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How should we manage a patient with invasive mucoromycosis who develops life-threatening reaction to amphotericin B? Report of two cases and literature review

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ABSTRACT

This report presents two cases of invasive rhino-orbital mucormycosis who had life-threatening reactions to amphotericin B. Both cases were treated with a combination of posaconazole–caspofungin favorably with no evidence of recurrence upon long-term follow-up. To our knowledge, this is the first report of successful treatment of invasive mucormycosis with azole–echinocandin combination. It may suggest that caspofungin exerts additional or even synergistic antimucoral effects to posaconazole.

1. Introduction

Mucormycosis is an aggressive, angioinvasive fungal infection caused by filamentous fungus *Rhizopus, Mucor*, and *Lichtheimia* species of the order Mucorales in the subphylum Mucormycotina [1]. This opportunistic fungal infection afflicts immunocompromised or severely hyperglycemic patients such as those with un-controlled diabetes mellitus with or without metabolic acidosis. Other known risk factors for invasive mucormycosis include high-dose glucocorticoid therapy, long-term neutropenia, intravenous drug use, malnutrition, stem cell or solid organ transplantation, treatment with deferoxamine and severe skin damages such as burns and surgical suture sites. Involvement of paranasal sinuses with extension to orbital area and central nervous system is a more common clinical feature of this potentially life-threatening fungal infection which requires urgent diagnosis and treatment. Diagnosis is usually made by clinical suspicion and histopathological examination. Treatment options for invasive mucormycosis are limited. Mucorales are inherently resistant to many antifungal drugs used to treat systemic mycoses, including ketoconazole, fluconazole, voriconazole, flucytosine and the echinocandins. Lipid formulations of amphotericin B are the drug of choice. Some patients can then be transitioned to oral posaconazole if absorption is adequate [1]. However, the variable results of treatment with different antifungal drugs, either alone or in combination, indicate more studies are required to find the regimens that suits special circumstances.

2. Case

Case 1.1. The first patient was a 64-year-old diabetic housewife, who was admitted to the hospital with the complaint of right facial palsies, swelling and paresthesia in the right cheek, and unilateral dark brown nasal discharge since few days ago. On admission, asymmetrical swelling of the right side of the face, right facial paralysis, decreased sensation in the distribution of the infraorbital nerve, and necrotic lesion of the nasal septum were observed. CT scan of the paranasal sinuses revealed right sided maxillary, ethmoid, and sphenoid sinusitis.

Histpathological examination of the endoscopic biopsy specimens revealed invasive mucormycosis. Brain MRI showed no evidence of spread of lesion to the brain. Diagnosis of rhino-orbital mucoromycosis was made and Amphotericin B deoxycholate (AmB) started at a dose of 1.5 mg/kg/day. During the first hour of infusion, patient developed acute respiratory distress, hypoxemia, tachycardia, bilateral wheezing, and chest pain. Because of serious adverse reactions, treatment stopped immediately. Intravenous hydrocortisone was administered and oxygen was started via nasal cannula. Her respiratory symptoms subsided within the next several hours, but she developed edema in the face and extremities. Possibility of AmB desensitization was proposed. On the

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next day, very slowly administering AmB at an extremely low dose started. A few seconds after starting AmB, patient developed similar but more intense symptoms. AmB stopped immediately and never restarted thereafter. Acute symptoms disappeared after a few minutes of intravenous administration of epinephrine. Therefore, a combination of Posaconazol 400 mg twice/day with a high-fat meal and Caspofungin IV 70 mg load, then 50–70 mg/day was started as salvage therapy. The patient also underwent debridement of necrotic and infected tissues several times, and her blood sugar level kept under control. Combination medical therapy continued for 4 weeks, until serial imaging showed no progression of the lesion and histopathological examination revealed no evidence of fungal invasion of tissue. At the end of week 4 of treatment, the patient was symptom-free except for mild facial paralysis. Posaconazole was continued for a further 6 weeks. The patient had no recurrence and remained healthy during the 12-month follow-up.

Case 1.2. A 43 year-old diabetic female patient presented with a history of unilateral facial swelling and numbness, and diplopia since 10 days ago. CT scan of the paranasal sinuses demonstrated right sided pan-sinus opacification with associated bone destruction of the orbital floor and medial maxillary sinus wall (Fig. 1).

