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## RESEARCH ARTICLE

# MANIFESTATION OF MUCORMYCOSIS IN PERIODONTICS

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**ABSTRACT**

Mucormycosis or black fungus is a non-septate filamentous fungal infection that causes potentially life-threatening conditions. This typical infection affects immunocompromised and diabetic patients most of the time and the symptoms of this deadly infectious condition depend on the site of origin, but generally facial structures (nose, sinuses, eye, and brain) are most involved. The major route of infection spread is via inhalation, which then involves the lungs and paranasal sinuses. The highest risk of fungal mucoromycetes infection is in those patients diagnosed and treated for COVID-19 with broad-spectrum antibiotics, non-invasive ventilation, and received corticosteroid therapies. Patients who had pre-existing diseases, such as asthma, diabetes mellitus, and chronic renal failure, and developed COVID-19 on top of it are particularly predisposed to contracting the mucormycotic infection. Any suspected case of mucormycosis requires rapid diagnosis and management due to its rapid progression as well as the destructive course of infection. This article reviews the taxonomy, risk factors, clinical features, pathogenesis, diagnosis, and various treatment modalities of Mucormycosis.

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# INTRODUCTION

Oral infection can be bacterial, viral, or fungal and can be evident in different forms affecting the hard and soft tissues of the oral cavity. Periodontium can be affected by such infections, often showing similar clinical features as that of periodontitis. Among fungal infections of the oral cavity are superficial infections candidiasis and deep fungal infections like mucormycosis which are life-threatening.

Mucormycosis is an opportunistic as well as angioinvasive fungal infection caused by a group of molds called mucoromycetes, which exist in soil, air, and food.[1]Mucormycosis ranked third after Candidiasis and Aspergillosis with high morbidity and potential mortality rate.[2] Furbringer described the disease for the first time in 1876, in a patient who died of cancer and in whose right lung showed a hemorrhagic infarct with fungal hyphae and a few sporangia in Germany.[3] The first case of disseminated mucormycosis was published by Arnold Paltauf and named "Mycosis mucorina" in 1885.[4] Mucormycosis is also designated as zygomycosis or phycomycosis.

**Nomenclature:**

Mucormycosis is caused by Mucorales species. Ajello et al. named the disease caused by these aetiologic agents "zygomycosis" and any invasive fungal infection caused by species of the phylum Zygomycota was termed as either "mucormycosis" or "entomophthoromycosis."[5,6]

**Classification**

**Depending on the clinical involvement[7]**

- Superficial
- Subcutaneous
- Deep

**Depending on the clinical presentation**

- Rhinocerebralal, pulmonary, cutaneous, gastrointestinal, disseminated, or other
- Rare forms- endocarditis, osteomyelitis, peritonitis, renal, etc.

**General Characteristics:** Mucoromycotina are monomorphic, fast-growing organisms, characterized by large, ribbonlike, and irregularly shaped, non-septate hyphae pathognomonically branching at right angles or rarely septate hyphae. The most common species all over the world is Rhizopus arrhizus (formerly Rhizopus oryzae). Other isolated fungi belong to the genera Lichtheimia, Mucor, Rhizomucor, Cunninghamella, Saksenaea, and Apophysomyces which are the main causative agents in human diseases.[8,9]

**Risk Groups:** The most important conditions that predispose to mucormycosis are diabetes mellitus, particularly with ketoacidosis, hematological malignancies, hematopoietic cell transplantation, solid organ transplantation, prolonged neutropenia, treatment with corticosteroids, treatment with deferoxamine, trauma(such as ulcer or extraction socket), iron overload, intravenous drug use, neonatal prematurity, malnourishment and recently COVID-19, whose underlying these diseases have disturbed function of their phagocytic cells.[10] Development of high risk of mucormycosis in those patients who either have decreased levels of mononuclear and polymorphonuclear phagocytes, that would prohibit germination of spores in healthy humans.[11] In diabetic ketoacidosis patients, increased level of glucose and acidic condition allows Rhizopus to survive. In serum increased levels of free iron are caused by a release of iron from binding proteins such as transferrin, which is due to a decreased pH level. The dysfunction of glucose and iron metabolism resulted in decreased phagocytic function and intracellular killing of R.oryzae.[12]

