

Review Article

Mucormycosis and its association with coronavirus disease – 19

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Received : 29 June 2021

Accepted : 31 August 2021

Published : 08 December 2021

DOI

10.25259/JADE_9_2021

Quick Response Code:



ABSTRACT

The pandemic coronavirus disease (COVID – 19) has been turning out to be an agonizing catastrophe among the human population all over the world. Among a perfect storm of the 2nd wave of COVID – 19, there is widespread and significant challenge due to the prevalence of the “MUCORMYCOSIS - the Black fungus infection.” It is a deadly but rare opportunistic fungal infection that mainly affects the immunocompromised people. It has been associated with COVID -19 as a Post – COVID manifestation among the recovered patients. The article provides information about Mucormycosis, its etiology, pathogenesis, predisposing factors, clinical manifestations, diagnosis, and management.

Keywords: COVID – 19, Mucormycosis, Black fungus, Post – COVID manifestation, Immunocompromised people, Management

INTRODUCTION

The COVID – 19 pandemic has been leading to a major health crisis all over the world. Over the course of the pandemic, to make matters worse, various post – COVID issues have been reported.^[1,2]

One such massively emerged post – COVID manifestation in the 2nd wave of Coronavirus disease in India is the “MUCORMYCOSIS – the Black Fungus Infection.” It is a potentially lethal and rare infection that is spotted in patients who have recovered from COVID – 19. While it is not contagious, delay in the diagnosis of the infection may prove fatal. In recent times, a large number of black fungus cases have been reported across the country, with hundreds hospitalized with at least 90 dead.

The State Government of Rajasthan, Gujarat, Odisha, Tamil Nadu and Telangana have already declared it an epidemic after the Centre’s Advisory.^[3]

It is prime time for the Dentists to beware of the clinical manifestations of the infection, its signs and symptoms, risk factors, and management because the patients first report to the dentists as the most common type of mucormycosis being the “rhino-maxillary disease” involves the oral cavity or the jaw bones and the patients may think that the pain or swelling is of Dental origin. The early diagnosis of the black fungus is crucial for optimal treatment and better prognosis.

This article provides a description on what Mucormycosis is, its association with COVID – 19 and its management.

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MUCORMYCOSIS

Mucormycosis^[4] (which was previously known as zygomycosis), widely known as the black fungus infection, is an outrageous but an infrequent fungal infection that is caused by the group of molds called mucoromycetes.^[5] It is caused by exposure to the spores of mucor mold which is commonly found in soil, plants, manure, and rotten fruits and vegetables. It is found everywhere in the environment and even in the nose and mucus of unaffected individuals.^[6]

Human zygomycosis caused by the Mucorales generally occurs in immunocompromised hosts as opportunistic infections and this have been the present noticeable cause for the prevalence of black fungus infection in the COVID – 19 recovered patients forging a scenario of “out of the frying pan into fire.” These forms of mucormycosis usually occur in people who have health problems or take medicines that diminish the body’s ability to fight microbes and sickness.^[4]

The Mucormycetes commonly affect the sinuses or lungs when a person inhales the fungal sporangiospores in the air. It can also affect the dermis following a topical injury like a cut wound or fire injury. It is non-contagious.

TYPES OF MUCORMYCOSIS

1. Rhino—oro-orbito-cerebral Mucormycosis^[7]
2. Pulmonary mucormycosis
3. Gastrointestinal mucormycosis
4. Cutaneous mucormycosis
5. Disseminated mucormycosis.

Mucormycetes can affect various organs (pulmonary, gastrointestinal,^[8,9] cutaneous, and disseminated mucormycosis). However, it is currently manifesting as an invasive Rhino-Oro-Orbito-Cerebral disease, entering via the sinuses to reach the brain affecting the eyes, ears, nose, throat, and mouth.

In a statement, the Indian Health Ministry said that the disease begins to manifest as skin infection in the air sinuses located behind the forehead, nose, cheekbones, and in between the eyes and teeth.^[10]

ETIOLOGY OF MUCORMYCOSIS

The fungi causing mucormycosis – Mucormycetes, belong to the order Mucorales. It has been reported that the most common species that cause mucormycosis are *Rhizopus* species and *Mucor* species. Other than *Rhizopus*, *Mucor*, and *Absidia*, species of Mucormycetes such as *Rhizomucor*, *Apophysomyces*, *Saksenaia*, *Cunninghamella*, *Cokeromyces*, and *Syncephalastrum spp.* also cause human diseases.

