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Deforming rheumatoid arthritis with vasculities

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Abstract
Rheumatoid vasculitis is a rare and late complication of rheumatoid arthritis and may affect small-to-medium-sized vessels. Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. Autoimmune diseases are illnesses that occur when the body's tissues are mistakenly attacked by their own immune system. The immune system contains a complex organization of cells and antibodies designed normally to "seek and destroy" invaders of the body, particularly infections. Patients with autoimmune diseases have antibodies and immune cells in their blood that target their own body tissues, where they can be associated with inflammation. While joint tissue inflammation and inflammatory arthritis are classic RA features, the disease can also cause extra-articular inflammation and injury in other organs. Because it can affect multiple other organs of the body, rheumatoid arthritis is referred to as a systemic illness and is sometimes called rheumatoid disease. Rheumatoid arthritis is a classic rheumatic disease. Rheumatoid arthritis that begins in people under 16 years of age is referred to as juvenile idiopathic arthritis or JIA (formerly juvenile rheumatoid arthritis or JRA).

Keywords: vasculitis, referred, juvenile, Rheumatoid, classic

Introduction
Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by chronic symmetric polyarthritis and by the presence of autoantibodies including rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) antibodies. Rheumatoid vasculitis (RV) is an unusual manifestation of chronic, deforming RA and may affect multiple systems [1, 2]. The active vasculitis associated with rheumatoid disease occurs in about 1% of this patient population. RV is a manifestation of “extra-articular” (beyond the joint) rheumatoid arthritis and involves the small and medium-sized arteries in the body. In many of its disease features, RV resembles polyarteritis nodosa. Other common extra-articular manifestations of rheumatoid arthritis, such as inflammation in the sac surrounding the heart (pericarditis), inflammation in the lining of the lungs (pleuritis), and interstitial lung disease (resulting in fibrosis or scarring of the lungs). Skin and the peripheral nervous system are the most commonly involved organ systems, followed by the eyes and pericardium. Involvement of other major organ systems such as lung, gastrointestinal (GI) tract, kidney, and central nervous system are rare but when occurs, can be organ or life threatening. Rheumatoid vasculitis is usually associated with seropositivity and represents a complication of long standing, erosive, and deforming RA [3].

Case presentation
59 year old female patient known case of deforming rheumatoid arthritis and hypertension since 5 years presented with recurrent ulcers over both the ankle with white discharge. She was referred to rheumatology due to painful swelling of her hand joints and edema and recurrent ulcers of both of her legs (image 1, 2), which insidiously developed over the past 2 months. She had 3 kg of weight loss during the 2 months period. On examination, she was afebrile and her blood pressure was normal. Joint exam revealed tender joint count of 15 and swollen joint count of 15 involving metacarpophalangeal, proximal interphalangeal, metatarsal, and ankle joints. Skin examination revealed livedo reticularis on lower extremities, but subcutaneous nodule was not noted. There was 2 + peripheral edema on lower extremities. Chest, heart, and abdominal examinations were not remarkable. Lab tests were as per table 1. Pus culture was sent which turned out to be negative for any organisms. Ultrasound Doppler of lower legs was scheduled and results were: both lower limb arteries show minimal intimal thickening; left side distal tibial and peroneal arteries show few plaques causing minimal narrowing. Also, biopsy of ulcer showed arterial wall necrosis with inflammatory cell infiltration consisting of lymphocytes, histiocytes, neurophils, and eosinophils. The vascular lumen is partially occluded by reactive intimal tissue. Patient was previously treated with methotrexate and hydroxycholoroquine. Upon diagnosis of rheumatic vasculitis, he received pulse dose of corticosteroids (1000 mg methylprednisolone for 3 days and then prednisone 60 mg daily while in the hospital), and total of two doses of Rituximab 1000 mg 2 weeks apart. In a follow-up visit 3 months later, the patient noted improvement of his skin lesions, right foot strength, paraesthesia, Raynaud's phenomenon and denied joint pain or swelling. (Image 3, 4)
The following laboratory values were significant for RF of 802 IU/mL, positive Anti-CCP antibodies with titer of 1:140, erythrocyte sedimentation rate of 70 mm/hour, C reactive protein of 10.23 mg/L, slightly. Antineutrophil cytoplasmic antibodies (ANCAs), HIV antibodies, acute hepatitis panel, scleroderma-70 antibody, double-stranded DNA antibody, anti-SSA/anti-SSB autoantibodies, anti-Smith, antiphospholipid antibodies and cryoglobulins were all negative. X-rays of bilateral hands and feet showed no erosive changes or joint space narrowing.

