

# Fungal osteomyelitis of maxillofacial bones: Rare presentation

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## Abstract

Osteomyelitis is defined as inflammation of the medullary cavities, haversian system and adjacent cortex of bone. Osteomyelitis involving maxilla is quite rare when compared to that of mandible. Fungal osteomyelitis is very rarely seen and documented in the maxillofacial area. It is devastating to patients if it is invasive in nature. A prospective study was undertaken from December 2011 to December 2013. Biopsied hard tissue bits were decalcified and sections were stained with H&E, periodic acid Schiff and Grocott methenamine silver. Culture sensitivity was carried out in all cases. Surgical intervention followed by antifungal therapy was advocated to treat the patients. The current series showed five cases of fungal osteomyelitis which included candidal osteomyelitis, aspergillosis and mucormycosis with slight predominance of maxilla over mandible. Osteomyelitis of facial bones needs to be investigated thoroughly as there is no difference in clinical presentation between bacterial and fungal osteomyelitis. The diagnostic workup with biopsy and culture sensitivity helps to identify the pathogen at the earliest. Appropriate antifungal treatment needs to be advocated for successful treatment.

**Key Words:** Aspergillosis, fungal infection, mucormycosis, osteomyelitis

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## INTRODUCTION

Osteomyelitis is defined as inflammation of the medullary cavities, haversian system and adjacent cortex of bone.<sup>[1]</sup> In the present era of antibiotics, osteomyelitis of facial bones is a rare condition. Osteomyelitis involving maxilla is quite rare compared to that of mandible because of the extensive vascularity and strut like nature seen in maxilla.<sup>[1,2]</sup>

Fungal osteomyelitis is very rarely seen and documented in the maxillofacial area. Here, we highlight five cases of fungal osteomyelitis presenting with diverse clinical presentation. The diagnostic workup with emphasis on special staining in

histopathological sections to identify the fungal nature has been discussed.

## CASE SERIES

A prospective study was undertaken from December 2011 to December 2013. Patients who reported for osteomyelitis were thoroughly screened and only five cases were obtained which showed characteristics of fungal osteomyelitis.

All five cases included in the series were primarily intraosseous with evidence of radiographic changes in bone. All cases had relevant clinical [Figure 1], radiological [Figure 2] and

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histopathological [Figures 3, 4 and 5] data. Biopsied tissue sections were stained with H&E, Periodic acid Schiff (PAS) and Grocott methenamine silver (GMS) stain. In all cases, microbiological confirmation by culture was obtained except in one case.

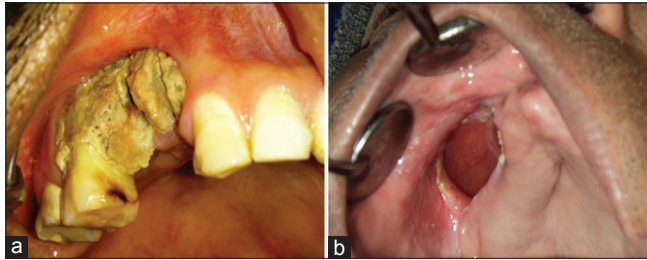
The clinical, radiological, histopathological and treatment data are illustrated in Table 1.

## DISCUSSION

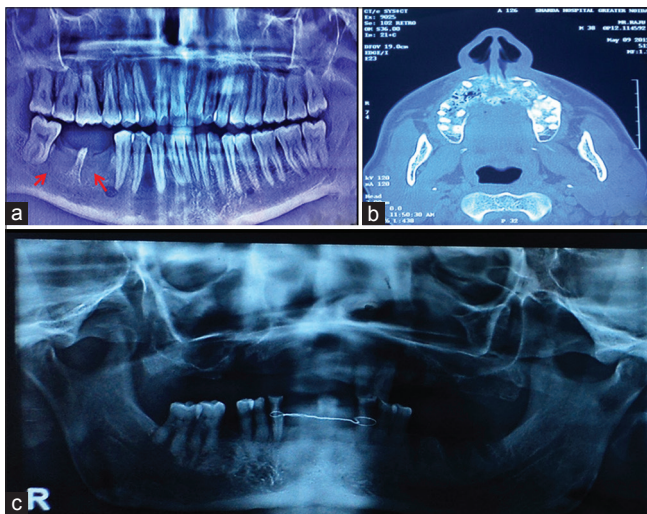
Osteomyelitis is an inflammatory condition of bone and bone marrow content which originates from chronic infection. Etiopathogenesis includes trauma, surgical intervention, bacteremia, fungal infection or a contiguous infectious focus and systemic diseases among the innumerable causes. It is further influenced by the immobility of stagnant blood which acts as nidus for the development of infection.<sup>[3]</sup>

