



## COVID-19 associated Mucormycosis: Prominent features, diagnoses, management, and treatment

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### Abstract

COVID-19-associated infections are increasing the burden on the overall health system. Mucormycosis is also related to coronavirus 2 disease and it is termed black fungus a life-threatening fungal infection caused by mucormycosis. Mucormycosis mostly affects diabetic and immunocompromised individuals. The major aim of this study is to discuss the features of COVID-19 associated mucormycosis, diagnosis, prevention, and treatment.

**Keywords:** Covid-19; Mucormycosis; Diagnosis; Oral manifestation

### 1. Introduction

Coronavirus 2 or severe acute respiratory syndrome (SARS-CoV-2) has been linked with a broad range of microbial or pathogenic infections [1]. The common manifestations of coronavirus 2 involve diarrhea, dyspnea, hyposmia, pharyngitis, and intraoral lesions [2]. Both aspergillosis and candidiasis have appeared as the major comorbidities in individuals with coronavirus 2 disease [3]. Recently, a number of mucormycosis cases have been reported in patients with COVID-19 around the world. Hypoxia, diabetes, metabolic acidosis, iron overload, and reduced activity of phagocytic cells due to improper functioning of the immune system are some of the fundamental reasons that help in the germination of Mucorales spores in COVID-19 patients. People with pre-existing medical illnesses such as diabetic ketoacidosis, organ graft, low neutrophil levels, iron buildup, and corticosteroids utilization are susceptible to mucormycosis [4] [5]. Pfizer-BioNTechs and Moderna COVID-19 vaccines were approved by the U.S. Food and Drug Administration (FDA) to fight against the SARS-CoV-2 pandemic [6].

### 2. Discussion

Mucormycosis also termed black fungus is a life-threatening fungal infection caused by micromycetes and mostly affects diabetic and immunocompromised individuals. The manifestations of mucormycosis involve the nose, nasal polyps, eyes, and nervous system. Blurred vision, facial edema, facial pain, pyrexia, and detachment of teeth are some of the manifestations related to rhino-orbital-cerebral mucormycosis (ROCM). Orofacial mucormycosis rarely affects healthy individuals but immunocompromised individuals are liable to these kinds of infections, the treatment of mucormycosis involves long-term IV antifungal drugs [7]. Mucormycetes are mostly found in soil, dead or decomposed leaves, fertilizers, and manure [8]. Inhalation is the considerable route of direct mucormycosis infection and involves the upper respiratory tract [9]. The treatment of coronavirus 2 consists of steroids, antimicrobial agents, and zinc and may cause an imbalance of microbiota which may cause mycotic disease. Presently, COVID-19 positive individuals treated with

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broad-spectrum antimicrobial drugs, corticosteroids, and noninvasive ventilation are at a higher risk for mucoromycetes infection. Individuals with pre-existing health issues such as diabetes, asthma, kidney failure, and also developed coronavirus disease are more susceptible to getting a mucormycotic infection. Several studies have discussed the management and manifestations of mucormycotic infection in the oral and maxillofacial areas. [10]. For this reason, mucormycosis can also be regarded as a diagnosis if cutaneous necrosis occurs in the orofacial area. Therefore, It is necessarily important to recognize the cause of mucormycosis to diagnose this disease earlier to give the most appropriate treatment and surgical intervention [11]. This study will discuss some of the crucial features of COVID-19-related mucormycosis, treatment, manifestations, and preventive measures.

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### 3. Mucormycosis

In 1957, the term “mucormycosis” was created by an American pathologist for an infection caused by *Rhizopus* fungi. It's a rare fungal condition that mostly attacks people with weak immune systems. The disease-causing fungi belong to the class Zygomycetes, genera *Rhizopus*, *Cunninghamella*, *Lichtheimia*, and *Mucor*. *Rhizopus Oryza* alone is responsible for a high percentage of mucormycosis infections and ROCM variants. Inhalation is considered a fundamental mode for the transmission of fungus spores. Mucormycosis disease has five different types according to the infected body area. Renal or kidney mucormycosis is also regarded as a type of mucormycosis.

