FEATURE ARTICLE

CE 1.5 Contact Hours | Rx 1.0 Pharmacology Contact Hour

Cutaneous Manifestations of Rheumatoid Arthritis

Marven Gerel Cabling

ABSTRACT: Rheumatoid arthritis is a chronic systemic autoimmune inflammatory arthritis with various extra-articular manifestations. In this first series examining the cutaneous manifestation of rheumatic diseases, we will discuss the most common dermatologic findings in patients with rheumatoid arthritis. Cutaneous lesions are the most common extra-articular findings. Rheumatoid nodules, accelerated rheumatoid nodulosis, and rheumatoid vasculitis are found especially in those with long-standing rheumatoid-factor-positive disease. Several neutrophilic dermatoses such as pyoderma gangrenosum, rheumatoid neutrophilic dermatoses, and Sweet's syndrome are also seen in association with rheumatoid arthritis. Patients may also present with various cutaneous adverse effects related to their arthritis therapy. It is important to recognize these dermatologic manifestations to better understand the underlying disease process, thus optimizing therapy and patient care.

Key words: Autoimmune Disease, Cutaneous Manifestations, Rheumatoid Arthritis

Rheumatoid arthritis is a chronic autoimmune inflammatory disease that mainly affects the joints. It is progressive and can lead to joint destruction, deformities, and, eventually, disability if not treated early on. In addition, it is also a systemic disease where extra-articular manifestations are found in about 40% of cases (Turesson et al., 2002). Multiple organ systems outside the musculoskeletal system can be affected. The most common findings include rheumatoid nodules, keratoconjunctivitis sicca, secondary Sjogren syndrome, pulmonary fibrosis, and pericarditis (Myasoedova et al., 2011). It is thus important for the clinician to be able to recognize the signs and symptoms for better patient outcomes.

Rheumatoid arthritis was first characterized in modern medical literature by Augustin Jacob Landré-Beauvais in 1800 (Landré-Beauvais, 2001). He described in his doctoral dissertation a cohort of predominantly female patients exhibiting severe joint pain. He hypothesized that they were experiencing a previously unrecognized condition, calling it primary asthenic gout. Although we now know that rheumatoid arthritis is not gout or a crystal arthropathy, Landré-Beauvais has paved the way for the study of this condition.

The exact pathogenesis of rheumatoid arthritis is yet to be elucidated. Studies have shown that patients with a high-risk genetic background who are exposed to various agents can trigger the development of rheumatoid arthritis. These agents can include cigarette smoking and, to a lesser degree, environmental hazards such as industrial pollution and pesticides (Calabresi et al., 2018). Cigarette smoking is strongly correlated with the development of rheumatoid arthritis in a dose-dependent manner. An increase in risk of 26% is noted in those who smoked 1–10 pack-years compared with those who never smoked, whereas it is twofold for those who smoked 21–30 pack-years (Di Giuseppe et al., 2014). The interaction between these factors leads to a cascade of events that ultimately lead to joint inflammation and, eventually, its destruction.

The main manifestation of rheumatoid arthritis is inflammation or synovitis of the joint. This leads to erosions on the cartilage and bone and then eventually on other intra-articular structures. Untreated, the disease will progress to result in bony deformities and disability. The classic disease presentation is a usually symmetric, slowly progressive development of pain, morning stiffness, and swelling of the joints. The metacarpophalangeal and proximal interphalangeal joints and wrists of both hands are most involved in the first year of diagnosis (Fleming et al., 1976).

Diagnosing rheumatoid arthritis first entails ruling out mimics and other inflammatory conditions such as infection,

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crystal arthritis, lupus, and psoriatic arthritis, among others, in a patient with observed joint swelling. One must then ascertain the duration of symptoms (usually >6 weeks) in which joints are involved and obtain laboratory tests. Recommended blood tests include the rheumatoid factor, anticitrullinated protein antibody (cyclic citrullinated peptide), erythrocyte sedimentation rate, and C-reactive protein. These are usually elevated or positive. Radiographs especially of the affected joints may show erosions that signal joint damage. An ultrasound of the affected joint to evaluate for synovitis and tenosynovitis may also aid in diagnosis. Rarely, extra-articular manifestations of the disease such as cutaneous lesions may precede the appearance of joint symptoms.

