Oral Mucormycosis Causing Necrotizing Lesion in a Diabetic Patient: A Case Report

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Abstract
Mucormycosis is an invasive and potentially lethal infection caused by fungi of the order mucorales. The microbiology, clinical forms and pathology of mucormycosis are well established but the rarity of the disease leads to difficulties in diagnosis and delays can result in a poor prognosis. The main risk factors for this disease are diabetes mellitus, renal insufficiency, organ transplantation and chronic use of iron-chelating agents and immunocompromised patients. Early recognition and aggressive treatment are of paramount importance and have reduced the mortality and morbidity. We present a case of oral mucormycosis in a patient with diabetes mellitus and ketoacidosis, who was saved by immediate diagnosis and medical treatment. What makes this case significant is the diagnosis and treatment of a neglected lesion accompanied by systemic diseases. All the diagnostic procedures, treatment and the relevant literature are discussed in detail.

Keywords: Mycoses; Zygomycosis; Mucormycosis; Fungi; Unclassified Mucorales; Diabetic; Ketoacidosis; Diabetes Mellitus.


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Introduction
Mucormycosis, also known as zygomycosis and phycomycosis was first described by Pautlauf in 1885.1 It is an acute opportunistic fungal infection with a high mortality rate that predominantly occurs in dehydrated and acidic patients caused by a group of distinctive Mycoses; all of which are ubiquitous, saprophytic fungi of the class Phycomycetes, order mucorales, family Mucoraceae.2 The most common genera isolated are Rhizopus, Rhizomucor and Absidia.3-5 Rhizopus is the predominant pathogen, accounting for 90% of the cases of rhinocerebral mucormycosis.6 It can be found in fruits, soil, dust, and manure and can be cultured from the nasal mucosa of normal persons, where it may not cause clinical signs of infection.7 The organisms are aerobic, but can live two to five days in vitro.8 Although infection usually occurs after inhalation through the nose or mouth, a skin laceration can also become an opening for mycotic entry.8

The terms phycomycosis and zygomycosis are occasionally used; however, mucormycosis is the most frequent term. There are at least six clinical entities of mucormycosis: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system (CNS), disseminated and miscellaneous like bone or kidney.3 The term rhinocerebral mucormycosis (RCM) should only be used if the facial, palatal, orbital, paranasal sinus or cerebral regions are involved and the patients generally present with signs and symptoms that may be primarily located in these regions.9 Up to 40% to 50% of patients who present with mucormycosis have Diabetes Mellitus (DM).10 The RCM is the most common form in patients with diabetic ketoacidosis (DKA), involving 70% of reported cases.3,10

Even though mucormycosis is ubiquitous and grows rapidly, it seldom causes an infection in immunologically competent patients. Therefore, if an infection with mucormycosis does occur, it usually indicates a serious underlying medical condition. Mucormycosis will commonly strike debilitated patients with conditions such as DM, DKA, neutropenia, immunosuppressive therapy, desferoxamine use associated with dialysis, malnutrition, leukemia, lymphoma, and renal failure.3,11-15 Therefore, a complete biochemical, radiographic, microbiological and histopathological study was carried out to diagnose and elucidate this highly mortal fungal infection, justifying the main aim of this report.

Case Report
A 68 year old male patient was referred to the surgery department with an extensive ulcer on the palate. He had noticed...
ulceration in the upper jaw, experienced difficulty in swallowing, facial pain, numbness and constant headaches for about two months but neglected his problems and postponed medical intervention. The ulcer progressed rapidly because of which he was referred to our hospital from a local hospital. He had a medical history of diabetes, diabetic ketoacidosis and was obese. Physical examination showed swelling and tenderness of the cheek, and there was extensive ulceration and necrosis of the hard palate. The affected mucosa appeared denuded and covered with brown foul-smelling debris. The ulcer had undermined edges, and a yellowish brown base. As low surgical debridement was done, there was an inability to all.