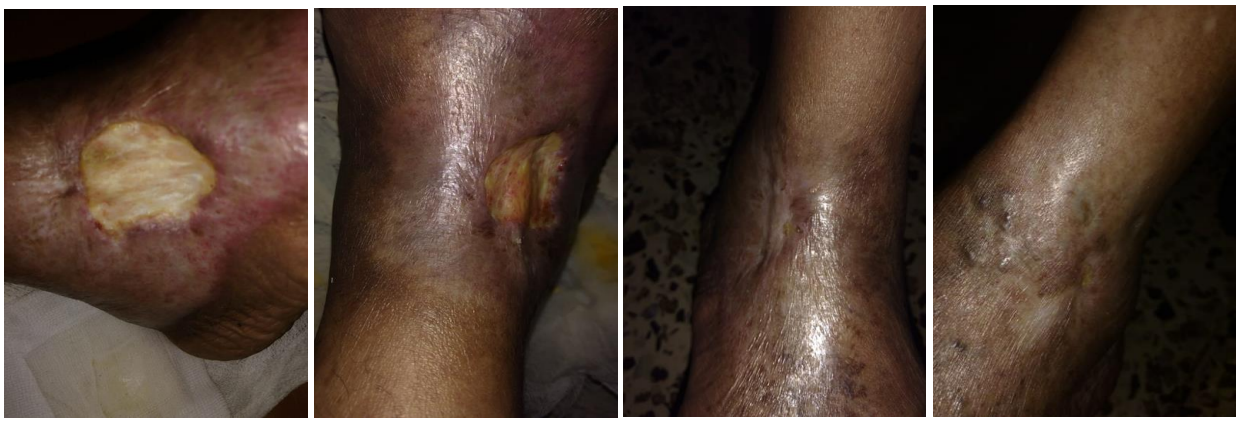

Fig (1, 2, 3, 4)

Table 1

Test	Result	Reference Range
Haemoglobin	11.6	12 - 16 gm%
Blood Group	A Positive	
RBC Count	3.72	3.8 - 4.8 million/cmm
HCT	34.8	36 - 48%
MCV	93.5	83 - 101 fl
MCH	31.2	26.4 -33.2 Pg
MCHC	33.3	31.8 – 35.9%
RDW-CV	12.8	11.6 – 14.0%
Total WBC Count	5780	4000 - 10000/cumm
Platelet Count	268	150 - 450 thou/cumm
Smear Examination	Microscopic Hypochromic RBC	
PS for MP	Not detected	
ESR	60	00-15 mm/hr
Total Bilirubin	1.0	0/1 – 20 mg/dl
Direct Bilirubin	0.4	0 – 0.4 mg/dl
Indirect Bilirubin	0.6	0 – 1.08 mg/dl
APTT	Test - 27.0, Control – 29.5	25.0 – 33.0 Seconds
Prothrombin Time	Test – 13.9, MNPT- 12.6	11.5 – 14.1 Seconds
INR	1.13	Non-Therapeutic: upto 1.2 Therapeutic Range: 2.0 – 3.0
Random Glucose	96	<140 mg/dl
S. Creatinine	0.8	0.52 – 1.04 mg/dl
HIV 1 and 2	0.07	<1.0 S/Co: Non-Reactive >=1.0 S/Co: Reactive