Fungal osteomyelitis is very rare and generally presents in an indolent fashion.<sup>[4]</sup> Fungal infections are devastating to patients if it is invasive in nature. These are opportunistic infections which frequently enter the body due to a decrease in host defense or through an invasive gateway, such as a dental extraction. Candidal infection is more often encountered when compared to other fungal infection, i.e. mucormycosis, aspergillosis etc.<sup>[5]</sup> Osteomyelitis mostly results from bacterial infection. However, fungi, parasites and viruses can also affect bone and bone marrow.<sup>[6]</sup>

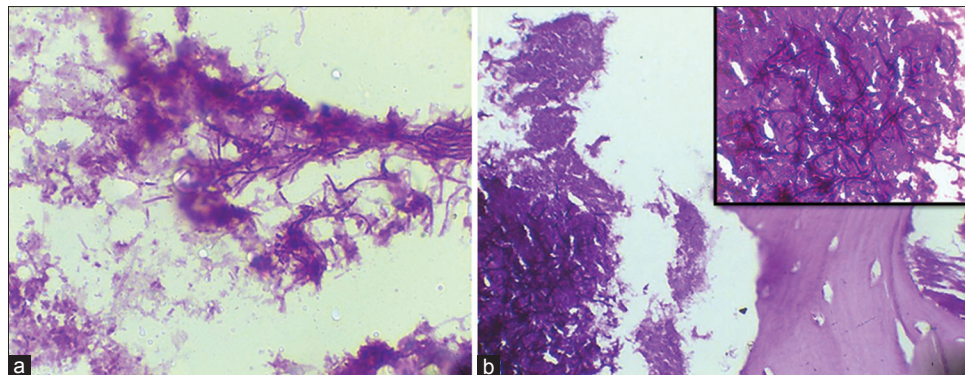
Since fungal infections involving bone occur infrequently, it can pose a diagnostic and therapeutic dilemma for those who are not familiar with its clinical presentation, hence leading to ineffective treatment or resolution. The clinical presentation of fungal osteomyelitis would be similar to the bacterial osteomyelitis. Exposed bone with history of varying pain intensity would be predominantly encountered.<sup>[3]</sup> Specific delineating features would be the involvement of maxillary sinus with a complaint of sinusitis in maxillary fungal osteomyelitis. An associated history of diabetes would generally be present in such cases.<sup>[7]</sup>



**Figure 1:** (a) Case 3-Clinical photographs showing exposed necrotic bone i.r.t. 14, 15 and 16; (b) Case 5-Clinical photograph showing oro-antral fistula in right maxillary vestibule, measuring 4x3 cm



**Figure 2:** (a) Case 1-Radiographs showing radiopaque interdentary septum i.r.t. 46 and 47 region in orthopantomogram. (b) Case 3- CT scan showing permeative bone destruction in anterior hard palate. (c) Case 5- Orthopantomograph shows necrotic bone i.r.t. 14,15 and 16 with haziness in right maxillary sinus in case 5



**Figure 3:** (a) Case 2- Section showing candidal pseudoseptate hyphae [Periodic acid Schiff (PAS) stain, x400]. (b) Case 4- Section showing empty lacunae in bone and candidal pseudoseptate hyphae [PAS stain, x40]. Inset: Higher magnification showing candidal pseudohyphae [PAS, x400]

Diabetes mellitus is usually a propagating factor for maxillary osteomyelitis.<sup>[8]</sup> Out of five cases, three were involving the maxilla with a history of diabetes in two out of three cases. Altered

immunity and compromised vascularity are well established and are commonly encountered facts related to uncontrolled diabetes mellitus (UDM).<sup>[7]</sup> The mechanism which facilitates

