Rhinocerebral Mucormycosis Treated with Amphotericin B Colloidal Dispersion in Three Patients

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Rhinocerebral mucormycosis (zygomycosis) primarily affects diabetic or immunosuppressed patients and typically progresses rapidly, necessitating surgical excision and antifungal therapy with amphotericin B. Large doses of amphotericin B are required for cure, causing significant renal toxicity. Amphotericin B colloidal dispersion (ABCD; Amphocil, Sequus Pharmaceuticals, Menlo Park, CA) is a 1:1 complex of cholesteryl sulfate and amphotericin B, which results in significant reduction of toxicity, especially nephrotoxicity. We describe three patients with life-threatening rhinocerebral mucormycosis treated with ABCD. All patients had high serum creatinine levels due to prior treatment with amphotericin B; these levels reverted to normal during treatment with ABCD. Two patients with diabetes mellitus were cured after receiving a combination of surgery and ABCD therapy. The third patient, who had myelodysplastic syndrome, had an initial good response, with cure of the fungal infection; however, he eventually died of his primary illness. To the best of our knowledge, this is the first detailed clinical description of the treatment of mucormycosis with ABCD.

Mucormycosis (zygomycosis) is a life-threatening infection caused by molds belonging to the order Mucorales of the class Zygomycetes. Members of this order are found in decaying vegetables, seeds and fruits, compost piles, animal excreta, soil, and stale bread. Members of the genera Rhizopus, Rhizomucor, Absidia, and Mucor are the main etiologic agents of mucormycosis and have a wide geographic distribution [1]. Mucormycosis is usually encountered as a secondary disease or an opportunistic infection in immunocompromised hosts, most of whom have underlying conditions such as diabetic ketoacidosis or major trauma [2].

The route of infection is either through inhalation of the spores or via abraded skin. Typically, in tissue the fungal hyphae invade blood vessels, which progressively leads to thrombosis followed by necrosis with the development of a black eschar that is the clinical hallmark of these infections. The clinical presentation may be specific to the host. Rhinocerebral mucormycosis caused by Rhizopus oryzae is seen most often in diabetics, and pulmonary infection is more common in patients with neutropenia secondary to chemotherapy for hematologic malignancies [2]. Patients with ocular involvement may present with proptosis, chemosis, and paralysis of extraocular muscles. It has recently been shown that treatment with the chelating agent deferoxamine poses a risk for acquiring the infection [2]. It is postulated that the chelating agent acts as a siderophore that enhances fungal growth.

Since its introduction four decades ago, amphotericin B has been the mainstay of therapy for invasive fungal disease [3]. The usual dosage is 1.0–1.5 mg/(kg·d). Some of the fungi, especially molds, are susceptible only to higher doses of amphotericin B, as can be demonstrated by MICs of >6 μg/mL for R. oryzae. Amphotericin B exerts its antifungal effects by binding to ergosterol, which is present in the cell membranes of susceptible fungi. This binding results in a change in permeability of the fungal cell membrane, allowing leakage of a variety of small molecules. An additional mechanism of action, at least in vitro, may include oxidative damage to fungal cells. Because of the renal toxicity associated with amphotericin B therapy, there has been interest in finding new formulations of the drug that would be less toxic but no less efficacious. The development of amphotericin B that is administered in association with a lipid moiety, such as a lipid colloidal dispersion of liposomal amphotericin B or lipid complex, rather than in association with bile salts, has made it possible to prescribe far higher dosages of amphotericin B with fewer subsequent side effects.

Amphotericin B colloidal dispersion (ABCD; Amphocil, Sequus Pharmaceuticals, Menlo Park, CA) is a novel assembly that combines amphotericin B and cholesteryl sulfate in a 1:1 molar ratio to form a lipid delivery system [4]. ABCD particles are a disk-like array, with diameters ranging from 120 nm to 140 nm. The formulation is dispensed in lyophilized form and is reconstituted by adding liquid.

