Case Report

Wound Zygomycosis: Two Cases with Unusual Manifestations

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Zygomycosis (mucormycosis) is an opportunistic fungal infection caused by fungi of the class Zygomycetes order Mucorales. Most human infections are caused by *Rhizopus, Mucor,* or *Absidia,* and less commonly *Rhizomucor, Apophysomyces, Cunninghamella* or *Saksenaea.* It usually affects hosts compromised by underlying hematologic cancer, renal failure, immunosuppressive therapy, diabetes mellitus, or burns, and patients receiving deferoxamine.[1-8] In addition, severe zygomycosis can occur in infants. Prematurity and malnutrition are common features, and infections are most commonly related to gastrointestinal involvement, with rare dissemination; however, primary pulmonary, cutaneous, and rhinocerebral involvement have been described. Gastrointestinal zygomycosis has been almost uniformly fatal in both children and adults.[9,10] Usually, clinical involvement in adults includes the classic rhinocerebral, invasive, pulmonary, disseminated or intestinal disease.[5,11-14] More recent reports have shown that primary cutaneous mucormycosis has emerged as an important form of the disease.[15-18] Other genera of the class Zygomycetes, for example *Basidiobolus*, have been implicated in primary subcutaneous infections in Uganda. Yet these fungi cause clinical syndromes clearly different from agents of mucormycosis.[19] The use of elasticized adhesive (Elastoplast®) dressing was implicated as a cause of *Rhizopus* infection in the 1970s, primarily in patients with underlying immunosuppressive conditions, although a few cases were described in previously healthy subjects.[20-22] Other cases have been related to extensive trauma.[23-25]

This report describes two cases of zygomycosis related to trauma. These cases presented with unusual features.

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CASE REPORTS

Patient 1

A 32-year-old male sustained an injury to his left cheek when a wall partially collapsed on him. Except for an abrasion on the left cheek, there was no other injury. There was no loss of consciousness. Two days following the injury the patient noted pain, redness, and swelling around the abrasion. After consulting a physician, he was started on oral clindamycin for facial cellulitis. There was no improvement, and therefore, he was admitted to the Aga Khan University Hospital on October 28, 1992. The patient had been previously healthy and was on no medication.

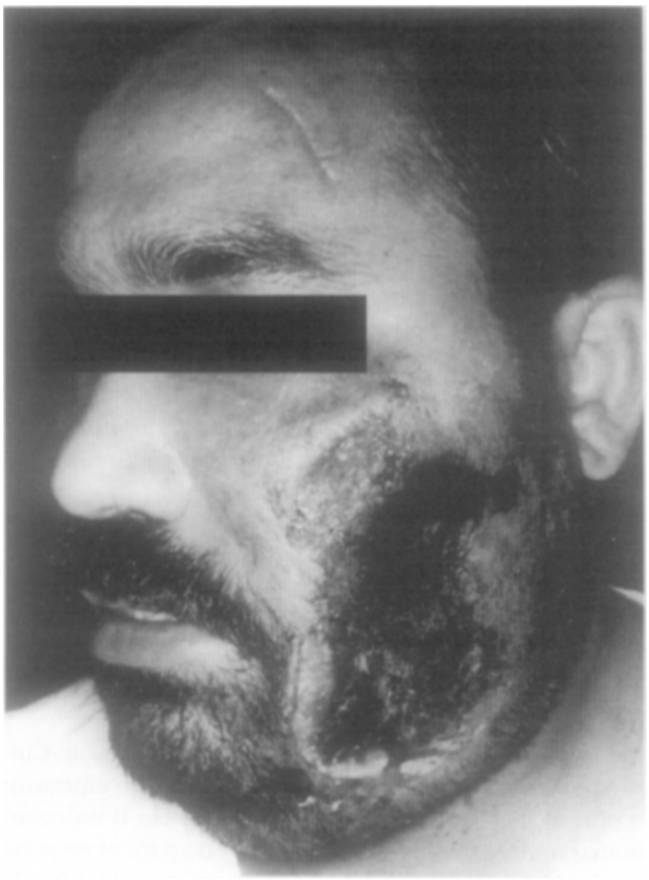

Figure 1. Large area of necrosis on the left cheek with minimal serous drainage.

