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Mucormycosis-related osteomyelitis of the maxilla in a post-COVID-19 patient

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ABSTRACT

Mucormycosis is a rare, invasive fungal infection that progresses aggressively and requires prompt surgery and appropriate treatment. The number of cases of mucormycosis in coronavirus disease 2019 (COVID-19) patients has recently increased, and patients with uncontrolled diabetes mellitus are particularly at an elevated risk of infection. This report presents a case of mucormycosis-related osteomyelitis of the maxilla in a 37-year-old man with diabetes mellitus. The patient complained of severe and persistent pain in the right maxilla, accompanied by increased tooth mobility and headache. On contrast-enhanced computed tomographic images, gas-forming osteomyelitis of the right maxilla was observed. Destruction of the maxilla and palatine bone then proceeded aggressively. Sequestrectomy was performed on the right maxilla, and the histopathological diagnosis was mucormycosis. Further investigation after the first operation revealed the patient's history of COVID-19 infection. ***(Imaging Sci Dent 2022; 52: 435-40)***

KEY WORDS: Mucormycosis; Maxilla; Osteomyelitis; Diabetes Mellitus; COVID-19

Mucormycosis is a fungal infection mainly introduced through the nasal and paranasal sinuses, which infiltrates into blood vessels, reduces blood flow to tissues, and causes thrombosis. Fungal involvement of the jaw bone can cause osteomyelitis, especially in the maxilla and maxillary sinuses adjacent to the paranasal sinus.[1,2] Mucormycosis of the jaw bone is very rare, and its clinical signs are also non-specific. Moreover, the characteristic imaging findings of mucormycotic osteomyelitis have not been detailed, making it difficult to diagnose on imaging. However, early diagnosis and aggressive treatment are essential because mucormycotic infections tend to expand aggressively, and the prognosis varies depending on the patient's underlying condition.[3,4]

Since around 2020 and 2021, reports of mucormycosis cases in coronavirus disease 2019 (COVID-19) patients have been increasing rapidly, especially in India.[1,2,5-9] Some literature has referred to this disease as COVID-19-associated mucormycosis.[2] COVID-19 is an infection caused by severe acute respiratory syndrome coronavirus 2, a pandemic disease that has been causing global problems since it was first reported in Wuhan, China in 2019. COVID-19 affects not only the respiratory system, but also various organs in the body, causing various complications and opportunistic infections that can lead to death. In particular, the elderly, immunocompromised, or patients with underlying diseases such as diabetes or hypertension are more likely to experience serious symptoms and complications.[10] The purpose of this report was to present a case of mucormycosis-related osteomyelitis of the maxilla with imaging findings in a patient with diabetes who had a history of COVID-19 infection.

Case Report

A 37-year-old male patient visited a local clinic with severe pain in the right maxilla. The pain was not relieved even after root canal treatment and serial extraction of the right maxillary first premolar and first molar. Due to per-

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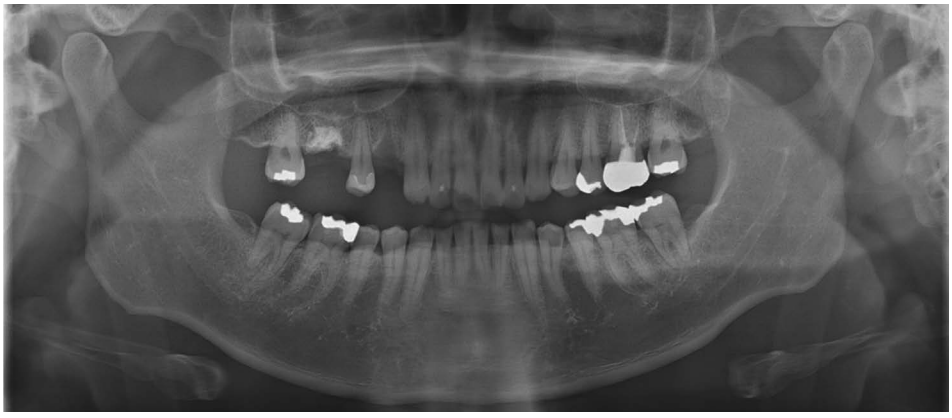

Fig. 1. Preoperative panoramic radiograph shows radiopaque foci thought to be a filling material at the extraction site of the right maxillary first molar, but there are no significant pathological findings in the right maxilla.

