CASE REPORT

Olgu Sunumu

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Post-COVID-19 Maxillary Actinomycotic Osteonecrosis: Diagnosis, Treatment, and Follow-Up Outcomes

Post-COVID-19 Gelişen Maksiller Aktinomikotik Osteonekroz: Tanı, Tedavi ve Takip Sonuçları

ABSTRACT
Osteonecrosis can be seen in post-Covid-19 patients due to the damage to their immune systems and the medications they take. This case report deals with the diagnosis, treatment and follow-up of actinomycotic osteonecrosis of the maxilla, which is one of the very rare post-covid conditions. The medical history of the 48-year-old patient, who had received treatment for Covid-19 in the intensive care unit about 1-year ago and had no systemic disease, revealed left palatinal and buccal bone exposure, suppuration and oroantral relationship. After limiting the lesion with pentoxifylline and alpha tocopherol, all necrotic bone tissue was removed and the area was closed with Bichat fat pad. The removed tissue was sent for histopathologic and microbiologic examination. The area was closed primerally. Postoperative follow-up of 1 year was completed and no new lesion was observed. Microbiologic evaluation was positive for actinomyces. This case may shed light on clinicians to give importance to the follow-up of patients with Covid-19 and its variants, especially if they have a history of hospitalization, to provide a differential diagnosis for PC-RONJ even if the interval is long, and not to skip the microbiological evaluation stage.

Key Words
Post Covid-19, Actinomycosis, Osteonecrosis

ÖZ
Bağışıklık sistemine verilen hasar ve kullanılan ilaçlar nedeniyle osteonekroz, COVID-19 sonrası hastalarda görülebilir. Bu olgu sunumu, nadir görülen post-COVID durumlarından biri olan maksiller aktinomikotik osteonekrozun tanı, tedavi ve uzun dönem takip sonuçlarını ele almaktadır. Yaklaşık bir yıl önce yoğun bakımda COVID-19 tedavisi gören ve herhangi bir sistemik hastalığı bulunmayan 48 yaşındaki hastada sol palatinal ve bukkal bölgede kemik ekspozisyonu, süpürasyon ve oroantral ilişki tespit edilmiştir. Lezyonun progresyonu pentoksifilin ve alfa-tokoferol ile kontrol altına alındıktan sonra nekrotik kemik dokusu tamamen uzaklaştırılmış ve defekt bölgesi Bichat yağ dokusu ile kapatılmıştır. Çıkarılan doku histopatolojik ve mikrobiyolojik incelemeye gönderilmiş, bölge primer olarak kapatılmıştır. Bir yıllık postoperatif takip sürecinde nüks veya yeni lezyon gözlenmemiştir. Mikrobiyolojik değerlendirme sonucunda Actinomyces varlığı doğrulanmıştır. Bu olgu, özellikle hastanede yatış öyküsü bulunan COVID-19 hastalarının uzun vadeli takibinin önemine dikkat çekmekte, geç dönemde dahi PC-RONJ ayırıcı tanısının göz önünde bulundurulması ve mikrobiyolojik değerlendirme aşamasının ihmal edilmemesi gerektiğini vurgulamaktadır.

Anahtar Sözcükler
Covid-19, Aktinomikoz, Osteonekroz

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INTRODUCTION

Covid-19, declared a pandemic by the World Health Organization in early 2020, is known to be associated with high morbidity and severe mortality rates. The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the coronavirus family of RNA viruses (1). The pathogenicity of viral infections is associated with viruses targeting Angiotensin Converting Enzyme 2 (ACE-2) receptors, facilitating viral entry into cells. ACE-2 receptors are distributed throughout the body in various tissues, including type II alveolar pneumocytes in the lungs, vascular endothelial cells, smooth muscle cells, and enterocytes in the intestines, as well as the oral and nasal mucosa (2). Complications related to Covid-19 in the oral cavity region have been reported as a consequence of high ACE-2 expression in epithelial cells within the oral cavity. This indicates that the oral cavity may be considered a potentially high-risk area for Covid-19 infection susceptibility (3).

