SKIN MANIFESTATIONS OF RHEUMATOID ARTHRITIS (RA)

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease presenting, not only with musculoskeletal disorders, but also with various extra-articular manifestations, such as cutaneous findings. These include rheumatoid nodules, accelerated nodulosis, purpuric rash and vasculitis especially in long-standing seropositive patients. Rash in adult -onset Still's disease, Felty's syndrome and drug – induced skin side - effects or neutrophilic dermatoses such us pyoderma gangrenosum, can also occur. The current article discribes in a precise and concise way the above skin entities, so that the clinical physician acquires the necessary insight to recognise these dermatological lesions, better understand the underlying disease process and thus provide optimal treatment and patient care.

INTRODUCTION

RA is an autoimmune, systemic , inflammatory disease that affects the joints and extra-articular tissues. Extra-articular or systemic manifestations are seen in up to 50% of patients. They generally predict a poor prognosis and an increased (more than double) risk of morbidity and mortality [1].

Today the frequency and severity of systemic manifestations are decreasing, probably because of treatment improvement. But, treatment practices are also associated with adverse effects that mimic the extra-articular manifestations of RA, such as osteoporosis, infections, pneumonitis, neurological complications.

The magnitude of clinical activity in RA patients reflects the overall burden of disease and is the variable which influences prognosis and treatment decisions the most. Joint inflammation is the major contributor to mobility impairment and is the most important cause of functional disability in the disease. Systemic (extra-articular) manifestations have even greater prognostic significance [2].
In this review we will focus exclusively on the dermatological manifestations of RA.

SKIN

The skin lesions of RA can be summarized in the following manifestations: Rheumatoid nodules, rash in adult-Onset Still's Disease (AOSD), purpuric and drug rashes, neutrophilic dermatoses and vasculitis manifestations, which are described below.

Rheumatoid nodules

They occur in 20%-30% of patients with active, seropositive RA, while nodules rarely precede arthritis.
They are most commonly developed on the extensor surfaces and pressure areas, including the forearm, Achilles tendon area, the sole of the foot and the joints of the fingers. Nodules grow singly or in groups (Fig. 1). Appearance of nodules in unusual locations can pose a major diagnostic dilemma such as in the sacrum, soleus and occipital bone (in bedridden patients), except in rare cases involving the heart, lungs, vocal cords or the sclera of the eye [3].

Upon examination, rheumatoid nodules are usually subcutaneous and stable. They may be mobile or attached to the underlying structures. Because nodules may be seen with other forms of inflammatory arthritis, biopsy may be needed to confirm the diagnosis in selected cases [4].

Other conditions that present with arthritis and nodules are SLE, gout (gouty tophi), multicentric reticulohistiocytosis (MRH), rheumatic fever, sarcoidosis, etc.

Histologically, rheumatoid nodules are characterized by a central area of necrosis surrounded by a corona of palisading fibroblasts, which are surrounded by a collagenous capsule with perivascular collections of inflammatory cells and accumulation of cells that expand centrifugally, leaving central necrosis of the connective tissue matrix.
Histologically the nodule consists of small inflamed arterioles [5] suggesting that it is a form of small vessel vasculitis. This is associated with other forms of extra-articular disease such as cardiovascular disease. A risk factor for the development of subcutaneous nodules is smoking, especially in men [6]. Rheumatoid nodules may resolve either spontaneously or with treatment. Increased nodular disease is an uncommon but well-recognized complication of methotrexate therapy, often occurring paradoxically in patients with well-controlled disease [7].

Fig.1. *Rheumatoid nodules: hand and forarm.*

Rash in adult-onset Still's disease.

It is a *non-pruritic* macular or maculopapular evanescent rash appearing during quotidian fever and disappearing in afebrile intervals. It is a 'salmon-coloured' lesion, mainly on the trunk (Fig. 2) and extremities, but may also appear on the palms, soles or rubbing areas (*Koebner* phenomenon*)*.
It should also be looked for in areas pressed by clothing or belt, such as under the breasts or even in areas of skin that have been irritated or scratched with nails or friction areas a sharp object (isomorphic response).
Adult-onset Still's disease is a form of rheumatoid arthritis. It is an autoinflammatory disease characterized by arthralgia or arthritis (erosive), generalized lymphadenopathy and hepatosple-nomegaly.

