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Case Report

Mixed and disseminated paracoccidioidomycosis after liver transplantation: Case report

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ABSTRACT

Paracoccidioidomycosis (PCM) is a systemic granulomatous fungal infection rarely associated with solid organ transplantation. We report the second case of PCM in an adult after liver transplantation. A 47-year-old woman who had undergone liver transplantation was hospitalized for flu-like symptoms and multiple erythematous ulcerated skin papules. There was lymphadenopathy, pulmonary compromise, and quickly progression to septic shock. PCM was confirmed by skin biopsy and serologic tests, and a satisfactory response to amphotericin B was achieved.

1. Introduction

Paracoccidiidioidomycosis (PCM) is an autochthonous systemic granulomatous infection in Latin America caused by fungi of the genus *Paracoccidoides*, such as *P. brasiliensis*, *P. americana*, *P. restrepiensis*, *P. venezuelensis* and *P. lutzii* [1]. The disease incidence varies from 3 to 4 cases/million/year in non-endemic regions versus 1 to 3 cases per 100, 000 inhabitants/year in endemic areas [2]. About 80% of cases occur in Brazil, affecting mostly men between 30 and 60 years old [3]. Usually, PCM is not related to immunosuppressive conditions, unlike other mycoses such as candidiasis, aspergillosis and cryptococcosis [2].

Brazil has the second-highest absolute number of hepatic and renal transplants in the world, and although PCM is rarely a consequence of either of them, its mortality may reach 33% [2,4–6]. To date, only 11 cases of PCM have been reported after solid organ transplantation (9 of them after kidney transplantation) [6].

The first case of PCM after liver transplantation was a 3-year-old girl who had biliary atresia. She presented with ulcerated papules on her face, trunk and abdomen associated with lymphadenopathy, evolving to pulmonary and hepatic disease [4]. In 2019, the first published case of an adult afflicted by PCM after liver transplantation described a 53-year-old man with alcoholic liver cirrhosis who had cutaneous abscesses, lymphadenopathy, pulmonary, bone and adrenal compromise 19 months after the surgery [6]. Both patients used Tacrolimus. We report the second case of PCM after liver transplantation in adults, affecting a woman who presented the mixed form of the disease.

2. Case presentation

The patient is a 47-year-old Brazilian woman living in a rural area of São Paulo state, who had worked as a coffee harvester. She had undergone liver transplantation due to alcoholic liver cirrhosis. Although the liver donor serological tests had shown no prior exposure to hepatitis B virus, she acquired acute hepatitis B immediately after the surgery.

On May 6th, 2019, one year after the liver transplantation, the viral infection was under control and she was taking Tacrolimus 1 mg/day, Mycophenolate 360 mg twice daily, Tenofovir 300 mg/day and Acetylsalicylic Acid 100 mg/day. However, she was hospitalized for

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asthenia, fatigue, generalized myalgia, dyspnea, dry cough, vomiting and fever (38-39 °C) during the last four days. On physical examination, she had multiple erythematous papules, some of them with ulcerated center, located on the chest, upper limbs, and face (Fig. 1A). She was in poor general condition, with tachycardia (118 bpm), blood pressure of 100/60 mmHg, dyspnea, oxygen desaturation, decreased vesicular murmur in the right pulmonary base and crackling in the inferior/lower third of the right lung.

Biopsies of the skin lesions were carried out on the same day (day 0). Chest X-ray showed hilar enlargement and right pleural effusion with diffuse alveolar opacities, preserving only the upper lobe of the right lung (Fig. 2A). Empiric therapy with cefepime 2 g/day was initiated aiming to treat a possible pneumonia. Opportunistic infections such as tuberculosis, atypical mycobacteriosis, histoplasmosis, cryptococcosis, PCM and aspergillosis were investigated.

The blood cell count revealed 6200 leukocytes/mm3 with no left shift, hemoglobin of 10.4 g/dl, hematocrit of 32.3% and 70,000 platelets/mm3. Urea and creatinine levels were 157 mg/dl and 2.9 mg/dl, respectively. The international normalized ratio (INR) was 2.39, whereas serum albumin was 2.1 g/dl. Total bilirubin and aspartate aminotransferase were increased (2.5 mg/dl and 69 U/L, respectively) and serum Tacrolimus concentration was 13.8 ng/mL (therapeutic level). Serologies for hepatitis C and human immunodeficiency virus (HIV) were negative.