However, the dysregulated immune response resulting from COVID-19 infection is known to predispose patients to opportunistic infections, especially fungal infections. COVID-19 infection represents an important risk factor for opportunistic infections due to associated immune system dysregulation and the use of immunosuppressive therapies such as corticosteroids or other immunomodulatory drugs (4). Among these opportunistic infections is actinomycosis, which is caused by species of Actinomyces (4,5). Actinomycosis is a rare anaerobic bacterial infection caused by gram-positive, immobile, filamentous bacterial rods that are acid-fast. Clinically, actinomycotic infections are classified into three subtypes: cervicofacial, thoracic, and abdominal. The cervicofacial subtype is the most common form of actinomycotic infection (6).

Some predisposing factors, such as secondary microbial infections and comorbidities, have been reported to contribute to jaw osteonecrosis in Covid-19 patients. Cases of osteomyelitis and osteonecrosis caused by actinomycosis infection in the jaws post-Covid-19 further underscore this scenario (2,5).

This case report aims to present the diagnosis, treatment, and follow-up process of actinomycotic maxillary osteonecrosis following Covid-19. This condition initially resembles MRONJ (medication-related osteonecrosis of the jaw) and underscores the importance for clinicians.

CASE REPORT

A 48-year-old man without known systemic diseases presented to our clinic in April 2022 with complaints of pain and swelling in the left palatal region. Examination revealed exposed bone tissue in the posterior palatal and buccal regions of the left maxilla. Intraoral assessment showed poor oral hygiene, suppuration at the borders of necrotic bone, and an oroantral fistula in the left maxillary region. The patient did not specify an exact onset time but reported that his symptoms had worsened over the past month.

In the patient's medical history, it was noted that he presented to the emergency department in August 2021 with complaints of dyspnea, general discomfort, and myalgia. Following diagnostic scans, he tested positive for COVID-19 PCR and subsequently received treatment in the intensive care unit due to diffuse pulmonary involvement and low SpO_2 levels. During his hospitalization, which lasted for a total of 12 days, he spent 5 days in the second-level intensive care unit of anesthesia and reanimation, followed by 7 days in the internal medicine service. To manage respiratory distress caused by Covid-19, he received intravenous methylprednisolone (Prednol-L 40 mg, Gensenta Drug Industry, Turkey) twice daily for 9 days, and budesonide (Pulmicort Turbuhaler 200 mcg/dose, Astra Zeneca Drug Industry, Sweden) via inhalation twice daily for 2 days. During his stay in the intensive care unit, his fasting blood glucose levels were measured as 161,8 mg/dl on two separate days and 133,2 mg/dl on another day.

During the week following discharge from the hospital, the patient observed bloody purulent discharge from his nose and noticed bone exposure. Seeking medical attention at a private clinic, he underwent debridement and was informed that this was likely a temporary complication related to sinusitis. Subsequently, he sought treatment at another facility for sinusitis management before being referred to the oral and maxillofacial surgery clinic.

On the day the patient was admitted to the Oral and Maxillofacial Surgery clinic, he was referred to the Periodontology clinic for improved oral hygiene and to the Hematology clinic for evaluation of his blood profile. On the same day, the patient was empirically treated with oral amoxicillin-clavulanic acid 1000 mg twice daily and oral ornidazole 500 mg twice daily for a 2-week course, followed by intramuscular clindamycin 600 mg twice daily for 5 days. This treatment successfully resolved suppuration in the affected area. Subsequently, the patient was prescribed pentoxifylline (Trentilin 400 mg tablet, Santa Farma Drug Industry Turkey) twice daily and alpha-tocopherol (Evicap Fort 400 E capsule, Kocak Farma Drug Industry, Turkey) twice daily for 2 months, which helped limit the area of bone necrosis. By the end of the first month of treatment, teeth 24 and 25, which were situated within the necrotic bone area and had lost significant bone support, were extracted due to their excessive mobility (Figure 1).

