

# 간이식 환자에서 발생한 하악골의 비침윤성 모균증: 범랑모세포종과 동반된 증례

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## 〈Abstract〉

## Non-invasive Mucormycosis Associated with Ameloblastoma of the Mandible in Liver Transplant Patients

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Mucormycosis is an aggressive opportunistic fungal infection that can be found in the oral cavity. The fungus usually affects the immunocompromised patients and tends to invade and block blood vessels, resulting in significant tissue necrosis and invasive mucormycosis. However, a non-invasive form of mucormycosis is mostly asymptomatic and found accidentally in the immunocompetent normal hosts, manifested by localized overgrowth of the fungus. Here, we report a rare case of asymptomatic non-invasive mucormycosis of the mandible that was incidentally diagnosed in wide resection specimen of liver transplant patient who had previously underwent surgery of excision and simultaneous alloplastic bone graft due to mandibular ameloblastoma. Histopathological examination of the specimen revealed that there was neither vasculitis nor tissue necrosis, but numerous fungal hyphae were located only within the alloplastic graft materials in decalcified tissue sections. Awareness of the possibility of life-threatening mucormycosis in immunocompromised patients should be emphasized because it can be inactive or reactivated depending on the immune state of patients.

**Key words:** Mucormycosis, Non-invasive, Mandible, Ameloblastoma, Alloplastic bone graft, Liver transplant

## I. INTRODUCTION

Mucormycosis is an aggressive opportunistic fungal infection that can be found in the oral cavity.<sup>1)</sup> The most common pathogens of mucormycosis are *Lichtheimia*, *Rhizopus*, *Rhizomucor*, and *Mucor* fungi of the order *Mucorales*.<sup>2)</sup> These fungi are widely distributed in nature, and predominantly

affect immunocompromised hosts with diabetes mellitus, immunosuppression, stem cell or solid organ transplant, hematologic malignancies, or prolonged corticosteroid therapy. The route of disease transmission is presumed to be via inhalation, traumatic implantation, ingestion of contaminated foods, and infiltration in blood vessels.<sup>3)</sup> In general, the fungi of mucormycosis tend to invade and block blood vessels, resulting in severe tissue necrosis and high morbidity and mortality rates.<sup>3,4)</sup> However, the disease might have rarely an isolated and localized focus in an immunocompetent

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host, which shows mostly asymptomatic and is manifested by localized overgrowth of the fungus.<sup>1-3)</sup>

The main types of mucormycosis occur at sinusitis/ rhinocerebral, pulmonary, cutaneous/subcutaneous gastrointestinal, and disseminated, while other forms including oral cavity occur at much lower frequencies.<sup>1,3)</sup> Mucormycosis of the oral cavity is reported usually in maxilla as a result of transpalatal extension of rhinocerebral infection,<sup>4,9)</sup> Mucormycosis associated with the mandible is a rare, but in the most cases, it is isolated only to mandible.<sup>5,10-15)</sup> It is reported that the oral lesions of mucormycosis developed after extraction of teeth or intraoral manipulations and mostly showed gingival involvement with ulceration and loosening of teeth.<sup>5,10-19)</sup> Among previous known articles, there were no case reports of non-invasive and inactive mucormycosis in mandible without fungal invasion into the blood vessels.

In this article, we report a rare case of non-invasive, inactive mucormycosis of the mandible that was accidentally found in liver transplant patient who had underwent surgery with recurrent ameloblastoma.