PREDISPOSING FACTORS OF MUCORMYCOSIS

According to the Indian Council of Medical Research advisory,^[11] the following conditions in COVID-19 patients increase the risk of mucormycosis infection:

- a. Uncontrolled diabetes
- b. Weakening of immune system due to use of steroids
- c. Prolonged ICU/hospital stay
- d. Comorbidities/post organ transplant^[12]/cancer
- e. Drug therapy (such as Voriconazole therapy used to treat serious fungal infections).

Diabetes mellitus

Diabetic patients are predisposed to mucormycosis because of the reduced phagocytosing ability of their neutrophils and thus the reduced ability of the neutrophils to adhere to the endothelial walls.

Furthermore, the ketoacidosis and hyperglycemia provide an excellent environment for the fungus to grow.

Steroids

Cytokines are produced by immune cells that are included in the innate immune response, including macrophages, dendritic cells, natural killer cells, and the adaptive T and B lymphocytes. An unchecked and exaggerated immune response which causes irreversible damage to the tissues is called a cytokine storm.

A sudden rapid increase in circulating levels of various pro-inflammatory cytokines such as IL-6, IL-1, TNF- α , and interferon, which have destructive effects on human tissue has been noticed in the severe and critical COVID – 19 patients.

Cytokine storm may cause acute respiratory distress syndrome (ARDS) and is the major cause of death in COVID-19 patients. An increased level of IL-6 can be an early indicator that shows that a patient is at risk of cytokine storm and ARDS.

Corticosteroids (*Dexamethasone*) have been prescribed in a wide range for its anti-inflammatory and immunosuppressive effects to the COVID – 19 patients in order to prevent the cytokine storm. The steroid prevents the progression of organ damage and thus serves as a life-saver.

On the other hand, indiscriminate use of high doses of steroids in COVID – 19 patients seems to trigger Mucormycosis in patients post-COVID – 19, even in minimally symptomatic patients.

High doses of corticosteroids amplify the hyperglycemia among the diabetics which in turn renders them vulnerable. Hence, the steroids act as a mixed blessing in post COVID – 19 patients with Diabetes Mellitus.

Prolonged stay in ICU (nosocomial infection)

People with severe COVID-19, such as those in an intensive care unit (ICU) undergoing Oxygen Therapy, are particularly vulnerable to Mucormycosis due to the prevalence of the moist ambience that is favorable for the growth of the fungi and makes them more prone to the opportunistic fungal infection.

Comorbidities/post organ transplant^[12]/cancer

Mucormycosis is also observed in patients with co-morbidities like post organ transplant and malignancies. Mucormycosis occurs in these patients as they become immune-compromised. This also correlates with the fact that the patients who undergo organ transplantation or patients with malignancies are prone to stay in hospitals for longer duration which paves a pathway for the development of the opportunistic Mucormycosis infection as a nosocomial infection.

Drug therapy (such as voriconazole therapy used to treat serious fungal infections)

Drug therapy using antifungal drugs like Voriconazole which is used to treat serious fungal infections such as Invasive Pulmonary Aspergillosis, and Candidiasis can also induce Mucormycosis.

Other predisposing factors include

Neutropenia (low number of white blood cells), iron overload in the body, skin injuries due to surgery, burns or wounds, prematurity and low birth weights, and usage of contaminated Industrial Oxygen Cylinders for oxygen therapy due to high demand during the pandemic.

PATHOGENESIS

The Mucormycete usually affects the sinuses or lungs when a person inhales fungal sporangiospores that are present in the environment, and can also affect the skin after a topical injury.

Mucormycosis begins to manifest as skin infection in the paranasal sinuses located behind our forehead, nose, cheekbones, and in between the eyes and teeth. It then follows its route to reach organs such as the eyes, lungs, and brain.

REASON BEHIND THE TERM BLACK FUNGUS INFECTION FOR MUCORMYCOSIS

The mucormycosis infection encompasses the circulation to the distal organs and thus produces necrosis (death of cells or tissue), which then becomes black.

A classic clinical sign of mucormycosis is the rapid onset of tissue necrosis with or without fever as the result of invasion of blood vessels (angioinvasion leading to gangrene) and

subsequent thrombosis. In severe cases, it leads to fatality due to septicemia.

Hence it was given the name black fungus infection.

