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# Successful Treatment of Maxillary Mucormycosis: Report of a Case and Literature Review

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## Abstract

Opportunistic fungal infections, such as mucormycosis, often occur in immunocompromised patients. Predisposing conditions include metabolic disorders (e.g. uncontrolled diabetes), corticosteroid or immunosuppressive therapy, desferoxamine therapy, burns, solid organ or bone marrow transplants, or neutropenic hematologic malignant diseases and their corresponding treatment. The infection begins in the nose and paranasal sinuses due to inhalation of fungal spores. The infection can spread to orbital and intracranial structures either by direct invasion or through the blood vessels. The fungus invades the arteries leading to thrombosis that subsequently causes necrosis of hard and soft tissues. We report a case of maxillary necrosis by mucormycosis in an uncontrolled diabetic patient and its successful treatment to emphasize that early diagnosis and prompt treatment can reduce the mortality and morbidity of this lethal fungal infection.

## Introduction

Mucormycosis or zygomycosis, also called phycomysosis, is an uncommon and aggressive fungal infection that usually affects patients with alteration of their immunological system. From its initial description by Paultauf, [1] this entity still has a high mortality. Mucormycosis is the most important invasive fungal infection behind aspergillosis and candidiasis; the associated overall mortality rate is approximately 50%. The zygomycoses are infections caused by fungi of the class Zygomycetes comprised of the orders Mucorales and Entomophthorales. The Entomophthorales are rare causes of subcutaneous and mucocutaneous infections known as entomophthoromycosis, which largely afflict immunocompetent hosts in developing countries. In contrast, fungi of the order Mucorales are causes of mucormycosis, a life-threatening fungal infection almost uniformly affecting immunocompromised hosts in either developing or industrialized countries [2]. Mucormycosis caused by filamentous fungi, generally saprophytic, characterized by large coenocytic hyphae that grow rapidly and are widely distributed in nature. They are commonly considered to be opportunistic pathogens, although such clinical manifestations are no longer regarded to be unusual, owing to their increase in diabetic subjects and in those receiving immunosuppressive therapies. Mucormycosis presents as an acute fungal infection with a typically fast and devastating course. It has gained increasing importance as a medical complication in immunocompromised patients. Historically, poorly controlled diabetes mellitus has been the most common underlying risk factor [3], but the increasing incidence of cancer and the rising use of modern medical treatment methods such as organ or hematopoietic stem cell transplantation in lifelong immunocompromised patients have led to increasing numbers of immunosuppressed individuals. This underlines the emerging influence of the risk of developing invasive fungal infections. [3,4]

## Pathogenesis

Host Defence: Both mononuclear and polymorphnuclear phagocytes of normal hosts kill Mucorales by the generation of oxidative metabolites and the cationic peptides defensins [5]. Clinical evidence demonstrates that these phagocytes are the major host defence mechanism against mucormycosis. For example, neutropenic patients are at increased risk of developing mucormycosis. Furthermore, patients with dysfunctional phagocytes are also at higher risk for developing mucormycosis. Hyperglycemia and acidosis are known to impair the ability of phagocytes to move toward and kill the organisms by both oxidative and nonoxidative mechanisms [6]. Additionally, corticosteroid treatment affects the ability of most broncho-alveolar macrophages to prevent germination of the spores in vitro or after in vivo infection induced by intranasal inoculation [7]. The exact mechanisms by which ketoacidosis, diabetes, or steroids impair the function of these phagocytes remain unknown.

