Treatment of disseminated coccidioidomycosis with diffuse pneumonia by caspofungin and fluconazole

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Abstract

**Background:** The current recommended therapy for diffuse coccidioidal pneumonia involves initial treatment with amphotericin B deoxycholate or high-dose fluconazole, followed by substitution with an azole after clinical improvement. Amphotericin B is more frequently used as initial therapy if deterioration is rapid.

**Case presentation:** A 31-year-old Korean male with coccidioidomycosis, who presented with a miliary pattern on a chest X-ray and a skin rash, did not clinically respond to amphotericin B deoxycholate therapy. Following combination treatment using caspofungin and fluconazole, the patient showed a favorable radiological, serological, and clinical response.

**Conclusions:** This appears to be the first case of successful treatment for diffuse coccidioidal pneumonia with skin involvement in an immunocompetent patient using caspofungin and fluconazole without any adverse effects. Combined therapy with caspofungin and fluconazole may, therefore, be an alternative treatment for diffuse coccidioidal pneumonia that does not respond to amphotericin B deoxycholate therapy.
**Background**

Diffuse coccidioidal pneumonia (caused by endemic fungi of the genus *Coccidioides*) is an unusual complication of an initial primary pulmonary infection in a host who is typically immunologically competent and can be a life-threatening systemic fungal infection [1]. The recommended therapy for diffuse coccidioidal pneumonia has been amphotericin B, replaced with an oralazole antifungal after clinical improvement [2, 3]. Recently, updated guidelines recommend high-dose fluconazole or amphotericin B for the treatment of diffuse coccidioidal pneumonia [4]. Although amphotericin B is more frequently used as initial therapy, the disease remains difficult to treat and treatment is often characterized by frequent failure and relapse and drug-associated toxicities, which also limit the clinical utility of amphotericin B [2–4].

We report a case of disseminated coccidioidomycosis with diffuse pneumonia in an immunocompetent Korean male treated successfully with combination of caspofungin and fluconazole, who previously had not improved after treatment with amphotericin B.
Case presentation

On 6 October 2004, a 31-year-old Korean male was admitted to hospital suffering from various symptoms, including fever, chills, general fatigue, cough, dyspnea, night sweats, and a weight loss of 2 kg, which he had experienced for the previous 4 weeks. The patient had smoked half a packet of cigarettes per day for the past 10 years and had been diagnosed 4 years previously with adrenoleukodystrophy. During August to September 2004, he traveled to Corona, California, where he developed his current symptoms and was treated for bacterial pneumonia. However, his symptoms worsened rapidly and he returned to Korea.

On admission to hospital, the following vital signs were observed: temperature, 37.8°C; blood pressure 130/70 mmHg; pulse 92 beats/min; and respiratory rate, 24 breaths/min. A clinical examination revealed a moderately ill looking appearance with multiple encrusted erythematous papular nodules on the face and trunk. There were no other remarkable findings in the examination. Laboratory tests revealed leukocytosis with eosinophilia (white blood cell count 23,460 cells/µl, eosinophils 22%), an increased erythrocyte sedimentation rate (100 mm/h), and increased levels of C-reactive protein (24.7 mg/dl). A chest X-ray and computed tomography scan revealed tiny multiple nodules in both lung fields (Fig. 1, top). A sputum acid-fast bacillus stain and
tuberculosis culture provided negative findings. The patient underwent bronchoscopy and a skin punch biopsy procedure, which revealed the presence of a chronic granuloma with thick-walled mature spherules containing endospores. *Coccidioides immitis* was grown from a skin tissue culture. The patient’s serum complement fixation (CF) titer was 1:16 and a serum coccidioidal immunodiffusion test for IgG antibody was negative (all coccidioidal CF antibody testing was carried out at the laboratory of Lynn A. Cheryk, Mayo Clinic, Minnesota, USA). Cerebrospinal fluid (CSF) parameters showed no evidence of meningitis.

