

Delayed Relapse of Paracoccidioidomycosis in the Central Nervous System: A Case Report

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Paracoccidioidomycosis is a dimorphic fungal infection endemic in Latin America. We report a patient with a history of pulmonary paracoccidioidomycosis who presented with relapsed disease in the central nervous system 4 years after initial treatment. We review current treatment strategies for paracoccidioidomycosis and neuroparacoccidioidomycosis.

Keywords. central nervous system; endemic mycosis; neuroparacoccidioidomycosis; *Paracoccidioides brasiliensis*; paracoccidioidomycosis.

CASE REPORT

A 49-year-old man presented to an outside hospital in fall 2017 with a 3-week history of headache, dizziness, and ataxia. He reported a past medical history of pulmonary paracoccidioidomycosis (PCM) diagnosed in 2011, for which he was treated with itraconazole for 2 years and underwent a right lower lobe wedge resection in 2013. The patient was originally from Brazil, where he worked in coffee and sugarcane plantations and in construction. He moved to the United States at age 29 with no international travel since immigration.

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He reported heavy alcohol consumption and a 40 pack-year smoking history. Before transfer to our hospital, a head computed tomography (CT) revealed a large right cerebellar mass with surrounding edema and mass effect.

Physical examination showed an awake patient with bradycardia (52 beats per minute), inspiratory crackles in the right mid lung, dysmetria on finger-nose-finger exam, and gait instability with falling to the right side. Admission laboratory tests were notable for a white blood cell count of 9600 cells/mL with normal differential, C-reactive protein of 16.9 mg/L (reference range 0.0–3.0 mg/L), negative human immunodeficiency virus (HIV) antigen/antibody, negative serum 1,3-β-D-glucan, and negative blood cultures. Brain magnetic resonance imaging (MRI) revealed a 5.0 × 3.5 × 3.0-cm multilocular, diffusion-restricting cystic mass in the right cerebellum with vasogenic edema and hydrocephalus (Figure 1). Chest and abdominal CT showed bilateral scattered pulmonary nodules and thickening of the adrenal glands (Figure 2). The patient underwent a right-sided posterior fossa craniotomy with subtotal resection of the cerebellar mass. The capsule was not entirely removed given that it was highly adherent to the brainstem and cranial nerves. Intraoperative frozen section pathology identified yeast forms suspicious for *Paracoccidioides brasiliensis*, confirmed by methenamine silver staining of permanent sections (Figure 3). Fungal cultures grew *P. brasiliensis* after 21 days. The patient began treatment with a planned 4-week induction course of liposomal amphotericin B (5 mg/kg per day) with normal saline prehydration [1].

The patient's course was complicated by acute kidney injury after 2 weeks of treatment with liposomal amphotericin B, which was subsequently transitioned to trimethoprim/sulfamethoxazole (TMP-SMX) dosed for glomerular filtration rate. After improvement in renal function, the patient was discharged on postoperative day 22 on oral TMP-SMX. One month after discharge, the patient reported alleviation of his presenting neurological symptoms. Repeat MRI obtained 2 months postoperatively demonstrated reduced edema with enhancement along the periphery of the surgical margin compatible with treatment-related involution of residual abscess (Figure 1). The target total duration of therapy was at least 18–24 months [1]. However, the patient was last seen in outpatient clinic almost 9 weeks after antifungal treatment initiation before he was lost to follow up.

DISCUSSION

Paracoccidioidomycosis is a dimorphic fungal infection caused by *Paracoccidioides* spp, which is endemic in Latin America. Paracoccidioidomycosis is acquired through inhalation of

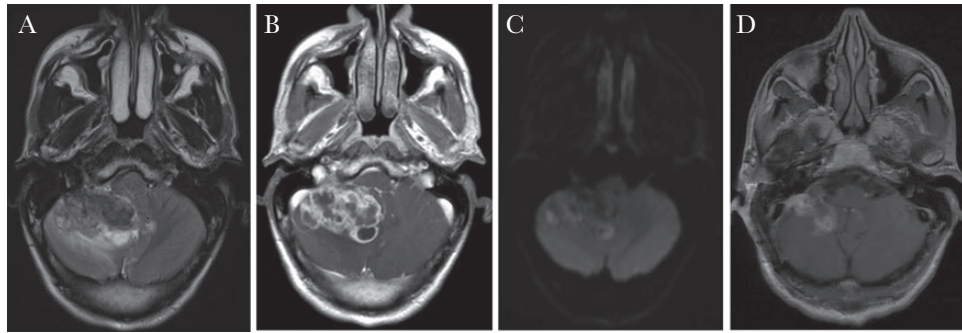


Figure 1. (A) Noncontrast T2-weighted, (B) contrast-enhanced T1-weighted, and (C) diffusion-weighted magnetic resonance (MR) images from the time of presentation demonstrate a large, rim-enhancing, multilocular cystic mass with areas of central diffusion restriction and adjacent edema. The mass effaces the fourth ventricle. Obstructive hydrocephalus with transependymal flow was also present (data not shown). (D) Contrast-enhanced T1-weighted MR image obtained 2 months postoperatively demonstrates resolved mass effect with heterogeneous enhancement along the margins of the resection cavity, consistent with treatment-related involution of the residual abscess.

conidia in soil [2]. Risk factors include agricultural work, male sex, smoking, and alcohol use disorder [1, 3]. Diagnosis relies upon serology, microscopy, and/or culture [1]. Microscopy using potassium hydroxide and calcofluor can identify the yeast form, appearing as a “pilot’s wheel” with round cells surrounded by budding daughter cells [4, 5]. Methenamine silver stain or periodic acid-Schiff stain can identify yeast forms and granulomatous inflammation in tissue samples. *Paracoccidioides* spp are cultured using Sabouraud agar incubated at room temperature, and the mold form usually grows within 20–30 days [5].