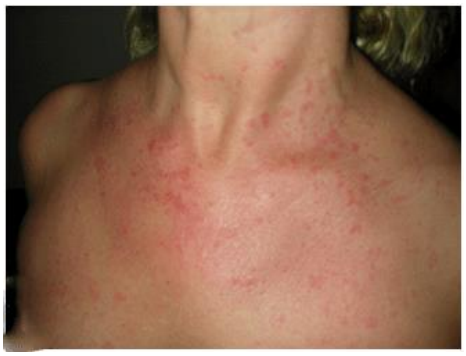

Fig. 2. *Rash in Still's Disease on trunk*

Laboratory findings are characteristic but not pathognomonic, hense their presence along with clinical manifestation is required to establish the diagnosis after exclusion of alternate causes. They include a marked inflammatory leucocytosis, nor mocytic normochromic anaemia and thrombocytosis as well as an increase in liver enzymes and inflammatory markers (CRP, ESR), as well as particulary high ferritin levels (more than 5 times the upper limit of normal).

Purpuric rashes

A purpuric rash is characterized by the presence of durk purple-colored lesions (4-10 mm in diameter) from bleding into the skin which do not blanch on pressure.
Secondary amyloidosis can also occur and exacerbate long-term uncontrolled inflammatory RA. The purpura of amyloidosis can be confused with skin fragility and "senile purpura". It appears on the lateral aspect of upper and lower limbs. Purpuric rash is also observed in patients who have received long-term glucocorticoid treatment. The diagnostic investigation of secondary amyloidosis in RA is based on the presence of renal disease, especially proteinuria, or malabsorption diarrhoea in a patient with long-term disease [10,11].

RA medications can cause skin petechiae due to platelet dysfunction, administration of steroids, NSAIDs or methotrexate or glucocorticoid – induced capillary fragility. Petechiae may also be a manifestation of thromobocytopenia from disease-modifying drugs, such as MTX, leflunomide or sulfasalazine [12,13].
The potential occurrence of the full spectrum of allergic reactions from RA treatment drugs is expected but is beyond the scope of this review.

Vasculitis in RA

It is one of the most serious skin manifestations of RA. It can present in many forms and with multiple cutaneous findings, such as livedo reticularis, leukocytoclastic vasculitis or vasculitis of small and medium vessels causing from nail fold infracts to a deep, erosive, scarring pyoderma (pyoderma gangrenosum).

Livedo reticularis, with its characteristic mottled reticulated vascular pattern (most prominent in the lower limbs), should raise concern for middle vessel vasculitis or a disease-related internal solid organ vasculitis, such as SLE or antiphospholipid antibody syndrome (APS) [14] (Fig. 3**)**

Vasculitis. In RA, vasculitis of small or medium vessels may occur. Its incidence in recent years has been reduced by the improvement of treatment [15]. Vasculitis in RA causes vascular occlusion and subsequent ischemic damage. The skin and peripheral nervous system are usually the most commonly involved organs. The lungs, gastrointestinal system, kidney and CNS are affected less frequently.

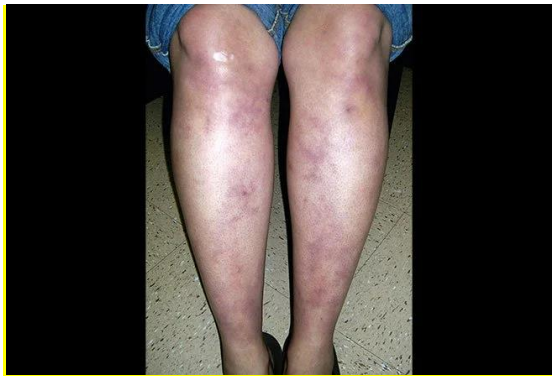

Fig. 3. *Livedo reticularis on lower limbs*

Risk factors. RA vasculitis is associated with male gender, RF positivity (high titer), smoking, long-term disease, extra-articular manifestations, subcutaneous nodules and radiological articular erosions.
Indications for the development of vasculitis are livedo **r**eticularis in the skin, circulating immune complexes and cryoglobulins as well as low serum complement [16].

