Long-term survival in rhinocerebral mucormycosis

Case report

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Mucormycosis refers to a group of rapidly progressive infections caused by fungi belonging to the order Mucorales. The causative agents are ubiquitous and typically present in soil, decomposing vegetation, and bread. These organisms are even saprophytic in the respiratory and digestive tracts in 2% of normal individuals. Entrance into the body is characteristically through the skin or mucosa of individuals who are immunologically or metabolically compromised. Specific clinical manifestations are associated with various predisposing factors. Rhinocerebral mucormycosis is the most common form and most frequently develops in individuals with poorly controlled diabetes mellitus. The extent of anatomical involvement and clinical course are unpredictable, depending on the intrinsic factors of the host. Over the past 20 years the prognosis for patients with rhinocerebral mucormycosis, once considered to be a uniformly fatal disease, has improved. Coordinated medical and surgical treatment, including rapid diagnosis, the advent of systemic antifungal agents, aggressive surgical debridement, and control of the underlying disease process, have been credited with its successful management. The range of survival rates recorded with the regimen of combined therapies is wide because the number of patients reported is limited and anatomical involvement is diverse. Survival with intracerebral abscess is rare.

The authors describe the successful management of a patient who developed a bifrontal fungal abscess during treatment for rhinocerebral mucormycosis associated with ketoacidosis and diabetes mellitus. The patient remains without radiographic or clinical evidence of infection more than 2 years after treatment. The authors review the characteristic clinical, radiographic, and pathological features of previously reported infections and emphasize the importance of early detection and aggressive treatment in the management of this frequently fulminant and fatal disease.

KEY WORDS • fungus • mucormycosis • brain abscess

Mucormycosis is an acute fulminant, often fatal, opportunistic infection caused by one of the fungi of the order Mucorales. The causative agents are ubiquitous and typically present in soil, decomposing vegetation, and bread. These organisms are even saprophytic in the respiratory and digestive tracts in 2% of normal individuals. Entrance into the body is characteristically through the skin or mucosa of individuals who are immunologically or metabolically compromised. Predisposing factors include diabetes mellitus, hematopoietic malignancy, renal disease, aluminum overload, or desferoxamine therapy. Fungal hyphae are angioinvasive and result in infarction and necrosis of the involved tissues. Spread is typically by direct invasion.

Mucormycosis is a polymorphic disease, with diverse clinical manifestations, that has traditionally been divided into rhinocerebral, pulmonary, cutaneous, cardiac, gastrointestinal, disseminated, and miscellaneous syndromes. Certain clinical presentations are more often associated with specific host conditions. Rhinocerebral mucormycosis, the most common form, most often develops in patients with poorly controlled diabetes but has also been reported in otherwise normal individuals. Without treatment the infection leads rapidly to death. Early diagnosis, administration of systemic antifungal agents, aggressive surgical debridement, and control of the underlying disorder have become the mainstays of treatment. The exact benefit of a coordinated medical and surgical treatment approach is unclear and remains controversial. A wide range of survival rates has been recorded for patients receiving combined therapies. The associated high morbidity found in patients with this disease makes it an extremely important entity for the neurosurgeon to recognize. We illustrate the successful treatment of a patient with rhinocerebral mucormycosis with involvement of the nose, sinus, orbit, and cerebrum who was managed with a combination of aggressive surgical and medical modalities.

Case Report

History. This 20-year-old man with a history of insul-
Mucor brain abscess

dependent diabetes mellitus since 14 years of age, which was treated without related complications, was admitted to another medical institution with a 2-day history of headache, malaise, and nasal discharge. On the morning of admission he became increasingly lethargic, feverish (38.5°C), hyperglycemic (664 mg/dl), and his blood pH was 6.83. He received intravenous hydration, broad spectrum antibiotic medications, and metabolic support for diabetic ketoacidosis. By the morning after admission, his level of consciousness had improved, but he was found to have a fixed, dilated right pupil with an associated loss of light perception and complete ophthalmoplegia. Computerized tomography (CT) scanning revealed opacification of the right ethmoid sinus cells without retroorbital abnormalities. A regimen of systemic amphotericin B was initiated. An intranasal ethmoidectomy was performed revealing only dried blood. The presence of fungal hyphae could not be detected in biopsy specimens. The vision in the patient’s left eye began to deteriorate and he was subsequently transferred to our institution for further care 7 days after the onset of his symptoms.