**Table 1: Clinical and radiological features with histopathological diagnosis and treatment details for cases 1-5**

Case number	Age/sex	Site	Chief complaint	Previous history	Clinical presentation	Radiograph	Culture	Histopathological diagnosis (H and E, PAS and GMS stained decalcified section)	Treatment, posttreatment and follow-up
1	26/M	Mandibular right posterior region	Nonhealing socket for 3 months	History of dengue fever-3 months since then mobility of 46 and 47 with pus discharge, extracted 46, 47	Exposed bone, erythematous area, mental nerve paresthesia	OPG Radio-opaque interdental septum i.r.t. 46 and 47	No growth	Zygomycosis Aseptate, flattened broad ribbon-shaped fungal hyphae admixed with few inflammatory cells in fibrous stromal tissue within nonvital bone	Debridement, curettage and Irrigation Amphotericin B + Metronidazole Follow-up (6 months) -satisfactory
2	50/M	Maxillary left posterior region	Unable to chew and pain for 2 weeks	Trauma Nondiabetic	Exposed bone Pain Tender on palpation	OPG Ill-defined radiolucency i.r.t. 25, 26 and 27 region	Growth +ve for <i>Candida</i>	Candidal osteomyelitis Trabeculae of bone with empty lacunae at places. The intervening connective tissue shows loosely arranged collagen fibers and fibroblasts with areas of necrosis. Clusters of thin pseudoseptate hyphae are seen	Sequestrectomy, curettage and irrigation Fluconazole Follow-up (6 months) -satisfactory
3	38/M	Maxillary right posterior region	Pain and foul breath for 6 months	Diabetic Underwent ATT for tuberculosis	15, 14, 21 were missing, exposed bone i.r.t. 14, 15 and 16 Pain	CT scan Punctate hyperdense foci i.r.t. maxillary sinus Premature bone destruction in anterior maxilla and hard palate	Growth +ve for mucormycosis	Mucormycosis Bony trabeculae with attached fungal sporangium. Broad, branching nonseptate fungal hyphae seen with replacement of marrow by sporangium	Complete removal of maxillary sinus lining with excision and closure of oroantral fistula by nasolabial flap. Amphotericin B, cefotaxime (taxim) and metronidazole Follow-up (6 months)-satisfactory
4	6/M	Mandibular right posterior region	Pain Since 3 months	Nondiabetic	Intraoral-exposed bone, Diffuse swelling of 4 cm×4 cm, hard in consistency, tender, poor oral hygiene Extra oral-tenderness of the right parotid gland and submandibular gland lymph node (tender)	OPG Irregular root resorption i.r.t. 84 and 85 with blunderbuss canal of 46	Growth +ve for <i>Candida</i> and <i>Staphylococcus aureus</i>	Candidal osteomyelitis superimposed by bacterial infection Clusters of pseudoseptate fungal hyphae along with numerous Gram-positive clusters of cocci in the marrow spaces. Few osteocytes within empty lacunae were also noted	Debridement, curettage and irrigation Itraconazole + amoxicillin + metronidazole Follow-up (6 months) -satisfactory

Contd...

Table 1: Contd...

Case number	Age/sex	Site	Chief complaint	Previous history	Clinical presentation	Radiograph	Culture	Histopathological diagnosis (H and E, PAS and GMS stained decalcified section)	Treatment, posttreatment and follow-up
5	72/M	Maxillary right posterior region and cheek	Pain Nasal regurgitation for 7 months	Diabetic Underwent treatment for actinomycosis History of tooth extraction, with subsequent oroantral fistula	A large oroantral communication present in the right maxillary vestibule extending from canine to molar region, measuring 4 cm×3 cm, ovoid in shape, well-defined margins, exposed and necrotic bone	OPG Bone with ill-defined border with respect to 14, 15 and 16 Haziness in right maxillary sinus	Growth +ve for aspergillosis, Candida and mucormycosis	Aspergillosis, mucormycosis with foci of actinomycosis, associated with superimposed candidiasis Foci of actinomycetes, thin septate hyphae and spores of aspergillosis with budding at 45° angle and few flat broad ribbon-shaped aseptate hyphae of mucormycosis were noticed along with few microbial colonies and inflammatory response	Sequestrectomy with reconstruction with buccal fat pad and irrigation amoxicillin + clavulanic acid + itraconazole Follow-up (6 months) -satisfactory up to 2 months Lost to follow up after 2 months

OPG: Orthopantomography, PAS: Periodic acid–Schiff, GMS: Grocott methenamine-silver, ATT: Antitubercular treatment, CT: Computed tomography