Discussion

RV is an unusual complication of long-standing, severe RA. It is characterized by an inflammatory process affecting small-to-medium-sized vessels and may involve any organ of the body. The mean duration between the diagnosis of RA and the onset of vasculitis is 10–14 years and it is unusual to be presented within the first 5 years of RA diagnosis though it has been reported before [1, 2]. The 30-year incidence of vasculitis in patients with RA was estimated to be 3.6% [1]. Over the past 15 years, with the widespread use of biological agents early in the treatment of RA, has led to a decline in the prevalence of RV [4]. Vasculitis usually develops in established disease with burnt out synovial inflammation implying that inflammatory burden over long period of time is important in the pathogenesis of rheumatoid vasculitis [3].

Rheumatoid vasculitis is a clinicopathologic condition. Definitive diagnosis of rheumatoid vasculitis usually requires histologic evidence of systemic necrotizing vasculitis involving small to medium-sized vessels. Histopathologic examination reveals fibrinoid necrosis and mononuclear and neutrophil infiltration of the vessel walls [5]. Rheumatoid vasculitis can involve any organ systems and clinical manifestations depend on size and types of the involved blood vessels. In a case control study, the skin or peripheral nerves were involved in more than 80% of the cases, and these organ involvements were shown to have a favorable prognosis [3]. Involvement of major organs such as lung, kidney, heart, central nervous system, and GI tracts are less common but often associated with poor prognosis [6]

Cutaneous manifestations of RV include palpable purpura, nodules, ulcers, nail fold infractions, digital necrosis, livedo reticularis and urticarial vasculitis.

Diagnostic criteria for systemic RV were proposed by Scott and Bacon as having one or more of the following in the presence of RA [1]: Mononeuritis multiplex or peripheral neuropathy [2], peripheral gangrene [3], biopsy evidence of acute necrotizing arteritis in addition to systemic illness (fever and weight loss) and [5], deep Cutaneous ulcers or extra-articular disease (eg, pleurisy, pericarditis and scleritis) if associated with typical digital infarcts or biopsy evidence of vasculitis [7, 8].

Management of rheumatoid vasculitis is largely empirical due to lack of randomized control trials. Corticosteroids and

cyclophosphamide have been historically used for severe forms of rheumatoid vasculitis [9]. Despite treatment with high dose glucocorticoids and cyclophosphamide, mortality rates are reported to be high with 12% at 1 year and 60% at 5 years [10]. The major cause of death was infection followed by organ damage from active vasculitis. The availability of biologic drugs for RA treatment has broadened treatment options for rheumatoid vasculitis. However, the role of these drugs in rheumatoid vasculitis management needs to be further investigated. There are case reports illustrating efficacy of biologic drugs, especially rituximab in severe refractory rheumatoid vasculitis patients, as efficacy of rituximab was proved in ANCA associated systemic vasculitis [11]. Anti-tumor necrosis factor (TNF) therapy seems to be a logical option for rheumatoid vasculitis treatment with their known efficacy in RA, but concerns were raised that these drugs may induce vasculitis [12]. Our patient responded well to the high dose corticosteroid and cyclophosphamide induction and methotrexate and tacrolimus maintenance treatment. However, considering high rates of infectious complications from aggressive immunosuppression, we need to develop a better and safer approach for managing rheumatoid vasculitis.

Conclusion

- RV, although it is a late complication of chronic RA, can be presented at any time during the disease process.
- Mononeuritis multiplex, manifested with foot drop in a patient with RA, could be a warning sign of RV.
- RV should be in the differential diagnosis of patients presenting with multiple organ dysfunction and high titer of rheumatoid factor.
- High-dose glucocorticoids and Rituximab help in inducing remission in active RA, while methotrexate or azathioprine might help in maintenance therapy. Rituximab has been shown to be effective in treating RV. The effect of tumor necrosis factor inhibitors and other biological agents in treating severe, active RV still require further investigations.

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