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Case Report

Paracoccidioidomycosis in a liver transplant recipient

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Abstract

Paracoccidioidomycosis is a granulomatous systemic mycosis that is endemic in Latin America; it is an extremely rare infection following solid organ transplantation. In this study, we describe the first report of disseminated paracoccidioidomycosis in a 3-year-old girl who underwent liver transplantation 2 years previously. The radiologic diagnosis and patient follow-up are described. In addition, we review the clinical evolution and treatment regimens for this infection.

Keywords: Paracoccidioidomycosis. *Paracoccidioides brasiliensis*. Organ transplant.

INTRODUCTION

Paracoccidioidomycosis, a systemic mycosis endemic in Latin America, usually affects previously healthy adults. It is an extremely rare infection following solid organ transplantation[1]. The diagnosis and clinical management of paracoccidioidomycosis in transplant recipients are challenging owing to the complexity of the disease and the paucity of published literature on this subject. In this study, we describe the first report of paracoccidioidomycosis in a liver transplant recipient. The patient developed disseminated paracoccidioidomycosis 2 years after undergoing liver transplantation. The radiologic diagnosis and patient follow-up are described. In addition, we review the clinical evolution and treatment alternatives for this infection.

CASE REPORT

This case study involves a 3-year-old girl who was diagnosed with congenital biliary atresia and subsequently received a living donor liver transplant when she was 9 months old. The surgical procedure was uneventful and the patient began receiving tacrolimus (2mg in the morning and 1mg at night) as immunosuppressive treatment, which was well tolerated. She lived in a rural area of Ribeirão Preto, SP. This area is in a region of Southeastern Brazil where paracoccidioidomycosis is endemic[1,2]. However, there were no prior cases of paracoccidioidomycosis in her family.

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The patient presented with a fever and dry cough approximately 24 months after undergoing liver transplantation. Physical examination revealed multiple skin lesions characterized by papular lesions, nodules, and ulcers covered in scabs involving multiple regions (upper limbs, abdomen, and face); hepatomegaly; splenomegaly; and peripheral lymphadenopathy in both axillary chains. The rest of the physical examination was unremarkable. Laboratory evaluation revealed a normal hemoglobin level (11.5g/dL) and platelet count (160,000/μL). The white blood cell count result showed eosinophilia (6.3%; 880 cells/mm^3). Serum liver function tests revealed high levels of the enzymes alanine transaminase (152U/L), aspartate transaminase (307U/L), and alkaline phosphatase (2,796U/L); elevated levels of direct and indirect bilirubin (15.9mg/dL and 2.46mg/dL, respectively); and a low serum albumin level (3.0g/dL). All serologic tests for viral antigens were negative. The antibody tests for syphilis and Chagas disease were non-reactive.

A contrast-enhanced multi-detector computed tomography (MDCT) scan of the abdomen was performed. The image demonstrated multiple clusters of enlarged lymph nodes in the retroperitoneal, perihepatic (around the common bile duct), and mesenteric chains. Several of the lesions displayed areas of central necrosis/liquefaction (**Figure 1A** and **Figure 1B**).

Additionally, a computed tomography (CT) scan of the chest and neck demonstrated lymphadenopathy involving the mediastinal, hilar, and diaphragmatic chains, and the submandibular, submentovertical, and supraclavicular spaces (**Figure 2A**). Interlobular septal thickening with associated ground glass opacification was observed in the lung parenchyma bilaterally (**Figure 2B**). The imaging and clinical findings suggested a lymphoproliferative disorder or opportunistic infection. Therefore, we considered infections caused by fungi, viruses, and mycobacteria as part of the differential diagnosis.

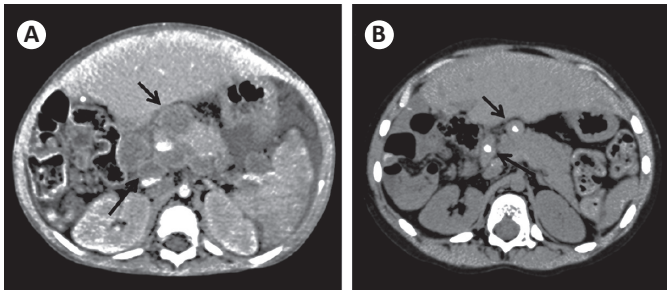

FIGURE 1 - (A) Axial contrast-enhanced MDCT image showing retroperitoneal and mesenteric lymphadenopathy with central areas of decreased attenuation representing liquefaction/necrosis, forming large conglomerates (black arrows). (B) Axial MDCT image after treatment, demonstrating marked decrease in the size of the lesions and gross calcification. MDC: multi-detector computed tomography.

