INTRODUCTION

Mucormycosis of the nose and paranasal sinuses is a rare invasive fungal infection, which often has a very fulminant course and characteristic clinical findings. Mucormycosis usually affects diabetics and immunocompromised hosts. Literature scanning usually revealed rarity of mucormycosis in immunocompetent host.

A case of maxillary paranasal sinus mucormycosis in an immunologically competent host that was successfully treated with surgery and combined liposomal amphotericin B and rHuGM-CSF, is described. We also review the literature and clinical spectrum of paranasal sinus mucormycosis in both immunocompromised and normal hosts and discuss the emerging incidence of invasive zygomycosis in immunocompetent patients.

CASE REPORT

A 68-year-old male has been recently admitted at our hospital because of a 3-months history of left maxillary sinusitis that did not respond to antibiotics and progressed to orbital cellulitis. His medical history included hypertension, but the patient had not diabetes or other systemic underlying conditions. After an extensive evaluation, no evidence of either diabetes mellitus or underlying immunologic abnormalities were found, however the patient had suffered from acute maxillary sinusitis two years earlier and was treated for maxillary apical granuloma one year earlier.

At the admission he was febrile and the general condition deteriorated. His temperature was 37.5°C. Laboratory findings disclosed the following data: white blood cell count 12,750/mm³ with 70% neutrophils, 20% lymphocytes, ESR 70 mm/h, C-reactive protein 3.2 mg/dl, alcaline phosphatase 355 UI/L, IgA 639 mg/dl, total proteins 7.87 g/dl with 17% beta globulin. He had not hyperglicemia, renal failure or metabolic acidosis.

A cranial CT scan showed a diffuse involvement of the left maxillary paranasal sinus with sinus obstruction (Figure 1).

Radiographs of the chest and an ultrasonogram of the abdomen were negative. Sinonasal endoscopy with biopsy for histopathological examination and culture showed acute and chronic inflammation, necrosis and fungal hyphae within necrotic tissue; on staining with hematoxylin and eosin the hyphae were broad and non septate.

Patient underwent left maxillary sinus exten-
teration and radical debridement of involved adjacent structures by the classic Caldwell-Luc procedure.

Pathological examination showed granulomatous inflammation with fungal hyphal forms that were broad, nonseptate, and irregularly branched; many blood vessels were plugged with hypae and inflammatory cells. A diagnosis of mucormycosis was made on the basis of the morphology of the fungal hyphae.

Combination therapy with liposomal amphotericin B (Ambisome®, 3 mg/kg/day, cumulative dose of 2.5 g), and subcutaneous rHuGM-CSF (Mielogen®, 150 µg daily for five consecutive days), resulted in a complete cure of the patient. A cranial CT scan and a new endoscopic sinus procedure performed after one month were negative. The patient remained free from relapse of invasive mucormycosis during a long-term follow-up of 24 months.

**DISCUSSION**

Invasive fungal infections have increased dramatically over the past several years, largely as a result of increasing numbers of immunosuppressed patients.

Immunosuppressive states secondary to chemotherapy, hematologic disorders, transplantation, and AIDS, place their hosts at risk for invasive mycoses.

Patients at high risk for acute invasive fungal sinusitis also include poorly controlled diabetics and those with conditions that predispose to metabolic acidosis such as chronic renal failure or diarrhea.

Fungal sinusitis is a well-documented disease in the immunocompromised patient, but in recent years it has been reported increasingly in immunocompetent patients.

In recent years invasive fungal diseases have been reported increasingly in immunocompetent patients. Environmental and local factors may predispose normal hosts to and increase a patient’s risk for developing fungal paranasal sinus infections, including frequent exposure to air or food contaminated with mycotic spores, domestic pets, root canal fillings, chronic or recurrent bacterial sinusitis, and long-term use of wide-spectrum antibiotics and/or topical steroid use.

The offending fungi originate from the classes Zygomycetes and Ascomycetes. Zygomycetes, divided into the orders Mucorales and Entomophthorales, include organisms characterized by the presence of sparsely septated, broad and polymorphic hyphae in tissue. The Zygomycetes are less common causes of invasive human infection compared to Aspergillus spp. and Candida spp.

Mucormycosis is an uncommon opportunistic disease caused by fungi belonging to the class Zygomycetes, order Mucorales. The causal agent is more frequently of the *Rhizopus*, *Absidia* or *Mucor* genera.

These organisms are ubiquitous, and mucormycosis can be acquired by inhalation, ingestion, or the deposition of spores in wounds. Although these fungi are frequently limited in their virulence, they may become highly invasive.

The Mucorales are associated with angioinvasive disease, often leading to thrombosis, infarction of involved tissues, and tissues destruction by fungal proteases, lipases and micotoxins [1].

Factors that contribute to the development of invasive mucormycosis include lowered resistance due to immunosuppressive states and/or metabolic disorders leading to acidosis, a local tissue defect due to trauma or burns creating a portal of entry, the administration of corticosteroids or antibiotics, deferoxamine therapy for iron or aluminum overload, and intravenous drug abuse.

Mucormycosis can also occur in patients suffering from malignancy, cirrhosis, and acute renal failure.

An extensive review of the English-language literature by MEDLINE and consulting the references of published articles revealed at least 24 reports describing 37 cases of mucormycosis in immunocompetent individuals from 1978 through 2003 [2-25].