We describe our experience with three patients who had severe, life-threatening rhinocerebral mucormycosis that was treated with surgical debridement and long-term administration of amphotericin B.
Case Reports

**Case 1.** A 44-year-old woman was admitted to another hospital for evaluation of left facial pain. Her medical history was significant for hypertension, alcohol abuse, and an 8-year history of non–insulin-dependent diabetes mellitus. Three days before admission she had complained of severe pain and swelling of her left cheek and forehead in association with visual disturbances. A diagnosis of diabetic ketoacidosis and invasive infection of the ethmoid and maxillary sinuses was made. Left ethmoidectomy and turbinectomy were performed. Broad (7–15 μm in diameter) nonseptate hyphae that branched at 90° angles, compatible with a zygomycete, were seen within the blood vessels and in pathological sections of the surrounding tissue. A culture yielded *Rhizopus* species. After 2 weeks of treatment with amphotericin B, clinical deterioration in the patient’s condition occurred that was manifested by the appearance of periorcular swelling. A CT scan disclosed spread of an invasive process of the sinus into the left orbit, penetrating the bone, and a cerebral abscess of the left frontal lobe. Extensive sinus debridement and left orbital enucleation were performed.

Over the next 2 days the patient’s renal function deteriorated, and her serum creatinine level increased to 230 μmol/L (normal range, 44–97 μmol/L); therefore, she was transferred to our hospital. Shortly after admission, massive debridement of the left maxillary and ethmoid sinuses was performed, and more soft tissue was removed from the left eye. The brain abscess was drained under stereotactic guidance, and a culture yielded *Pseudomonas aeruginosa* that was susceptible only to imipenem and gentamicin.

Pathological examination of the aspirated material disclosed wide-angle, branching, broad nonseptate hyphae, consistent with mucormycosis, although no fungi were recovered in culture. Treatment with ABCD, administered at a dosage of 5 mg/(kg · d), together with imipenem and gentamicin, was started. Dexamethasone therapy was initiated for brain edema. Over the next 2 months the patient’s condition improved slowly, but repeated superficial debridement of her sinuses was needed. The fungal infection remained under control, and her renal function returned to normal. She was discharged to receive amphotericin B, 1 mg/kg, once every other day.

The patient received a 2-month course of therapy with imipenem, until complete resolution of the abscess cavity was noted on a CT scan. An ocular prosthesis was placed in the left eye socket. She then continued to receive amphotericin B twice a week for 2 more months. Thus, the total amount of ABCD administered was 12.3 g over a period of 8 weeks, with an additional 2 g of amphotericin B. Three years after completion of therapy, there is no evidence of recurrent fungal disease.

**Case 2.** A 72-year-old woman with insulin-dependent diabetes mellitus was admitted to another hospital for treatment of a necrotic oropharyngeal lesion. Biopsy of the soft palate revealed necrotic tissue invaded by nonseptate hyphae that branched at a 90° angle, characteristic of mucormycosis. Consequently, she was transferred to our hospital for further treatment. A CT scan disclosed an infiltrating lesion of the ethmoid, maxillary, and sphenoid sinuses, with involvement of the base of skull. Extensive surgery with extirpation of the soft and hard palate was performed by surgeons from the department of oral and maxillofacial surgery in collaboration with staff from the department of otolaryngology. The patient concurrently started receiving amphotericin B at a dosage of 1 mg/(kg · d). Within 4 weeks she developed moderate renal failure, with a serum creatinine level of 170 μmol/L. Therapy was changed to that with ABCD. The dose was gradually increased to 4 mg/(kg · d), with complete resolution of the renal failure (figure 1).

Over the next 4 weeks, the patient’s course was complicated by line sepsis due to *P. aeruginosa*, from which she recovered. After 3 months of therapy with ABCD, she was discharged to a day care center. Because of the initial involvement of the base of skull, which could not be debrided, treatment with ABCD was continued for an additional 3 months, three times per week at 4 mg/kg per dose. Thus, she received a total of 30 g of ABCD. The treatment was then changed to that with amphotericin B, 1 mg/(kg · d), once a week. Repeated MRI scans disclosed no new lesions.