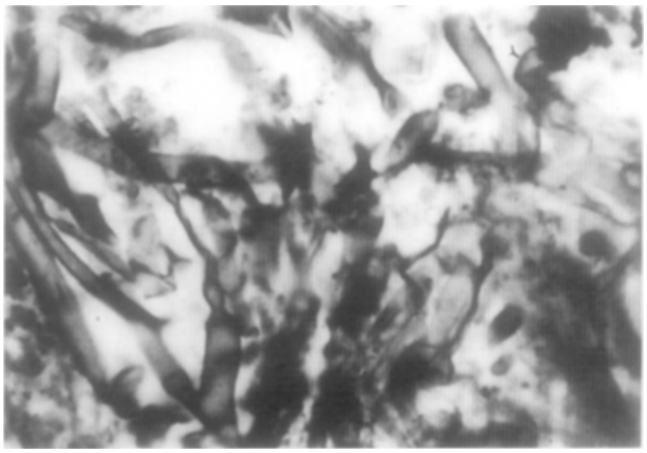

Figure 2. Broad, thin-walled, irregularly contoured branched hyphae present consistent with mucormycosis (H&E, original magnification ×100).

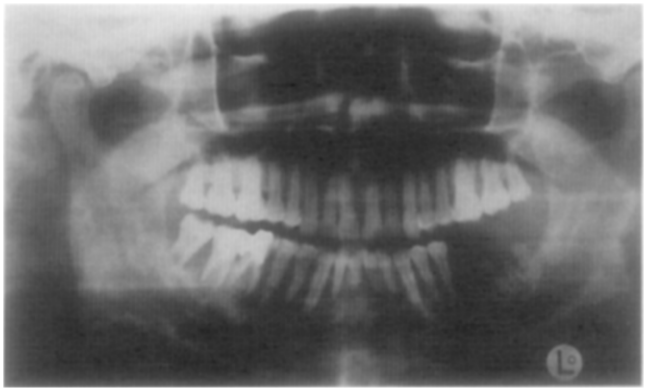

Figure 3. Pantomograph showing an osteolytic lesion of the left body of the mandible with absorption of teeth.

On examination, the patient was noted to be febrile at 38°C with swelling and erythema of the left side of his face, a central necrotic area and a small amount of serous discharge but no pus (Figure 1). The area was tender to touch. The rest of his physical examination was unremarkable. On admission, pertinent laboratory tests included a total white blood cell count (WBC) of 26,000, with 83% neutrophils and 7% lymphocytes; hemoglobin of 14.4; creatinine of 0.7; sodium (Na) 137; potassium (K) 3.5; and normal serum glucose and bicarbonate levels. Skull and chest radiographs were unremarkable. Parenteral clindamycin, metronidazole, and amikacin were started. On pantomography there was an area of lucency at the root of the first right lower molar but no other abnormality. Superficial cultures of the serous discharge were negative. Cultures from the oral cavity grew *Candida tropicalis*. On November 11, 1992, the patient underwent surgical débridement, and tissue was sent for mycology and histopathology. In spite of antibiotic treatment, the necrotic area continued to increase in size. Cultures grew *Rhizopus* species, and histopathology demonstrated gangrenous inflammation with extensive fungal infiltration (Figure 2).