One week after admission (day 7), she developed hypotension, bradycardia, impaired consciousness, hemoptysis, hematuria, hematoma in the left upper limb, periorbital ecchymosis, and bilateral subconjunctival hemorrhage (Fig. 1B). A progressive worsening was also detected through laboratory tests that showed anemia, leukopenia, lymphopenia, and thrombocytopenia. The INR was 3.45, the activated partial thromboplastin time was 3.78 seconds, and the platelets count was 24,000/mm3. Fibrinogen consumption (91 mg/dL) and increased D-dimer (2328 ng/mL) were also registered, confirming the presence of disseminated intravascular coagulation (DIC). She was transferred to the intensive care unit, where hemodialysis was started. Daily transfusion support was provided and the antibiotic treatment was expanded to meropenem and vancomycin.

Chest computed tomography (CT) revealed lymph node enlargement of up to 15 mm in the prevascular, infracarinal, paraesophageal and paratracheal areas (Fig. 2B). Consolidations of nodular aspect, poorly defined, were mainly observed in the right lower lobe and at the base of the middle lobe, with air bronchograms. A cavitation of 2.1 × 2.5 × 1.7 cm in the posterior segment of the right upper lobe was also detected (Fig. 2C), as well as the inverted halo sign (Fig. 2D), suggesting fungal etiology. Tacrolimus was stopped and intravenous amphotericin B lipid complex 5 mg/kg/day was initiated in the same day (day 7).

The skin biopsy showed a suppurative granulomatous inflammatory process with multinucleated giant cells in the Hematoxylin & Eosin staining, while leveduriform structures with birefringent capsule and multiple sporulations were found in the Grocott-Gomori silver metenamine staining, enabling the diagnosis of PCM (Fig. 3). Serological double immunodiffusion test was also positive for PCM (1:8 titration). After 28 days of hospitalization (day 28), amphotericin B was replaced by sulfamethoxazole/trimethoprim 160/800 mg PO twice daily, with significant renal function recovery. One month after admission (day 30), the patient was discharged taking only this latter antibiotic, with clinical and radiological improvement, and the immunosuppressants were reintroduced.

3. Discussion

Opportunistic infections are the leading cause of death in the first three years after liver transplantation [7], either by bacteria (48%), virus (12%) or fungi (22%) [8]. In the latter group, Candida and Aspergillus infections are the most frequent, followed by *Histoplasma capsulatum*, *Coccidiodes immitis* and *Blastomyces dermatitidis* [7]. PCM is seldom associated with immunosuppression. However, there are reports related to HIV infection, neoplasms, and rarely to immunobiological usage and organ transplantation [2]. Labor activities related to soil and harvesting, as in the case reported herein, are the major risk factor due to the inhalation of fungal infecting propagules (conidia), which are the transmissible form of PCM [2,6]. The disease is more frequent between 30 and 60 years, affecting 10 to 15 men for each woman.

The acute/subacute (juvenile) form is common in children, adolescents, and young adults, representing 5–25% of cases. This form is characterized by rapid evolution, affecting multiple organs and leading to high fever, hepatosplenomegaly and lymphadenopathy [2]. The chronic form (adult) can be found in more than 80% of cases and may be silent [2], but often has an insidious onset followed by symptoms that last longer than four months until the disease is discovered, occasionally simulating other diseases, including neoplasms [9]. As in the acute/-subacute form, it may present with mucosal and skin lesions, but pulmonary involvement occurs in more than 90% of cases. In contrast, in the acute/subacute form the pulmonary lesions are limited or absent.

According to the new classification proposed in the most recent 2017 Brazilian consensus on PCM, there is a third type characterized by the overlapping of the two classical forms that is the so-called mixed form. The manifestations are usually severe, disseminated, and linked to

