Invasive Fungal Sinusitis Caused by *Scytalidium dimidiatum* in a Lung Transplant Recipient

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We describe a case of invasive fungal sinusitis caused by *Scytalidium dimidiatum* in a lung transplant recipient. Treatment was complicated by renal failure with amphotericin B therapies. Following 6 months of voriconazole treatment, the patient remained radiographically and clinically stable for a short time before dying of respiratory failure precipitated by graft rejection.

CASE REPORT

A 51-year-old female, who underwent lung transplantation two and a half years ago for end-stage chronic obstructive pulmonary disease, was admitted for management of suspected left maxillary fungal sinusitis. The patient had a long history of chronic rhinosinusitis treated with multiple trials of antibiotics and sinus surgery 10 years ago. During the month prior to presentation, the patient complained of increasing left maxillary sinus tenderness, sinus drainage with thick yellow discharge, dental pain, and subjective fever and chills. An endoscopic sinus evaluation done at an outside facility revealed chronic inflammatory changes and a marked amount of necrotic tissue. Pathology revealed branching fungal elements with septate hyphae suggestive of *Aspergillus* spp. infection. She was transferred to the University of Utah hospital in stable condition for further management.

The patient was from and lived in Salt Lake City, Utah. Additional social history was notable for the absence of tobacco, alcohol, or illegal drug use, recent domestic or foreign travel, and exposure to ill contacts. The patient’s medications included tacrolimus (5 mg orally twice a day), methotrexate (10 mg orally once a week), ganciclovir (1,000 mg three times a day), and trimethoprim-sulfamethoxazole (one tablet Mondays and Thursdays).

On admission to the University of Utah hospital, the temperature was 35.7°C, blood pressure 88/55 mm Hg, pulse was 92/min, respirations 12/min, and the oxygen saturation was 92% on room air. She was awake and oriented. There was marked tenderness over the left maxillary sinus without any obvious nasal discharge. She had no proptosis, and the extraocular muscles movements were intact. Her visual acuity was intact, and the tympanic membranes were clear. The left lung was clear to auscultation and percussion, but the right hemithorax had decreased lung sounds. Examination of the heart, abdomen, and extremities revealed no abnormalities. Likewise, the skin revealed no rash or lesions.

Initial laboratory testing results included a white blood cell count of 1,400/μl (28% polymorphonuclear leukocytes, 1% bands, 69% lymphocytes, 1% eosinophils), hemoglobin level of 8.1 g/dl, hematocrit result of 23.1%, mean cell volume of 100 fl, and platelet count of 228,000/μl. Chemistry results included a normal chemistry panel with the exception of a blood urea nitrogen level of 28 mg/dl and a creatinine level of 2.4 mg/dl. Serum protein was at 4.8 g/dl, and the albumin level was 2 g/dl. Liver function tests were normal.

A computed tomography scan of the sinuses without contrast revealed postoperative changes of the bilateral maxillary and ethmoid sinuses with chronic mucopurulent change, left greater than right (Fig. 1). There was mild collapse of the anterior left maxillary wall but no orbital involvement. There was no acute air/fluid level or evidence to suggest a destructive process in the skull base or facial structure.

The patient was stable upon admission and received empirical lipid formulation amphotericin B (10 mg/kg of body weight once a day). Endoscopic sinus surgery for further biopsy and debridement revealed copious amounts of necrotic tissue in the left maxillary sinus. There was a linear erosion from the left maxillary sinus into the facial tissues. Erosion of the orbital floor was noted, as well as two areas of bony sequestrum, which were somewhat liquefied and necrotic. The patient tolerated the surgery well and remained on antifungal treatment postoperatively.

Biopsy results of the left maxillary sinus revealed severe acute and chronic inflammation with associated giant cell reaction. There was focal necrosis with fungal hyphae and yeast forms identified with periodic acid-Schiff stain and silver staining (Fig. 2). Fungal organisms were also seen within bone marrow spaces. Calcofluor white staining showed budding yeast cells. Culturing of maxillary sinus material revealed a dematiaceous mold identified as a *Scytalidium dimidiatum*. The organism grew rapidly within 4 to 6 days on several types of medium, including inhibitory mold agar and brain heart infusion agar with gentamicin and chloramphenicol (Hardy Diagnostics, Santa Maria, Calif.), at both 30 and 35°C. Colonies on potato dextrose agar (ARUP Reagent Laboratory, Salt Lake...
City, Utah) were initially olivaceous grey, becoming dark brown to black with a greyish-black reverse. Microscopic examination of a slide culture showed branched, septate hyphae and barrel-shaped, subhyaline to dark brown, nonseptate or one-septate arthroconidia (Fig. 3). Confirmatory identification and susceptibility testing were performed at the Fungus Testing Laboratory, University of Texas Health Science Center (San Antonio, Tex.). The isolate was sensitive to amphotericin B (MIC ≤ 0.5 μg/ml; minimum lethal concentration = 1 μg/ml) and resistant to flucytosine (MIC = 16 μg/ml), fluconazole (MIC of >64 μg/ml), and itraconazole (MIC of >8 μg/ml).

After discontinuation of methotrexate, ganciclovir, and trimethoprim-sulfamethoxazole and the addition of folate to the patient’s regimen, her neutropenia resolved within a week after admission (white blood cell count = 3,260/ml; 79% polymorphonuclear leukocytes) and remained stable. A peripherally inserted central catheter line was placed, and the patient was discharged from the hospital with lipid formulation amphotericin B (5 mg/kg once a day). Three weeks later when the patient returned for sinus reconstruction, the otolaryngologists reported no gross evidence of necrosis, continued inflammation, or fungal infection. Due to significant renal toxicity (serum creatinine = 3.5 mg/dl), amphotericin B therapy was halted after approximately 4 weeks of therapy.