After 8 months, a permanent oral prosthesis was prepared for the patient. She gradually regained weight and resumed normal activities. After a total of 18 months of weekly therapy with amphotericin B, the treatment was stopped. Repeated MRI scans were obtained initially after 1 month and then every 3–6 months for 1 ½ years, and no new findings were observed. Two and one-half years after cessation of all therapy, the patient remains well.

**Case 3.** A 62-year-old man was admitted to another hospital for evaluation of periorbital pain and swelling of 3 days’ duration. His medical history was remarkable for myelodys-
plastic syndrome of 6 months’ duration. He was known to be a carrier of hepatitis B surface antigen and had anti-hepatitis C antibodies and abnormal liver function. After receiving treatment with steroids, he developed diabetes mellitus. Mucormycosis was diagnosed on the basis of histological findings in sections from his maxillary sinus, and cultures of the biopsy specimens yielded Rhizopus species. Because of severe hemorrhagic diathesis, an attempt to completely debride the involved area was aborted, and he was transferred to our hospital.

On admission the peripheral WBC count was 4,200/mm³, the hemoglobin level was 8.2 g/dL, and the platelet count was 60,000/mm³. The serum creatinine level was 270 μmol/L. A CT scan showed soft-tissue swelling in the left maxillary sinus area where the operation had been performed. There was a suspected destructive bony lesion of the ethmoid sinuses on the left. All the sinuses showed increased tissue density. Therapy with high-dose ABCD (the dosage rapidly reached 6 mg/(kg·d)) was started. After initial improvement in the patient’s condition, which lasted for several days, the swelling worsened. Single donor platelets were prepared, and the patient underwent debridement of the left maxillary sinus and ethmoido-dosphenoidostomy. After the operation, the facial swelling almost completely resolved. The diplopia and pain disappeared.

While receiving ABCD at a dosage of 6.0 mg/(kg·d), the patient developed nausea and vomiting and lost his appetite. His liver function deteriorated: the alanine aminotransferase level rose to 251 U/L (normal level, 53 U/L), the aspartate aminotransferase level rose to 269 U/L (normal level, 40 U/L), and the γ-glutamyltranspeptidase level rose to 273 U/L (normal level, 80 U/L). Reduction of the dosage of ABCD to 4.5 mg/(kg·d) led to an immediate improvement in his liver function. After 42 days of therapy, he was discharged to receive amphotericin B twice a week at home. At this stage a CT scan still showed a soft-tissue density filling the nose and nasopharynx and extending into the left sphenoidal sinus with interruption of its floor and anterior wall. Complete debridement was never attempted because of the patient’s tendency toward severe bleeding.

After 8 weeks of treatment with amphotericin B at home, the mucormycosis flared up but rapidly responded to an increase in the dosage of a commercial liposomal amphotericin B preparation that was given for 10 weeks. After 1 year during which the patient remained symptom free, he died of a complication of myelodysplastic syndrome, without any evidence of mucormycosis.

Discussion

The incidence of invasive fungal infections has risen in the last several years [5, 6]. This increase is due to the availability of more-aggressive chemotherapeutic protocols and to the use of broad-spectrum antibiotics. The empirical use of amphotericin B for treatment of fever in neutropenic patients has become common practice in the past 10 years because of the increasing incidence of disseminated candidiasis. Several years after the introduction of empirical therapy with amphotericin B, there has been an increase in the number of infections with relatively resistant fungi such as species of Fusarium and Aspergillus and members of the Zygomycetes. Eradication of these infections necessitates high-dose, long-term therapy with amphotericin B, with more frequent adverse effects.

Rhinocerebral mucormycosis is often a rapidly progressive infection that may be fatal in a short period. This infection is most often seen in diabetics or immunocompromised hosts. Early, extensive surgical debridement of the focus of infection, combined with antifungal therapy, provides the only prospect for cure. For the three patients described herein, an aggressive surgical approach was combined with high-dose amphotericin B therapy. All three patients started receiving ABCD because of renal failure, which occurred in two days after treatment with amphotericin B was initiated. Renal function reverted to normal in all three patients despite treatment with ≤6 mg/(kg·d) of ABCD.

