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CASE REPORT

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Extrapulmonary Tuberculosis: Unusual Presentation with Bone Marrow Involvement

Tuberculosis extrapulmonar: Presentación atípica de compromiso de la médula ósea

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ABSTRACT

The leading cause of death from a contagious infectious disease worldwide is attributable to Mycobacterium tuberculosis infection. Extrapulmonary tuberculosis accounts for 20-25% of cases of tuberculous disease. Frequently, in order to reach the diagnosis of these sites, invasive diagnostic tests have to be used.

We present the case of a 17-year-old patient with extrapulmonary tuberculosis with bone marrow involvement. The patient wasn't immunocompromised, and had the following symptoms: fever, asthenia, weight loss, tricytopenia and hepatosplenomegaly, without other significant clinical findings. The diagnosis was reached by positive culture for tuberculosis in bone marrow puncture aspiration/biopsy material

After one month of treatment with isoniazid, pyrazinamide, ethambutol and rifampicin, the patient evolved with fever episodes, even after having received antibiotics for urinary tract infection caused by *Klebsiella pneumoniae*. Thus, oral corticosteroid therapy was started, with good response. The patient discontinued treatment after three and a half months due to poor adherence.

Key words: Extrapulmonary tuberculosis; Bone marrow; Cytopenia; Tuberculosis

RESUMEN

La primera causa de muerte por enfermedad infecto-contagiosa a nivel mundial es atribuible a la infección por Mycobacterium tuberculosis. La tuberculosis extrapulmonar representa entre un 20-25% de los casos de enfermedad tuberculosa. Frecuentemente, para arribar al diagnóstico de dichas localizaciones, se debe recurrir a pruebas diagnósticas invasivas.

Se presenta el caso de un paciente de 17 años de edad con compromiso extrapulmonar de tuberculosis en médula ósea sin inmunocompromiso conocido, con síntomas de fiebre, astenia, pérdida de peso, tricitopenia y hepatoesplenomegalia, sin otros hallazgos clínicos significativos.

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Se arriba al diagnóstico por cultivo positivo para tuberculosis en material de punción/biopsia de médula ósea.
Luego de un mes de tratamiento con Isoniacida, Pirazinamida, Etambutol y Rifampicina evoluciona con registros febriles, aún después de recibir antibióticos por infección urinaria por Klebsiella pneumoniae, por lo cual se inicia corticoterapia oral con buena respuesta. El paciente abandona tratamiento luego de tres meses y medio por mala adherencia al mismo.

Palabras clave: Tuberculosis extrapulmonar; Médula ósea; Citopenias; Tuberculosis

INTRODUCTION

Infection by *Mycobacterium tuberculosis* (MTB) still remains the leading cause of death from a contagious infectious disease worldwide.[1] Up to 25% of the tuberculosis cases show extrapulmonary involvement.[2-3] It is caused by hematogenous and lymphatic dissemination of the MTB bacillus to other organs. The most frequent extrapulmonary sites are the lymph node, pleural and osteo-articular sites.[2-3] The problem with these forms of tuberculosis (TB) lies in the difficulty in reaching a definitive diagnosis, since both clinical symptoms and direct bacteriological (paucibacillary forms) and imaging tests can be non-specific. Most of the time it is necessary to resort to invasive diagnostic tests for the collection of biological samples for the genotypic diagnosis, culture in liquid or solid media or anatomic pathology.[2-3]

In immunocompetent and immunocompromised patients, the presentation in the bone marrow as the only form of extrapulmonary involvement is very rare, and there is little information in the literature.[4-10] In general, it is associated with disseminated miliary forms.[7-11]

The aim of this presentation is to describe the case report of a patient in whom bone marrow involvement was the only extrapulmonary site of tuberculosis.

CASE REPORT

Male patient, 17 years old, with no relevant history. The patient was admitted with one month of clinical evolution characterized by fever episodes, unquantified weight loss, night sweats, and adding in the last four days epistaxis and bleeding flictenas in the jugal mucosa. He did not report cough or expectoration. He had no close contact with people with respiratory symptoms.

He presented tricytopenia in the admission laboratory tests, so it was decided to admit him to the General Medicine Ward. There were no significant findings on physical examination. There was no history of immunocompromised disease.

Complementary tests were performed, blood cultures and urine culture (without bacteriological rescue), negative serological testing for human immunodeficiency virus, hepatitis A, B and C, cytomegalovirus and Parvovirus B19; negative PPD (purified protein derivative); echocardiogram with no vegetations, abdominal ultrasound showing hepatosplenomegaly without pathological findings, chest X-ray without pleuropulmonary pathology. A full body CT scan was performed and the only relevant finding was homogeneous hepatosplenomegaly. A positron emission tomography was requested with evidence of splenomegaly without pathological uptake. As the patient continued with fever episodes and tricytopenia, a consultation was made with the Hematology Department: a bone marrow puncture aspiration and biopsy were performed, showing hypercellularity for age with dysplasia in the erythroid and megakaryocytic series. A sample was sent for culture in Lowenstein Jensen's solid medium, which reported growth of *Mycobacterium tuberculosis*, so self-administered treatment was started with isoniazid 5 mg/kg/day, rifampicin 10 mg/kg/day, pyrazinamide 25 mg/kg/day and ethambutol 20 mg/kg/day orally. The antibiogram reported sensitivity to isoniazid and rifampicin. The patient evolved with daily fever episodes despite receiving anti-tuberculous treatment, so blood cultures without rescue, and urine culture (*Klebsiella pneumoniae*) were performed. He completed seven days of treatment with imipenem without changes in the thermal curve. After being evaluated by the Hematology Department, other causes of hematological involvement were discarded. On day 32 of anti-tuberculous treatment, it was decided that the patient should be started on oral corticosteroid therapy (meprednisone 40 mg/day orally) with good response. The patient evolved afebrile and without complications, with improvement of hematological parameters twenty days after starting meprednisone. He was discharged from hospital after 52 days of anti-tuberculous treatment and on replacement therapy with hydrocortisone. He continued treatment on an outpatient basis with regular adherence and clinical improvement. Subsequently, he discontinued anti-tuberculous treatment after three and a half months. A bone marrow biopsy was still pending.

