Cutaneous manifestations in rheumatoid arthritis

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Summary

Rheumatoid Arthritis (RA) is a potentially invalidating, immuno-mediated, chronic inflammatory disease affecting selected joints. Its numerous extra-articular manifestations predominantly involve skin, with a number of clinical manifestations (1).

Non-specific cutaneous manifestations

Non-specific cutaneous changes can be identified (Figure 1) which are characterized by diffuse skin atrophy with edema of the skin covering interphalangeal joints, a bluish coloring of the fingertip that may suggest rheumatoid vasculitis and palmar erythema presentation (2). In literature, a case of localized acral cutis laxa in a patient with severe rheumatoid arthritis was reported (3). Among non-specific manifestations which may occur in patients with RA, there are nail changes, including onychorrhexis, clubbing, erythema and periungual telangiectasias, bleeding associated with nail bed thrombosis, lunula erythema, onycholysis and pterygium inversum (2).

Raynaud’s phenomenon can affect 5 to 17% of patients with RA and its onset can be predictive of a more aggressive course of the disease (4,5). Clinical manifestations of chronic ulcers localized in the lower limbs in patients with RA are also reported in literature; these ulcers are characterized by a vascular-based, venous but also mixed (arterial and venous) multifactor etiopathogenesis, as well as by specific presentations of pyoderma gangrenosum and necrotic vasculitic lesions (6).

Chronic spontaneous urticaria can be associated with RA according to the pathogenetic hypotheses.

Rheumatoid Arthritis (RA) is a potentially invalidating, immuno-mediated, chronic inflammatory disease affecting selected joints. Its numerous extra-articular manifestations predominantly involve skin, with a number of clinical manifestations (1).

KEY WORDS: rheumatoid arthritis; spondyloarthritis; neutrophilic dermatoses; cutaneous vasculitis; TNF-α antagonists.

Figure 1 - Main non specific cutaneous manifestations in patients with Rheumatoid Arthritis (RA).
defined by Grattan et al. in 2002 and still widely accepted (7).

Urticarial vasculitis is a chronic-recurrent disease which is typically characterized by wheals that usually persist for more than 24 hours, accompanied by burning or itchy symptoms, that evolve into ecchymoses and hyperpigmentation, that may be associated with a number of skin manifestations characterizing cutaneous small-vessel vasculitis; it can be associated with more or less severe systemic symptoms, including fever and other extra-cutaneous symptoms (lymphadenopathy, hepatosplenomegaly, abdominal pain, dyspnoea, chronic obstructive lung disease, glomerulonephritis, conjunctivitis, episcleritis and uveitis) (8).

With regard to this, two different profiles may be identified: a normocomplementemic form (NUV) characterized by a low-to-absent systemic involvement and a benign course, and a hypocomplementemic form (HUV) characterized by a multisystemic involvement and a more aggressive course, with the presence in the blood stream of antibodies directed against the collagen-like region of C1q, and consequent C1q reduction and complement cascade activation (8, 9) (Figure 2).

Moreover, RA is associated with an increased risk of epithelial non-melanoma skin cancer (10).

### Specific cutaneous manifestations

Specific RA-associated cutaneous manifestations (Figure 3) are characterized by the appearance of subcutaneous nodules, including classical rheumatoid nodules, the peculiar accelerated rheumatoid nodulosis, as well as rheumatoid nodulosis (2). The numerous group of specific manifestations also includes rheumatoid vasculitis, neutrophilic dermatoses and granulomatous dermatitides.