When rheumatoid arthritis is suspected, an early referral to the rheumatologist is warranted. It is recommended that the patient see the specialist within 6 weeks of onset of symptoms for evaluation, diagnosis, and initiation of treatment. Treating the patient within this "window of opportunity" may alter the natural history of rheumatoid arthritis and prevent disease progression and joint damage in the long run. Treatment with disease-modifying antirheumatic drugs (DMARDs) work better in the early stages of disease (Cush, 2007).

In this article, we focus on the most common cutaneous manifestations of rheumatoid arthritis. The lesions may range from nonspecific skin changes to ones that have been classically associated with the disease. Nonspecific lesions are common in patients with rheumatoid arthritis. These include skin atrophy, xerosis, and nail findings such as nail discoloration, longitudinal groves, and onycholysis (Ziemer et al., 2016).

RHEUMATOID NODULES

Rheumatoid nodule is the most common localized extra-articular manifestation of rheumatoid arthritis with cumulative incidence of about 31% in 10 years (Myasoedova et al., 2011; Figures 1 and 2). These subcutaneous nodules are firm to doughy, nontender and usually found on extensor surfaces such as the olecranon and areas frequently subjected to pressure (Tilstra & Lienesch, 2015). Ninety percent of patients presenting with nodules are positive for rheumatoid factor (Kaye et al., 1984). The presence of these nodules is associated with a worse prognosis, higher disease activity, and progression of joint damage on radiographs (Nyhäll-Wåhlin et al., 2010). These lesions are also linked with a higher likelihood of developing rheumatoid vasculitis (Makol et al., 2014). On histology, the rheumatoid nodules show a pattern of central area of necrosis surrounded by palisading cells enclosed by granulation tissue containing lymphocytes and histiocytes (Tilstra & Lienesch, 2015).

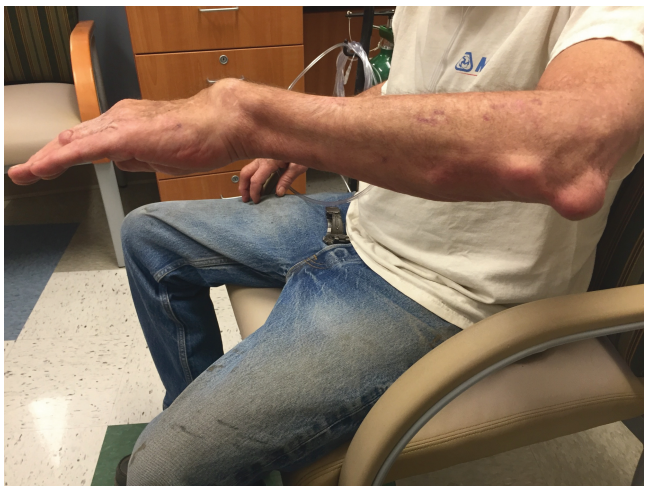

FIGURE 1. Rheumatoid nodules: arm and hand.

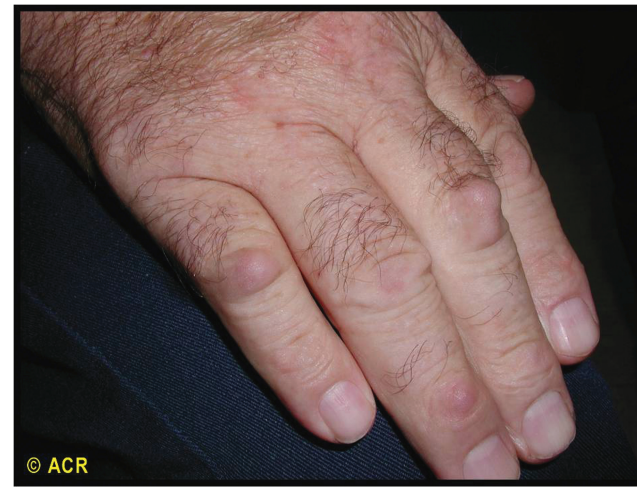

FIGURE 2. Rheumatoid nodules on the hand of a patient who developed accelerated rheumatoid nodulosis because of methotrexate.