- ROCM (orbital); is common in individuals with brittle diabetes or after a renal transplant.
- Lungs; is common in patients with cancer or those who undergo surgery (organ transplant)
- Gastrointestinal tract; common in preterm, underweight, and immunocompromised infants receiving treatment or undergoing surgery.
- Leukemia patients with tissue or skin damage, uncontrolled diabetes, Graft-versus-host syndrome, HIV/AIDS, or substance abuse.
- Any infection disseminates from one region or part of the human body to another through blood circulation. [10].

#### 3.1. Pathogenesis of Mucormycosis

Inhalation corrupted food and damaged skin aid the entry of Mucorales into the human body. Mucorales can cause infection in the lungs, gastrointestinal tract, ROCM, and the integumentary system. These complex fungi have several features including heat tolerance, quick growth, power to fuse with the endothelial membrane, feature to get iron from the body of the host, and tissue healing, all these features are responsible for the aggressiveness of this disease [12, 13]. *R. Oryzae* is also associated with improper functioning of interferon. Hyperglycemia, ketogenesis, and iron have a crucial role in the pathogenicity of Mucorales [10].

Mucorales affect an individual's body in two different ways:

- Harmful bacteria evade the human body's immune system and live inside the host.
- Impairment of host cells due to a less efficient defense mechanism. Infections traits of pathogens also play a crucial role in this process [14].

Spores enter the host tissue through skin or alveoli and attach themselves to the endothelium by identifying glucose regulatory protein present on the host receptor [15]. Due to this, *Rhizopus* can permeate tissues of the host and cause infection in diabetic and individuals treated with deferoxamine. Nevertheless, a large number of researches were carried out to find the connection between ketoacidosis and the infection caused by micromycetes. Resistance to antimycotic drugs such as amphotericin B, itraconazole, and Posaconazole is also associated with the poor predictability of infection. In addition to this, Mucorales can easily disseminate through exhalation, ingestion, and local inoculation. Inhibition of Mucorales germination can be achieved by decreasing the levels of phagocytic cells. Patients receiving high-dose of steroids had any transplants and HIV patients are included in this group [10].

#### 3.2. Diagnosis of Mucormycosis

Biopsy and fungal culture techniques to detect the spores are considered necessary to diagnose mucormycosis [16,10]. Because fungus can be present everywhere, cultivation alone is not helpful [17]. Culture testing and detection of the infection-causing agent in body fluids are also considered beneficial. A complete blood count should be performed to find out neutropenia, other tests include blood glucose level, iron, and electrolytes. Endoscopic evaluation can also be helpful [10].

### 3.3. Clinical diagnosis

The clinical diagnosis of mucormycosis requires recognition of host properties, assessment of clinical manifestations, and a good index of suspicion. Some manifestations of mucormycosis include pleurisy in patients with neutropenia and double vision in diabetic individuals which suggest the use of imaging techniques for the diagnosis of mucormycosis infection. Tissue necrosis is also regarded as a distinguishing factor for Mucormycosis. However, the manifestations and symptoms are not adequate to diagnose this disease because some fungi such as *Aspergillus* are also associated with a similar presentation [18]. In addition to this, tuberculosis and mucormycosis can coexist [10]. Corzo-Leon et al. suggested an efficient method to detect ROCM in individuals with diabetes. He concluded that diplopia, exophthalmos, sinus pain, puffy eyes, abducens nerve, and peptic ulcers should be considered the prominent manifestations of mucormycosis [19].

Dental health providers and clinicians should be careful and alert because mostly the presentation of symptoms is not related to fungal sinusitis. The maintenance of a low threshold is necessary for the maxillofacial surgeon especially if an individual has a medical history of coronavirus infection, and was treated with high-dose steroids and antimicrobial agents. This could be helpful to save crucial human organs (e.g eyes) in patients with COVID-19 associated mucormycosis [20, 10]

### 3.4. Microscopic examination

Microscopic evaluation can be used for the presumptive diagnosis. Fluorescent brighteners along with KOH aid to visualize the features of fungal hyphae. Microscopic evaluation is a cheap but extremely useful method to obtain a presumptive diagnosis of fungal infection. This technique is also suggested by "European Confederation of Medical Mycology" experts. However, these methods are not effective enough to recognize the genus of fungus. Immunohistochemistry is another technique that uses monoclonal antibodies, it is beneficial to identify mucormycosis. Furthermore, it can also be useful to differentiate between aspergillosis and mucormycosis [21].