Clinical picture.

Rheumatoid vasculitis can clinically occur in the following forms:

Leukocytoclastic vasculitis with the clinical manifestation of palpable purpura is one of the most common cutaneous vasculitic lesions of RA (Fig. 4). It may also be of pharmacogenic etiology. All patients should be examined for possible systemic involvement of internal organs, especially the kidneys, and for the presence of neurological disorders. Ischemic skin ulcers (Fig. 5) are often seen with severe systemic involvement and prognosis [17,18].

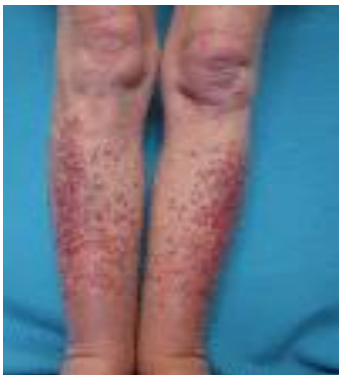

Fig. 4. *Leukocytoclastic vasculitis of the lower extremities*

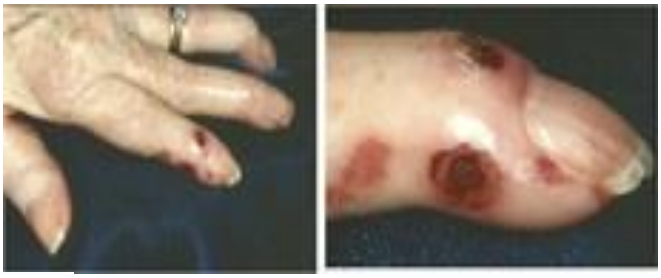

Fig.5. *Cutaneous finger ulcers*

- **Arteritis** with nail infarcts (Fig. 6), splinter hemorrhages, and possible gangrene.
- **Skin ulcers**, including gangrenous pyoderma (Figs 7,8).
- **Peripheral neuropathy** as either multiple mononeuritis or polyneuropathy, associated with "glove or sock" type sensory disorders. Multiple mononeuritis is indicative of an unfavourable prognosis [19].
- **Coronary arteritis**

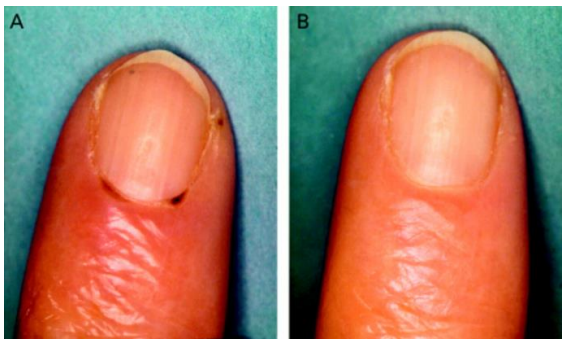

Fig. 6. *Arteritis with nail infarcts*

- **Pulmonary capillaritis**
- **Visceral arteritis** is similar to polyarteritis nodosa, involving the viscera or solid organs, without microaneurysms.

