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Mucormycosis a Rare & Life Threatening Cause of Sinus Infection in Diabetes

KEYWORDS: Mucor, Mucormycosis

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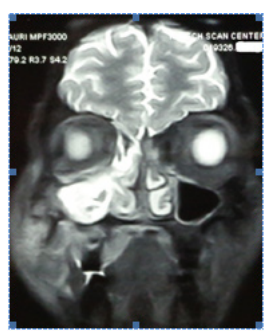
ABSTRACT *We report a case of a middle aged male diabetic, presented with right maxillary sinusitis. Radiological and histopathological findings confirmed mucormycosis. Conventional Amphotericin therapy combined with surgical debridement resulted in complete resolution. Mucormycosis infrequently presents as sinus infection in diabetics. Mucormycosis is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality (>40%) than many other infections. A high index of suspicion is critical for diagnosis, and early initiation of therapy—often before confirmation of the diagnosis—is necessary to optimize outcomes. CT scan and histopathological examination usually clinch the diagnosis. Amphotericin B is the drug of choice. Surgical debridement is usually required.*

Introduction:
Mucormycosis (or zygomycosis) is an infection caused by fungi of the order Mucorales in the phylum Zygomycota. Rhinocerebral mucormycosis is the most common form of the disease. It typically develops in diabetic or immunocompromised patients and presents as an acute fulminant infection, which is often lethal. The Mucorales are saprophytic fungi frequently found in the upper respiratory tract and are non-pathogenic in normal hosts. [1] Patients with diabetes, malignancies, solid organ or bone marrow transplants or iron overload and those receiving immunosuppressive agents, desferoxamine therapy or broad-spectrum antimicrobial drugs are at highest risk for mucormycosis. Based on clinical presentation and the involvement of a particular anatomic site, mucormycosis can be divided into at least six clinical categories: i) Rhinocerebral, ii) pulmonary, iii) cutaneous, iv) gastrointestinal, v) disseminated and vi) miscellaneous.[2,3]

Case:
40 years/ Male, K/C/O Diabetes Mellitus for 4 years admitted with painful swelling of right cheek since 10 days which was progressively worsening in nature. H/O fever with chills was also present since 10 days. His vital parameters and systemic examination were normal. He was conscious and oriented with no neurologic deficit. His vision & eye examination was normal. Locally, he had swelling over right half of face. Total leucocyte count, Renal function tests, Liver function tests and Serum electrolytes were normal. CT scan showed soft tissue density lesion in right maxillary sinus likely to be fungal (Image I). He underwent biopsy which was suggestive of Mucormycosis. He was started on Amphotericin B 1mg/kg/day. BSL was controlled with insulin and renal functions were monitored. Repeat CT was done after 2 weeks which didn't show significant resolution of the lesion. He was referred to maxillofacial surgeon for surgical intervention. Right subtotal maxillectomy was performed. Amphotericin B was continued. Histopathological examination of the operative tissue confirmed mucormycosis of maxillary sinus. Post operative CT scan at later date (after 5 weeks of therapy) showed complete resolution (Image II).



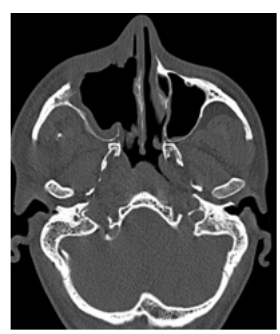


Image I **Image II**

Epidemiology: Mucormycosis is extremely rare, the true incidence is unknown, but an estimated 500 cases occur in the United States annually.The incidence of mucormycosis appears to be increasing secondary to rising numbers of immunocompromised persons. Further, there are increasing reports of breakthrough mucormycosis in the setting of antifungal prophylaxis or treatment (e.g, voriconazole, echinocandins) that is effective against most fungi (e.g, Aspergillus) but not mucormycosis. No racial or age factors that predispose people to mucormycosis exist, and a patient's sex is not likely to affect the occurrence of mucormycosis, because the underlying conditions are the major predisposing factors.[4]

