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CASE REPORT

DISSEMINATED FUNGAL INFECTION WITH ADRENAL INVOLVEMENT: REPORT OF TWO HIV-NEGATIVE BRAZILIAN PATIENTS

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SUMMARY

Paracoccidioidomycosis and histoplasmosis are systemic fungal infections endemic in Brazil. Disseminated clinical forms are uncommon in immunocompetent individuals. We describe two HIV-negative patients with disseminated fungal infections, paracoccidioidomycosis and histoplasmosis, who were diagnosed by biopsies of suprarenal lesions. Both were treated for a prolonged period with oral antifungal agents, and both showed favorable outcomes.

KEYWORDS: Paracoccidioidomycosis; Histoplasmosis; Systemic mycoses.

INTRODUCTION

Paracoccidioidomycosis (PCM) and histoplasmosis are systemic infections caused by dimorphic fungi endemic in Brazil. In Latin America, these infections target rural male workers with limited access to public and private health systems. Most of these individuals are therefore diagnosed only when they are severely ill[5]. Disseminated clinical forms are not uncommon in immunodeficient individuals, particularly in HIV infected patients, who show involvement of almost all organ systems throughout the body, including the reticuloendothelial system, lungs, gastrointestinal tract, renal tract, central nervous system, bone marrow and adrenal glands[2,13,15]. Disseminated disease is much less common in immunocompetent hosts, and it is known that immunosuppression increases the aggressiveness of these fungi[4,13]. These systemic mycoses have distinctive clinical presentations, resulting in early suspicion and appropriate clinical management.

We describe two immunocompetent patients, serologically negative for HIV, who presented disseminated forms of PCM and histoplasmosis mimicking neoplasms. Both patients were diagnosed by adrenal biopsies.

Patient 1: A forty-five-year-old male was admitted to our hospital with seizures. Physical examination showed three skin lesions on his face and scalp (Fig. 1). Previous medical history included treatment for skin PCM three years earlier and alcoholism. He never worked in a rural area, but two years before developing PCM skin lesions, he had been in a car accident in the rainforest, which resulted in several hours of exposure to the forest environment, in an injured state. Magnetic resonance imaging (MRI) showed lesions in the left frontal area of his face (Fig. 2) and in the right inferior cerebellar peduncle. Thoracic computed tomography (CT) showed areas of mediastinal lymphadenomegaly and areas of ground glass attenuation with small centrilobular nodules, and abdominal CT showed a left suprarenal lesion measuring 5 x 3 cm. His cerebrospinal fluid (CSF) was normal. Double radial immunodiffusion serology for PCM showed a titer of 1:4. Direct examination of skin lesion specimens clarified with 20% KOH showed typical round to elongated, thick-walled, gemulation cells of *Paracoccidioides* spp.

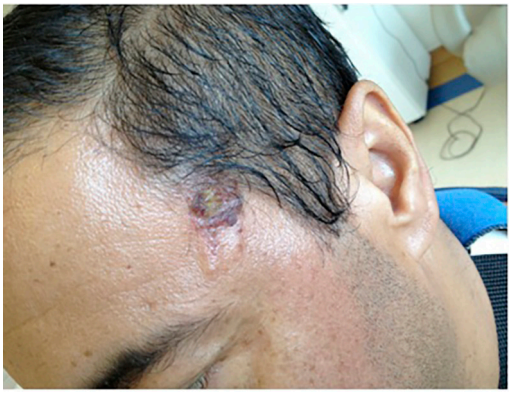

Fig. 1 - Skin lesions on face.

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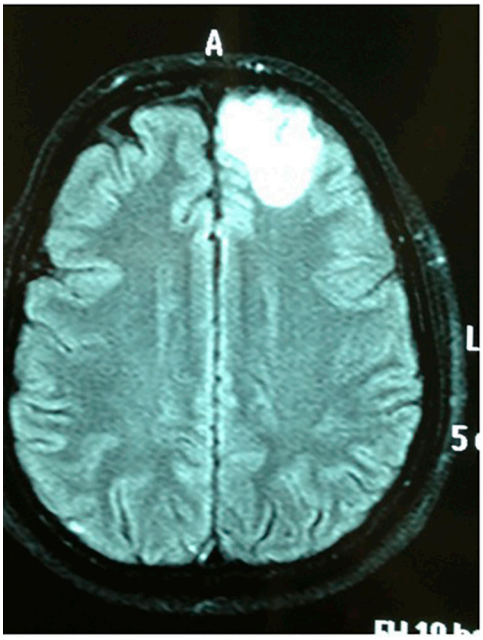

Fig. 2 - Magnetic resonance imaging of the brain showing an expansive left frontal.

