

Case Report and Review of Articles: Rheumatoid Vasculitis

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Summary:

We describe here a case of a 70 yr old man with long-standing rheumatoid arthritis who presented with low grade fever, fatigue, loss of appetite and weight, bluish discoloration of the fingers and patches of gangrenous skin on the fingers. There was intense pain in the fingers which prevented him from sleep. Along with these symptoms he developed loss of sensation in the dorsum of left foot, then left foot drop. We give below full account of the case and review of the causes of vasculitis. We want to emphasize on the importance of identifying vasculitis as one of the complications of rheumatoid arthritis and intensive treatment of this complication, as it is a life-threatening complication.

Key words: Rheumatoid Arthritis, Vasculitis, Complications, Systemic involvement, vasculopathy, arteritis, Raynaud's phenomenon, neuropathy, gangrene.

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Introduction:

Rheumatoid vasculitis (RV) is a severe extra-articular manifestation of RA that develops in a minority of patients with this disease¹. Clinical reports have estimated the prevalence of RA vasculitis at less than 1% to 5%^{2,3}. RV develops relatively frequent in males and its estimated lifetime risk is 9:1 compared to 38:1 for females⁴. RV has become increasingly uncommon in recent years⁵. This decline in rheumatoid vasculitis is likely related to marked improvement in therapy resulting from widespread use of methotrexate and new biologic agents. RV typically occurs in patients with longstanding, seropositive, destructive RA. In one study, the mean duration between the diagnosis of RA and the onset of vasculitic symptoms was 13.6 years⁶.

Case Report:

A.D.A, 70- year- old man was admitted to the Baghdad Teaching Hospital, Medical City, with 2 weeks history of painful discoloration of the fingers. Diagnosis of Rheumatoid arthritis (RA) was done 25 years prior to admission following one year of pain, stiffness, and swelling in multiple joints. The patient was non adherent to the prescribed therapies, and in the last 16 years he was on irregular treatment with prednisolone 10-20 mg daily. Two months before admission, the patient developed multiple joint pain and swelling of gradual onset, with simultaneous, symmetrical involvement of the upper and lower limbs joints. Pain was continuous, most severe in the morning, relieved partially by activity. Night pain was also present. The patient described morning stiffness of 1 hour duration, fatigue, loss of appetite, and weight loss (not documented). The patient also has low grade fever;

intermittent, mainly at night, associated with mild sweating, but there was no rigor. The patient consulted a physician who prescribed him Methotrexate (MTX) tab 10 mg weekly, folic acid, and prednisolone 10 mg daily. Two weeks before admission the patient developed bluish discoloration of the fingers. To start with, the discoloration was mild, involving only 3 fingers in each hand, associated with pain and coldness. With time, the discoloration became more severe, involved more fingers bilaterally, with patches of blackish discoloration of some fingers. Pain was continuous, became so intense that interfered with the patient's sleep. At the same time, the patient started to complain of numbness and pricking sensation over the dorsum of left foot, followed in short time by foot weakens, with associated difficulty in walking, and frequent tripping.

The patient didn't admit history of eye redness, pain, or dryness. There was no history of oral ulceration or dry mouth. History of frequency, nocturia, and burning micturation for the last one month was obtained, but there was no loin pain or hematuria. Otherwise, review of other systems was unrevealing. Past medical and surgical history was unremarkable. The patient is ex-smoker for the last 10 years. He smoked about 10 cigarette/day for more than 30 years.

General examination revealed an old age man, conscious, looking ill and distressed, not tachypneic. He was pale, not jaundiced, with no palpable lymph nodes, or palpable goiter. Right eye showed ptosis and converging squint (congenital). Examination of the upper limbs revealed tender red streaks on forearms, and few bruises. Finger tips (2nd-5th) of both hands were cyanosed, cold and extremely tender, with gangrenous patches (2nd, 3rd, 4th) on right side, (2nd, 3rd) on the left side. Examination of the lower limbs revealed mild cyanosis of the right 2nd and 3rd toes with coldness and severe tenderness.

