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Systemic Rheumatoid Vasculitis: Differential Diagnosis of Consumptive Syndromeina Patient with Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis is a systemic chronic autoimmune disease, where systemic rheumatoid vasculitisis potentially the most severe form of extra-articular manifestation. It is characterized by ischemic-inflammatory tissue damage histologically defined as vasculitis, which can affect different systems, particularly skin and peripheral nervous system.

Our report describes a case of systemic rheumatoid vasculitis in a 74-year-old man, who presented with prolonged clinical picture (4 months) of consumptive syndrome with fever, without any signs/symptoms associated with articular rheumatoid arthritis activity.

Keywords

consumptive syndrome, Fever, Rheumatoid arthritis, Rheumatoid vasculitis

Introduction

Rheumatoid arthritis is a systemic chronic autoimmune disease, in which systemic rheumatoid vasculitisis potentially the most severe form of extra-articular manifestation. It is characterized by ischemic-inflammatory tissue damage histologically defined as vasculitis, which can affect different systems, particularly skin and peripheral nervous system. Depending on its form of expression, it can be difficult to diagnose, requiring high level of suspicion, so that appropriate treatment can be initiated as soon as possible.

With the emergence of disease-modify in ganti-rheumatic drugs (DMARDs), particularly biological drugs, the incidence of systemic rheumatoid vasculitis has decreased considerably [1,2], but it still occurs, especially in high-risk cases such as seropositive rheumatoid arthritis (affecting almost exclusively this population), chronic progressive articular phenotype, smoking, male gender, older age at diagnosis, long-duration disease, occurrence of rheumatoid nodules and presence of HLADRB1 and HLAC3 [3-6]. Nowadays, prevalence is less than 1-5% among the total rheumatoid arthritis population [7,8], with a mortality rate about 30-50% in case series reported [9-10].

We report here a case of an elderly male patient who developed an a typical clinical picture of systemic rheumatoid vasculitis, characterized by prolonged and severe constitutional symptoms, with only late on set of cutaneous necrotizing vasculitis, which made the diagnosis possible.

Case Presentation

JDM, a 68-year-old, white, male, Brazilian, was admitted to Hospital Renascentistain November 2013 because of malaise, appetite loss, poorly characterized sporadic holocranial headache, weight loss of 15 kg and occasional episodes (twice a week) of evening/night fever (Tmax: 38.4°C), which had started about 2 months after an episode of herpes zoster in the right upper arm and shoulder. He had been treated incompletely with oral acyclovir. Concomitant with improvement of skin lesions, he developed severe local neuropathic pain, requiring the use of multiple analgesics for prolonged periods without significant response. On admission to the hospital, the pain in the right upper arm and shoulder slowly fading out was in the process of being resolved, using simple analgesics as needed for headache. He had chronic coronary heart disease with percutaneous angioplasty 2 years prior for the proximal 1/3 of the anterior descending artery because of acute coronary syndrome (unstable angina), hypertension, dyslipidemia, hypothyroidism, left renal cell carcinoma with radical nephrectomy 15 years prior (cure criteria), calculous cholecystitis, renal cortical cyst on the right (BosniakI) and benign prostatic hyperplasia. For 35 years, he had rheumatoid arthritis, characterized by long-standing joint involvement only, with no recurrence of events after the start of treatment. The patient was a chronic user of valsartan (160 mg), bisoprolol (5 mg), simvastatin (20mg) and levothyroxine (100 μg), once a day. Two months prior to his admission, he had stopped taking methotrexate 2.5mg once a week (it had been prescribed by a doctor not known) due to herpes zoster, and previously on his own, he quit using acetyl salicylic acid(100mg) once a day. He was an ex-smoker (4 pack-years), and it had been 16 years since he quit. He had no history of drinking alcohol. On physical examination, he was edemaciated, with mucocutaneous pallor (2/4+) and healing lesions of herpes zoster on the right upper arm and shoulder. He did not show any other change in general clinical and neurologic examination. The result of complementary admission examinations were: Hb: 10.2g/dL, Ht: 30.6%,WBC: 12,900 cells/mm^3 (neutrophilic leukocytosis without left shift), platelets: 320,000/mm^3, AST: 16 IU/L, ALT: 18IU/L AP: 30 IU/L GGT: 28 IU/L, total bilirubin: 0.8 mg/dL, albumin: 3.2 g/dL, CRP: 73mg/L, ESR: 98mm/h, coagulation: normal, electrolytes: normal, blood gas analysis: normal, urinalysis: normal, chest X-ray: increased cardiothoracic index, electrocardiogram: sinus rhythm with no dynamic changes in ST-T segment in the inferior wall, transthoracic echocardiography: discrete tricuspid and mitral regurgitation, urine culture (6 samples): negative, blood cultures (8 samples): negative, and CSF: normal.