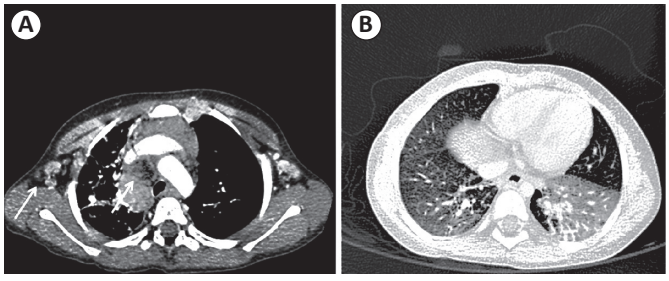

FIGURE 2 - (A) Axial MDCT image showing multiple enlarged mediastinal and axillary lymph nodes (white arrows). (B) Bilateral ground glass opacification, most evident in the superior segment of the lower left lobe. MDC: multi-detector computed tomography.

The patient underwent ultrasound-guided biopsies of the skin lesions, cervical lymph nodes, and liver. Examination of the cervical lymph node biopsy demonstrated chronic granulomatous inflammation with numerous fungi and giant cells, compatible with *Paracoccidioides brasiliensis* infection (**Figure 3**).

The biopsy of the liver showed granulomatous hepatitis with *Paracoccidioides brasiliensis*. Anti-*Paracoccidioides* antibodies were present in the serum, detected by quantitative counterimmunoelectrophoresis (titer: 1/64). The patient was treated with sulfamethoxazole/trimethoprim (200/40mg 12 hourly). However, the fever and dyspnea persisted for 6 weeks; hence, amphotericin B was introduced (1mg/kg/24 hours). Tacrolimus was suspended during antimicrobial treatment. The child was subsequently transferred to an intensive care unit for 3 months, and combined treatment with both drugs (sulfamethoxazole/trimethoprim + amphotericin B) was continued for 5 months. During hospitalization, the child received a cumulative dose of 2,745mg of amphotericin B.

An MDCT scan, repeated after complete remission of all symptoms, showed substantial reduction in the size of the enlarged lymph nodes scattered throughout the neck, chest, and abdomen, with gross calcification of the residual lesions (**Figure 1B**). After treatment, the titer of anti-

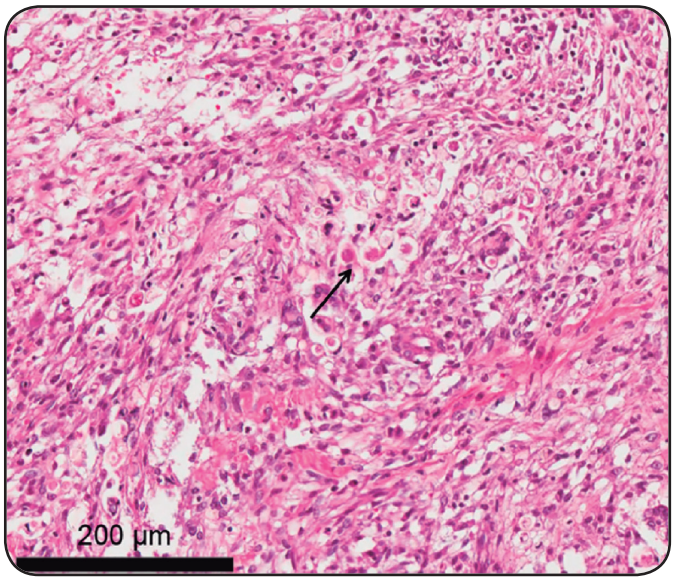

FIGURE 3 - Photomicrograph of a hematoxylin-eosin stain of a cervical lymph node specimen demonstrating collections of epithelioid macrophages with small round structures (black arrow), consistent with *Paracoccidioides brasiliensis*.

Paracoccidioides antibodies in the serum by quantitative counterimmunoelectrophoresis had decreased to half. After hospital discharge, the patient received sulfamethoxazole/trimethoprim (100/20mg 12 hourly) for another 6 months. After 3 years of follow up, the patient has remained asymptomatic with regression of jaundice, but residual calcified lymph nodes are evident on imaging surveillance. She continues to receive tacrolimus as immunosuppressive therapy.

