Surgery and Treatment with High-Dose Liposomal Amphotericin B for Eradication of Craniofacial Zygomycosis in a Patient with Hodgkin’s Disease Who Had Undergone Allogeneic Hematopoietic Stem Cell Transplantation

Michelle A. Barron,* Margaret Lay, and Nancy E. Madinger
University of Colorado Health Sciences Center, Denver, Colorado

Received 18 October 2004/Returned for modification 20 November 2004/Accepted 9 December 2004

This case report describes craniofacial zygomycosis in a 24-year-old male with Hodgkin’s disease who underwent chemotherapy and autologous hematopoietic stem cell transplantation, followed by a nonmyeloablative allogeneic transplant. Empirical therapy with itraconazole and amoxicillin-clavulanate failed to resolve the infection. Postdiagnosis, surgery and treatment with high-dose liposomal amphotericin B eradicated the disease.

CASE REPORT

A 24-year-old male was first diagnosed with stage 4B Hodgkin’s lymphoma (nodular sclerosing subtype) in December 1998 after presenting with fever, chills, and weight loss. The patient underwent eight cycles of chemotherapy and completed treatment in August 1999. This initial treatment failed to produce complete remission, and the patient experienced disease recurrence, which was treated with an additional two cycles of chemotherapy.

In January 2000, the patient underwent high-dose chemotherapy with busulfan and cyclophosphamide, followed by autologous hematopoietic stem cell transplantation (HSCT) without complications. The patient then underwent a 6/6 HLA-matched related sibling nonmyeloablative allogeneic transplant in February 2000 and was placed on cyclosporine (300 mg given orally [po] twice a day [bid]; Abbott Laboratories) and mycophenolate mofetil (MMF; 1,500 mg po bid; Roche Pharmaceuticals) for graft-versus-host disease (GVHD) prophylaxis. On day 30 following his nonmyeloablative HSCT, the patient’s MMF was discontinued. One week later, the patient developed fever, diarrhea, and an erythematous, maculopapular rash over his chest and trunk. In addition, his serum creatinine was elevated at 4.7 mg/dl.

The patient was admitted to the hospital for evaluation. The rash was biopsied, and histopathology was consistent with grade I GVHD of the skin. In addition, he underwent colonoscopy for evaluation of his diarrhea, which revealed congested mucosa in the transverse colon and multiple ulcerations in the descending colon. Histopathology of the colon biopsies were consistent with acute GVHD (immunohistochemical stains for cytomegalovirus and herpes simplex virus were negative).

Treatment of GVHD was initiated with high-dose steroids (2 mg/kg/day methylprednisolone; Pfizer, Inc.) and continuation of his cyclosporine (300 mg po bid) without improvement in his rash or diarrhea. Renal function slowly improved with intravenous hydration and low-dose dopamine. On day 41, MMF at 500 mg po bid was added with minimal improvement. Cyclosporine was subsequently changed to tacrolimus (Fujisawa Healthcare, Inc.) at 5 mg po bid secondary to oral intolerance of the cyclosporine on day 44. Symptoms rapidly improved, and the patient was discharged on high-dose prednisone (125 mg po bid), tacrolimus (5 mg po bid), and MMF (750 mg po bid). This regimen was slowly tapered to prednisone (50 mg po bid), MMF (750 mg po bid), and tacrolimus (1 mg po bid) without recurrence of symptoms; however, the patient did develop steroid-induced diabetes mellitus requiring insulin.

On day 71, the patient presented to the bone marrow transplant clinic with symptoms of right-sided facial pain and numbness. His medications at that time included levofloxacin (Ortho-McNeil Pharmaceuticals) at 500 mg po once a day (prophylaxis), pentamidine nebulizer every 2 weeks (prophylaxis), acyclovir at 400 mg po bid (prophylaxis), prednisone at 50 mg po bid, tacrolimus at 1 mg po bid, and MMF at 750 mg po bid. A computed tomography scan of the sinuses revealed extensive left-sided sinus disease and right maxillary sinus hypoplasia. The patient was evaluated by an otolaryngologist, and an aspirate of the left maxillary sinus was taken for culture. Empirical therapy with oral itraconazole (Janssen Pharmaceuticals) at 200 mg bid and oral amoxicillin-clavulanate (GlaxoSmithKline) at 875 mg bid was administered, with some clinical improvement. Gram stain of the sinus aspirate revealed heavy red blood cells, rare leukocytes, and no organisms. Sinus cultures yielded Veillonella species with no aerobic growth.