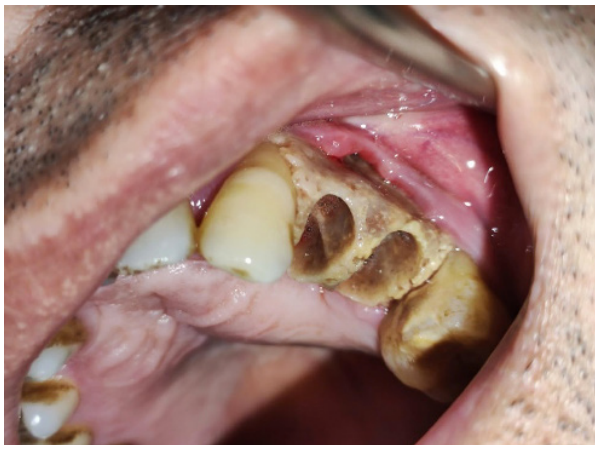

Figure 1. Intraoral photograph demonstrating exposed necrotic bone

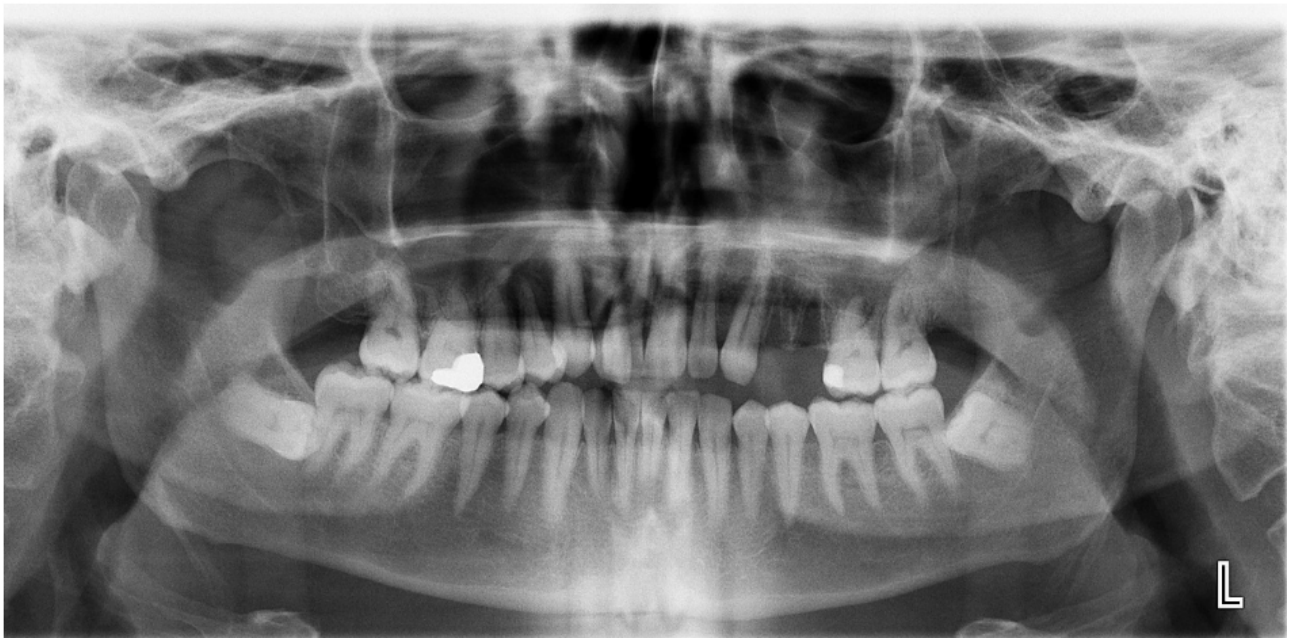

Figure 2. Panoramic radiographic image showing osteolytic and destructive lesions in the left maxillary and anterior region