Pathophysiology: The Mucorales are saprophytic fungi frequently found in the upper respiratory tract and are non-pathogenic in normal hosts. When spores are converted into hyphae, they become invasive and may spread through the paranasal sinuses into the brain and orbits. Direct soft-tissue invasion and formation of cerebral abscesses are frequent. Extension along blood vessels is followed by invasion and thrombosis. In addition to this classical fulminant presentation a chronic form of mucormycosis exists.[1,2] In the diabetic ketoacidotic patient, there is a high incidence of mucormycosis caused by Rhizopus oryzae, also known as Rhizopus arrhizus, because they produce the enzyme ketoreductase, which allows them to utilize the patient's ketone bodies. It is also likely that the hyperglycaemia stimulates fungal growth, and the diabetic reduction in chemotaxis and phagocytic efficiency permit these otherwise innocuous organisms to proliferate. Mucormycosis of head and neck region results from inhalation of airborne spores. In the nasal mucosa, germination ensues and the hyphal elements penetrate, by direct extension or through vascular channels, the paranasal sinus, orbit brain and occasionally even the eye. Destructive

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lesions of the palate and maxilla should suggest a peripheral T-cell lymphoma (formerly termed midline lethal granuloma), nasopharyngeal carcinoma and tertiary syphilis. Some might be concerned about a Wegener's granulomatosis, but this disease is limited to the palatal soft tissue and does not necrose the palate or maxilla. Fungal sinusitis generally affects only debilitated patients. The Phycomycetes and Aspergillus organisms are common opportunistic pathogens in the milieu of immunologically compromised patient; so mucormycosis should also be differentiated from aspergillosis. Radio graphically in aspergillosis, radiopaque concretions may be identified whereas mucormycosis shows opacification of sinus. Suspicion of mucormycosis requires a CT scan of the maxilla orbits and brain. In particular, evidence of intracranial brain abscesses and orbital extensions is critical. Sinus and orbital extensions are recognized by membrane or periosteal thickenings as well as bony disruption.[5] Perineural spread with invasion of nerves, blood vessels, cartilage, bone and meninges is common and may result in thrombosis and nerve dysfunction. Rhinocerebral mucormycosis is the most common type.

Mucormycosis Clinical Presentation: Rhinocerebral disease may manifest as unilateral, retro-orbital headache, facial pain, numbness, fever, hyposmia, and nasal stuffiness, which progresses to black discharge. Initially, mucormycosis may mimic sinusitis. Late symptoms that indicate invasion of the orbital nerves and vessels include diplopia and visual loss.

Other disseminated forms of mucormycosis may involve the kidneys, bones, heart, and other locations, with symptoms attributed to these organ systems. Peritonitis in the setting of continuous ambulatory peritoneal dialysis has also been described. Central nervous system (CNS) disease manifests as headache, decreasing consciousness, and focal neurologic symptoms/signs, including cranial nerve deficits. Patients with CNS involvement may have a history of open head trauma, intravenous drug use, or malignancy. Mucormycosis is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality (>40%) than many other infections. A high index of suspicion is critical for diagnosis, and early initiation of therapy—often before confirmation of the diagnosis—is necessary to optimize outcomes.[2-4]

Investigations: Haemogram should be done to asses leucocyte & neutrophil count. Blood sugar level and other metabolic parameters are also checked. In case of suspected CNS involvement neuroimaging & CSF studies should be done.[6] Plain X ray films may show sinus involvement with mucosal thickening, air-fluid levels, and/or bony erosions. Head and facial computed tomographic (CT) scanning should be used as the initial investigation in rhinocerebral infections. CT scans may show sinusitis of the sinuses, as well as orbital and intracranial extension. As the disease progresses, bony erosion may occur and the infection may spread into the brain or orbits. In addition, because mucormycosis organisms have a predilection for vascular involvement, thrombosis of the cavernous sinus or internal carotid artery may occur. Magnetic resonance imaging (MRI) of the facial sinuses and brain may be superior to a CT scan.[4-6] The critical test procedure for diagnosing mucormycosis is obtaining a biopsy specimen of the involved tissue. A rapid histologic assessment of a frozen tissue section can be performed in order to promptly institute surgical and medical management for the infection. Biopsy of necrotic tissue may be obtained from nasal, palatine, or paranasal sinuses. Stains of fixed tissues with hematoxylin and eosin (H&E) or specialized fungal stains, such as Grocott methenamine-silver or periodic acid-Schiff (PAS) stains, show pathognomonic changes of broad-based (typically 10- to 20-µm diameter), irregular, ribbon like, nonseptate hyphae with irregular branching that may occur at right angles. Vascular invasion and necrosis are the characteristic consequences of the infective process. Thus, neutrophil infiltration, vessel invasion, and tissue infarction are often observed. A granulomatous reaction may also be observed.[2,4,6] Culture of biopsy samples is required to determine the species of Mucorales.