Approximately 5 days following the initial visit, the patient returned with complaints of worsening symptoms that included right-sided facial pain with right eye involvement, numbness and tingling of the right upper palate, and loss of taste on the same side. He also complained of fatigue and weakness in the right upper extremity. The patient denied having fevers, chills, rhinorrhea, sore throat, or visual disturbances. There were no

* Corresponding author. Mailing address: University of Colorado Health Sciences Center, 4200 E. Ninth Avenue, Box 168, Denver, CO 80262. Phone: (303) 315-1113. Fax: (303) 315-8681. E-mail: Michelle_Barron@UCHSC.edu.
complaints of nausea, vomiting, or diarrhea. The patient was admitted to hospital for further workup and treatment.

During the patient’s hospitalization period, he remained stable and afebrile. A nasal wash culture was plated to brain heart infusion agar with blood, brain heart infusion agar with blood plus gentamicin and chloramphenicol, and Sabouraud dextrose agar. At 48 h, a mold was recovered, which was initially white and then grey with a cream reverse. Mycelia were wide and nonseptate, with rhizoids coming off directly from the stolon and sporangio- phore. The sporangium was round and filled with spores. The mold was identified as a *Rhizopus* spp. using standard criteria (7). Identification to the species level was not performed.

Following isolation of the mold, sinus debridement was performed and Gomori methenamine silver staining of a maxillary aspirate and sinus tissue showed broad, nonseptate hyphae consistent with a zygomycete. Hyphae present in the walls and lumen of necrotic blood vessels were highly suggestive of angioinvasion. Radiological investigations included magnetic resonance imaging scans of the brain and sinuses and showed extensive sinus disease and an unusually aerated right sphenoid wing. Magnetic resonance imaging of the cervical spine found no evidence of lesions or other abnormalities.

Following confirmation of infection with a zygomycete, liposomal amphotericin B (AmBisome; Gilead Sciences, Inc., Fuji- sawa Healthcare, Inc.) was initiated at a dose of 10 mg/kg/day for approximately 2 weeks (total dose of 13,706 mg), with concurrent, often daily, surgical debridement of the sinuses and nasal washes with amphotericin solution (1 mg/5ml bid). In addition, very aggressive management of his diabetes mellitus was undertaken. He was initially placed on an insulin drip and was later changed to injectable insulin. His prednisone dose was slowly tapered (decreased by 10 mg/week) to 5 mg po every other day in an effort to better control his glucose. His tacrolimus was increased to 4 mg po bid, and he remained on MMF at 750 mg po bid without evidence of recurrence of his GVHD.

The patient responded well, and clinical improvement was observed. The dose of AmBisome was reduced to 5 mg/kg/day secondary to renal insufficiency for a treatment course of 79 days (total dose of 35,155 mg). Debridement of isolated necrotic tissue was performed on an outpatient basis as needed.

A follow-up visit 3 months later revealed no evidence of zygomycosis. The frequency of AmBisome dosing was decreased to twice weekly, at a dose of 5 mg/kg/day for a 2-month period (total dose of 8,010 mg). Ongoing follow-up visits for routine nasal debridement revealed the presence of necrotic bone, but with no active signs of infection. The decision was made to discontinue AmBisome, and the patient resumed standard prophylactic treatment with itraconazole (200 mg po bid) for prevention of aspergillosis. At 3 years after initial presentation, the patient was doing well and there was no evidence of disease recurrence.

Zygomycosis is an uncommon infection caused by fungi in the *Zygomycetes* class. This class is subdivided into two orders, *Mucorales* and *Entomophorales*. The members of the order *Mucorales* have most often been implicated as pathogens in human disease and include the genera *Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces, Saksenaea, Cunninghamella, Syncephalastrum*, and *Cokeromyces* (2, 12). The zygomycetes are hyaline fungi found in air, soil, and food and produce wide, ribbon-like, nonseptate or sparsely septate hyphae in human tissue. The primary route of transmission is inhalation of spores from the environment; however, cutaneous or percutaneous routes of exposure have also been implicated in disease (2, 12). Demonstration of invasive disease due to these organisms generally requires growth from a specimen obtained from a normally sterile site or identification of fungal elements within tissue, as colonization and laboratory contamination have been reported (12).