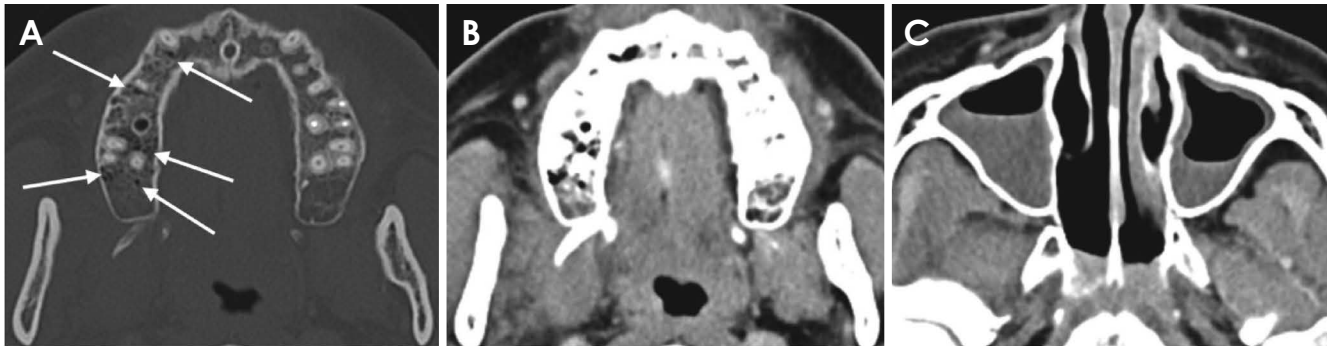

Fig. 2. A. A bone setting computed tomographic (CT) image shows multiple air voids (arrows) throughout the right maxilla and inside the extraction socket of the maxillary first molar. B. An axial enhanced CT image shows no significant inflammatory changes in the soft tissue surrounding the right maxilla. C. An axial enhanced CT image shows mucosal thickening with air-fluid level in both maxillary sinuses.

sistent pain and a sudden increase in the mobility of the right second premolar and molar, he was transferred to the Department of Oral and Maxillofacial Surgery at Seoul National University Dental Hospital 2 days later. The patient complained of extreme pain and a feeling of paralysis extending up to the head. The patient had been taking diabetes medication for 2 years and had mild hypertension. Panoramic radiography showed no significant pathological findings such as bone destruction in the right maxilla, other than radiopaque foci thought to be a filling material at the extraction site of the right maxillary first molar (Fig. 1). In an oral examination, pale bone exposure was found in the extraction socket of the right maxillary first molar, but there was no pus discharge. A blood test showed a serum glucose level of 185 mg/dL. At first, based on clinical findings such as bone exposure limited to the extraction site, increased tooth mobility, and persistent pain, osteomyelitis was suspected, and contrast-enhanced computed tomography (CT) of the paranasal sinuses was performed.

The enhanced CT scans were acquired by multi-detector CT (SOMATOM Definition Edge, Siemens, Erlangen, Germany), using a tube voltage of 120 kV, tube current of 400 mA, 3-mm slice thickness, and intravenous administration of non-ionic iodinated contrast material. The CT scans showed multiple air voids throughout the alveolus from the lateral incisor to the second molar of the right maxilla, presumed to be gas-forming (Figs. 2A and B). However, there was no evidence of destruction or isolation of cortical bone, or periosteal new bone formation. Inflammatory changes in the surrounding soft tissues were not evident. Mucosal thickening with air-fluid level blocking the ostium was also observed in both maxillary sinuses, and it was especially severe on the right side (Fig. 2C). The first imaging diagnosis was emphysematous osteomyelitis caused by gas-forming microbes. Based on clinical and imaging findings, sequestrectomy was performed in the right maxillary first molar area (Fig. 3). After the first operation, co-administration of antibiotics and analgesics, wound dressings, and saline washing were continued for about 2 weeks before a histopathological diagnosis was obtained. However, after 3 days, a buccal gingival fistula was observed with a percussion response of the right maxillary lateral incisor.