At the conclusion of pentoxifylline treatment, the patient's overall condition improved, and intraoral hard and soft tissues became suitable for surgery. Following examination of panoramic and CBCT (cone beam computed tomography) images (Figure 2, Figure 3A, Figure 3B), resection of the necrotic bone was recommended. This statement clarifies that the patient's condition and tissue suitability improved after treatment, leading to the decision for surgical intervention based on diagnostic imaging.

Under local anesthesia, a horizontal incision was made extending from tooth 14 to the mesial border of tooth 27, and a full-thickness flap was raised. Teeth 11, 12, 13, 21, 22, 23, and 26 were extracted along with the necrotic alveolar bone (Figure 4). Dense granulation tissue observed in the perforated sinus area was carefully curetted to integrate with the sinus membrane.

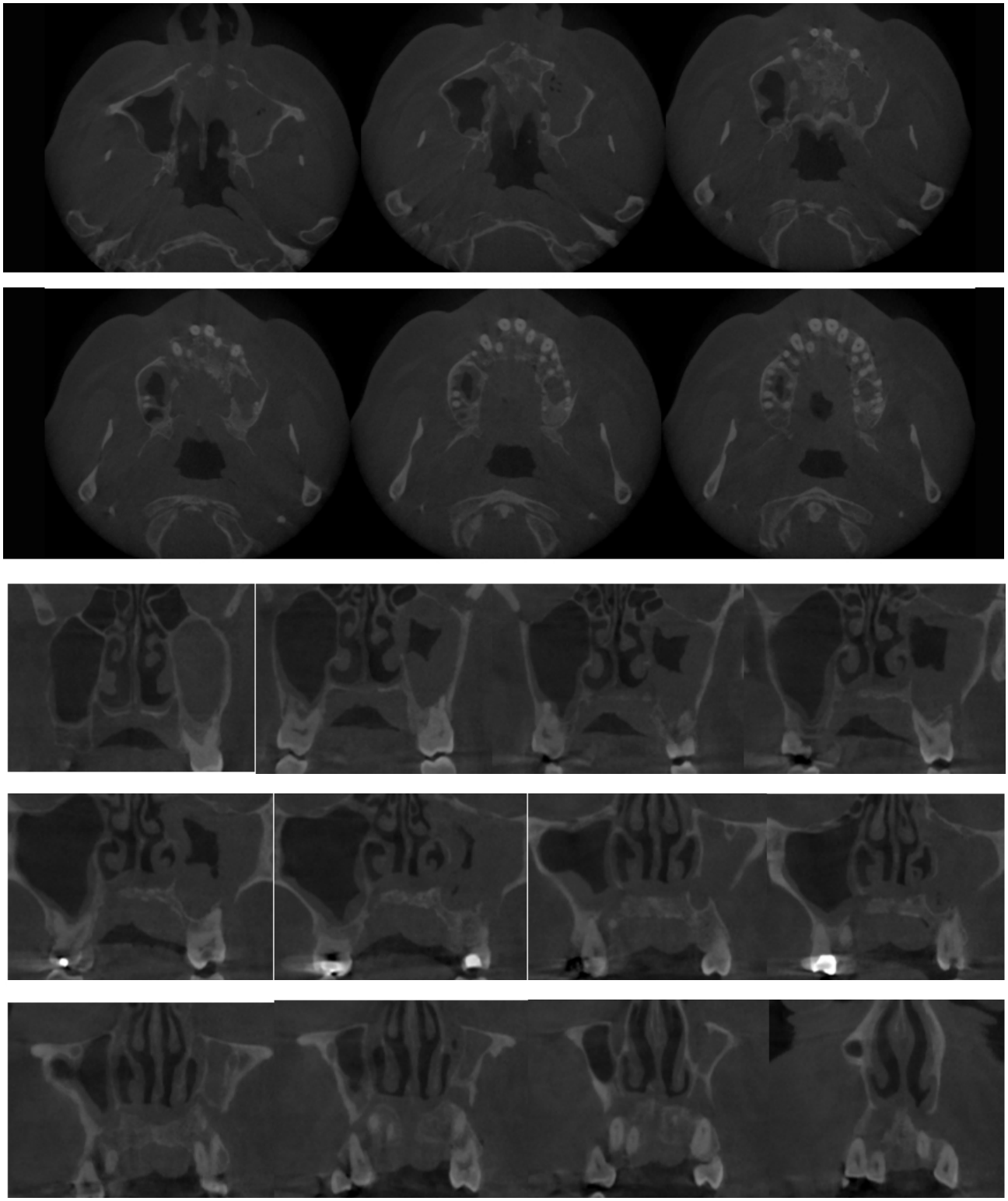

Figure 3. Cone beam computed tomography images depicting the lytic and destructive lesion in the left maxillary and anterior region, shown in (A) axial and (B) coronal sections.

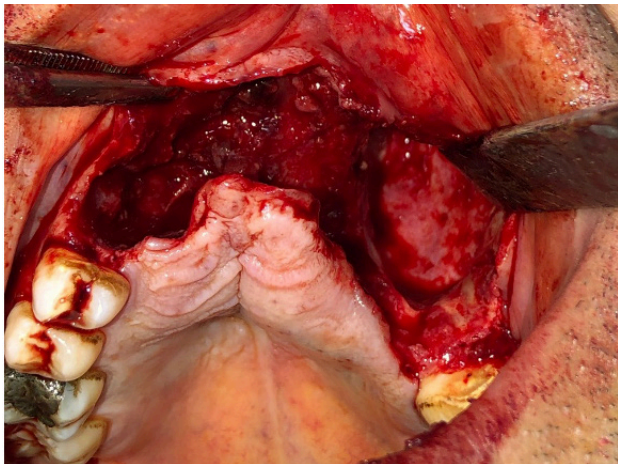

Figure 4. Extraction of teeth numbered 11, 12, 13, 21, 22, 23, and 26 along with necrotic alveolar bone

To reconstruct the anterior region, a half-thickness flap was elevated from the palatal region and rotated to suture onto the buccal mucosa in the anterior region. For the posterior region, Bichat adipose tissue was used to achieve primary closure (Figure 5).

