Case Report

Maxillary Mucormycotic Osteonecrosis as a Manifestation of Post-COVID-19 Infection in Non-diabetic Patients: Report of Two Cases

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Abstract

Mucormycosis is a rare, opportunistic fungal infection prevalent in the elderly, especially in patients with uncontrolled diabetes or a compromised immune system. However, the outbreak of the pandemic declared by the World Health Organization in late 2019 increased the incidence of mucormycosis cases in COVID-19 patients due to increased steroid usage that resulted in an immunocompromised state. The current report presents two cases of oral mucormycotic osteomyelitis in patients who developed diabetes post-COVID infection, along with a review and relevant literature.

Keywords: COVID-19, mucormycosis, non-diabetic, osteonecrosis

Introduction

A pandemic outbreak caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a member of the coronaviridae family, resulted in a global emergency worldwide when it affected individuals in 206 countries. The novel disease manifests a myriad of symptoms with numerous complications that are being identified with time. The patients infected with this virus tend to present with various other bacterial and fungal infections, as the severity of the infection increases. The incidence of fungal co-infection in the orofacial region due to COVID-19 is a major complication of great clinical significance due to the increased risk of morbidity and mortality of the patient.[1]

Mucormycosis is one of the most common fungal co-infection in the orofacial region caused by *Mucorales* sp, mainly *Rhizopus arrhizus*. It has been identified that diabetes and diabetic ketoacidosis are the primary predisposing factors for the development of mucormycosis in immunocompromised patients.[2] Uncontrolled diabetics, immunocompromised patients, and patients on steroids were considered at high risk of developing mucormycosis. The organism gains entry into the paranasal sinus, invades the blood vessels and causes thrombosis, leading to tissue necrosis. Oral manifestations include pain, mobility of teeth associated with pus discharge and osteonecrosis of the jaws.[3] In this paper, we report two non-diabetic patients with post-COVID-associated mucormycosis (CAM) of the maxilla after obtaining informed consent and approval from institutional review board.

Case Reports

Case 1

A 63-year-old male patient reported to the surgeon with a complaint of mobility of teeth in the upper anterior region of the jaw for the past 2 weeks. The patient had a history of COVID infection and had undergone functional endoscopic

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sinus surgery before 1 month. On intra-oral examination, 11, 22, 23, and 24 were mobile. Grade II mobility was found in relation to 11, 22, 23, and 24 with tenderness. The left upper anterior alveolar segment was found to be floating from the maxillary arch. On radiographic examination, 11, 22 were root canal treated, 21 was missing, and a fixed partial denture was seen in relation to 11, 21, and 22. Ill-defined radiolucency was seen in relation to the periapical region of the upper anterior teeth [Figure 1]. Considering post-COVID status and the floating upper anterior segment from the maxillary jaw, a provisional diagnosis of CAM was made. Alveolectomy of the upper anterior maxilla along with extraction of 11, 22, 23, and 24 were done and sent for histopathological examination. On gross examination, the hard-tissue specimens were brownish-black in color [Figure 2]. Microscopically, multiple fragments of lamellar bone with empty osteocytic lacunae were seen in association with branching aseptate, broad hyphae suggestive of mucormycotic maxillary osteonecrosis [Figure 3]. No episode of recurrence was noticed after a follow-up period of 6 months.

Case 2

A 56-year-old male patient presented with a complaint of pain in the upper right jaw region following the extraction of his front teeth. On eliciting the history of the presenting illness, the patient was diagnosed as COVID positive 2 months ago and was administered steroid (Posaconazole 300 mg). A few days later, the patient developed pain and difficulty in opening the right eye. A diagnosis of Rhino–Orbital Mucormycosis was given, and orbital exenteration was done. Two weeks later, the patient developed pain and mobility in the upper front tooth, for which extraction was done. Approximately 7 days following extraction, the patient again developed pain in the extraction site. Intra-oral examination revealed a necrotic lesion on the right side of the palate [Figure 4]. Considering the past medical history, a provisional diagnosis of mucormycosis was given. A partial right maxillectomy with 15, 16, 17, turbinectomy, and maxillary sinus debridement were done under general anesthesia [Figure 5]. On gross examination, the specimens were brownish-black in color and hard in consistency. The tissue section showed nonseptate, broad, ribbon-like hyphae in the fibrous connective tissue stroma [Figure 6]. Fragments of lamellar bone with empty osteocytic lacunae suggestive of sequestrum were also evident. The connective tissue stroma exhibited chronic inflammatory cell infiltrate, predominantly plasma cells, and macrophages. Thus, post-COVID mucormycosis associated osteonecrosis was considered as the final diagnosis. Follow-up imaging study was done after 6 months and was found to be uneventful.