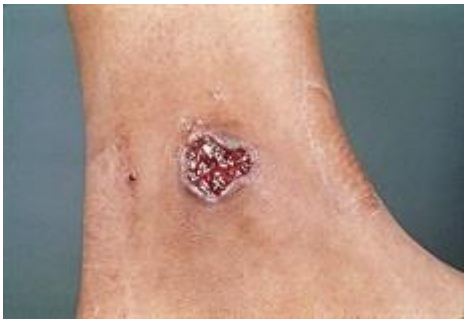

Fig. 7. *Cutaneous leg ulcer*

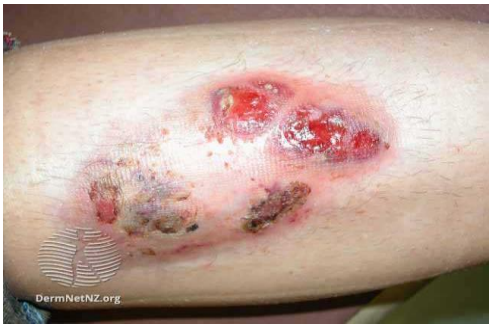

Fig. 8. *Ulceration, rupture of pustules with well-defined purple border*

Intestinal vasculitis usually manifests as abdominal pain due to bowel obstruction. In biopsy or tissue excision, histopathology in rheumatoid vasculitis usually shows a "panarteritis" with fibrinous necrosis or an obstructive endarteritis (gangrene) [20].

Treatment of rheumatoid vasculitis begins with conventional DMARDs, which can be used in splinter hemorrages or palpable purpura. High doses of glucocorticoids and cytotoxic drugs are reserved for threatening conditions. Therapeutic success has been achieved with biologic DMARDs, including TNF inhibitors and rituximab. Prognosis remains relatively poor with 5-year mortality ranging from 26% to 50% [15,21]. The use of biologic agents has significantly improved disease outcomes in recent years.

Accelerated rheumatoid nodulosis. This dermatopathy has been associated with methotrexate administration and presents as an accelerated rate of development of multiple rheumatoid nodules, despite improvement of the underlying joint disease. Histologically, these nodules do not differ from rheumatoid nodules. The fingers are the most common site of involvement, but elbows, knees and feet can also be affected, as well as other organs, including the lungs and larynx (Fig. 9) [22]. Other drugs that have been implicated are azathioprine, etanercept, infliximab and tocilizumab.

Although the exact pathophysiology of these lesions is still unclear, it appears that methotrexate increases monocyte production of adenosine both intra- and extra-articularly, promoting the formation of multinucleated giant cells through stimulation of the A1 receptor.

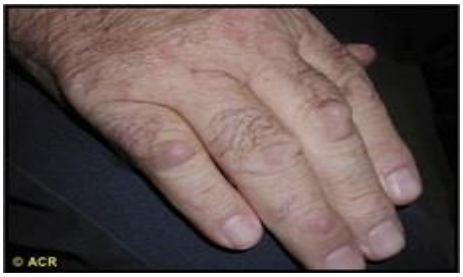

Fig.9. *Accelerated rheumatoid nodulosis on hand from methotrexate*

Treatment is limited, as there are no specific recommendations from the literature. According to available evidence, it is indicated to discontinue the underlying drug and consider other drugs to better control the underlying arthritis [23].

Neutrophilic dermatoses

Neutrophilic dermatoses are a heterogeneous group of non-vasculitis, inflammatory, skin diseases, presenting mainly with sterile lesions and predominantly neutrophilic skin infiltrates. They may be idiopathic or secondary to rheumatoid arthritis, malignancy or other systemic inflammatory conditions such as inflammatory bowel disease. Some of the

neutrophilic dermatoses found in rheumatoid arthritis include: gangrenous pyoderma, rheumatoid neutrophilic dermatoses and Sweet's syndrome.
Gangrenous pyoderma is a refractory skin disruption which usually presents as a deep ulcerative lesion, usually affecting the lower legs in women [24].

Rheumatoid neutrophilic dermatoses are rare, but they are usually found in patients with long-term severe rheumatoid arthritis as scattered papular, nodular, urticarial, or plaque lesions on the limbs, trunk and extensor surfaces. They are usually asymptomatic and resolve without treatment within weeks [25].
Sweet syndrome is a neutrophilic dermatopathy that can be idiopathic, or associated with drugs or malignancy. It is characterized by systemic symptoms such as fever with acute onset of multiple painful tender erythematous plaques or nodules mainly on the limbs, trunk and face (Fig. 10) [26].