Amphotericin was started at 1 mg/kg per day. Although the patient continued to complain of pain, there was a decrease in swelling and erythema over the week. Repeat WBC on November 16, 1992, showed a WBC of 9,300 with 60% neutrophils and 35% lymphocytes; hemoglobin of 10.5; and creatinine of 0.2. The ear, nose, and throat surgeon decided on split thickness grafting over the left cheek wound, which showed granulation. Cultures were all negative. The graft was subsequently reported as having taken well. Amphotericin B was continued up to a total dose of 2 grams. The patient insisted on discharge. Three months later, he presented with a 1-week history of swelling and redness over the graft and a 2-day history of severe pain and pus oozing from the lower part of the lesion. On examination the patient was afebrile and trismic. Intraorally there was mucosal edema. Laboratory tests showed a hemoglobin of 11.6, total WBC of 10.2 with 63% neutrophils and 33% leukocytes. Cultures of pus were negative. Repeat pantomography showed extensive destruction of the left mandible (Figure 3). The patient was scheduled for surgery and amphotericin B was restarted at 1 mg/kg per day; however, after 2 days the patient left the hospital against medical advice. No further follow-up was available.

Patient 2

A 25-year-old previously healthy male was admitted to the Aga Khan Hospital on December 20, 1991, with inability to move all four extremities following a road traffic accident. There was no history of loss of consciousness; examination confirmed a level at C4 vertebra and quadriplegia. A small abrasion was noted on the forehead, but there was no other injury. Chest radiograph and skull films were normal (Figure 4, *A*), and computed tomography (CT) of the cervical spine demonstrated a grossly comminuted fracture of C5 and C6 with posterior subluxation of C4 and cord compression. Pertinent laboratory tests were a hemoglobin of 16.4 g/L, a WBC of 10,100 with 80% neutrophils and 18% lymphocytes, and normal electrolytes and blood sugar as well as renal and liver function.

The patient was started on Decadron® (4 mg every 6 hr) and cervical traction. Three days later, the patient was noted to be febrile and complained of pain at the site of the abrasion. Cloxacillin (2 g every 6 hr) was started parenterally. The area around the abrasion became red and tender with a central necrotic area that increased in size over the next 2 days. The area was débrided under general anesthesia. Cultures obtained during surgery of the débrided tissue grew *Rhizopus* species. Decadron was stopped and amphotericin started at 1 mg/kg per day. The patient tolerated amphotericin B poorly, with chills and fever, and insisted on several occasions that the antifungal agent be held for a few days. Therefore,