Discussion

The term "coronavirus" was derived from the crown-like morphology of the virus. SARS and Middle East Respiratory Syndrome outbreaks have emerged in China and Middle East countries, respectively. Belonging to the beta-corona virus subgroup, the COVID-19 pandemic is still continuing worldwide with subsequent mutations in the virion.[4] The devastation caused by the COVID-19 pandemic also led to a rise in secondary infections in patients with severe forms of infection. Mucormycosis has been described

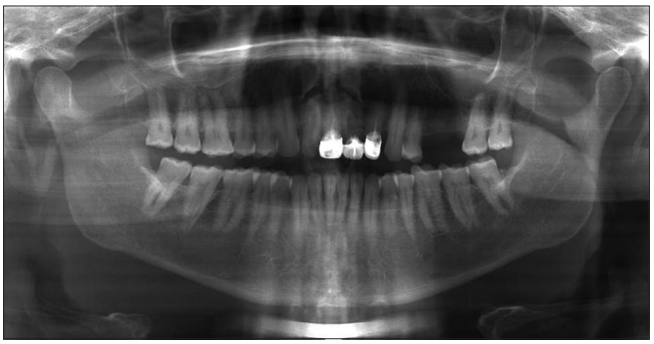

Figure 1: Orthopantomogram depicting ill-defined radiolucency in the periapical region of upper anterior teeth

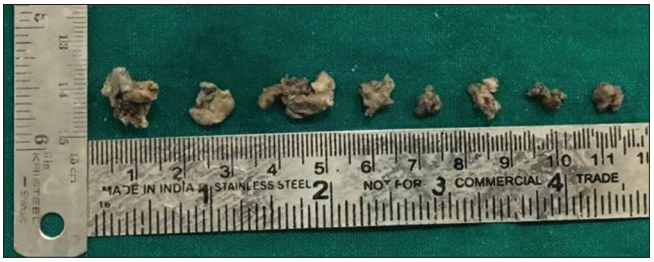

Figure 2: Gross specimen from the maxillary anterior region

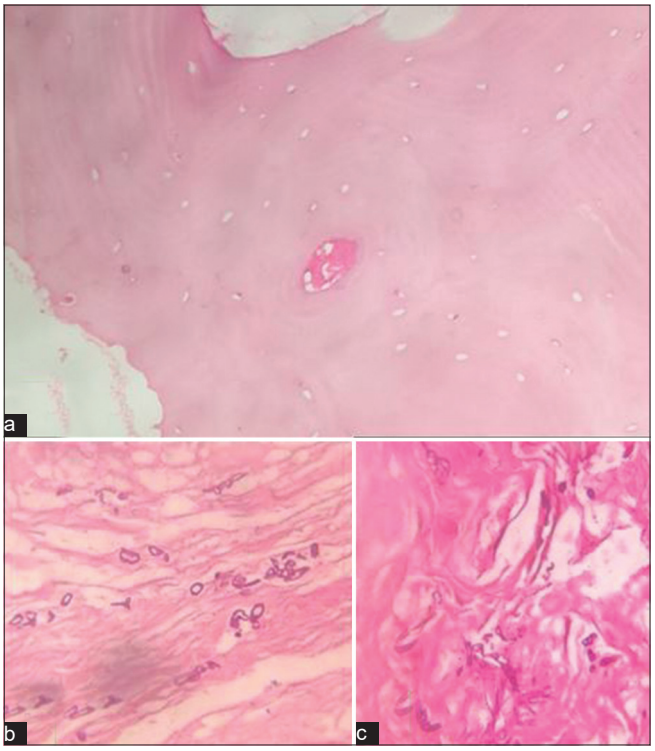

Figure 3: (a) Lamellar bone with empty osteocytic lacunae (×10), (b and c) dispersed branched, aseptate hyphae along with few circular to oval spore forms in the stroma (×40)

