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CASE REPORT

An Early and Advanced Oral Mucormycosis Lesions: Case Series

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ABSTRACT

Introduction: Mucormycosis is a deep fungal infection caused by *Mucorales*. It is commonly found in immunocompromised patients and is considered the third most common fungal infection after candidiasis and aspergillosis. **Case report**: This paper reports 2 cases of mucormycosis, which involve the oral cavity, lung, maxillary sinus, orbital and cerebral. The first case had haematology disorder with long-term corticosteroid therapy. The brownish oral pseudomembrane was unresponsive to nystatin and mycafungin therapy. The second case had type 2 diabetes mellitus with perforated hard palate, rhinosinusitis, orbital infection and cerebral abscess. Direct mycology from oral specimens showed coenocytic hypha consistent with the *Mucorales* in both cases. Both cases showed responsiveness to Amphotericin B therapy. **Discussion**: Mucormycosis can be invasive to adjacent sites or angioinvasive to distant sites. Thus, an interdisciplinary team approach must be taken. Early diagnosis and prompt treatment are essential in mucormycosis to prevent the further spreading of infection and tissue destruction. A diagnostic procedure using an oral specimen is an option. **Conclusion**: Management of mucormycosis cases requires interdisciplinary teamwork. Early recognition of oral lesions of mucormycosis and diagnosis of mucormycosis is very important to prevent further damage and even death. Identifying *Mucorales* from oral lesions is beneficial since it is more accessible and non-invasive.

Keywords: mucormycosis; deep fungal infection, oral lesion, oral mycology smear

INTRODUCTION

Mucormycosis, formerly known as zygomycosis, caused by *Mucorales,* is an important fungal infection due to its high ability to destroy tissue.[1–3] Compared to other oral deep fungal mycosis, such as Aspergillosis, which is more common than mucormycosis, most cases of mucormycosis are lethal, and the prevalence increases with the increase in cases of diabetes and immunosuppressive therapy.[2,3] The definite prevalence of mucormycosis is unknown but is estimated to be low.[2–5] The estimated worldwide incidence of mucormycosis in 2005 was about 430 to 1700 cases per million people per year, while Chakrabarti et al. showed a rising trend of up to 50 cases per year in a single centre in India.[2,3] The mortality rate of mucormycosis was around 30% to 90%, depending on the underlying condition and site of infection, making it a very lethal disease.[2,4] One of the factors that contribute to the high mortality rate is the delay in diagnosis and Mucorale's resistance to the most available antifungal

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therapy.[6] There has been a rising trend of mucormycosis due to an increase in cases of diabetes mellitus, increasing use of immunomodulating agents in cancer, organ transplant and autoimmune patients, increased awareness among health professionals, and better diagnostic methods.[7]

Members of the order Mucorales are abundant in the human environment, and some are utilized in making cheese and soy products.[1,2,13] The spores can easily fly and be inhaled.[1,2] Mucorales can be cultured from the nose and oral cavity without clinical signs and symptoms in immunocompetent individuals.[1] Three main routes of mucormycosis infection: (1) respiratory system, (2) direct inoculation, and (3) oral.[2] The characteristics of *Mucorales* are the ability to cause thrombosis and tissue necrosis through an angioinvasion mechanism.[1]

Based on location and distribution, there are six types of mucormycosis: rhino-orbital/cerebral/rhinomaxillary, pulmonary, cutaneous, gastrointestinal, and disseminated.[1] Symptoms of mucormycosis include malaise, headache, black eschar, fever, swelling, and facial pain.[1] *Mucorales* spores are very easy to fly and are inhaled, causing Mucorales to infect the nasal or palatal mucosa and then spread to the surrounding sinus cavities and orbital.[1] Orbital involvement can cause proptosis, ptosis, pupillary dilatation, orbital cellulitis, and blindness due to damage to cranial nerves III, IV, and V caused by hyphae penetration.[1]

In this case report, the authors will report two cases of mucormycosis in inpatient ward X Hospital, Jakarta, Indonesia, with early and advanced features of oral lesions.

