INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused by coronavirus disease 2019 (COVID-19) has been linked to a variety of opportunistic bacterial and fungal diseases. As we all know, mild COVID-19 may be treated with symptomatic and supportive care such as antipyretics, analgesics, non-steroidal anti-inflammatory drugs (NSAID), and oxygen therapy. However, other drugs such as tocilizumab and corticosteroids have been recommended for the treatment of severe cases and progressive illnesses. Corticosteroids, such as dexamethasone and methylprednisolone, are used to reduce inflammation. In previous research, both of these medicines were demonstrated to enhance outcomes in patients with COVID-19 pneumonia. Invasive fungal infections, especially aspergillosis and cerebral rhino mucormycosis, have recently increased in Iran in the new wave of COVID-19. A saprophytic fungus of the family Mucoraceae is the causal agent of rhino-cerebro-orbital...
mucormycosis. Its spores infect the host’s paranasal sinuses, causing vascular invasion and thrombosis, which leads to extensive tissue necrosis. Immuno-compromised patients, uncontrolled diabetic mellitus, and patients taking steroids are more susceptible to these infections.

The clinical manifestation of mucormycosis depends on the site of entry of the fungus and the organs involved. The most common form includes rhinocerebral, which involves the oral cavity, paranasal sinuses, orbits, and cranial. Other forms of mucormycosis are cutaneous, gastrointestinal, respiratory, and disseminated. Oral cavity mucormycosis is usually caused by inhalation of spores or direct contamination of an open oral wound. This infection affects immunosuppression patients, especially those with diabetes mellitus (DM) and corticosteroid therapy, as has been described in the literature. Here, we report two rare cases of maxillary destruction with mucormycosis following post-COVID-19 in diabetic patients.

2 | CASE PRESENTATION

2.1 | Case 1

A 35-year-old man with a 5-year history of uncontrolled diabetes, after improving from a coronavirus infection, was referred to a dentist with complaints of swelling and numbness on the right side of his face and periorbital, an ulcer on the nose, and a floating 2nd premolar tooth in the upper jaw. In orthopantomography (OPG) performed, maxillary osteonecrosis was diagnosed. The patient was referred to an ear, nose, and throat (ENT) specialist and a maxillofacial surgeon. The computed tomography (CT) scan and cone-beam computed tomography (CB-CT) requested for him confirmed the diagnosis of osteonecrosis and he underwent surgery. Then, the tissue debridement samples were sent to the pathology laboratory to rule out possible mucormycosis and malignancy (shown in Figure 1). Pathological findings showed fibroconnective tissue lining by squamous epithelium with necroinflammation and mucormycosis. Also, the patient was treated with drugs such as clindamycin (900 mg/TDS for 4 weeks), ciprofloxacin (400 mg/BD for 2 weeks), and liposomal amphotericin B (a dose of 5 mg/kg; a total dose of 400 mg daily for 10 weeks). He was discharged in good general condition and followed up six months later to prevent a recurrence.

2.2 | Case 2

A 40-year-old man with a 6-year history of diabetes under treatment with hypoglycemic agents following respiratory problems and a diagnosis of COVID-19 was admitted to the infectious ward. He was discharged after 10 days in good general condition. He returned 20 days later with

**FIGURE 1** (a) Photomicrograph showing broad and septate fungal hyphae with areas of osteonecrosis (head of blue arrow) and necrosis with acute and chronic inflammation (head of green arrow) (H & E stained section; 40x magnification); (b) CB CT is showing destruction of the bony wall of the alveolar, inferior cortex maxillary sinus and as well as mild resorption at the 2th premolar teeth in the right upper jaw; (C) CT scan (axial section) of the right maxillary sinus showing osteonecrosis (head of white arrow) in alveolar ridge
complaints of swelling on the left side of his face and the loss of six maxillary teeth. An OPG X-ray was performed, and there was no evidence of tooth decay (shown in Figure 2). Again, a CT scan was requested, and the upper jaw necrosis was reported. Finally, six teeth were extracted and the maxilla was debrided. Several debrided samples were sent to the pathology laboratory to rule out possible mucormycosis and malignancy. Laboratory findings showed fibroconnective tissue lining by squamous epithelium with necroinflammation and fungal elements compatible with mucormycosis. Next, the patient was treated with clindamycin (900 mg/TDS for 4 weeks), ciprofloxacin (400 mg/BD for 4 weeks), and liposomal amphotericin B (a dose of 5 mg/kg; a total dose 300 mg daily for 10 weeks). He was discharged in good general condition and followed up six months later to prevent a recurrence.