#### Subcutaneous nodules

**Classical rheumatoid nodules**

Classical rheumatoid nodules are the most common extra-articular manifestation in patients with RA; they are subcutaneous lesions, skin-like colored, with a diameter generally ranging from >5mm to several centimeters. They typically appear in RA, usually in the advanced phase and there is a strict association with HLA DR4 and DRB1 haplotypes. The characteristic areas affected are the extensor surfaces of the forearms, the back of the hands, the occipital regions, the auricular regions and the nasal pyramid, but these nodules can also affect other regions. From the histological point of view, there is a characteristic distribution in three areas: a central necrotic area of degenerated collagen, an intermediate area made of macrophage palisade and a peripheral area characterized by a mainly lymphohistiocytic and plasmacellular infiltration surrounding the remaining part of the nodule (2).

A number of pathogenetic hypotheses have been formulated until the publication of a paper in 2003 which documented high levels of TNF-alpha and especially of interleukin 1-beta in rheumatoid nodules, to support the autoinflammatory and Th1-mediated pathogenetic hypothesis (11).

The treatment of rheumatoid nodules is not required and usually there is a spontaneous regression or reduction when a specific RA treatment is administered. Nodules can sometimes remain or even worsen with the treatment; in this case, surgical excision may be considered especially for lesions which are considered to be invalidating (2).

Figure 4 reports the main differential diagnoses to be considered when clinically approaching a patient with RA and nodular lesions.

**Accelerated rheumatoid nodulosis**

Accelerated rheumatoid nodulosis is a particular variant characterized by the onset of nodules which cannot be distinguished either clinically or histopathologically from classical rheumatoid nodules; they occur in RA patients being treated with methotrexate (8-11%).
Other medicinal products have been described as triggers, including azathioprine, leflunomide, but also anti-TNF-α drugs; typically, the areas involved are metacarpophalangeal and proximal interphalangeal joints. From the therapeutic point of view, a good response to hydroxychloroquine and colchicine was documented (12, 13).

### Rheumatoid nodulosis

Rheumatoid nodulosis is characterized by usually multiple rheumatoid nodules; it is associated with clinically and radiologically mild joint manifestations, and with the presence of subchondrial bone cysts in the hands and feet and a usually benign course, with no or mild systemic involvement (14).

### Rheumatoid vasculitis

Another cutaneous manifestation which is considered to be disease specific is rheumatoid vasculitis (Figure 5). Its incidence is supposed approx. 0.1 to 5.4% in patients with RA. The skin is the most commonly affected organ, with manifestations generally occurring in patients with long-term disease and positive rheumatoid factor (RF) and anti-citrullinated peptide antibodies. The clinical presentation is cutaneous small-vessel vasculitis: this dictum is preferable to necrotizing vasculitis which is merely descriptive or to the histopathologic one of leukocytoclastic vasculitis. The clinical polymorphism is typical: purpura, bruise-like lesions, ulcerative-necrotic lesions, until occurrence of an evident ulcer usually covered with eschars. The presentation may be similar to urticarial vasculitis. The course is usually benign, but a systemic involvement is possible leading to relevant morbidity and mortality (8).

Bruise-like and ulcerative-necrotic digital lesions are the most common, and most frequently occur in the advanced phase, but can also be early manifestations (15). From the histopathologic point of view, it is possible to observe fibronoid necrosis of the vassal wall, proliferation of intima with perivasal inflammatory infiltration, suggesting the typical leukocytoclastic pattern, showing neutrophil granulocytes and nuclear dust surrounding the small dermal vessels; direct immunofluorescence on recent lesion reveals immunoglobulin perivasal deposits, predominantly IgG, and complement (C3).

The cutaneous lesion pathogenesis has a Type III hypersensitivity mechanism, due to immune complexes. Immune complexes activate the complement, triggering chemotactic recruitment of neutrophils; actually the physiopathology is more complex, with a co-factorial role of T-CD4+ lymphocytes. Moreover, a direct damage on endothelium occurs, and the role of antiphospholipids antibodies which can lead to coagulation activation is still being studied; coagulation involvement may be an ancillary physiopathologic mechanism in the pathogenesis of cutaneous lesions (16). The therapeutic armamentarium in case of rheumatoid vasculitis (Figure 6) includes, besides systemic corticosteroids, the possible use of medicinal products, i.e. dapsone, having neutrophil anti-chemotactic activity, and a classical immunosuppressor, cyclosporine, that can be used in the treatment of dermatological manifestations; on the other hand, cyclophosphamide is certainly the gold standard in...

