ABSTRACT

In a dental hospital, patients reporting with exposed bone in the palate/maxilla with or without pus discharging sinuses are generally clinically diagnosed as osteomyelitis which can occur as a complication of odontogenic bacterial infections, traumatic injuries, herpes zoster infection, aspergillosis, mucormycosis or iatrogenic infections. We present a series of four cases, all of which were initially clinically diagnosed as osteomyelitis and later confirmed to be mucormycosis following histopathological examination. Although rare, the common form of this opportunistic fungal infection is seen in the rhinomaxillary region and in people with an underlying systemic disease like diabetes mellitus (DM). This case series of rhinomaxillary mucormycosis is being reported to increase awareness among dental surgeons to regard the occurrence of osteomyelitis in the maxilla occurring in an immunocompromised patient especially with poorly controlled DM, with suspicion of an aggressive, fulminant, fatal fungal infection so as to ensure an early diagnosis and prompt treatment thereby reducing the morbidity and mortality associated with this disease.

Keywords: Rhinomaxillary mucormycosis, Uncontrolled diabetes mellitus, Maxillary osteomyelitis, Immunocompromised status.


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INTRODUCTION

Mucormycosis is a rare opportunistic fungal infection which affects less than two people in a million.1 However, it is a life-threatening infection and the fatality rate can be as high as 50 to 100%.2 This infection is usually seen in patients with an immunocompromised status and there are different clinical forms of which the rhinomaxillary or rhinocerebral form is the most common type.3 There are no pathognomonic clinical or radiologic features of this disease and the diagnosis is based on histopathology. Since mucormycosis is a rare condition, it may pose a diagnostic challenge for dental surgeons who may not be familiar with its clinical presentations even though they may occasionally encounter such cases reporting with maxillary osteomyelitis. As immunocompromised or diseased individuals are more likely to suffer from this disease, early diagnosis aided by a careful history, meticulous clinical examination, hematologic, biochemical and radiologic investigations lead to prompt and aggressive surgical management, with the institution of specific antifungal therapy to ensure a good prognosis, thereby reducing the fatal complications associated with this disease.

CASE REPORTS

Case 1

A 63 years old male patient reported to the dental hospital with a complaint of fluid discharge from the right side of nose, change in voice and severe halitosis for the past 3 months. History revealed that 9 months back he had developed a swelling on the right side of the palate for which incision and drainage was done. Six months later he gradually noticed a change in voice and on drinking fluids, discharge of the same from the right nostril. He also had foul odor in his mouth with mild pain in right side of the palate. There was watery discharge from his right eye with loss of visual acuity.

On clinical examination, there was epiphora from the right eye, mild swelling in the region of body of maxilla which was tender on palpation.

Intraorally, an area of necrosis of the right palatal mucosa, with exposure of underlying bone with a perforation at the junction of hard and soft palate was seen. The surface of the lesion was rough, covered by granulation tissue and surrounded by erythema, firm in consistency and tender on palpation (Fig. 1).
Since, the lesion started 3 months back with necrosis and perforation of the palate associated with areas of inflammation and pain, a provisional diagnosis of osteomyelitis of the palate was made.

Routine hematologic and biochemical investigations revealed hyperglycemic state and anemia.

Occlusal radiograph showed rarefaction on the right side of maxilla. Posteroanterior view of the skull revealed haziness in the right maxillary sinus. Computed tomographic (CT) scan of the paranasal sinuses (PNS) was done. Coronal view revealed a heterodense soft tissue mass in the right maxillary antrum perforating and infiltrating into the nasal cavity and erosion of the roof of the antrum (Fig. 2). The left maxillary antrum also is partially filled with fluid. Axial view showed a hyperdense mass filling the right maxillary antrum by a heterodense mass with perforation of the medial wall (Fig. 3).

Histopathologic examination revealed areas of necrosis along with fungal hyphae branching at 90° angle. There was the presence of moderate chronic inflammatory cell infiltrate, areas of hemorrhage, mild vascularity and evidence of overlying parakeratinized stratified squamous cell epithelium of variable thickness. Histopathologic features were suggestive of maxillary mucormycosis (Fig. 4).

Correlating clinical, radiological and histopathological findings, a final diagnosis of osteomyelitis with mucormycosis was made.

Patient underwent surgical debridement of the necrotic tissues with glycemic control and was administered liposomal amphotericin B 1 mg/kg body weight as an infusion in 100 ml of 5% dextrose over 1 to 2 hours once daily for a period of 2 weeks continuously monitoring the renal function. The patient was then given a maxillofacial prosthesis following uneventful healing.

