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Dermatologic Manifestations of Rheumatoid Arthritis

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Abstract

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease which can involve tissues and organs other than the synovial joints. RA patients with skin manifestations usually have severe disease. Rheumatoid nodule is the most common skin manifestation seen in RA. Other skin conditions commonly described in RA are rheumatoid vasculitis, raynaud's phenomenon and neutrophilic dermatoses. Drugs used to treat RA could also cause skin changes. In this review we will discuss the various cutaneous complications associated with RA.

Keywords: Rheumatoid arthritis; Skin manifestation

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease which can present with extra-articular manifestations apart from joint inflammation. Non-articular manifestations of RA occur in nearly 40 percent of patients with RA over a lifetime of disease [1]. Skin is commonly involved in RA and is usually seen in patients with severe RA. The most common cutaneous manifestation seen in RA patients is rheumatoid nodule [2,3]. In this review article, we will discuss the various skin conditions seen in RA as physicians treating patients with RA should be aware of these manifestations. We have divided the various skin manifestations as specific and non-specific.

Specific Manifestations

Rheumatoid nodule

Rheumatoid nodule (RN) is the most common cutaneous manifestation of RA. Palpable nodules are present in up to 20 to 35 percent of patients with RA at some point during their disease course [2,4]. Rheumatoid nodules are superficial lesions in the deep subcutaneous tissues, commonly found on the olecranon (Figure 1) and extensor surfaces of the forearm, hands, and other areas of repetitive trauma however rarely they can appear in internal organs [4-6]. Rheumatoid factor is almost always present in patients with nodules and RA pts with nodules are more likely to develop vasculitis [6]. The size of nodules varies from 2 mm to 5 cm, they are firm, non-tender and movable in subcutaneous tissue [3]. Cigarette smoking may increase the risk of developing rheumatoid nodules [7]. Although the pathogenesis of RN is not clear, complement activation following immune complex deposition on vessel walls, fibrin deposition and pro-inflammatory cytokines have been implicated in the pathogenesis of RN [2].

Histopathologically rheumatoid nodule is composed of three parts, namely inner zone of central necrosis, a surrounding cellular palisading zone and an outer area with perivascular infiltration of chronic inflammatory cells (Figure 2) [8].

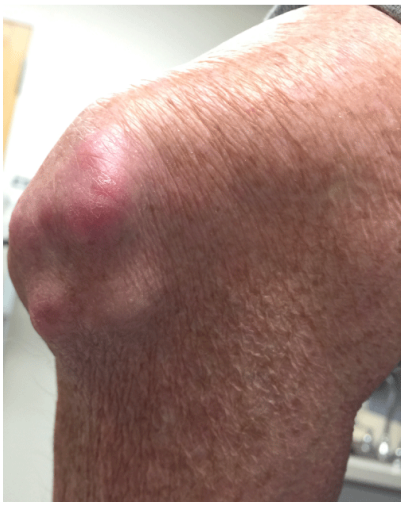

Figure 1: Rheumatoid nodules are superficial lesions in the deep subcutaneous tissues, commonly found on the olecranon.

These findings are similar to those seen in granuloma annulare but the presence of mucin within the area of collagen degeneration, a paucity of giant cells, and lesser degree of fibrosis will favor the diagnosis of granuloma annulare [9]. These nodules are mostly asymptomatic and usually do not require any treatment but occasionally they might ulcerate and become infected. Patients may request treatment in cases of ulceration, infection, nerve compression or limitation of motion. Local glucocorticoid injection could be used to decrease the size and surgical excision is an option in patients who do not respond to the local steroid injection but recurrence at the same site is possible [10,11].

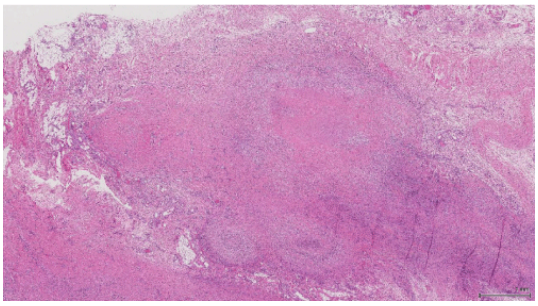

Figure 2: Histopathologically rheumatoid nodule.