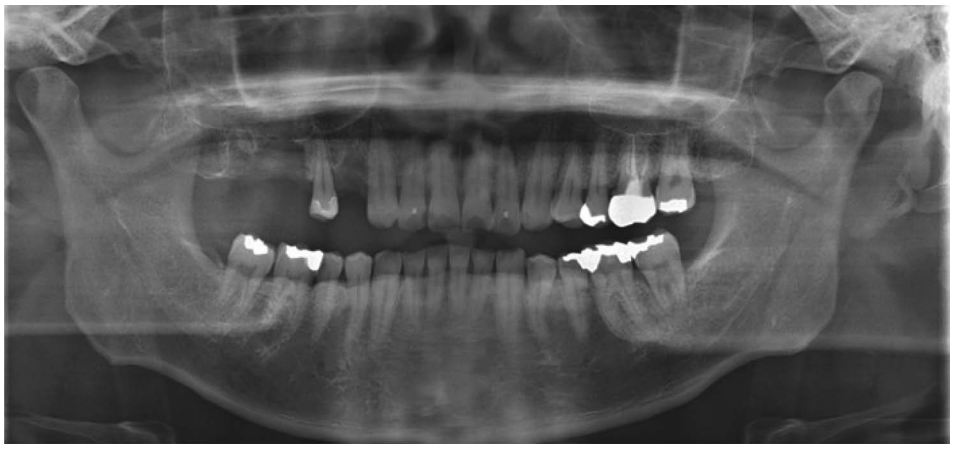

Fig. 3. Panoramic radiograph after sequestrectomy in the maxillary first molar area shows no significant pathological findings other than the postoperative findings.

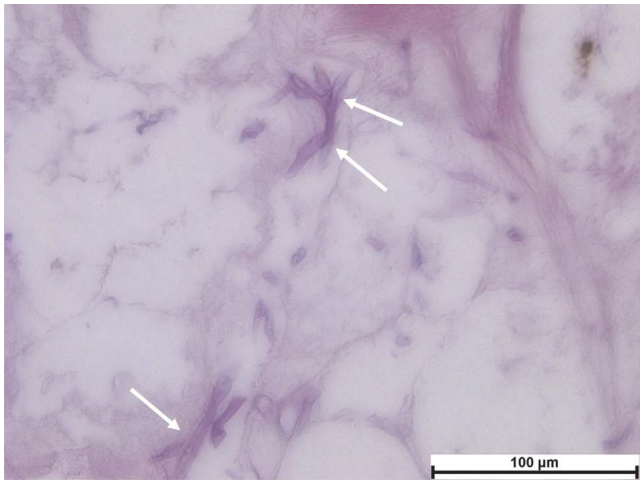

Fig. 4. Periodic acid-Schiff-stained section shows broad, irregularly branching hyphae characteristic of mucormycosis-causing organisms (original magnification ×40).

Palatal fistula formation was also observed. A few days later, the mobility of the right maxillary second molar increased rapidly, and a slight pus discharge was observed in the gingival sulcus. The histopathological findings led to a diagnosis of an invasive fungal infection, consistent with mucormycosis (Fig. 4). Meanwhile, in the course of surgery and supportive care, it was found that the patient had been infected with COVID-19 about 2 weeks ago and received home treatment, and the COVID-19 infection was presumed to be related to the onset of mucormycosis. The patient was referred to the Department of Infectious Diseases and started antifungal medication (amphotericin B). Additional sequestrectomy was then performed on the right maxilla, including the anterior and premolar region, maxillary tuberosity, and right maxillary sinus (Fig. 5).