3 | DISCUSSION

Mucormycosis is a rare fungal infection that can cause widespread necrosis of orofacial tissues in susceptible hosts. Though the incidence of mucormycosis secondary to tooth extraction and floating is extremely low, when it occurs, it may cause significant morbidity and mortality. Recently, the Indian Council of Medical Research (ICMR) suggested that clinicians and medical centers should consider clinical manifestations of mucormycosis such as sinus pain, nasal congestion on one side of the face, unilateral headache, swelling or numbness of the face, toothache, and floating of the teeth.9

Because both corticosteroids and tocilizumab have anti-inflammatory and immunomodulatory properties, it is possible that combining the two medicines might cause fungal infection or aggravation of pre-existing fungal illness in susceptible people.10 Mucormycosis is a rare opportunistic fungal infection caused by mucorales. It was first reported in humans by Paultaufin in 1885.7 These fungi are quite invasive, and their intra-orbital and intra-cranial expansion are linked to a high rate of morbidity and mortality. As a result, in these COVID patients, regular follow-up should be scheduled, not only to maintain glycemic control but also to detect early symptoms of invasive fungal infections.5 Medication-related osteonecrosis of the jaw (MRONJ) is a condition characterized by the necrosis of the jawbones in patients who have been exposed to a variety of drugs, including bisphosphonates, antibodies to receptor activator for nuclear factor kappa-beta ligand (RANKL), angiogenic inhibitors, tyrosine kinase inhibitors, and vascular endothelial growth factors.10

Concomitant steroid therapy and systemic diseases such as diabetes and a weakened immune system have also been shown to aggravate jaw osteonecrosis.11 Compared to the mandible, osteomyelitis is rare in the maxilla due to its extensive vascularity and porous architecture.12 But in both our cases, with a history of DM and COVID-19 infection, maxillary involvement was observed. Also, in multiple specimens obtained from bony tissue necrosis, fibroconnective tissue lined by squamous epithelium with necroinflammation and rhinocerebral mucormycosis is characterized by urgent, irreversible diseases, and often lethal opportunistic infections.7 Since the fungus enters the oral cavity and paranasal sinus, it can cause necrotizing fasciitis in the oral tissue and sinus, infecting an immunocompromised or diabetic host, which can quickly develop into the orbit, muscles of the face, and cranial cavity.8

Osteonecrosis from paranasal sinus mucormycosis often has no symptoms despite severe invasive disease, and even if the disease manifestations are symptomatic, they appear with a delay.13,14 This seems to be due to the vascular permeability of fungi and their tendency to develop into the soft tissues of the orbit, muscles of the face, and brain through blood vessels. The treatment of chronic rhinocerebral mucormycosis is unknown, but the treatments used include debridement of the lesion with surgery, infusion of high-dose liposomal amphotericin B, resuscitation of the metabolic and electrolyte disturbance, and hyperbaric oxygen.15

FIGURE 2 (a) OPG X-ray showing losing of six tooth in right maxillary jaw (b) Photomicrograph showing broad ribbon-like hyphae with haphazard branching (H & E stained section; 40× magnification)
CONCLUSION

So, we can conclude that corticosteroids and tocilizumab regimens used alone or in combination for the treatment of progressive COVID pneumonia should be prescribed with caution, and the medical community should be aware of the potential risks of invasive maxillofacial fungal infections and jaw osteonecrosis. Diabetic individuals, as well as those who take any of the medications linked to MRONJ, are at a higher risk of developing these diseases. As a whole, dentists, ENT surgeons, and maxillofacial surgeons should be aware of the possibility of this serious complication, so as to avoid undesirable results.

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Declared none.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

MF, ZZ, MG and RP were involved in the interpretation and collecting of data and editing of the manuscript. ASH, ESB involved in writing and preparing the final version of the manuscript. MS was responsible for collecting data and submitting the manuscript. All authors reviewed the paper and approved the final version of the manuscript.

ETHICAL APPROVAL

The study was approved by our local ethics committee.

CONSENT

Written informed consent for publication of this case report was obtained from the patients.

DATA AVAILABILITY STATEMENT

The data are available with the correspondence author and can be achieved on request.

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