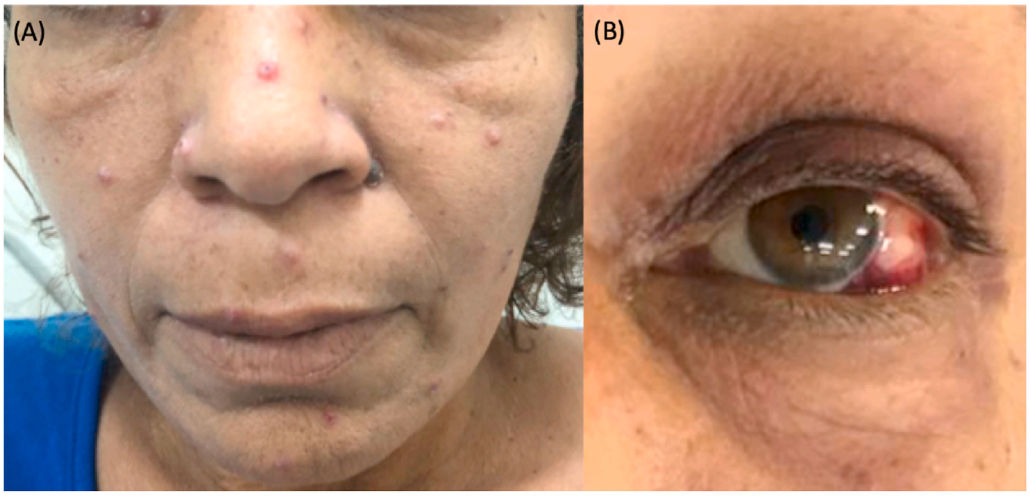

Fig. 1. Clinical presentation of paracoccidioidomycosis after liver transplantation. A: multiple erythematous papules on the face, some of which exhibit ulcerated center. B, periorbital ecchymosis and subconjunctival hemorrhage due to disseminated intravascular coagulation caused by the fungal infection.

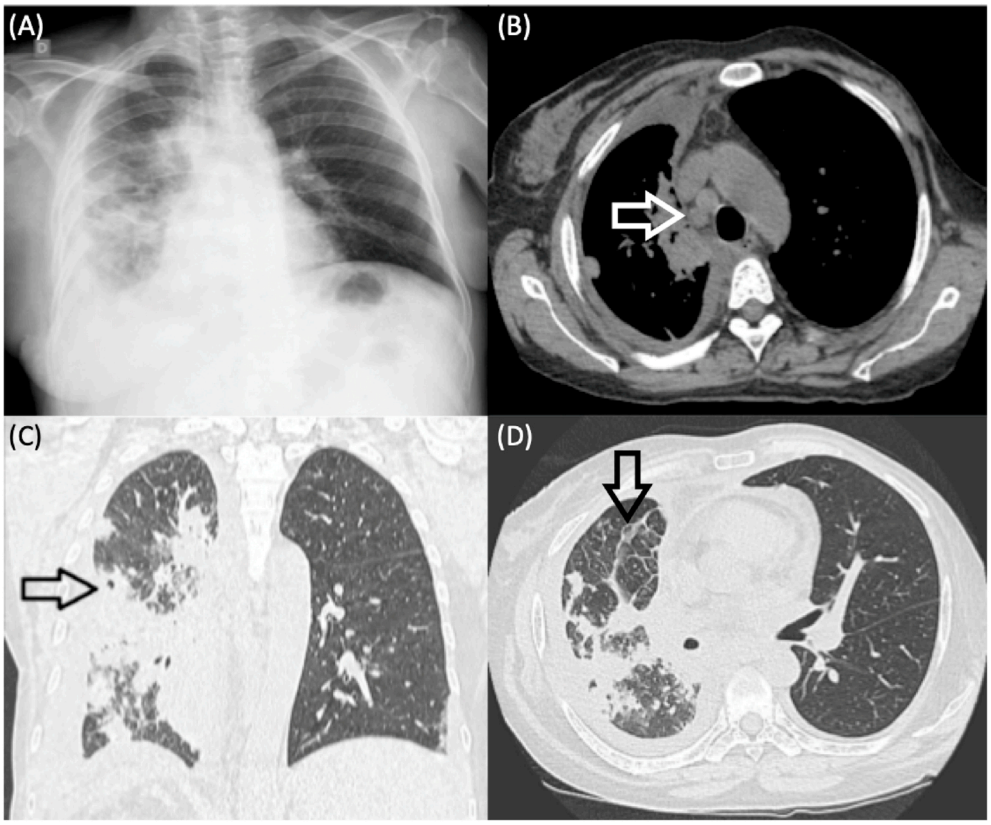

Fig. 2. Radiological findings in the liver transplant recipient with Paracoccidioidomycosis. A: chest X-ray displaying right pleural effusion associated with poorly delimited and diffuse alveolar opacities, preserving only the periphery of the right upper lobe, whereas the left lung showed preserved radiolucency. B: axial image from chest computed tomography (CT) displaying enlarged hilar and paratracheal lymphadenopathy (arrow). C: coronal image from chest CT showing a cavitated nodule (arrow). D: axial image from chest CT highlighting the inverted halo sign (arrow).