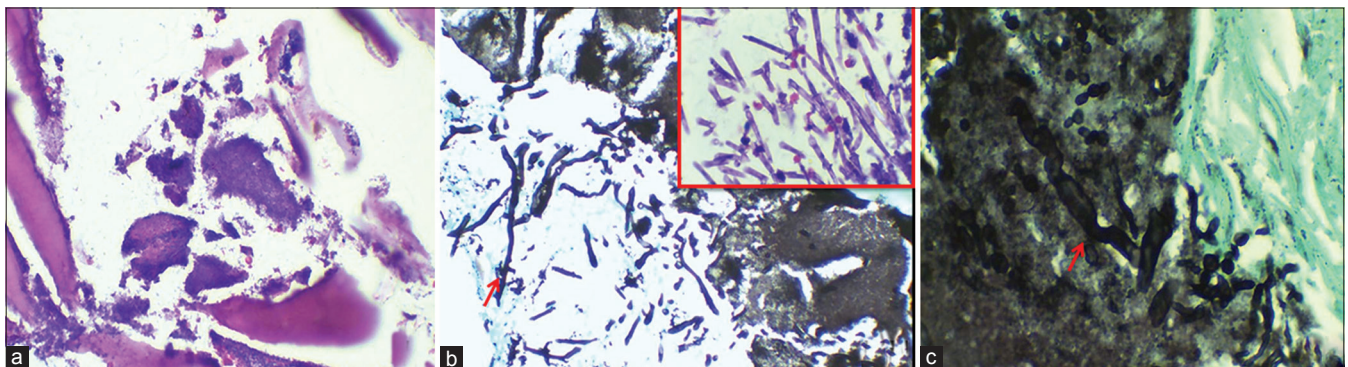


Figure 4: Case 4- Section showing actinomycotic foci within bone (H&E stain, ×200), (b) Grocott methenamine silver (×200) and H&E (Inset, ×400) stained section showing septate and dichotomous hyphae of aspergillosis, (c) Grocott methenamine silver stain showing aseptate broad, ribbon shaped hyphae of mucormycosis (×400)

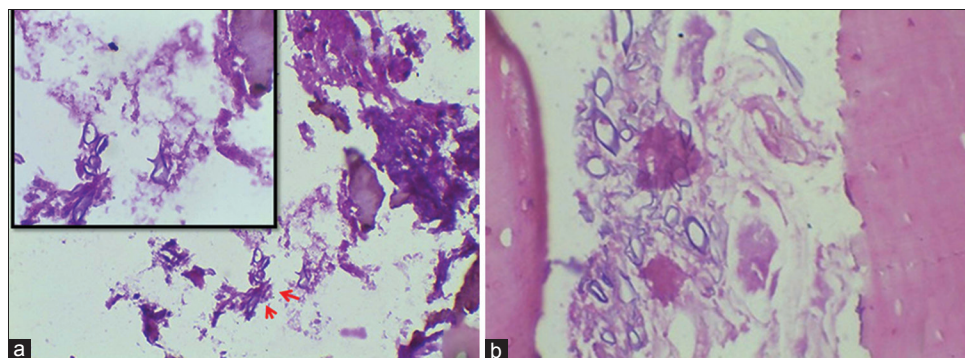


Figure 5: (a) Case 1- Section showing necrotic bone with aseptate hyphae (H&E stain, ×200), (b) Case 3- Sections showing broad aseptate hyphae and spores (H&E stain, ×400)

bone infection includes diminished leukocyte chemotaxis, phagocytosis and life span; and diminished vascularity, thus reducing tissue perfusion. Defective glucose utilization causes delayed wound healing.<sup>[9]</sup> An incidence of 45.1% of maxillary osteomyelitis has been reported by Koorbusch *et al.* among UDM patients in a rural Indian population.<sup>[10]</sup>

Collateral blood supply, porous nature and thin cortices of maxilla, reduces the chance of osteomyelitis in maxilla when compared to the mandible.<sup>[1]</sup> However, the current series showed a slight predominance of fungal osteomyelitis in maxilla over mandible. According to Niranjana *et al.*, 52% cases of fungal osteomyelitis and 48% of nonfungal osteomyelitis were observed in a 10 year study conducted on North Karnataka population. Maxillary involvement was seen in 80.76% of cases with male predominance associated with diabetes mellitus.<sup>[11]</sup> A thorough review of literature showed that the incidence ratio of maxilla: Mandible osteomyelitis was 1.07:1 by Peravali *et al.*, whereas the incidence of 1:6.5 and 1:6 was noted by Koorbusch *et al.* and Rangne and Ruud.<sup>[7,10,12]</sup>

The diagnostic workup is of paramount importance to differentiate between bacterial and fungal osteomyelitis. The biopsied bony tissues on decalcified sections show irregular bony trabeculae with empty osteolytic lacunae. The presence of fungal hyphae within the bone would essentially highlight the fungal nature. Culture sensitivity should be followed in all cases irrespective of its nature.