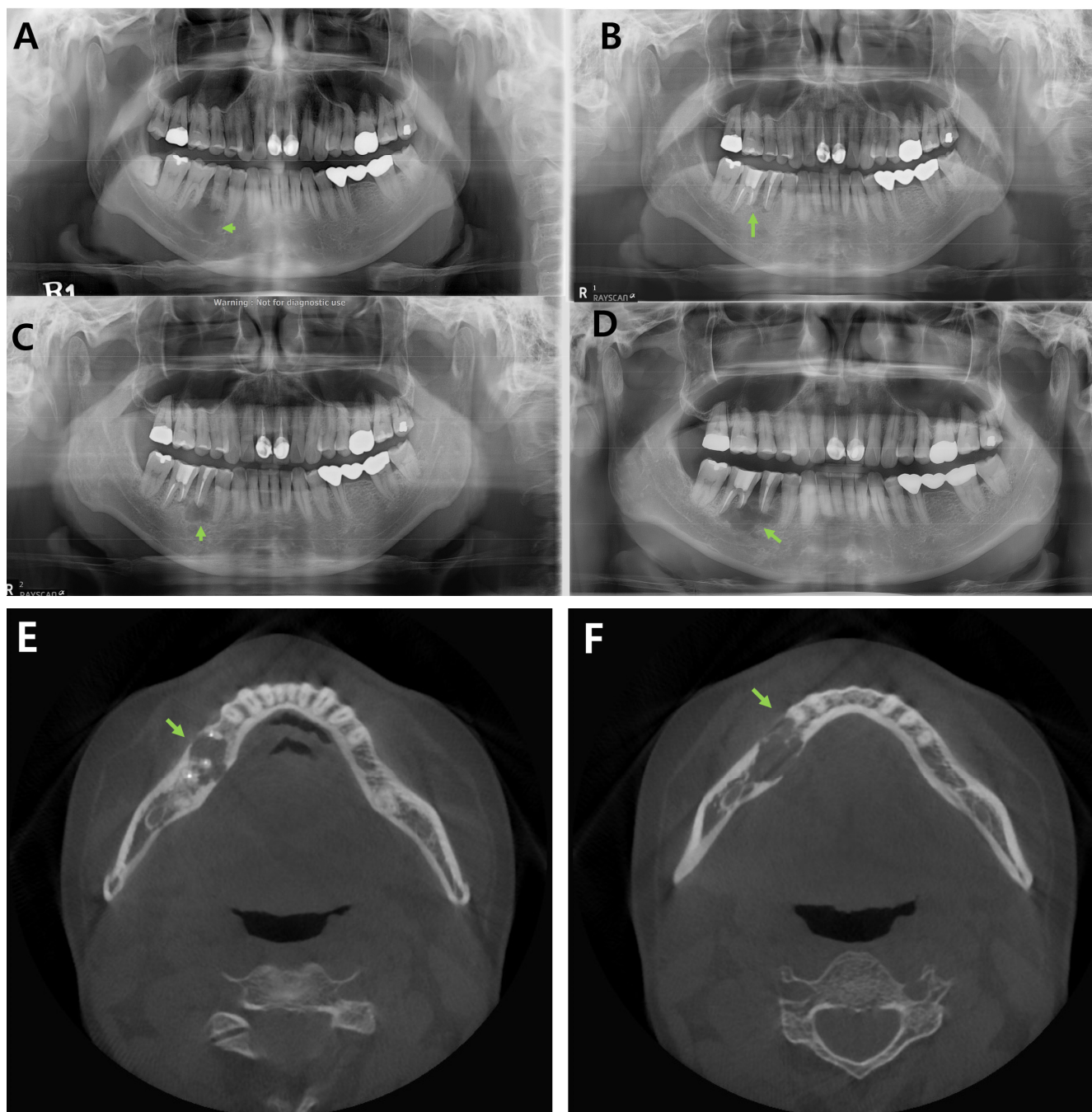
## II. CASE REPORT

A 53-year-old male initially visited dental hospital with gingival tenderness of right mandible area in February 2015. The radiolucent lesion of the right lower jaw and external root resorption of 2<sup>nd</sup> premolar was observed and the result of the incisional biopsy was ameloblastoma. (Fig. 1.A) The mass excision and apicoectomy were performed after the root canal therapy of related teeth. After about a year, the patient had liver transplantation surgery for liver cirrhosis on June, 2016, and had been taking immunosuppressive drugs and steroids since then. In November 2017 (1 year 5 months after liver transplantation), the patient revisited the dental hospital due to the discomfort of the right lower second premolar. On the radiograph, increased radiolucent le-

