Mucormycosis in the Jaw: A Report of 2 Cases and Literature Review

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Abstract: Mucormycosis is a rare fungal infection with high morbidity and mortality and a very poor prognosis. However, aggressive medical and surgical management can result in survival rates exceeding 80%. The most common sites involved in mucormycosis infection are the sinus, lung, skin and soft tissues, gastrointestinal system, central nervous system, and rarely the mandible. Systemic risk factors for mucormycosis are diabetes mellitus (DM), neutropenia, corticosteroid use, hematologic malignancies, organ transplantation, metabolic acidosis, deferoxamine use, and advanced age. Local risk factors are a history of trauma, burns, surgery. We report on two patients with mucormycosis of the jaw. While one case presented as mucormycosis involving the maxillary sinus in a patient with uncontrolled DM, the other was a rare case of mandibular mucormycosis in a patient with acute myeloid leukemia.

Key words: jaw, mucormycosis, necrosis, zygomycosis

Mucormycosis is an infection by fungi of the Mucorales order,\textsuperscript{3} characterised by vessel invasion and tissue necrosis that occurs mainly in immunocompromised patients. Several immunosuppressive conditions, such as poorly controlled diabetes mellitus (DM), hematologic malignancy, solid-organ transplantation, chronic renal failure, nutritional deficiency, severe burns, and trauma act as predisposing factors for opportunistic fungal infections.\textsuperscript{2} The first case of mucormycosis in humans was reported in 1885 by Peltauf, and a case of rhino-orbital cerebral mucormycosis was reported by Gregory et al in 1943.\textsuperscript{9} Mucormycosis presents with various clinical features and mainly involves rhinocerebral lesions, the skin, lung, central nervous system, and gastrointestinal tract. Mucormycosis can secondarily extend from the primary infection site via hematogenous dissemination,\textsuperscript{10} and in uncommon cases, it infects the kidney, heart, and oral cavity.

The most frequently involved site in oral and maxillofacial regions is the maxillary sinus, where it presents with tissue necrosis. Without appropriate treatment it can extend to the orbit and brain, which has a poor prognosis. Mucormycosis can also occur in the maxillary alveolar ridges, lips, tongue, and mandible,\textsuperscript{11} but mandibular mucormycosis is extremely rare. Mucormycosis has a very poor prognosis, but appropriate treatment that includes active antifungal therapy and aggressive surgical debridement can increase the survival rate to 80%.\textsuperscript{25} However, even after successful treatment, mucormycosis can become dormant and then recur during chemotherapy or neutropenia.\textsuperscript{23}

This report of two rare cases of oral mucormycosis involves one originating from the maxillary sinus and infiltrating the palate in a patient with uncontrolled DM, and the other of mucormycosis infection in the gingiva and alveolar bone of the mandible in a patient with acute myeloid leukemia.
CASE REPORTS

Case 1
A 44-year-old man was referred to the Department of Advanced General Dentistry at Yonsei University College of Dentistry from the Department of Infection Medicine, Severance Hospital, to address mobility of the left maxillary incisor. Clinical and radiographic examinations showed grade-2 mobility of the maxillary left central incisor, lateral incisor, and canine, and enlargement of periodontal ligament space. The patient had been admitted to the Department of Otorhinolaryngology, Severance Hospital, after receiving endoscopic sinus surgery and Caldwell-Luc surgery for sinus fungal infections before the present referral. The initial pathologic diagnosis was invasive aspergillosis, and the patient was transferred to the Department of Infection Medicine for antifungal therapy and was maintained on intravenous voriconazole. This patient also had systemic diseases: hypertension, hyperlipidemia, hypothyroidism, and uncontrolled DM (glucose: 377 mg/dl, HbA1c: 14.4%).

We also observed swelling and yellowish-white elongated tissue on the left hard palate (Fig 1). The patient mentioned...
that it did not subside on the left hard-palate tissue after
eating hot food, but we diagnosed it as being associated
with the existing sinus fungal infection related to the medi-
cal history of the patient. Computed tomography (CT) and
wide resection through cooperation with an oral maxillofa-
cial surgeon was necessary. Thus, we recommended
prompt intervention to the Department of Infection Medi-
cine. CT revealed bony erosion of the left hard palate and
maxillary sinus walls (Fig 2).