Longitudinal cohort studies of patients with rheumatoid arthritis in Olmsted County, Minnesota, show that the cumulative incidence of rheumatoid nodules remained the same between 1985–1994 and 1995–2007 despite introduction of advanced biologic therapies (Myasoedova et al., 2011). However, multiple case reports suggest that rheumatoid nodules regress with treatment using sulfasalazine, tocilizumab, or rituximab (Al-Attia, 2013; Englert et al., 1987; Sautner et al., 2013). More studies are needed to assess the impact of newer therapies and its wider use on the incidence of these nodules.

Management of rheumatoid nodules is largely conservative and often focuses on observation as the nodules are usually asymptomatic and may diminish with use of antirheumatic drugs. Treatment may be indicated when the nodules impair function such as in cases when there is nerve impingement or limitation of joint motion because of the nodule. Other indications include presence of nodule ulceration, infection, or significant pain. If intervention is necessary, surgical excision or local injection may be performed. Only a few have looked at the efficacy and safety of these approaches. Two double-blind trials reported diminution of nodule volume after steroid injection with minimal local adverse effects (Baan et al., 2006; Ching et al., 1992).

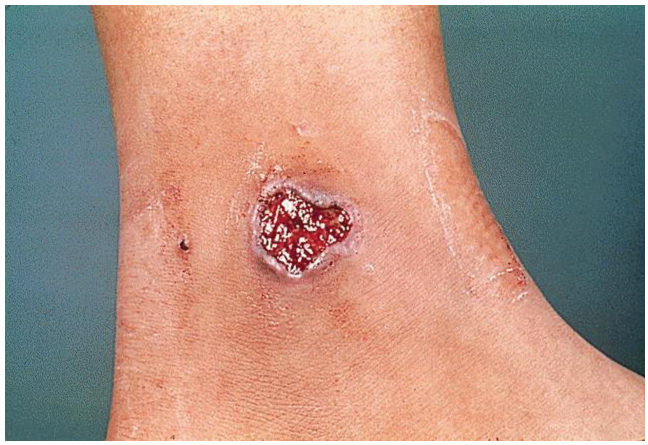

FIGURE 3. Rheumatoid vasculitis ulcer: foot.

However, these studies are limited because of their extremely small sample size and not enough to draw definitive recommendations from.

ACCELERATED RHEUMATOID NODULOSIS

This condition was first described by Kremer and Lee in 1986 in three of 29 patients treated with methotrexate. They noted there was an accelerated pace of development of multiple rheumatoid nodules, despite an improvement in their joint disease. Multiple reports have since associated methotrexate with the development of accelerated rheumatoid nodulosis. Histologically and physically, these nodules are not different from the rheumatoid nodules described above. A systematic review of methotrexate-induced accelerated nodulosis showed that 78% of patients were positive for rheumatoid factor with fingers as the most involved site 64% of the time (Patatanian & Thompson, 2002). Nodulosis can also develop on the elbows, knees, and feet as well as on other organs including the lungs and larynx (Akiyama et al., 2015).

Other drugs have been implicated in the development of accelerated rheumatoid nodulosis. These include azathioprine, etanercept, infliximab, and tocilizumab (Kellet et al., 2015; Mackley et al., 2004; Talotta et al., 2018). Furthermore, there are a few case reports indicating that methotrexate-induced accelerated nodulosis can also occur in other diseases such as psoriasis and systemic lupus erythematosus (Berris et al., 1995; Rivero, 2004).

The exact pathophysiology of the accelerated growth of these lesions is still unclear. A study by Merrill et al. (1997) proposes that methotrexate increases adenosine production by monocytes both intra-articularly and extra-articularly, promoting multinucleated giant cell formation via A1 receptor stimulation.

Treatment of accelerated rheumatoid nodulosis is limited as there are no specific recommendations from literature. The review by Patatanian and Thompson in 2002 showed the possibility of using azathioprine, hydroxychloroquine, colchicine, or D-penicillamine in addition to or as a replacement for methotrexate to regress nodule size. However, no significant conclusions can be made especially because the case reports reviewed were fragmented and incomplete. Despite the lack of strong data, it is only prudent to discontinue the offending medication and consider other agents to better control the underlying arthritis.