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**Figure 4** - Classical rheumatoid nodules: main differential diagnoses.

Other medicinal products have been described as triggers, including azathioprine, leflunomide, but also anti-TNF-α drugs; typically, the areas involved are metacarpophalangeal and proximal interphalangeal joints. From the therapeutic point of view, a good response to hydroxychloroquine and colchicine was documented (12, 13).

**Figure 5** - Rheumatoid vasculitis: main clinical features.

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Neutrophilic dermatoses

With regard to the big chapter of neutrophilic dermatoses, a starting point can be the recently published classification reported in Figure 7 referring to the approach by Wallach's French group, in which the following forms of neutrophilic dermatoses are distinguished: epidermal, dermal, hypodermal and mixed (17).

Neutrophilic dermatoses are a wide group of diseases characterized by neutrophil accumulation in the skin and in extra-cutaneous sites.

Pyoderma gangrenosum

Around 12% of patients with pyoderma gangrenosum, a rare neutrophilic dermatosis with chronic evolution, develop seropositive AR (18); at onset pyoderma gangrenosum typically shows one or more sterile pustules which rapidly evolve in painful ulcers, variably wide and deep, characterized by well-defined and raised edges of erythematous-purple coloring (19).

Figure 8 reports the main clinical variants of pyoderma gangrenosum: besides the classical ulcerative form, also the pyoderma gangrenosum vegetans – that is often the evolution of an ulcerative lesion – and bullous Pyoderma gangrenosum are reported (20, 21).

The pattern of the so-called neutrophilic disease, with extra-cutaneous neutrophilic involvement, is particularly interesting; it is rarely observed and its incidence is unknown; any organ can be involved, but usually joints are specifically affected: in the synovial fluid of these patients neutrophilic polymorphonuclear leukocytes (PMNs) are found, with seronegative destructive polyarthritis and acute monoarthritis. The systemic involvement can also affect lungs (with PMNs in BAL), kidneys (nephrotic syndrome, more rarely glomerulonephritis), bones (chronic-recurrent multifocal osteomyelitis, peculiar in children), central nervous system (aseptic meningitis, encephalitis, cerebral abscesses), eyes (uveitis, episcleritis, ulcerative keratitis); neutrophilic disease can also be associated with multi-organ aseptic abscesses affecting liver, spleen, pancreas, lymph nodes and the gastro-enteric system (22, 23).

The physiopathological mechanism proposed in neutrophilic dermatoses has been recently studied: innate immunity-regulating gene mutations can induce the inflammosome assembly, a sort of molecular platform responsible for activating caspase-1, the enzyme determining the proteolytic clivage of functionally inactive pro-interleukin-1-beta, into interleukin 1-beta, a cytokine regulating a number of mechanisms including the stimulus to release chemokines and proinflammatory cytokines. This process would translate into a chemotactic recruitment of neutrophils, that is central pathomechanism of neutrophilic dermatoses: this is the physiopathological model of autoinflammation applied to neutrophilic dermatoses (17, 24).

An important aspect generally concerning neutrophilic dermatoses, but that can be also observed in association with RA, is the overlapping presentation of several neutrophilic dermatoses. Some cases were reported showing association between pyoderma gangrenosum and Sweet's syndrome, and between pyoderma gangrenosum and rheumatoid neutrophilic dermatitis (25, 26). Another aspect to consider is the possible onset of pyoderma gangrenosum in patients with RA being treated with an anti-TNF-α agent, which can be explained as a paradoxical effect or as the inability of the anti-TNF-α treatment to prevent the onset of a pyoderma gangrenosum (27).

