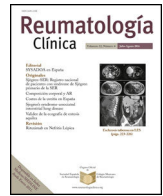




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Case Report

Visceral leishmaniasis in a patient with rheumatoid arthritis treated with methotrexate[☆]

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ABSTRACT

A large number of complications have been associated with rheumatoid arthritis (RA), those of infectious aetiology being of special relevance. Their high incidence is closely linked to the use of immunosuppressive medication.

The spectrum of agents causing opportunistic infections in patients with RA is very broad; however, there are relatively few cases of *Leishmania* infection, especially in patients not being treated with biological drugs.

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Leishmaniasis visceral en un paciente con artritis reumatoide en tratamiento con metotrexato

RESUMEN

Los pacientes con artritis reumatoide (AR) pueden presentar un número amplio de complicaciones, siendo de especial importancia las de etiología infecciosa. Su elevada incidencia está muy ligada al uso de inmunosupresores.

El espectro de agentes causantes de infecciones oportunistas en pacientes con AR es muy amplio; sin embargo, son relativamente escasos los casos de infección por *Leishmania*, especialmente en pacientes sin tratamiento con fármacos biológicos.

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Palabras clave:

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Introduction

Leishmaniasis is a protozoal intracellular infection caused by the bite of a dipteran insect. The development of the disease depends on the virulence of the parasite and host risk factors, essentially the state of their immune system. Patients with rheumatoid arthritis (RA) are chronically treated with methotrexate and other immunosuppressants and are therefore at risk of developing infections.¹ The spectrum of opportunistic infections is very broad in these

patients, however, cases of leishmaniasis are rare, especially in patients treated only with methotrexate.

Clinical case

We present the case of an 84-year-old male, resident of a southern area of Madrid (an area with a high rabbit population), with a personal history of hypertension, diabetes mellitus, dyslipidaemia, heart failure with atrial fibrillation, with pacemaker implantation due to a third degree atrioventricular heart block, diagnosed 6 years earlier with RA with positive rheumatoid factor, positive anti-cyclic citrullinated peptide antibodies, treated with weekly methotrexate 15 mg, with good clinical response. Admitted due to fever, shivering and chills over one week. On physical examination slight bibasilar crackles were observed. No adenopathies, visceromegaly or other data of infectious disease were observed. Analytical tests

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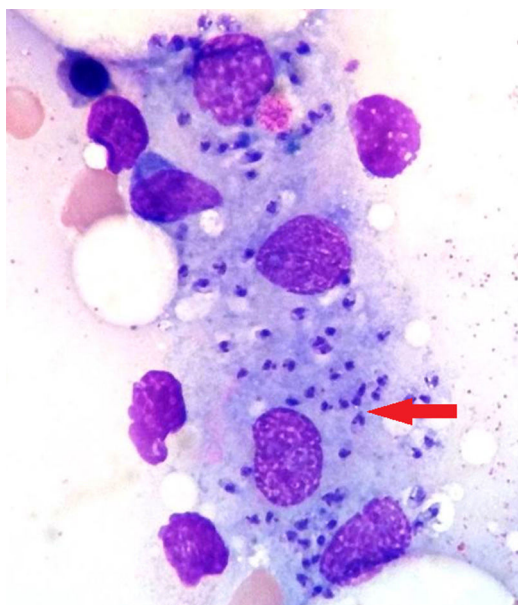


Fig. 1. Bone marrow biopsy: several macrophages can be seen with *Leishmania* amastigotes in their interior (arrow).

revealed pancytopenia (haemoglobin 10.9 g/dl, 2050 leukocytes with 1310 neutrophils/ μ l and 49,000 platelets/ μ l), C reactive protein (CRP) 104 mg/l and erythrocyte sedimentation rate 110 mm/h. Initially medullary toxicity by methotrexate was suspected, with probable bacterial superinfection.

The methotrexate was suspended and several microbiological tests (blood cultures, urine culture, sputum culture, viral and bacterial serologies) and imaging tests (thoracic-abdominal computed tomography, transthoracic and transoesophageal echocardiography) were requested, all of which were not diagnostic of the patient's current condition. Treatment with folic acid and broad-spectrum empirical antibiotics was initiated. Given the persistence of fever and pancytopenia, a bone marrow biopsy was performed to diagnose visceral leishmaniasis (Fig. 1). Serology for *Leishmania* was positive (titre 1/640) as was polymerase chain reaction (PCR) in the bone marrow biopsy and peripheral blood culture. By contrast, peripheral blood culture was negative. Treatment was started with liposomal amphotericin B 200 mg IV initially every 4 days until reaching a cumulative dose of 2400 mg. When the treatment was completed, the patient had recovered from the pancytopenia,

showed a decrease in antibody titres, and CPR in blood remained negative.