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There was mild bilateral pitting edema, with intact peripheral pulses. Vital signs were normal; pulse rate: 90 /min, blood pressure 130/80 (no postural change), temperature 37.1oC, and respiratory rate 15 breath/min. Examination of Chest, heart, and abdomen showed no detectable abnormalities. Examination of the nervous system was normal in the upper limbs. However, lower limbs examination revealed left complete foot drop with absent ankle jerk, and diminished knee jerks bilaterally. Planter response was down bilaterally. There was decrease in pin prick and touch sensation over the dorsum of the left foot (L5 dermatome). Position sense was intact. Steppage gait was observed. Cranial nerves were intact apart from markedly decreased visual acuity in the left eye, corneal opacity, ptosis and converging squint of left eye. There was loss of lateral movement of the left eye but no diplopia. Regarding musculoskeletal examination, in the hands there was wasting of dorsal interossei, ulnar deviation at MCP level, swelling and tenderness of the 2nd and 3rd proximal interphalangeal joints (PIPs) and metacarpophalangeal joints (MCPs) bilaterally. Wrists showed Swelling and tenderness, pain with motion, mild limitation of both flexion and extension. Elbows examination revealed flexion deformity of both elbows, tender joint line bilaterally, pain with motion, and limitation of extension of the right elbow (10-15 degree) and left (10 degree). Shoulders examination revealed tender joint line bilaterally, pain with motion in all directions, but no limitation. On examination of feet there was clawing of the 2nd toe bilaterally, tender MTP joints bilaterally; and ankles showed bilateral swelling and tenderness, pain with motion, and limitation of dorsiflexion of left ankle joint. Knees were normal apart from palpable crepitus with motion. Hips and spine were normal.

Investigations:

Laboratory tests revealed the following results: erythrocyte sedimentation rate (ESR) of 85 mm/hour, C-reactive protein (CRP) of 48mg/l(normal: <6). Hemoglobin was 11g/dL, white blood cell count was 20.100 mm³, with 91.7% neutrophil, and platelets count was normal. Blood film revealed normochromic, normocytic anemia, and neutrophil leukocytosis, with no immature cells. Fasting blood sugar was elevated on 2 occasions (157mg/dL, 200mg/dL). Diagnosis of diabetes mellitus was made. Blood urea was elevated (98 mg/Dl). However, serum creatinine, serum electrolytes, liver function tests, and serum lipid profile were all normal. General urine examination revealed one plus albumin, 8-15 R.B.C, 15-20 Pus cell. Test for rheumatoid factor was strongly positive (1:512). Anti CCP antibodies, lupus anticoagulant, anticardiolipin antibodies, and ANCA were all negative. Hepatitis B and C serology was negative. X-ray of hands and wrists revealed osteopenia, soft tissue swelling, and loss of cartilage width at radiocarpal, intercarpal, carpometacarpal, and PIP joints.

Multiple erosions at intercarpal joints, PIP joints, base of the right 2nd and the left 3rd proximal phalanx. ECG revealed left axis deviation. Chest radiograph, echocardiography, abdominal ultrasound and DXA were normal. Our diagnosis was **active rheumatoid arthritis with rheumatoid vasculitis**.

Treatment: The patient was treated with pulse methylprednisolone 500mg/day intra-venously (3 doses), followed by prednisolone 40 mg daily in 3 divided doses, Cyclophosphamide 50 mg tab twice daily. In addition, the patient was kept on soluble insulin, analgesia, antibiotic, and clopidogrel 75 mg daily. Within 2 days joint symptoms improved markedly. In addition there was significant improvement of pain and to less extent other ischemic features of fingers and toes. Blood sugar was controlled, and blood urea came back to normal.





