Maxillary Necrosis: A Sequelae of Fungal Osteomyelitis

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ABSTRACT
Osteomyelitis is designated to a variety of bone diseases having inflammation as a common denominator. Persistent infection progresses to inflammation of marrow space, haversian system and periostium of affected region. Thrombosis of endothelial vessels cause necrosis and sequestrum formation. Both pyogenic and nonpyogenic infections of jaw lead to this condition. Immunosuppressed patients are more prone to mycelial infections, whereas their occurrence in immunocompetent individuals are highly unusual.

Keywords: Mucor, Rhizopus, Ulcer, Necrosis, Diabetes Mellitus, Antifungal therapy.

INTRODUCTION
Mucormycosis is caused by fungal species belonging to mucorales order. Predisposing medical conditions include diabetes, long-term steroids, pneumonia, AIDS, leukemia, lymphoma, and organ transplant. The most common factor is diabetes mellitus, affecting 40% of cases. The mode of spread is through inhalation of sporangiospore from the environment, which travels via blood vessels and disseminated to various organs. Mucor is recognized as the most rapidly progressive and lethal form in immunosuppressed patients, while it is exceedingly rare and less fulminant in immunocompetent patients.

CASE 1
A 35-year-old female patient reported with a complaint of sudden exfoliation of maxillary teeth over a period of two weeks. Medical history revealed that the patient is apparently healthy and not under any medication. Intraoral examination demonstrated a single well-defined, 2.5 × 1 cm ulcer on the mid palatine region with well-defined borders. The base was covered by yellow, pseudomembranous slough. The ulcer was nottender and on removing the slough with gauze, palatal bone was exposed (Fig. 1). Maxillary anterior teeth and premolars were missing with necrosed bony sockets. Upper labial mucosa was denuded exposing the necrosed anterior alveolar bone (Fig. 2). We considered lesions which may cause progressive ulceration, leading to midfacial destruction like Wegener’s granulomatosis, localized form of angiocentric lymphoma and deep seated fungal infection secondary to HIV as differential diagnosis.

Wegener’s granulomatosis is a multisystem disease of unknown etiology, and occasionally oral lesion may be the first indicator. Palatal ulceration and spontaneous exfoliation of teeth are reported. However, special stains for organisms will be negative, and oral epithelium demonstrates pseudoepithelial hyperplasia and vasculitis of small arteries on histopathological examination.

Angiocentric lymphoma is a malignant proliferative process often with angiocentric and angiodestructive features. Aerodigestive tract is often involved and manifest mucosal ulcers (nasal, oral, pharyngeal laryngeal and tracheal) progressing to destruction of soft tissue and bone.

Deep fungal infections in HIV are clinically nonspecific ulcers and should be confirmed with histopathological investigations.

At the time of admission the patient’s vital signs were unremarkable and her hematological analysis was within normal limits. An incisional biopsy was carried out and the tissue was sent for histopathological examination.

INVESTIGATIONS
Patient’s blood glucose estimation revealed that FBS was 79 mg/dl and PPBS was 132 mg/dl. Patient was seronegative for HIV. Patients CD4 + level are 560 cells per cubic mm. Plain CT scan of paranasal sinuses showed nasal septal deviation, bilateral maxillary polyp, bilateral frontal, ethmoidal and maxillary sinuses. Multiple areas of perforation are evident in the anterior aspect of hard palate (Fig. 3).
A section of soft tissue specimen demonstrated granulation tissue with chronic inflammatory cells. On using special PAS staining to isolate fungus, the fungus has not taken PAS stain but taken counter hematoxylin stain and demonstrated broad aseptate branching hyphae (Fig. 4).

A section of bone tissue specimen on Grocot-Gomari methénamine silver (GMS) demonstrated necrotic bone islands surrounded by chronic inflammatory cells with few aseptate fungal hyphae branching at approximately 90 degree (Fig. 5). Features suggestive for mucormycosis.

**DISCUSSION**

Mucors are ubiquitous in the environment and can grow on bread, fruit, leaves and soil. It may manifest in five clinical forms, such as rhinocerebral, gastrointestinal, pulmonary, cutaneous, and disseminated mucormycosis. Nose is the most frequent portal of entry for rhinomaxillary form, which is a subtype of rhinocerebral form. Following acquisition from the environment, these fungi have a tendency to erode and invade small blood vessels that leads to thrombosis, ischemia and tissue necrosis. Infection extending from the sinuses into the mouth and oral lesions are generally ulcerative and limited to the hard palate. From the palate and nasal mucosa, it starts spreading via the angular, lacrimal and ethmoidal vessels. Direct extension from the sinuses into the retro-orbital region is also possible. Functional impairment of cranial nerves II, III, IV, and VI are characteristic sequelae. Hematogenous spread to the cavernous sinus and cavernous sinus thrombosis also has been reported. Initial symptoms may manifest as sinusitis, peri orbital cellulitis, facial pain or numbness followed by blurred vision and soft tissue swelling.

Mucor is often recognized as a triad of symptoms, such as uncontrolled diabetes mellitus, periorbital infection and meningoencephalitis. Normal human serum usually can inhibit the growth of rhizopus, while diabetes mellitus alters the immunologic capability to resist rhizopus by reducing the phagocytic ability of granulocytes during hyperglycemia and acidosis. In addition, rhizopus species flourish well in glucose rich environment and in elevated serum iron conditions. Patients with renal disease and on desferoxamine (which increase serum iron level) are also prone to similar condition and at risk of mucor.

