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Chronic Candida osteomyelitis of hard palate and nose: A diagnostic quandary

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ABSTRACT

Candida induced osteomyelitis is infrequent. There is scarcity of literature on this entity in maxillofacial region and thus there is possibility to mismanage such cases. We are presenting a case of chronic maxillofacial *Candida tropicalis* osteomyelitis causing palatal and septal perforation with saddle nose deformity in a young lady with commencement and progression of disease process over two pregnancies. Diagnosis was established by histopathology and repeated isolation on culture. Debridement followed by adequate antifungal therapy instituted.

1. Introduction

Osteomyelitis is defined as the inflammation of the medullary cavities, Haversian system and adjacent cortex of bone [1]. Fungal osteomyelitis usually occurs in immunocompromised individuals but it can affect immunocompetent individuals also. In maxillofacial region, *candida* induced osteomyelitis is seen very rarely. The extensive vascularity of the maxilla compared to the mandible makes it a less preferred site of involvement [2]. Isolated nasal disease is extremely uncommon. Nasal involvement is usually seen in conjunction with primary maxillary osteomyelitis [3]. Proper diagnosis with the help of special stains on histopathology and fungal culture is essential since there are high chances of misdiagnosis and thus improper and inadequate treatment of such cases. Early institution of antifungal therapy is of foremost importance.

2. Case

A 29 year old thin built, married female patient presented to us (Day +0) with a painless, gradually progressive perforation in the hard palate with nasal regurgitation of food and halitosis. She gave history of development of septicemia eight years back with acute liver and renal disease during the 34th week of first pregnancy for which she received prolonged antibiotics and two rounds of hemodialysis. A week into the post-partum period, she developed a necrotizing ulcer over the hard palate which later turned into a perforation around 1 × 1 cm in size. A biopsy was taken from the margins which revealed chronic inflammation and vasculitis. Tuberculosis workup was non-contributory. Serology for Hepatitis B, Hepatitis C, Hepatitis E and HIV was negative. Her blood sugar level was normal during the gestational period. There was no other immunocompromising status in the patient.

Four years later during her second pregnancy, the size of the palatal perforation increased with the appearance of new symptoms such as crusting, foul smelling discharge and nasal regurgitation of food. She also developed saddle nose deformity. She had a history of miscarriage prior to first pregnancy and had received Progesterone and hCG injections during both pregnancies as per obstetrical norms.

On day + 0, at the time of presentation, local examination revealed a 6 × 4 cm defect involving almost whole of the hard palate with yellowish crusting all around its margins. There was a large septal perforation leading to saddle nose deformity, however, the turbinates were normal (Fig. 1a). There was no other significant clinical finding. On routine blood investigations, her Hemoglobin was 9.2 g% while Erythrocyte Sedimentation Rate (ESR) was raised (22 mm in 1st hour). Her renal function and liver function tests were normal, VDRL and Viral markers were non reactive, antinuclear antibodies (ANA), cANCA and pANCA were negative. Serum Angiotensin Converting Enzyme (ACE) levels were also in normal range. Debridement of all the necrotic tissue was done on day + 5 (Fig. 1b) and tissue was sent for histopathology, KOH mount, aerobic bacterial and fungal culture and sensitivity on the same day.

Histopathology revealed necrotic trabeculae with fungal hyphae

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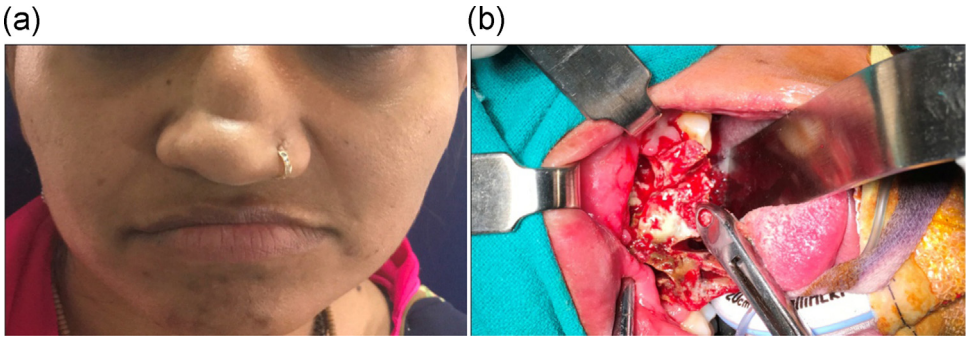

Fig. 1. a Saddle nose deformity in the patient and b: Intraoperative picture showing debridement of necrotic and infected bone.