Discussion and review of literatures:

Rheumatoid vasculitis (RV) is considered one of the important, life-threatening manifestations of RA, that is fortunately rare, affecting nearly 1-5%(2,3) . Male gender, longstanding disease, high-titer RF in serum, hypocomplementemia, erosive disease, circulating cryoglobulin, and extra-articular features such as subcutaneous nodules are variables associated with the development of rheumatoid vasculitis(7). In our case, the patient is an old age man, has long standing, seropositive, erosive RA, but he has no extraarticular features like nodules. RV may involve both small blood vessels and medium-sized arteries(8). RV may target virtually any organ of the body. The most common sites of involvement are the skin and peripheral nerves(9). Major organ system involvement of the heart, bowel, or kidney is much less common but can lead to significant morbidity and mortality, including myocardial infarction, bowel ischemia, and renal failure. Central nervous system involvement is rare(10). Skin vasculitis occurs in as many as 90 percent of patients with RV(6). The classic skin lesions of RV are deep cutaneous ulcers on the lower extremities. Medium-vessel vasculitis can also lead to digital ischemia, necrosis, and gangrene. Clinical manifestations of small-vessel vasculitis (eg, palpable purpura) may also be present in RV, but the clinical picture and most challenging problems are dominated by disease in medium-sized arteries and arterioles (11,12). The next most common organ involved is the peripheral nervous system. Distal symmetric sensory polyneuropathy, distal motor or combined neuropathy, or mononeuritis multiplex encompass the range of peripheral nervous system manifestations. Mononeuritis multiplex is very specific to systemic vasculitis¹. In our case, both digital gangrene and mononeuritis multiplex were present, indicating involvement of small and medium sized vessels. However, internal organ involvement was not clinically evident in our case. The two main ocular manifestations of RV are necrotizing scleritis and peripheral ulcerative keratitis(13,14). ANCA-associated renal vasculitis and/or necrotizing glomerulonephritis, similar to that seen with Wegener's granulomatosis or microscopic polyangiitis, may occur (15,16). Laboratory tests may support, but do not confirm, a diagnosis of systemic RV. Laboratory findings may include elevations in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), thrombocytosis, hypoalbuminemia, and the anemia of chronic disease. RV is also associated with a number of serological abnormalities, including autoantibodies and hypocomplementemia¹. Among the autoantibodies that have been noted in patients with RV are Rheumatoid factor, Anti-CCP antibodies, antinuclear antibodies, and antineutrophil cytoplasmic antibodies. (ANA) are present in the majority of patients with RV. The ANA are non-specific, however, and do not contribute to either making the diagnosis of RV or following the disease activity in RV(6). ANCA assays do not have an important role in the evaluation of either RA or RV patients (aside from their utility in the exclusion of other conditions). With immunofluorescence testing for ANCA, significant percentages of both RA and RV patients are ANCA positive. The usual immunofluorescence

patterns observed in RA are perinuclear (P-ANCA) and atypical (A-ANCA). Cytoplasmic (C-ANCA) patterns are very rare. In nearly all cases, however, ANCA positivity in RA is caused by one of the “minor” ANCA antigens, eg, lactoferrin, elastase, cathepsin G, or others, not by proteinase-3 or myeloperoxidase, the two antigens strongly associated with systemic vasculitis(17). In our case, there were non-specific features of inflammation, and high titer RF.

RV is suspected on the basis of the presence of compatible clinical features. A diagnosis is most easily attainable when it involves the skin or peripheral nerves¹. Diagnostic criteria for systemic rheumatoid vasculitis were proposed in 1984 by Scott et al⁶. The diagnosis of RV depended on the presence of one or more of the following: (1) mononeuritis multiplex; (2) peripheral gangrene; (3) biopsy evidence of acute necrotising arteritis plus systemic illness;(4) deep cutaneous ulcers in the absence of significant atherosclerosis or active extraarticular disease if associated with typical digital infarcts or biopsy evidence of vasculitis. Our case fulfills 2 of the above mentioned criteria, making RV the most correct diagnosis. Confirmation of RV by biopsy of a clinically involved organ is recommended whenever it is feasible to do so.