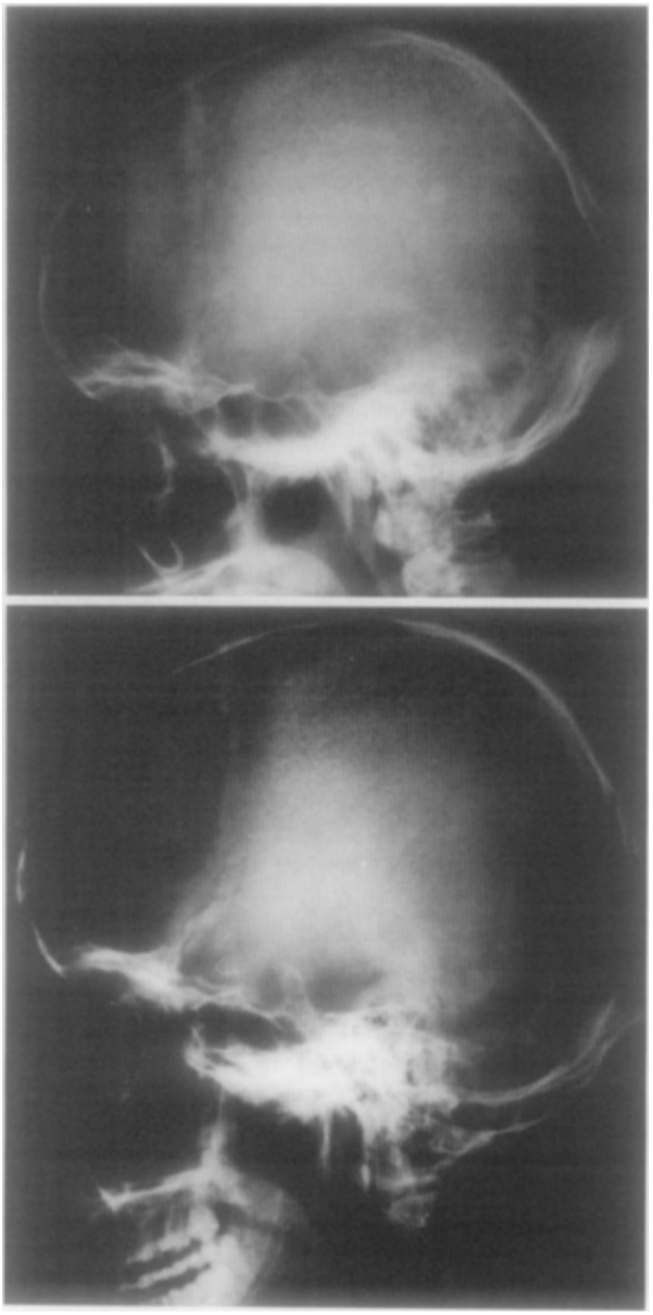

Figure 4. Skull radiographs. *A*, December 20, 1991, normal skull; *B*, May 1, 1992, lytic lesion of the frontal bone.

after receiving daily therapy for 2 weeks, he received a total dose of 1 gram over the next 4 months. However, despite therapy, the necrotic margins of the area continued to extend, requiring repeated surgical débridement. Finally, a repeat skull radiograph on May 1, 1992, demonstrated numerous lucent defects consistent with fungal involvement (Figure 4, *B*). The infected bone was surgically removed, the fungal tissue debulked, and the dura repaired. Cultures obtained at surgery again grew *Rhizopus*, and pathology confirmed invasive zygomycosis. The patient subsequently received an additional 2 grams of amphotericin B. Three months later, when readmitted for elective cranioplasty he had no evidence of fungal infection and was discharged after a few days. When last seen in February 1993, he was doing well.

MATERIALS AND METHODS

Mycology

Specimens were streaked heavily in duplicate onto Sabouraud dextrose agar (oxoid code CM42, Oxoid Ltd., UK) and Sabouraud with 2% dextrose containing chloramphenicol and polymyxin B (chloramphenicol 0.05 g/L; polymyxin B 0.1 g/L). The plates were incubated at 25°C and 37°C under aerobic condition. The growth of *Rhizopus* was observed in 2 to 3 days. The mold grew rapidly and filled the petri dish with grayish-white mycelium. Identification by macroscopic and microscopic examination was performed as previously described.[26]

DISCUSSION

The Zygomycetes are widespread in nature, living on decaying vegetation and organic materials. Asexual sporangiospores are the infective particles, and direct inoculation occurs into wounds. Organisms germinate in tissues, and invasive mycelial forms with thick nonseptate hyphae spread preferentially in the lumen of blood vessels, leading to ischemia and infarction of tissue. The angioinvasiveness of this fungus determines the rapid progression of necrosis, as seen in the cases presented here.[1,8]

Progressive infection with Zygomycetes in normal hosts is rare. Keys and colleagues first described a nosocomial outbreak of skin and subcutaneous *Rhizopus oryzae* infection in six patients complicating the use of Elastoplast bandage.[21] This was later confirmed by Gartenberg and co-workers, who grew *Mucor* from an Elastoplast strip.[23] Johnson and colleagues reported three cases in nondiabetic patients with extensive trauma, all of whom developed rapidly progressive severe wound infections caused by *Rhizopus* species.[24] Two cases of wound zygomycosis attributable to *Rhizopus* species were described in healthy adults by Vainrub and colleagues; however, these patients had extensive soft tissue damage together with soil contamination.[25] The authors postulated that devitalization of tissue allowed for germination of organisms. Although detailed immunologic parameters were not available, white blood cell function, immunoglobulin levels, and metabolic parameters were normal in these patients, and there was no history of use of alcohol or immunosuppressive therapy. Many recently reported cases of wound zygomycosis in immunocompetent patients have been caused by *Apophysomyces elegans* or *Saksenaea vasiformis*.[27]

