Case report

Testicular vasculitis – a rare manifestation of rheumatoid arthritis

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ABSTRACT

Testicular vasculitis is a very rare extra-articular manifestation of rheumatoid arthritis (RA). We describe the case of a 53-year-old man diagnosed with RA for eight years, who was poorly controlled and developed rheumatoid vasculitis, which manifested as leg ulcers and peripheral polyneuropathy. The patient also had acute neutrophilic meningitis and was treated with antibiotics and intravenous pulse therapy with methylprednisolone (500 mg daily) for three days, followed by oral cyclophosphamide (2 mg/kg daily) and prednisone. Overall improvement was observed, and the patient was discharged. But 15 days later, the meningitis recurred, and the patient was readmitted and treated again with antibiotics. Three days later, he developed pain and enlargement of his left testicle with gangrene. Unilateral orchiectomy was performed, revealing lymphocytic vasculitis. The patient died two days later due to aspiration pneumonia. This case illustrates a rare and severe manifestation of rheumatoid vasculitis.

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Introduction

Rheumatoid vasculitis (RV) is considered a complication associated with longstanding rheumatoid arthritis (RA), usually of more than 10-year duration. RV is associated with a worse prognosis due to the increased morbidity and mortality. It is often manifested by digital infarcts, leg ulcers, systemic manifestations and mononeuritis multiplex, but may involve any blood vessel bed, especially mesenteric, coronary and cerebral arteries. RV is more common in men and some predictors such as smoking, rheumatoid nodules and genetic factors have been recognized. The 30-year incidence of RV is estimated to be 3.6% among patients with RA. A possible approach to the diagnosis of RV is the use of the proposed diagnostic criteria; although helpful, these criteria have not been validated yet.

Testicular inflammation has been recognized as a manifestation of several systemic vasculitides such as Henoch-Schönlein purpura and polyarteritis nodosa or it may occur in an isolated form of testicular vasculitis. In RV testicular involvement is an extremely rare manifestation and to our knowledge there is one case report describing this complication in a patient with RA and another in juvenile chronic arthritis. Herein, we describe a case of RV in a patient with a seropositive and poorly-controlled RA.

Case report

A 53-year-old, white male was admitted in the university hospital because of leg ulcers, tingling, numbness and weakness on distal lower limbs and a worsening of pain and swelling in small and large joints over the last three weeks. Five days before admission he started to present symptoms of fever, severe headache and vomiting. He had been diagnosed with RA for 8 years with symmetrical polyarthritis and a positive rheumatoid factor (RF) 640 IU/mL. In addition, he had a past medical history of systemic hypertension, type 2 diabetes mellitus and smoking. Following the RA diagnosis, he was treated with glucocorticoids (GC) and methotrexate and then with methotrexate and lefunomide 20 mg/day with some improvement of joint complaints that lasted four years. He did not attend the follow-up consultations for the next three years and remained only on prednisone 20 mg QD without any associated immunosuppressive agent.

On examination, the patient was febrile and had mild cushingoid features. Two deep leg ulcers with elevated margins and fibrin were observed on his left leg. Swelling and tenderness were observed over proximal interphalangeal and metacarpophalangeal joints, wrists, elbows and knees, and calculated DAS-28 score yielded a result of 5.0. Neurological examination revealed normal mental status, neck stiffness, decreased deep tendon reflexes in lower limbs, impaired sensitivity below the knees and drop left foot. Cerebrospinal fluid (CSF) analysis was suggestive of bacterial meningitis with 2,832 cells/mm³ (98% of neutrophils), protein 376.5 mg/dL and glucose 69 mg/dL. Gram stain, CSF cultures for aerobic bacteria, fungi and mycobacteria were negative. CSF serologic tests for toxoplasmosis, syphilis, cytomegalovirus, herpes simplex and Cryptococcus were also negative. An incisional skin biopsy showed a non-specific ulcer with neutrophilic vasculitis in a small artery and an electromyography showed motor and sensitive axonal polyneuropathy. RF remained positive (1,280 IU/mL) and anti-profilagrin antibodies were positive (titer 1/320), antinuclear antibodies (ANA), antineutrophil cytoplasmic antibody (ANCA), cryoglobulins and serum tests for HIV, hepatitis B and C were all negative.

