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Effective Treatment of Cerebral Mucormycosis Associated with Brain Surgery

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Abstract

Isolated cerebral mucormycosis is rare. We describe a patient with a brain tumor and a surgically-related *Rhizopus oryzae* brain abscess. Her abscess was effectively treated with posaconazole, micafungin, and colony-stimulating factor followed by posaconazole alone. To our knowledge, cerebral mucormycosis secondary to brain surgery had not been previously reported.

Keywords

brain tumor; Mucormycosis; surgery; chemotherapy

Introduction

Isolated cerebral mucormycosis is a rare entity usually seen in intravenous drug users¹. *Rhizopus oryzae* is the most common organism isolated from patients with mucormycosis². Surgical debridement and systemic antifungals are the mainstay of therapy despite which related morbidity and mortality are high^{1, 3}. The optimal choice of antifungals for treatment of mucormycosis remains controversial^{4, 5}. We describe the effective treatment of a surgically-related cerebral mucormycosis in a patient with an extensive astrocytoma and discuss the therapeutic approach taken.

Case report

A 15 year-old female was referred to a neurologist with a 6-week history of headaches, diplopia, and blurred vision. A magnetic resonance imaging (MRI) of the brain showed hydrocephalus and extensive, infiltrative T₂-weighted hyperintense abnormalities involving both thalami, left temporal lobe, and brainstem. An external ventricular drain (EVD) was placed in the frontal horn of the right lateral ventricle and 3 days later a stereotactic biopsy

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of the left thalamic tumor revealed a diffuse astrocytoma (WHO grade II). The EVD was replaced by a ventriculo-peritoneal (VP) shunt inserted into the frontal horn of the left lateral ventricle 3 days following the biopsy. Dexamethasone was initiated peri-operatively to reduce cerebral edema and was continued after tumor biopsy. The patient developed high-grade fever and decline in mental function and affect 7 days after the biopsy. Broad-spectrum antibiotics were initiated and the patient was transferred to our institution for further therapy. The patient was febrile, had a flat affect, slow mental processing, sluggish pupillary reflexes bilaterally, left facial palsy, and left-sided hemiparesis at presentation. A repeat brain MRI showed no change in tumor size. However, it demonstrated a new enhancing area suspicious for an abscess in the right anterior basal ganglia at the area of the previous biopsy. Absolute neutrophil count (ANC) at this time was 8400 cells/mm³. Empiric antifungal therapy with posaconazole (Noxafil®, Merck & CO., Inc; Whitehouse Station, NJ) 400 mg PO twice daily and micafungin (Mycamine®; Astellas, Northbrook, IL) 2 mg/kg/day was initiated due to high index of suspicion for a fungal infection. A biopsy of this new enhancing lesion was done and Grocott's methenamine silver (GMS) stain showed many broad, aseptate hyphae. Based on this finding, dexamethasone was rapidly tapered and stopped over a 9-day period. The patient's clinical condition improved and fever subsided 4 days after starting antifungal therapy. Preliminary results of the culture 5 days after the biopsy suggested a mucormycete. Two decisions were made to optimize antifungal treatment in this patient. Micafungin dosage was increased to 4 mg/kg/day to maximize central nervous system (CNS) penetration. Additionally, sargramostim (Leukine®, GM-CSF; Genzyme Corporation, Cambridge, MA) at a dose of 100 mg/m²/day was added to enhance phagocytic function. Final tissue culture results, 8 days after the biopsy, identified the fungi as *Rhizopus oryzae*. Posaconazole minimum inhibitory concentration was 1 µg/mL. A repeat brain MRI 8 days after initiating antifungal therapy showed reduction in the size of the abscess. Sargramostim and micafungin were discontinued after 34 days of therapy. The patient tolerated administration of sargramostim well with ANC ranging from 7900 to 28400/mm³. Posaconazole steady-state trough level obtained at two weeks of treatment was 2.06 µg/mL. Anticancer therapy with oral erlotinib (Tarceva®, Astellas, Northbrook, IL; Roche, Basel, Switzerland; Genentech, South San Francisco, CA), an oral inhibitor of epidermal growth factor receptor and whole-brain radiotherapy were started 14 days following initiation of antifungal therapy. The patient's clinical condition continued to improve and her brain MRI demonstrated a stable tumor size and increasing necrosis at the abscess 6 weeks after the start of anticancer therapy. Posaconazole 400 mg PO twice daily and erlotinib were continued as the sole antifungal and anticancer agents, respectively, after completion of radiotherapy. Follow-up MRI done 7 months after starting antifungal treatment showed enlargement of a cystic lesion within the abscess with possible intra-cystic hemorrhage and overall stable size. The patient underwent surgical drainage of the cyst and placement of an Ommaya reservoir. Analysis of fluid from the cyst revealed no tumor cells and no evidence of fungal infection. Concomitant, random assessment of posaconazole level in the fluid aspirated from the brain cyst, cerebrospinal fluid, and blood were 0.66 µg/mL, undetectable, and 0.95 µg/mL, respectively. The patient remained clinically stable for 19 months while receiving erlotinib and posaconazole, after which she had clinical and radiological signs of tumor progression. She died of tumor progression 21 months after