Methotrexate has been postulated to cause accelerated nodulosis in patients on Methotrexate and a possible mechanism for this is the agonist stimulation of adenosine A1 receptors by Methotrexate leading to enhanced giant cell formation [12]. If there are other options available, patients could be switched to another DMARD but some rheumatologists might decide to continue the patient on Methotrexate if the disease is well controlled.

Rheumatoid vasculitis

Rheumatoid vasculitis (RV) is an inflammatory process that primarily effects small to medium sized blood vessels usually occurring in patients with long standing and severe RA. A clinicopathological study of 81 autopsied patients with RA suggested RV in an average of 30 percent patients [13] but the incidence of RV has been decreasingdue to aggressive treatment; a large retrospective study of 141 RA patients found vasculitis in 2 percent patients [14]. The mean duration between the diagnosis of RA and the onset of RV is around 10 to 14 years [15,16]. Pathogenesis of vascular involvement in RA is not completely understood, but an association between RV and DRB1*0401 locus has been suggested [17]. The proposed mechanisms for wall destruction in RV include endothelial cell antibodies targeting against the endothelial cells, immune complex deposition and cell mediated immunity [18-20]. In a case control study by Makol et al. 86 RV cases were compared with 172 controls to determine the risk factors of RV which were younger age at diagnosis, current smoking status, peripheral vascular disease, cerebrovascular disease, severe RA and the use of other DMARDs (besides hydroxychloroquine and Methotrexate) and biologics for RA treatment [15].

The common cutaneous manifestations of RV include leg ulcers, digital infarcts, petechiae (Figure 3) palpable purpura, peripheral gangrene and bowel ulcers/bowel perforation [21]. Oien et al. studied twenty patients with RA and leg ulcers and the causation of leg ulcers was found to be multifactorial with vasculitis and venous insufficiency as the main determinants [22]. Skin biopsy is a useful tool for diagnosis and has a 75% yield. Histologically all layers of vessel wall are infiltrated by inflammatory cells in addition to fibrinoid necrosis, erythrocyte extravasation and nuclear dust [18,19] Isolated nail fold infarcts also known as Bywaters lesions are benign lesions and do not require immunosuppressive treatment due to low risk of progression [23]. The options for treatment of RV are high dose glucocorticoids plus rituximab [24]. The other option is high dose glucocorticoids plus cyclophosphamide with azathioprine as maintenance treatment [25].

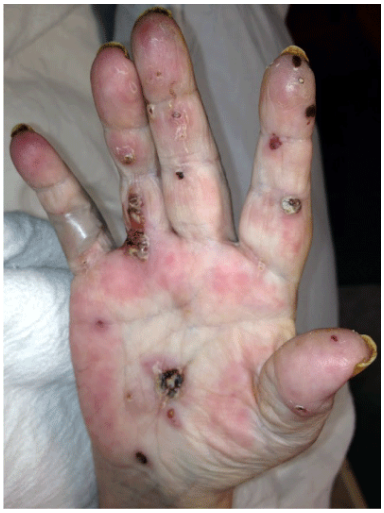

Figure 3: Cutaneous manifestations of rheumatois vasculitis.