Partial maxillectomy with extraction of the left lateral inci-
sor, canine, and first and second premolars was then per-
formed (Fig 3). The specimens were sent to the Department
of Oral Pathology, and the histopathological results con-
firmed the presence of mucormycosis, which manifests as
a broad and irregular form of nonseptate branching hyphae
(Fig 4). Intravenous voriconazole administered following the
initial pathologic diagnosis was changed to intravenous Am-
Bisome (amphotericin B) in accordance with the final patho-
logic diagnosis. Its rapidly spreading behaviour had resulted
in it extending to the orbital and cavernous sinus in this
patient. However, the application of active and appropriate
antifungal therapy improved the patient’s condition, and at
the last study follow-up, he was undergoing prosthetic treat-
ment of the maxillary region (Fig 5).

Case 2
A 61-year-old man diagnosed with acute myeloid leukemia
(AML) was admitted to the Department of Hematology, Sever-
ance Hospital, for chemotherapy. This patient was referred to
the Department of Advanced General Dentistry due to swell-
ing, soreness, and a heat sensation in the left cheek area.
Other systemic diseases of this patient were hypertension
and poorly controlled DM (HbA1c: 8.0%). The patient had not
been to a dentist for 20 years. Clinical and radiographic ex-
aminations showed grade-3 mobility of the mandibular left
first and second molars. Root caries were also present.

The patient’s teeth were extracted and chemotherapy
was resumed for AML. One month after the extraction, the
patient was referred again for swelling and pain in the gin-
giva of the right mandibular second premolar and the first
molar region. Clinical and radiographic examinations showed
fibrous gingiva and bone loss under the mandibular
second premolar and first molar. An incisional biopsy was
planned (Fig 6), but at the time of referral the patient had a
WBC count of 240/μl, hemoglobin level of 9.1 g/dl, hema-
tocrit of 25.7%, and platelet count of 23,000/μl, meaning
that a biopsy procedure was not possible. After 15 days the
blood counts had improved to within the normal ranges and
so the biopsy was performed. The gingiva in the posterior
part of the right mandible was necrotic, and the necrosis
extended to the anterior part (Fig 7). The biopsy specimen
was sent to the Department of Oral Pathology and was con-
formed as mucormycosis. Intravenous AmBisome (ampho-
tericin B) 200–320 mg/day was administered. In the pa-
thology specimen, a mycelium with an obtuse angle without
a septum was observed in the blood vessels (Fig 8).

At 5 days after the biopsy, the patient underwent extrac-
tion of the mandibular right first premolar, second premolar,
first molar, and second molar followed by sequestrectomy.
After the diagnosis of mucormycosis, intravenous ampho-
tericin B was administered for 4 weeks to prevent recur-
rence. However, amphotericin B induced a shock response
and so the medication was changed to Noxafil (posacon-
zole) 300 mg/day for about 35 days. Prophylactic therapy
and chlorhexidine rinse were also applied periodically to
prevent further infections. At 1 month after the operation,
there were no signs of mucormycosis or necrotic tissue in
the infected area of the patient, and no sign of additional
infection was observed (Fig 9).

The patient was referred again at 2 months after the op-
eration for right maxillary gum pain and oedema. A clinical
examination showed a whitish lesion and gingival recession
under the maxillary right first and second molars, and mu-
cormycosis was confirmed by the subsequent biopsy
(Fig 10). There was no loss of alveolar bone in the infected
area radiographically; thus, it was considered that mucor-
mycosis was limited to the gingiva. Periodic scaling and
chlorhexidine rinse were therefore performed, but the re-
sponse was poor. Hence, both maxillary right first and sec-
ond molars were extracted. The patient was subsequently
monitored for recurrence of mucormycosis in periodic visits.