**Pathogenesis:** Due to their relatively bigger dimensions as compared to other species fungi are easily retained in the paranasal sinuses. However, some small size bodies of certain fungal species may also reach the lungs.[13] If the epithelium is disrupted, the fungal spores adhere to the extracellular matrix proteins present in the basement membrane, laminin, and collagen VI. These fungal spores adhere by specific binding and subsequently secrete lipolytic/glycosidic enzymes and proteases that degrade the underlying stroma ultimately facilitating fungal invasion into the host tissues.[14,15] Frank angioinvasion by colonies of fungi causing thrombosis of the involved blood vessels resulting in subsequent tissue ischemia and necrosis is the most characteristic process in the pathogenicity of mucormycosis.[16] The occlusion of blood vessels by the fungi causes a lack of blood supply which protects the fungi by preventing systemic antifungal drugs and host inflammatory cells from reaching the site of infection.[17]

**Virulence Traits:** To achieve thrombosis the fungi need to adhere to the endothelial cells and disrupt their integrity to enter the bloodstream. Mucorales exclusively express spore coat homolog proteins on their surface. These proteins enable the spores to effectively bind utilizing adhesins to glucose regulator protein 78 (GRP78) receptors present in the endothelial cells. After binding to the blood vessels, secondary metabolites are released during phagocytosis of *R. oryzae* by the endothelial cells. These metabolites were identified as the cause for disruption of the endothelial lining, rather than viable fungi.[18] Platelet-derived growth factor receptor (PDGFR) was shown to permeate endocytosis and induce angiogenesis which subsequently aids in the dissemination of the fungi to other organs via the bloodstream.[19] Therefore, PDGFR inhibitors could be potential molecules to limit the endothelial damage caused by the fungi and their dissemination to other organs. In addition, Another important virulence characteristic observed in *Mucorales* fungi is the presence of distinct interactions that enable evasion of host defense. Mendelian and epigenetic mutations majorly account for this evasive potential. These mutations allow the fungi to evade the inflammatory response by the host and survive in a hostile environment.[20] The fungi also can counteract antifungal drugs for which calcineurin has been identified as a virulence factor.[21] Mucorales can grow at 37ºC, some at even higher temperatures as they are thermotolerant. No clear correlation between growth speed at host temperature and differences in virulence potential was detected, according to Schwartze et al.[22] Iron is an important element needed for the survival, growth, and development of the fungal cell. Therefore, iron acquisition is considered a virulence factor. Reductive iron uptake, a siderophorepermease that facilitates the uptake of siderophore-sequestered iron, and an uptake system for acquiring iron from heam are three general mechanisms of iron uptake that have been identified in fungi.[23]

**Clinical Features:** Oral mucormycosis usually develops after the transpalatal extension of rhinocerebral infection. The early stage of mucormycosis might be manifested as sinus pain, nasal congestion, fever, soft tissue swelling, headache, and sometimes nasal ulceration. Untreated cases are more invasive and the rate of progression is rapid, further leading to necrosis of tissues causing pathognomonic brown-black eschar on the maxilla or nasal mucosa. Some other clinical manifestations of the disease are verrucous or granulomatous lesions, indurated and painful ulcers, especially of the tongue, gingiva, or palate, multiple abscesses in the gingival tissues, loosening of teeth, gangrenous inferior turbinates, paresthesia over half of the face, blackish discoloration of the skin over a nasolabial groove or alae nasi, periorbital swelling. Extension to the eyes may lead to blurred vision ophthalmoplegia, ptosis, periorbital edema, and loss of vision along with infection can progress towards the central nervous system resulting in altered consciousness, cranial neuropathies, or cerebral abscesses.[24] Some cases manifested as the presence of mobile teeth and swelling with no eschar feature are misdiagnosed with advanced periodontitis.

**Periodontal Mucormycosis and COVID-19:** Besides the death of millions of lives all over the world by itself, the aftereffects of COVID-19 infection and its therapy have created a unique scenario that is in favour of mucormycosis.[25] Due to the large number of cases of COVID-19 cases, the hospitals were preoccupied and the majority of healthcare resources were shifted to combat the harmful effects of the pandemic which might be accounted for the delay in diagnosis of mucormycosis cases. Since the organism consists of virulence factors, it can grow and disseminate very rapidly. Thus the "window of opportunity" to diagnose and resolve the condition is extremely short, particularly in cases of COVID-19 patients. Delay at the beginning of the treatment has been reported to result in a doubled mortality rate in patients with mucormycosis infection[26.] A higher (87.5%) mortality rate has been reported in cases of mucormycosis associated with COVID-19 patients.[27] However, patients may avoid reporting to the hospitals during post-recovery from COVID-19 due to financial or psychological reasons, and therefore, COVID-associated mucormycosis might have a much higher mortality rate.[28]

**Identification:** Early diagnosis of mucormycosis is difficult. A correct diagnosis needs direct identification of the characteristic hyphae or the recovery of organisms in culture from specimens obtained from the site of infection.