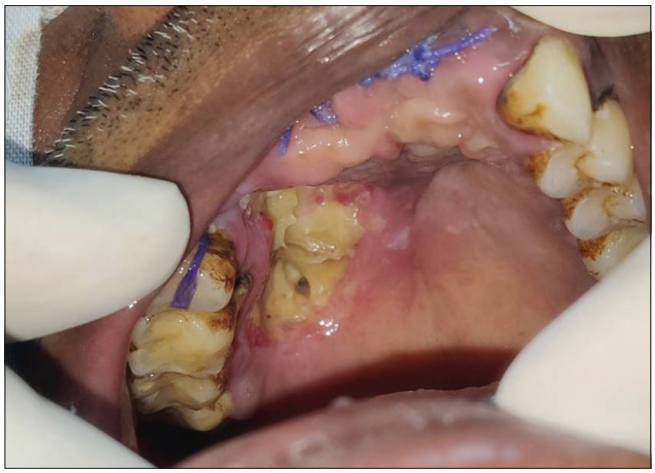

Figure 4: White necrotic lesion on right palatal aspect postextraction

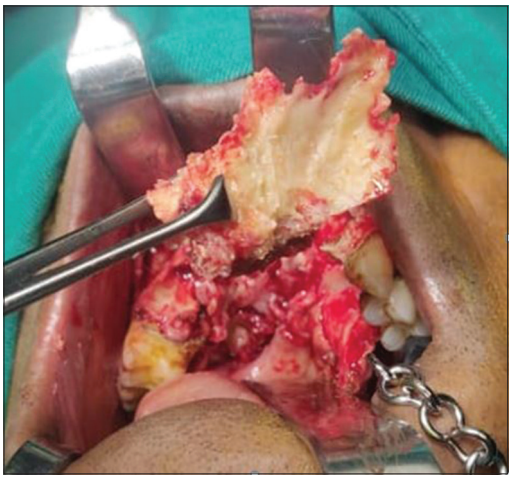

Figure 5: Partial right maxillectomy in relation to 14, 15, 16 and sinus debridement

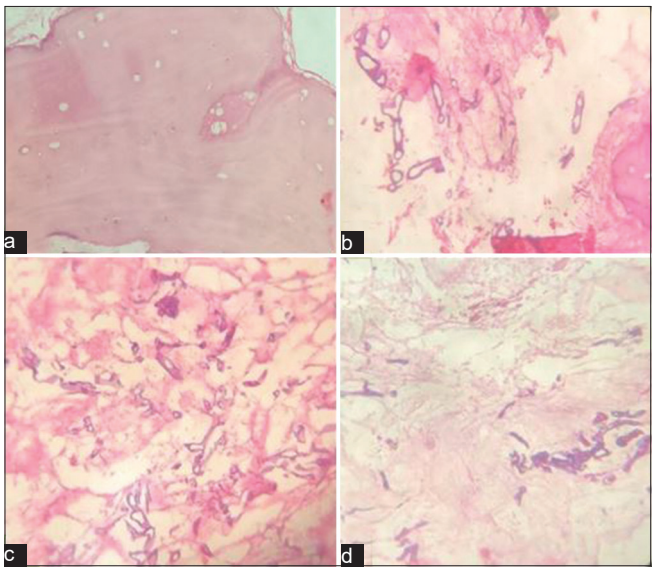

Figure 6: (a) Fragmented lamellar bone with empty osteocytic lacunae (×10), (b-d) Broad, aseptate hyphae with right-angled branching (×40)

as COVID-19-related comorbidity in various countries. An alarming increase in the number of reported cases of mucormycosis in post-COVID patients was reported in India in 2021. It was also commonly referred to as "Black fungus" as the affected region appeared black.[5,6]

Mucormycosis (Zygomycosis/Phycomycosis) is an acute opportunistic fungal infection caused by *Mucorales*. *Mucor* and *Rhizopus* are the most common organism causing the noncontagious, angio-invasive fungal infection. As the fungal spores are ubiquitously present in air, they can be easily inhaled. Since the patients' principal innate immune response, nasociliary clearance, is impaired, the spores readily infiltrate the nose and paranasal sinus.[6,7] These fungi undergo a change in morphology from sporangiophore to coenocytic hyphae after invading the host cell, thereby suppressing the host immune response.[8] Angioinvasion is the hallmark of mucormycosis. The organism has a higher affinity for blood vessels and multiplies within the vessel wall. Eventually, it causes thrombosis, ischemia, and necrosis of tissues such as nasal mucosa, palate, and turbinates. Necrosis of bone might be the sequelae in untreated cases with involvement of orbit, cranium, and jaw bones. The organism invades the bloodstream to be seeded into visceral organs such as the brain and lungs causing cerebral and pulmonary forms of mucormycosis.[9,10]