sion was observed in interdental area of 1<sup>st</sup> molar and 2<sup>nd</sup> premolar. (Fig. 1.B). In the out-patient dental clinic, excisional biopsy was performed under local anesthesia, and bone graft using alloplastic graft material was performed. The histopathologic result was recurrent ameloblastoma. In November 2018 (2 year 5 months after liver transplantation), periodic radiographic examination showed an increase in radiolucency in the apical area of 2<sup>nd</sup> premolar and mass excision was performed in the out-patient dental clinic. (Fig. 1.C) The histopathologic result was recurrent ameloblastoma. In subsequent regular checkups, the patient has no signs and symptoms of recurrence, but he revisited in June 2020 (4 years after liver transplantation) with tenderness of lingual gingiva of right lower molar area. In clinical examination, the presence of low-grade discomfort and mild gingival swelling was seen in lingual area of lower molar without gingival ulceration or tooth mobility. On radiographic examination, irregular radiolucent multilocular lesion was observed in right lower premolar and molar area (Fig. 1.D,E,F) and tentative diagnosis was made with recurrent ameloblastoma. Marginal mandibulectomy was performed under general anesthesia and the acquired specimen was submitted for histopathological evaluation.

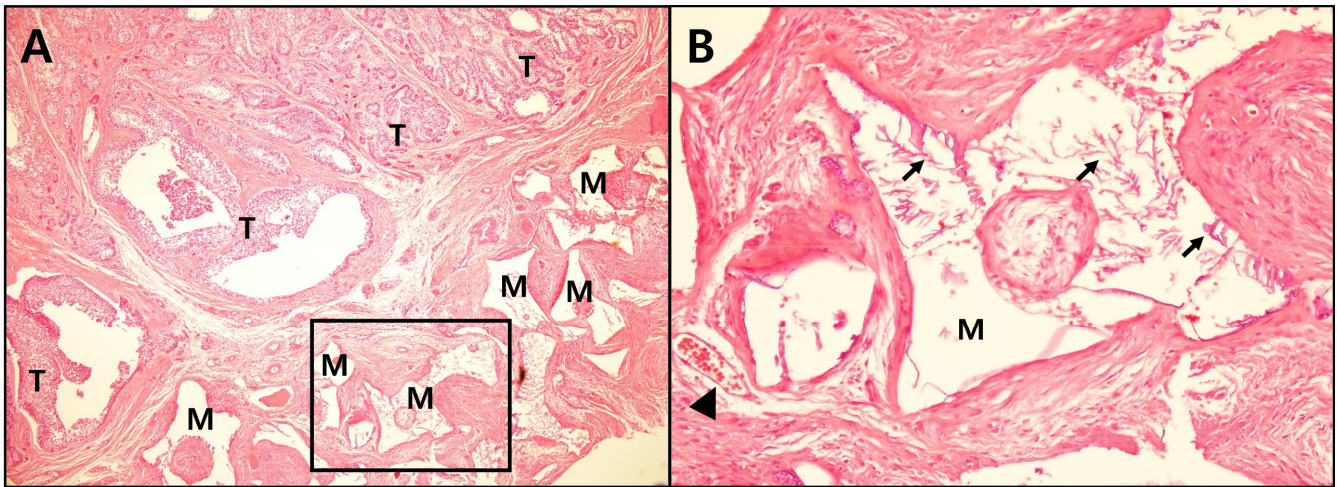
Histopathologic examination of decalcified tissue sections shows the numerous spaces of alloplastic graft materials associated with ameloblastoma. Tissue necrosis or fungal invasion into the blood vessels is not observed. (Fig. 2.A,B) In Periodic-acid Schiff stain, within the empty spaces of graft materials, the numerous fungus with various size are located, which shows the broad non-septate hyphae with rightangled branching. However, the amounts of branching hyphae were very small. (Fig. 3. A,B) The lesion was diagnosed as recurrent ameloblastoma and inactive mucormycosis.

Because surgical debridement (marginal mandibulectomy) has already been performed on the fungus infection site, and histologically it was diagnosed as inactive, no additional antifungal agent such as amphotericin B was prescribed.