Following a diagnosis of diffuse coccidioidal pneumonia with skin involvement, the patient was treated with amphotericin B deoxycholate (total dosage, 1970 mg; ~1 mg/kg) for 40 days, from day 5 to day 45 of hospitalization. However, the patient complained of persistent fever (temperature of 38.6–39°C), and night sweats, with no improvement of his cough and skin rash, and his general condition progressively deteriorated. The patient developed a right pleural effusion and no improvement in the miliary shadows on a chest X-ray was observed. A follow-up CF titer performed on day 27 of hospitalization showed that the CF titer had increased to 1:64. On day 45 of hospitalization the therapy was changed to a combined treatment with caspofungin (initially 70 mg and then 50 mg/day, given intravenously) and fluconazole (400 mg/day,
given orally). Sixteen days after the combination treatment (day 60 of hospitalization), a chest X-ray revealed a reduction in both the miliary nodes and pleural effusion. The patient began to improve; however, he still developed occasional fevers. Forty-nine days after the combination therapy, his peak body temperature had decreased to below 38°C and dyspnea had subsided and his serum CF titer had decreased to 1:8. However, his cough still remained. By day 125 of the combination treatment, the patient had defervesced and all his respiratory symptoms subsided. Moreover, his skin lesions were nearly resolved, although some still remained on his face, and a serum CF titer was undetectable, and on day 131, caspofungin therapy was stopped. There were no drug-related side effects observed during treatment with caspofungin and fluconazole. The patient was subsequently treated with fluconazole at a dose of 400 mg/day. On day 194, his follow-up CF titers increased to 1:256 without any worsening of respiratory symptoms, skin rash and chest X-ray. A follow-up examination, performed 5 months following completion of the combination treatment, revealed minimal residual nodules visible on a chest X-ray and computed tomography scan (Fig. 1, bottom) and CF titers decreased to 1:128. The patient remains clinically healthy and without any respiratory symptoms and fever as of September 2005; however, he is still receiving treatment with suppressive fluconazole.
**Discussion**

We report an immunocompetent patient with diffuse coccidioidal pneumonia with extrapulmonary manifestation who has been treated successfully with caspofungin and fluconazole without any adverse effects.

In 2000, the Infectious Diseases Society of America (IDSA) published guidelines for the treatment of coccidioidomycosis [3]. Amphotericin B was recommended as first-line therapy for diffuse pneumonia caused by *Coccidioides* organisms. Despite the use of amphotericin B therapy, diffuse coccidioidal pneumonia remains difficult to treat, and treatment is often characterized by frequent failure and relapse.

Recently, a number of new antifungal agents have been evaluated for their activity against *C. immitis*, in both *in vitro* and *in vivo* studies. Agents that have been shown to be potentially useful in the treatment of coccidioidomycosis include voriconazole, caspofungin, and posaconazole [2, 5–7].

Lutz et al. [7] published *in vitro* data for posaconazole showing fair fungicidal activity against *C. immitis*. They also noted that posaconazole showed superior activity to fluconazole or itraconazole in a murine model of disseminated non-meningeal coccidioidomycosis. Anstead et al. [5] reported a successful outcome in six patients who had refractory coccidioidomycosis treated with posaconazole. Another recent report
described the successful treatment of a human case of disseminated non-meningeal coccidioidomycosis with voriconazole [6]. However, both these agents were not available to us to treat this particular patient.