One month after discharge, the patient came to the hospital for follow-up and complained of increased mobility and pain in the right anterior and canine areas. No signs of infection were observed on an oral examination. However, enhanced CT scans showed that bone destruction had progressed to the palatine bone and the left anterior maxilla (Figs. 6A and B). In addition, erosive bone changes had progressed upward to the sphenoid bones (Fig. 6C) on both sides of the middle cranial fossa, and mucosal thickening was also noted in the bilateral maxillary and sphenoid sinuses. Extraction and sequestrectomy were performed in the anterior maxilla and left maxillary premolar region (Fig. 7). Antifungal medication was then continued for 3 months after discharge. No additional bone destruction or signs of infection were observed on follow-up CT images 2 months after the third operation.

Discussion

This report described a case of maxillary mucormycosis osteomyelitis in a 37-year-old man with diabetes. Initially, when the patient's history of COVID-19 infection was unknown, he was first diagnosed with emphysematous osteomyelitis based on imaging findings. Small et al.[11] described the characteristic imaging findings of emphysematous osteomyelitis as multiple intramedullary gas clusters with irregular sizes on the scale of millimeters, which they called the "pumice stone" sign. A secondary imaging feature is emphysema of the adjacent soft tissue without cortical destruction. Ram et al.[12] reported that intramedullary gas findings were the result of infiltrating gas-forming bacteria from the surrounding soft tissue into the bone. In this patient, however, there was no extraosseous gas formation. Unlike the initial diagnosis, this case was histopathologically confirmed as mucormycosis after the first operation.

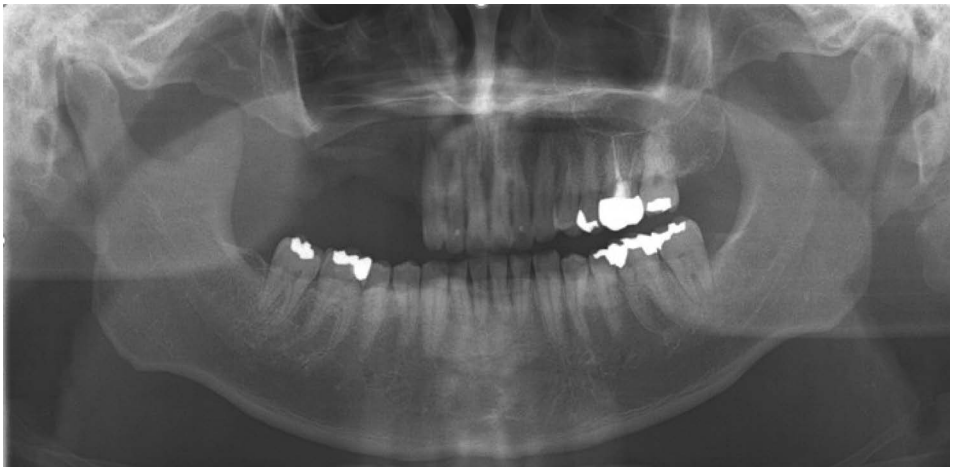

Fig. 5. Panoramic radiograph shows the postoperative condition after additional sequestrectomy in the right maxilla, including the maxillary tuberosity and maxillary sinus.

