Mucormycosis: A Case Report and Review of Literature

Guem-Sug Lee¹, Kyung-Hwa Lee², Byung-Gook Kim³, Yeong-Gwan Im⁴

¹Department of Dentistry, Chonnam National University Hwasun Hospital, Hwasun, Korea
²Department of Pathology, Chonnam National University Hwasun Hospital, Hwasun, Korea
³Department of Oral Medicine, School of Dentistry, Chonnam National University, Gwangju, Korea
⁴Department of Oral Medicine, Chonnam National University Dental Hospital, Gwangju, Korea

Mucormycosis is a rare but fatal fungal infection with low survival rate in immune-compromised patients. It is caused by a fungus belonging to the Mucoraceae family of the Zygomycetes class. Mucormycosis is classified as rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous types according to its clinical manifestations. Early diagnosis and treatment along with correction of the underlying medical condition is important for favorable results. This case presentation describes mucormycosis involving the anterior maxillary region in a leukemic patient with prolonged neutropenia. The patient benefited from a timely biopsy and immediate treatment with amphotericin B, and was successfully managed with an interdisciplinary team approach consisting of dental and several medical specialists.

Key Words: Amphotericin B; Head; Leukemia; Mucormycosis

INTRODUCTION

Mucormycosis is a rare but life-threatening opportunistic fungal infection caused by a fungus belonging to the Mucoraceae family of the Zygomycetes class. It is associated with high morbidity and high mortality rate in susceptible individuals who are immune-compromised from various medical conditions. We describe a case of mucormycosis involving the anterior maxillary region in a leukemic patient with prolonged neutropenia.

CASE REPORT

A 58 year-old man was referred from the Department of Hematology to the Department of Dentistry for evaluation and treatment of oral ulceration and pain. History taking revealed that he had fallen down on a dirt slope and developed facial lacerations and bruising about a month earlier. He had visited a local medical clinic and the laceration had been sutured. Then, he was referred to the Department of Hematology, Chonnam National University Hwasun Hospital, for further hematologic evaluation due to a finding of pancytopenia in his blood studies. Initial hematologic screening showed low blood cell counts (white blood cell 1.5×10⁵/mm³; red blood cell 1.56×10⁶/mm³; platelet 39×10⁴/mm³). During the following two weeks, he received several diagnostic examinations including bone marrow biopsy, peripheral blood smear, and genetic tests. The peripheral blood smear indicated pancytopenia without definitive abnormal cells. The bone marrow biopsy showed hypocellular marrow with leukemic cell infiltration in focal cellular areas. During the third week of hospitalization, the patient suffered from severe pain associated with oral ulceration and his maxillary teeth became loose and at risk of dislocation. At the time of the patient’s first visit to the Department of Dentistry, he had already lost two maxillary incisors on the right side and had necrotic ulcers with swelling on the pre-maxillary region, extending to the maxillary anterior vestibule on the right side. Close oral examination showed that the ulcerative lesion was irregular in shape and demarcated by elevated margins. The marginal oral mucosa was separated from the supporting bone, indicating necrosis of the
periosteal membrane. The gingival mucosa in the necrotic region was detached from the underlying alveolar bone and showed tattered borders (Fig. 1).

Because acute necrotizing ulcerative gingivitis was suspected as one of the diagnoses responsible for the pathology, local antimicrobial agents were chosen and applied for the first-line therapy. For definitive diagnosis, incisional biopsy samples were taken from the palatal and gingival sites within the necrotic lesion. Four days after the biopsy, the diagnosis of mucormycosis was confirmed by histopathologic exam results. The exam revealed characteristic aseptate fungal hyphae occasionally branching at a right angle (Fig. 2). Antifungal therapy with intravenous infusion of amphotericin B was initiated immediately after the biopsy results at the Department of Hematology. Referral to an otolaryngologist for an evaluation of the nasal cavity and paranasal sinuses indicated no fungal infection of the examined area. The patient was screened for the spread of infection to the bronchus and lung at the Department of Pulmonary Medicine, and no infection was identified. Ten days later, tissue necrosis accompanying severe pain...
symptoms extended into the maxillary canine and premolar region on the right side despite the ongoing antifungal therapy (Fig. 3).