We were able to find 16 cases of rhino-cerebral mucormycosis, 16 cases of cutaneous and soft-
tissue infections, 2 cases of pulmonary infections and 1 case of liver, gastrointestinal or disseminated diseases, respectively. *Apophysomyces elegans* resulted as the zygomycete most frequently isolated in these cases. All patients had been previously healthy. Patients with cutaneous and soft-tissue infections had suffered from trauma or skin lesions. An Indian patient developed necrotizing fasciitis after a postinguinal herniorrhaphy [8].

There were six fatal cases attributed to rhinocerebral mucormycosis in two patients, cutaneous and soft-tissue infections in two patients and to gastrointestinal and disseminated disease in two other patients. In most cases patients underwent extensive surgical debridement, and they were treated with high doses of amphotericin; some patients also received liposomal amphotericin B.

There was a single and fatal case of disseminated disease due to *Saksenaea vasiformis* in a 59-year old man with signs of sepsis. The patient died 24 h after admission, and postmortem examination showed disseminated mucormycosis with endocarditis involving the mitral valve, bronchopneumonia, and pulmonary embolism, and involvement of the thyroid and the skin. The manifestations of mucormycosis include primary rhino-cerebral, pulmonary, abdominopelvic, cutaneous or subcutaneous, disseminated disease and miscellaneous. Prognosis is poor with overall mortality reaching 50% [26].

The nose, paranasal sinuses, or both serve as the portal of entry for rhino-cerebral mucormycosis.

Mucor sinusitis usually involves a single sinus; most often the maxillary sinus.

Definitive diagnosis requires histologic demonstration of tissue invasion with characteristic broad nonseptate hyphae with right-angle branching on hematoxylin-eosin staining.

The mainstay of treatment includes correction of the underlying disorder, a decrease of immunosuppression, surgical debridement of necrotic tissue where the fungus proliferates, and antifungal therapy.

Amphotericin B, the only antimicrobial agent with evidence of antifungal efficacy in mucormycosis, is the first-line therapy of choice for most cases of zygomycosis, but its use is limited by its potentially severe side effects. Despite optimal therapy with amphotericin B combined with surgical intervention, morbidity and mortality remain high.

In the last decades there has been the introduction of several new antifungal drugs, however practical options for the treatment of mucormycosis remain limited.

Lipid-based amphotericin B is increasingly being used, as it is much better tolerated than conventional amphotericin B [27-32].

Liposomal amphotericin B resulted more effective than amphotericin B in treating murine disseminated zygomycosis, improving survival of diabetic mice infected with *Rhizopus oryzae* [33]. Triazoles and echinocandins are usually inactive as single agents. Although the use of azole antifungal drugs for the treatment of mucormycosis does not appear to be effective, some studies have demonstrated the potential for azole drugs to be useful in the therapy of mucormycosis alone or in combination. The combination of an azole with the quinolone topoisomerase inhibitors demonstrated significant effects in treatment of murine pulmonary mucormycosis [34-36].

Combination of antimicrobial agents tested against strains of zygomycetes showed synergistic interactions between amphotericin B and terbinafine for 20% of the strains, and an interaction between terbinafine and voriconazole synergistic for 44% of the isolates [37].

An in vitro antifungal susceptibility testings study has recently showed that posaconazole, a new antifungal triazole, has significantly potential for clinical development against the zygomycetes [38].

Salvage therapy with the new azole antifungal posaconazole resulted in dramatic clinical improvement in a diabetic patient with invasive infection due to *Rhizopus* species after a duel heart/kidney transplantation [39].

Eradication of invasive mucormycosis attributable to the use of the echinocandin FK463, a newly available antifungal agent, has been recently reported [40].

The combination of excisional surgery, liposomal Amphotericin B, and adjuvant immunotherapy with rHuGM-CSF resulted in an excellent response in our patient. The effects of GM-CSF on the function of monocyte/macrophages against fungal pathogens have been well described in previous studies. The major effect of GM-CSF is to enhance phagocytic and metabolic functions of monocytes and macrophages, resulting in inhibition and killing of a variety of intracellular microbes including fungal pathogens. rHuGM-CSF used in combination with liposomal amphotericin B was well
tolerated and effective in the treatment of mucormycosis in our patient that was non-neutropenic and immunocompetent.

To our knowledge, this is the first report of a case of mucormycosis that was successfully treated with liposomal amphotericin B associated with low-dose rHuGM-CSF in an immunocompetent patient without diabetes or any of the common systemic underlying conditions for invasive mycoses.

In a previous report, three diabetic patients who had non-neutropenic rhinocerebral zygomycosis have been successfully treated with a combination of aggressive surgical debridement, a prolonged course of amphotericin B (1 patient) or amphotericin B lipid complex (2 patients) and GM-CSF [41].

Although the clinical experience with GM-CSF for invasive mucormycosis is limited to our case reports, GM-CSF should be considered as adjuvant treatment for both immunocompromised and immunocompetent patients with invasive mucormycosis.

The clinical application of immunotherapy as adjunctive therapy for fungal infections is largely limited to anecdotal case reports and small studies and is currently investigational [42-46]. However, much of the available information on the clinical use of immune-modulating therapies for invasive mycoses is encouraging and need more extensive clinical investigation to define specific indications.

Keywords: mucormycosis, liposomal amphotericin B

**REFERENCES**


