

Puerperal brain cryptococcoma in an HIV-negative woman successfully treated with fluconazole: a case report

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ABSTRACT

Cryptococcus spp. cerebral abscesses are uncommon in immunocompetent subjects. The recommended induction treatment is the administration of amphotericin B plus flucytosine combined with resection for lesions ≥ 3 cm. In this paper, we describe an HIV-negative woman diagnosed with a large cryptococcoma in the immediate postpartum period. The lesion was not resected, and due to amphotericin B intolerance, she received an extended course of fluconazole monotherapy. There was no disease recurrence during the 4 years of follow-up. The abrupt onset of her symptoms following delivery suggests that she developed a postpartum immune reconstitution syndrome. This case also demonstrates that in specific situations fluconazole monotherapy can be attempted in immunocompetent patients with cryptococcoma.

Keywords: *Cryptococcus*. Immune reconstitution inflammatory syndrome. Treatment.

INTRODUCTION

Most cases of central nervous system (CNS) infection caused by *Cryptococcus* spp. manifest as meningitis. In sporadic cases, *Cryptococcus* spp. CNS infection can result in the formation of a cryptococcoma, which can resemble a neoplastic mass. Cryptococcal disease typically occurs in immunocompromised individuals. Although *Cryptococcus gattii* infections have been increasingly recognized in immunocompetent hosts¹⁻³, the incidence of brain cryptococcoma remains very low in healthy individuals³. We report a novel case of a large CNS cryptococcoma in an human immunodeficiency virus (HIV)-negative woman that was successfully treated with fluconazole. Her symptoms developed during the immediate postpartum period, suggesting a presentation exacerbated by postpartum immune reconstitution.

CASE REPORT

In December 2006, a 25-year-old female, who worked as a primary school teacher in a small city in northeast Brazil, was referred to a neurologist with complaints of progressively worsening right-sided paresthesias and muscle weakness. She denied having

any other symptoms, including pulmonary complaints. Her current symptoms began abruptly in the week following an otherwise uneventful pregnancy and spontaneous vaginal delivery of a healthy baby. She was previously healthy, but recalled that six years prior she had experienced a two-week episode of right-sided paresthesias and headache that resolved spontaneously.

The initial physical exam was unremarkable except for word-finding difficulties and weakness and numbness of the right-sided extremities. There was no papilledema on fundoscopic examination, and routine laboratory studies were normal. A computed tomography scan of the brain without contrast revealed a heterogeneous mass that was further evaluated by magnetic resonance imaging (MRI). Post-gadolinium infusion images revealed a 3cm x 2cm heterogeneously enhancing lesion arising in her left thalamus with a well-defined rim of enhancement and central hypointense areas suggestive of necrosis (**Figure 1A and 1B**). Based on the radiographic appearance, the patient was presumptively diagnosed with glioblastoma multiforme. While awaiting surgical evaluation, prophylaxis with dexamethasone and phenytoin was initiated, resulting in some initial improvement in her symptoms. A non-stereotactic biopsy of the mass was performed without resection. The pathological examination revealed numerous budding encapsulated organisms consistent with *Cryptococcus* sp. without granulomata or multinucleated giant cells (**Figure 1C**). The tissue was not sent for microbiologic studies due to a primary suspicion of CNS malignancy; therefore, the species and serotype could not be determined.

A chest X-ray revealed no evidence of active lung disease, scarring, or calcified granulomata to suggest prior pulmonary cryptococcosis. An enzyme-linked immunosorbent assay (ELISA) test for HIV I/II was negative. Additional testing for inherited immunosuppression was not performed. A routine

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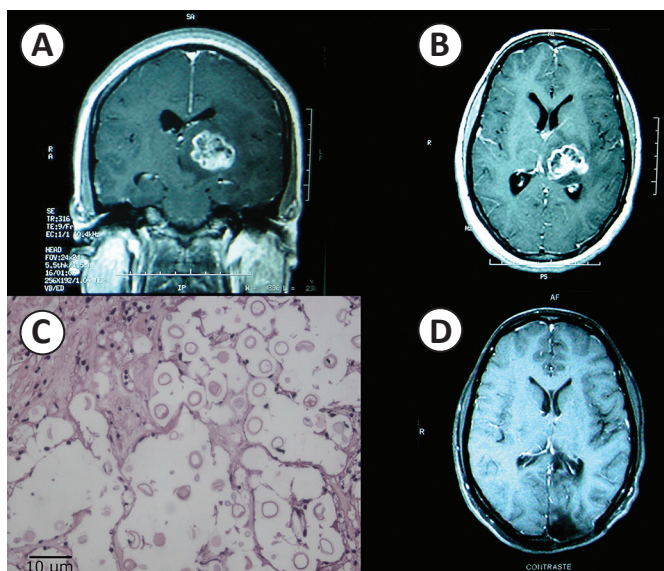