Examination. On arrival, the patient was feverish (39°C) but alert. He had proptosis of the right eye with associated periorbital edema, chemosis, and ecchymosis. There was no perception of light or pupillary response, and he had complete ophthalmoplegia of the right eye. Funduscopic examination revealed a pale right optic disc with diffuse retinal edema consistent with an occlusion of the central retinal artery. The visual acuity in the left eye was reduced (20/200), with an associated paralysis of lateral rectus and superior oblique. Facial sensation was impaired in the distribution of the opthalmic division of the trigeminal nerve on the right. The remainder of the neurological examination was normal. Magnetic resonance (MR) imaging and repeated CT scanning demonstrated radiographic progression of the opacification and mucosal thickening of the maxillary and ethmoid sinuses bilaterally and of the sphenoid sinus. No intracranial extension was detected.

Operation. The patient underwent surgery for radical sinus debridement. A total septotomy with resection of the vomer, bilateral maxillotomies, left external ethmoidectomy, and sphenoidectomy were performed. Black necrotic eschar filling the sinuses was removed. The cribiform plate was not violated. Histopathological examination of the necrotic tissue revealed the characteristic nonseptate branching hyphae of mucormycosis. Subsequent cultures confirmed the diagnosis. The patient was maintained on daily intravenous infusion of amphotericin B deoxycholate along with local paranasal debridement and packing. Strict control of his blood sugar was maintained and the patient steadily improved.

Second Operation. Four weeks after his initial presentation, the patient developed progressive cognitive changes that included apathy and abulia as well as urinary incontinence. Magnetic resonance imaging revealed bilateral cerebritis of the basal frontal lobes, suggesting intracranial extension. In spite of intensive efforts at further control, serial MR imaging revealed progressive maturation of a bilateral subfrontal abscess with a thickened capsule (Fig. 1). The patient was returned to surgery and a bifrontal craniotomy was performed, after which sectioning of the anterior falx, complete resection of the abscess, and repair of the anterior cranial fossa with vascularized pericranium and fat were achieved (Fig. 2). His mental status improved and his incontinence resolved.

Postoperative Course. Seven months after the patient’s initial presentation, the systemic antifungal therapy was discontinued. The patient received a total of 6.7 g of amphotericin B deoxycholate without significant renal impairment. The vision in his left eye had returned to near normal (20/30) with normal extraocular movement. Thirty months following presentation, the patient is free of disease as confirmed by serial MR imaging and endoscopic examination. He has returned to independent living and full-time work.

Discussion

Mucormycosis refers to a group of rapidly progressive infections caused by fungi belonging to four families of the order Mucorales, which is a member of the class Zygomycetes. Most infections are caused by the three genera of the family mucoraceae: Rhizopus, Mucor, and Absidia. The causative organisms are ubiquitous within the environment. Infection most often develops in individuals with immunologically compromising conditions, which are frequently the result of diabetes mellitus, cancer chemotherapy, or administration of immunosuppressive medications following organ transplantation. Other predisposing factors include renal failure, severe burns, malnutrition, neutropenia, and treatment with the metal chelator desferoxamine. Patients without an underlying abnormality or apparent predisposition have also been affected. The incidence of the disease has not been demonstrated to vary based on age or gender. The spectrum of disease varies among different patient populations. Certain predisposing conditions seem to be more commonly associated with specific manifestations of mucormycosis. Pulmonary and disseminated disease often develop in patients with hematological malignancy during

Fig. 1. Coronal T2-weighted postcontrast MR image demonstrating the rim-enhancing subfrontal fungal abscess.
periods of neutropenia. Cutaneous manifestations develop in those receiving treatment of extensive burns. The gastrointestinal form is prevalent in underdeveloped countries where children are often malnourished. The rhinocerebral form is usually associated with diabetes mellitus and ketoacidosis but has increasingly been reported with other sources of immunosuppression. Intracerebral infection in the absence of sinus disease or endocarditis is rare, but it is most frequently encountered in intravenous drug users. In these patients, there seems to be a predilection for the basal ganglia.

The clinical manifestations of the rhinocerebral form, which seems to be the most common entity, depend on the specific intracerebral locations involved and the rate of progression of the infection. The clinical course, which is often determined by intrinsic factors of the host, is unpredictable and metabolic or immunological aberrations play a critical role. The predisposition of patients with diabetes to acquire the disease may be partially related to hyperglycemia, and the presence of ketoacidosis is presumed to induce a neutrophil defect, resulting in reduced phagocytosis and chemotaxis. Experimental studies suggest that iron increases the susceptibility of the host to mucormycosis. An active ketone–reductase system allows fungi of *Rhizopus* species to thrive in an acidic, glucose-rich environment with reduced oxygen tension typical of diabetes.

