Introduction

Mucormycosis is an uncommon acute and often fatal opportunistic fungal infection that is classically seen with poorly controlled diabetes mellitus with acidosis, acute leukemia, or other immunosuppressive conditions. A relatively new association of mucormycosis occurring in patients with iron and aluminum excess who receive deferoxamine therapy has been reported with increasing frequency. While most commonly noted in patients receiving hemodialysis, mucormycosis develops in patients with various iron overload states such as thalassemia, sideroblastic anemia, and myelodysplasia where deferoxamine may be used. We report a case of mucormycosis in a patient with acute myelogenous leukemia who underwent allogeneic bone marrow transplantation and was treated with deferoxamine for transfusion-induced iron overload.

Case Report

A 32-year-old man received an allogeneic bone marrow transplant in May of 1995 for relapsed acute myelogenous leukemia (M₃). The patient developed acute graft-vs-host disease (GVHD) that was treated with corticosteroids. Subsequent development of chronic GVHD was controlled with 75 mg of azathioprine once daily. Iron overload from multiple blood transfusions was confirmed by liver biopsy and treated with 2,000 mg of deferoxamine twice daily for five days a week. Approximately one year following bone marrow transplantation, hemoptysis and a dry cough developed. Bronchoscopy at an outside institution revealed an endobronchial lesion in the left lower lobe. Bronchial washings revealed hyphal elements consistent with a filamentous fungus. These hyphae were irregular and hyposeptated and resembled "moose antlers (Figs 1A-B)." Cultures revealed Mucor sp, Candida albicans, Candida tropicalis, and Aspergillus fumigatus.

On physical examination, the temperature was 36.8 degrees Celsius (98.24 degrees Fahrenheit), the pulse rate was 98 beats per minute, and the blood pressure was 100/70 mmHg. Fine rales were audible at the left lung base.

Laboratory studies yielded the following values: hemoglobin, 6.5 g/dL; white blood cell count, 4.81 x 10⁹/L; absolute granulocyte cell count, 3.96 x 10⁹/µL; and platelet count, 137 x 10⁹/L. Liver enzymes were elevated, with an alkaline phosphatase of 2,054 U/L, gamma-glutamyl transferase of 765 U/L, bilirubin of 2 ng/dL, and SGOT and SGPT of 193 and 221 U/L, respectively. The blood urea nitrogen and creatinine levels were 22 mg/dL and 1.8 mg/dL, respectively.

Chest radiography revealed a left lower lobe infiltrate, which was seen more clearly on a computed tomography scan of the chest (Fig 2). Repeat bronchoscopy showed a white, friable, hemorrhagic endobronchial lesion. Culture and stains for multiple microbial entities of the biopsy of the endobronchial lesion and bronchoalveolar lavage (BAL) remained negative. The initial use of amphotericin B was changed to 5 mg/kg per day of liposomal amphotericin B due to progressive renal insufficiency. Deferoxamine was discontinued.

Due to the localized nature of the infection, the left lower lobe of the lung was surgically resected for definitive diagnosis and therapy. Pathologic findings included abundant pulmonary hemorrhage with occasional organized fibrous thrombi in the lamina of bronchi, as well as patchy areas of fibrosis alternating with relatively normal-appearing pulmonary parenchyma. A poorly developed localized necrotizing granuloma, which appeared grossly as a small abscess and was originally identified during surgery, revealed fragmented, irregular, ribbon-like pieces of hyphal material suggestive of the morphology of a zygomycetous fungus (Fig 3). These hyphal elements were consistent with mucor present in the bronchial washings obtained from the first bronchoscopy.
Six areas from the lobectomy specimen remained culture-negative for fungal, bacterial, and viral pathogens. The patient was discharged in stable condition five days after thoracotomy. He completed six weeks of 5 mg/kg per day of liposomal amphotericin B followed by three months of 200 mg of itraconazole twice daily. He remains symptom-free six months later. Long-term follow-up revealed no recurrence of the fungal infection.

Discussion

Mucormycosis is an opportunistic infection caused by organisms belonging to the order Mucorales and the class Zygomycetes.¹ The organisms most commonly implicated in clinical disease belong to the genera Mucor, Rhizopus, Absidia, and Cunninghamamella. These organisms are widely disseminated in the environment, and most of the infections are due to the inhalation of spores.

The clinical manifestations of mucormycosis consist of rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated infection. Invasive infection usually occurs in patients with underlying diseases, especially acute myelogenous leukemia and poorly controlled diabetes mellitus. The rhinocerebral form is the most common presentation.