CASE REPORTS

Case 1

A 62-year-old woman who was referred from a private hospital in Jakarta to Dr. Cipto Mangunkusumo General Hospital Hospital with aplastic anaemia and had received therapy with methylprednisolone 44 mg/day for two weeks and continued with regular dose reduction while hospitalized in the hospital. The patient admitted to the hospital complained of coughing up brown sputum mixed with blood. The complete blood count showed haemoglobin levels ranging from 9 to 11 g/dl, platelet <500,000/uL, and neutrophils ranging from 16% to 36%. The intraoral examination found yellowish-white pseudomembranous lesions with a brownish-black area at the centre of the lesion (Figure 1).

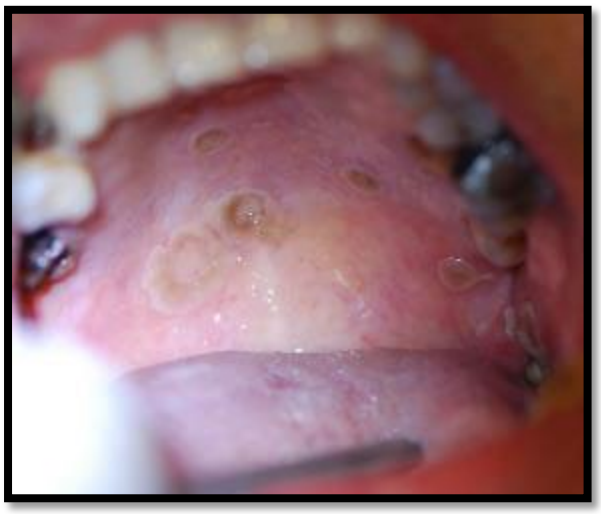
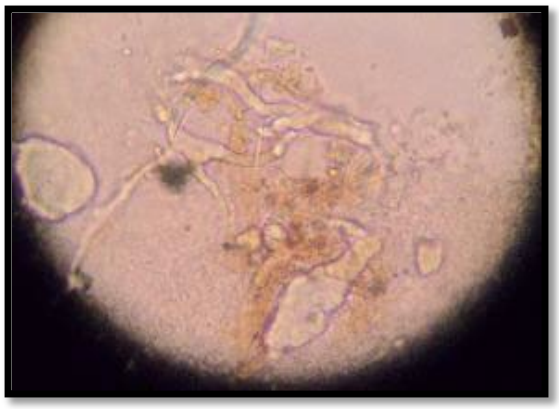


Figure 1. Yellowish white pseudomembrane with the brownish black central area before administration of Amphotericin B on the first patient

The patient was already on nystatin oral suspension 4x1 ml for three days and continued with micafungin 2x50 mg intravenously for one week, all given by the Internist, but there was no improvement. Subsequently, a specimen was taken by scraping off pseudomembranous lesions for fungal examination. Direct examination revealed coenocytic hyphae (ribbon-like hyphae) consistent with mucormycosis and large numbers of yeast cells (Figure 2). The patient was then treated with

amphotericin B. The oral lesion was improved, and the yellowish-white pseudomembranous lesions with a brownish-black area at the centre of the lesion subsided, leaving a shallow reddish ulceration (Figure 3).



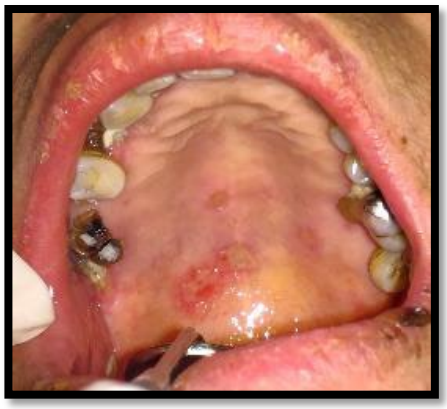
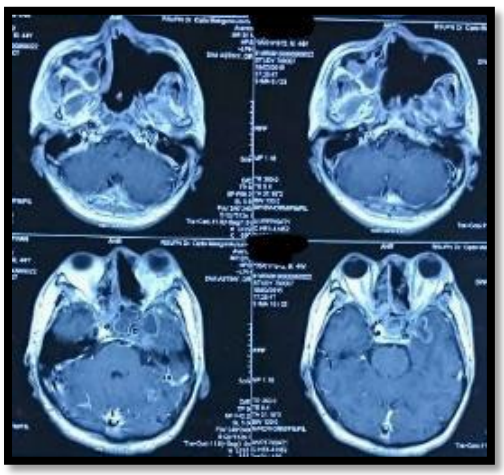