Suprarenal glandular histopathology showed granulomatous inflammatory infiltrates with necrosis, as well as several structures typical of *Paracoccidioides* spp. Hematoxylin and eosin staining of skin biopsy sections showed clusters of *Paracoccidioides* cells into giant cells, while Gomori methenamine silver staining showed typical peripheral buds (Fig. 3).

The patient was treated with liposomal amphotericin for two weeks. After discharge, he was treated with itraconazole (200 mg/day) and trimethoprim-sulfamethoxazole (160 mg/800 mg three times per day). After three months of treatment, MRI showed a 50% reduction in the intracranial lesion and his clinical symptoms had improved. He was treated for a total of two years.

Patient 2: A fifty-eight-year-old man presented fatigue, anorexia, drowsiness and moderate weight loss for four months. He had worked in rural areas for 40 years before developing these clinical symptoms. He denied having a history of smoking, alcoholism, or other risk factors. Abdominal and thoracic CT scans, performed to determine whether he had a tumor, showed a left suprarenal lesion, 3 cm in diameter, but no pulmonary lesions. Histologic examination of a suprarenal biopsy sample showed granulomatous inflammatory process with histiocytes and necrosis, as well as round and small (3-5 µm) budding structures suggestive of *Histoplasma capsulatum* (Fig. 4). Immunohistochemistry showed that he was positive for *Histoplasma* but serologically negative for histoplasmosis. Treatment with itraconazole (400 mg/day) for 30 days improved his clinical symptoms. This patient was treated for a total of 12 months.

DISCUSSION

We have described two patients, who were apparently not immunosuppressed, with disseminated fungal diseases that mimicked

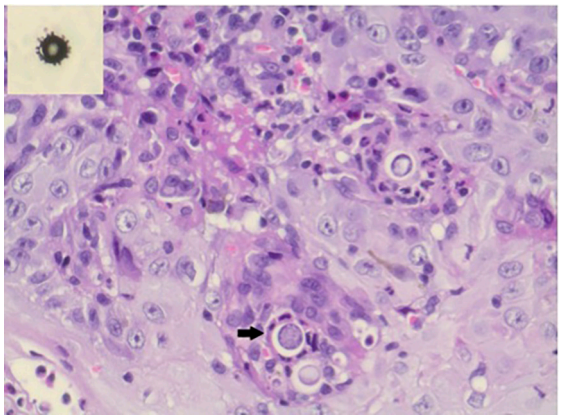

Fig. 3 - Paracoccidioidomycosis in skin's sections. Clusters of *Paracoccidioides* spp. in giant cells (arrow). Gomori methenamine silver stain demonstrates peripheral buds (upper left).

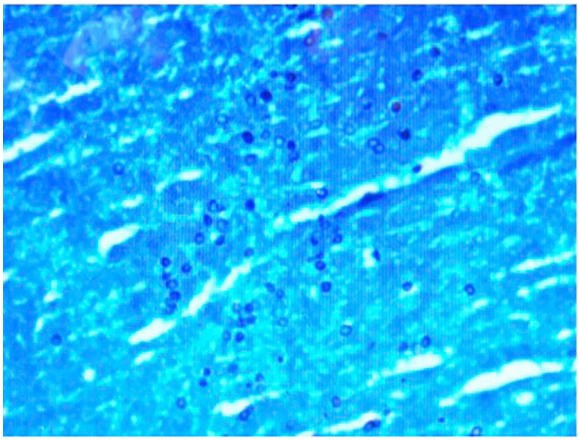

Fig. 4 - Histoplasmosis in suprarenal's sections. Granulomatous inflammatory process with histiocytes, besides necrosis with suggestive *Histoplasma* spp. structures.

neoplasms. Skin and adrenal biopsies of patient one were positive for *Paracoccidioides* spp. The infection was attributed to the trauma experienced by the patient, followed by contact with rain forest vegetation, the natural habitat for this etiologic agent. Many years after first being successfully treated for PCM, this patient presented the disseminated form of the disease. This patient was at higher risk of fungal infection, due to his close contact with native plants and exposure to fungal conidia through inhalation or inoculation following transcutaneous trauma. Epidemiological studies using intradermal paracoccidioidin tests showed a wide variation of exposed individuals in Brazil, with as many as 82% of patients showing positive results, demonstrating their potential risk of infection[5].