The patient was treated with ceftriaxone 4 g/day during 10 days and received intravenous pulse therapy with methylprednisolone 500 mg daily for three days followed by oral prednisone 60 mg/day and oral cyclophosphamide 2 mg/kg/day. An overall improvement was observed for leg ulcers, meningitis, joint complaints and peripheral neuropathy.

Fifteen days after discharge, the patient experienced the recurrence of fever, headache and vomiting. He returned to hospital, underwent another lumbar puncture and CSF analysis showed 4,640 cells/mm³ (84% of neutrophils), protein 276.5 mg/dL and glucose 116 mg/dL. These results confirmed the new onset of meningitis. An infection caused by Listeria monocytogenes was suspected and he was treated with meropenen and ampicillin while the combination of prednisone and cyclophosphamide was temporarily withdrawn. Three days after admission, he complained about scrotal pain and enlargement of his left testicle with the development of signs of gangrene a few hours later. Urologic consultation recommended the surgical procedure and a unilateral radical orchietomy was performed. The evaluation of pathological specimen showed transmural lymphocytic vasculitis in justa-funicular arterial branches with myointimal proliferation (Fig. 1). The patient developed aspiration pneumonia and sepsis after surgery and despite the treatment with antibiotics, vasactive drugs and mechanical ventilation; he died two days later due to septic shock.

Discussion

This case report illustrates the onset of a biopsy-proven RV involving the skin, peripheral nerves and testicular arteries in a patient presenting a poorly-controlled RA with high titers of RF. Although an overall improvement was observed after the initiation of immunosuppressive therapy with a cyclophosphamide and GC, the patient developed life-threatening infection that was considered the leading cause of death. To our knowledge, this is the second case report of RV with testicular involvement in an adult patient with RA. This case is similar to the previously reported regarding RV onset in a middle-aged male patient with a long-term seropositive RA and poor compliance to treatment. Skin and peripheral nerves were involved in both cases and testicular involvement became apparent after an initial improvement with GC and cyclophosphamide. However, our patient presented lymphocytic vasculitis in justa-funicular arterial branches of the testis instead of leukocytoclastic vasculitis observed in the testis in the previously report case. Histopathological demonstration of vasculitis is considered the gold standard for the diagnosis of RV and in the majority of cases pathological specimens demonstrate leukocytoclastic vasculitis. The most typical pathological finding of RV is medial necrosis surrounded by proliferating...
intimal and adventitial cells in a radial fashion similar to the appearance of a rheumatoid nodule. Perivascular infiltrates around normal and necrotizing vessels are also often seen in patients with RV.4,13

Another point worth mentioning regarding our patient is the difficulty to manage his RV due to the several infectious complications observed, including bacterial meningitis before the immunosuppressive therapy, its recurrence after initiating the treatment for RV with the suspicion of listeriosis and the aspiration pulmonary infection that evolved into sepsis and death. Unfortunately, these facts acted as hurdles for the appropriate treatment of RV in our patient and the effects of combining GC and cyclophosphamide may have elicited the recurrence of meningitis. The treatment of RV is largely empirical and the combination of high-dose GC with cyclophosphamide is a well-recognized therapy. In one open-label study,7 21 patients on IV methylprednisolone and cyclophosphamide were compared to 24 patients on other therapies that included azathioprine, D-penicillamine, chlorambucil and high-dose prednisolone. Clinical response was significantly better and the rate of relapses was lower in the cyclophosphamide group.7 Biological therapies with anti-TNFα agents and rituximab have been employed to treat RV in case reports and case series with some success.7,14,15 They may be an alternative in patients with severe RV when cytotoxic agents are contraindicated or fail to control the vasculitic manifestations.1

In conclusion, testicular involvement is a rare manifestation of RV and rheumatologists should be aware of this potential complication especially when the patient complains about pain and testicular enlargement in the context of vasculitic manifestations in RA. Although most patients with RV present cutaneous vasculitis and peripheral neuropathy, internal organs may be affected and prompt investigation and treatment are important for the achievement of better outcomes.

**Conflicts of interest**

The authors declare no conflicts of interest.

**REFERENCES**