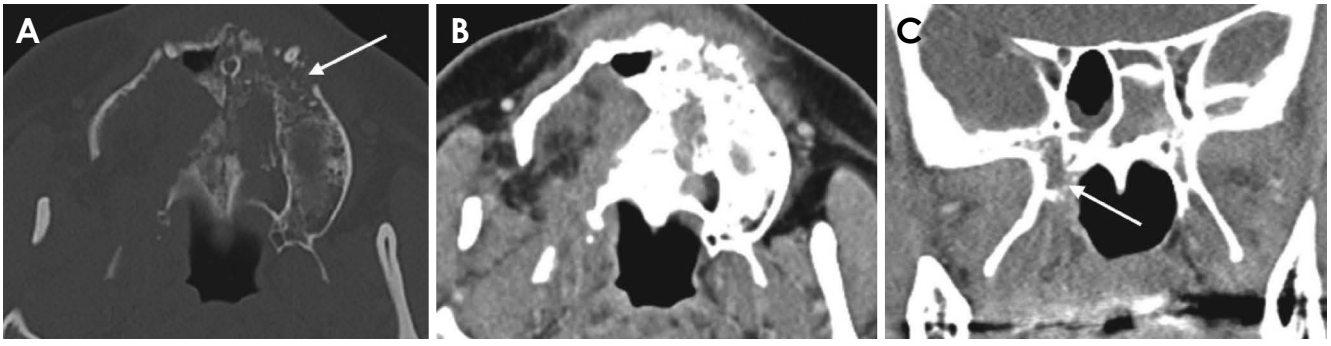

Fig. 6. Axial bone setting (A) and enhanced computed tomographic (CT) (B) images taken at a 1-month follow-up after discharge show bone destruction extending to the palatine bone and the left anterior maxilla (arrow). C. A coronal enhanced CT image shows erosive bone changes upward to the sphenoid bone (arrow).

In healthy individuals, mucormycosis is an extremely rare infection, but immunocompromised patients are susceptible to opportunistic infections. Mucormycosis is classified into 6 types according to the anatomical site affected.[13] In particular, rhino-orbital-cerebral mucormycosis is most prevalent in patients with diabetes mellitus or patients who have undergone a renal transplant.[14] Similarly, in this case, diabetes mellitus was a predisposing factor that induced rhinocerebral mucormycosis. The patient was on medication for diabetes, but a blood test at the time of admission showed uncontrolled hyperglycemia. Hyperglycemia and ketoacidosis in patients with diabetes lead to phagocyte dysfunction, impaired antioxidant mechanisms, and increased serum levels of free iron.[1,8,14] These conditions probably contributed to the morbidity of fungal growth, especially mucormycosis.

The imaging findings of mucormycosis are difficult to distinguish from bacterial infection, so a diagnosis based on imaging studies is challenging.[13,15] Most cases reported by imaging were rhinosinusitis due to rhinocerebral mucormycosis or pulmonary mucormycosis. In addition, there are few reports of imaging findings of mucormycosis developing in the jaw bone. Characteristic imaging findings have not been specifically documented, but sinus CT usually shows features such as mucosal thickening, air-fluid level, and bony erosion.[3] In this case, the first contrast-enhanced CT scan showed air-fluid level in both maxillary sinuses, but bony erosion was not evident. However, multiple air voids were observed within the bone marrow space of the maxilla, which has also been described in several reports of mucormycosis affecting the jaw bone. In these cases, osteolysis with multiple small air voids was observed in the medullary space, resulting in loss of the normal trabecular bone pattern.[16-19] These intramedullary air traps progressed to extensive or multiple bone necrosis as the infection worsened. In this case as well, bone destruction was aggravated as the infection expanded. In other words, although very few cases of mucormycosis of the jaw bone have been reported to date, the intramedullary air traps may be regarded as a characteristic imaging finding. Nevertheless, these

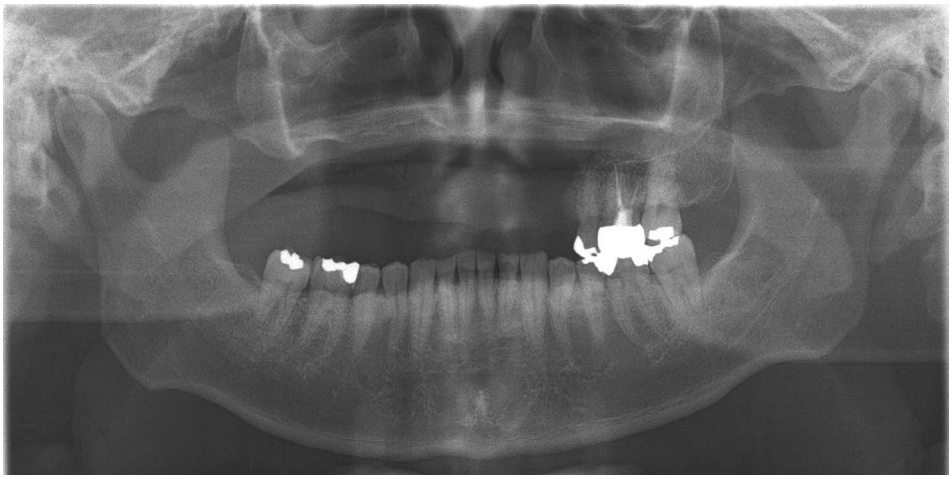

Fig. 7. Panoramic radiograph showing the postoperative condition after the third sequestrectomy in the anterior maxilla and left maxillary premolar region.

radiographic findings may appear somewhat later than the clinical progression.[3] Therefore, for an accurate early diagnosis, an aggressive biopsy is needed considering not only imaging findings, but also clinical symptoms and patient history.