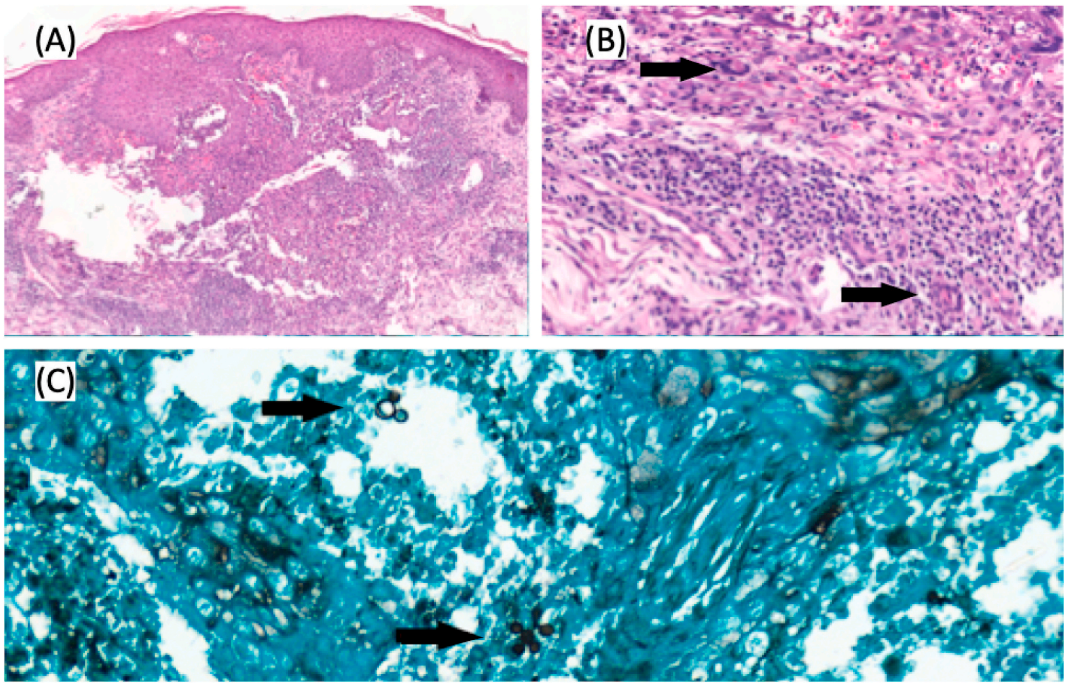

Fig. 3. (skin biopsy). A: hematoxylin/eosin staining × 100 magnification showing intense suppurative granulomatous inflammatory process with necrotic foci affecting the dermis. B: hematoxylin/eosin staining × 400 magnification displaying the acute inflammatory process with multinucleated giant cells (arrows) located in the dermis. C: Grocott-Gomori silver methenamine staining × 400 magnification revealing the *Paracoccidioides spp*. yeast-like rudder wheel-shaped structures (arrows) with birefringent capsule and sporulations.

intense cellular suppression [2], as illustrated in the current case report by the presence of acute symptoms, disseminated lymphadenopathy, splenomegaly, and rapid worsening, suggesting juvenile presentation. Nevertheless, she was 47 years old and had a remarkable pulmonary involvement, which are characteristics of the chronic form, thus fulfilling the criteria for the mixed presentation. In 90.5% of cases

compromised by the chronic form, the lung involvement is diffuse, predominates in the middle third, and affects both lungs, with a "butterfly wing" pattern in the chest X-ray [10,11]. Additional findings observed in CT are irregular ground-glass opacities, consolidations, nodules, cavitations, interlobular septum thickening and fibrotic lesions [12]. None of these findings are observed in the acute form, in which only mediastinal enlargement due to lymphadenopathy is identified on the chest X-ray [10]. It should be noted that the case presented herein had a distinct pattern, which is the atypical unilateral lung involvement (Fig. 2), probably because it was a mixed form of PCM in an immunosuppressed patient. Another unusual presentation was the "inverted halo sign" (Fig. 2D), defined as a rounded focal area with ground-glass attenuation surrounded by a complete or partial consolidation ring [13]. It has been identified in only 10% of patients afflicted by active PCM infection [12].