Figure 2. Orthogonal, non-septate, coenocytic hyphae from the oral specimen of the first patient (courtesy of Mycology Laboratory, Department of Parasitology, Faculty of Medicine Universitas Indonesia) Figure 3. Shallow reddish ulcers, three days after administration of Amphotericin B on first patient.

Case 2

A 44-year-old man was referred from a private hospital in Tangerang to Dr. Cipto Mangunkusumo General Hospital in Jakarta with a complaint of redness, swelling, numbness in the neck and left face, soreness on the left palate and visual disturbance in the left eye. The patient was known to have had diabetes mellitus for two years and was on Metformin 500 mg twice daily. Cerebral MRI with Gadodiamide contrast showed abscess and oedema in the left temporal lobe, pansinusitis extending to the infratemporal to intracranial fossa in the left paracella, anterior temporal base and left frontal lobe, and causing left bulbar ptosis (Figure 4). The sagittal view of the cerebral MRI showed defects in the nasal septum, medial wall of the left maxillary sinus, left anterior ethmoid sinus, nasal concha and left ostiomeatal complex (Figure 5).



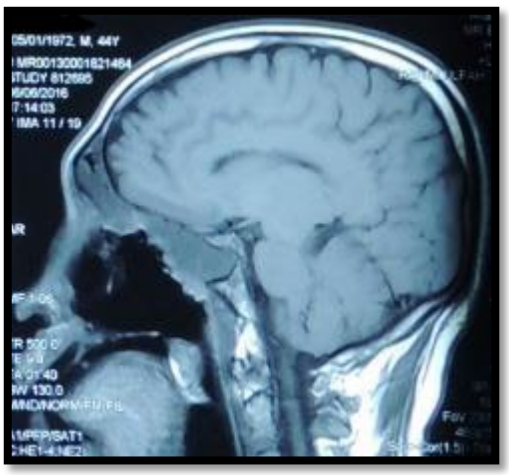


Figure 4. Axial view of cerebral MRI with the contrast of the second patient. Figure 5. The sagittal view of cerebral MRI with the contrast of the second patient

CT scan of the paranasal sinuses showed the lesion extending to the infratemporal fossa to the intracranial, extending to the left orbital cavity, causing left bulbar ptosis, extending to the left para pharynx, destroying the inferomedial orbital wall, left sphenoid wing, anterior-posterior-lateral-medial wall of the left maxillary sinus, wall of the left maxillary sinus, left ethmoid sinus and left cranial base. On intraoral examination, a perforation of the left palate was noticed with black eschar around it and an exposed palatal bone (Figure 6). Specimens were taken by scrapping off necrotic tissue to the border of

the non-necrotic area for fungal examination. Direct fungal examination showed coenocytic hyphae consistent with Mucorales hyphae (Figure 7). The patient received Amphotericin B and necrotic tissue debridement. After debridement, palatal perforation was seen with exposed palatal bone and healthy tissue margin (Figure 8). Perforation of the left orbital nasal was also found (Figure 9).