Case 2
A 55 years old female patient reported to the dental hospital with the complaint of swelling on the right side of the face for the past 7 months.

History revealed that the patient noticed mild swelling on the right side of the face which had gradually increased in size, did not subside on taking medications and was asymptomatic. She also had nasal stuffiness, mild dyspnea and fatigue.

On clinical examination, diffuse swelling of the face was seen, more pronounced on the right side obliterating the infraorbital rim. Bilaterally the nasolabial fold was obliterated with diffuse swelling in the malar region and the upper lip (Fig. 5). The facial swelling was nontender and firm in consistency. A single ulcer was observed in the midline of the hard palate, measuring 8 × 3 mm in size, covered with necrotic slough with central area of exposed underlying bone, nontender and the base appeared indurated on palpation (Fig. 6).
Correlating with the clinical, radiologic and histopathologic findings a final diagnosis of maxillary mucormycosis was made.

The patient could not opt for treatment due to financial constraints.

**Case 3**

A 38 years old female patient reported to the dental hospital with pain and swelling on the left side of face with pus discharge for the past 2 months.

History revealed that she had pain in the left side of the palate 4 months back following which she had undergone for extraction of 26, even after the extraction the pain was persistent, and there was difficulty in chewing on the left side. Two months after the extraction she developed a swelling in the left side of face in the zygomatic region which was gradually increasing in size and was accompanied by pain.

Since the swelling was slow growing, nontender with a necrotic palatal ulcer a provisional diagnosis of chronic maxillary osteomyelitis was made.

Hematologic and biochemical investigations revealed a hyperglycemic state.

Water’s view of the skull revealed haziness in the maxillary antra bilaterally.

Contrast enhanced CT scan of the PNS revealed nonenhancing soft tissue density in sphenoidal, bilateral ethmoidal and frontal sinuses (Fig. 7). Bilaterally concentric soft tissue densities were seen in the maxillary antra with obliteration of osteomeatal openings (Fig. 8). There was no evidence of bone erosion or intracranial extension of the lesion (Fig. 9).

Histopathologic investigation revealed nonseptate hyphae branched at 90° with foci of organism and areas of necrosis formation. PAS staining also showed nonseptate hyphae.
On clinical examination, a diffuse swelling was seen in the left zygomatic region, lifting the lower eyelid and the skin over the swelling was erythematous with an extraoral pus discharging sinus (Fig. 10). On palpation, the swelling was warm to touch and the bone in the zygomatic region is slightly thickened, irregular with severe tenderness. Intraorally, extraction socket had partially healed, slightly erythematous with mild obliteration of the buccal sulcus. The clinical findings were suggestive of chronic suppurative osteomyelitis.

Hematologic and biochemical investigations revealed hyperglycemia with high serum urea and creatinine levels.

Posteroanterior view of skull showed opacity in the left maxillary antrum and bony destruction, with obliteration of trabecular pattern in the maxilla near the zygomatico-maxillary suture and destruction of part of the zygoma.

CT scan, coronal section revealed bony expansion of left lateral orbital wall, zygomatic arch, anterior wall of left maxillary sinus, with osteolysis resulting pieces of bone associated with periosteal new bone formation with soft tissue swelling. Laterally there was destruction of infraorbital margin on the left side (Fig. 11). The axial section also showed osteolysis and thickening of the anterior wall of the left maxillary antrum and the zygoma (Fig. 12). Histopathologic examination revealed subcutaneous tract lined by granulation tissue with dense chronic inflammation and areas of necrosis. Bony islands were surrounded by chronic inflammation along with areas of necrosis. The necrotic tissue showed fungal hyphae with branching (Fig. 13).

Local surgical debridement was done and the serum glucose levels were controlled. The patient was given fluconazole 150 mg orally for a month. Amphotericin B was not used due to nephrotoxicity. The lesion healed and there was no recurrence.

Case 4

A 56 years old male patient reported to the dental hospital with the complaint of swelling and ulceration in the right side of the anterior maxillary region.

History revealed that the patient underwent extraction of a mobile maxillary molar tooth 3 months back. Subsequently, the socket did not heal and gradually there was swelling around the socket with mild intermittent pain. He was suffering from type 2 diabetes mellitus (DM) for the past 2 years with poor glycemic control.

On intraoral examination a diffuse swelling was seen in the right anterior maxilla, measuring 3 × 2 cm in size, with surface lobulation, ulceration and exposure of bone (Fig. 14).
The swelling was firm in consistency, tender and there was purulent discharge on palpation.