The total quantity of ABCD that was administered ranged between 10 g and 32 g. The duration of ABCD administration ranged between 6 weeks and 6 months and was followed by treatment with low-dose amphotericin B for prolonged periods. The patient in case 2 had involvement of the base of skull that could not be completely debrided, and the infection was unquestionably cured with ABCD, since she remains healthy >2 years after cessation of therapy.

Studies in mice, rats, and dogs have shown that ABCD is safer than amphotericin B. The LD₅₀ of ABCD in mice has been shown to be >10 mg/kg, compared with 0.6–0.8 mg/kg for amphotericin B [7]. In these studies in mice, organ distribution was compared between the different formulations of amphotericin B. The concentration of amphotericin B delivered by ABCD in the liver was 12 times that delivered by amphotericin B; in the spleen, it was four times that delivered by amphotericin B; and in kidneys and plasma, it was less than that delivered by amphotericin B. The concentration in normal brain tissue is usually low but was slightly higher with amphotericin B than with ABCD. In contrast, concentrations of ABCD in infected brain tissue were slightly higher than those of amphotericin B.

The experience in the treatment of deep mycotic infections with lipid formulations of amphotericin B has been growing since the introduction of these formulations in 1985 [8]. Ten patients with invasive fungal infection, including aspergillosis (four patients), deep candidiasis (four), and zygomycosis (two), have recently been described [9]. Liposomal amphotericin B therapy was associated with little nephrotoxicity in these patients. The overall survival rate was 50%. Of the two patients with mucormycosis, the one with rhinosinusal zygomycosis survived, and the one with surgical wound zygomycosis died. Lim et al. [10] described a 71-year-old diabetic with rhinocerebral mucormycosis who was treated with surgical debridement and liposomal amphotericin B. The patient underwent surgical...
intervention 4 weeks after beginning therapy; however, despite surgical removal of necrotic tissue and treatment with liposomal amphotericin, this patient died 2 days after surgery.

A chronic variety of rhinocerebral mucormycosis has occasionally been observed [11]. In one such case, in which the patient presented with a 3-month course of gradual deterioration of an orbital lesion, the infection was finally treated successfully with surgical debridement and an 8-month course of liposomal amphotericin B [12]. Transplant recipients treated with cyclosporine are especially prone to develop renal failure during amphotericin B therapy. Munckhof et al. [13] described a case of rhizopus sinusitis in a transplant recipient who was treated successfully with debridement and a 4-week course of liposomal amphotericin B.

Our three cases were successfully managed with a combination of extensive surgery and administration of ABCD. This formulation has recently been tried in phase 1 clinical studies. Seventy-five bone marrow transplant recipients with invasive fungal infections (primarily aspergillosis or candidiasis; two patients with mucormycosis) treated with ABCD were noted to have no appreciable renal toxicity at any dosage [14]. There was complete or partial response in 52% of these patients. ABCD was safe at dosages of ≤7.5 mg/(kg·d). This dosage was associated with tolerable infusion-related toxicity. ABCD has been also used recently to treat 10 patients with kala-azar [15]. They were given 2 mg/(kg·d) for 5 days. All of our patients had initial resolution of disease, and two recovered completely. One patient relapsed at 5 months (case 3). We believe that the relapse of mucormycosis in this patient with myelodysplastic syndrome could be attributed primarily to his underlying disease with neutropenia and thrombocytopenia, which precluded adequate debridement.

The treatment of rhinosinusial or cerebral mucormycosis with ABCD has not been described previously in detail. The extremely high cost of lipid formulations of amphotericin B warrants the continued search for new and effective treatments that will induce competition between companies and thus will affect drug prices. The description of the two patients in the phase 1 study [14]—one with pneumonia and one with sinus disease—only states that the first patient’s response to therapy was not evaluable and that the other had a partial clinical response. Our experience has shown that prolonged administration of high-dose ABCD, combined with appropriate surgical excision, is both safe and efficacious in producing long-term cure for invasive mucormycosis in patients whose underlying disease can also be controlled.

References

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