**MANAGEMENT**

Amphotericin-B at 1 mg/kg in 5% dextrose was infused over 6 to 8 hours/day and continued for 2 months. Renal and liver function tests were done periodically. Subtotal maxillectomy was carried out at the end of first month of therapy and palatal obturator was given, which resulted in remission of the lesion and the subsequent postoperative period was uneventful.
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Once the fungus starts establishing its hyphae, as having rich affinity for blood vessels, penetrates and starts growing on the walls of blood vessels causing thrombosis and tissue necrosis.\textsuperscript{9} Thrombosis of internal maxillary artery or descending palatine artery results in necrosis of maxilla.\textsuperscript{10} Cranial involvement leads to meningoencephalitis, resulting in patient’s death, and hence the time between diagnosis and initiation of treatment is critical for prognosis.

The unique feature in our patient is, no evidence of any predisposing factors, rapid exfoliation of multiple teeth and bilateral necrosis of the maxillary alveolus. Patient continued her routine life without making any compromises.

Radiographic findings of rhinocerebral mucormycosis include nodular thickening of sinus mucosa, sinus opacification without fluid levels, and spotty destruction of paranasal sinus wall, resembling sinusitis\textsuperscript{11} and at later stage may mimic sinus malignancy.\textsuperscript{12} Definitive diagnosis of mucormycosis is possible by tissue biopsy. Histopathologically mucormycosis is characterized by extensive tissue necrosis and numerous large nonseptate hyphae with budding and nondichotomous branching, approximately at 90° angle.\textsuperscript{13} Fungal angioinvasion and neutrophilic infiltrate in the necrotic tissue are also seen. The Grocott-Gomori methenamine silver (GMS) stain is the most appropriate stain for histopathological examination. Also hematoxylin and eosin, Periodic acid Schiff (PAS) or calcofluor stains may be used.\textsuperscript{14}

Ideal culturing technique requires the mincing of infected tissue with a sterile scalpel and using sabouraud dextrose, brain heat infusion or potato dextrose agar incubation at 25 to 30° C. Successful outcome depends on resolution of predisposing problem, if present followed by systemic antifungal therapy and débridement of necrotic tissue.

The gold standard antifungal agent is Amphotericin-B.\textsuperscript{15} This drug alters the membrane permeability of fungi by binding to ergosterol and acts as fungistatic agent. The highly refractory nature of rhizopus requires 1.0 to 1.5 mg/kg/day dosage continued for 8 to 10 weeks. Variability in sensitivity among isolates, spores and hyphae forms, and poor immunocompetence may complicate the drug efficacy. Long-term use may lead to nephrotoxicity, acidosis, anemia, hypocalcemia and bone marrow suppression. Pretreatment with 0.6% hydrocortisone or antihistamines are preferred to reduce the adverse effects. Periodical evaluation of liver and renal functions are mandatory. Guidelines for RFT are BUN (normal value 8-18 mg/100 ml) and Creatinine (normal value 0.6-1.2 mg/100 ml) which may arise to 50 and 3 mg/100 ml, respectively before the dose needs to be reduced.\textsuperscript{16}

To summarize the pathogenesis:

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<tr>
<th>Susceptible Hosts</th>
<th>Normal Hosts</th>
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<tr>
<td>Defects in phagocytic defence mechanism</td>
<td>Phagocytes, endothelial cells and binding proteins</td>
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<tr>
<td>Endothelial adherence of mucor</td>
<td>Sequestration of serum iron</td>
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<td>Fungal angioinvasion</td>
<td>Regulation of vascular tone and permeability</td>
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<td>Vessel thrombosis</td>
<td>Prevention of tissue infection and endothelial invasion</td>
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<td>Tissue necrosis</td>
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<td>Dissemination of fungal infection</td>
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Fig. 4: H and E stained photomicrograph reveals broad aseptate fungal hyphae

Fig. 5: Photomicrograph of GMS stained bone specimen showing fungal hyphae

Once the fungus starts establishing its hyphae, as having rich affinity for blood vessels, penetrates and starts growing on the walls of blood vessels causing thrombosis and tissue necrosis.\textsuperscript{9} Thrombosis of internal maxillary artery or descending palatine
Liposomal formulation of Amphotericin-B (LAMB)\textsuperscript{17} has developed to reduce renal toxicity specifically and the recommended dosage is 4 mg/kg/day.

Pasaconazole is a promising alternative\textsuperscript{18} or adjunctive drug to LAMB. This combination gives favored prognosis over monotherapy and can be used successfully without surgical intervention.

Ketoconazole, Rifampin or tetracycline can be considered but not as single primary choice.

In drug therapy, clearing the fungi in necrotic tissue is challenging, and hence surgical intervention like maxillectomy or anterectomy is unavoidable.

Use of adjunctive therapy, such as hyperbaric oxygen may reduce tissue necrosis and also augment the effect of Amphotericin-B. The mutagenic effects associated with CNS and pulmonary toxicity restricts its use unless it is mandatory.

The use of Amphotericin-B and subtotal maxillectomy in our patient provided desired results and frequent follow-up is given for the past eight months of postoperative period, though recurrence is not common in mucormycosis.

**CONCLUSION**

Mucormycosis causing maxillary necrosis in an immunocompetent individual, as reported in our case is extremely unusual. This emphasized the need to include mucor infection as differential diagnosis in otherwise healthy patients. In clinically suspected patients, the extent of lesion should be studied with the aid of radiographs, followed by histopathological examination to confirm the diagnosis. Any reversible predisposing factors, if present should be dealt initially to reduce the level of immunosuppression. The immunity against fungi is not long lasting, unlike in bacteria and viruses. Also, the antigenic potential being variable and nonspecific makes the host prone for reinfection by the same fungus. Antifungal therapy and surgical débridement are essence in the management. The survival rate ranges between 50 to 85%. The variability in outcome is due to various forms of diseases, delay in the initiation of treatment and abysmal rate of success of monotherapy.

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**REFERENCES**