Meanwhile, in the past 1-2 years, the number of cases of mucormycosis caused by co-infection after COVID-19 has been on the rise. About 1% of reported cases occurred in the oral region.[1,14] According to systematic reviews of COVID-19-associated mucormycosis,[1,8] the majority of reported cases were in male patients, showing a distinct sex bias of 7 : 2. However, the age of affected patients varied from young adults in their 20s and 30s to the elderly in their 60s to 80s. In more than 80% of cases, the patients had diabetes mellitus. Consistent with these reviews, the patient presented herein, a 37-year-old man, had pre-existing diabetes mellitus and was quarantined for treatment of COVID-19 approximately 2 weeks before the onset of mucormycosis. The predisposing factors for mucormycosis in COVID-19 include long-term use of drugs such as steroids and broad-spectrum antibiotics, diabetes or hyperglycemia, and hypertension. Glucose level control is particularly important in COVID-19-associated mucormycosis, as COVID-19 may worsen the glucose profile of patients with diabetes, making them more susceptible to infection development.[1] John et al.[20] reported that patients with both uncontrolled DM and severe COVID-19 had a very high chance of developing rhino-orbital or rhinocerebral mucormycosis, which induces necrosis of nasal structures, including the nasal mucosa and palate.[7] Extension to the maxilla via vascular invasion results in insufficient blood flow and necrotic osteomyelitis.[8,21] When differential diagnosis is made in patients with a history of diabetes, hyperglycemia, and COVID-19, it should be considered that the likelihood of mucormycosis is high.

The main principles of treatment for mucormycosis are surgical debridement and supportive antifungal medication.[14,22] Timely repeated and extensive debridement is essential to prevent infection spread and improve prognosis.[23] The first-line antifungal medication is amphotericin B.[22-24] Antifungal treatment should be continued until all symptoms of infection are resolved, and signs of recurrence should be evaluated through follow-up images.[3,24] Initially, this patient described herein was diagnosed with emphysematous osteomyelitis based on his clinical and imaging findings, and antibiotic treatment was continued for 2 weeks after the first operation. Antifungal medication was started only after the pathologic diagnosis of mucormycosis. Although the patient underwent multiple sessions of sequestrectomy and surgical debridement, the infection progressed along the anterior and posterior alveolus of the maxilla. Missing the timing of appropriate antifungal treatment might have been one of the reasons for the exacerbation of the infection. In summary, timely and active surgery, along with antifungal treatment based on an accurate early diagnosis, is essential for a favorable prognosis and infection control. Therefore, if evidence of gas-forming osteomyelitis is observed in images of patients with certain clinical conditions, including predisposing factors such as diabetes mellitus or COVID-19 infection, mucormycosis should be included in the differential diagnosis list.

This report presented the imaging findings of mucormycosis in the maxilla, a very rare condition. In particular, patients with diabetes mellitus have a high risk of developing mucormycosis. It is expected that this case will help radiologists diagnose mucormycosis in the maxilla. Since mucormycosis progresses aggressively, prompt diagnosis and treatment are important, but the clinical and imaging

findings of mucormycosis are difficult to differentiate from those of a bacterial infection. In patients with risk factors such as diabetes or immunosuppression, if air voids in the intramedullary space of the maxilla are observed on radiographic images such as paranasal sinus CT at an early stage, mucormycosis should be suspected at the time of initial diagnosis. It should also be noted that mucormycosis can occur as a sequela of COVID-19.

Conflicts of Interest: None

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