Successful Treatment of Cerebral Blastomycosis with Voriconazole

Division of Infectious Diseases, Department of Neurology, Mayo Clinic College of Medicine, Rochester, Minnesota

Blastomycosis can occasionally involve the central nervous system (CNS). Amphotericin B deoxycholate is considered the drug of choice for the treatment of CNS blastomycosis. Significant toxicity may be associated with its use. We describe a case of cerebral blastomycota that was successfully treated with voriconazole.

Blastomycosis is an uncommon mycosis endemic in the southeastern and central United States. It is primarily a disease of the lung, but CNS involvement is seen on rare occasions. CNS blastomycosis usually presents with meningitis, subdural focal leptomeningeal abscess, or intraparenchymal abscess [1]. The latter 2 pathological entities are encompassed under the rubric of cerebral blastomycota. The recommended treatment for CNS blastomycosis is amphotericin B deoxycholate at a total dose of at least 2 g [2]. Lipid formulations of amphotericin B are effective in animal models, but other than case reports [3], there are limited human data. In general, azoles are not considered for primary treatment of patients with CNS blastomycosis. Some authors suggest administration of high doses of fluconazole in cases of CNS infection because of the excellent CNS penetration [4, 5]. We describe a case of CNS blastomycosis successfully treated with voriconazole.

A 57-year-old, right-handed woman from western Wisconsin presented to the hospital in May 2003 for evaluation of headaches. In January 2003, the patient developed bilateral, frontal, and infraorbital pressure and pain, which also extended to the right ear. It was believed that this possibly represented rhinosinusitis; thus, the patient was treated with courses of amoxicillin, amoxicillin/clavulanate, and, subsequently, clarithromycin. Subsequent to this, her symptoms changed by early March, at which time she described them as more of a generalized pressure-like sensation diffusely involving her head and her ears, with brief episodes of pulsatile tinnitus. During this time, she felt as though her hearing had decreased bilaterally. The patient also reported some aching and stiffness of the neck posteriorly.

The patient’s medical history was significant for non-Hodgkin lymphoma that had occurred 6 years before presentation and had been treated with chemotherapy without any evidence of relapse. Near the completion of her initial chemotherapy regimen, she developed disseminated blastomycosis with pulmonary disease and osteomyelitis of 1 foot and 1 hand. She was treated with amphotericin B deoxycholate for 1 month, followed by oral itraconazole, which was later changed to fluconazole because of gastrointestinal intolerance and was continued for 6 months. The findings of her neurological examination were normal except for decreased hearing bilaterally, more marked on the right side. There were no other focal neurological abnormalities.

The patient’s leukocyte count was 5.1 × 10⁶ cells/dL. The serum creatinine level was 1.1 mg/dL, and the serum transaminase levels were normal. Chest radiograph findings were normal. MRI of the head revealed an irregular enhancing bifrontal lesion (size, 2 cm) involving the anterior falx with extension into frontal lobes bilaterally (figure 1). The patient underwent CT-guided stereotactic brain biopsy to establish the diagnosis. Histopathologic examination revealed granulomatous inflammation, and Gomori methenamine silver staining revealed budding yeasts characteristic of Blastomyces dermatitidis. Fungal culture of the brain biopsy specimen grew B. dermatitidis.

The patient was treated initially with amphotericin B deoxycholate but developed significant nephrotoxicity. The serum creatinine level increased from a baseline level of 1.1 mg/dL to 2.7 mg/dL after receipt of only 170 mg of amphotericin B. The regimen was switched from amphotericin B to liposomal amphotericin B (AmBisome; Gilead). Shortly after receipt of the first dose of liposomal amphotericin B, the patient developed severe chest tightness and respiratory distress, requiring discontinuation of the drug. Given her previous intolerance to itraconazole, the patient was then treated with voriconazole, 200 mg orally twice per day, which was increased to 300 mg orally twice per day after 4 weeks in an attempt to achieve a higher CNS concentration. She tolerated voriconazole therapy well. The headache and hearing loss resolved after 1 month of treatment, and the brain mass diminished in size on follow-
Figure 1. A, Coronal T1-weighted MRIs with gadolinium enhancement show focal, dural, leptomeningeal, and intraparenchymal enhancing abnormality in the frontal lobes and interhemispheric fissure. B, Resolution of these changes after treatment.

Voriconazole therapy was continued for a 12-month course. Follow-up head MRI performed 1 month after discontinuation of therapy revealed nearly complete resolution of the mass (figure 1). The patient has remained asymptomatic as of 9 months after completion of therapy.

To our knowledge, this was a unique case of CNS blastomycosis successfully treated with voriconazole. Approximately 5%–10% of patients with blastomycosis have CNS disease. CNS blastomycosis presents as meningitis, focal leptomeningeal abscess, or intraparenchymal abscess [1]. Amphotericin B deoxycholate is considered the drug of choice for the treatment of CNS blastomycosis [2]. Despite being the drug of choice, the CSF level of amphotericin B is <1% of the plasma level after intravenous administration of amphotericin B [6]. Nephrotoxicity and infusion-related reactions are common adverse effects of amphotericin B use. Liposomal products of amphotericin B are better tolerated, but few data exist about use of these products for blastomycosis [3]. Chest pain, dyspnea, and other symptoms are known adverse effects that can occur during liposomal amphotericin B infusion [7]. A few case reports have suggested that fluconazole is effective for treatment of CNS blastomycosis [4, 5]. Fluconazole was ineffective in 13%–35% of patients with non-CNS blastomycosis [8, 9]. Because of this high failure rate, we elected to treat the patient with voriconazole. Voriconazole is a newer triazole with broad-spectrum antifungal activity. Animal and human studies indicate that high concentrations of voriconazole can be achieved in the CSF and brain tissue [10]. In vitro investigations demonstrate that voriconazole is effective against B. dermatitidis and other dimorphic fungi [11]. A Murine model of pulmonary blastomycosis shows that voriconazole is effective in decreasing fungal burden in the lungs and prolonging survival [12]. The clinical and radiographic improvement with voriconazole therapy and absence of recurrence 9 months after completion of therapy suggest that voriconazole may be effective in the treatment of CNS blastomycosis when amphotericin B cannot be used.

Acknowledgments

Financial support. Mayo Clinic College of Medicine.
Potential conflicts of interest. All authors: no conflicts.

References

3. Chowfin A, Tight R, Mitchell S. Recurrent blastomycosis of the cen-