Paracoccidioides spp. has recently been reclassified as two main species, *P. brasiliensis* and *P. lutzii*. These agents usually cause benign pulmonary infections that progress to acute forms. Alternatively, they may remain latent, followed months or years after fungal inoculation by primary complex reactivation, and resulting in the development of chronic and insidious disease. PCM can occur in immunocompetent hosts, although immunosuppression increases its aggressiveness. Primary infection is self-limiting and asymptomatic, whereas the progressive,

disseminated form of this disease is characterized by fever, generalized lymphadenopathy, and lesions in the lungs, brain and several other organs[4]. Recent studies in Brazil found that the most affected anatomical sites were the lungs and oral mucosa; generalized lymphadenopathy and skin lesions were more frequent during the first decades of life, whereas the central nervous system and adrenal glands were rarely affected[1,3]. Our patient presented adrenal involvement despite being immunocompetent. PCM with brain involvement is usually treated with amphotericin B and trimethoprim/sulfamethoxazole, the drugs of choice in the treatment of neuroparacoccidioidomycosis, and triazoles for at least nine months[10,11]. Our patient was treated with trimethoprim/sulfamethoxazole, to improve drug penetration into the CSF, and itraconazole. Although a newer triazole, voriconazole, has shown good *in vitro* activity, it is too expensive to be used in developing countries. Moreover, there is limited clinical experience with this agent in PCM, although this drug may be an option for salvage treatment[12].

The second patient lived in a rural area for 40 years prior to developing the disseminated form of histoplasmosis. Histoplasmosis has a wide spectrum of clinical manifestations, ranging from asymptomatic infection to severe disseminated disease. Prolonged contact in a rural environment, smoking, and alcoholism have higher rates among patients with disseminated form of histoplasmosis and paracoccidioidomycosis[6]. The first patient had a history of alcoholism and the second patient only had contact with a rural environment.

Non-pathognomonic clinical symptoms and serological tests for histoplasmosis usually do not yield a correct diagnosis, mainly because of cross reactions encountered in such tests. Thus, a diagnosis requires tissue biopsy and culture procedures. SEVERO *et al.* have described that, in disseminated histoplasmosis, only 62% of patients had a positive immunodiffusion test[14]. *Histoplasma* species grow slowly (> 20 days) and there is frequent contamination with fast-growing molds and yeasts. Grocott methenamine silver (GMS) staining of direct smears has been found to be a more sensitive diagnostic test than the cell block assay[7]. Although antibody titers and detection of antigens are limited in the diagnosis of histoplasmosis, the best approach consists of a combination of these methodologies[8]. The standard treatment for the disseminated form of histoplasmosis consists of amphotericin B for one to two weeks, followed by itraconazole for at least 12 months, although patients with mild to moderate disease are frequently treated with itraconazole alone[9,16]. The treatment of our patient with itraconazole 400 mg for one year resulted in the disappearance of symptoms and the adrenal lesion.

In conclusion, we have described two immunocompetent patients, seen at two different hospitals, with clinical suspicion of neoplastic diseases. Both patients had suprarenal lesions and were finally diagnosed histopathologically with fungal lesions. Both patients were successfully treated with antifungal agents. These findings indicate that immunocompetent patients in tropical countries can present disseminated fungal infections mimicking neoplasms. Endemic mycosis must be included in the differential diagnosis of this type of patients, especially in those with suprarenal lesions, even without confirmation by laboratory tests.

RESUMO

Infecções fúngicas disseminadas com acometimento das supra-renais: descrição de dois pacientes brasileiros HIV-negativos

A paracoccidioidomicose e a histoplasmose são infecções fúngicas sistêmicas endêmicas no Brasil. As formas clínicas disseminadas são incomuns em pacientes imunocompetentes. Nós descrevemos dois pacientes HIV-negativos com infecções fúngicas disseminadas, paracoccidioidomicose e histoplasmose, que foram diagnosticadas por biópsias de lesões de supra-renal. Ambos foram tratados por períodos prolongados com antifúngicos orais, evoluindo com boa resposta terapêutica.

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