Discussion

Leishmaniasis is a zoonosis caused by more than 20 species of intracellular protozoa of the genus *Leishmania*. It is transmitted through the bite of an infected female diptera (*Phlebotomus* and *Lutzomyia* genera). Mammals act as reservoirs, the most important in our environment being dogs and rodents.

The infection may be asymptomatic, localised or disseminated (mucocutaneous or visceral). According to the World Health Organisation, there are between 900,000 and 1.3 million new cases each year worldwide; of these, between 200,000 and 400,000 have the visceral form. In the Mediterranean basin the infection is due to *Leishmania infantum* (*Leishmania donovani* complex), responsible for the visceral form. This is characterised by fever, weight loss, hepatosplenomegaly and pancytopenia. Progression of the disease depends on the aggressiveness of the parasite and on host risk factors such as immunosuppression. The activation of the cell-specific immune response of T helper 1 lymphocytes and the production of macrophage-activating cytokines, such as gamma interferon, interleukin 12 and tumour necrosis factor alpha (TNF- α), play an essential role in defence against the disease. Methotrexate inhibits neutrophil chemotaxis and T lymphocyte proliferation, decreasing macrophage activation and response against the parasite.

Diagnosis can be made from tissue samples (skin, spleen, bone marrow or lymph nodes) by direct visualisation of the parasite, culture or quantification of DNA by CRP. CRP and antibody detection by ELISA or indirect immunofluorescence are performed from peripheral blood.¹

Conclusions

RA affects .5%–1% of the world's population and most patients are treated with methotrexate.² Multiple cases of visceral leishmaniasis have been described in patients with RA on biological therapy, especially in treatment with anti-TNF, but after a review of the literature we found only 9 cases published on patients treated with methotrexate alone, almost all of them in the Mediterranean area (Table 1) and, given the few cases, it is difficult to establish a subgroup of patients that is more susceptible to the infection.

Between 2009 and 2012 there was an outbreak of leishmaniasis in the Community of Madrid, affecting 446 people. Of the 160

Table 1

Cases of visceral leishmaniasis in patients treated with methotrexate described in the literature.

Case	Author, year	Age, sex, country	Comorbidity	Treatment (drug, dose, duration)
1	Toqeer et al., 2012 ⁵	64 years, male, United Kingdom (trips to Spain)	18-Year history of RA	Methotrexate, unknown dose, 3 years
2	Venzelos et al., 2009 ⁶	65 year, female, Greece	8-Year history of RA	Methotrexate, unknown dose, 8 years
3	Harms et al., 2003 ⁷	67 years, male, Italy	Unspecified rheumatological disease	Methotrexate, unknown dose and duration
4	Harmset al., 2003 ⁷	68 years, male, Italy	Unspecified rheumatological disease	Methotrexate and steroids, unknown dose and duration
5	Garcia Olid et al., 2012 ⁸	67 years, male, Spain	5-Year history of RA	Methotrexate, 15 mg/week, unknown duration
6	Garcia Olid et al., 2012 ⁸	51 years, male, Spain	16-Year history of RA	Methotrexate, 10 mg weekly, leflunomide 10 mg daily, unknown duration
7	Karagiannidis et al., 2012 ⁹	79 years, female, Greece	3-Year history of RA	Methotrexate, 10 mg weekly, one year
8	Reina et al., 2016 ¹⁰	64 years, female, Spain	10-Year history of RA	Methotrexate 15 mg weekly, prednisone, unknown duration
9	Trigkidis et al., 2017 ¹¹	71 years, female, Greece	5-Year history of RA	Methotrexate 2.5 mg weekly, 3 years, methylprednisolone 4 mg/day, 3 years

patients with visceral leishmaniasis, 25 were on immunosuppressive therapy.^{3,4}

In conclusion, the presence of fever and pancytopenia in a patient with cell immunosuppression in an endemic area makes it necessary to rule out leishmaniasis. Exclusive therapy with methotrexate (without biological treatments) in RA may be sufficient to increase the risk of this infection. Bone marrow biopsy enables diagnosis of visceral leishmaniasis, as well as ruling out other causes of pancytopenia.¹

Ethical disclosures

Protection of human and animal subjects. The authors declare that neither human nor animal testing has been carried out under this research.

Confidentiality of data. The authors declare that they have complied with their work centre protocols for the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is held by the corresponding author.

Conflict of interests

The authors have no conflict of interests to declare.

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