The chronicity of the lesion, exposure of the necrotic bone with pus discharge was suggestive of chronic suppurative osteomyelitis.

Periapical, panoramic and skull radiographs revealed a mixed radiolucent-radiopaque lesion in 12 to 14 regions and haziness in the right maxillary antrum. Hematologic and biochemical examination revealed a raised ESR of 68 and 262 mg/dl fasting blood sugar.

An incisional biopsy was taken from the swelling and histopathologic examination revealed large amount of necrotic tissue with cellular degeneration and debris. Fungal hyphae were seen with neutrophil infiltration and generalized chronic inflammatory cell infiltrate within connective tissue. Hyphae were aseptate, branched and resembled mucormycosis (Fig. 15).

The patient did not turn up for further diagnostic evaluation or treatment.

**DISCUSSION**

In 1885, mucormycosis was first reported as a human disease by Paultau. Mucormycosis is one of the most sudden, severe and fatal fungal infection in humans, with a high mortality rate. It is most often caused by the *Rhizopus*, *Rhizomucor* and *Cunninghamella* genera of the family *Mucoraceae*. These fungi have broad, aseptate, hyphae of uneven diameters with long sporangiophores. They are saprophytic, ferrophillic and ubiquitous in nature.

Rhinomaxillary (rhinocerebral), pulmonary, gastrointestinal, central nervous system, cutaneous and disseminated mucormycosis are the six clinical subtypes of mucormycosis.

Mucormycosis is a disease of the diseased and is not commonly seen in healthy people. However, immuno-competent individuals as a result of trauma or surgery might get infected by mucormycosis. The rhinomaxillary form is the most common form of infection, predominantly occurring in patients with uncontrolled DM with ketoacidosis as seen in all the four cases presented here.
The low pH, hyperglycemic state and iron rich environment in diabetics’ favors fungal growth. Also in diabetic patients, mucormycosis is caused by *Rhizopus arrhizus* species, due to their ability to produce the enzyme ketoreductase, which allows them to utilize the patient’s ketone bodies for their nutrition. Immunocompromised patients with organ transplants, hematologic malignancies like leukemias and lymphomas, patients having severe burns, patients on chemotherapy for cancer, long-term glucocorticoid therapy and end stage renal disease also suffer from this infection. Surprisingly HIV/AIDS patients, though immunosuppressed do not commonly get infected with mucormycosis.

Hemodialysis patients who are treated with deferoxamine to chelate iron and aluminum have been associated with an explosive form of mucormycosis. It seems iron is an important growth factor for mucorales. The fungus cannot utilize iron from the host as it is bound to transferrin. Hence, they secrete their own iron-binding compounds known as siderophores. Deferoxamine is obtained from *Streptomyces pilosus* and is a naturally occurring hydroxamate siderophore. Therefore, deferoxamine provides the iron to the fungus to grow and spread. So it is essential to monitor patients under deferoxamine therapy for warning signs of mucormycosis.

RM infection is presumed to occur by asexual spores. These minute spores are present in the atmosphere and are either inhaled or ingested by humans. Normally in immunocompetent individuals such spores coming into contact with the nasal or oral mucosa are phagocytized by immunocompetent individuals such as polymorphs and macrophages, however in immunocompromised hosts, the spores germinate and grow into hyphae. In poorly controlled diabetics the glutathione pathway is impaired; hence the macrophages are rendered hyphae. In poorly controlled diabetics the glutathione pathway is impaired; hence the macrophages are rendered ineffective. Therefore, the infection progresses with the angioinvasive hyphae entering the vascular channels invading the arteries, growing within the vessel walls, occluding the lumen, causing stasis which gradually results in thrombosis, ischemia, and infarction with dry gangrene of the affected tissues. Hematogenous spread occurs to other organs like the lungs and brain or there may be a disseminated sepsis. The infection is noncontagious and does not spread from person to person. Besides being angioinvasive, their spores are resistant to temperature changes. The organisms are able to thrive at or above the human body temperature, producing destructive enzymes, thereby active ketone reductase system and hydroxamate siderophores; all these factors contribute toward the extreme virulence of this fungus.

The clinical presentation of RM is variable and may consist of low-grade fever, maxillary sinusitis, nasal stuffiness, epistaxis, palatal ulcer or perforation of the palate, facial swelling, decreased vision, epiphora and ophthalmoparesis. Sometimes it may be associated with triad of symptoms of poorly controlled DM, antral sinusitis and facial gangrene. Black necrotic eschar on the palate or nasal cornet may be typically seen due to gangrene of the infected tissues. In the present case series, three patients had palatal ulcers among which two had exposed necrotic bone, one had diffuse facial swelling and one with osteomyelitis involving the zygoma which is very rarely reported in the English literature (Table 1).