DISCUSSION

Mucormycosis is a rare but life-threatening infectious dis-
ease with a high mortality rate. The risk factors for mucor-
mycosis are poorly controlled DM, neutropenia, hematopo-
etic malignancy (leukemia, lymphoma, and multiple
myeloma), solid-organ transplantation, multiple traumas,
and use of corticosteroids. Reports of mucormycosis have
recently increased worldwide, especially in patients
with DM or malignant tumors.20 Mucormycosis presents in
various forms: rhino-orbito-cerebral, pulmonary, gastroin-
testinal, cutaneous, and disseminated.14 The oral form of mu-
cormycosis is relatively rare.19 The main affected area
in the oral and maxillofacial region is the maxillary sinus, and
it can present with invasion and necrosis of the palate.
Without appropriate treatment, it will expand to the orbit
and brain, which has a very poor prognosis.22 Besides the
maxillary sinus, mucormycosis in the alveolar bone of the
maxilla, lip, tongue, and mandible has been reported. How-
ever, cases involving the mandible are very rare.2,4,8,11,23
The first case of mandible-affected mucormycosis was re-
ported by Eisenberg et al,13 and to date, 12 such cases
have been reported, as presented in Table 1.

Despite the relatively favourable prognosis of mucormy-
cosis with adequate surgical resection and antifungal ther-
apy, it is difficult to define treatment or the case of mucor-
mycosis in the mandible. Due to suboptimal blood supply,
it is easily transmitted to the necrotic gingiva and bone in
spite of the early diagnosis; appropriate surgery as well as
repeated dormancy and recurrence will prolong the time to
complete healing. Also, mucormycosis in the mandible is
more likely to be associated with hematologic malignancy
than with diabetes mellitus, corticosteroid use, and trauma.
As shown in Table 1, the patient had acute leukemia in 8 out of 13 cases, including 12 reported cases and 1 case in this case report. Especially acute leukemia patients who are undergoing chemotherapy or bone marrow transplantation suffer from neutropenia. Neutrophils have an important role in host defense system against fungal colonisation. In patients with leukemia, bone marrow fails to produce healthy red or white blood cells or platelets. Moreover, myelosuppression and neutropenia occur during remission and induction before and after chemotherapy. These situations render patients relatively vulnerable to fungal infections and make them prone to opportunistic infections. Close follow-up is necessary, because it reveals the process of dormancy and reappearance in the treatment of mucormycosis. In case 2, the unfavourable condition of acute myeloid leukemia combined with uncontrolled diabetes and age factor led to invasive mandible mucormycosis, despite close follow-up. The diverse clinical presentations of mucormycosis make early diagnosis difficult. However, patients with risk factors and deteriorating progress despite taking empirical antibiotics must be examined for the possibility of mucormycosis infection. Unlike aspergillosis, it is difficult to diagnose mucormycosis using serological and imaging techniques, so that histopathological examination and culturing are necessary. The histopathological hallmarks of mucormycosis are broad and
irregularly shaped nonseptate branching hyphae 10–50 μm in size with vessel invasion by thrombosis and tissue necro-
sis.3,10,24 Successful early diagnoses were recently reported
based on C-reactive protein and the polymerase chain re-
caction, but further investigations are essential.21
The principles of mucormycosis treatment are early diag-
nosis, removal of risk factors, debridement of infected tis-
sue, surgical resection, and effective antifungal therapy.12
Characteristics of mucormycosis such as vessel invasion
with thrombosis and tissue necrosis impede the ability of
antifungal agents to reach an infectious region, and so ag-
gressive surgical resection and systemic antifungal therapy
for removing the infection source is necessary. A lipid am-
photericin B formulation (5–10 mg/kg/day) is the first-
choice antifungal treatment agent, while amphotericin B
deoxylcholate is no longer recommended due to renal toxic-
ity. If treatment failure or drug side effects occur when ad-
ministering liposomal amphotericin B, posaconazole or li-
posomal amphotericin B combined with posaconazole is
recommended.6 Because a shock event occurred in case 2
when liposomal amphotericin B was prescribed for 4
weeks, the medication was changed to posaconazole.
Mucormycosis is a life-threatening infectious disease
whose mortality rate depends on the invasion area.20 The
survival rate could be increased by early diagnosis, ap-
propriate antifungal therapy, and management of predisposing
factors.16

CONCLUSION
The two patients presented here represent very rare cases
of mucormycosis originating from the maxillary sinus with
invasion to the palate and mandible. Because no accurate
guideline exists about surgical resection due to a paucity
of reported cases, the applied treatment might depend on the
experience of the clinician. The present case series demon-
strates the importance of early detection, diagnosis, and
appropriate treatment of mucormycosis.

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