Neutrophilic dermatoses

Neutrophilic dermatoses constitute a group of disease which has neutrophil predominance in its inflammatory infiltrate. It can be seen in patients with RA and other connective tissue diseases. The neutrophilic dermatoses associated with RA include rheumatoid neutrophilic dermatosis (RND), palisaded neutrophilic granulomatous dermatitis (PNGD), pyoderma gangrenosum (PG) and sweet's syndrome [26-29]. The pathogenesis of neutrophilic dermatoses is unclear but they probably represent an altered immunologic reactivity. In a study of skin manifestations in 215 turkish patients with RA, PNGD was seen in 6.5% patients and RND in 0.9% patients [30]. Classical lesions of RND are papulo-nodules and/or plaques distributed on the extensor surfaces of extremities particularly the hands and forearms as well as the neck and trunk. It is thought to be an immune complex disease. Histopathologically there is a dense neutrophilic infiltrate without vasculitis [26]. The lesions are usually asymptomatic and tend to resolve spontaneously with improvement in RA. Treatment option include topical steroids, systemic steroids, dapsone, colchicine and hydroxychloroquine [31,32].

Early lesions of PNGD may appear as urticaria-like annular plaques and may even have a livedoid appearance. In later stages of the disease, the lesion is more infiltrative and may present as violaceous annular plaques, waxy papules, painful subcutaneous nodules or indurated linear bands. The histopathologic findings of early lesions include a small-vessel leukocytoclastic vasculitis and a dense neutrophilic infiltrate. Mature lesions exhibit palisaded granulomas and dermal fibrosis (Figure 4) [27,33]. As with RND treatment of RA might help in resolving the lesions of PNGD. Other treatment options are topical corticosteroids, intralesional corticosteroids, dapsone, hydroxychloroquine and anti-TNF drugs [27,34,35].

PG is a painful, recurring, chronic neutrophilic disease of the skin which comes in four clinical variants namely ulcerative, bullous, pustular and superficial granulomatous out of which ulcerative is most commonly associated with RA.

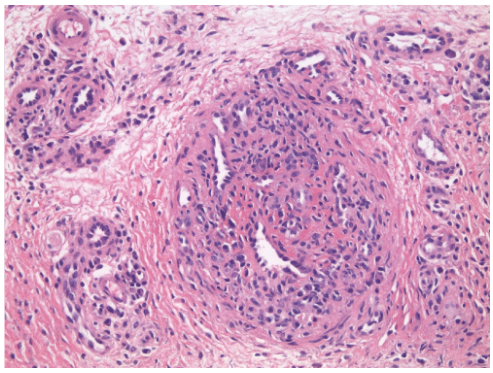

Figure 4: Mature lesions exhibit palisaded granulomas and dermal fibrosis.

Although these lesions typically affect the lower limbs, they can also affect the entire body. Classic forms of PG associated with arthritis present as aggressive ulcers, which quickly involve the skin, fascia, tendons, and muscles, and typically have a diameter exceeding 10 cm. The ulcers appear as necrotic pus-covered lesions surrounded by a distinctive purple-red, undermined surrounding skin (Figure 5) [28]. The histopathology of PG ulcers is nonspecific and is usually a diagnosis of exclusion. In a retrospective study of 86 patients with typical and atypical forms of PG, RA was the second most common disease association among patients with PG (14%) and seronegative inflammatory arthritis was the second most common association among patients with atypical PG (13.6%). Atypical PG is a more superficial form of PG characterized by hemorrhagic bullae that arise rapidly and are frequently located on the upper extremities [36]. For treatment in mild and localized PG, high potency topical corticosteroid, topical tacrolimus or dapsone can be tried [37]. In patients with extensive PG, options include systemic glucocorticoids, cyclosporine or infliximab [38,39].

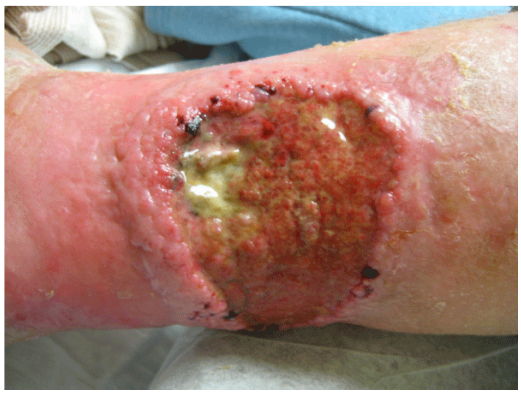

Figure 5: The ulcers as necrotic pus-covered lesions surrounded by a distinctive purple-red, undermined surrounding skin.