Role of Iron in Pathogenesis: A recently identified important clinical feature is the increased susceptibility to mucormycosis of patients with elevated available serum iron. It has been known for two decades that patients treated with the iron chelator deferoxamine have a markedly increased incidence of invasive mucormycosis [8]. However, it is now clear that iron chelation is not the mechanism by which deferoxamine enables mucormycosis infections. Patients with diabetic ketoacidosis are at high risk of developing rhinocerebral mucormycosis [9]. Multiple lines of evidence support the conclusion that patients in systemic acidosis have elevated levels of available serum iron, likely due to release of iron from binding proteins in the presence of acidosis [10]. Finally, simulated acidotic conditions decreased the iron-binding capacity of sera collected from normal volunteers, suggesting that acidosis temporarily disrupts the capacity of transferrin to bind iron [10]. Therefore, the increased susceptibility to mucormycosis of patients with diabetic ketoacidosis is likely due at least in part to an elevation in available serum iron during diabetic ketoacidosis.

Fungal-Endothelial Interactions: A hallmark of mucormycosis infections is the virtually uniform presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis. This angioinvasion is associated with the ability of the organism to hematogenously disseminate from the original site of infection to other target organs. Hence, damage of and penetration through endothelial cells lining blood vessels is likely a critical step in the organism's pathogenetic strategy. The clinical hallmark of mucormycosis is vascular invasion resulting in thrombosis and tissue infarction/ necrosis. Mucormycosis virtually always occurs in patients with defects in host defence and/or with increased available serum iron, although rare cases have been reported in apparently normal hosts [2]. In most cases, the infection is relentlessly progressive and results in death unless treatment with a combination of surgical debridement and antifungal therapy is initiated promptly.

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Imaging techniques are not usually diagnostic and cultures are not totally reliable. Definitive diagnosis is exclusively obtained by means of histological examination. Even with a prompt diagnosis, treating underlying diseases and aggressive medical and surgical management is often not effective, leading to an extension of the infection and death.

## Case presentation

A 57-year-old female patient referred for assessment of palatal ulceration that had not responded to the treatment since 2 months (Figure 1A). The patient had complaints for pain and swelling in the left cheek for the past 1 month. The patient had a medical history of uncontrolled diabetes for more than 10 years. On general examination vital signs were within normal limits. The patient's blood sugar level was high (450 mg/dl) and she had acidosis (pH 7.30). The presence of ketones was noted on urinary analysis. On examination, a diffuse swelling noted in the middle third of face on left side, which was warm and tender. Intraoral examination revealed a suspicious palatal ulcer under an old denture associated with necrotic palatal bone. The ulcer was subsequently biopsied and diagnosed as consistent with Mucormycosis (Figure 1B). A radiograph (sinus view) was advised that showed haziness of left maxillary sinus with erosion of lateral sinus wall. Computerized tomography (CT) indicated necrotic perforation in the palatal bone together with severe erosion of the left maxillary sinus wall and thickening of the mucosal sinus (Figure 2A-C). Treatment plan consists of reversing immunosuppression by improvement of the general health status and the underlying disease, systemic and local antimycotic treatment, surgical debridement and adjunctive therapy by hyperbaric oxygen.

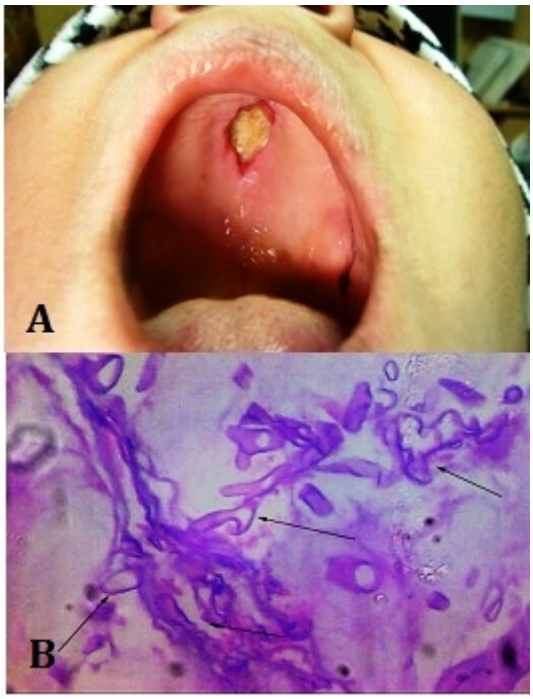


Figure 1: (A) Large palatal ulceration; (B) Mucormycosis hyphae (arrows on left side) & spores (arrows on right side) (Hx & E - x400).