Weinberg and co-workers noted the frequency of invasive cellulitis attributable to *Apophysomyces elegans* in immunocompetent hosts as opposed to that caused by other species. Inoculation generally followed local trauma with definite or possible contamination from soil and occurred predominantly in warmer areas.[28] Contiguously spread osteomyelitis attributable to zygomycetes is rare and is difficult to treat. Meis and colleagues describe an immunocompetent patient with trauma-introduced zygomycosis. Despite 7.9 grams of amphotericin B, the patient required an interthoracoscapular amputation because of rapid spread of infection.[29]

In a previous review of 117 patients with cutaneous zygomycosis, local factors (i.e., surgery, burns, motor vehicle-related trauma, spider bites) were associated with most cases, 50% of patients who did not have systemic illnesses, 97% had local risk factors.[16] The two patients presented here did not have any systemic illnesses, obvious immune defects, or extensive local trauma. In these two cases, neutrophil function tests could not be done because of the expense involved. However, the patients were on no medications and had not had frequent previous infections. Metabolic parameters were normal. Neutrophils are the most important component of the host response to Zygomycetes. As yet undefined defects of macrophages and neutrophils present in diabetic and steroid-treated patients allow replication of the fungus.[1] There are few cases in patients with human immunodeficiency virus (HIV), attesting to the importance of the neutrophil. Nevertheless, HIV testing was not done in the patients presented here. In a recent review of cases, Sanchez and colleagues noted that eight of ten HIV-positive patients with zygomycosis were intravenous drug users.[30] Cutaneous infections occurred in four of their patients. Nagy-Agren and colleagues reviewed 15 HIV-positive patients with zygomycosis. The majority of patients had a history of intravenous drug use and several had episodes of neutropenia.[31]

Of interest, one of the patients presented here sustained minimal trauma with no fractures and only an abrasion of the cheek. The second patient had serious trauma and quadriplegia, yet the abrasion on his forehead was almost imperceptible at the time of admission. However, he did receive steroids for 3 days, which may have predisposed him to invasive fungal disease.[32]

That cutaneous mucormycosis is rare cannot be explained by lack of exposure to the infecting spores, because they are ubiquitous. It remains possible that suppression of immune responses by acute trauma enables this sequence of events in otherwise normal hosts. The lung was unlikely to be a portal of entry, because skin involvement secondary to disseminated mucormycosis is widespread, involving many other organs besides the lungs.[13,33] The present cases indicate that when progressive necrosis at the margin of a wound is noted, a diagnosis of invasive zygomycosis should be considered and is likely if appropriate antibiotic therapy for bacterial pathogens is ineffective. Culture and histologic examination of biopsied tissue taken from the margin of the wound is diagnostic. The prognosis for cutaneous mucormycosis is distinctly better than that of other forms. However, long-term morbidity and mortality rates are still high. Many patients require amputation of affected extremities.[16] Treatment requires an aggressive combined surgical and medical approach. Surgical treatment is important. Review of cases revealed that death resulted from extension of the infection into vital regions. Once local control had been attained, relapse rarely occurred.[16] Amphotericin B is the only agent thought to have activity against Mucorales. Occasional response to amphotericin B administered alone suggests that use of this drug is beneficial.[34] Higher than usual doses of amphotericin B have been recommended. Interpretation of in vitro susceptibility tests is problematic.[35] There is a lack of standardization of susceptibility testing. Reliable in vitro susceptibilty data are available for yeasts and not for molds, such as zygomycosis.[36] Eng and colleagues found that most strains, including *Rhizopus*, were inhibited but not killed by 0.5 μg/mL of amphotericin B. In serum, all were resistant to the imidazoles.[35] Christenson and co-workers found synergistic activity of amphotericin B and rifampin against *Rhizopus* in vitro.[37] However confirmatory in vivo data are scarce.

In patient 1, 3 grams of amphotericin B were used in daily doses of 1 mg/kg, yet relentless progression occurred. Several newer antifungal agents that are not yet available in conjunction with cytokines may show promise for the future.[38,39] As these cases illustrate, an immunologic defect may not be evident, and the introduction of spores into devitalized tissue in the setting of trauma and, in particular, with the use of steroids for a few days, may be sufficient for invasion.

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