Several studies show that zygomycosis represents approximately 5% to 12% of all fungal infections in high-risk patient groups and are considered opportunistic pathogens (12). Similar to *Aspergillus* spp., zygomycetes cause a spectrum of clinical diseases that affect a variety of systems, including the sinonasal, rhinocerebral, pulmonary, cardiac, gastrointestinal, and cutaneous systems (14). Rhinocerebral or craniofacial zygomycosis is the most frequently encountered form and is usually fulminant and rapidly fatal. *Rhizopus* spp. are the most commonly implicated organisms causing craniofacial zygomycosis, accounting for about 90% of all infections with the *Zygomycetes* (12). The host is typically immunocompromised, with granulocytopenic and acidic patients being at highest risk. Diabetes mellitus is the single most common predisposing illness associated with the development of this infection (2, 12).

In this report, we present a case of craniofacial zygomycosis in a patient with Hodgkin’s disease—caused by *Rhizopus* sp.—that responded to surgical treatment and high-dose therapy with liposomal amphotericin B.

Identification of the mold as a zygomycete was important in terms of clinical management. Histopathologic examination of biopsied sinus tissue revealed characteristic aseptate branching hyphae with invasion of the blood vessels consistent with zygomycosis. Microbiological confirmation allowed assignment to the genus *Rhizopus* as has been previously described (7). Of note, the recovery rate of zygomycetes in culture is enhanced if the tissues are sliced into small pieces (2).

This case highlights the difficulty and potential delay in diagnosing zygomycosis as the patient was initially thought to have a bacterial sinusitis. This delay can translate into complications and treatment failures (11). Zygomycosis, although a rare fungal infection in immunocompetent hosts, most frequently develops in patients with diabetes mellitus or hematologic malignancies and is characterized by a mortality rate of approximately 70% (11). Reported cases of zygomycosis in the literature include patients with acute leukemia or lymphoma and other hematologic malignancies, as well as organ or stem cell transplant recipients with their associated immunosuppressive treatments (11, 12).

In a study examining 5,589 HSCT recipients, Marr and colleagues reported that zygomycosis generally occurred late after transplantation, when patients had chronic GVHD (8). Several authors have since reported findings of breakthrough invasive fungal infection by zygomycetes as an emerging problem in patients who have undergone allogeneic HSCT and received empirical or prophylactic treatment with voriconazole (6, 9, 13).

Clinical practice experience dictates that successful treatment of zygomycosis requires (i) early and aggressive surgical excision of necrotic lesions, (ii) recovery of immune function or...
control of underlying disease, and (iii) intensive antifungal therapy (12, 14). A multivariate analysis of data from 59 patients with hematologic cancers with proven or probable zygomycosis revealed that the only factor significantly correlating with recovery from infection was treatment with liposomal amphotericin B (11). A recent study by Miller et al. comparing amphotericin B deoxycholate to lipid formulations of amphotericin B reported that in certain patient populations, amphotericin B is significantly better tolerated when a lipid formulation is given as first-line therapy (10).

Zygomycetes are resistant in vitro to all currently available triazoles and the echinocandins (5). To date, the literature supports the use of intravenous amphotericin B as the primary antifungal treatment for all forms of zygomycosis (1, 3, 4). However, there are in vitro data to suggest that the new investigational agent posaconazole (Schering-Plough) may be useful in the treatment of zygomycosis (15). Clinical data are still needed to confirm this activity in vivo.

In this case, cranial nerve abnormalities on presentation, combined with the patient’s history of Hodgkin’s lymphoma, HSCT, and immunosuppression, placed zygomycosis at the top of the differential diagnosis. Considering that cultures revealed *Rhizopus* species as the offending organism, the drug of choice was liposomal amphotericin B, which enabled aggressive and continuous antifungal therapy. Treatment with Ambisome was both appropriate and effective against craniofacial zygomycosis in this patient.

This effort was supported by an educational grant from Fujisawa Healthcare, Inc., Deerfield, IL.

REFERENCES