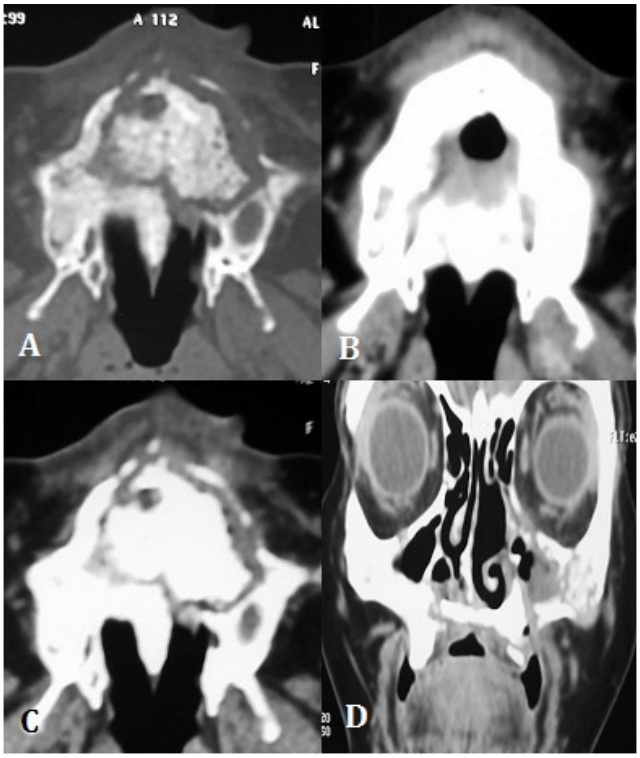


Figure 2: (A) Axial Bony Window Computerized tomography indicated necrotic perforation in the palatal bone; (B & C) Axial Soft-Tissue Window Computerized tomography indicated necrotic perforation in the palatal bone; (D) Coronal Computerized tomography indicated severe erosion of the left maxillary sinus wall and thickening of the mucosal sinus.

The patient was admitted to the hospital for adjustment of the uncontrolled diabetes and improvement of the general health condition simultaneously with systemic and local administration of antifungal medications. Amphotericin B (fungilin) was used at a dose of 3 mg/kg, once daily with regular checkup for the renal function test. Endoscopic surgical debridement was done for removal of all the necrotic tissue. The operation was performed by using the standard endoscopic sinus surgery technique with 4 mm rigid endoscopes with deflection angles of 0 and 30 degrees. Haemostasis was usually achieved with nasal packing under the middle turbinate. Aggressive surgical debridement to remove all the diseased sinus mucosa and necrotic bone was performed. The patient was discharged from the hospital and the systemic antifungal treatment was continued for another one month simultaneously with hyperbaric oxygen therapy (HBO). After another one month, the patient appeared to be in remission. Intraoral palatal ulcer showed significant improvement with significant reduction of the ulcer size (Figure 3). The radiographic evaluation by CT showed significant improvement with reduction of the palatal perforation and formation of new palatal bone (Figure 4).

