Successful Treatment of Disseminated Nonmeningeal Coccidioidomycosis with Voriconazole

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A 31-year-old Jamaican man with disseminated nonmeningeal coccidioidomycosis that involved the spine, ribs, pelvis, liver, and spleen did not clinically respond to a prolonged course of both amphotericin B deoxycholate and liposomal amphotericin B therapy. After institution of voriconazole monotherapy, the patient had a favorable (albeit slow) radiological and clinical response without adjunctive surgical intervention.

Less than 1% of patients infected with Coccidioides immitis develop chronic pulmonary or disseminated coccidioidomycosis [1, 2]. For patients unfortunate enough to develop disseminated coccidioidomycosis, successful management often requires a combined medical and surgical approach [3–5]. We report the case of an HIV-negative Jamaican man with severe disseminated nonmeningeal coccidioidomycosis who did not respond to amphotericin B therapy but appeared to clinically respond to voriconazole monotherapy without surgical intervention.

Case report. On 19 March 2003, a previously healthy 31-year-old black Jamaican man incarcerated in Taft, California, was admitted to a local hospital with a nonproductive cough, shortness of breath, fever, chills, back pain, and a 9-kg weight loss over the preceding 2 months. A chest radiograph revealed diffuse pulmonary infiltrates. Coccidioidomycosis was diagnosed by histopathological examination of specimens obtained by transbrachial biopsy. The findings of an examination of a CSF sample were unremarkable. On 29 March 2003, after 5 days of antifungal therapy, a once-daily, 40-mg regimen of amphotericin B (~1 mg/kg) was substituted for fluconazole.

On day 24 of therapy, the patient was transferred to the Federal Medical Center and Saint Mary's Hospital in Rochester, Minnesota, for further management. He complained of fever, chills, night sweats, and neck pain. Physical examination revealed a small, cachectic-appearing man (weight, 44 kg) with tachycardia, bilateral basilar rales, tenderness to palpation along the cervical spine, and normal neurological findings.

The findings of CT and MRI scans and microbiological studies confirmed disseminated coccidioidomycosis (figures 1–3). Multiple lesions were present in the lungs, liver, spleen, ribs, pelvis, left femur, and paraspinal and pelvic musculature. MRI of the head and spine revealed a right cerebellar infarct; an inflammatory mass encasing the right vertebral artery; extensive vertebral osteomyelitis with paravertebral abscesses at C4, C5, T2, and T4; epidural abscesses at T2, T8, and T9, causing spinal cord displacement; and paraspinal muscle abscesses at T7, T8, L5, S2, and S3.

A second examination of CSF samples revealed a WBC count of <1 cell/µL, a glucose level of 61 mg/dL, and a total protein level of 30 mg/dL. Complement-fixation antibody titer to Coccidioides species was 1:2 in the CSF sample and 1:1024 in the serum sample. The patient’s leukocyte count was 21,200 cells/µL, with an erythrocyte sedimentation rate (ESR) of 102 mm/h, an alkaline phosphatase level of 663 U/L, an alanine aminotransferase level of 171 U/L, and an aspartate aminotransferase level of 32 U/L. The patient’s condition was believed to be inoperable because of the widespread nature of the disease. The orthopedic surgery department placed him in a custom Cervical-Thoracic-Lumbar-Sacral-Orthosis.

On day 43 of therapy, the patient was switched to a once-daily, 250-mg regimen (~5.7 mg/kg) of liposomal amphotericin B (AmBisome; Gilead Sciences). On day 50 of therapy, fluconazole (600 mg q.d. po) was added to the patient’s regimen due to persistent fever (temperature, 38.6°C–39.2°C). On day 61 of therapy, he was readmitted to St. Mary’s Hospital for persistent fever, malaise, continued weight loss (weight, 39.5 kg), and persistently elevated leukocyte count (25,200 cells/µL), ESR (123 mm/h), and C-reactive protein (CRP) level (21 mg/dL). On day 65 of therapy, an additional MRI of the head and cervical spine showed a slight increase in the size of the previously documented epidural and prevertebral abscesses and a new large pleghm around the C7 spinous process. Treatment with liposomal amphotericin B was continued, and itraconazole (200 mg b.i.d. iv)
and caspofungin (50 mg q.d.) were added to the regimen. A gastrostomy tube was placed for enteral nutrition.