RHEUMATOID VASCULITIS

Rheumatoid vasculitis is a known complication and extra-articular manifestation of rheumatoid arthritis (Figures 3 and 4). This condition affects the small- or medium-sized blood vessels. The most usual presentation is with patients who have long-standing active seropositive disease. Male patients and older adults seem to be more affected.

The disease presents in various ways depending on which blood vessels and organs are involved. However, about 90% of patients have skin manifestation (Kishore et al., 2017). The underlying pathogenesis is deposition of immune complexes and complement activation. In a study by Chen et al. (2002), the clinical and histological spectrum of rheumatoid arthritis was analyzed. Histologically, they have found the pattern of rheumatoid vasculitis predominantly of

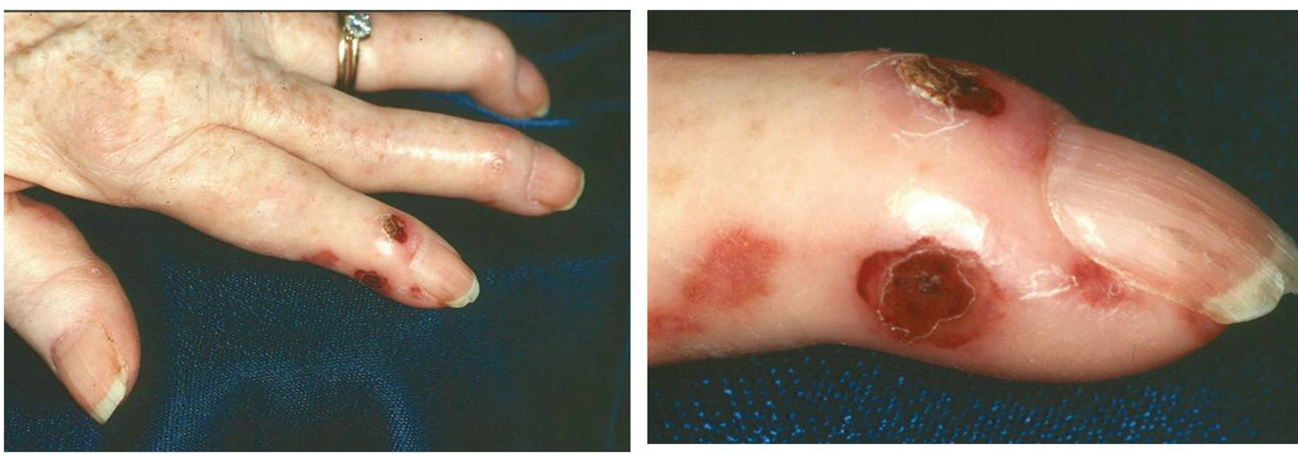

FIGURE 4. Rheumatoid vasculitis ulcer: finger.

leukocytoclastic vasculitis. Arteritis similar to cutaneous polyarteritis nodosa has been found as well. In the same study, the predominant physical findings are palpable purpura, subcutaneous nodules, livedo reticularis, and ulcers.

Treatment of rheumatoid vasculitis requires controlling the patient's underlying rheumatoid arthritis. Mild cases of cutaneous vasculitic lesions may improve with the addition of either colchicine or dapsone (Carlson et al., 2006) or use of methotrexate. However, if there is systemic vasculitis with multiple organ involvement (i.e., ocular, neurologic, cardiac, renal), a more aggressive approach is needed. High-dose systemic corticosteroids with either cyclophosphamide or rituximab are used as treatment (Coffey et al., 2019).

NEUTROPHILIC DERMATOSES

Neutrophilic dermatoses are a heterogenous group of nonvasculitic inflammatory skin diseases that mainly present with sterile lesions and a predominantly neutrophilic dermal infiltrate on histology. These can be idiopathic or found in association with rheumatoid arthritis, malignancy, or other systemic inflammatory conditions such as inflammatory bowel disease. Pyoderma gangrenosum, rheumatoid neutrophilic dermatoses, and Sweet's syndrome are some of the neutrophilic dermatoses found in association with rheumatoid arthritis.