Among skin manifestations occurring in RA, the PAPA syndrome (Pyogenic sterile Arthritis, Pyoderma gangrenosum, Acne) should be mentioned: this is a rare autosomic dominating form, for which two mutations in exons 10 and 11 of PSTPIP1 gene on chromosome 15 have been described, which translate into an abnormal activation of the innate immune response associated with the related immunopathological events (28).

The acronym SAPHO (Synovitis, Acne, Pustolosis, Hyperostosis, Osteomyelitis), defines a syndrome characterized by the association, that can be also not simultaneous, of skin and osteoarticular manifestations, with articular presentation characterized by pain onset on the anterior thoracic wall. Another very interesting recent case is that of a PA-...
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PASH syndrome, considered as a new pathological variant from the combination of PAPA and PASH (Pyoderma gangrenosum, Acne, Suppurative Hidradenitis) syndromes, especially interesting from a dermatological point of view, being characterized by a new mutation of exon 11 of the PSTPIP1 gene (29) (Figure 9).

Sweet’s syndrome

Sweet’s syndrome, also known as “acute febrile neutrophilic dermatosis”, was first described in 1964 and is clinically characterized by the onset of fever, neutrophil leukocytosis, and painful plaque erythematosus skin lesions, preferably localized on the cervical area, with a tendency to surface detachment. A series of atypical variants may be possible, including bullous, pustular, subcutaneous and giant cellulitis-like forms (30). It is rarely seen in patients with rheumatoid arthritis, and is histologically characterized by a dense neutrophilic infiltrate in the superficial derma, with considerable edema; another possible variant is the “histiotic” form, while the presence of eosinophils in the infiltrate suggests a drug-induced form. In literature, the case of a patient with a recurrent form of Sweet’s syndrome, associated with rheumatoid arthritis treated with etanercept is reported to have achieved good clinical response (31).

Rheumatoid neutrophilic dermatosis

Rheumatoid neutrophilic dermatosis – closely related to RA – is clinically polymorph, with the appearance of papules, erythematous plaques, nodules and also urticarial lesions having a typical symmetric distribution, on joints, on extensor surfaces of the extremities and the trunk; the infiltrate – just like in Sweet’s syndrome – is localized in the derma, without vasculitis (32).

Interstitial granulomatous dermatitis

Interstitial granulomatous dermatitis is a distinct entity from the nosological point, having a chronic-persistent clinical course; in the past, it was also defined as interstitial granulomatous dermatitis with arthritis (currently considered as a distinct nosological entity), in order to highlight its association with rheumatic diseases (33). From the clinical point of view, it is characterized by papules and erythematous plaques, erythematous-purple lesions, in 10% of the cases with a typical “cord-like” appearance, with symmetric distribution; the most affected sites being the axillary area, the trunk and the medial surface of thighs. From the histological point of view, it is characterized by the presence of interstitial histiocytic granulomas without vasculitis and mucin deposits (34). In literature, the presence of joint manifestations is reported in over 50% of patients, with spondyloarthritis, RA or common arthralgic manifestations (35).

Cutaneous manifestations associated with spondyloarthritis

Figure 10 summarizes the main skin manifestations associated with spondyloarthritis.

It is interesting to highlight that a percentage of patients ranging from 10 to 25% of cases of ankylosing spondylitis have a concomitant pattern of psoriasis and that the presence of psoriasis is related to a more aggressive clinical course of the rheumatological disease (Figure 11).

Cutaneous manifestations associated with spondyloarthritis

Figure 10 - Cutaneous manifestations associated with spondyloarthritis.

Figure 11 - Ankylosing Spondylitis: clinical features.
In conclusion, the BADAS syndrome (Bowel-Associated Dermatosis-Arthritis Syndrome) should be briefly mentioned: an interesting pattern characterized by arthritis, often spondyloarthritis, proteiform skin manifestations resembling those of different neutrophilic dermatoses (17, 36, 37).

References

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