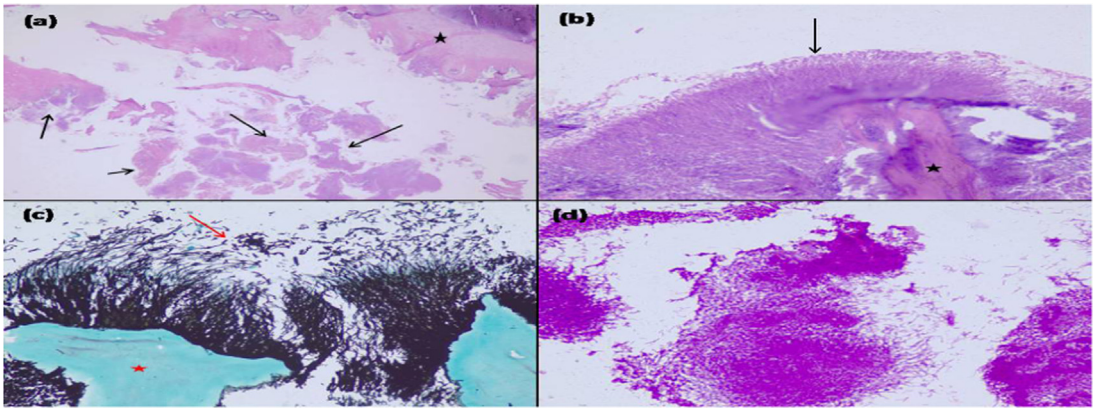

Fig. 2. (a) H&E stain showing on 100× and (b) on 400× numerous fungal hyphae (arrow) causing bone destruction (black asterisk), (c) and (d) showing Positive for special stain Gomori's methenamine silver stain (red arrow) and Periodic acid-Schiff stain (magenta color), indicating that these are fungal hyphae respectively.

positive for Periodic Acid Schiff (PAS) and Gomori Methenamine Silver (GMS) stains suggestive of mycetoma (Fig. 2a–d).

On KOH mount, budding yeast cells with pseudohyphae were seen (Fig. 3).

Candida tropicalis was grown on culture (Fig. 4a-b) which was sensitive to Caspofungin (MIC 0.125 μg/ml) and Amphotericin B (MIC 1 μg/ml) and showed MIC > /= 256 μg/ml for fluconazole and MIC > /= 32 μg/ml for itraconazole i.e. resistant to fluconazole and itraconazole by E-strip method (HIMEDIA) which was also confirmed by VITEK-2 automated system.

Additional growth of Group A β- hemolytic *Streptococci* and *Enterococcus* species was obtained. Both organisms showed sensitivity to Co-trimoxazole, so oral co-trimoxazole 160/800 mg was given twice a day along with a trial of oral Itraconazole 200 mg twice a day on outpatient basis on day + 10. In view of lack of clinical improvement after ten days of treatment (day + 20), patient was re-admitted on day + 20 and again necrotic tissue was partially debrided and sent for culture which again shown growth of *Candida tropicalis* sensitive to Amphotericin B. Parenteral Liposomal Amphotericin-B was administered in a dose of 100 mg/day (3 mg/kg/day) to cumulative dose of 3000 mg over one month from day + 23 to day + 53 with continuous renal function monitoring. The dose was kept on lower side as patient had past history of renal disease. There was significant local improvement after one month of therapy in terms of control of infection, absence of discharge and crusting and presence of healthy granulation tissue (Fig. 5a) after which patient was discharged on day + 55. Patient was not given any oral antifungal (fluconazole/itraconazole) at the time of discharge as it came resistant on sensitivity testing and also, there was no clinical improvement on giving trial of itraconazole to the patient earlier. On day + 260, after approximately 7 months of follow up (Fig. 5b), patient was having no necrotic tissue or debris. An opinion from prosthodontist was sought on day + 260 and patient was fitted with a palatal obturator. Patient has been on regular follow-up.