After a full work up, the diagnosis of rhino-orbital mucormycosis with right CN 6th palsies was documented histopathologically, and patient started AmB 1.5 mg/kg/day. A few minutes after starting the first dose of AmB, she began to experience uncontrollable shaking chills that cause her teeth broke. Second dose of AmB started twenty minutes after premedication with acetaminophen, antihistamines, and dexamethasone, but a few minutes after starting infusion, she developed severe respiratory distress and bilateral wheezing. *AmB* stopped but she then developed severe toxic epidermal necrolysis (TEN)-like skin lesions. Two days later, she developed severe generalized edema, increased alkaline phosphatase (ALP), Gamma-glutamyl transpeptidase (GGT), and lactate dehydrogenase (LDH), and progressive anemia. Despite AmB being stopped, serum creatinine increased progressively up to 3 mg/dL. However, she did not require renal replacement therapy.

Patient received combination of Posaconazol 400 mg twice/day with a high-fat meal and Caspofungin IV 70 mg load, then 50–70 mg/day as salvage therapy. Several courses of endoscopic and surgical debridement of devitalized and necrotic tissues performed. Combination therapy continued for 6 weeks during which symptoms gradually resolved, until repeated CT scan of para-nasal sinuses showed no progression of the lesions and histological specimen from the debrided tissue showed no fungal invasion. After discharge from hospital, patient received Posaconazol for a further 6 weeks. At the end of treatment, patient fully recovered with minimal right lateral rectus palsies. Long-term follow-up showed no recurrence.

3. Discussion

Both reported cases had life-threatening adverse reactions to Amphotericin B deoxycholate (AmB). After first thinking, posaconazole monotherapy was considered as salvage therapy. However, based on favorable preliminary results using combination lipid polyene–echinocandin therapy including in vitro and animal model studies and observational clinical data, in addition to the safety profile of echinodandins, trial of combination azole–echinocandin was proposed and started. Both patients had favorable outcome with this combined regimen with no recurrence during long-term follow-up. The efficacy of this combination of antifungal drugs in patients with mucormycosis has not been evaluated before. Two hypotheses can be put forward to explain the favorable outcome of patients: [1] posaconazole alone had favorable antifungal effect, or [2] caspofungin exerts additional or even synergistic antifungal effects.

Reversal of underlying risk factors (e.g., diabetes control) is important in the treatment of mucormycosis [2]. Surgical resection is also a critical component of the management of mucormycosis. Surgery was found to be an independent predictor for improved outcome in a retrospective study of cases of mucormycosis [3]. However, the mortality of mucormycosis without antifungal drugs is unacceptably high. Even with antifungal therapy, crude mortality is 40% among patients with mucormycosis [3].

AmB remains the only licensed antifungal agent for the treatment of mucormycosis [4]. Posaconazole is an option for second

