

Mucormycosis: A Challenge for Diagnosis and Treatment - 2 Case Reports and Review of Literature

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Abstract

To present two clinical rare case reports of mucormycosis, an opportunistic fungal infection of maxilla presenting as necrosis in palate.

The cases reported were two females with known immunodeficiencies. One patient was uncontrolled type 1 diabetic and the other was acute myeloid leukemic patient on chemotherapy. Both the patients showed necrosis of hard palate. After histopathologic and culture report confirmation with a diagnosis of mucormycosis, they underwent surgical resection of involved bone and amphotericin B therapy. There was complete cure of disease.

The oral physicians and surgeons play an important role in early detection of disease. Apt multimodal treatment strategy and prophylaxis for mucormycosis in all immune-deficient patients will help us to combat this dreaded disease. The antifungal prophylaxis for all chemotherapy patients should be reviewed so that prophylaxis for mucormycosis should also be included.

Key Words: Mucormycosis, Fungal infections, Amphotericin-B (Ampho-B)

Introduction

Mucormycosis is rare fulminant infective disease caused by fungi of order mucorales [1]. It is an opportunistic infection usually occurring in immuno-compromised patients such uncontrolled diabetes, hematological malignancies, renal failure, patients on chemotherapy, patients on long term steroids and AIDS [2]. Nevertheless, there are few reported cases of mucormycosis occurring in immune-competent patients. The genera associated with mucormycosis are Rhizopus, Absidia, and Mucor, of this Rhizopus being the most common cause for rhinocerebral Mucor. Once infested it invades the vascular system, thereby occluding the arterial blood flow causing rapid thrombosis and ischemia. This is followed by necrosis of hard and soft tissues, hence it invades the surrounding tissues rapidly.

In past few years there has been rapid increase in incidence of mucormycosis, especially in diabetic patients [3-6]. Here we present two cases of maxillary mucormycosis with different clinical course. One of the cases showed a rare combination of two different fungal strains infecting maxilla and lungs. The aim is to alert clinicians about the importance of early diagnosis and management of mucormycosis. As oral signs are among the first few clinical manifestations of cranio, rhino, orbital mucormycosis, oral physicians and surgeons play an important role in early detection and prompt treatment [7].

Case 1

A thirty three year old known uncontrolled type I diabetic female patient reported to the Department of Oral and Maxillofacial Surgery, with the complaint of pain and pus discharge from palate since 2 months. There was a positive history of nasal congestion and head ache since 4 months, which gradually lead to pain and mobility in upper anterior teeth and was followed by pus discharge, bone exposure in anterior teeth and exfoliation of all the upper incisors (*Figure*

1). Examination revealed mild tenderness in right maxillary sinus and septal perforation. Intra orally, upper incisors were missing and rest of the teeth in upper arch were mobile except for left upper I and II molars. There was minimal pus discharge from anterior teeth sockets. The right maxillary segment was mobile on palpation with necrosed bone of hard palate being exposed (*Figure 2*). A provisional diagnosis of maxillary osteomyelitis was made and investigated with CT of face, bone scan, blood glucose levels, glycosylated haemoglobin (Hb1Ac) level and fungal culture swab from pus discharge site, blood cultures and biopsy of necrosed alveolar portion of pre maxilla were done on the second day of admission. The Hb1Ac level was 9.4 which were considerably high. CT scan showed pan sinusitis involving even sphenoid sinus (*Figure 3a*) with extensive destruction of adjacent bones. SPECT scan (*Figure 3b*) and NM bone scan revealed increased uptake in right maxilla and ethmoid region indicating inflammatory process. Her blood glucose levels were unexceptionally high. Biopsy revealed invading non septate, haphazardly branched, thick,



Figure 1. Necrotic anterior alveolar bone with missing teeth.

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fungal hyphae, which are characteristic of *Mucor* colonies (Figures 4a & 4b). Multimodal therapy was from 5th day of admission. Injection lipid complex Ampho-B 35mg once daily as initiated from day one of admission and was gradually increased to 45mg under continuous check of electrolyte imbalance for 6 weeks. Blood glucose was controlled. After obtaining consent for surgical intervention and possibility of data usage for publishing in scientific journals, extensive surgical debridement with subtotal maxillectomy and ethmoidectomy was done on 9th day of admission. Patient showed good recovery but had oronasal communication on right side (Figures 5 & 7) which was, addressed with temporary obturator (Figure 6). In future zygomatic implant supported prosthesis is planned for complete rehabilitation.

Case 2

A 39 year old, known acute myeloid leukemic, Afghani



Figure 5. Post-operative oronasal communication of palate.



Figure 2. Necrotic bone in hard palate.



Figure 6. Post-operative prosthetic rehabilitation.