***Cytopathology:*** Calcoflour, Fungi-flour, or Blancoflour which are chitin-binding stains are used along with a fluorescent microscope to identify hyphal elements on Potassium hydroxide wet mounts.[29]

***Histopathology:*** Periodic acid Shiff and Gomori methenamine silver stains are used for a microscopic characterized appearance such as non-septate hyphae, rhizoids, columellae, sporangia, and sporangiospores of the organism.

***Culture:*** To optimize growth, clinical specimens should be inoculated onto appropriate media, such as Sabouraud's dextrose agar medium used to inoculate clinical specimens and incubated at room temperature and 37ºC. Blood culture results are rarely positive when there is luminal involvement of a vascular catheter. Colonies typically appear within 24-48 hours and fill a culture disc in 3-5 days which demonstrates a grayish-white, aerial mycelium with a wooly texture.[30]

***Radiography/ Imaging Techniques:*** Computed tomography is useful in marking the extent of the disease which involves edematous mucosa, fluid-filled sinuses, and destruction of the peri-orbital tissue and bony margins. Magnetic Resonance Imaging is useful in defining the intradural and intracranial extent of the disease.[31]

**Table 1. Updated taxonomy of medically important mucoralean species**

| | Updated Species Names | Former Names of Species |
|---|---|---|
| 1 | Rhizopus arrhizus | Rhizopus oryzae |
| 2 | Rhizopus microsporus | Rhizopus microsporus var. azygosporus, var. chinensis, var. oligosporus, var. rhizopodiformis, var. tuberosus |
| 3 | Lichtheimia corymbifera | Absidia corymbifera, Mycocladus corymbifer |
| 4 | Lichtheimia ornata | Absidia ornate |
| 5 | Lichtheimia ramosa | Absidia ramosa, Mycocladus ramosus |
| 6 | Mucor ardhlaengiktus | Mucor ellipsoideus, Mucor circinelloides f. circinelloides |
| 7 | Mucor irregularis | Rhizomucor variabilis |
| 8 | Mucor janssenii | Mucor circinelloides f. janssenii |