Four months after her initial presentation, the patient began to complain of increasing left facial pain and swelling. Repeat computed tomography imaging revealed persistent sinusitis, and due to concerns about invasive infection, she was taken back to the operating room. The maxillary sinus was nearly completely obliterated by scar tissue. Biopsy material again revealed the presence of S. dimidiatum, and liposomal amphotericin B therapy was reinitiated (5 mg/kg once a day). Since renal dysfunction had been noted previously, alternative agents were considered and evaluated for their activity against S. dimidiatum. Susceptibility testing revealed that the original isolate was more sensitive to voriconazole (MIC = 1 μg/ml) than caspofungin (MIC = 16 μg/ml) or posaconazole (MIC = 4 μg/ml).

It was again necessary to discontinue systemic liposomal amphotericin B treatment after approximately 3 weeks when the patient’s serum creatinine peaked at 6.7 mg/dl. Shortly thereafter, oral voriconazole was made available from the manufacturer (Pfizer, Inc., New York, N.Y.) under a compassionate-use protocol, and the patient received 200 mg orally twice a day for almost 6 months (note: the Food and Drug Administration approved general use of voriconazole in May 2002). During this time, some renal toxicity was noted due to the interaction of voriconazole with tacrolimus. With appropriate adjustment of tacrolimus dosing, the patient’s renal function improved significantly.

The patient was clinically and radiographically stable for several months after voriconazole treatment. However, biopsy-proven acute rejection of the lung graft ensued, and the patient...
died of respiratory failure. No autopsy was performed pursuant to the wishes of the family.

*S. dimidiatum* (sylnanomorph *Nattrassia mangiferae*) is a dematiaceous mold that has been observed predominantly in patients from tropical and semitropical regions, such as South America, Southeast Asia, India, the Caribbean, and West Africa (6). In temperate zones, infections have been noted in immigrants from endemic areas. *S. dimidiatum* has been identified in many woody hosts in North America, including citrus trees in Arizona, and can cause significant disease in susceptible plants and fruit trees (6).

Most reports of human infection due to *S. dimidiatum* involve superficial skin infections and onychomycosis (4, 5, 7). In immunocompromised hosts, the feet, palms, and nails are the most common sites of infection. Infection results from direct or indirect contact with contaminated soil or plants. Generally, superficial infections caused by *S. dimidiatum* are difficult to distinguish from those caused by dermatophytes. Like dermatophytes, *S. dimidiatum* possesses factors such as keratinase that allow for skin invasion (6).

Invasive infections have been noted primarily in immunocompromised hosts. Diabetes was an underlying condition in deep tissue infections and a case of maxillary sinusitis (11, 12). In a patient with advanced AIDS, genital and foot abscesses developed secondary to *S. dimidiatum* (10). As well, there is a case report of a 13-year-old boy who developed an abdominal skin lesion and fungemia with *S. dimidiatum* while he was neutropenic secondary to cytotoxic treatment for lymphoblastic B-cell lymphoma (2). In an immunocompetent patient, persistent eye infection with *S. dimidiatum* following trauma resulted in enucleation despite extensive therapeutic and surgical treatment (1).

Invasive fungal sinusitis is a life-threatening condition in immunocompromised patients. The extent and duration of neutropenia in these patients is a major risk factor for development of invasive disease. Patients treated intensively for hematologic malignancies are at high risk for fungal sinusitis. Over a 10-year period, Iwen et al. identified 17 patients with invasive fungal sinusitis (8). All but two patients with end-stage renal disease were initially diagnosed with hematologic malignancies.

Aspergillus flavus was the most commonly identified pathogen in that series of patients as well as others (8). Additional *Aspergillus* spp., *Pseudallescheria boydii*, *Rhizopus* spp., *Mucor* spp., *Fusarium* spp., and *Alternaria* have also been reported to cause sinus disease in immunocompromised patients (3, 8, 13). Those patients treated with systemic antifungal agents and surgery had the best chance for survival (8).

We have described the first case of invasive *S. dimidiatum* infection in a solid organ transplant patient. In addition to her immunosuppressive regimen, the patient was also neutropenic on admission and had acute and chronic renal failure. The management of her sinistis not only included surgical debridement and the initiation of amphotericin B but also required adjusting the immunosuppressive regimen, correcting the neutropenia, and improving renal function. In spite of the above measures, symptomatic disease recurred and necessitated additional debridement and retreatment with antifungal therapy. Clinical and radiographic studies 6 months after a combination of surgery and voriconazole treatment suggested at least stabilization of the patient’s sinus disease. This illustrates that complete eradication may require a multifaceted approach of extensive surgery, prolonged antifungal therapy, and correction of predisposing risk factors.

Our patient had no history of travel to areas to which *S. dimidiatum* is endemic. Other cases reported in the United States, such as those from Arizona and Ohio, have been linked to those patients’ travel in areas of endemicity (4, 12). The identification of *S. dimidiatum* from a posttraumatic hand wound infection in a 32-year-old male from North Texas suggests that the distribution of this mold in North America may be more widespread than previously described (9).

Despite in vitro susceptibility to several agents within the range of achievable serum and tissue levels, the clinical response of *S. dimidiatum* to treatment is typically very poor. For superficial infections, topical treatments or systemic agents used for onychomycosis are usually ineffective. Treatment outcomes for deep infections are unpredictable, since no one agent has proven efficacious. For subcutaneous and soft-tissue infections, a combination of amphotericin B and topical antifungal cream has been somewhat beneficial. Effective treatment of invasive disease in immunocompromised patients has required management of neutropenia and administration of amphotericin B. More promising are newer agents, such as voriconazole, that may provide options for treating those patients with invasive disease who are unable to tolerate amphotericin B formulations due to poor renal function.

REFERENCES