Review Article

# Maxillary Fungal Osteomyelitis: A Review of Literature and Report of a Rare Case

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## Abstract

Fungal osteomyelitis is a life-threatening and seldom seen opportunistic infection. It is commonly an affectation of the nose and paranasal sinuses within the orofacial region. It is an aggressive infection that needs to be addressed promptly to prevent fatal consequences. Here, we present a case of a 62-year-old female who presented with complaints of pain and pus discharge from the extraction socket of the left maxillary 23, 24, 25, 26 teeth. She had a history of uncontrolled diabetes mellitus. On further investigation, using diagnostic and Interventional aids, a final diagnosis of maxillary fungal osteomyelitis was made. The infective fungal agents were a mixture of *Mucorales* and *Aspergillus* species. A review of all literatures on the subject in the past 13 years using different search engines showed that craniofacial fungal infections with primary maxillary involvement are a rare phenomenon. The primary aim of reporting this case, therefore, is to highlight its rarity, presentation, management and most importantly the outcome of management.

**Keywords:** Aspergillosis, concomitant infection, fungal osteomyelitis, mucormycosis, opportunistic infection

## Introduction

Concomitant fungal infection of mucormycosis and aspergillosis is a rare, invasive, rapidly progressive, and life-threatening fungal disease of the maxillofacial region.[1] There is a paucity of incidence of such combination opportunistic infections within the maxillofacial region as a result of the rich vascularity of this specific anatomy. Fungal organisms such as *Mucorales* and *Aspergillus,* however, can evade this defense mechanism in view of their potential virulence.[2] This is more common among patients with a depressed immune system or with immunocompromised clinical states. Attributable risk factors for such infections are: uncontrolled diabetes mellitus; long-term steroid therapy; hematological conditions like leukemia and lymphomas; and renal failure and Acquired Immune Deficiency Syndrome (AIDS).[3] These fungi gain entry into the body through different portals such as the nose, breached skin, and tooth extraction sockets. Pulmonary affectation and rhino-orbito-cerebral involvement are the most common form of mucormycosis. However, other primary sites of infection include the skin, ears, gastrointestinal tract and there could be disseminated forms involving multiple sites.[1]

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According to published literatures, mortality rates of mucormycosis ranges from 10% to 100% depending on the site of infection and underlying predisposing factors.[2] Maxillary sinus mucormycosis have a poor prognosis and high mortality rate (46%).[4] Aspergillosis has a mortality rate of 30% with a poor prognosis in pediatric cases (with a mortality rate as high as 85%).[5] Early diagnosis and immediate intervention are essential for such patients. Treatment modality includes control of the underlying risk factors, antifungal therapy, surgical debridement, supportive therapy, and surgical or prosthetic rehabilitation (RECONSTRUCTION) is very important in view of the restoration of quality of life to the premorbid state.

We present a review and our experience of concomitant *Mucorales* and *Aspergillus* infection of the maxilla causing extensive necrosis in a female with uncontrolled diabetes who had a history of tooth extraction. Through this article, it is our

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effort to bring awareness among clinicians regarding such a rare but potentially fatal fungal infection.

## Materials and Methods

We did the literature search to analyze the site specificity and types of immunocompromised conditions that may be associated with a rare concomitant occurrence of mucormycosis and aspergillosis. A database search in PubMed, ScienceDirect, EBSCO, Medline, and Google Scholar was carried out using MeSH terms such as "mucormycosis," "concomitant infection," "aspergillosis," "fungal infection," and "orofacial." Only reports of concomitant infection of *Mucorales* and *Aspergillus* were included in the review. Reports with other fungal infection were excluded. All articles published in English were included in this analysis.

## Results

We reviewed 35 literatures on the subject (orofacial fungal infection) over the past 13 years (2005–2018). Using the inclusion and exclusion criteria, 14 relevant literatures were included. Of the total 14 literatures involving mixed fungal infections of both *Mucorales* and *Aspergillus* species, there were 12 case reports and 2 case series (2 + 2) making a total of 16 cases. Out of these, 15 cases had underlying debilitating disease or immunocompromised condition according to the following distribution; uncontrolled diabetes mellitus ($n$ = 6, 40%); leukemia ($n$ = 3, 20%); postrenal transplant infection ($n$ = 2, 13.3%). Other conditions were Castleman disease, lymphomas, and tetralogy of Fallot [Diagram 1]. The paranasal sinuses were the most common sites of involvement in this review ($n$ = 14, 87.5%). None of the cases showed primary involvement of maxilla [Table 1], but in our case, maxilla was primarily involved most likely through the extraction socket.