During hospitalization, which lasted three months, he continued losing weight rapidly and had weekly episodes of fever and headache. He also showed malaise, significant worsening of hyporexia in need of enteral nutrition, worsening anemia and slight worsening of neutrophilic leukocytosis (reaching 16,300 leukocytes/mm^3), without any skin-articular and/or systemic involvement suggestive of rheumatoid arthritis activity. Because of the lack of definite diagnosis, we performed the following complementary tests: CT of paranasal sinuses, chest, abdomen and pelvis with contrast: no noteworthy changes; fecal occult blood: negative; upper endoscopy: presence of esophageal candidiasis; colonoscopy: normal; cranial MRI: normal; US thyroid: normal; 24-hour urinary cortisol: normal; serum cortisol at 08:00hour: normal; TSH/FT4: normal; serum folic acid: normal; serum vitamin B12: normal; PPD: negative; CEA: normal; CA19-9: normal; alpha-fetoprotein: normal; B-HCG: normal; PSA: normal; anti-HIV: negative; HBsAg: negative; anti-HCV: negative; rheumatoid factor: 124 IU/mL; anti-CCP:

>340 IU/mL; ANA: negative; anti-DNA: negative; anti-ANS: negative; C3/C4: normal; p-ANCA: negative; c-ANCA: negative; serum cryoglobulins: negative; serum IgA: normal; FTA-ABS (IgG and IgM): negative, VDRL: negative; protein electrophoresis: polyclonal hypergammaglobulinemia; toxoplasmosis/CMV/epstein-barr virus/brucellosis/psittacosisserologies (IgM): negative; direct testing and culture for fungi at various sites: negative; direct testing and culture for mycobacteria in various places: negative; iron: 24.6 µg/dL; ferritin: 972 ng/mL; IST: 24%; bone marrow: granulocytic and megakaryocytic hyperactivity and erythrocytic hypoactivity; nasopharyngoscopy: without changes; complete eye examination: without changes.

Because of the single positive finding of esophageal candidiasis, the patient was treated with intravenous fluconazole 200 mg per day for 14 days, without any clinical improvement. At the end of the second month after admission, and after 4 months of the disease, the patient developed an acute decrease in level of consciousness, being referred to the intensive care unit for better support. At this time he developed petechiae in the distal third of leg (Figure 1), which rapidly turned into confluent palpable purpuras with major areas of necrosis (Figure 2). Skin biopsy showed ulcerated skin with dense neutrophilic inflammatory infiltrate, leukocytoclastic, associated with fibrinoid necrosis of perivascular arrangement (Figure 3).

Due to the evidence of necrotizing cutaneous vasculitis, a definitive diagnosis of systemic rheumatoid vasculitis was made and treatment was begun with intravenous methylprednisolone 1g/day for 3 days followed by prednisone 60 mg/day (1g/kg/day) combined with six cycles of intravenous cyclophosphamide 15 mg/kg (every two weeks for the first three cycles and then three-week cycles). The patient´s evolution showed resolution of leukocytosis and fever, as well as significant improvement in general condition, the neurological level and lesions on legs; he was discharged after the third pulse of cyclophosphamide with prednisone 60 mg/day and told to return to the hospital for 3 more cyclophosphamide pulses every three weeks.

After six months, the patient was in excellent general condition, asymptomatic and on prednisone alone (weaning off phase), as he refused further use of the disease-modifying anti-rheumatic drug for chronic treatment of rheumatoid arthritis, which is usually necessary to maintain stable disease and prevent relapse.

Discussion

Systemic rheumatoid vasculitis is a rare complication of rheumatoid arthritis nowadays, mainly due to the effective long-term therapeuties available, the so-called disease-modifying anti-rheumatic drugs (DMARDs) [1,2]. However, the possibility of its occurrence should always be considered in the differential diagnosis in cases of consumptive syndrome associated with fever [11], since this is a potentially fatal condition if not properly treated. Despite its reduced incidence as described above, the clinical course is still unchanged, and mortality of systemic rheumatoid vasculitis has remained high in recent decades, despite the progress in our knowledge and approach of rheumatoid arthritis [2].