In the current study, two cases of mucormycosis were seen. All histopathological sections were stained with H&E, PAS and GMS. Special staining with GMS specially identifies the nature of hyphae whether septate or aseptate. Identification can be accurately done on histopathological sections itself and the culture will confirm the exact species.<sup>[13]</sup> Mucormycosis is an opportunistic fulminant fungal infection, which mainly infects immunocompromised patients.<sup>[14]</sup> The fungus invades the arteries leading to thrombosis that subsequently causes necrosis of hard and soft tissues.<sup>[15]</sup> Mucormycosis is frequent in diabetic patients because a favorable environment is created due to an excess of ketone bodies in diabetic patients. *Rhizopus arrhizus*, produces the enzyme ketoreductase, which allows them to utilize the patient's ketone bodies. The increase in the levels of free iron ions favors fungal growth.<sup>[16,17]</sup> Literature reveals that zygomycosis is less documented in mandible with only five cases of mandibular zygomycosis being reported until date.<sup>[18]</sup>

The evidence of candidal osteomyelitis is scarce in the reported literature. The current series showed few cases of candidal osteomyelitis. PAS stained histopathological sections showed pseudoseptate hyphae in clusters with budding at focal areas (case# 2 and case# 4). This was confirmed by

culture sensitivity. Peravali *et al.* have analyzed 31 cases of osteomyelitis in which there appears to be only one case of candidal osteomyelitis, along with three cases of mucormycosis and one case of aspergillosis.<sup>[7]</sup>

It is extremely rare to find candidal osteomyelitis in the maxilla and because of nonspecific symptoms, diagnosis is very challenging.<sup>[19]</sup> Case#4 was a pediatric patient diagnosed with candidal osteomyelitis. It is very rare to find candidal osteomyelitis as compared to bacterial osteomyelitis. Incidence in children ranges from 1:5000 -1:10,000 as documented by Weichert *et al.* and Dahl *et al.*<sup>[20,21]</sup>

Aspergillosis is the second most common fungal infection after candida. It is usually invasive in nature when involving maxillary sinus though noninvasive forms have also been reported<sup>[22]</sup> and does not cause bone destruction when compared to mucormycosis.<sup>[17,23]</sup> Case#5 had a combination of mucormycosis, aspergillosis, actinomycotic foci and superimposed candidiasis. A thorough search in PubMed reveals only one case of trirungal osteomyelitis reported till date.<sup>[18]</sup> Case#5 in the current series appears to be the second case being reported. The identification of these hyphae are quite characteristic with aspergillosis showing narrow septate hyphae of 3–6  $\mu\text{m}$  in size having dichotomous branching between 45° and 90°.<sup>[24]</sup> Mucormycosis which belongs to zygomycetes family typically shows broad aseptate hyphae of size 6–20  $\mu\text{m}$  with branching at > 90°. Histopathological identification can be considered as the gold standard in such cases.<sup>[25]</sup>

Appropriate treatment of antifungal regime needs to be initiated as the culture sensitivity results could take up to 6 weeks. Early identification and prompt treatment with the identification of underlying systemic disease would lead to successful outcome. In the present study, two cases of candidal osteomyelitis (case#2 and case #4) healed with appropriate antifungal regime of itraconazole and fluconazole along with surgical debridement.

Case#3 was administered with amphotericin B, cefotaxime and metronidazole which was followed by the complete removal of maxillary sinus lining with excision and closure of oroantral fistula by the nasolabial flap. A similar drug regime was followed for case#1.

Case#5 underwent sequestrectomy with reconstruction with buccal fat pad and irrigation, followed by drugs, i.e. amoxicillin, clavulanic acid and itraconazole.

All cases were followed up for renal toxicity for 6 months with an interval of 1 month. There were no aberrant changes in serum creatinine and urea levels. However, case#5 was lost to follow-up.

## CONCLUSION

Osteomyelitis of facial bones needs to be investigated thoroughly as there is no difference in clinical presentation between bacterial and fungal osteomyelitis unless accompanied by maxillary sinusitis. The diagnostic workup with biopsy and culture sensitivity helps to identify the pathogen at the earliest. Fungal osteomyelitis is very rare and appropriate treatment with antifungal regime and timely surgical intervention, i.e., debridement, curettage, sequestrectomy will lead to successful resolution of the disease process.

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## Conflicts of interest

There are no conflicts of interest.

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