## Case Report

A 62-year-old female patient reported to the Dental Surgery Outpatient Department (OPD) of All India Institute of Medical Sciences Bhubaneswar, Odisha, India, with a chief complaint of pain, pus discharge, and diffuse swelling of the left midfacial region following the extraction of teeth from the left maxillary quadrant. The extraction was performed 2 months before this visit. She was a known case of type II diabetes mellitus, and the exodontia was performed by a general dental practitioner. Her past dental records revealed that she had chronic generalized periodontitis with high fasting blood sugar (FBS) and postprandial blood sugar (PPBS (i.e., 139 mg/dl and 193 mg/dl, respectively) at the time of exodontia. Few days

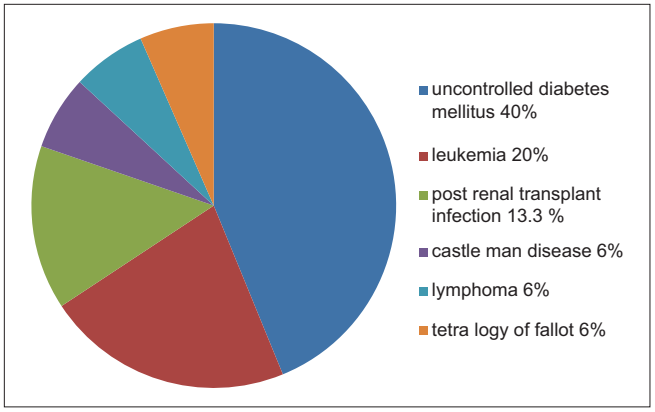


**Diagram 1:** Distribution of underlying debilitating diseases

**Table 1: Review of the last 13 years of concomitant mucormycosis and aspergillosis in orofacial region**

| Author | Years | Type of study | Site of lesion | Underlying disease |
|---|---|---|---|---|
| Maiorano *et al*.[6] | 2005 | Case report | Palatal mucosa and paranasal sinuses | Castle man disease |
| Lador *et al*.[7] | 2006 | Case report | Mandible | Acute lymphoblastic leukemia |
| Alfano *et al*.[8] | 2006 | Case report | Paranasal sinuses and brain | Diabetes mellitus |
| Pellacchia *et al*.[9] | 2006 | Case report | Para nasal sinus and brain | Diabetes mellitus |
| Chua and Cullen[10] | 2008 | Case series (two cases) | Orbit and left maxilla, bilateral ethmoid sinus, and sphenoid sinus | Diabetes mellitus |
| Kishel and Sivik[11] | 2008 | Case report | Pansinusitis | Acute myeloid leukemia |
| Suwan *et al*.[12] | 2012 | Case series (two cases) | Case 1: Left maxillary, frontal, ethmoid<br>Case 2: Left maxillary and ethmoid sinus | Case 1: T-cell lymphoma<br>Case 2: Tetralogy of fallot |
| Vaidya and Shah[13] | 2011 | Case report | Nose, paranasal sinus, orbit, and brain | No associated immunocompromised condition (hypertension) |
| Shashir *et al*.[14] | 2014 | Case report | Rhinocerebral region | Postrenal transplant diabetic patient |
| Davoudi *et al*.[15] | 2014 | Case report | Brain, lungs, spleen, and bones | Hematopoietic stem cell transplant with acute myeloid leukemia |
| Nitin *et al*.[16] | 2014 | Case report | Nasal cavity, left side of hard palate | Uncontrolled diabetes mellitus |
| Mahomed *et al*.[17] | 2015 | Case report | Right orbit, right maxillary sinus, bilateral ethmoid, right sphenoid sinus and cavernous sinus | Insulin-dependent diabetes mellitus |
| Goswami *et al*.[18] | 2016 | Case report | Right side frontal, sphenoidal, ethmoid, maxillary sinus, and osteomeatal complex | Postrenal transplant patient |
| Habroosh *et al*.[19] | 2017 | Case reports | Orbital infection | Silicon intubation of nasolacrimal duct for dacryocystitis |

following the exodontia of the left upper quadrant (21–26), she developed regurgitation of water and other oral fluids through the left nostril along with nasal congestion which was also later associated with pain and discomfort in the same region for which she reported to our OPD.

