REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Case report

Testicular vasculitis – a rare manifestation of rheumatoid arthritis

Alexandre Wagner S. de Souza, Daniela Pereira Rosa, Ana Letícia Pirozzi Buosi, Ana Cecília Diniz Oliveira, Jamil Natour*

Division of Rheumatology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil

ARTICLE INFO

Article history:
Received 20 November 2011
Accepted 14 May 2013

Keywords:
Arthritis, rheumatoid
Rheumatoid vasculitis
Testicular diseases
Sepsis

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.

Vasculite testicular – uma rara manifestação da artrite reumatoide

Palavras-chave:
Artrite reumatoide
Vasculite reumatoide
Doenças testiculares
Sepse

RESUMO

A vasculite testicular é uma manifestação extra-articular muito rara da artrite reumatoide (AR). Descrevemos o caso de um homem de 53 anos com diagnóstico de AR por oito anos, sem controle adequado da doença. O paciente desenvolveu vasculite reumatoide, manifestada por úlceras de membros inferiores e neuropatia periférica. Apresentou ainda meningite neutrofílica aguda, tendo sido tratado com antibióticos e posterior pulsoterapia endovenosa com metilprednisolona (500 mg/dia) por três dias, seguida de ciclofosfamida (2 mg/kg/dia) e prednisona orais. O paciente apresentou melhora do quadro, mas 15 dias após a alta hospitalar, houve reativação da meningite bacteriana. O paciente foi reinternado e tratado novamente com antibióticos. Três dias depois da segunda admissão hospitalar, o paciente apresentou dor, aumento de volume do testículo esquerdo e posteriormente gangrena. Foi realizada orquiectomia unilateral e o exame anatomopatológico revelou vasculite linfocítica. O paciente faleceu dois dias após a cirurgia devido a pneumonia aspirativa. Esse caso ilustra a vasculite testicular como uma manifestação rara e grave da vasculite reumatoide.

* *Corresponding author.*
E-mail: alexandre_wagner@uol.com.br (A.W.S. Souza).

0482-5004/$ - see front matter.

Introduction

Rheumatoid vasculitis (RV) is considered a complication associated with longstanding rheumatoid arthritis (RA), usually of more than 10-year duration.[1] RV is associated with a worse prognosis due to the increased morbidity and mortality.[2,3] 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.[1,4] The 30-year incidence of RV is estimated to be 3.6% among patients with RA.[5] 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.[4,6,7]

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.[8-10] 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.[11,12] 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 leflunomide 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 predinisone 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/mm^3 (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-profillagrin 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/mm^3 (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 orchiectomy was performed. The evaluation of pathological specimen showed transmural lymphocytic vasculitis in justafunicular arterial branches with myointimal proliferation (Fig. 1). The patient developed aspiration pneumonia and sepsis after surgery and despite the treatment with antibiotics, vasoactive 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.[11] 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.[4] The most typical pathologic finding of RV is medial necrosis surrounded by proliferating

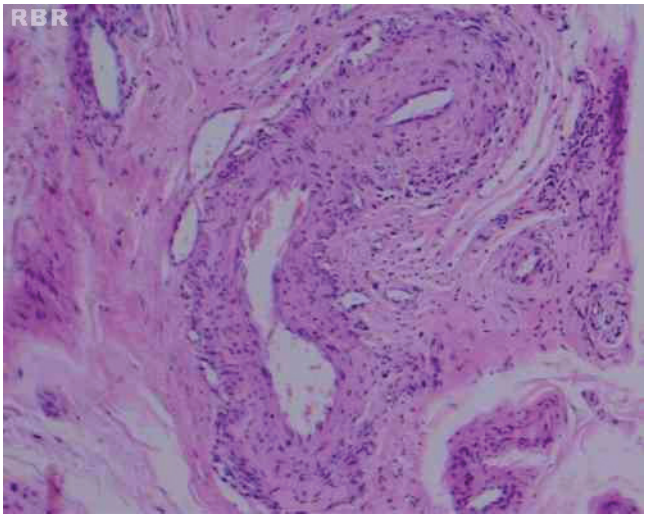

Fig. 1 – Photomicrograph (original magnification x20; hematoxylin-eosin stain) of a section of the left testicle showing transmural lymphocytic vasculitis in justa-funicular arterial branches and intimitis with myointimal proliferation. Seminiferous tubule is atrophic.

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.[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 cutaneuos 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

1. Turesson C, Matteson EL. Vasculitis in rheumatoid arthritis. Curr Opin Rheumatol. 2009;21(1):35-40.
2. Erhardt CC, Mumford PA, Venables PJ, Maini RN. Factors predicting a poor life prognosis in rheumatoid arthritis: an eight year prospective study. Ann Rheum Dis. 1989;48(1):7-13.
3. Puechal X, Said G, Hilliquin P, Coste J, Job-Daslandre C, Lacroix C, et al. Peripheral neuropathy with necrotizing vasculitis in rheumatoid arthritis: a clinicopathologic and prognostic study of thirty-two patients. Arthritis Rheum. 1995;38(11):1618-29.
4. Genta MS, Genta RM, Gabay C. Systemic rheumatoid vasculitis: a review. Semin Arthritis Rheum. 2006;36(2):88-98.
5. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis. 2003;62(8):722-7.
6. Scott DG, Bacon PA, Tribe CR. Systemic rheumatoid vasculitis: a clinical and laboratory study of 50 cases. Medicine (Baltimore). 1981;60(4):288-97.
7. Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. Am J Med. 1984;76(3):377-84.
8. Ben-Sira L, Laor T. Severe scrotal pain in boys with Henoch-Schönlein purpura: incidence and sonography. Pediatr Radiol. 2000;30(2):125-8.
9. Stroup SP, Herrera SR, Crain DS. Bilateral testicular infarction and orchiectomy as a complication of polyarthritis nodosa. Rev Urol. 2007;9(4):235-8.
10. Hernández-Rodríguez J, Molloy ES, Hoffman GS. Single-organ vasculitis. Curr Opin Rheumatol. 2008;20(1):40-6.
11. Mayer DF, Matteson EL. Testicular involvement in rheumatoid vasculitis. Clin Exp Rheumatol. 2004;22(Suppl.36):S62-4.
12. Tangney NJ. Testicular complications in connective tissue disease. Arch Dis Child. 1981;56:651-2.
13. Sokoloff L, Bunim JJ. Vascular lesions in rheumatoid arthritis. J Chron Dis. 1957;5(6):668-87.
14. Puéchal X, Miceli-Richard C, Mejjad O, Lafforgue P, Marcelli C, Solau-Gervais E, et al. Antitumor necrosis factor treatment in patients with refractory systemic vasculitis associated rheumatoid arthritis. Ann Rheum Dis. 2008;67(6):880-4.
15. Assmann G, Pfreundschuh M, Voswinkel J. Rituximab in patients with rheumatoid arthritis and vasculitis-associated cutaneous ulcers. Clin Exp Rheumatol. 2010;28(1Suppl 57):81-3.