Other non-neutrophilic dermatopathies in RA include: palmar erythema, dry skin, Raynaud's phenomenon, skin atrophy, nail ridging and onycholysis.

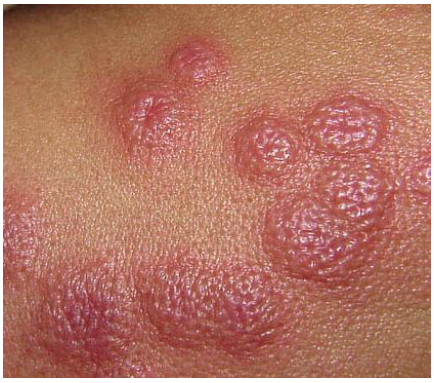

***Fig. 10**. Sweet syndrome, erythematous plaqueson upper back*

Skin manifestations associated with RA treatment

Treatment of RA involves the use of DMARDs and biologic agents. However, some of them are associated with cutaneous adverse effects such as accelerated rheumatoid nodulosis, oral ulcers or increased hair loss due to methotrexate, while the administration of injectable biologic agents may cause the development of a delayed-type hypersensitivity reaction at the injection site, which is usually self-limiting and decreases with continued use [27]. Administration of biologic agents has also been associated with worsening of existing psoriatic disease, or even the development of new lesions in a patient with no history of psoriasis [28]. Treatment of these lesions should be performed with appropriate modification of the dose of the imlpicated drug taking into consideration the control of the underlying arthritis and the severity of the resulting skin eruption [29]. Biologic agents have been associated with an increased risk of developing skin cancer, particularly squamous cell carcinoma [30].

Felty syndrome

Felty syndrome (FS) is characterized by the triad: arthritis, leukopenia and splenomegaly [31]. It occurs in 1% of patients with RA, usually after long-term disease, and affects almost exclusively the Caucasian race [31, 32]. Patients with Felty syndrome tend to have more frequently positive RF, circulating immune complexes, rheumatoid nodules and erosive arthritis, despite the presence of less active and/or inactive synovitis than other RA patients [33,34]. They usually present with extra-articular manifestations, such as cutaneous lesions which include rheumatoid nodules, occurring in 76% of patients, and secondary leg ulcers associated with venous insufficiency and resultant hyperpigmentation (Fig. 11). Patients have an increased risk of malignant melanoma in the first year of diagnosis, as well as lymphomas and leukaemias, as do all RA patients [35]. The association of FS with malignancy has been

attributed to neutropenia, spleen dysfunction, relatively aggressive rheumatoid disease and increased susceptibility to Epstein-Barr infection [35]. FS patiens have a poor prognosis and a mortality rate of up to 25%, mainly due to sepsis [36].

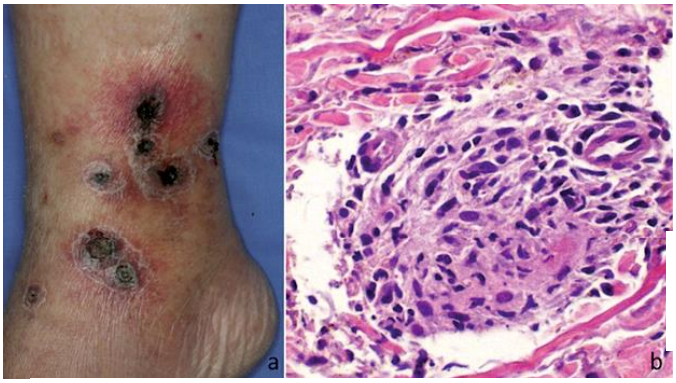

Fig. 11. *Felty syndrome, skin ulcer of the lower limb*

Conclusion

RA is a systemic inflammatory disease associated with the development of cutaneous manifestations especially in patients with long-standing seropositive disease with poorer prognosis. These include rheumatoid nodules, accelerated rheumatoid nodulosis, rash in AOSD, purpuric rash, vasculitis or rash in Felty's syndrome. The recognition and accurate diagnosis of these skin findings is of vital importance for better patient assessment and treatment interventions.

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