As other extra-articular rheumatoid arthritis manifestations, the development of systemic rheumatoid vasculitis appears to be more common in certain groups of patients with rheumatoid arthritis, especially seropositive (affecting almost exclusively this population) and more severe cases,

smokers, males, diagnosed at an advanced age, long disease duration, presence of rheumatoid nodules and presence of HLA DRB1 and HLA C3 [3-6]. The possible association with these factors is the result of an analysis of series cases, and pathogenic mechanisms are not well established, although the severity of chronic disease and its consequential effects, such as increased incidence of extra-articular manifestations, are probably the main risk determinants [12-14].

The pathophysiology of systemic rheumatoid vasculitis is still target of studies and controversies, but it is believed that high serum titers of autoantibodies with consequent activation of the complement cascade and immune-mediated inflammatory tissue injury are fundamental mechanisms of disease development [14,15]. Cellular immune involvement, as well as inflammatory mediators (interleukin-1, interleukin-6 and tumor necrosis factor) seems to play important role in this process, on the basis of evidence of successful treatments with the biological agents anti-TNF (infliximab) and anti-CD-20 (rituximab) [14, 16-18].

The histological finding that characterizes systemic rheumatoid vasculitis is a predominantly neutrophilic inflammatory response, sometimes lymphomononuclear, of blood vessel walls, especially of small- and medium-size vessels, although vessels of any diameter can be affected. The inflammatory lesions usually affect the entire length of the wall and determine vascular and perivascular fibrinoid necrosis and/orleukocytoclasia, with consequent disruption of vascular architecture and formation of intramural thrombi, which impairs local blood perfusion [14].

Systemic rheumatoid vasculitis commonly occurs in patients with severe and long-standing rheumatoid arthritis, with a history of extra-articular involvement, requiring often combined DMARDs therapy. The clinical picture is based on: constitutional symptoms (82%) with or without associated fever; skin involvement (88%), which can happen in the form of petechiae, palpable purpuras developing into necrotizing lesions, ulcers and live doreticularis, among others; involvement of the peripheral nervous system, which can occur mainly in the form of symmetrical distal sensory neuropathy and mononeuritis multiplex (42%); and less frequent involvement of other systems, such as eyes (16%), heart (34%), lungs (34%), kidneys (12%) and gastrointestinal system (10%) [19]. Articular activity of RA is not necessarily present when vasculitis develop, a fact that makes the diagnosis more difficult, requiring high levels of suspicion and a thorough workup. If not promptly recognized and treated, it can lead to progressive organ dysfunction and fatal outcome.

The diagnosis of systemic rheumatoid vasculitis is based on the histopathological finding of vasculitis in patients with rheumatoid arthritis, particularly through skin and peripheral nerve biopsy, tissues that are most affected and easily accessed [14]. However, by the systemic character of the disease, diagnostic systems have been established, especially those of Scott and Bacon [20], which define systemic vasculitis in patients with rheumatoid arthritis who meet at least one of the following criteria: mononeuritis multiplex or acute peripheral neuropathy, peripheral gangrenous lesion, biopsy showing acute necrotizing arteritis in patients with constitutional symptoms, typical deep skin ulcers or extra-articular involvement in a patient with typical digital infarcts and/or biopsy showing vasculitis. Additional nonspecific findings may aid in the diagnostic evaluation, such as neutrophilic leukocytosis, increased CRP and ESR, hyperferritinemia, polyclonal hypergammaglobulinemia in protein electrophoresis, normocytic and normochromic anemia, and hypoalbuminemia, among other changes

linked to systemic involvement, such as pericardial effusion in cases of cardiac involvement. Importantly, virtually all patients who develop rheumatoid vasculitis have increased rheumatoid factor and anti-CCP titers, which must be verified during the investigation.

There is no established treatment protocol for systemic rheumatoid vasculitis. Different forms of therapy are used and their choice is based on individual experience and the severity of the condition. In milder cases with cutaneous involvement, prednisone combined with methotrexate [21,22] or azathioprine [23] can be considered. In more severe cases, the greater results have been described with the use of corticosteroids and cyclophosphamide for a long time (3 – 6 months)(20,24), with different schemes available. Of note is the "CYCLOPS Protocol," used in our case report and described herein. Biological drugs, such as infliximab and rituximab, have been used as a therapeutic alternative in the treatment of the disease, especially in cases refractory to traditional schemes, with reported satisfactory results [14, 16-18].