Sweet's Syndrome also known as acute febrile neutrophilic dermatoses was first described by Robert Sweet in 1964. Lesions present as erythematous, raised plaques. The lesions are often tender and sharply demarcated. Case reports have shown association of Sweet's Syndrome with RA [29,40]. Systemic steroids seem to have been considered as the gold standard treatment for Sweet's Syndrome; other options include topical steroids, colchicine, potassium iodide, and clofazimine [41,42].

Erythema elevatum diutinum (EED), a chronic form of leukocytoclastic vasculitis consisting of violaceous, red-brown, or yellowish papules, plaques, or nodules that favor the extensor surfaces and may resemble RND and PNGD. EED has been associated with RA in few case reports [43,44].

Intralymphatic histiocytosis

Intralymphatic histiocytosis is a rare condition characterized by the presence of dilated lymphatic vessels containing aggregates of mononuclear histiocytes within their lumina. There is a frequent association of this condition with RA. The skin lesions of intralymphatic histiocytosis associated with RA (IHRA) are almost asymptomatic and usually presents with irregularly shaped papules, patches or plaques some with livedo-like erythema; they have typically been seen overlying or in close proximity to a joint. The pathogenesis is not clear but given its association with RA, it has been proposed that inflammation could be promoting lymph stasis with subsequent development of lymphagiectases [45-47]

Felty's syndrome

Felty's syndrome (FS) is characterized by a triad of seropositive RA with severe joint involvement, splenomegaly and neutropenia. The life time risk for a patient with RA to develop FS is 1%. Increased splenic sequestration and neutrophilic destruction leads to neutropenia however spleen size does not always correlate with degree of neutropenia or clinical course [48]. Binding of IgGs to neutrophil extracellular chromatin traps (NET) leading to neutrophil death plays an important role in pathophysiology of FS [49]. Cutaneous manifestations which could be evident in FS include eye lid necrosis, skin hyperpigmentation, leg ulcers and vasculitis [50].

Patients with FS have more risk for developing NHL compared to general RA population [51]. Treatment of the underlying RA with DMARDs may improve granulocytopenia and thus reduce risk of infection. Methotrexate is the initial drug of choice [52] but in resistant cases glucocorticoids and IV rituximab have been used [53,54]. Few case reports have shown benefit with sulfasalazine, hydroxychloroquine, leflunomide and cyclophosphamide [55-57].

LGL (large granular lymphocytic) leukemia

RA is the most common autoimmune disease associated with LGL leukemia, occurring in approximately 25 percent of patients with Tcell-LGL leukemia. On the other hand, LGL leukemia is much less common in patients with RA, occurring in less than 1 percent of patients. In some cases these diseases may be simultaneously diagnosed whereas in others LGL leukemia might precede RA by several years. Patients with both LGL leukemia and RA may resemble felty's syndrome. T-LGL leukemia usually manifests as neutropenia (84%) and recurrent infections, followed by anemia (50%) and thrombocytopenia (20%). The skin manifestations include recurrent bacterial infections such as cellulitis and peri-rectal abscesses [58,59].

Adult onset still's disease

Adult onset still's disease (AOSD) also known as is an inflammatory disorder is characterized by daily spiking fevers, arthritis and

evanescent salmon colored rash. The rash is usually non pruritic macular or maculo-papular and tends to occur with the fever. Skin biopsy shows mild perivascularinflammationof the superficial dermis with lymphocytes and histiocytes. Treatment options include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, non-biologic DMARDs (sulfasalazine, methotrexate, hydroxychloroquine) and biologics [60,61].

