Successful Use of Combination Antifungal Therapy in the Treatment of Coccidioides Meningitis

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Coccidioidal meningitis is a highly lethal condition with a high morbidity and relapse rate caused by *Coccidioides immitis*.[1] This case report highlights the difficulty in diagnosing and treating coccidioidal meningitis, and discusses a novel combination antifungal therapy (voriconazole and liposomal amphotericin B), which was used to treat this patient.

Key words: *Coccidioides immitis* ■ meningitis ■ treatment

CASE REPORT

A 39-year-old Hispanic male with a history of failed renal transplants, chronic renal failure, hypertension, diabetes and a previous history of disseminated coccidioidomycosis was hospitalized in 2002 with low-grade fevers, headaches, neck stiffness and photophobia. Clinical examination revealed an alert male with a T_{max} of 100.2°F. A significant clinical finding included neck stiffness. The rest of the physical examination was unremarkable.

A spinal tap revealed cerebrospinal fluid (CSF) glucose levels of 62 mg/dl (with serum glucose of 180 mg/dl), CSF protein of 59 mg/dl, and a white blood cell count of 68 cells/mm^3, with a differential of 26 polynuclear cells and 74 monocytes per 100 cells. Bacterial and fungal smears and cultures were negative. Serum coccidioidal antibody immunodiffusion IgG levels were elevated. The initial MRI of the brain was unremarkable; however, due to clinical suspicion of coccidioides meningitis, he was treated with itraconazole and liposomal amphotericin B for six weeks.

Despite receiving antifungal therapy, the patient's headaches persisted. He also experienced weight loss, instability of gait and memory loss as well as grand mal seizures. A MRI scan performed three months postinitial hospitalization showed a 5-mm nonenhancing lesion immediately adjacent to the anterior limb of the internal capsule. Repeat spinal tap demonstrated CSF protein of 54 mg/dl and 25 white blood cells/mm^3, with a differential of 29 polymorphonuclear cells and 71 mononuclear cells per 100 cells. Bacterial and fungal smears were negative.

Subsequent MRIs revealed an increased number and size of the brain lesions. Multiple biopsies of the brain lesions 11 months after initial hospitalization revealed inflammatory tissue, but fungal and AFB stains and cultures were negative. No evidence of malignancy was noted. Due to a continued suspicion of coccidioides meningitis, his antifungal regimen was changed to liposomal amphotericin B3 mg/kg/day intravenous in combination with intra-

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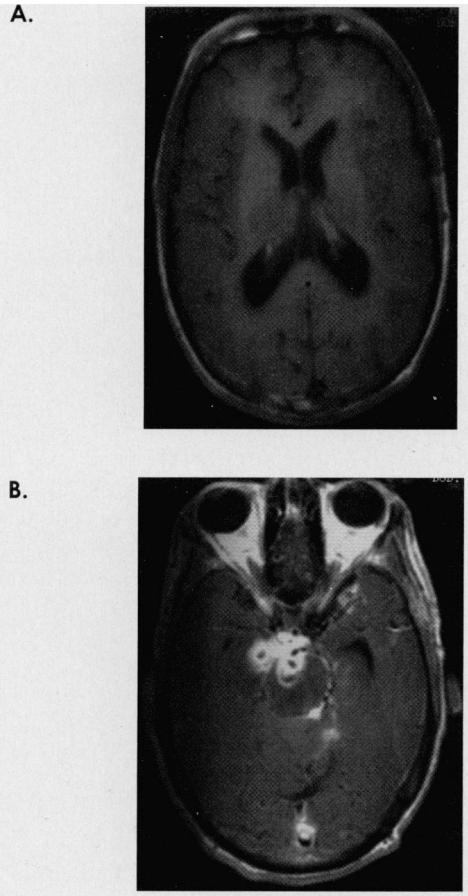
venous voriconazole 200 mg daily. A few weeks later, his headaches and gait dysfunction started to improve. An MRI of the brain performed one month later showed that his lesions had started to regress in size, and they eventually resolved (Figure 1) after one year of treatment. The clinical symptoms of headaches, dizziness and ataxia also resolved.