Differential diagnosis: When evaluating a patient with suspected rhinocerebral mucormycosis, also consider the following:

Bacterial orbital cellulitis

Cavernous sinus thrombosis

Aspergillosis & other fungal infections

Pseudallescheria boydii infection (Pseudallescheriasis)

Rapidly growing orbital tumour

Treatment: Patients with mucormycosis should be treated in a center with experience in the care of the condition and the underlying causes. Correction of the underlying abnormality (like uncontrolled diabetes, neutropenia, glucocorticoids & immunosuppressant therapy) and prompt institution of amphotericin B therapy and surgical resection are critical.[2-4] Antifungal treatment consists of lipid formulations of amphotericin (e.g, liposomal amphotericin), amphotericin B deoxycholate, or posaconazole. Amphotericin B has proven efficacy in the treatment of mucormycosis, and the conventional form (deoxycholate) is typically administered at 1-1.5 mg/kg/d (the total dose given over the course of therapy is usually 2.5-3 g). High doses of this drug are required, and nephrotoxicity may result. A lipid formulation of amphotericin B has now replaced amphotericin B deoxycholate as the drug of choice, owing to improved efficacy and safety of these formulations, increased cost may be an issue. Lipid preparations of amphotericin B are typically used at 5 mg/kg/d or more doses. Posaconazole, a triazole, is currently considered a second-line drug for treatment of mucormycosis, and the typical dose is 400 mg orally twice daily (total of 800 mg/d). Most commonly, posaconazole is used as sequential therapy after the initial administration and control of the disease with amphotericin B.[7] Other medications: Other azoles (e.g, fluconazole, voriconazole) have not shown significant activity against these fungi.[6,7] Of note, despite the use of voriconazole prophylaxis in high-risk patients (e.g, transplant recipients), breakthrough zygormycosis has been reported. Limited data suggest that combination therapy with lipid formulations of amphotericin and an echinocandin (e.g, micafungin, caspofungin) may improve survival. **Surgical treatment** is usually necessary, with extended resection until bleeding tissue is found. Efforts to save the ocular globe with conservative resections may lead to a delayed enucleation and worsening of the patient. One must ensure the paranasal sinus drainage. It is quite frequent to perform repeated resections of small residual fungus foci from the margins of the wound during the postoperative period; in these cases, the frozen section analysis is extremely useful. There is agreement in the use of amphotericin irrigation of the surgical field, as well as the amphotericin embedded gauze. The aim is to ensure the drug biodisponibility in the surgical field, where the vascularisation is compromised because of the thrombosis. Surgical reconstruction is usually deferred until the infection is completely resolved.[4-9] Other therapeutic modalities includes hyperbaric oxygen therapy and nasally nebulised amphotericin B.[8] It is advisable to avoid administration of iron to patients with active mucormycosis, as iron exacerbates infection in animal models.[2,4]

Duration of Therapy and Long-Term Monitoring: Ongoing clinical surveillance and diagnostic imaging are required to ensure complete resolution of mucormycosis and to detect relapse. The duration of therapy is highly individualized and should encompass the resolution of associated symptoms and findings, normalization of radiographic findings (with the exception of radiographic findings thought to be the result of post inflammatory or postoperative scar formation), negative cultures from the affected site, and resolution of immunosuppression[5,7,9]. Successful courses of therapy typically last 4-6

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weeks and require cumulative doses that are equivalent to greater than 2 g of amphotericin B deoxycholate.

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