FIGURE 1 - Central nervous system cryptococcoma. T1-weighted post-gadolinium coronal (A) and transverse (B) MRI images revealing a 3cm x 2cm enhancing mass in the left thalamus with central hypointensity suggestive of necrosis. C: Hematoxylin and Eosin stain of brain biopsy tissue at 40x revealing numerous budding encapsulated organisms consistent with *Cryptococcus* species. D: T1-weighted post-gadolinium transverse magnetic resonance imaging (MRI) image revealing post-craniotomy changes but no evidence of an intra-parenchymal mass.

peripheral blood culture was negative for bacteria and fungus. A cerebrospinal fluid (CSF) examination revealed no cells, glucose level of 58mg/dL (normal=50-80), and protein level of 33mg/dL (normal=15-45). An India ink stain was negative, and a CSF cryptococcal antigen latex agglutination assay (IMMY, Norman, Oklahoma, USA) was positive.

Dexamethasone therapy was discontinued, and treatment with amphotericin B was initiated due to a diagnosis of CNS cryptococcoma. Flucytosine was not commercially available in Brazil at the time. Her hospital course was immediately complicated by a pruritic body rash, severe hypokalemia and hypomagnesemia, and ventricular arrhythmia; all of these symptoms resolved after the withdrawal of amphotericin B. She was, therefore, treated with fluconazole, 800mg/day i.v. for 2 months, which was well tolerated until her discharge from the hospital. The patient's symptoms resolved over 17 months of continuous oral fluconazole therapy (8 months of 600mg/day and 9 months of 300mg/day), and a follow-up brain MRI showed complete resolution of the lesion (Figure 1D). The patient was followed for four years after her treatment, during which time she experienced mild residual neuromotor symptoms but displayed no evidence of disease recurrence.

DISCUSSION

Our patient was negative for HIV and did not have any prior or subsequent history of recurrent infection, suggesting that she did not have a significant undiagnosed humoral or

cellular immunodeficiency. Although we could not determine the *Cryptococcus* species that caused her disease, our patient lived in the northeast region of Brazil, where *Cryptococcus gattii* accounts for 66% of the cryptococcal isolates⁴. In Brazil, 75% of the cryptococcal infections in HIV-negative patients are due to *Cryptococcus gattii*⁴, which is increasingly recognized worldwide as a cause of infection in immunocompetent hosts^{2,3}. In these patients, cryptococcal disease is more likely to manifest as a cryptococcoma, as compared to immunosuppressed patients³. Nevertheless, the likelihood of a brain mass caused by *Cryptococcus* in immunocompetent individuals is extremely low compared with immunocompromised patients^{1,3}.

Our patient's symptoms began within the first week after delivering a healthy baby. Although several cases of cryptococcal meningitis in immunocompetent pregnant women have been described^{5,6}, to our knowledge, only two cases of cryptococcoma during pregnancy have been previously reported^{7,8}. The presence of antecedent symptoms six years before this illness suggests the possibility of a prior infection that was spontaneously controlled until recrudescence and growth of the cryptococcoma during the relative immunosuppression of pregnancy, in which cell-mediated immunity is particularly affected. Additionally, the abrupt onset of her symptoms following delivery may suggest an inflammatory response related to postpartum immune reconstitution. This inflammatory response occurs rapidly after delivery and may result in the unmasking of previously occult infectious diseases, such as mycobacterial infections, including tuberculosis; viral infections; and fungal infections, such as *Cryptococcus*. This phenomenon has been described in several case reports, in which symptoms of previously quiescent cryptococcal disease presented or significantly worsened during the late third trimester or immediate postpartum period⁹.

The recommended therapy for CNS cryptococcoma includes induction therapy with amphotericin B and flucytosine for at least 6 weeks, followed by 6-18 months of consolidation therapy with fluconazole. Surgical excision and debulking are indicated as adjunct therapies for lesions that are greater than or equal to 3cm¹⁰. Our patient was intolerant of amphotericin B and did not undergo surgical resection but was successfully treated with 2 months of i.v. and 17 months of oral fluconazole. Fluconazole monotherapy is effective for cryptococcal meningitis in immunocompetent patients¹¹ and has been successfully used without surgical resection in both invasive pulmonary and thyroid cryptococcoma^{12,13}. However, fluconazole monotherapy without surgical resection has not been previously described in the successful treatment of CNS cryptococcoma. Our patient had complete resolution of the brain lesion in a follow-up MRI and remained free of disease recurrence for 4 years of follow-up. This finding suggests that extended fluconazole monotherapy can be attempted in immunocompetent patients with cryptococcoma caused by a susceptible organism who are intolerant of amphotericin B and who are not good candidates for surgical resection.

Finally, this case illustrates the potential of CNS cryptococcoma to be mistaken for glioblastoma multiforme and other intracranial neoplasms and also reveals the importance of considering fungal infection, including cryptococcoma, in the differential diagnosis of a CNS mass in immunocompetent pregnant women.

Ethics approval to publish this case report was granted by the Hospital Couto Maia Ethics Committee. The patient provided written informed consent to have her case details published.

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