Liposomal amphotericin B was tapered off after 16 months of therapy; however, the patient remains on lifelong oral voriconazole therapy, 200 mg daily. His meningeal symptoms have completely disappeared as have his brain lesions, with slight meningeal edema remaining.

DISCUSSION

The onset of clinical signs of coccidioides meningitis is usually subacute. Most common symptoms include headache, nausea, vomiting, altered mental status, nuchal rigidity and, occasionally, cranial neuropathies. These symptoms vary according to the affected sites and according to the extent of parenchymal damage. Occasionally, brain abscesses may complicate the process.[3]

Figure 1. Pretreatment MRIs of the brain showing parenchymal lesions and marked degree of edema



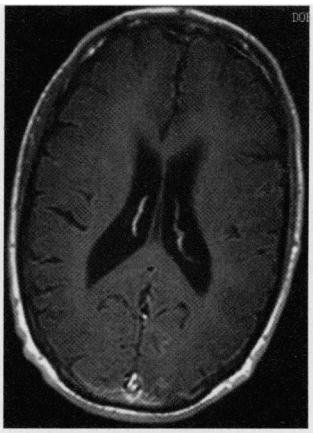
Although establishing a definitive diagnosis is important for therapy, it is not always possible. The diagnosis is usually made during primary (pulmonary) illness and by isolating the organism *Coccidioides immitis* from a clinical specimen. Modes of detection include DNA-specific probes, antibody tests, culture or microscopy. CNS involvement is generally diagnosed by the meningitis-associated clinical symptoms, by MRI or CT scans, and rarely by detection of the organism by direct observation in the spinal fluid. As mentioned by Johnson and colleagues, serology remains the mainstay in confirming the diagnosis although a negative test cannot exclude the diagnosis.

Debate still remains over the optimal treatment of coccidioides meningitis. Two animal models have been developed in order to study efficacies of various drugs and in order to obtain a better understanding of pathologic processes.[4,5] Although two subsequent studies conducted on rabbits were performed concerning drug efficacy,[6,7] optimal treatment has still not been defined. Administration of amphotericin B is the mainstay of therapy for CNS coccidioidomycosis; addition of itraconazole or fluconazole has also been used. Therapy is to be continued indefinitely.[8] Failures have been reported and alternatives sought. In such instances, there have been case reports of successful use of voriconazole in coccidioides meningitis.[9,10]

Voriconazole (Vfend®) has not been approved for the treatment against *Coccidioides immitis*, although it has shown good in vitro activity against this pathogen.[13] and with its ability to penetrate the CSF and brain tissue, may be a good alternative to fluconazole or itraconazole.

Liposomal amphotericin B (AmBisome®) has

Figure 2. Posttreatment MRIs of the brain with voriconazole and liposomal amphotericin B showing resolution of lesions



also demonstrated excellent efficacy in a rabbit model of coccidioides meningitis.[14] Furthermore, its successful use in managing disseminated coccidioidomycosis has been demonstrated clinically.[15] Combination therapy of both liposomal amphotericin B and voriconazole thus seems logical but in vivo and in vitro studies are still lacking.

In conclusion, we believe this case to be important due to two major aspects: 1) This case report exemplifies the difficulties encountered in diagnosing and treating coccidioidal meningitis. A high level of suspicion for coccidioides meningitis must be maintained in patients presenting with signs of meningitis and history of coccidioidomycosis; 2) This case report illustrates that the optimal treatment regimen for coccidioides meningitis still has not been defined. New drugs such as posaconazole, voriconazole and lipid solutions of amphotericin B may prove to be equally or possibly even more beneficial in the management of such patients as described herein. Especially when standard therapy fails, combination therapy with voriconazole and liposomal amphotericin B may be an option.

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