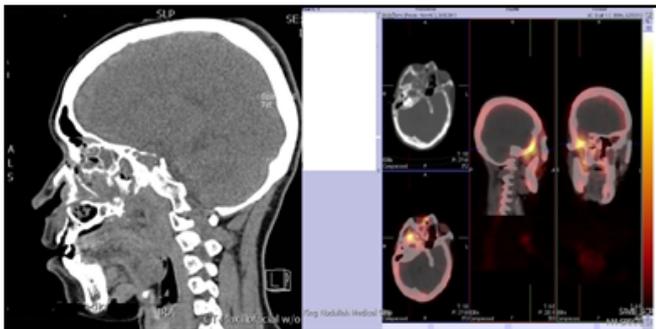


Figure 3. a) Pre-operative CT showing pan sinusitis including sphenoidal sinusitis and bony destruction. b) SPECT scan of Case 1 showing hyper intake in right maxilla.

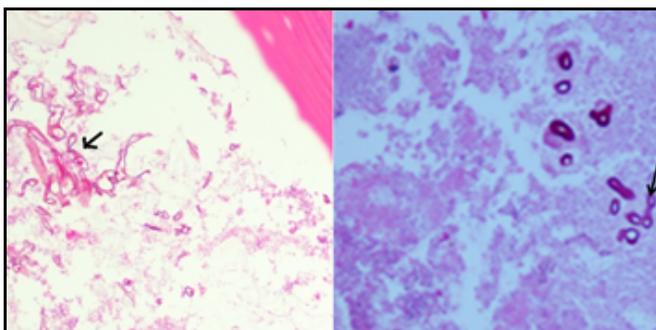


Figure 4. a) Bony erosion and fungal hyphae, (black arrows denoting fungal hyphae), H&E stain, magnification: 200X, b) Non septate hyphae (Black arrow denoting fungal hyphae, PAS stain, magnification: 400X



Figure 7. Post-operative CT showing maxillary defect and resolution of infection in Case 1.

female admitted to haematology department for treatment of leukemia, complained of pain and swelling in right upper back teeth region and fever since 1 week after admission. The pain was continuous and of throbbing type. The chest

x-ray which was taken as routine per admission protocol on the day of admission had revealed circular radio-opaque lesion in right lung, further investigated with CT lungs which showed circular hyper intensity indicating fungal ball in right lung. CT PNS showed features of fungal sinusitis. After 9 days of admission repeat CT maxillofacial showed mucosal thickening in right and left maxillary sinuses. She was on prophylactic antibiotic and antifungal since the time of admission. Upon examination carried out on the seventh day of admission, there was mild diffuse swelling in right mid face, soft to firm in consistency and non-tender on palpation. Intraoral examination revealed inflamed attached gingiva and palatal mucosa in relation to right posterior teeth. An ulcer in palatal gingival in relation to right maxillary first molar was noticed, with sloping edges and the surface was covered with scrapeable greyish white patch. Surrounding mucosa appeared inflamed. Right first molar to first pre molar teeth were tender on vertical percussion, second premolar was grade II mobile with deep proximal caries. A provisional diagnosis of acute apical periodontitis was made but extraction of second premolar tooth had to be delayed because of her acute Neutropenic and thrombocytopenic condition. The antibiotics did not help to reduce the clinical symptoms, hence a scrape biopsy and culture swab was done from the ulcer on day eleventh of admission to rule out fungal involvement. CT chest was reported with high suspicion of fungal ball in right lung. The scrape biopsy and culture swab confirmed of having invading mucormycosis. After obtaining consent for surgical intervention and possibility of data usage for publishing in scientific journals, early and aggressive treatment with injection lipid complex at a dose of 100 mg once daily was started on the thirteenth day of admission and continued for 6 weeks. Surgical debridement and extraction of involved teeth was planned under GA, on fifteenth day of admission, along with right lung lobectomy from cardiothoracic surgeons at the same time. The histopathologic report confirmed the diagnosis of having mucormycosis of right maxilla. But the histopathology of lung showed Aspergillosis. Patient dramatically improved following surgery with very minimal morbidity.

Discussion

The mucorales fungi is found in mouldy bread, soil, decaying matter, & oral, nasal, & pharyngeal mucosa of asymptomatic normal patients [7-9]. The route of infection could be via inhalation, ingestion or traumatic inoculation [9]. The disease can manifest in five major clinical forms as rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated [7]. The most common form of disease is rhino-cerebral which is characterized by progressive fungal invasion of hard palate, paranasal sinuses, orbits and brain [1]. As per the new taxonomy, the class Zygomycota is replaced by Glomeromycota. Mucormycotina and Entemophthermycotina are the two subphyla [3]. 66 percent of rhino-cerebro-orbital mucormycosis was seen in diabetic patients, whereas cutaneous manifestation is common in immuno competent patients [3].