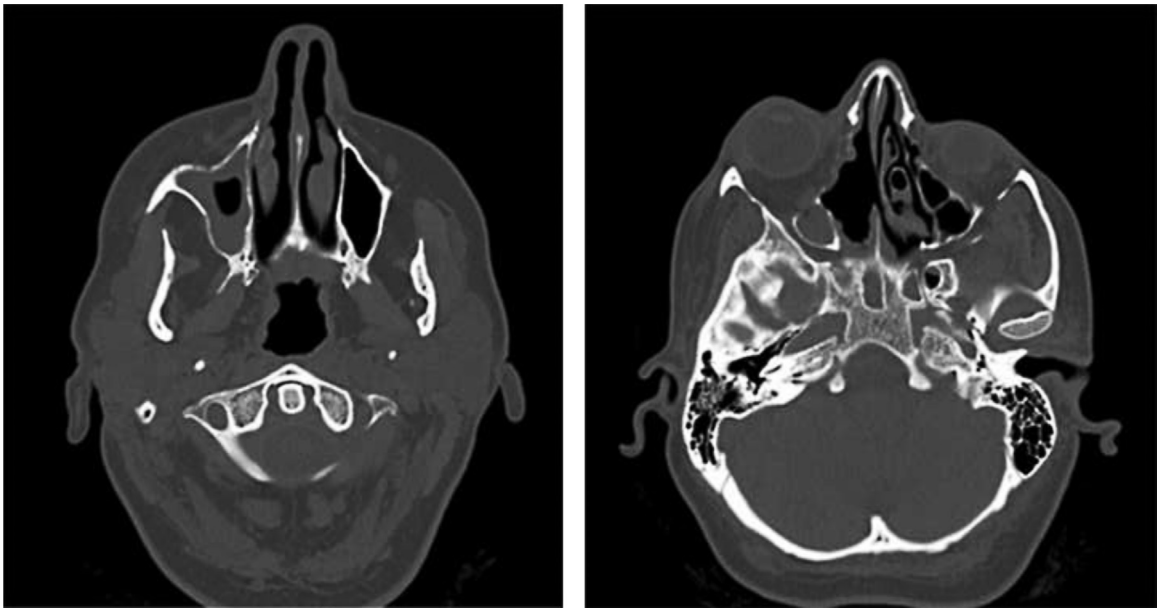

Fig. 1. CT scan of the paranasal sinuses demonstrated right sided pan-sinus opacification with associated bone destruction of the orbital floor and medial maxillary sinus wall.

line-treatment [2]. Numerous studies have tried to establish the efficacy of combination therapy in mucormycosis hoping to increase the response rate of available treatment in patients who tolerate first line antifungal agents. Accordingly, three potential strategies are proposed including combination lipid polyene–echinocandin, combination lipid polyene–deferasirox, and combination lipid polyene–posaconazole (or isavuconazole). However, until randomized clinical trials are conducted, no definitive conclusion about their efficacy is possible [3].

Echinocandins do not have in vitro activity against the Mucorales in standard susceptibility tests [3]. No clinical data are available with echinocandin monotherapy in mucormycosis and occurrence of mucormycosis has been documented in patients with hematologic malignancies who currently receiving or recently exposed to caspofungin [2]. In the study of Spellberg et al. combination polyene–echinocandins therapy improved survival of diabetic ketoacidotic mice with disseminated zygomycosis compared to that of mice given monotherapy and that of untreated controls [5]. Comparable results were observed in the studies in which combination of polyene plus other echinocandins were used in murine models [6]. There are also several case reports of favorable outcome in patients with mucormycosis who treated with combination polyene–echinocandins in the literature [7,8]. In a small, retrospective study, combination LFAB–caspofungin therapy was associated with significantly improved outcomes for rhino-orbital-cerebral mucormycosis among patients with diabetes, compared with polyene monotherapy [9].

There has been little research on the appropriate treatment for patients who does not tolerate AmB. Severe allergic reactions (including anaphylaxis) to AmB are extremely rare but have been reported and considered a contraindication to further AmB [10,11]. Available clinical data from open-label salvage studies suggest that posaconazole is a reasonable option for patients with mucormycosis who are refractory to or intolerant of polyenes [4]. As a salvage regimen, posaconazole was associated with response rates of 60–80% or greater [12–14]. No clinical studies have evaluated combination posaconazole–polyene therapy for mucormycosis [4].

To our knowledge, this is the first report of using combination posaconazole–caspofungin as salvage therapy in mucormycosis. If the hypothesis of additional or synergistic effect of caspofungin is well-documented, the combination of posaconazole–echinocandin therapy can be proposed as more effective treatment for use in patients who do not tolerate polyenes. By validating this hypothesis, possible triple therapy with polyene plus echinocandin plus azole might also be proposed as a regimen with more effective response rate in patient with mucormycosis who can tolerate polyene antifungal drugs. Spellberg et al. noted the possible triple combination therapy with a polyene plus echinocandin plus deferasirox, which would represent maximal aggressiveness of treatment [15].

As stated by Spellberg et al., if combination therapy is superior but is not used, it may lead to undertreatment. On the other hand, if it is not superior but is used, it causes unacceptable toxicity and cost [15]. Therefore, it seems necessary to search for the effective treatment options for affected patients hoping to improve their survival and quality of life.

Conflict of interest

None.

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