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Spleen and Liver Enlargement in a Patient With Rheumatoid Arthritis☆

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ABSTRACT

We describe the case of a 51-year-old woman with a seropositive, erosive, and non-nodular rheumatoid arthritis of 15 years of evolution. The patient had poor compliance with medical visits and treatment. She came to the clinic with persistent pancytopenia and spleen and liver enlargement. Liver and bone marrow biopsies were carried out and amyloidosis, neoplasias and infections were ruled out.

We discuss the differential diagnosis of pancytopenia and spleen and liver enlargement in a long-standing rheumatoid arthritis patient.

Hepatomegalia y esplenomegalia en una paciente con artritis reumatoide

Palabras clave:
Hepatomegalia
Artritis reumatoide
Esplenomegalia

RESUMEN

Se describe a una paciente de 51 años de edad con artritis reumatoide de 15 años de evolución, seropositiva –factor reumatoide positivo y anticuerpos antipéptido citrulinado positivos–, erosiva, no nodular, con poca adherencia al tratamiento y controles médicos, que presentó un cuadro caracterizado por pancitopenia persistente y hepatoesplenomegalia. La biopsia hepática y de médula ósea descartó tumores, amiloidosis e infecciones.

Se discute el diagnóstico diferencial de pancitopenia y hepatoesplenomegalia en una paciente con artritis reumatoide de larga evolución.

Case Presentation

The patient is a 51-year-old female diagnosed with rheumatoid arthritis (RA) who met the criteria of the American College of Rheumatology 1987, with disease onset 15 years prior, seropositive (rheumatoid factor [RF] and anti-peptide antibodies citrullinated), erosive disease, non-nodular, who had a family history of lymphoma. She denied substance abuse and toxic tobacco or alcohol use. This patient had been under treatment with leflunomide (6 years), methotrexate (3 years) and hydroxychloroquine (1 year) without response, for which she received 2 months of treatment with etanercept, which was suspended due to a skin reaction. She later received adalimumab during 5 months in 2010, lost to follow-up.

In September 2012 she complained of fatigue, loss of 8 kg of weight in 4 months, grade III dyspnea and abdominal distention for 10 days. On physical examination the patient had no fever (37 °C), was normotensive (blood pressure 110/80 mmHg), presented tachycardia (110 bpm), tachypnea (28 cycles/min), thin skin and pale mucous membranes with multiple bruises. The remainder of the examination showed the presence of a pulmonary systolic multifocal murmur 2/6, bibasal hypoventilation and dullness, globular abdomen with hepatomegaly and splenomegaly, ascites and collateral circulation, and a painful ulcer, 5 cm in diameter on the trochanter of the right hip, and purpura on the legs below the knees. There was hypotrophy of interosseous muscles, ulnar deviation, swan neck deformity and arthritis of the metacarpophalangeal joints of the third right and fourth bilateral fingers. The clinimetry showed HAQ: 2375 and DAS28: 7.29 (ESR: 142 mm in the first hour, 3 swollen joints, 12 tender joints, patient assessment of activity: 100 mm).

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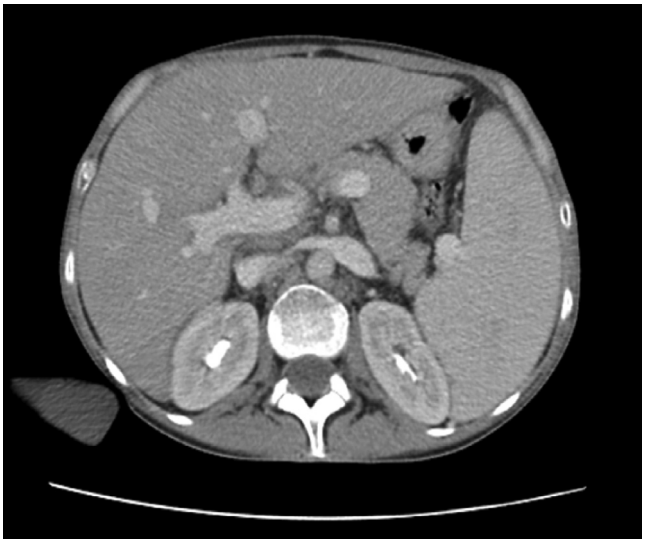

Fig. 1. CT scan of the abdomen showing hepatomegaly and dilated portal and splenic veins.

Laboratory data showed: hematocrit 25%, hemoglobin 7.6 g/dl, WBC 1900 cells/ml, neutrophils 1140 cells/ml, platelets 82 000 cells/ml, CRP 17.4 mg/l, erythrocyte sedimentation rate 142 mm in the first hour, increased alkaline phosphatase (997 U/l), RF (latex: 1/1280), anti-citrullinated peptide antibodies (53.7 U/ml) and anti-nuclear antibodies (Hep2): 1/2560. Renal function, alanine aminotransferase (13 U/l), aspartate aminotransferase (19 U/l), anticardiolipin antibodies, lupus anticoagulant, anti-DNA (*Crithidia*), C3 and C4, and serology for histoplasmosis, HBV and HCV were normal.