The patient was diagnosed with acute lymphoblastic leukemia at the Department of Hematology. When the patient’s systemic condition improved and he was fully recovered from pancytopenia, he was sent to the Department of Otolaryngology for a partial maxillectomy with the complete removal of necrotic tissues (Figs. 4, 5). To eliminate the possibility of the fungal remnants being infected, amphotericin B was administered for an additional one month following the surgical treatment. Finally, the patient was referred to a prosthodontist for prosthetic restoration of the lost teeth and supporting tissue.

**DISCUSSION**

In recent decades, acute fulminant mold infections have been increasing. Candida species have been the most common fungal pathogen among all fungal infections. Aspergillosis is the second most common fungal infection, followed by mucormycosis. In 1865, Cohnheim reported a fungal infection by *Mucor* for the first time, describing widespread infection involving ear, lung and stomach. The second case was reported in 1885 by Paltauf. After Gregory et al.’s report in 1943 about a case in an uncontrolled diabetes mellitus patient, reports of mucormycosis have been steadily increasing.

Mucormycosis is a fatal disease with a high mortality rate in immunocompromised patients with uncontrolled diabetes, acute and chronic renal failure, hemodialysis using deferoxamine, burns, immunosuppressive drug use, solid organ transplantation, intensive chemotherapy and radiation therapy, AIDS, etc. Invasive infection often occurs in patients with hematologic malignancy, iron overload and hematopoietic stem cell transplantation as well. Mucormycosis is one of the emergency conditions with 20%-80% mortality.

Such primary diseases and systemic conditions, as predisposing factors, make a favorable environment for fungal infection. In the present case, mucormycosis developed in a patient with acute leukemia and preceding neutropenia.

The pathogens that cause mucormycosis are commonly found in the environment—organic debris decaying in soil, leaves, fruits, rotten wood, and composts. In the *Mucoraceae* family of the *Zygomycetes* class, the *Rhizopus*, *Mucor*, and Absidia genera have been associated with human diseases. Overall, the *Rhizopus* genus is the most commonly implicated organism causing mucormycosis in humans, accounting for 90% of infections.

Infection usually occurs by inhalation through the respiratory route or by direct skin contact. When spores come into one’s body with normal immunity, their proliferation is inhibited by the immunologic functions of macrophages, neutrophils, and complements. But in immune-suppressed patients, fungi rapidly proliferate and the characteristic tissue responses such as thrombus formation, infarction, and necrosis are provoked.

Clinical manifestations are varied and mucormycosis is classified as rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous types. In patients with diabetes, rhino-orbital-cerebral mucormycosis is common and the pulmonary type is rare. Lung infection with the rhino-orbital-cerebral type often occurs in patients with neutropenia.

Dissemination of fungal hyphae along the blood stream to major organs such as brain and lung can lead to death. Vascular invasion by fungal hyphae induces blood clots in the vessels and results in tissue necrosis. Thrombus formation within the internal maxillary artery or the inferior palatal artery, for example, can cause tissue necrosis of the maxillary region, which could be an explainable disease process for the present case. When both the alveolar bone and the palatal bone are destroyed, oral-nasal fistula can be formed.

Diagnosing necrotizing ulcerative lesions of the palate with only clinical signs and symptoms is very difficult. Differentiation is required due to pathologies with similar clinical appearance, such as necrotizing granulomatosis, Wegener’s granulomatosis, tertiary syphilis, tuberculosis, lymphoma, squamous cell carcinoma, and malignant diseases of the minor salivary glands. Thus biopsy is mandatory for definitive diagnosis.