Rhinocerebral mucormycosis is found commonly in uncontrolled diabetics³ with ketoacidosis and is associated with the development of sinusitis with involvement of the orbit leading to proptosis and ophthalmoplegia. Pulmonary mucormycosis more often occurs in patients with leukemia, lymphoma, or severe granulocytopenia.² Symptoms of pleuritic chest pain, fever, cough, and hemoptyis with radiographic findings of consolidation and cavity formation are indistinguishable from pulmonary aspergillosis.

Hematogenous dissemination can result in brain, spleen, kidney, heart, liver, and omentum metastatic infection. Pulmonary mucormycosis has a predilection to spread to the brain. Cerebral forms of mucormycosis are more characteristic of patients with a hematologic malignancy and associated neutropenia. Regardless of the anatomical site of the lesion, invasion of blood vessels results in downstream tissue necrosis, and a black necrotic eschar develops if the skin is involved.

Neutrophils and monocytes/macrophages are the essential host defense factors against the zygomycetes.⁴ Patients with acute leukemia are at high risk of developing mucormycosis as a result of prolonged neutropenia. The neutrophil count was within normal limits in our patient, who remained in hematologic remission. However, immunoospressive treatment for GVHD and deferoxamine therapy were significant risk factors for pulmonary mucormycosis.

Treatment with the iron chelator deferoxamine is a risk factor for developing mucormycosis due to its effects on iron storage and metabolism. In human plasma or on the mucosal surfaces, the amount of free iron available for microbial growth is low; almost all of the iron is bound to proteins such as transferrin and lactoferrin or is inaccessible in tissue stores. Microorganisms have developed complex mechanisms to compete for the iron in the host, usually by secreting sidero-phores that trap iron and deliver it to the microorganism, thus enhancing growth. One of these siderophores is deferoxamine B mesylate (deferoxamine) which is produced by Streptomyces pilosus.⁵ The organisms responsible for causing mucormycosis are not known to produce siderophores of their own but are capable of extracting iron from them to support their growth and thus result in infection.

Daly et al⁶ compared 26 patients who developed mucormycosis associated with deferoxamine therapy with 20 patients who received deferoxamine following dialysis. The mean duration of deferoxamine therapy related to mucormycosis was 9.3 months (range = 19 days to 20 months). The dose of deferoxamine ranged from 1 g to 14 g per week. Of the 26 patients, 14 (54%) had a disseminated infection with lung and brain as the most prominent sites of infection. Two patients (7%) had isolated pulmonary infection, and one patient each developed cerebral, small bowel, and skin infections. The presentation was acute in all but one patient. Twenty-three (88%) of the 26 patients died. An international registry on mucormycosis in dialysis patients registered 59 cases in which an antemortem diagnosis was made in only 23 (39%) of the patients with an 86% mortality rate.¹

The diagnosis of mucormycosis is best made by biopsy of involved tissues with histopathology and fungal culture.⁴ Microscopy will reveal broad, irregularly shaped, nonseptate hyphae with right-angled branching. The fungi are often seen invading through tissue planes and blood vessels. Thrombosis and resultant infarction of the surrounding tissue ensues.⁶ The diagnosis of pulmonary mucormycosis is rarely made antemortem, as the yield from sputum fungal smears and culture and bronchoalveolar lavage are low.⁷ In spite of these limitations, an antemortem diagnosis in our patient was made followed by an aggressive approach of wide surgical resection.

Without early aggressive therapy, mucormycosis is almost always fatal. Therapy consists of early surgical debridement, administration of amphotericin B or liposomal amphotericin B, and correction of the underlying disease process. If surgical debridement or the correction of the underlying condition is not possible, then the response from medical treatment alone is poor. A better therapeutic response is obtained in patients with diabetic ketoacidosis and mucormycosis than in patients with underlying leukemia and lymphoma, because ketoacidosis can be quickly corrected and because the sinus rather than the lung is affected.

Conclusions

An association between deferoxamine therapy and mucormycosis is evident even in settings without hemodialysis,⁴ and thus, the potential benefits of deferoxamine must be weighed against the risk of developing such infections. Although prophylactic antifungal therapy is not warranted for all patients receiving deferoxamine, early recognition of mucormycosis in high-risk patients receiving deferoxamine may improve outcomes. A promising development is the newer class of chelator hydroxypyridone,⁸ which is associated less often with infectious complications.

References