On day 68 of therapy, due to persistent fever and failure to respond to multiple antifungal agents (including 6500 mg of liposomal amphotericin B and 1400 mg of amphotericin B deoxycholate), the patient was switched to voriconazole (100 mg b.i.d. po). Low-grade fever persisted for the next 2 months; however, the patient gained weight (weight, 53 kg). On day 170 of therapy, Coccidioides species complement-fixation antibody titer was undetectable. On day 191 of therapy, the gastrostomy

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**Figure 1.** CT scan of abdomen/pelvis showing destructive lesions of ilium, sacrum, and soft-tissue abscesses

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**Figure 2.** T1-weighted MRI with gadolinium enhancement of the cervical and upper thoracic spine performed on 22 April 2003 and demonstrating widespread, multifocal vertebral body involvement, along with anterior inflammatory masses at C4, C5, T2, and T4 and epidural abscess at the T2 level (A), and a follow-up MRI performed on 1 March 2004 and showing improvement of multifocal abscesses and destruction of T2 vertebral body (B).
Figure 3. T1-weighted MRI without gadolinium performed on 23 April 2003 and demonstrating widespread involvement of the thoracic spine, with epidural abscesses present at T8 and T9 and paraspinous abscesses at T2–5 (A), and a follow-up MRI showing significant reduction in the multiple paraspinous and epidural abscesses (B).

tube was removed. On day 219 of therapy, the ESR was 0 mm/h, CRP level was 0.04 mg/dL, and leukocyte count was 9000 cells/μL. Additional spinal MRIs on day 176 and day 255 of therapy revealed significant radiological improvement, with resolution of epidural abscesses and significant reduction or resolution of the paraspinous abscesses (figure 3). The patient continued to receive voriconazole under inpatient medical supervision at the Federal Medical Center until day 242 of therapy. During the next 2 weeks, he developed low-grade fevers and lost 3 kg after not consistently taking voriconazole; his ESR (69 mm/h), CRP level (19.4 mg/dL), leukocyte count (16,300 cells/μL), and coccidioidal complement-fixation antibody titer (1:128) all increased. After supervised administration of voriconazole at an increased dosage of 200 mg administered twice daily, the patient quickly showed clinical improvement. On day 344 of therapy, his ESR was 18 mm/h, his CRP level was 0.04 mg/dL, his leukocyte count was 9900 cells/μL, and his coccidioidal complement-fixation antibody titer remained at 1:128. An additional spinal MRI revealed stable disease (figure 2). At the time of writing, the patient remains clinically healthy and without neurological deficit after 10 months of voriconazole therapy. He will continue to receive voriconazole for the foreseeable future.

Discussion. The risk of disseminated coccidioidomycosis is believed to be higher among patients with HIV, hematological malignancy, or solid-organ transplantation, and among those of African or Filipino descent [1–3]. Our patient’s infection appeared refractory to amphotericin B therapy. Relapse rates after treatment with amphotericin B alone have not been well defined in the medical literature [6]. In a retrospective review of 24 patients with skeletal infection, Bried and Galgiani [5] found that patients with high complement-fixation antibody titers (≥1:128) had a greater chance of experiencing failure of medical therapy alone with amphotericin B and/or ketoconazole (P<.01). Bisla and Taber [7] reported a relapse rate of 22% for coccidioidomycosis of bone and/or joints with intravenous amphotericin B and surgical debridement. Response rates to fluconazole or itraconazole for disseminated nonmen-
Ingestal coccidioidomycosis remain far from satisfactory, and relapses rates are high after discontinuation of therapy [8, 9]. Catanzaro et al. [9] reported a response rate of 86% (12 of 14 patients) with fluconazole (200 or 400 mg daily) in patients with skeletal involvement, but relapse rates were high (50%) once therapy was discontinued. However, no details were given with regard to the extent of skeletal involvement or to indicate whether surgical debridement was performed. Galgiani et al. [8] found an overall response rate of 50% for fluconazole (400 mg q.d.), compared with 63% for itraconazole (200 mg b.i.d.) for disseminated nonmeningeal coccidioidomycosis after 8 months of treatment. Only 5.2% of patients underwent surgery to manage *C. immitis* infection [8]. For patients with skeletal infection, 37% responded to fluconazole, compared with 70% who responded to itraconazole, after 12 months of treatment (*P* = .03) [8].

Our patient was switched to voriconazole and had a slow, yet favorable, clinical response. Administration of enteral nutrition may have contributed to this response. Voriconazole has emerged as a viable treatment option for invasive pulmonary aspergillosis and other fungal infections, such as candidiasis, cryptococcosis, scedosporiosis, and fusariosis [10, 11]. Little clinical data have been published concerning voriconazole’s potential role in treating *C. immitis* infection [10, 12]. Voriconazole has better in vitro activity against *C. immitis*, compared with itraconazole or amphotericin B [13]. Both agents, however, are fungistatic [13]. Our patient was initially treated with a lower dosage of voriconazole due to his initial low body weight. Skeletal involvement with *C. immitis* does not have a reliable response to fluconazole, and itraconazole has issues with oral bioavailability. Voriconazole holds promise as an alternative agent, but more clinical experience is needed.

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**References**