On clinical examination, the patient was of average built and was in obvious painful distress. Extraoral examination revealed diffuse swelling on the left side of the midface, extending anteroposteriorly from the nasolabial fold to the left tragal region and superoinferiorly from infraorbital rim to the level of the oral commissure. The overlying skin appeared to be smooth, shiny, and mildly erythematous and it was soft and tender to digital palpation. Intraoral examination revealed an exposed necrotic alveolar bone in the area from 23 to 26 tooth sockets [Figure 1]. The surrounding labial and palatal mucosa were inflamed, edematous, with irregular borders. Foul smelling pus oozed from the extracted teeth sockets.

The panoramic view revealed a moth-eaten appearance of the left maxillary alveolar bone and haziness of the maxillary antrum of the same side. Noncontrast computerized tomographic scan of the craniomaxillofacial region revealed osteolytic lesions involving the left maxillary alveolar bone and maxillary antrum [Figures 2 and 3]. Based on clinical and radiological findings, a provisional diagnosis of osteomyelitis of the left maxilla was made presuming to be of bacterial origin. A pus sample was appropriately taken and sent to the microbiology department for routine culture and sensitivity test.

The patient was hospitalized and planned for sequestrectomy and saucerization of the affected region under general anesthesia. Before the intervention, routine biochemical, serological, and hematological examinations were done. All test reports appeared within normal limits except a significantly elevated FBS and PPBS levels (230 and 450 mg/dl, respectively). These were monitored and controlled in consultation with the endocrinologist by initiating appropriate insulin regime.

Antibiotic prophylactic regime was initiated including intravenous (IV) injections of Monocef 1 g (Aristo India) at 12 h interval and Metrogyl 500 mg (Unichem India) at 8 h interval. Under general anesthesia and total aseptic condition, sequestrectomy and debridement of necrotic bone were done through the intraoral approach [Figure 4]. The excised hard and soft-tissue specimen was put in 10% formal saline and sterile distilled water and sent for histopathological and microbiological examination, respectively. The microbiological examination involved screening for fungal hyphae using the Gomori methenamine silver (GMS) staining technique. The postoperative period was uneventful. The antibiotic regime was continued for 5 days with regular twice daily dressings.

### Microbiological examination

The aspirated pus sent for culture before surgery was sterile. The tissue was homogenized under aseptic condition and subjected to bacterial (aerobic and anaerobic), tubercular, fungal culture, Gram-stain, Ziehl–Neelsen (ZN) stain, and potassium hydroxide (KOH) mount examination. Gram-stain revealed good number of pus cells and no bacteria. ZN smear was also negative for acid-fast bacilli. However, KOH preparation showed hyaline broad nonseptate hyphae. The bacterial and tubercular culture reports were sterile. Fungal culture report showed grayish white, cotton-like floppy growth on the 7$^{th}$ incubation day. By lactophenol cotton blue mount from the growth, it was identified to be *Mucor* species. A repeat fungal culture from the same sample was undertaken to rule out contamination. However, a mixed growth of *Mucor* and *Aspergillus* spp. was obtained on the 8$^{th}$ day.

### Histopathological examination

Histopathology of the tissue under special stains such as hematoxylin and eosin (H and E), Periodic acid–Schiff (PAS), (GMS) highlighted the presence of broad nonseptate hyphae and acute angle branching septate hyphae and yeast forms [Figures 5-7]. The features were consistent for the fungal invasion of bone with *Mucor* and *Aspergillus* species.

### Final diagnosis

Taking into account the microbiological and histopathological evidence, a diagnosis of fungal osteomyelitis secondary to *Mucor* and *Aspergillus* species tissue invasion was made.

Thereafter, antifungal treatment of IV amphotericin B (1 mg/kg/day) and oral voriconazole (200 mg 12 hourly) was started with a monitoring of renal function test, liver function test, complete blood count, and blood sugar level. After 8 doses of amphotericin-B infusions, the patient developed neutrophilic leukocytosis, hence amphotericin B was stopped, and oral voriconazole was continued for 12 weeks. The patient was given an obturator and was kept on follow-up. Postoperative healing was satisfactory. There was no recurrence of disease after 2 years of follow-up [Figure 8].