The isolation of fungal elements on a fresh examination of sputum or another clinical specimen (needle aspiration of lymph node content or tissue sample of affected organs) is the gold standard for PCM diagnosis. Histopathological findings are characterized by intense inflammatory response and epithelioid granulomas containing multinucleated giant cells, occasionally forming epidermal microabscesses. The fungus has a round or oval shape, with birefringent capsule and multiple sporulations attached to the mother cell through narrow fixation points, conferring to the pathogen a "rudder-wheel" or "Mickey-Mouse-head" shape [14]. Although in this case the objective identification of the fungus was done only in the skin biopsy, the infection was probably disseminated, thus explaining the multiorgan failure. Despite the disease severity, it was completely reversible after antifungal treatment.

Another exceptionality of this case was its evolution to DIC. Inflammation can lead to pathological and unbalanced activation of procoagulant systems, which are not counteracted by anticoagulant factors such as C protein, antithrombin and/or tissue factor pathway inhibitor. The result is an excessive formation of thrombin and clots into small vessels, causing thrombosis and infarctions that lead to consumption of plasmin activators, coagulation factors, and platelets so that hemorrhagic and thrombotic events can occur at the same time [15,16]. The triggering factor in this case was the fungal infection, leading to endothelial inflammation. According to The International Society on Thrombosis and Haemostasis score [17], the hemorrhagic manifestations (ecchymosis, hematomas, hemoptysis and hematuria) associated with fibrinogen consumption, thrombocytopenia, D-dimer elevation and extended prothrombin time confirm the diagnosis of DIC.

Serology can be helpful for diagnosing PCM, especially when fungus isolation is not possible. In addition, it is also useful to evaluate therapeutic response, with sensitivity of up to 80–95% [2,4]. Double immunodiffusion is the gold standard for detecting anti-paracoccidioidal antibodies, and the titration of specific anti-PCM antibodies is correlated with the disease severity [18]. However, cross-reactivity with other systemic mycoses can occur, such as cryptococcosis, histoplasmosis, aspergillosis and candidiasis [4]. False-negative results constitute another concern among immunosuppressed patients [2]. In the case reported, PCM was confirmed by both skin biopsy and double immunodiffusion test in agar gel. Despite the immunosuppression, confirmed by serum Tacrolimus concentration, the antibody titration was positive, suggesting a severe infection.

PCM can be treated with amphotericin B, sulfamethoxazole/trimethoprim and azole derivatives such as ketoconazole, itraconazole and fluconazole. Itraconazole 200 mg/day for 9–18 months is the drug of choice in mild and moderate forms, for which sulfamethoxazole/trimethoprim is the second option. In severe/disseminated forms, amphotericin B deoxycholate 0.5–0.7 mg/kg/day or lipid formulation 3–5 mg/kg/day (liposomal or lipid complex) is indicated for two to four weeks [2]. In the case described currently, amphotericin B was prescribed due to the disease severity and the immunosuppression. The lipid complex was the only drug available and is potentially nephrotoxic but was essential for controlling the disease.

The treatment duration should be based on body weight recovery, resolution of symptoms and radiological findings, and the decrease of serum PCM antibody titers [2,4,6]. The scarcity of studies and published cases of PCM after liver transplantation makes the disease management a challenge. The withdrawal or maintenance of the immunosuppressant regimen, the choice of the best antifungal for each case, the right time for antifungal withdrawal and the need of secondary prophylaxis for immunosuppressed patients are still debatable. Replacing amphotericin with sulfamethoxazole/trimethoprim in this case was a reasonable choice to remove a potential cause of renal toxicity. In addition, the risk of interaction between Tacrolimus and itraconazole would pose a problem for reintroducing the immunosuppressant medication [19]. Therefore, sulfamethoxazole/trimethoprim was the best choice in this case.

To date, there is no routine recommendation for screening PCM in living donors and solid organ recipients, because the disease is rare [5]. Nevertheless, PCM after liver transplantation should be considered in refractory infectious conditions with lymphadenopathy and skin lesions without defined etiology, especially in endemic regions. Furthermore, clinical manifestations in these patients can be atypical, requiring a high degree of clinical suspicion to make the diagnosis. Since serological tests are usually negative in immunosuppressed patients, the isolation of fungal elements should be actively sought. Intravenous antifungals seem to be necessary in severe forms, but they should be used under close monitoring due to adverse events such as renal toxicity. Treatment length depends on disease severity and can be better estimated through serum PCM antibody titers. Reporting cases such as the one described herein is imperative to decide whether PCM screening should be done in solid organ donors and recipients in endemic areas.

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Ethical form

The authors have obtained written and signed consent to publish the case report.

Declaration of competing interest

There are none.

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