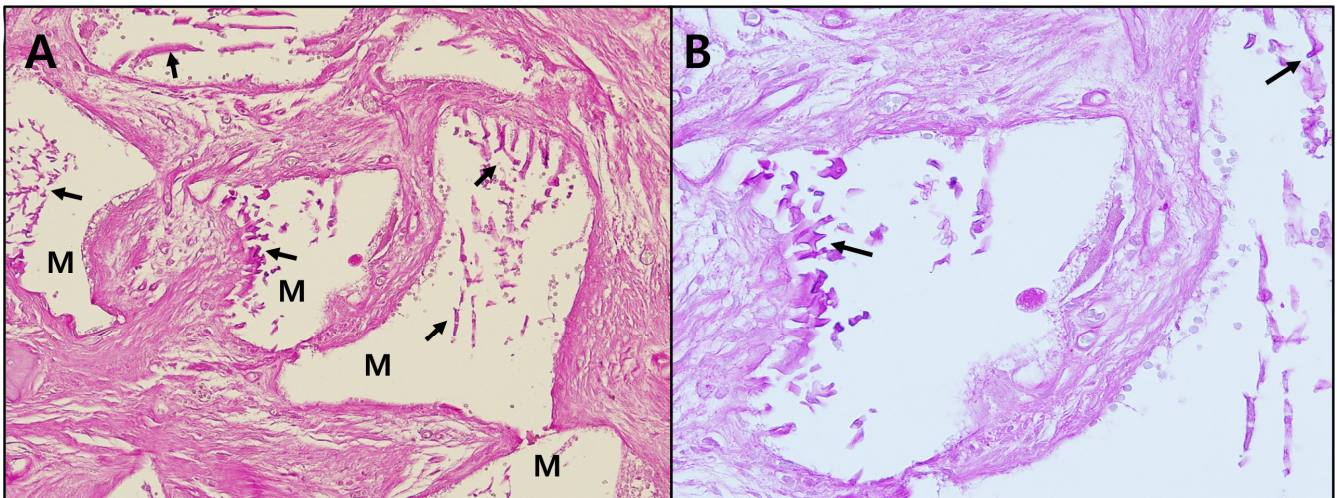
**Fig. 1.** Radiographic image of the right mandibular lesion.

- A. Initial visit. The radiolucent lesion of the right lower jaw and external root resorption of 2<sup>nd</sup> premolar (arrow) were observed, and the result of the incisional biopsy was ameloblastoma.
- B. 2 year 6 months after 1st operation (1 year 5 months after liver transplantation): Increased radiolucent lesion was observed in interdental area of 1<sup>st</sup> molar and 2<sup>nd</sup> premolar (arrow)
- C. 1 year after 2<sup>nd</sup> operation (2 year 5 months after liver transplantation): Periodic radiographic examination showed an increase in radiolucency in the apical area of 2<sup>nd</sup> premolar (arrow)
- D,E,F. 1 year 7 months after 3rd operation (4 years after liver transplantation): The scalloped multilocular lesion (arrow) was observed in right mandible. (D: Panoramic view E,F: Computed tomography axial view)



**Fig. 2.** Hematoxylin and eosin stain

- (A) Histopathologic examination of decalcified tissue sections shows the numerous spaces of alloplastic graft materials (M) associated with ameloblastoma (T). No tissue necrosis is observed around the graft materials (square box). (original magnification, 40).
- (B) High power view of the square box shows numerous fungal hyphae (arrow) within the spaces of alloplastic graft materials (M) without fungal invasion into the blood vessels (arrowhead). (original magnification, 200).



**Fig. 3.** Periodic-acid Schiff stain

- (A) Within the empty spaces of graft materials (M) of decalcified tissue sections, the numerous fungus with various size are located (arrow). (original magnification, 200).
- (B) High power photograph shows the broad nonseptate hyphae with right-angled branching (arrow). (original magnification, 400).

### III. DISCUSSION

Our case report has two characteristics different from the mucormycosis reported so far. First, this case was accompanied by ameloblastoma, and second, it showed an inactive

form in immunocompromised patient.

In the English literature, only one case of mucormycosis associated with ameloblastoma has been reported.<sup>20)</sup> Molero et al reported aggressive rhinocerebral mucormycosis with silent ameloblastoma which present quick spread, eye in-

volvement, necrotic scar and inflammatory response in the form of granulomas. However, on the contrary, our case was aggressive ameloblastoma with recurrence in the mandible, but mucormycosis showed an inactive histological form. The mucormycosis of mandible is a rare but most of them appear isolated only to mandible. When it involved to mandibular bone, their histological findings were mostly active, showing hyphae branching and penetration into surrounding tissues and blood vessels.<sup>5,11,13,19)</sup> However, this case shows a completely different pattern from the previous cases. The lesion didn't progress clinically fast and there was no change in gingiva such as ulcer and necrosis, except for slightly discomfort in lingual gingiva. Microscopically, histologic findings consistent with ameloblastoma were predominant, and non-septate hyphae were observed only in some areas suspected to be the bone graft site without penetration of surrounding tissue. There were little hyphae branching and no intravascular infiltration or inflammatory reactions were observed, meaning low activity of hyphae.

