a definitive diagnosis.

#### ***Cryoglobulinemic vasculitides***

Cryoglobulins are monoclonal or polyclonal immunoglobulins that share the common property of precipitating at temperatures of less than 37°C and re-dissolving on warming (38). The consequent deposition of circulating IC (cryoglobulins and complement) together with hemodynamic and local factors are the main components of the disease pathogenesis (39). Essential mixed cryoglobulinemia (MC) shows a prominent association with HCV infection (>90%). It is a systemic vasculitis (leukocytoclastic vasculitis) affecting cutaneous vessels and multiple visceral organs. CV are characterized by the presence of palpable purpura (40). The histological characteristics include: occlusive thrombotic diathesis comprising eosinophilic refractile deposits within vessel lumina with extension into the intima, with or without associated characteristic granulomatous vasculitic component (41).

#### ***Behçet disease***

Behçet's disease (BD) is an inflammatory multisystem disease of unknown aetiology with unpredictable exacerbations and remissions. Mucocutaneous lesions constitute the hallmark of the disease. Among

classification diagnostic criteria, oral and genital ulcers and skin hyperreactivity are included. The skin pathergy test is considered highly sensitive and specific for BD (42). Together with oral and genital ulcers, various cutaneous lesions can be observed, such as: erythema nodosum-like lesions (15-78%) and papulopustular lesions (28-96%). Lesions such as hemorrhagic blisters, infiltrated erythema, Sweet's syndrome-like eruptions and extragenital ulcerations may also be observed (42). Combinations of various skin lesions are commonly seen in the same patient.

Histological features include: leukocytoclastic vasculitis and lymphocytic vasculitis with extension to focal localized fibrinoid necrosis of vessel walls. Mucocutaneous lesions often present features of leukocytoclastic vasculitis or, in many cases, a neutrophilic vascular reaction without true vasculitis (43, 44).

#### **■ OTHER SKIN MANIFESTATIONS IN RHEUMATOLOGICAL DISEASES**

Rheumatoid arthritis (RA) is a systemic inflammatory disorder that primarily affects the joints, but may exhibit extra-articular manifestations, including cutaneous ones that are the most frequent, and often the initial feature of extra-articular involvement in RA patients (45). They include rheumatoid vasculitis, rheumatoid nodules, granulomatous skin disorders, and neutrophilic dermatoses. Rheumatoid vasculitis displays features of both cutaneous necrotizing venulitis (leukocytoclastic vasculitis) and cutaneous polyarteritis nodosa. Associations with mononeuritis multiplex and bowel involvement has a fatal prognosis, while patients with superficial dermal venulitis without other extra-articular involvement may have a favourable prognosis (45-47).

Histopathology of rheumatoid nodules is characterized by granulomatous tissue reaction pattern. Well-formed necrobiotic granulomas appear within the dermis frequently with deep extension. There is a



surrounding palisade of histiocytes and a mixed infiltrate of lymphocytes, plasma cells, multinucleated giant cells and occasional eosinophils (48).

Lyme disease is a disorder caused by *Borrelia burgdorferi* infection and may involve many organs, including the skin. The early skin lesion around the tick bite is an expanding area of redness on the skin, known as erythema migrans. It shows edema, vascular dilatation, extravasation of erythrocytes and an inflammatory infiltrate of neutrophils. If the causative organisms persist in the skin, there is a superficial and deep perivascular and interstitial infiltrate of lymphocytes and, in many cases, plasma cells and rare eosinophils, especially at the site of tick bite (49). A special stain is the Warthin-Starry silver, used to identify the spirochetes in the papillary dermis at the dermoepidermal junction. Diagnosis may be confirmed by using an indirect immunofluorescence or immunoperoxidase techniques (49).