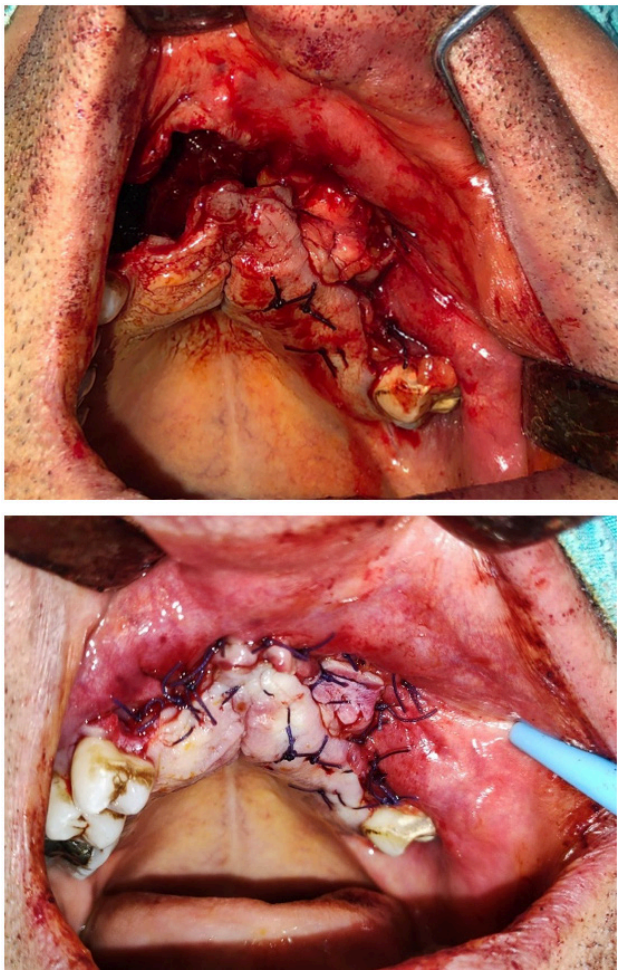

Figure 5. Half-thickness flap harvested from the palatal region for anterior area reconstruction, utilization of Bichat's fat pad for posterior area reconstruction, followed by primary closure with buccal mucosal flap

Postoperatively, the patient was prescribed amoxicillin-clavulanic acid 1000 mg twice daily for 7 days, cetirizine, oxymetazoline, etodolac sodium, and chlorhexidine. Soft and bone tissue samples removed from the region were sent for histopathological examination. Histiocytes within the granuloma structure stained positive for CD 68 on immunohistochemistry. The epithelium showed positive staining with Pan CK. Histochemically, actinomycetes were identified and stained positive with PAS (Periodic Acid-Schiff) and GMS (Gomori Methenamine Silver).

At the 1-year postoperative follow-up, intraoral and radiographic examinations showed that the soft tissue was intact, and there were no signs of infection or osteonecrosis (Figure 6). The patient is still under follow-up.

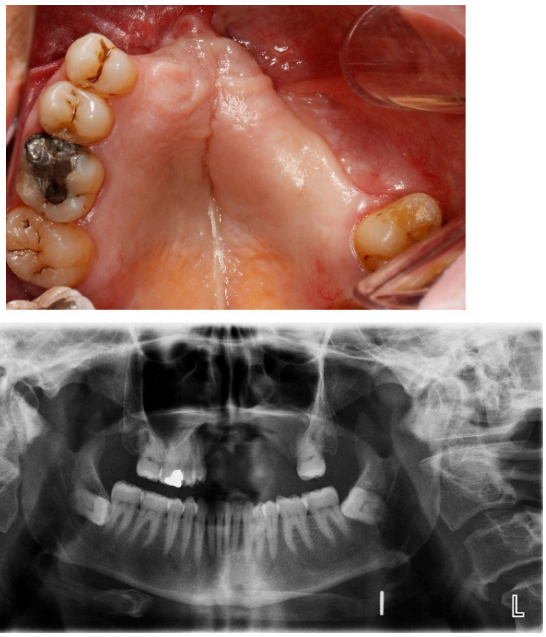

Figure 6. Intraoral view of the maxillary region and panoramic radiographic image at the 1-year follow-up postoperatively

DISCUSSION

COVID-19 has caused a large number of deaths and serious health problems globally, and many first-time clinical cases have been reported in the literature. This case report is one of the rare reports of actinomycetes-induced osteonecrosis of the jaw in a patient hospitalized and treated with corticosteroids due to COVID-19 (5,7). Considering the length of time between the patient's hospitalization due to the outbreak and his presentation to our clinic with maxillary osteonecrosis, we believe that there may be more cases of osteonecrosis that have not been associated by clinicians, missed in microbiological evaluation, or not reported. With this case report, we aim to contribute to the literature, encouraging clinicians to review the characteristics of the cases they encounter and to develop perspectives for treatment protocols.