Risk factors for mucormycosis include immunosuppression, stem cell or solid organ transplant, hematologic malignancies, corticosteroid, uncontrolled diabetes, and the breaking of cutaneous or mucous membrane barrier due to trauma and surgical wounds.<sup>3)</sup> A study involving organ transplant recipients showed that mucormycosis accounted for 5.7% of all opportunistic mold infections.<sup>21)</sup> The patient of this case had three risk factors: liver transplantation, immunosuppression and steroid therapy, so it was highly likely to show invasive or active mucormycosis, but in actually it was not. We think of the pathogenesis of inactive mucormycosis as follows.

Although the patient has three risk factors, he might be slightly immunocompromised or immunocompetent state. Neutrophils are known to play a crucial role in protective host response to fungal colonization. They are chemotactically attracted to the hyphae and used their oxidative cytotoxic system, and neutrophils damage the fungal elements without accompanying phagocytosis. The neutropenia is a

well-known risk factor for infection and is known to have absolute neutrophil count of less than  $1/\mu\text{L}$  for one week or more than a week, increasing the risk of fungal infection.<sup>1)</sup> In the third surgery, 2 year 5 months after liver transplantation, the period of suspected infection, the patient's white blood cell count (WBC) was  $3.59 \times 10^3/\mu\text{L}$  and an absolute neutrophil count was  $1.64 \times 10^3/\mu\text{L}$  (59.1 %), indicating a value below the normal range. In the last surgery, 4 years after liver transplantation, his WBC and neutrophil values were in the normal range,  $6.24 \times 10^3/\mu\text{L}$  and  $5.13 \times 10^3/\mu\text{L}$  (82.1%) respectively. This values showed a better his condition than in the past, although he was still taking immunosuppressant drugs after liver transplantation. Therefore, we speculated that the infection of mucormycosis was likely to occur in third surgery at the out-patient clinic before the neutrophil fully recovered after liver transplantation. After that, the adequate numbers of functional neutrophils restoration might make neutrophil to prevent the activity and reproduction of the fungus, which could lead to inactivity of mucormycosis.

The susceptibility of corticosteroids to develop mucormycosis is known to be probably twofold, potentially mediated through macrophages/neutrophil dysfunction or hyperglycaemia.<sup>1,3)</sup> Thus, it could be inferred that prolonged steroid administration after liver transplantation affect phagocytosis function of macrophage and, as a result, the hyphae remains inactive without being removed. Particularly, hyphae were mainly observed in the area suspected of graft material. It is presumed that the phagocytosis of hyphae did not occur properly due to the phagocytic function of macrophage against the graft material. This implies that if the patient's immune status is worse, the fungus could change to an active form.

Since the spores can be found in many environment, including air, dust, soil, and surfaces, and may be invisible, the source of the mucormycotic infection in this case is certainly undetermined.<sup>1)</sup> The first surgery for ameloblastoma was performed in the operating room, but the second and third minor surgery was performed in the out-patient dental

clinic. The marginal mandibulectomy for recurrent ameloblastoma was undergone in the operating room and fungi hyphae were found only in the last surgical specimen. The operation room are often isolated with hepafilter treatment of the air supply and positive pressure to exclude the recruitment of dust into the ward, so dust can be kept to a minimum in the environment.<sup>1)</sup> Thus, it could be assumed that the hyphae were implanted into injured tissue at the time of the operation in out-patient dental clinic and remained inactive state until last surgery.

Mucormycosis usually extends into adjacent normal structures and results in significant tissue necrosis, but the disease may have an isolated, localized and inactivated focus based on the host's immune status. Therefore, awareness of the possibility of life-threatening mucormycosis in immunocompromised patients should be emphasized because it can be inactive or reactivated depending on the immune state of patients.

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