*Sarcoidosis* is a systemic disease characterized by non-caseating granulomas that can involve any tissues or organs. Cutaneous sarcoidosis develops in 20-35% of patients with systemic sarcoidosis although it may represent the only clinical manifestation of the disease. Recognition of cutaneous involvement is important because it provides an easier and fast diagnosis since the skin represents an accessible tissue source for histological examination. The lesions may show different morphologies, so that differential diagnosis can be difficult, the disease being known as the great imitator (50). The cutaneous eruptions are divided into specific, distinguished by classic non-caseating granulomas, and aspecific when they arise as a reactive process without granuloma formation. Among the former, the most common clinical manifestation is papular sarcoidosis, which usually appears on the face although it can occur anywhere. Papules are often associated with acute disease (51). The plaques, instead, are localized at the trunk, face and extensor surfaces of the arms and legs and they often arise during chronic and extrathoracic sarcoidosis (52, 53). Some patients may present lu-

pus pernio. In a small percentage of cases, it results in a mucous infiltration obstructing the upper respiratory airways (54). The lesions can develop in pre-existent areas of trauma and scars and can be confused with keloids (55). The most common aspecific lesion is erythema nodosum. It is a benign condition with >80% complete regression within two years (56). Less common presentations of cutaneous sarcoidosis are verrucous, annular, lichenoid, psoriasiform, subcutaneous, ichthyosiform ulcerative, atrophic, hypopigmented, erythrodermic, nail and the alopecia associated variants (57-59). The great clinical variety of lesions also reflects the variety of histopathological characteristics examined. Granulomas are characterized by an infiltrate of lymphocytes, epithelioid cells, giant cells, neutrophils and plasma cells. In many cases Schaumann bodies, necrosis and fibrosis can be found. Epidermal changes include atrophy, parakeratosis, acanthosis and telangiectasia (60). The number of granulomas is not related to the extension or severity of the disease (61). No differences have been found in the depth and cellular density of granulomas between patients with papules and those with plaques. In both groups the infiltrate appears to be superficial with moderate density. In contrast, in patients with nodules, granulomas are deeper, while patients with scar sarcoidosis seem to have both deeper and heavier infiltrates (62).

Pyoderma gangrenosum (PG) is an immune-mediated cutaneous disease, characterized by the development of one or more necrotic ulcers with distinctively ragged, undermined, erythematous borders (63, 64). Ulceration may be preceded by the occurrence of papulopustular or nodular lesions (65). Development of PG lesions may occur on sites of previous trauma (*i.e.*, pathergy) (64). Clinical subtypes of PG include the common ulcerative presentation as well as the bullous, pustular, vegetative, and the rare superficial granulomatous variants (66). Histopathological findings in PG are variable, being contingent on lesion duration and anatomic location; accordingly, a diagnosis of PG or exclusion thereof should not rely only on histological

findings, but it always requires appropriate correlation with clinical and anamnestic data (64, 66).

A histological classification of PG has been proposed, which identifies ulcerative, pustular, bullous, and vegetative PG lesions (67). Such histological subtypes, however, may be interpreted as different stages of the same disease, accounting for significant overlapping observed between different subtypes. Early lesions of PG are characterized by follicular and perifollicular inflammation along with development of intradermal abscesses (65). Later, necrosis of superficial dermis and epidermis ensues, resulting in ulceration (65). Fully developed PG ulcers are almost indistinguishable from ulcers due to other causes, with mixed inflammatory cells and abscess formation being observed at the base of the lesion (63, 65). Superficial edema at the advancing edge is a frequent finding, along with a tight perivascular lymphoplasmacytic infiltrate, at times with signs of evident vasculitis. Pustular lesions of PG are characterized by subepidermal edema and a diffuse dense neutrophilic infiltrate, resulting in subcorneal pustules formation (63, 64); in bullous lesions of PG, conversely, massive subepidermal edema leads to subepidermal bullae with neutrophils (67). Finally, a special acknowledgement should be given to the vegetating subtype, the distinctive features of which include pseudoepitheliomatous hyperplasia, dermal abscesses with sinus tracts formation, and an associated palisading granulomatous infiltrate (63, 64, 67).

## ■ CONCLUSIONS

Rheumatological systemic autoimmune diseases include, in most instances, skin manifestations as a key component of the disease. Rheumatologists often have the primary privileged position of suspecting, recognizing and treating extra-articular manifestations of autoimmune diseases as skin diseases (68). In this context, it is useful for the rheumatologist to better understand skin diseases and their histopathological features (69). Evaluation of skin

biopsy specimens can be helpful not only to confirm the diagnosis of skin disease in both classic and atypical clinical variants, but also to further improve knowledge of the pathogenesis and the close link between skin and articular diseases (70).

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