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Laboratory studies were carried out to confirm diabetes with values as high as 300 mg/dl and diabetic ketoacidosis with traces of acetone. HIV infection was ruled out. Hematology investigations suggested a WBC count 14,000 cells/mm³. Computed tomography showed absence of normal bone trabecular pattern, replaced by radiolucent areas. Multiple sequestra involving the hard palate and few areas of maxillary bone were noticed.

The cause of necrotic lesion was unclear therefore an incisional biopsy was done to reach to the exact diagnosis and the tissue was sent for 10% KOH wet mount preparation (Figure 1b) and (Figure 1c) hematoxylin & eosin and periodic acid Schiff stained sections were prepared. The stained sections show the presence of granulation and necrotic tissues which contain colonies of large hyalinised basophilic hyphae that are devoid of septa. Inflammatory cells, chiefly neutrophils and eosinophils, prevailed in the granulation tissue that is located peripheral to widespread zones of necrosis. All the above findings confirmed the diagnosis of Mucormycosis.

Antifungal chemotherapy consisting of amphotericin B, 50 mg daily intravenously was started immediately after the reports of incisional biopsy were received to confirm mucormycosis. The dose was gradually increased to 40mg twice a day. His Diabetes was controlled with daily insulin. Six days later, his condition was considerably stable enough to allow surgical debridement (Figure 1d). The dressings were changed daily, and the wound irrigated with Hydrogen peroxide. Post operatively, the patient was given amphotericin B for two weeks and treated for diabetes. His recovery was smooth and was discharged from the hospital after a month from the hospital.

Discussion

Studies have shown that DM alters the immunologic capability to resist mucormycosis through reduction of the phagocytic ability of granulocytes during acidosis and the inability of diabetic serum to inhibit Rhizopus in vitro. 4,5,16,17 In addition, Rhizopus species thrive best in an acidic and glucose-rich environment. 12 Patients with RCM will present with facial pain, headache, and fever. 10 If the infection extends to the nasal turbinates, the orbit can become involved. Infection can lead to proptosis, periorbital oedema, chemosis, ophthalmoplegia, and loss of vision if the orbital apex becomes involved. Infection of the CNS is usually attributed to direct extension of the nose or paranasal sinuses or through vascular channels, the supraorbital fisure, or the cribiform plate. 10 If the disease invades the mouth, a black, necrotic eschar is often found on the palate, and ischemic, necrotic turbinates may be found in the nose. As mucormycosis often invades blood vessels, infarction, necrosis, and thrombosis are the major characteristics. 3,11,16

Mucormycosis of the oral cavity can be of 2 origins. One is from disseminating infection where the portal of entry is by inhalation (usually through the nose); the other is from direct wound contamination with dissemination to other viscera as a common complication. When arising from the nose and paranasal sinuses, the infection may cause palatal ulceration progressing to necrosis. The area appears black in the large majority of the cases. When the infection spreads from direct wound contamination, the clinical findings may appear anywhere in the oral cavity, including the mandible. An important prognostic difference between infection involving the maxilla and infection of the mandible is cavernous sinus thrombosis, a serious complication of maxillary infections. Another difference is the rarity of the mandibular infections as compared to the maxillary. More than 60 reports of jaw infection have been found in the English literature, all but four with maxillary involvement. 12

RCM is opportunistic; infecting humans whose systemic health is compromised.
Human infection is felt to be caused by asexual spore formation. The tiny spores then become airborne and land on the oral and nasal mucosa of humans. In the vast majority of immunologically competent hosts, these spores will be contained by a phagocytic response. If this fails, germination will ensue and hyphae will develop. Because polymorphonuclear leukocytes are less effective in removing hyphae, the infection can then become established. It progresses as the hyphae begin to invade arteries, where they propagate within the vessel walls and lumens causing thrombosis, ischemia, and infarction with dry gangrene of the affected tissues (Chart 1). Hematogenous spread to other organs can occur (lung, brain, and so on), as well as overt sepsis.\textsuperscript{18}

The initial medical approach to mucormycosis is to treat aggressively any underlying predisposing disorder.\textsuperscript{3} Surgical management also should be initiated early in the course of treatment. This should involve debridement of all infected tissues. In some cases, radical resection may be required, which can include partial or total maxillectomy, mandibulectomy and orbital exenteration.\textsuperscript{17}