Based on the site of involvement, mucormycosis is classified as rhino–orbito–cerebral mucormycosis, pulmonary, gastrointestinal, renal, cutaneous and miscellaneous forms affecting parotid, bones, and lymph nodes. Although osteomyelitis is rare in the maxilla owing to the rich vascular supply and thin cortical plates, maxillary mucormycosis was reported to be the common form in the head-and-neck region. This can be attributed to vascular insufficiency caused by the invasion of the endothelial lining of the blood vessels by fungi.[9-11]

Major predisposing factors for developing mucormycosis include uncontrolled diabetes, ketoacidosis, immunosuppressant drugs, use of corticosteroids, hematologic malignancies, and organ transplantation.[12,13] In patients with COVID-19, Song *et al*. reported diabetes and the use of corticosteroids to be the most common cause of mucormycosis.[1] Co-incidence of diabetes mellitus, COVID-19 infection, and steroid medication reckons up immunosuppression and hyperglycemia that can result in fatal fungal colonization.[14] Concomitant systemic disease, steroid therapy and immune deficiency have also been documented to cause osteonecrosis. Bindakhil and Mupparapu reported medication-related osteomyelitis of the mandible in a patient with a history of tocilizumab.[15] Dogra *et al*. reported that treatment with monoclonal antibodies such as tocilizumab and itolizumab also causes immunosuppression and makes the patient susceptible to fungal infection.[6] Fakhar *et al*. reported two cases of floating upper teeth with maxillary mucormycosis as post-COVID sequelae in a 35-year-old male patient with a 5-year history of diabetes and a 40-year-old male patient with a 6-year history of diabetes. Our first patient had a similar floating anterior segment of the upper jaw, as reported

by Fakhar *et al*.[16] Rao *et al*. reported 10-15 days as the time interval between diagnosis of COVID-19 and mucormycosis in their case series of 28 patients of CAM from Bengaluru and Kalaburagi districts. The study also reported that nasal or paranasal symptoms were the earliest presentation in the COVID recovery period rather than dental symptoms, which is in concordance with both of our patients.[14] Indian Council of Medical Research also suggested that nasal congestion, paranasal sinus pain, headache, numbness, dental pain, floating of teeth, and avascular necrosis could be considered as clinical presentations of mucormycosis.[17] Pauli *et al*. reported a case of mucormycosis in a 50-year-old diabetic female patient with a painful lesion on the hard palate approximately 8 days after the diagnosis of COVID-19. It was also described that the permeability of the cell wall to these pathogens and avascular osteonecrosis may be attributed to the increased prevalence of oral lesions in COVID patients.[18]

Steroids have been identified to cause drug-induced hyperglycemia resulting in dysfunction of the immune system. The steroid-induced hyperglycemia results in defective phagocytic activity and immunosuppression. Bellanger *et al*. reported that a 55-year-old male patient who was treated with steroids during COVID infection, developed mixed mold infection with *Rhizopus microsporus* and *Aspergillus fumigates*.[19] Said Ahmed *et al*. reported 14 cases of maxillary mucormycotic osteomyelitis in post-COVID patients ranging from 29 to 76 years of age; among them, 9 were known diabetic, whereas 5 of them developed temporary post-COVID hyperglycemia.[11] Kontoyiannis and Lewis proposed that a high dose of corticosteroids for a period of 3 weeks predisposes a patient to risk of developing opportunistic mucormycosis from immunosuppression.[20] Mohammadi *et al*. reported post-COVID mucormycosis from *Rhizopus oryzae* in a 59-year-old non-diabetic male patient who was treated with methylprednisolone for COVID.[21] Thus steroids are responsible for causing hyperglycemia in non-diabetic patients as it increases insulin resistance, lipolysis, gluconeogenesis and also decreases the peripheral glucose uptake by muscles, adipose tissue. Drug-induced hyperglycemia from steroid administration depends upon the duration and dosage.[22]

Conclusion

Oral mucormycotic osteomyelitis is a rare condition that is predisposed by uncontrolled diabetes mellitus and immunocompromised state. Even though it is less prevalent, clinicians must be aware of this condition and assess for the same in patients with post-COVID-19 manifestations as they initially present with minor symptoms such as pain, swelling, and mobility of teeth. If left untreated or diagnosed at a later stage, the rapid course of the disease may prove to be fatal for the patient.

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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