Disseminated form is common in hematologic malignancy patients [3]. Increased occurrence in diabetic ketoacidotic patients as in our first case could be attributed to ferrophilic

nature of Mucor. Acidosis reduces the iron binding capacity of transferrin leading to increased levels of iron in blood, which intern is utilized by Mucor for proliferation [11]. Aggressive spread of this infection is due to its Angio-invasive nature causing thrombosis, ischemia and necrosis of tissues [12]. Usually early diagnosis of this infection is not possible and difficult because of following reasons:

1. Late presentation of associated symptoms like pain, fever etc., as fungal infections does not generate exuberant inflammation.

2. Extensive tissue and bone necrosis will lead us to think first in terms of osteomyelitis unless proved by culture or failure of antibiotic therapy.

3. Cultures of fungus take approximately three weeks and the confirmatory diagnosis is delayed. Hence histopathology of scrape biopsy or tissue biopsy can be promising in early detection of fungi.

The mortality rate due to mucormycosis has dropped dramatically from 84 % in 1950s to 40 percent in 1990s. This change is because of early diagnosis and multimodal treatment therapy, which include reduction of immunocompromised status, reversal of underlying risk factors, prompt and aggressive antifungal therapy, and most important surgical debridement [3,13]. Surgical debridement reduces mortality rates from 55 % to 27%, whereas medical treatment alone has a mortality rate varying from 39% to 70% [14]. Angio-invasion, thrombosis and tissue necrosis of Mucor leads to poor penetration of antifungal agents at the site of infection and compromises the efficacy of the same [7].

Aggressive and radical surgical resection causes significant morbidity in patients who survive, because treatment usually requires extensive and often disfiguring, facial surgery [9]. In the first case, extensive involvement of facial bones lead to disfiguring surgery, but a good prosthetic rehabilitation resulted in reduced morbidity. Morbidity can be reduced by following conservative-aggressive approach with intraoperative use of frozen section [15].

Aggressive medical treatment with conventional antifungals and non-conventional therapeutics are corner stone for successful treatment [3]. Polyenes like amphotericin-deoxycholates and lipid complex are primary therapeutic agents for mucormycosis. The dosage varies from 0.5-1.0 mg/kg body weight once daily for not less than 4 weeks. There should be close monitoring of serum electrolytes, as polyenes are known to cause potassium imbalance [3,11,13]. Data from comparison of lipid complex Ampho-B and deoxycholate Ampho-B showed improved survival rates less side effects with lipid complex Ampho-B [3]. Data on use of Triazoles as first line of treatment are sparse. Two studies with use of Triazoles have shown 60% and 67% success rates [16,17]. These results cannot be relied on as the number of patients is small. Trail studies have shown posaconazoles are not effective against rhizopus Oryzae strain of Mucormycotina in neutropenic, diabetic mice, thus Triazoles are not recommended as primary therapy for mucormycosis [18]. These can be used as supportive treatment when patients are intolerant to amphotericin or in whom the use is limited by nephrotoxicity.

Non-conventional therapeutic agents like anti diabetics, iron chelating agents, statins, granulocyte transfusions,

cytokines, and hyperbaric oxygen have increased the survival rates to 94 % [3].

Prevention always remains a gold standard. Maintenance of immune balance especially in immunocompromised patients plays an important role in preventing this fulminant infection [3]. Use of suitable antifungal regimen in all severely immunocompromised patients may help us in prevention of disease. As shown by Trifilo et al. there is increase in number of Zygomycosis in patients with regular antifungal prophylaxis which could be due to the fact that most of the prophylactic antifungals do not cover mucormycosis [19]. The use of Posoconazole as prophylaxis in hematologic malignancy patients is suggested by Cornely et al. and Ullmann et al. in their two randomised trials of Posoconazole as antifungal prophylaxis in graft versus host disease patients and patients on chemotherapy related neutropenia, no cases of mucormycosis were seen [20]. This prophylaxis is questionable as Posoconazole has little or no effect on rhizopus *Oryzae* strain and use of non-selective Posoconazole

could increase risk of fungi becoming resistant, hence routine use remains controversial [18].

Summary

Mucormycosis is subtle but aggressive fungal infection. It is an essential task for clinicians to pick these infections at early stage. In this regard, oral physicians and surgeons can play an important role as the oral manifestations are first to appear especially in severely immunocompromised patients. Histopathological studies are of great help in determining the diagnosis. Multimodal therapy including medical and surgical efforts will help in reducing morbidity and mortality of patients. One should seriously think of revising the anti-fungal prophylactic regimens for immunocompromised patients.

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Conflict of Interest

We declare that we have no financial or personal relationship(s), which may have inappropriately influenced me in writing this paper.

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