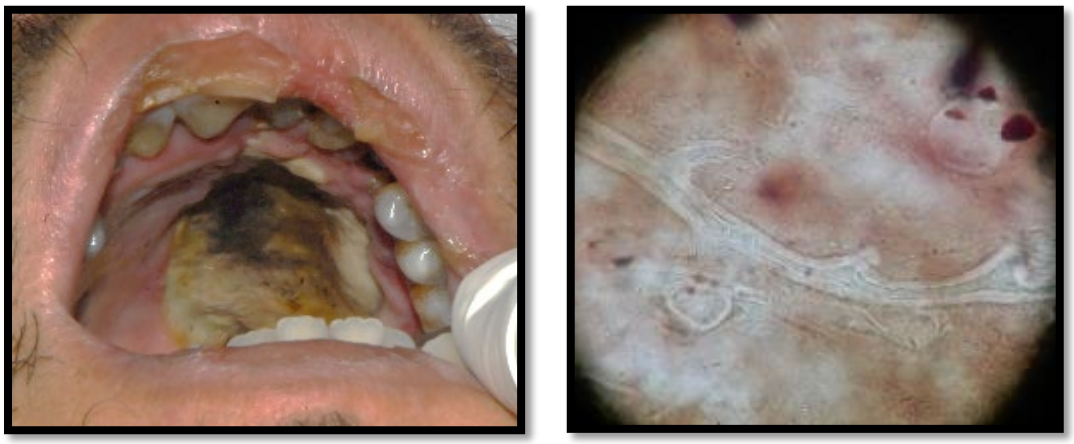


Figure 6. Necrotic tissue with black eschar and palate perforation before administration of Amphotericin B on the second patient Figure 7. Orthogonal, non-septate, coenocytic hyphae from the oral specimen of the second patient (courtesy of Mycology Laboratory, Department of Parasitology, Faculty of Medicine Universitas Indonesia)

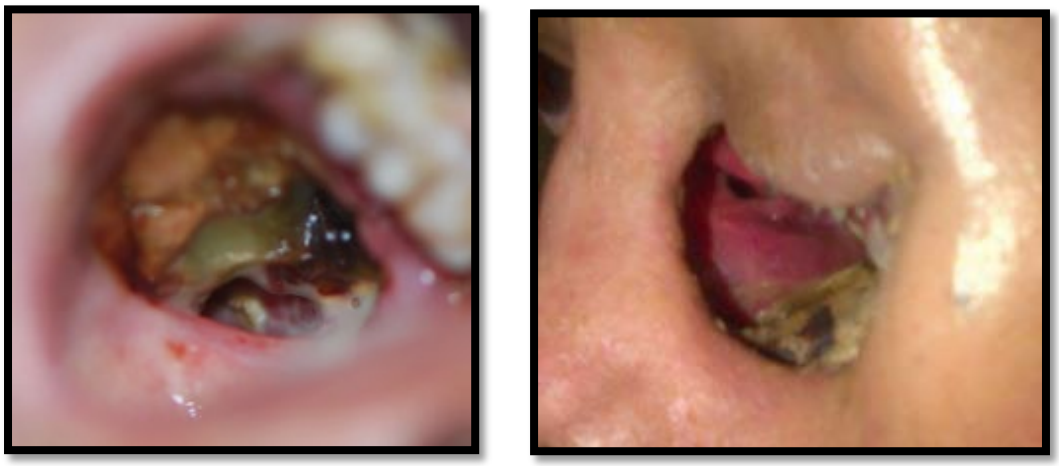


Figure 8. Perforated palate with healthy surrounding tissue without black eschar after administration of Amphotericin B on the second patient. Figure 9. A perforation of the left lateral orbito-nasal wall of the second patient.