DISCUSSION

Opportunistic infections are the leading cause of death in the first three years following liver transplantation[2]. The most common types of infections are bacterial (48%), fungal (22%), and viral (12%)[3]. Fungal infections caused by *Candida* species are the most common and those caused by *Aspergillus* species are the second most common[2]. Other endemic mycoses, such as *Histoplasma capsulatum*, *Coccidiodes immitis*, and *Blastomyces dermatitidis*, may also occur. However, the patient described herein represents the first report of paracoccidioidomycosis following liver transplantation.

Paracoccidioidomycosis is a relatively common fungus found in Latin America; approximately 80% of cases occur in Brazil, where the incidence is 1-3 cases per 100,000 inhabitants[4]. *P. brasiliensis* is a thermally dimorphic fungus that typically infects healthy adults. Infection primarily involves the lungs and then disseminates to other organs[5]. Paracoccidioidomycosis is very rare in transplanted patients and a limited number of reports have been described in kidney transplant recipients. In our case, the lungs, skin, and lymph nodes were involved. These findings are consistent with the pattern of involvement in children, described by Pereira et al., in which the reticuloendothelial system, especially lymph node enlargement, hepatomegaly,

and splenomegaly, are encountered[6]. This differs from the pattern observed in adults, where lung involvement is most common; most children present with reticuloendothelial system involvement[7]. Hepatic abnormalities are also associated with paracoccidioidomycosis and occur in almost half of the cases[6].

In this report, we used repeat imaging investigations to reveal decreased lymph node size and progressive gross lymph node calcification after 5 months of follow-up. Similarly, calcified lymph nodes were reported in three (11.5%) patients in a series of 26 cases of paracoccidioidomycosis who underwent abdominal CT[8]. However, this previous study did not describe the current or previous use of medication to treat paracoccidioidomycosis.

The epidemiologic characteristics of the current case are also important because the patient was 3 years old at diagnosis. Paracoccidioidomycosis typically manifests between the third and sixth decades of life and is more frequent in men living in rural areas due to their exposure to soil (fungal habitat). Factors that probably contributed to this infection were residency in a rural area and exposure to logging of extensive areas of forest, especially for agricultural purposes. A previous review of 524 patients found that only 16% of patients were younger than 25 years; the youngest was a 5-year-old boy[9]. In another report, Pereira et al. described a case of fatal disseminated paracoccidioidomycosis in a 2-year-old child; this is the youngest reported case[7].

Our patient had high levels of direct bilirubin, probably related to hepatitis and obstructive jaundice, caused by enlargement of the hilar lymph nodes around the common bile duct. These findings are consistent with the patterns described by Chaib et al. who reported that hepatic abnormalities occurred in almost half of the episodes of paracoccidioidomycosis[6,10]. The gold standard for the diagnosis of paracoccidioidomycosis is isolation of fungal elements by direct mycologic culture of materials allegedly affected. In such cases, histopathologic examination shows a proliferative and/or exudative reaction with granulomas containing *Paracoccidioides* spp[11]. Serologic tests can be performed if the lesions are not easily accessible; these methods show specificity values of 85-100%, depending on the technique. Immunodiffusion and immunoelectrophoresis can be used to detect anti-*Paracoccidioides* antibodies, however cross-reactivity may occur with other systemic mycoses, such as cryptococcosis, histoplasmosis, aspergillosis, and candidiasis[11-12].

Paracoccidioides brasiliensis is sensitive to most antifungal agents including amphotericin B, sulfamethoxazole/trimethoprim, and the azoles (ketoconazole, itraconazole, fluconazole). However, the azoles should be avoided in patients with impaired liver function (liver enzyme levels more than 4 times above the normal limit); these patients can be treated with sulfamethoxazole/trimethoprim or amphotericin B deoxycholate[11]. Treatment should continue until all cure criteria are achieved. These criteria include the following: symptom resolution, stabilization or regression of radiologic findings, and negative/stabilized immunodiffusion titers (to less than 1:2)[11,13].

In conclusion, paracoccidioidomycosis is extremely rare in organ transplant recipients. However, this infection must be considered in patients from Latin America presenting with enlarged lymph nodes and concurrent lung and skin lesions.

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