Nasal infection follows the inhalation of aerosolized fungal spores that may deposit in the nasal turbinates and extend into the adjacent paranasal sinuses and orbit. The pathogens are prone to invade and spread along blood vessels, particularly arteries. The fungus proliferates within the internal elastic lamina, dissecting it away from the media. As the hyphae penetrate the endothelium, thrombotic arteritis, infarction, hemorrhage, and extensive tissue necrosis follow. Involvement of the internal carotid artery, cavernous sinus, and opthalmic artery is common. Involvement of venous and lymphatic structures occurs later in the course of the disease. Infection with *Aspergillus* and *Pseudomonas aeruginosa* also carries with it a propensity toward vascular invasion with production of black infarcted tissue, which should be considered in the differential diagnosis.

Patients with rhinocerebral mucormycosis usually present with lethargy, fever, and headache or facial pain. A black necrotic intranasal or palatal eschar is highly suggestive of the disease, but it occurs in only 40% of those affected. Periorbital cellulitis, extraocular muscle paresis, proptosis, and chemosis frequently develop as a result of disease extension into the orbit or cavernous sinus. Cranial nerves are progressively infarcted as the infection spreads. Visual loss may develop from central retinal artery occlusion or direct orbital extension. Intracranial infection may result from spread through the vasculature or contiguous progression through the cribriform plate or orbital apex. Radiographic imaging is helpful in establishing the extent of sinus, orbital, or intracranial progression of mucormycosis and in determining the efficacy of treatment. Precise anatomical localization of the infection is important for guiding the choice of treatment modalities and for the overall prognosis. Therapy in our patient was clearly guided by the abscess appearance on MR imaging. Amphotericin B therapy was discontinued only after radiographic confirmation of disease eradication. The appearance on plain radiographs and CT scans can reflect the degree of soft-tissue destruction and bone destruction. Computerized tomography frequently exhibits nodular thickening of the mucosa of multiple sinuses, particularly the ethmoids, “cloudy” sinuses without air-fluid levels, fo-

![Fig. 2. Intraoperative photograph of the subfrontal bilateral fungal abscess.](image-url)
Mucor brain abscess

Fig. 3. Photomicrograph showing the broad, nonseptate hyphae branching at right angles, which are characteristic of the tissue appearance of mucormycosis. Gomori’s methenamine silver stain, original magnification × 1250.

cal bone erosion of multiple sinuses, and it is also very sensitive in detecting orbital involvement. Cerebral infarction may be difficult to distinguish from fungal cephalitis or abscess on CT scanning because associated edema is often minimal and ring enhancement may be absent. The improved sensitivity of MR imaging compared with CT scanning provides early detection of meningeal, intraparenchymal, and intracranial vascular occlusion, often before the patient develops clinical signs. Soft-tissue changes in the fat planes of the face and orbit and abnormal signal changes within the walls of the paranasal sinuses may be observed on MR imaging with fungal invasion. Fungal sinusitis may display a spectrum of signal characteristics.

The diagnosis of mucormycosis is suggested by the aggressive clinical features of the disease in the compromised host but needs to be confirmed by histopathological examination of a transnasal or cerebral biopsy specimen. The diagnosis is established with the demonstration of vascular invasion by irregular, broad, nonseptate hyphae that branch at right angles (Fig. 3). The presence of vascular invasion is necessary for diagnosis because these organisms can be present as colonizers or contaminants. The fungus is often difficult to isolate from infected tissue. Although culture is necessary to identify the involved fungal species, it is an unreliable diagnostic procedure because of the saprophytic nature of these fungi and the difficulty in isolating them. Serological testing has not been useful.

Over the past 20 years the prognosis for patients with rhinocerebral mucormycosis has improved with reported survival rates of up to 85%. There has been no major shift in the disease’s pattern of anatomical involvement to account for the improved prognosis. Successful therapy for infection involving craniofacial structures includes a combination of medical and surgical treatment modalities. Rapid control of the underlying disease process, systemic antifungal therapy, and aggressive surgical debridement of necrotic tissue have been the hallmarks associated with improved outcomes.