## Discussion

Aspergillosis and mucormycosis of the orofacial region are rare, but aggressive, opportunistic infections which may lead to fatal consequences.[20] They belong to the group of Aspergilli and Zygomycetes, respectively. The most common species forms associated with mucormycosis are *Rhizomucor*, *Rhizopus*, and *Absidia*.[21] Mucormycosis is the third most prevalent opportunistic fungal infection after candidiasis and aspergillosis.[22] Paul Tauf in 1885 reported the first case of human mucormycosis.[23] Scheld had reported a case of simultaneous disseminated aspergillosis and zygomycosis in a leukemic patient in 1979.[24] Most common sites for the manifestation of mucormycosis infection are the nasal cavity, orbit, and cerebral tissues.[25] Other systemic sites of involvement are pulmonary, gastrointestinal, cutaneous, and disseminated forms.[4]

In the literature review by Chermetz *et al*., 51 cases were reported to have a concomitant infection with *Aspergillus*

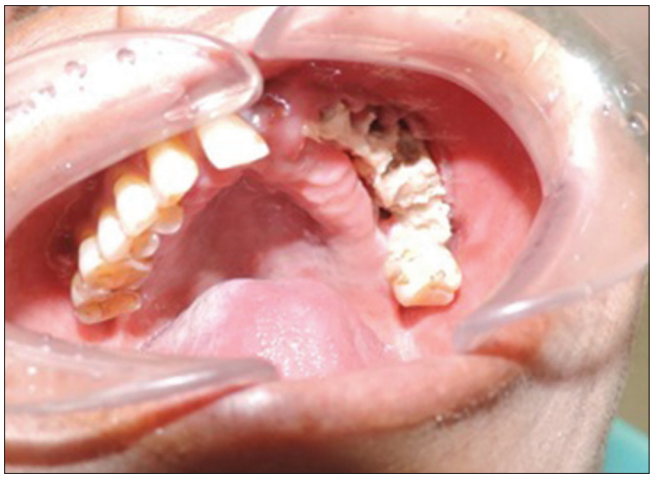

**Figure 1:** Image showing osteomyelitic changes of the left maxillary alveolus

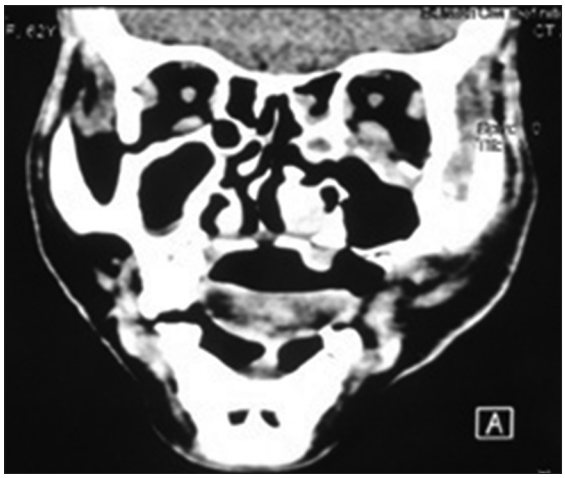

**Figure 2:** Noncontrast computerized tomographic scan of face showing osteolysis of maxilla (Left) involving maxillary antrum

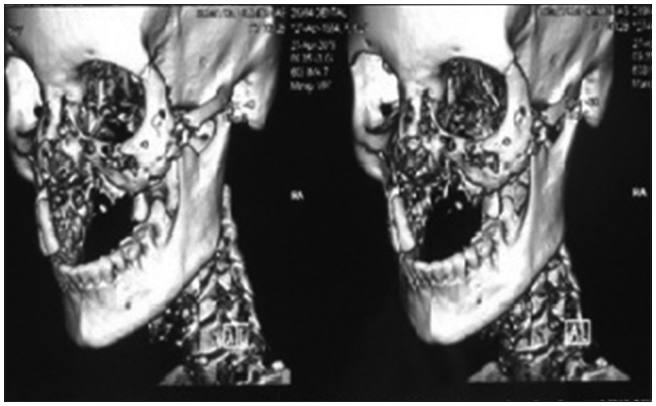

**Figure 3:** Three-dimensional reconstruction of computed tomography showing bone destruction and erosion of the left maxilla with antral involvement