DISCUSSION

Due to the biological characteristics of the MTB bacillus, it is able to affect almost any tissue. Extrapulmonary TB can present with various he-

matological manifestations frequently associated with the involvement of other organs, including pancytopenia.[2-3] Pancytopenia could be due to hypersplenism, maturation arrest, hemophagocytic lymphohistiocytosis, and infiltration of the bone marrow by caseating or noncaseating granulomas that cause reversible or irreversible fibrosis.[10-13]

Extrapulmonary TB is defined according to the classification criteria of the World Health Organization as an infection produced by MTB that affects tissues and organs outside the pulmonary parenchyma. It accounts for 20-25% of the cases of tuberculous disease.[1] It is the result of hematogenous and lymphatic dissemination of the MTB bacillus. As a result of this dissemination and thanks to the development of specific cellular immunity, including the formation of anti-tumor necrosis factor antibodies, interleukin-12 and interferon gamma, protective immunity is created against the bacterium, with the consequent formation of encapsulated granulomas containing viable bacilli inside.[1]

In our service between 1979 and 2019, 4,283 patients were diagnosed with various forms of TB presentation, but there was only one case with bone marrow involvement as unique site of disease presentation (prevalence 0.02%). We present the case of a 17-year-old patient with hematological alterations (tricytopenia), asthenia, fever and weight loss, with no other positive findings on physical examination, no known immunocompromise, negative cultures, negative serology and hepatosplenomegaly. Bone marrow puncture aspiration was performed and Lowenstein Jensen's solid medium culture allowed the diagnosis of TB.

Extrapulmonary TB can present with various hematological manifestations. Various hematological manifestations in patients with pulmonary and extrapulmonary TB have been described.[7-11] Normochromic normocytic anemia was the most common abnormality observed in all studies.[7,11] Other hematological abnormalities of white blood cells include leukopenia, neutropenia, lymphocytopenia, monocytopenia, leukocytosis, neutrophilia, lymphocytosis and monocytosis.[3,7] Pancytopenia was observed only in patients with disseminated TB and can be explained by granulomatous TB infiltration, macrophage activation syndrome or hemophagocytic lymphohistiocytosis syndrome.[5-6] This often fatal syndrome responds to an ineffective inflammatory response, characterized by excessive macrophage and T-cell activation, as well as decreased activity of natural killer and cytotoxic lymphocytes to attack infected cells. This results in uncontrolled histiocytic phagocytosis of mature blood cells and their precursors in the reticuloendothelial system. Our patient had hepatosplenomegaly. This disproportionate response leads to cytokine-mediated multiple organ dysfunction.[5-6] Another explanation that we ruled out which could explain hepatosplenomegaly is as a clinical form of presentation of disseminated TB.[7,11] In general, when there is hepatic involvement due to TB, liver enzymes tend to be elevated (this was not the case in our patient), and if the spleen is also involved, hepatosplenic radiological lesions can often be observed (for example, single or multiple nodules) on abdominal CT scan or abdominal ultrasound (again, this was not the case).

In a series of 22 cases in Saudi Arabia reported by Hakawi et al, 55% had no history of immunocompromise, as did some reported cases and our patient.[8,11]

Thrombocytopenia was also very common in patients with disseminated TB and thrombocytosis in patients with pulmonary TB.[6,7] Bone marrow puncture aspiration or biopsy are useful to confirm the bacteriological and/or histological diagnosis.[9] Late diagnosis of extrapulmonary forms is frequent and leads to increased morbidity and mortality. Symptoms and signs can be relatively vague and sometimes present on normal chest X-rays and in patients with negative bacilloscopy, making it difficult to consider the disease in the initial approach.[3]

In many case reports or the Indian series of 32 cases with disseminated forms and 23 pulmonary cases with bone marrow involvement, evolution with anti-TB treatment was favorable, but in the series of 22 cases of Hakawi et al 45% of patients died probably due to immunocompromise associated with disseminated forms.[7-11] Our patient began treatment with four first-line drugs for TB and due to the lack of response after the first month, systemic corticosteroids were added, and the patient evolved until the fever disappeared. Unfortunately, follow-up was lost after multiple dropouts due to poor adherence and social vulnerability of the patient.

Regarding the use of corticosteroid therapy in TB, only with a high level of evidence it can be recognized for the treatment of tuberculous

meningitis and pericarditis.[13] There is *in vitro* evidence that corticosteroids in MTB infection can protect pulmonary fibroblasts from mycobacterial death and reduce intracellular bacterial growth in human monocyte-derived macrophages.[14-16] They would prevent necrotic cell death of MTB-infected cells by facilitating mitogen-activated protein kinase-dependent dephosphorylation. These findings could explain how the use of corticosteroids could be beneficial in specific cases of TB treatment.[12-14] However, there is no evidence for their use in a clinical situation as that of our patient.

In conclusion, we present a very rare case of extrapulmonary TB with bone marrow involvement without known immunocompromise. A high index of suspicion of TB is required and other hematological diseases must be discarded. In our case report the diagnosis was made by culturing bone marrow puncture aspiration/biopsy material for TB in a patient presenting with tricytopenia under study and symptoms of fever, asthenia and weight loss without any other significant clinical finding.

Conflict of interest: Authors have no conflicts of interest to declare.

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