Control of the primary disorder is paramount to improved prognosis. Blitzer, et al., found that the underlying disease was the most important determinant of survival in a retrospective analysis of 179 patients treated for rhinocerebral mucormycosis. In patients without an underlying compromised state the survival rate was 75%. The survival rate decreased to 60% in patients with diabetes mellitus and to only 20% in those with other systemic disorders. Appropriate medical management of the preexisting condition, therefore, seems to contribute significantly to outcome. Elder and Baker have demonstrated that rabbits are more susceptible to experimental mucormycosis during the acute acidotic stage of alloxan-induced diabetes mellitus. Acute ketotic diabetes in rabbits and mice permits fungal invasion, decreases the phagocytic activity of polymorphonuclear leukocytes, and depresses the local inflammatory response. Perhaps the poor prognosis seen in patients with hematological malignancy, chronic renal failure, or following organ transplantation reflects the difficulty in treating the underlying disorder.

Systemic antifungal chemotherapy, limited to amphotericin B, has significantly improved the survival rates of patients with mucormycosis. This drug remains the only proven and effective medical therapy. Azole derivatives do not have a place in the treatment of these infections. In vitro, Mucor and Rhizopus are highly resistant to itraconazole. In vitro testing of isolates of the
Mucoraceae to amphotericin B has produced variable results and may not necessarily correlate with the clinical response. Amphotericin B is often associated with the potential for nephrotoxicity and other adverse reactions. Although renal toxicity is directly related to serum concentrations and total dosage, our patient received nearly 7000 mg of this drug with no renal impairment. Cessation of treatment was based on clinical evidence of absence of disease. The dose was altered during therapy to prevent irreparable renal failure and the serum creatinine level was maintained below 3 mg/ml. Lipid formulations of amphotericin B, which have different physical and kinetic characteristics, have been developed to provide less toxic alternatives. Although the successful treatment of rhinocerebral mucormycosis has been reported with the use of these lipid formulations, it is not clear whether they are equally effective or therapeutically better than standard preparations. Synergism between amphotericin B and rifampin has been suggested, but remains unproven. Similarly, cases have been reported in which success has been demonstrated with the addition of hyperbaric oxygen therapy.

Surgical procedures have become an important adjunct to the successful treatment regimens for rhinocerebral mucormycosis. Therapeutic response to antifungal therapy alone is unreliable. In addition to playing a role in diagnosis, early and, if required, repeated surgery has been necessary to treat extensive disease. Because the fungus thrives in devitalized and necrotic tissue and because ischemic tissue is difficult for chemotherapy agents to penetrate, debridement has been recommended. Drainage and debridement of parasanal sinuses, exenteration of necrotic orbital contents, palatectomy, and craniotomy have all been associated with cure. According to Blitzer, et al., radical resection appeared to enhance survival from 57.5 to 78% of diabetic patients. Although in many reviews it has been suggested that surgical debridement statistically improves survival, in others the value of aggressive surgical pursuit in the presence of intracranial disease has been questioned.

Although the survival rates for patients treated for rhinocerebral mucormycosis appear to be increasing, the exact benefit of combined surgical and medical treatment for intracranial involvement remains unclear. Appropriateness of therapy is limited by the relative paucity of clinical material. In addition, conclusions on adequacy of treatment are difficult to derive when there does not appear to be a significant effort in the literature to differentiate or classify the extent of anatomical involvement or the nature of disease. Although craniorrhaphy has reportedly improved survival rates, direct fungal invasion or abscess formation is not often differentiated from inflammatory or ischemic events. Survival associated with fungal brain abscess is rare. In a review of the management of rhinocerebral mucormycosis at a single institution, Nussbaum and Hall reported that all seven individuals treated for intracranial disease died, in contrast to four others with disease localized to the sinuses or orbits. Successful results, and hence alternative or new management strategies, are limited to small groups of patients and individual case reports.

Rhinocerebral mucormycosis was previously considered uniformly to cause death. However, over the past 20 years the prognosis for patients with the disease has dramatically improved. Patient survival rates of up to 85% have been reported with the advent of chemotherapeutic agents, early diagnosis, and aggressive surgical intervention. Outcome may depend on several factors, especially extent of disease, host resistance, and predisposing conditions. Successful management of intracranial mucormycosis abscess is possible, as we describe in this report. However, because rhinocerebral mucormycosis is rare, the success of new management regimens and antifungal agents will continue to be reported in small groups and as individual cases.

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