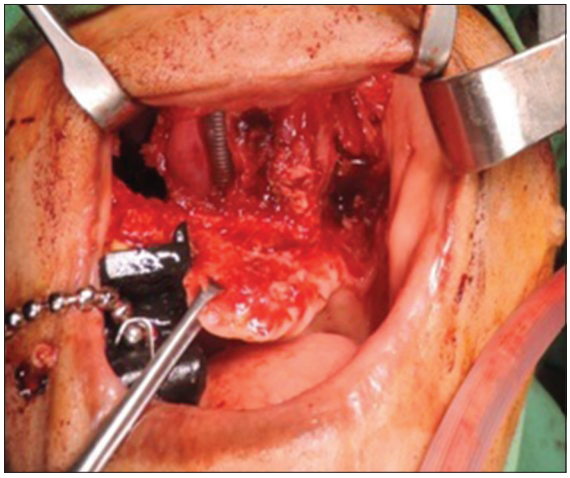

**Figure 4:** Photograph of the patient following debridement and sequestrectomy performed from the palatal aspect

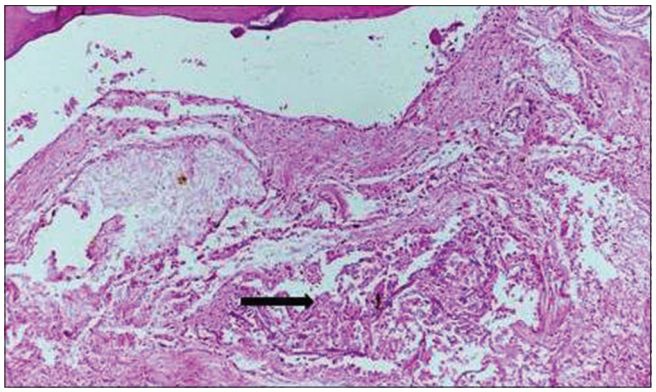

**Figure 5:** Microscopic view showing branching fungal hyphae and spores (Hematoxylin and Eosin Stain with, ×10)

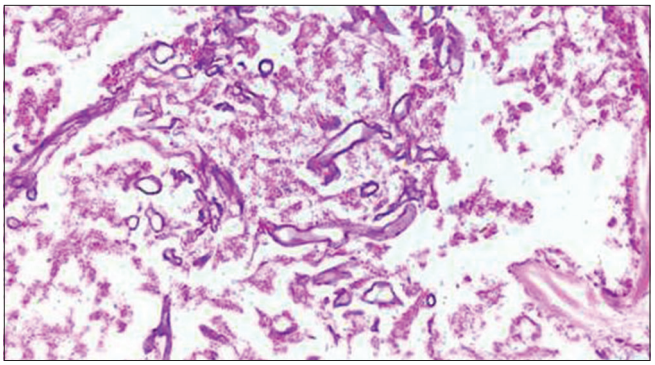

**Figure 6:** Microscopic view showing non septate wide branched hyphae (PAS, ×40)

and *Mucorales* of which only 9 cases had sino-orbito-oral involvement. The remaining 42 cases had other systemic involvement, particularly of the skin and lungs.[5]

Immunocompromised individuals are more vulnerable to such opportunistic infections.[26] Commonly involved predisposing factors are uncontrolled diabetes, lymphomas, leukemia, renal failure, immunosuppressive or long-term steroid therapy, organ transplant, renal failure, protein-energy malnutrition, and AIDS.[27,28] Rarely, does it involve healthy individuals.[29] Recipients with bone marrow transplant are