Drug related skin manifestations

Tumor necrosis factor (TNF) antagonists have been successfully used to treat RA but these TNF antagonists can induce psoriasis. In a study of 9826 anti-TNF-treated and 2880 DMARD-treated patients with severe RA from The British Society for Rheumatology Biologics Register, the incidence rate of psoriasis in those treated with anti-TNF alpha therapy was elevated at 1.04 (95% CI 0.67 to 1.54) per 1000 person years compared to the rate of 0 (upper 97.5% CI 0.71) per 1000 person years in the patients treated with DMARDs. This study also noted that adalimumab might lead to a higher incidence of psoriasis compared to other TNF inhibitors. TNF-alpha inhibits PDCs (plasmacytoid dendritic cells) maturation and interferon-alpha production; TNF inhibition could give an uncontrolled production of interferon-alpha by PDCs. PDC derived IFN is essential in activating pathogenic T cells leading to the development of psoriatic skin lesions [62]. Other cutaneous manifestations include infections such as viral (herpes zoster, varicella), bacterial and fungal (granulomatous infections), eczematous dermatitis, drug induced lupus, leukocytoclastic vasculitis, lichenoid eruptions and erythema multiforme [62,63].

Methotrexate as mentioned earlier is postulated to cause accelerated nodulosis [12]. 10 percent of patients on hydroxychloroquine (HCQ) can develop a skin reaction presenting as pruritic maculopapular lesions. Patients on long term HCQ can also develop hyperpigmentation over the shins, hyper or hypopigmentation of the hair and oral mucosa and alopecia [64,65]. Leflunomide can cause alopecia in 9% to 17% of patients and a maculopapular skin rash in 10% to 12% of patients [66].

Nonspecific Manifestations

Raynaud's phenomenon

Raynaud's phenomenon (RP) is an exaggerated response to cold temperature or stress. An episode of RA is characterized by onset of cold fingers followed by sharply demarcated skin color changes (white, blue and red). Primary RP usually includes patients with no underlying cause and secondary RP also known as Raynauds syndrome (RS) refers to patients with an associated disease; RS can be associated with various autoimmune diseases including RA. The exact mechanism of RS in patients with RA is unclear but the proposed mechanisms are a procoagulant tendency, endothelial injury and reduced vasodilatation [67,68].

A meta-analysis comprising of 3730 patients showed that patients with RA have a greater prevalence of RS than the general population (a pooled prevalence of 12.3% and 95% CI were obtained) [69]. Treatment options include calcium channel blocker, phosphodiesterase (PDE) inhibitor and topical nitroglycerine. In patients resistant to initial therapy, recurrent digital ulcers, threatened digital loss, IV infusions of prostaglandins (eg: iloprost), endothelin-1 inhibitors (eg: bosentan) or chemical/surgical sympathectomy has been used [70].

Nail changes

In a case control study of 50 patients suffering from RA and 50 controls, the only nail abnormalities significantly associated with RA was the presence of longitudinal ridging on the finger nails [71]. Another prospective observational study in which 205 RA patients were compared with 144 non RA patients showed a significant increase in nails signs (nail ridging and onycholysis) in patients with RA compared to controls [72]. Yellow nail syndrome characterized by the triad of pulmonary disease, lymphedema, and slow-growing, yellow nails without a cuticle or lunula has also been described in patients with RA [73].

Palmar erythema

Palmar erythema also known as liver palms is characterized by non-pruritic, non-tender symmetric erythema mostly involving thenar and hypothenar eminences. It can sometimes involve the palmar aspect of phalanges and periungual areas. In a study of 152 patients with RA, palmar erythema was found in 61% patients [74]. In another study comparing 100 RA patients with 100 patients with various other internal diseases, palmar erythema was significantly higher in RA. Age of the patients, gender, and duration of disease, titer of rheumatoid factor, disease severity, erythrocyte sedimentation rate and frequency of volar tenosynovitis of the hands did not differ between patients with and those without palmar erythema [75].

Miscellaneous

Other cutaneous manifestations described in case reports and case series in patients with RA include pruritus, diffuse cutaneous atrophy, acral cutis laxa, urticarial/urticarial vasculitis, athletes foot and xerosis [72,76].

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