Osteonecrosis of the jaws is defined as necrosis of the jaw bones resulting from decreased blood supply to bone tissue due to radiation, drug therapy, trauma, infection, and malignancy (5). Many factors in the biological course of COVID-19 have the potential to contribute to the development of osteonecrosis of the jaw. Primarily, SARS-CoV-2 infection causes endothelial dysfunction, leading to excessive thrombin generation and increased hypercoagulability (8). The virus also induces a hyperinflammatory state with ACE-2 downregulation, which increases microvascular thromboses and hypercoagulability, thereby raising the risk of osteonecrosis (9). Corticosteroids and biologic drugs (e.g., Tocilizumab) used in the treatment of COVID-19 contribute to the development of osteonecrosis due to their effects on the immune system (8,10,11). Additionally, bacterial and fungal co-infections (6,12) and concomitant diseases such as diabetes can weaken the immune system and promote osteonecrosis (10,13). All these factors are directly linked to the development of osteonecrosis of the jaw, either independently or through their interactions.

Among these factors, corticosteroids and immunosuppressant drugs used in the treatment of COVID-19 are the most commonly encountered and are frequently implicated in patients' medical histories. In a systematic review by Daltro et al. (10), the relationship between COVID-19 and osteonecrosis was evaluated. They concluded that there is sufficient evidence that COVID-19 patients are at risk for developing corticosteroid-associated avascular osteonecrosis. In the present case, it was noted that the patient had used high doses of corticosteroids both intravenously and via inhalation during hospitalization. We believe that inhaled corticosteroids may have increased the potential for osteonecrosis in the oral cavity and maxillary sinus. Kudva et al. reported a case initially thought to be mucormycosis in the maxilla; however, mucormycosis was not identified bacteriologically. The patient was treated with nintedanib for COVID-19, and both steroid use and diabetes were present in the medical history (14). The drugs used in our case did not include nintedanib, a tyrosine kinase inhibitor used for pulmonary fibrosis.

All patients who develop actinomycosis of the jaw as a secondary infection after COVID-19 have at least one comorbid factor, such as diabetes mellitus, hypertension, cardiac diseases, or cancer (5-7,15). Our patient, however, did not have any systemic diseases other than a history of COVID-19 infection.

All reported cases of a potential association between COVID-19 and osteonecrosis of the jaw have occurred in the maxilla. This may be related to the anatomical proximity of the maxilla to the nasal mucosa and maxillary sinus. Additionally, the high expression of ACE-2 receptors on nasal and oral mucosa epithelial cells should be considered a risk factor (2,3,16). In our case, as with all other cases of osteonecrosis following COVID-19 infection, maxillary osteonecrosis was observed.

As a result of the immunosuppression caused by COVID-19, opportunistic actinomycetes may invade deeper tissues and increase the risk of infection due to disruption of the mucosal barrier (5). When actinomycotic infection is combined with osteonecrosis, it presents a clinical condition similar to MRONJ cases. Therefore, considering possible predisposing factors for differential diagnosis, a specific guideline for the prevention, early diagnosis, and management of PC-RONJ (2) should be considered for patients at risk of developing osteonecrosis after infections caused by COVID-19 and its variants. In addition to a history of current or previous radiotherapy, intake of antiresorptive or antiangiogenic agents, trauma, and malignancy, a recent COVID-19 infection with concurrent cumulative corticosteroid/immunosuppressant drug therapy may be considered as accelerating factors for the occurrence of osteonecrosis of the jaw. Bacterial and fungal infections due to immune system dysregulation as a result of COVID-19 infection and treatment should also be considered during and after treatment.

CONCLUSION

In conclusion, it is important to recognize that individuals infected with COVID-19 and its variants may develop multifactorial clinical conditions. Therefore, patients should be closely monitored for potential long-term complications, particularly those affecting the maxilla.

Author Contribution Statement

Case preliminary diagnosis and follow-up, article writing: C.N.E., M.A.A., B.K., S.U.D.

Conflict of Interest

None of the authors mentioned in this case report are or there is no conflict of interest with the organization.

Ethics Committee Approval

Consent was obtained from the patient. Ethics Committee Approval Certificate was not required.

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