Most patients initially develop an asymptomatic pulmonary infection, which may reactivate months or years later into chronic disease. Paracoccidioidomycosis may disseminate to the oral mucosa, skin, adrenals, and in 9%–25% of cases, to the central nervous system (CNS) [5, 6]. Neuroparacoccidioidomycosis (NPCM) most frequently localizes to the cerebral hemispheres (67%), cerebellum (25%), brain stem (25%), and spinal cord (4%) [7]. Neuroparacoccidioidomycosis has a mortality rate of 44%; among survivors, 50% develop long-term neurological sequelae including motor deficits [8]. Individuals coinfecting with HIV, with solid organ transplantation, active malignancies, or on biologic therapy have greater risk for disseminated

disease, relapse, and mortality [1, 9–11]. Few randomized trials have been conducted to characterize the optimal treatment of PCM [12, 13]. There are no treatment guidelines available from professional or governmental bodies in the United States. For severe or disseminated infection, Brazilian guidelines recommend initial use of amphotericin B for 2–4 weeks followed by transition to oral antifungals, usually itraconazole or TMP-SMX [1]. Brazilian guidelines recommend TMP-SMX for 18–24 months or longer for the treatment of NPCM, given its greater CNS penetration than itraconazole [1, 14]. Ensuring regular follow up and adherence to protracted treatment regimens, particularly in the setting of disseminated disease, can be challenging for patients and clinicians.

CONCLUSIONS

The present case is remarkable for the development of relapsed CNS disease 4 years after antibiotic treatment and resection of affected lung in an immunocompetent patient with no repeated exposures. Although PCM is rare in the United States, practitioners should consider it in immigrants from endemic areas. Past treatment does not preclude future relapse [15], and a significant fraction of cases can involve the CNS.

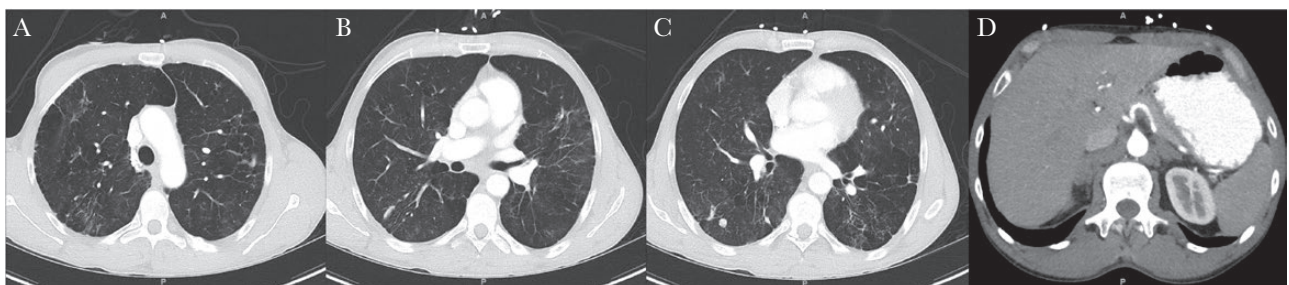


Figure 2. Axial contrast-enhanced computed tomography images from the time of presentation demonstrate (A–C) several scattered pulmonary nodules in bilateral lungs, some of which are tubular in configuration and peribronchial in distribution, and (D) thickening of the adrenal glands.

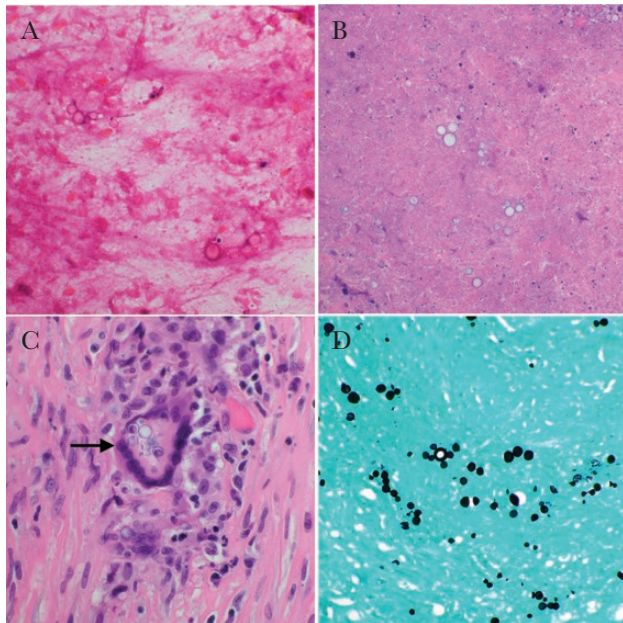


Figure 3. Histopathologic findings from right cerebellar mass resection. (A) Hematoxylin and eosin (H&E)-stained smear preparation from the intraoperative pathology consultation showed scattered medium to large-sized yeast with multiple buds. Permanent sections (B, C, and D) showed numerous yeast (negatively stained by H&E) in a background of necrosis (B) and associated with granulomatous inflammation (C), including engulfment by multinucleated giant cells (arrow). (D) Grocott's methenamine silver stain highlighted multiple yeast forms including the classic "pilot's wheel" appearance characteristic of *Paracoccidioides brasiliensis*. All images were taken with $\times 40$ objective.

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