DISCUSSION

Mucormycosis, formerly known as Zygomycosis or Phycomycosis, was first introduced by Paultauf in 1885 with the term "mycosis mucorina."[3] Globally, some species are most isolated from the order of *Mucorales* of Mucoraceae, i.e. *Rhizopus sp, Mucor sp*, and Lichtheimia sp.[3] *Rhizopus sp* is responsible for more than 70% of all cases of mucormycosis, specifically *Rhizopus arrhizus* (formerly *Rhizopus oryzae*).[7]

The most important predisposing factors for mucormycosis are diabetes mellitus (with or without ketoacidosis), haematological malignancy and other malignancies, transplantation, neutropenia, corticosteroid, trauma, malnutrition, iron overload, and trauma.[3,7] In stem cell transplant recipients, mucormycosis is the third most common fungal infection after candidiasis and aspergillosis.[7] There is a demographic difference in the epidemiology of mucormycosis between developed and developing countries.[6] This difference is thought to be related to socioeconomic status and malnutrition.[2] There is only limited data available regarding mucormycosis in Indonesia, which roughly estimated 530 cases annually in immunocompromised, trauma burn and diabetic patients group in a single diagnostics facility.[15] Reflecting India as a developing country, even before the COVID-19

pandemic, the number of cases of mucormycosis was predicted to be more than 200,000 per year, accounting for 24% of global invasive fungal infections.[7]

In the first case, the predisposing factor for mucormycosis was a haematological disorder with long-term corticosteroid therapy, while in the second case, diabetes mellitus. Corticosteroids affect the work of neutrophils and decrease their activity against fungal infections, as neutrophils have an important role in inhibiting the proliferation of fungal spores.[2,8] Hyperglycemia is favourable for fungal proliferation in diabetes mellitus. It also impairs the host's chemotaxis and phagocytic activity, which allows the fungi to survive in the acid-rich environment.[9] Hyphae from *Mucorales* produce rhizoferrin, a specific siderophore with a high affinity for iron. Mucorales use the iron-rhizoferrin complex for their survival and also for its virulence properties.[1,10,14] In diabetic ketoacidosis (DKA), increased levels of ferric iron, low pH, and hyperglycemia play an important role in the growth of *Mucorales*.[1,10] In DKA, the availability of keton bodies increases the risk of mucormycosis. This is because *Rhizopus oryzae* produces enzyme ketoreductase, which can use the patient's ketone bodies as nutrients.[1,9,10]

Mucorales are abundant in the environment (food, fruit, and plants), and the spores can fly very easily and are inhaled.[1,2] As a commensal, *Mucorales* can be cultured from the nose and oral cavity without clinical signs and symptoms in immunocompetent individuals.[1] There are three main routes of mucormycosis infection: (1) respiratory system, (2) direct inoculation, and (3) oral.[2] The characteristics of *Mucorales* are the ability to cause thrombosis and tissue necrosis through an angioinvasion mechanism.[1] Necrotic blood vessels will inhibit leukocytes' migration to the area of infection.[8] Angioinvasion plays a vital role in the ability of *Mucorales* to disseminate hematogenously to reach other target organs.[8]

Based on location and distribution, there are six types of mucormycosis: rhino-orbital/cerebral/rhinomaxillary, pulmonary, cutaneous, gastrointestinal, and disseminated.[1] Symptoms of mucormycosis include malaise, headache, black eschar, fever, swelling, and facial pain.[1] *Mucorales* spores in the air infect nasal or palatal mucosa and disseminate to the sinus and orbit.[1] Orbital involvement can cause proptosis, ptosis, pupillary dilatation, orbital cellulitis, and blindness due to damage to cranial nerves III, IV, and V caused by hyphae penetration.[1]

In the first case, the clinical picture was a diffuse yellowish-white pseudomembranous lesion on the oral mucosa with a brownish-black centre. There was no black eschar, swelling or facial pain, a characteristic of mucormycosis. Scraping off the pseudomembrane left reddish superficial ulcers without any evidence of tissue necrosis nor palatal perforation. The patient also had impaired lung function, but due to the patient's condition, it was not possible to perform broncho-alveolar-lavage (BAL) or lung tissue biopsy to confirm the diagnosis of lung mucormycosis.