Sweet's syndrome is a neutrophilic dermatosis that can be found in patients with rheumatoid arthritis. In addition, this condition can also be idiopathic, drug induced, or associated with a malignancy. This disease features systemic symptoms such as fever with acute onset of multiple painful tender erythematous plaques or nodules especially on the extremities, trunk, and face (Villarreal-Villarreal et al., 2016).

Pyoderma gangrenosum causes a refractory and significant disruption in the skin. It usually presents as a deep ulcerative lesion but is also less commonly in bullous, pustular, or vegetative/superficial verrucous forms (Yamamoto, 2015). Seventy-six percent of female patients are affected, and the lower leg is the most frequently affected area of the body. Pyoderma gangrenosum is associated with systemic diseases in 56.8%. Inflammatory bowel disease is seen in 17.6%; arthritis (rheumatoid arthritis and other seronegative arthritis), in 12.8%; and hematological malignancies, in 8.9% (Kridin et al., 2018).

Rheumatoid neutrophilic dermatoses are rare but usually found in patients with long-standing severe rheumatoid arthritis. These usually present as scattered papular, nodular, urticarial, or plaque lesions on the extremities, trunk, and extensor surfaces. The lesions are usually asymptomatic and may resolve over weeks even without therapy (Cugno et al., 2018).

SKIN MANIFESTATIONS ASSOCIATED WITH RHEUMATOID ARTHRITIS TREATMENT

The treatment of rheumatoid arthritis includes the use of DMARDs including methotrexate and biologic agents such as tumor necrosis factor inhibitors (TNFis). However, these medications are associated with cutaneous adverse effects.

Methotrexate has been considered the anchor medication for the management of rheumatoid arthritis. Aside from the development of accelerated rheumatoid nodulosis, other more common adverse effects are notable. Oral ulcers are common and occur in about 30% of patients. The medication is also associated with increased hair loss in up to 29.4% of patients (Łukasik et al., 2019).

Biologic medications can be administered through either a subcutaneous injection or an intravenous infusion. Injection site reactions are the most common side effect of injectable biologics and are estimated to occur in at least 10%–20% of cases. These are usually self-limited and decrease even with continued use. One study by Zeltser et al. (2001) found that injection site reactions occurred in 20% of patients, usually within the first 2 months of drug initiation. Furthermore, immunohistochemical analysis of punch biopsy samples shows that the reactions may be because of a T-lymphocyte-mediated delayed-type hypersensitivity reaction with eventual induction of tolerance.

TNFi biologics are known treatments for rheumatoid arthritis and psoriasis, among other indications. However, this class of medication has been reported to be associated with a paradoxical development of psoriasis and psoriasiform eruptions. Three patterns of cutaneous eruptions have been described: induction of psoriasiform eruption, induction of new psoriasis in a patient with no history of psoriasis, and exacerbation of preexisting psoriasis with possibility of a new type of psoriasis appearance (Wollina et al., 2008). A systemic review showed that this phenomenon is found in a variety of indications that TNFis are used for: most commonly rheumatoid arthritis, psoriasis, and Crohn's disease. Infliximab has been implicated in 62.5% of cases; adalimumab, in 21.8%; and etanercept, in 14.4%. The extremities, especially the soles and palms, are affected in about 45% of cases. More than half would show a classic psoriasis histology on biopsy, whereas about a third would show pustular psoriasis (Brown et al., 2017).

Treatment of these TNFi-induced lesions depends on various factors, including the control of the underlying disease process and the severity of the resulting skin eruption. Discontinuing the medication is an option, but this may be at the expense of causing a flare-up of the underlying rheumatoid arthritis. A balance of controlling the arthritis with the TNFi and treating the resulting cutaneous eruption has to be met. A treatment algorithm has been proposed by Li et al. in 2019. They recommended classifying the eruptions to whether the lesions are mild or moderate to severe and then classifying according to the control of the underlying disease (i.e., rheumatoid arthritis, inflammatory bowel disease, psoriasis, and psoriatic arthritis). The treatment of those with mild eruptions and controlled disease is to