Disorders that must be considered in the differential diagnosis of RV include mimics of vasculitis like Infection, thromboembolic diseases, and malignancies(18). The presence of ongoing tissue ischemia without evidence of systemic inflammation should lead to consideration of ischemia related to arteriosclerotic or diabetic microvascular disease¹. In our case the presence of features of systemic inflammation, together with intact peripheral pulses, in proper clinical setting make RV is the most likely diagnosis. Other causes of vasculitis in a patient with RA must also be considered. Polyarteritis nodosa (PAN) shares many features with RV. The key to distinguishing these two disorders is the clinical setting. PAN does not lead to a destructive arthritis. In our case of longstanding history of seropositive, erosive RA, the correct diagnosis is likely RV. ANCA-associated diseases have many features in common with RA. A significant proportion of patients with ANCA-associated vasculitides are rheumatoid factor positive. However, the clinical setting, and the lack of characteristic clinical features of ANCA-associated vasculitis will make RV the most correct diagnosis in our patient. Hypersensitivity vasculitis is usually caused by a reaction to a medication. The presence of systemic signs and symptoms, vasculitic neuropathy, and high titer RF in patient with longstanding, erosive RA will shift the diagnosis toward RV rather than hypersensitivity vasculitis. Patients with Type II and Type III cryoglobulinemia are almost always rheumatoid factor positive. Cutaneous features of small-vessel vasculitis (purpura, pustules), nearly universal in cryoglobulinemia, are not evident in our patient.

Systemic vasculitis has a poor prognosis without immunosuppressive therapy. The combination of daily cyclophosphamide and high-dose glucocorticoids is recommended for patients with severe visceral involvement, including deep cutaneous ulcers, vasculitic neuropathy,

scleritis, digital ischemia, and other significant manifestations of RV(19,20). It is recommended that patients with severe RV receive 1-3 days of pulse methylprednisolone (1 gram IV daily). Pulse glucocorticoid therapy should then be followed by 1 mg/kg/day of prednisone, up to 80 mg/day. In many patients, these high initial doses of glucocorticoid therapy need to be modified because of existing steroid-related morbidity. In our case, the presence of diabetes made us reduce the dose of pulse steroid to 500 mg/day, and subsequently to keep the patient on prednisolone 40 mg/day. The goal of the prednisone taper should be to lower patients' prednisone doses to 20 mg/day by two months of treatment, and then to 5 mg/day or less by six months of therapy. There are no trials in patients with RV that directly compared daily oral cyclophosphamide to intermittent (or pulse) intravenous (IV) cyclophosphamide. However, it is recommended that patients with severe RV begin therapy with daily cyclophosphamide, up to 2 mg/kg per day, assuming normal renal function. For patients who need an alternative to cyclophosphamide for initial therapy of systemic RV, the combination of high-dose glucocorticoids plus azathioprine is a reasonable option(21). An initial dose of azathioprine of 2 mg/kg per day is typically used, although a higher in the absence of contraindications and in the presence of severe disease manifestations. Failure of the combination of high-dose glucocorticoids and azathioprine could be followed by the addition of a TNF inhibitor (22,23). In the rare case that RV appears to progress despite these measures, rituximab is probably the next best option(24), reserving chlorambucil as a last resort. Regarding maintenance therapy the usual practice is to induce remission with cyclophosphamide (typically after three to six months) and then to switch to a less toxic drug, such as azathioprine, to maintain the remission.

Conclusions:

Disorders that must be considered in the differential diagnosis of RV include mimics of vasculitis like Infection, thromboembolic diseases, and malignancies.

Aggressive therapy with immune suppressive drugs is needed to relieve the intense pain caused by this condition, as well as lifesaving, as this manifestation is considered one of the most important poor prognostic features of this disease if untreated.

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