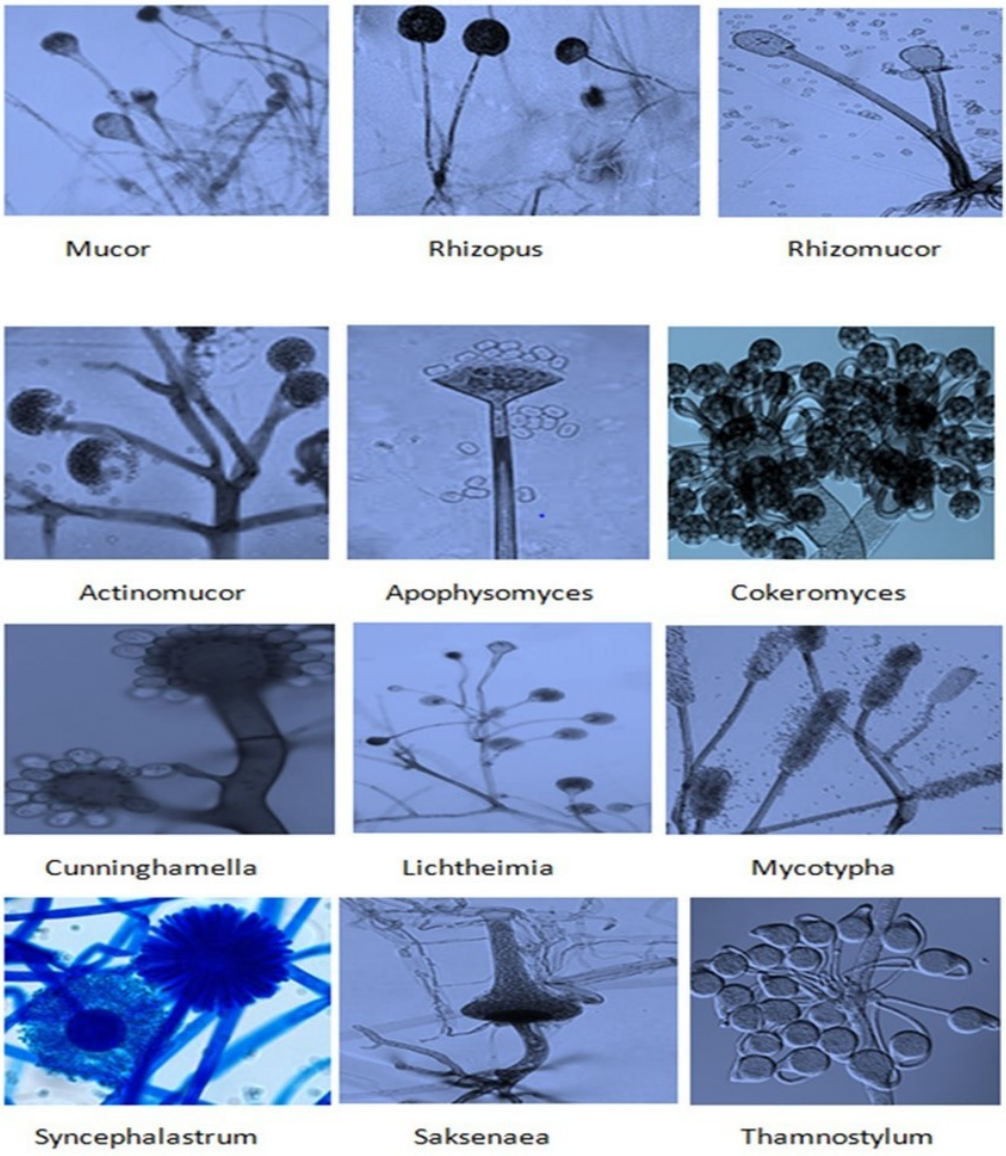


**Figure 1. Mucoralean species**

**Other Methods:** Past medical history, biochemical tests, and molecular analysis like Polymerase Chain Reaction may be used for rapid diagnosis.

**Treatment Modalities:** Aggressive medical treatment with conventional antifungals and non-conventional therapeutics are cornerstones for successful treatment.[32] Immunosuppressive medications, particularly corticosteroids, should be stopped or the dose should be reduced, if at all possible. Aggressive management to rapidly restore euglycemia and normal acid-base status is critical in diabetic patients with ketoacidosis. Administration of iron should be avoided because it exacerbates the severity of infection in animal models. For complete eradication of mucormycosis debridement of necrotic tissues may be critical.[33]

Polyenes like Amphotericin-deoxycholates and lipid complexes are primary therapeutic agents for mucormycosis. The dosage varies from 0.5-1.0mg/kg once daily for 4 weeks. There should be close monitoring of serum electrolytes, as polyenes are known to cause potassium imbalance.[34,35]

Salvage therapy by Posaconazole or Deferasirox can be used when patients are refractory or intolerant to polyene therapy.[36] Non-conventional therapeutic agents like antidiabetics, iron chelating agents, statins, granulocyte transfusions, cytokines, and hyperbaric oxygen have increased the survival rates to 94%.

# CONCLUSION

The immunocompromised state of the person opens the way for various secondary bacterial and fungal opportunistic infections. Mucormycosis is life-threatening fungal infection that often targets immunocompromised individuals. The higher number of reported cases of COVID-associated mucormycosis warrants more attention from healthcare facilities, especially dental surgeons. As dental surgeons would be most efficiently able to identify the disease in an early stage, minimizing the ensuing damage. The clinicians need to pick these infections at an early stage. Histopathological studies are of great help in determining the diagnosis. Successful treatment of mucormycosis requires four steps 1) early diagnosis; 2) reversal of underlying predisposing risk factors, if possible; 3) surgical debridement where ever applicable, and 4) prompt antifungal therapy. A thorough understanding of pathogenesis would further augment the ability of healthcare facilities and workers to develop precautionary and prophylactic measures against the developing malice.

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**Glossary of Abbreviations**

R.oryzae - Rhizopus oryzae
GRP78 - Glucose regulator protein 78
PDGFR - Platelet-derived growth factor receptor
mg/kg – Milligram per kilogram

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