Caspofungin is the first of a new class of antifungal agents, the echinocandins, which target the fungal cell wall itself via interruption of the β-(1,3)-D-glucan synthesis pathway [8, 9]. This mechanism of action is different from that of amphotericin B and azoles. β-(1,3)-D-glucan synthase is absent from mammalian cells. Caspofungin has received US Food and Drug Administration approval for the treatment of mucosal and invasive candidiasis and salvage therapy of invasive aspergillosis [8]. Caspofungin was therapeutically effective in a murine model of C. immitis infection [10], despite its limited in vitro activity against the fungus when minimum inhibitory concentrations (MICs) were determined. However, an improved correlation between in vivo activity and the minimum effective concentration (MEC) – the lowest dose of drug that causes morphologic effects on fungal hyphae – was observed [10]. In this study, mice infected with one of two strains of C. immitis, each with an MEC of 0.125 mg/mL but one with an MIC of 8 mg/mL and the other with an MIC of 64 mg/L, responded equally well to treatment with caspofungin. A recent report has described the successful treatment of disseminated coccidioidomycosis in a renal transplant recipient with caspofungin [11].
Furthermore, another report described a treatment failure for coccidioidal meningitis because the large molecular mass, water solubility, and high protein binding of caspofungin limited penetration into the CSF [12].

Amphotericin B therapy had failed to prevent progression of our patient’s illness. At that time the recommended regime was initial treatment with amphotericin B, substituted with an azole if clinical improvement was achieved [2, 3]. The only new antifungal agent available to us was caspofungin. Since clinical and in vitro data for caspofungin were limited, caspofungin monotherapy could not be selected because of the severity of the illness. The scarcity of evidence of in vitro antagonism when combined with other antifungal agents led us to consider combination therapy [8]. We considered fluconazole or itraconazole as combination antifungal with caspofungin. Itraconazole has absorption problems and we could not measure serum levels, so we chose fluconazole. Combined treatment against C. immitis is currently not recommended. In addition, the possibility of antagonism or synergism between caspofungin and fluconazole has not yet been fully evaluated. However, an in vitro study has reported that although synergy was low between caspofungin and fluconazole, synergism was the pattern most often observed [13]. The mechanisms proposed for its synergy may be simultaneous inhibition of different fungal cell targets, such as the cell
wall and membrane targets.

These data, the limited treatment options and the severity of the illness prompted us to carry out a trial of combined therapy with caspofungin and fluconazole. While we are preparing the manuscript, the updated IDSA guidelines published in September 2005 and recommend amphotericin B or high-dose fluconazole for the treatment of diffuse coccidioidal pneumonia [4]. However, the high-dose fluconazole therapy was not suitable to treat some Korean patients for fungal infections, because of frequent elevation of hepatic transaminase level.

On day 16 after initiating combined therapy with caspofungin and fluconazole, a chest X-ray revealed a reduction in both the miliary nodes and pleural effusion, and the patient began to improve. Our patient had a favorable clinical response and the combined therapy resulted in a successful outcome.

Combined therapy with caspofungin and fluconazole may, therefore, represent an alternative treatment for diffuse coccidioidal pneumonia with non-meningeal extrapulmonary involvement that does not respond to amphotericin B therapy. However, determining the best course of therapy in treating coccidioidomycosis remains a therapeutic challenge. Further clinical studies evaluating this combination are required.
Conclusion

Although combined therapy with caspofungin and fluconazole against *C. immitis* is not currently recommended, it may represent an alternative treatment for cases that are not responsive to amphotericin B deoxycholate.

List of abbreviations

CF, complement fixation; CSF, cerebrospinal fluid

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

HJC, WJK, and MJK advised on the management of the patient and assisted in editing of the manuscript. JHK and CS performed the bronchoscopic biopsy and provided clinical details. DWP and JWS drafted the manuscript and were involved in patient management and follow-up. All authors read and approved the final manuscript.

Acknowledgement

Written consent was obtained from the patient for the publication of this case report.
References


Figure legend

Fig. 1. Chest X-ray and high-resolution computed tomography (CT) findings on admission and at 5 months following combined treatment. Top (on admission): (A) posterior–anterior chest radiograph showing multiple tiny reticular nodules on both lungs; (B) tiny centrilobular and subpleural nodules are evident in both lungs on the chest CT. Bottom (5 months after combined treatment): (C) a follow-up chest X-ray showing that the multiple reticular nodules are much improved; (D) follow-up computed tomography scan revealing minimal residual nodules, which are much improved.