### 3.5. Antifungal Susceptibility examination

Identification of fungus specie is crucial for outbreak investigations. *Aspergillus* and Mucorales can be easily distinguished with the help of cultivation techniques. It was concluded that specie recognition and morphological traits alone are significant in terms of accuracy [22]. However, antifungal susceptibility testing may be associated with some specific drawbacks. ID32C and API 50CH kits were considered useful to identify *Mucor* species but both testing kits cannot distinguish between *M. Circinelloides* specie and *M. Rouxii* specie. Furthermore, it is suggested to use molecular-based tests. The minimum inhibitory concentration (MIC) of *M. Circinelloides* is greater than that of *Rhizopus*. Some *Apophysomyces* variables also have substantial MIC for amphotericin-B. Further investigations are mandatory to obtain data for the relevance of the Antifungal Susceptibility examination in health care [10].

### 3.6. Radiological diagnosis

CT scan technique is used for the examination of lungs and nasal polyps. The usual signs of fungal infection are wedge-shaped shadows, transudative effusions, abnormal tissues, and vascular invasion. Individuals with a compromised level of neutrophils show atoll signs or RHS. The pictures of the CT scan can be used to distinguish between orbital zygomycosis and orbital cellulitis. MRI is also considered beneficial together with gadolinium contrast to diagnose ROCM. In addition to this, 'black turbinate' like presentation indicates rhino-sinusitis fungal infection. Contrast enhancement in computerized tomography (CT-Scans) is helpful to evaluate devitalized regions around the paranasal and ethmoidal sinuses. Similarly, the intracranial extension may be found as hypointense neoplastic lesions. Partial or total opacified paranasal cavities and presence of separation line indicate fungus presence on CT scan. [10].

### 3.7. Serology (Serum examination)

Serology testing and immunodiffusion examination are successful ways to diagnose mucormycosis. ELISpot also called enzyme-linked immunospot technique was shown to identify specific T-lymphocytes for mucormycosis. More studies should be conducted related to the ELISpot technique [10].

### 3.8. Clinical Cases and oral manifestations

The oral manifestations of ROCM include dental pain, halitosis, stuffed nose, epistaxis, black purulent drainage from the nose, Periocular edema, cellulitis, ocular pain, vision abnormalities, and facial erythema [23]. Ahmed et al. conducted a study on 21 post-COVID19 individuals (after 2 weeks of recovery) with mucormycosis of the oral cavity. The study included 11 males and 10 females, it was determined that oral manifestations of mucormycosis are most prominent on the mouth roof and include mucosal stains, edema, oral ulcers, necrotic bone, and appearance of black eschar. Therefore,

palatal ulcers may appear as the first presenting manifestation, encouraging the individual to consult a dental care provider. A dentist may be the first caregiver to identify mucormycosis [10,24,25].

### 3.9. Prevention and treatment of Mucormycosis infection

It is possible to prevent the ROCM infection post-COVID-19 by careful utilization of steroids, prudent usage of tocilizumab, minimizing the risk of mucormycosis contamination, and use of effective mouth rinses. Posaconazole can be utilized as a prophylactic treatment for susceptible individuals. Management of mucormycosis surgical procedures and anti-fungal agents [10,26,27].

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## 4. Conclusion

The goal of this review was to present the prominent features of COVID-19 associated mucormycosis, individuals affected with COVID-19 must follow the preventive measures to avoid mucormycosis infection. Patients with uncontrolled diabetes and immunocompromised individuals are more susceptible to this deadly infection. Therefore, early diagnosis with efficient diagnostic techniques and treatment is necessary to prevent surgical intervention.

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## Compliance with ethical standards

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All of the authors have read this manuscript, and there is no conflict of interest.

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