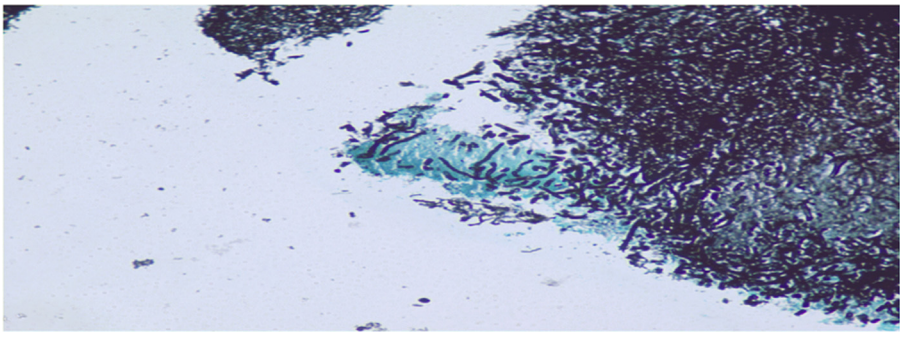

Fig. 3. Tissue showing budding yeast forms, true hyphae and pseudohyphae consistent with *Candida species* on GMS stain (400X).

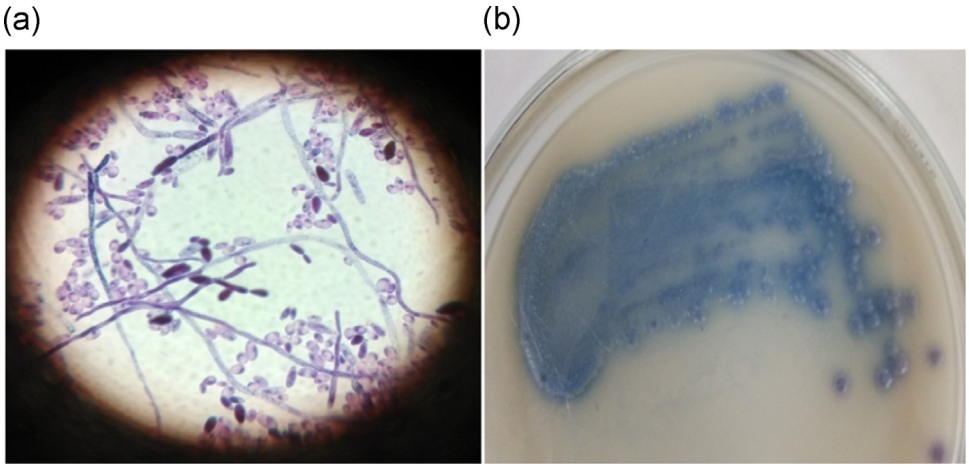

Fig. 4. (a) Gram stain showing budding yeast cells, pseudohyphae and true hyphae (1000 ×) (b) Teal blue colonies of *C.tropicalis* on chromagar.

3. Discussion

Osteomyelitis is an inflammatory condition of the bone that starts as an infection of medullary cavity, involves Haversian canal rapidly and then progresses to involve the periosteum [1]. Due to this inflammatory process, there occurs compression of blood vessels resulting in development of ischemic and necrotic bone [4]. *Candida* is ubiquitous in nature and is present as normal flora in the oral cavity [5]. Osteomyelitis may develop due to contiguous infection, trauma, surgery and overuse of broad spectrum antibiotics or certain systemic conditions like diabetes, malnutrition, malignancy, radiation or other immunocompromised states [3]. Although its pathogenicity is said to be enhanced by immunocompromised state of the patient, *Candida* osteomyelitis is seen in a large number of immunocompetent individuals also [6]. There is ample evidence supporting the surge of vaginal candidiasis during pregnancy but the association of systemic candidiasis or candida induced osteomyelitis with pregnancy is largely unexplored. In comparison to bacterial infection, fungal osteomyelitis is much less common and much more debilitating. Fungal infection can be devastating if it is invasive as in mucormycosis. Unlike bacterial osteomyelitis, *candida* osteomyelitis has an indolent course but can cause significant destruction and morbidity if not recognized in time and not treated properly. Vertebra, femur, ribs and humeri are the most common bones to get involved as per literature with rare description of maxillofacial involvement [6]. Osteomyelitis involving maxilla is quite rare compared to that of mandible (the latter being the most commonly affected bone in the head and neck region) because of the extensive vascularity, porous nature and thin cortices in maxilla [1,3]. Clinical presentation may vary from an isolated discharging sinus to extensive bony destruction.