The use of amphotericin B in patients with mucormycosis has been a widely published and accepted treatment, with a survival rate of up to 72%. Although combined treatment of surgery and amphotericin B has a survival rate of 80%, 70% of those who do survive will encounter some type of functional deficit (i.e., blindness or cranial nerve palsy).\textsuperscript{3}

Hyperbaric oxygen (HBO) has also been used to treat rhinocerebral mucormycosis. A few studies have shown that HBO has direct in vitro fungistatic activity and reduces tissue hypoxia, which may reverse the hypoxic acidosis that helps the fungus to proliferate.\textsuperscript{19} However, a retrospective study showed no significant difference between the effectiveness of therapy with and without HBO.\textsuperscript{6} Although some studies have shown that the most important effect of hyperbaric oxygen is to aid neovascularization, with subsequent healing in poorly perfused acidic and hypoxic but viable areas of tissue. Tissue changes caused by microvascular insufficiency secondary to obliteratorive arteritis occurring after radiotherapy is similar to the changes seen with the vascular occlusion by mucormycosis, as well as other fungal infections.\textsuperscript{20-22} Rifampin also has been used to treat mucormycosis because of the reported synergistic effect of amphotericin B

Figure 1: The intraoral examination revealing an extensive ulcer and necrosis of the hard palate (a). The photomicrograph of KOH wet mount (b) and periodic acid schiff stained section (c) showing basophilic hyphae. The photograph showing the site of surgical debridement (d).
and rifampin against Rhizopus in vitro.\textsuperscript{23} However, other studies have shown minimal, if any, increased activity in vivo when amphotericin B is combined with rifampin.\textsuperscript{24} Therefore, some authors do not recommend these therapies for general use in most patients diagnosed with mucormycosis. Proper treatment of CST includes appropriate antibiotic coverage and elimination of the source of infection.

![Chart 1: The Pathophysiology of Mucormycosis.](image)

Anticoagulants have been used; however, their use is still controversial. Although it has been postulated that anticoagulants will prevent further thrombosis, those who do not favor this approach believe that the clot confines the infection and that anticoagulants may cause or increase intracranial bleeding.\textsuperscript{25}

Computed tomography of patients with rhinocerebral mucormycosis typically shows opacification of the paranasal sinuses and thickening of the sinus mucosa and bone destruction, without an air-fluid level.\textsuperscript{26} In addition, the CT scan will also show soft tissue swelling, proptosis, and swelling of the extraocular muscles.\textsuperscript{27} However, a definitive diagnosis of mucormycosis can only be made by a biopsy that identifies the characteristic hyphae and by culturing the fungus in the laboratory.\textsuperscript{3}

Histologically, mucormycosis is characterized by extensive tissue necrosis and the presence of numerous large fungal hyphae, which are nonseptate and have a ribbon-like appearance, with budding and dichotomous branching.\textsuperscript{28} Magnetic resonance imaging is currently the imaging method of choice in diagnosing CST.\textsuperscript{29} However, CT scanning can be useful for diagnosing CST if contrast is used. The CT scan may reveal irregular filling defects or radiolucency of the cavernous sinus. Therefore, the diagnosis of the disease is mainly based on history, high index of suspicious diagnostic imaging and biopsy. This case reinforces the concept that awareness and complete knowledge of potentially fatal complications may help in rapid diagnosis and prevention of disease dissemination.

**Conclusions**

Early recognition of mucormycosis is necessary to limit the spread of infection, which can lead to high morbidity and mortality. Therefore, health practitioners should be familiar with the signs and symptoms of the disease and should maintain a high level of suspicion in patients with diabetes. These patients should have a plasma glucose level measured before surgery. Hence, early diagnosis, aggressive surgical intervention, reversal of the underlying disorder, and use of amphotericin B are keys to improved outcome for patients with mucormycosis. As all the above criteria were considered and administered, the patient was treated and saved even after the prior postponed and neglected medical treatment.

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