Our report describes a case of systemic rheumatoid vasculitis in a74-year-old man, who presented with a prolonged clinical picture (4 months) of consumptive syndrome with fever, without any signs/symptoms associated with classic rheumatoid arthritis activity. Only four months after the first symptoms, patient developed cutaneous vasculitis of the legs with subsequent diagnosis of systemic rheumatoid vasculitis (confirmed on biopsy and filling the Scott and Bacon criteria). We then decided to treat him with corticosteroids (initial pulse therapy with methylprednisolone 1 g/day for three days followed by prednisone 1 mg/kg/day) combined with six regular pulses of cyclophosphamide 15 mg/kg (every two weeks in the first three cycles and then every three weeks), with excellent therapeutic response.

Figures

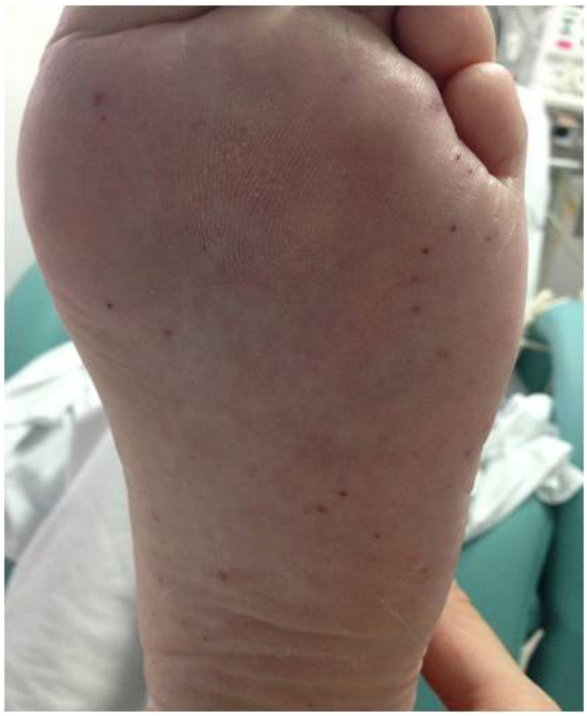

Figure 1: Photograph of sole of left foot of patient: Petechial lesions on sole of left foot of patient.

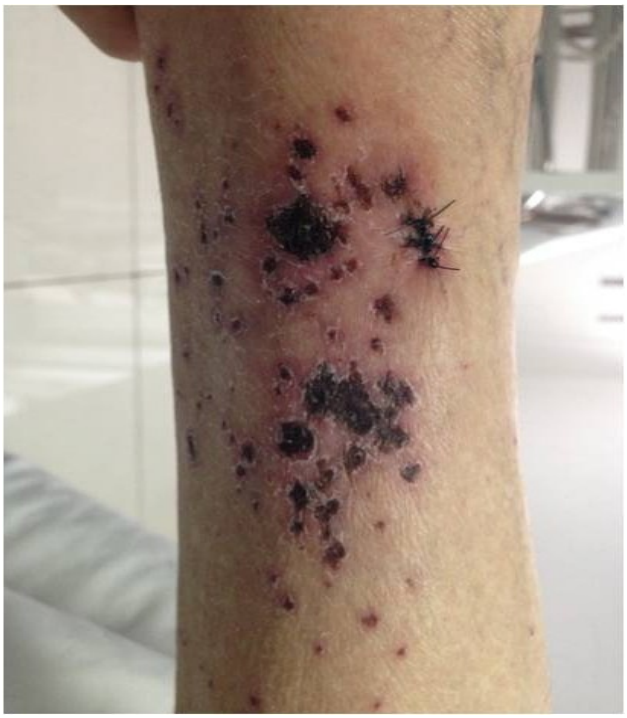

Figure 2: Photograph of side of left leg of patient: Confluent palpable purpuras with substantial areas of necrosis on the side of left leg of patient.

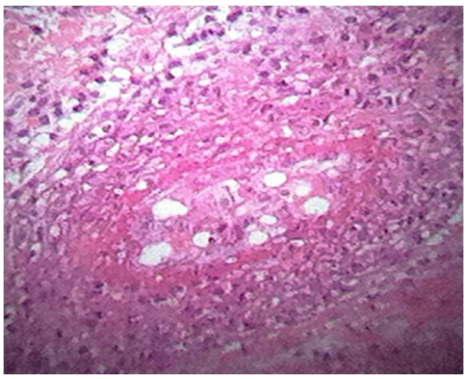

Figure 3: Biopsy of skin lesion on left leg of patient: Histological section (10x) showing vascular structures in dermis that indicate inflammatory infiltrate with frequent neutrophils, sometimes leukocytoclastic, besides fibrinoid necrosis in perivascular arrangement.

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