Diagnosis of fungal osteomyelitis is quite challenging due to its rarity and a clinical presentation that mimics bacterial osteomyelitis. If not worked up properly, these patients usually are misdiagnosed. Histopathology with special stains for fungus such as PAS and GMS is essential along with fungal culture for establishing the diagnosis. The most common *candida* species involved in osteomyelitis is *Candida albicans*. However with improved diagnostic techniques, a surge of cases caused by non albicans candida species has been reported. Among non albicans Candida species, *Candida tropicalis* is the main culprit followed by *Candida glabrata*. Others are *Candida lusitaniae, Candida paratropicalis, Candida pseudotropicalis, C. parapsilosis, Candida holmii, C. krusei* and *Candida guilliermondii* [6]. In our case, tissue was positive for PAS and GMS stains and *Candida tropicalis* was grown in culture. *Candida tropicalis* is considered to be more virulent and offers greater resistance to commonly used antifungals than *Candida albicans.* The increased virulence may be attributed to bio film formation, expression of tissue damaging enzymes (e.g. proteases, phospholipases and haemolysins) and dimorphism [8].

Since there are aesthetic concerns involved, treatment of osteomyelitis of face remains challenging as along with treatment of osteomyelitis, aesthetic corrections are also required.

For correcting chronic osteomyelitis caused by *Candida*, Infectious disease Society of America guidelines suggest liposomal amphotericin B (fungicidal) in a dose of 3–5 mg/kg for 2–6 weeks followed by oral fluconazole (fungistatic) 6 mg/kg for 6–12 months as first line treatment [7]. In our case, since there was resistance to fluconazole and

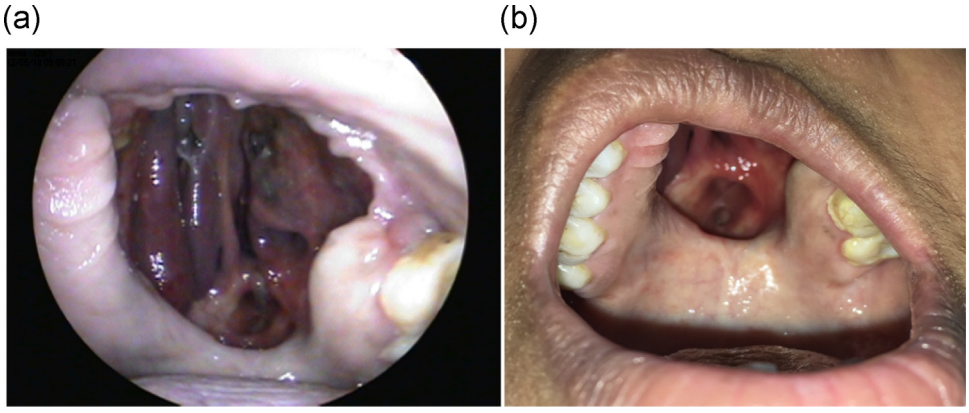

Fig. 5. (a) Postoperative picture (at one month) showing presence of healthy granulation tissue and absence of crusting and necrotic bone (b) Follow up picture after 7 months.

itraconazole, we have given only parenteral liposomal amphotericin B. Whenever feasible, it is necessary to complement the medical management with appropriate surgical treatment viz. debridement. Correction for aesthetics can be done later.

Patient should be kept under strict observation for at least 6 months after stopping the treatment and in case of clinical suspicion of residual/recurrent disease; patient should be subjected to radiology and/or histopathology of the suspicious area to prevent any relapse.

4. Conclusion

Candida osteomyelitis is very rare and can lead to extensive bony destruction as seen in our case. There is possibility to misdiagnose such cases especially in immunocompetent individuals, as such extensive bony destruction is usually seen in immunocompromised individuals and is caused by either bacterial or mucorales. To identify causative agents, always send biopsy tissue for fungal culture. Appropriate treatment as per antifungal sensitivity report should be administered early with an emphasis on adequate dosage. Follow up of patient should be ensured. Possibility of hormonal influence on invasive candidiasis should be explored.

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Conflict of interest

There are none.

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