Often there is a history of extraction of a maxillary tooth with pus discharge from an unhealed extraction socket and exposure of necrotic bone or a solitary palatal ulcer with exposed maxillary bone as the sole oral manifestation. Usually the antrum is infected first and then through the sphenopalatine and greater palatine arteries, the palate is affected. Since, solitary palatal ulcer with exposed necrotic bone can occur in different diseases, a differential diagnosis may be considered (Flow Chart 1). In long standing diabetics with poor glycemic control, there is atherosclerosis and microangiopathy of blood vessels which further compromises the vascularity and predisposes the patient to osteomyelitis.

The infection may spread from the antrum to the orbit through the nasolacrimal duct, blood vessels or the lamina papyracea. Even perineural invasion has been reported in some cases. Further extension of the infection from the orbit to the brain occurs via orbital vessels or the cribiform plate. Through the apex of the orbit, invasion of the lateral

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<td>Uncontrolled diabetes mellitus with anemia</td>
<td>Palatal ulcer, necrosis and exposed bone</td>
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<td>2</td>
<td>55 years female</td>
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<td>4</td>
<td>56 years male</td>
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wall of the cavernous sinus can occur, leading to cavernous sinus thrombosis, ischemia of the internal carotid artery, cerebral ischemia and subsequently death (Flow Chart 2).20-22

Plain film radiography is nonspecific and showing haziness in the antrum unilaterally. With the help of CT scan, multiplanar imaging of the antrum and orbit, the extent of the infection and the amount of bone destruction can be observed.25 CT findings are usually nonspecific showing unilateral or bilateral mucosal edema, fluid in the sinus and destruction of bony margins. As the infection spreads destruction of antral walls with soft tissue mass extending into the orbits is observed.26 Though the extent of bone destruction and invasion is seen in CT images, the features are similar to that of carcinoma.

Magnetic resonance imaging (MRI) is used to diagnose the involvement of the cavernous sinus and vascular complications like ischemia can also be detected.27,28 The infected necrotic tissue is depicted as lack of enhancement seen on MRI, with a characteristic ‘black turbinate sign’, which may help in early diagnosis of this disease.29 Given the fulminating and invasive nature of the disease CT or MR images may be taken at frequent intervals disease to monitor the therapeutic response.

Mucormycosis is aptly diagnosed histologically when broad, irregularly shaped, nonseptate hyphae with right angle branching are seen invading the tissue with hematoxylin and eosin (H&E); but they are better visualized with PAS or silver stains.30,31 They are found mostly in areas
adjacent to clinical necrosis, especially necrotic vessel wall. Culture on Sabouraud’s agar can also be helpful in diagnosis but positive results alone are not sufficient to make the diagnosis, as mucorales can be grown from specimens taken from uninfected mucosal and skin surfaces.32

RM is a life-threatening infection and warrants emergency treatment. Management is based on prompt diagnosis and institution of early aggressive surgical and medical therapy. Treatment of the underlying systemic disease, especially control of the glycemic state or modification/cessation of immunosuppressive drugs help in decreasing the morbidity and mortality associated with mucormycosis.33 Amphotericin B is the polyene antifungal drug commonly used, which binds to ergosterol in the fungal cell membrane altering its permeability. It is a very toxic drug hence the patient has to be monitored for renal damage and anaphylaxis. Posaconazole is another antifungal drug, a triazole which is also very effective besides being safe for patients with renal disease. Since the involved blood vessels are ischemic, the antifungal drugs do not reach their target tissues hence extensive surgical debridement to remove necrotic tissue and establish sinus drainage is essential.34 Hyperbaric oxygen therapy has been used as an adjunct to aggressive surgical debridement, amphotericin B therapy, control of any underlying predisposing conditions by aiding neovascularization and subsequent healing.35 Granulocyte colony-stimulating factor may also be administered to improve host defences and also to enhance leukocyte count to promote immunity.36

To conclude, a poorly controlled diabetic or immune compromised patient having exposed necrotic bone in the maxilla/palate with or without pus discharge and possibly a history of tooth extraction should warn the oral physician of a supposed RM infection which if diagnosed early can minimize the complications. A prompt diagnosis ensures a better prognosis for the patient suffering from this otherwise fulminant, fatal fungal infection.

REFERENCES

Rhinomaxillary Mucormycosis Masquerading as Chronic Osteomyelitis: A Series of Four Rare Cases with Review of Literature


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