TABLE 1. Available Therapies for Rheumatoid Arthritis

Tumor Necrosis Factor Inhibitors	Conventional DMARDs	Janus Kinase Inhibitors	Anti-Interleukin-6 Inhibitor	B-Cell Depleting Agent
Etanercept	Methotrexate	Tofacitinib	Tocilizumab	Rituximab
Infliximab	Sulfasalazine	Baricitinib	Sarilumab	
Adalimumab	Hydroxychloroquine	Upadacitinib		
Golimumab	Leflunomide			
Certolizumab	Azathioprine			
Nonsteroidal Anti-Inflammatory Drugs	**T-Cell Costimulatory Blocker**		**Anti-Interleukin-1 Inhibitor**	
Corticosteroids	Abatacept		Anakinra	

Note. DMARDs = disease-modifying antirheumatic drugs.

continue the TNFi and add conventional psoriasis therapy, including ultraviolet therapy, topical steroids, and methotrexate, among others. In those with an uncontrolled underlying disease and/or moderate-to-severe skin eruptions, a change of therapy is warranted. They recommended either a change to another TNFi agent or use of a different class of medication altogether.

The use of TNFi drugs has been found to be associated with an increased risk of nonmelanoma skin cancer in patients with rheumatoid arthritis. A recent systematic review and meta-analysis by Wang et al. (2020) evaluated the risk of development of nonmelanoma skin cancer. The study found that patients with rheumatoid arthritis on TNFis are at an increased risk (relative risk: 1.28) compared with those who were never on the drug. Furthermore, the use of TNFi drugs in rheumatoid arthritis is associated with a 30% higher risk of developing squamous cell cancer, but not basal cell cancer.

TABLE 2. Summary of the Common Cutaneous Manifestations of Rheumatoid Arthritis

Rheumatoid nodules

Accelerated rheumatoid nodulosis

Rheumatoid vasculitis

Neutrophilic Dermatoses

- Sweet's syndrome
- Pyoderma gangrenosum
- Rheumatoid neutrophilic dermatoses

Nonspecific Lesions

- Skin atrophy
- Palmar erythema
- Xerosis
- Raynaud's phenomenon
- Nail ridging
- Onycholysis

DMARD-related cutaneous side effects

- Methotrexate: oral ulcers, hair loss, methotrexate-induced accelerated nodulosis
- TNFi: infusion and injection reactions, psoriasis/psoriasiform eruptions, skin cancer

Note. DMARD = disease-modifying antirheumatic drug; TNFi = tumor necrosis factor inhibitor.

TREATMENT

The ultimate goal of treatment for rheumatoid arthritis is to improve quality of life as well as prevent progression and complications of the disease. With this in mind, a treat-to-target approach has been adopted as the guiding principle in the management of the disease. This approach entails setting a target (i.e., low disease activity or remission), initiating therapy to reach the target, and reevaluating at prespecified time points to determine if the target is reached. If not, a revision of therapy should then ensue (Smolen et al., 2010).

The treatment of rheumatoid arthritis has evolved significantly over the past 30 years, especially with the introduction of methotrexate as the initial drug of choice in 1988. Methotrexate, along with other DMARDs such as hydroxychloroquine, leflunomide, and sulfasalazine, has been beneficial in decreasing the inflammatory activity of rheumatoid arthritis (Table 1). However, there is a subset of patients who will not respond to these therapies or will not tolerate the drugs. They would then need to use newer medications such as the biologics, either as monotherapy or in combination with the conventional DMARDs. Etanercept was the first biologic approved by the FDA in 1998, and other TNFi drugs and classes of medications for rheumatoid arthritis followed shortly thereafter. Table 2 shows the available classes of drugs currently available for the treatment of rheumatoid arthritis.

CONCLUSION

Rheumatoid arthritis is a systemic inflammatory arthritis that may present with various cutaneous lesions. Rheumatoid nodules, accelerated nodulosis, rheumatoid vasculitis, and neutrophilic dermatosis are some of the classic lesions found in rheumatoid arthritis. These findings are usually found in patients with long-standing rheumatoid-factor-positive rheumatoid arthritis and may indicate worse

prognosis. Recognizing these lesions would lead the clinician to better assess the patient and optimize therapy. ■

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