diagnosis. No signs of enlargement of her abscess were observed throughout the entire follow-up period. Her parents declined permission for an autopsy.

Discussion

Fungi of the order Mucorales are ubiquitous, typically causing life-threatening infections in severely immunocompromised hosts, diabetics, and intravenous drug (IVD) users^{1, 3, 6}. The site of infection, clinical course, and outcome is influenced by the patient's underlying immune status and route of infection¹.

Three clinical forms of mucormycosis involving the CNS have been described³. Rhino-cerebral and sino-orbital infections are the most common presentations of invasive mucormycosis and typically occur in diabetics⁶. Isolated CNS mucormycosis is very uncommon and was previously noted as an abscess or meningoencephalitis in patients with penetrating head traumas or attributed to hematogenous spread in IVD users^{1, 3}. The location of the abscess along the biopsy tract in our patient is highly suggestive of an iatrogenic introduction of the infection during one of her preceding surgeries. While deep fungal infections secondary to traumatic disruption of the skin have been described^{2, 3}, to our knowledge our case is the first with isolated CNS mucormycosis suspected to be an iatrogenic infection related to surgical procedure.

Treatment of patients with mucormycosis is challenging and related mortality is high despite treatment^{1, 4-6}. Typical treatment strategy consists of aggressive surgical debridement of the necrotic tissues with systemic antifungal therapy, the duration of which is defined by the clinical and radiological response in addition to recovery of the host immune system^{1, 4, 7}. In most retrospective studies, amphotericin B deoxycholate (AmB) and its lipid formulations were the first choice of therapy with response rates ranging between 23 and 58%^{1, 3}. Currently, AmB is the only antifungal agent licensed by the United States Food and Drug Administration for primary therapy of mucormycosis and its use is proposed as part of any potential combination therapy for this group of invasive fungal infections^{4, 5}. Posaconazole at a maximum daily dosage of 800 mg alone or in combination with other agents is recommended as salvage therapy of mucormycosis^{4, 8}. Response rates of 72–80% with posaconazole in patients with mucormycosis including those failing or not tolerating polyene-based therapy have been described⁷. While echinocandins lack *in vitro* activity against the order Mucorales, *Rhizopus oryzae* expresses a target enzyme for echinocandins⁹. Therefore, echinocandins have been used as part of combination antifungal therapy for treatment of mucormycosis. GM-CSF was shown to increase neutrophil count and improve phagocytic function in patients with mucormycoses¹⁰. We applied many of the principles underlying the various treatment approaches described in the literature for our patient. The choice of posaconazole as the backbone of antifungal therapy was based on its reported efficacy in the treatment of mucormycosis and better tolerability compared to AmB. The combination with micafungin aimed to add antifungal activity without compromising the tolerability of this therapy. We used higher than normal dosage of micafungin to overcome the low CNS penetration of this agent. Addition of GM-CSF and weaning of steroids were to optimize the qualitative function of phagocytes¹⁰. Although we will not be able to tease out the relative contribution of each of these planned interventions in the effective therapy of

our patient's CNS mucormycosis, we attribute her outcome to a great extent to the limited immunosuppression associated with her underlying disease and anticancer therapy. Our patient succumbed to her brain tumor, although she had no clinical, radiologic or microbiologic evidence of active fungal infection. The outcome of patients with cerebral mucormycosis varies remarkably depending on the underlying disease and site of infection. Patients with disseminated disease have the worst outcome while localized disease confers a better prognosis^{1, 3}. In our patient, the localized fungal infection, combined with anticancer therapy that minimally affected the neutrophil count/function, were favorable factors.

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