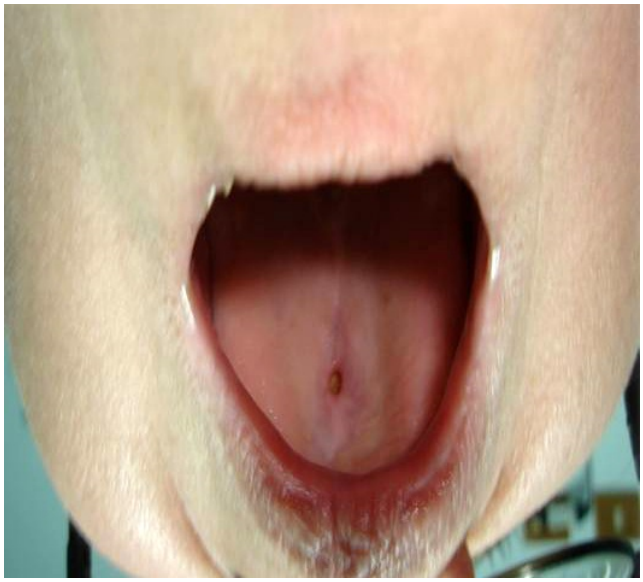

Figure 3: Significant improvement with significant reduction of the ulcer size.

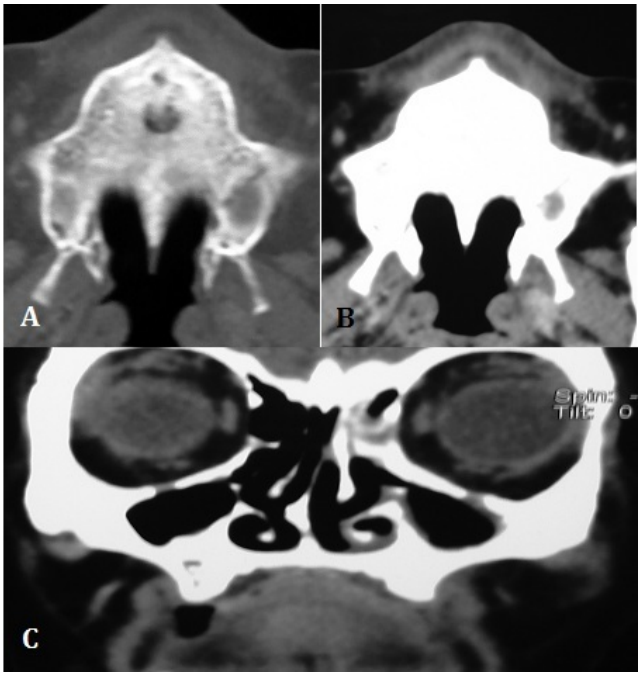


Figure 4: The radiographic evaluation by CT showed significant improvement with reduction of the palatal perforation and formation of new palatal bone.

On follow up visits, patient's condition improved, diabetes was controlled, and patient was strongly advised regarding control of diabetes. Small residual palatal defect was covered by the denture which used as obturator for the patient. The patient was disease free for the next 3 yrs.

## Discussion

Mucormycosis is the term used to refer to a rare and lethal fungal infection caused by the family of Mucoraceae, which belongs to the class of Phygomycetes or Zygomycetes [11,12]. These saprophytic fungi exist widely in nature and their spores may be found in soil, air, spoilt food, and other decaying organic material. Due to their low virulence potential, it may be present in the nasal mucosa of normal people as a commensal [13]. If the patient has some form of immunosuppression of his immune system (diabetes, ketoacidosis, severe burns, solid organ transplant) the fungus may germinate within the paranasal sinuses and spread to nearby structures (for example the palate, orbit, brain,) with the possibility of intracranial extension and death [11]. Skin lacerations or even trivial injuries of the skin surface can also be a portal for mycotic infection [14].

Several recent reviews identify factors that are critical to successful treatment of zygomycosis included; rapid diagnosis, Remove or reduce risk factors, antifungal therapy, surgical debridement and adjunctive therapies. [15,16].