Cultures of blood, urine, stool and bone marrow were negative for common bacteria, typical and atypical mycobacteria and fungi. Thoracentesis reported an uncomplicated exudate. Computed tomography with contrast (oral and IV) of the head, neck and pelvis were normal; the scan showed the presence of a bibasal pleural effusion, and the abdomen (Fig. 1) showed homogeneous hepatomegaly (230 mm of longitudinal diameter) and splenomegaly (200 mm of longitudinal diameter). Hepatic vessels on an eco Doppler ultrasound showed dilation of the portal vein (14 mm in diameter) with no evidence of thrombosis. Upper gastrointestinal fiberoptic endoscopy ruled out the presence of esophageal varices.

The peripheral blood smear showed leukopenia and thrombocytopenia, so a bone marrow biopsy was performed, finding hypercellularity with megakaryocytes, myeloid hyperplasia and isolated clusters of mature lymphocytes. The patient began treatment with methylprednisolone 50 mg/day orally for 1 month, with subsequent gradual decline, methotrexate 15 mg/week, calcium, vitamin D and folic acid. However, despite the immunosuppressive therapy, pancytopenia persisted (hematocrit 28.4%, hemoglobin 9.2 g/dl, WBC 3200 cells/ml, platelets 44 000 cells/ml) and the patient showed worsened liver function (alanine aminotransferase: 62 U/l; aspartate aminotransferase: 47 U/l), leading to a liver biopsy.

Based on the results it was decided to treat the patient with prednisone 10 mg/day, methotrexate 10 mg/week, leflunomide 20 mg/day, folic acid, calcium and vitamin D, presenting inactive RA with pancytopenia, but no neutropenia or bleeding.

Differential Diagnosis

Faced with a patient diagnosed with longstanding RA who develops persistent pancytopenia and hepatosplenomegaly, the first step in diagnostic reasoning should be to ask whether it is due to concomitant conditions, treatment, or if it is secondary to the underlying disease.

Infections

Patients with RA have an increased risk of infection.[1] The major risk factors for their development is the presence of extra-articular manifestations, comorbidities, advanced age, leukopenia, and therapy with corticosteroids and biologics, among others.[2] The most common infections are the upper respiratory tract, skin and soft tissue, bones and joints.[3]

Concern about the risk of severe opportunistic infections (histoplasmosis, tuberculosis, leishmaniasis, *Pneumocystis carinii*) among patients with rheumatic diseases has increased, especially since they share several clinical features such as fever, fatigue, chest pain, pleural effusion, diffuse pulmonary infiltrates, pericarditis, myalgia, epistaxis, joint pain, arthritis, erythema nodosum, diffuse papules, lesions in the oropharynx, hepatosplenomegaly, lymphadenopathy, stroke, seizures, endocarditis, anemia, leukopenia, thrombocytopenia, elevated liver enzymes and bilirubin, and uveitis.

Occasionally, histoplasmosis is first manifested by extrapulmonary organ involvement. These isolated lesions are usually considered manifestations of disseminated disease, despite the lack of lung involvement. This situation may mimic other diseases, such as Felty's syndrome, and it is important to suspect it as an unusual manifestation of the disease when it occurs[4,5] in an outpatient setting.

Therefore, although our patient came from an endemic area (the Argentine coast) and histoplasmosis may mimic a flare of RA or an extra-articular manifestation of it (Felty's syndrome: fatigue, joint pain, arthritis, pleural effusion, hepatosplenomegaly, pancytopenia and abnormal liver function), serology, blood, bone marrow and liver cultures were negative for histoplasmosis and deep mycoses, allowing us to rule out this diagnosis.

Neoplasms

RA is characterized by persistent immune stimulation, which could lead to polyclonal lymphocytic proliferation, increasing the potential for malignant transformation.[6] According to some reports, the risk of cancer is two times higher in RA patients compared with the general population, with the estimated risk in these patients for developing lymphoma[7] ranging from 1.5 to 8.7, while the relative risk of developing non-Hodgkin's lymphoma in Felty's syndrome is closest to 13.[8] Anti-TNF drugs do not seem to increase the incidence of lymphoma.[9] Current disease in this case includes a series of hematological symptoms (weight loss, hepatosplenomegaly, leukopenia, anemia, thrombocytopenia) that made us suspect lymphoma. However, the absence of lymphadenopathy confirmed by a CT scan and negative results on bone marrow and liver biopsy allowed us to exclude them.

Amyloidosis

Another rare disease with a poor prognosis associated with longstanding RA patients who present with systemic symptoms, hepatomegaly, cardiomyopathy, neuropathy, purpura and proteinuria, is amyloidosis.

It is characterized by the extracellular accumulation of amorphous, eosinophilic hyaline material.[10] The diagnosis is established by Congo Red staining of rectal mucosa, abdominal fat, and tissues involved.[11] In this patient, no such amorphous material was found in the liver tissue.