In the second case, the patient had uncontrolled type 2 diabetes mellitus and developed palatal-rhino-orbita-cerebral mucormycosis. Among uncontrolled diabetic patients, the most prevalent form of mucormycosis is rhino-cerebral (rhino-maxillary).[9] Rhinocerebral mucormycosis starts from the palate or nasal mucosa, which extends to paranasal sinuses and spreads through angular, lacrimal, and ethmoidal vessels.[9] The clinical findings in the second patient were palatal perforation with black eschar, left sinonasal necrosis, ptosis and loss of left eye vision, left facial paralysis, and cerebral abscess. A cerebral biopsy was prepared to determine the organism causing extensive damage involving palatal-rhino-orbita-cerebral.

Ideally, diagnosis is made by biopsy of necrotic and non-necrotic tissue. Hematoxylin & Eosin (H&E) or Periodic Acid Schiff (PAS) staining are performed, as well as KOH wet slide investigations and culture using Sabouraud dextrose agar (SDA) medium for 48-72 hours. Histopathologically, *Mucorales* can be seen in the walls of the necrotic blood vessels.[1,7] Structurally, *Mucorales* have a broader hyphal structure (6-16 μm), coenocytic and orthogonal hyphae compared with Aspergillus, which has a narrow hyphae structure (2-3 μm), septated and branched hyphae.[2,3,11] However, in cases where a biopsy is not possible, direct examination and culture of any specimen could be performed, for example, from sputum.[3,12] The discovery of the hyphae on direct examination is very important because this result can be obtained relatively quickly and strongly supports the diagnosis of mucormycosis.[3,12] Thus, health professionals need to recognise oral lesions of mucormycosis and perform sample collection from oral lesions, particularly when the biopsy of other organs involved cannot be done. Scraping of oral lesions is more accessible and non-invasive.

Direct fungal examinations were performed from oral lesions in both cases by scraping off necrotic tissue. The scraping material was placed into a sterile tube containing 1-2 drops of 0.9% sodium

chloride solution, and KOH direct fungal examination and culture were carried out in the parasitology laboratory immediately. Direct examination found the presence of broad, coenocytic, and orthogonal hyphae consistent with the description of *Mucorales* hyphae. In both cases, Amphotericin B therapy was given as the drug of choice for mucormycosis immediately after the presence of Mucorales hyphae was proved. Amphotericin B works on *Mucorales* by targeting ergosterol and functions by binding and sequestering the ergosterol, resulting in cell membrane instability and pore formation.[13] The response of this regime to both cases was positive.

Early diagnosis, accompanied by radical debridement of necrotic tissue, appropriate systemic antifungal administration, and management of risk factors, determines the success of mucormycosis management.[10,11] An oral medicine specialist has an essential role in establishing an accurate diagnosis of mucormycosis as early as possible, accelerating the diagnosis, and subsequently administering appropriate antifungal therapy to prevent fast deterioration of the patient or even death. A thorough clinical examination is needed to distinguish the initial lesion of mucormycosis, a yellowish-white pseudo membrane with brownish-black areas, from the oral pseudomembranous candidiasis. The absence of response to nystatin and micafungin reinforces the suspicion that the lesion might be mucormycosis.

In both cases where systemic conditions did not support immediate biopsy, a quick decision was needed to take a specimen from a yellowish-white pseudomembranous lesion with a brownish-black area in the centre in the first case and scrape off necrotic tissue on the hard palate in the second case. The successful identification of *Mucorales* hyphae from oral scraping dramatically helps speed up the diagnosis, avoids or replaces more invasive diagnostic procedures (BAL in the first case and cerebral biopsy in the second case), and accelerates the administration of appropriate antifungals for mucormycosis. Tissue necrosis and perforation of the palate in the first case and death from cerebral abscess in the second case could be prevented by the active role of an oral medicine specialist in the interdisciplinary team.

CONCLUSION

Management of mucormycosis requires interdisciplinary teamwork because of the predisposing factors and the extent of infection, which can involve multiple organs. Early recognition and diagnosis of oral lesions of mucormycosis are very important to prevent further damage and even death. Oral mycological smear of oral lesions and direct pathologic examination that follow are non-invasive methods to identify the etiologic agent and establish a diagnosis. They could be beneficial steps in the immediate management of this fungal infection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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