Initial symptoms of sinus mucormycosis include nasal congestion, nasal bleeding, headache, retro-orbital pain, fever, and malaise. Infection often spreads to paranasal sinuses, the orbital cavity, and the brain in immunologically compromised individuals. Infection of the ethmoid sinus easily spreads to the orbit, extraocular muscles, eye, and ophthalmic nerve via the orbital plates. The infection can further extend to the cavernous sinus and eventually to the
brain through the ethmoid veins or ophthalmic veins.\textsuperscript{17-23} At this advanced stage of infection, which is called the rhino-orbital-cerebral mucormycosis, clinical features are manifested, such as cellulitis of facial and orbital areas, paresthesia, visual disorders, tears, diplopia, ptosis, proptosis, paralysis of ophthalmic muscles, loss of vision, discharge of nasal exudate, turbinate necrosis, fever, headache, and lethargy.\textsuperscript{17-22}

Histopathological features of mucormycosis are very similar with those of aspergillosis, but they differ in the morphological characteristics of hyphae. In the microscopic view, the fungal hyphae in aspergillosis have septa and branches. In contrast, the hyphae in mucormycosis show wide ribbon-like form and thick walls without septa. Branching of hyphae is rare in mucormycosis and, if any, occurs at approximately right angles. Because the \textit{Mucorales} can be found in the nasal mucosa of normal individuals, the histopathological confirmation of vascular invasion is important for diagnosis. A histopathological exam is also valuable at the early stage of disease progression when the result of the blood culture is negative.\textsuperscript{15,24}

The widely accepted method of managing mucormycosis is a multi-faceted treatment strategy including administration of proper antifungal agents, correction or removal of the underlying disease, and surgical excision of necrotic tissues. The treatment results largely depend on the degree of immune suppression, infection depths and sites, the time until suitable treatment is provided, and the form of treatment. According to Blitzer et al.,\textsuperscript{19} the survival rate of rhino-orbital-cerebral mucormycosis was 75\% without systemic disease, 60\% in patients with diabetes, and only 20\% when it accompanies other systemic diseases.

The underlying disease must be corrected before surgical procedures are performed. For example, hyperglycemia in patients with diabetic acidosis needs to be actively corrected. In transplant recipients and patients with blood cancer, corticosteroids or other immunosuppressive agents should be temporarily stopped until the infection is controlled. For the recovery of immune function, administration of granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon-\(\alpha\) can be considered. G-CSF and GM-CSF facilitate the generation of neutrophils and various immune cells, and promote the effect of the antifungal agent.\textsuperscript{25}

Amphotericin B is the first drug of choice for mucormycosis. Long-term use of amphotericin B is necessary because it is not fungicidal but fungistatic.\textsuperscript{21} It is usually administered for two to three months although the exact treatment period, and the total dose varies according to the factors, including the patient’s response and the degree of renal toxicity. Side effects of amphotericin B include fever, nausea, vomiting, hypokalemia, and nephrotoxicity. To prevent such side effects, acetaminophen, diphenhydramine, and hydrocortisone can be administered as pre-treatment.\textsuperscript{25-26}

Posaconazole has demonstrated treatment efficacy in the case of mucormycosis experimentally induced by \textit{Mucor} but not by \textit{Rhizopus}. According to some reports,\textsuperscript{27,28} posaconazole shows activity in some mucormycosis that do not respond to amphotericin B therapy. However, oral administration of posaconazole is not recommended for the early treatment of mucormycosis.

Successful surgical treatment cases for mucormycosis of the hard palate have been reported, and the operative procedures varied from simple resection of the hard palate to total maxillae/mandible resection.\textsuperscript{19-21,29} More extensive infection, such as rhino-orbital-cerebral mucormycosis, is optimally managed with an interdisciplinary team approach consisting of an ophthalmologist, a neurosurgeon, an oral-maxillofacial specialist, and an otolaryngologist.

In conclusion, early diagnosis with biopsy, correction of the underlying disease that compromises the immune system, and appropriate pharmacological and surgical therapy is important for the management of mucormycosis. Multidisciplinary team treatment is often required. The role of dentists is to identify and diagnose infection of the oral and maxillofacial region as early as possible, and to provide effective local surgical, pharmacological, and restorative treatments, in cooperation with other medical specialists.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**