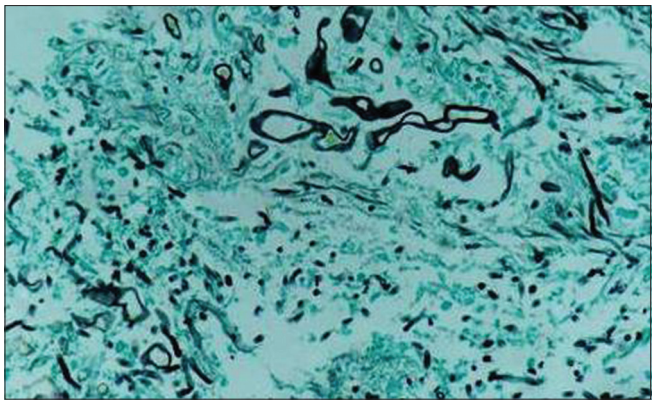

**Figure 7:** Microscopic view showing nonseptate wide branched and septate acute angle branching hyphae (GMS, ×40)

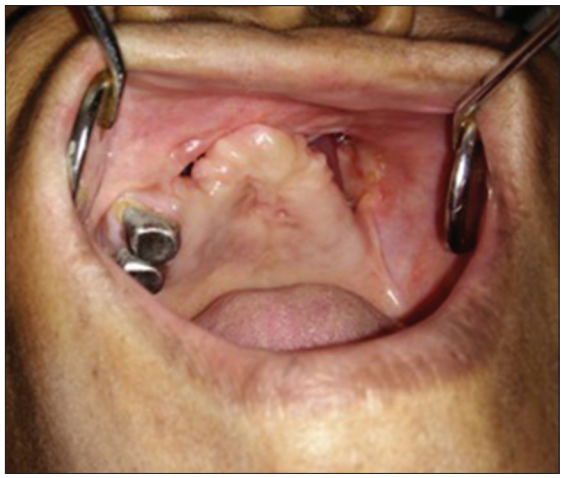

**Figure 8:** Follow-up image after 2 years

exclusively susceptible to infection with an incidence of 5%–14%.[30] Attributable risk factor in our case is uncontrolled diabetes mellitus. The common portal of entry for pathogens is nose and paranasal sinuses through inhalation or breached skin and mucous membrane. An uncommon, but invasive portal site is the dental extraction socket.[31] The portal of entry in this case could be through the extracted tooth socket due to extraneous contamination. Vascular invasion is the key pathophysiological feature of human *Mucorales* infection.[32] Spores or vegetative forms of *Mucorales* invade the arteries and form a thrombus within the vessel resulting in ischemic infarcts and subsequently necrosis of regional hard and soft tissues.[2,26,32] The destruction of tissues as a result of *Aspergillus* infection is due to the action of inflammatory cells recruited to the affected site.[5] High glucose levels, acidic environment, low oxygen, and high iron levels facilitate germination and growth of fungal spores.[33]

In case of diabetes mellitus, primary contributing factors are deranged granulocyte-phagocytic ability and altered polymorphonuclear leukocyte response.[34] Second contributing factor is microangiopathy and atherosclerosis (peripheral vascular diseases), resulting in local tissue ischemia and increased vulnerability to infection.[35] Cases of diabetic ketoacidosis are at higher risk of developing mucormycosis due to the elevation of serum iron. Moreover, fungal hyphae produce "rhizoferrin" which binds to the available serum iron and forms iron-rhizoferin complexes. This is the nutrient element for growth, development, and multiplication of *Mucorales* spores.[36]

In orofacial region, clinical manifestation of mucormycosis and aspergillosis are rhinorrhea, facial cellulitis, nasal discharge, and turbinate necrosis along with lethargy fever and headache.[37] Ophthalmic involvement occurs in later stages and includes painful eyes, blurred vision, conjunctival suffusion, ptosis, proptosis, and chemosis.[38] Loss of vision has also been reported indicating retinal artery thrombosis.[33] Our case did not show any ophthalmic involvement.

According to the joint clinical guidelines by the European Confederation of Medical Mycology, direct microscopy, culture, and histopathology are recommended diagnostic aids in the management of this disease entity.[39] Further advanced techniques used in the diagnosis of *Aspergillus* infection include detection of galactomannan, beta-D-glucan and DNA by Polymerase Chain Reaction-based methods.[40] According to the Infectious Disease Society of America, detection of galactomannan, beta-D-glucan and various stains like H and E , PAS, Grocott-GMS nitrate and fluorescent stains are frequently used to reveal characteristic hyphae content in tissues.[20]

Radiographic techniques serve as a supportive diagnostic aid rather than being a definitive diagnostic modality. Radiographic picture of the affected area may show erosion of underlying bone, mucosal thickening, or opacification of sinus cavity.

Treatment includes sequestrectomy with proper wound debridement. Antifungal drug regime includes amphotericin B, voriconazole and posaconazole. Postdebridement defect if created can be rehabilitated by soft tissue and hard tissue reconstruction or by providing an obturator for the patients.[41]

## Conclusion

Immunocompromised patients are vulnerable for fatal fungal infections involving bones and soft tissues of the oral cavity. Such infections always create a dilemma for the clinicians to reach a definitive diagnosis due to paucity of occurrence and reporting. Early diagnosis and treatment can save such consequences. The possibility of such kind of fungal osteomyelitis should be taken into account as a differential diagnosis for similar clinical situations.

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### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients

understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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