### Rapid diagnosis

The starting point is to recognize patients at increased risk and early signs of infection. Initially, clinical features may be similar to those of other invasive mould infections, but it is the consideration of zygomycosis as a diagnosis that may lead to timely confirmation by successful biopsy and/or culture of the causative organism. Early diagnosis is important because small, focal lesions can often be surgically excised before they progress to involve critical structures or disseminate. Unfortunately, there are no serologic or PCR-based tests to allow rapid diagnosis. The patient may complain of a combination of headache, visual disturbance, facial and/or orbital swelling. Urgent radiological imaging to localize and determine the extent of the infection is crucial (although this may initially be falsely negative) and should be followed by surgical review to consider a biopsy, or therapeutic surgical debridement. Any diabetic patient with a headache and visual changes is a candidate for prompt evaluation with imaging studies and nasal endoscopy to rule out mucormycosis. Furthermore, to reiterate a concept that is frequently poorly grasped by clinicians inexperienced with mucormycosis, the initial imaging study is frequently negative or has subtle findings. Radiographic findings lag behind clinical progression in this disease, and a negative imaging study does not provide a rationale to delay more aggressive diagnostic manoeuvres (e.g., endoscopy with biopsy) if clinical suspicion is high. The appearance of tissue at endoscopy may also lag behind invasion, as the mucosa can appear pink and viable during the initial phase of fungal invasion. Therefore, if the suspicion for disease is high, blind biopsy of sinus mucosa is warranted to make the diagnosis.

### Remove or reduce risk factors

The second consideration is to deal with any reversible predisposing factors by, for example, rectifying diabetic ketoacidosis, withdrawing desferrioxamine therapy or reducing the level of immunosuppression. Because there is a relationship between the high mortality rates and predisposing conditions, the improvement of those factors of comorbidity will influence the patient's prognosis. In diabetic ketoacidosis patients, Hyperglycemia and acidemia should be corrected. Discontinuation of deferoxamine or immunosuppressive

therapy, particularly steroids, should be strongly considered when the diagnosis of mucormycosis is made.

### Antifungal therapy and surgical debridement

Unfortunately, because of the relative rarity of this infection, formal comparative studies of different systemic antifungal agents have not been feasible. Choice of therapy has therefore been based on experience, supplemented by information gleaned from animal model studies and in vitro susceptibility data. The agent of choice was conventional Amphotericin B used at higher than normal doses of up to 1.5 mg/kg/day. [15] Mucormycosis is frequently rapidly progressive, and antifungal therapy alone is often inadequate to control the infection. The numerous agents of mucormycosis have a broad range of susceptibilities to antifungal agents; some strains may be highly resistant to amphotericin B. Furthermore, the hallmark angioinvasion, thrombosis, and tissue necrosis of this disease result in poor penetration of anti-infective agents to the site of infection. Surgical debridement to remove all necrotic and septic tissue because systemic therapy may not reach or destroy the entire population of fungal organisms. Surgical debridement should always be considered as an option early in management as Antifungal therapy and surgery were independently associated with a decreased risk of mortality. Finally, surgery is necessary due to the massive amount of tissue necrosis occurring during mucormycosis, which may not be prevented by killing the organism. Surgical debridement of infected and necrotic tissue should be performed on an urgent basis.

### Adjunctive therapies

The role of hyperbaric oxygen (HBO) treatment of zygomycosis has recently been reviewed. It is hypothesized that hyperbaric oxygen might be useful for treating mucormycosis in conjunction with standard therapy because higher oxygen pressure improves the ability of neutrophils to kill the organism. Additionally, high oxygen pressure inhibits the germination of fungal spores and growth of mycelia in vitro. Whether hyperbaric oxygen actually improves the outcome of patients with mucormycosis remains to be established through appropriately controlled prospective clinical trials. In a series of 28 cases, a significant association was found between survival and treatment with HBO ($P = 0.009$) provided patients received an adequate course. Nearly all the patients treated had also received Amphotericin B. Survivors were more likely to be diabetic than have a malignancy and to have had the predisposing condition rectified [17].

## Conclusion

Lesions, such as small ulcerations of the palate, may be the first signs of a mucormycosis. Early and prompt planed treatment is crucial for improvement in the patient's prognosis. General treatment of a patient's basic disease may lead to a positive outcome and complete rehabilitation.

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