SYMPTOMS AND CLINICAL MANIFESTATIONS**Common clinical manifestations**

1. The nasal manifestations of the mucormycosis include black discoloration (eschar) over the nasal bridge, black purulent nasal discharge with epistaxis, and congestion of nose and paranasal sinuses
2. One-sided facial swelling, headache, fever, and malaise
3. Pulmonary Manifestations such as difficulty in breathing (shortness of breath), chest pain, and cough
4. The visual manifestations include diplopia, ptosis, blurring of vision, periorbital erythema and edema and loss of vision in the most severe cases which creates a “gaping hole” in the face.

Oral Manifestations detected in the Mucormycosis include loosening of teeth, osteomyelitis, dental pain, palatal ulceration, halitosis, and intraoral draining sinuses.

DIAGNOSIS

Medical history, symptoms, physical examinations, and laboratory tests are considered for the diagnosis of Mucormycosis.

In the initial case of pulmonary Mucormycosis, a sample of fluid from the respiratory system is sent to the laboratory.

The diagnosis of Mucormycosis is also done by biopsy using the tissue sections to demonstrate focal areas of necrosis and hemorrhage in histopathology.

Fungal selective staining techniques that are used in the diagnosis of Mucormycosis are KOH mounting, Lactose phenol cotton blue mount, and Hematoxylin and Eosin staining.

RADIOGRAPHIC DIAGNOSIS OF MUCORMYCOSIS

CT or MRI scans of lungs, sinuses, or other parts of the body are taken for the diagnosis depending on the location of the suspected infection.

Features on contrast-enhanced CT scans are mucosal thickening, inflammation of nasal turbinate, bony erosion, fluid-filled sinus, and sequestered bone.

Features on MRI include peri-sinusal spread on T2-weighted images, black turbinate sign (First Sign), high-intensity signal in fat-suppressed T2 image in pterygoid bone, and osseous

erosion as T2 weighted hypointense signal & mucosal thickening.

SIGNIFICANT MICROSCOPIC FEATURE OF MUCORMYCOSIS

Demonstration of aseptate hyphae with wide-angle branching (90°) with angioinvasion is the chief characteristic of the *Mucor* species.

The microscopic features of mucormycosis can be differentiated from other fungal infections such as Candidiasis and Aspergillosis by observing the following characteristics: In aspergillosis, the hyphae are septate and dichotomously branched, and in Candidiasis, yeast cells and hyphae are present in the superficial and deep layers of the affected epithelium. *Candida albicans* is also characterized by the presence of pseudohyphae.

TREATMENT

As a blessing in disguise, mucormycosis can be treated to maximize survival rates if diagnosed earlier. Once the mucormycosis is suspected, it requires immediate intervention due to its rapid progressive and destructive nature.

DRUG TREATMENT

Initially, Amphotericin B was prescribed as the first-line antifungal monotherapy for Mucormycosis. At present, Isavuconazole and Posaconazole have also been declared as the first-line antifungal drugs used in the treatment of mucormycosis according to a recommendation from the European Confederation of Medical Mycology (ECMM), together with the Mycoses Study Group Education and Research Consortium (MSG ERC ECMM).^[13]

Amphotericin B, Isavuconazole and Posaconazole are administered via intravenous transfusion. Oral suspension of Posaconazole has also been used successfully in the treatment.

SURGICAL TREATMENT

In severely affected patients of mucormycosis, surgical treatment is prescribed to treat the Mucormycosis in which case, the highly infected tissue or organ is excised.

A combined team approach of surgeons from various fields such as ENT surgeons, maxillofacial surgeons, ophthalmologists, and neurosurgeons is required.

PREVENTION

Mucormycosis can be prevented by following the below-mentioned rules

1. Usage of masks should be mandatory while visiting dusty areas like construction or excavation sites
2. Maintain personal hygiene including proper scrub bath, wearing shoes, long trousers, long sleeve shirts, and gloves while handling soil, moss, or manure
3. Control diabetes and diabetic ketoacidosis. The blood glucose level should be monitored post-COVID-19 discharge and also in diabetics
4. Steroid, antibiotics/antifungal drugs must be used judiciously in the correct timing, correct dose, and duration of administration
5. Immuno-modulating drugs can be discontinued
6. Oxygen therapy must be provided using clean and sterile water for the humidifiers.

Protocols for preventing mucormycosis in the post- COVID-19 patients in a dental setting

- i. Oral hygiene should be maintained using gargles such as 2% povidone-iodine gargles
- ii. Steam inhalation and 0.5% Betadine nasal irrigation are recommended to enhance ciliary function and sinus health
- iii. Patients should be educated regarding the early signs and symptoms of mucormycosis to encourage early reporting by the patients
- iv. Defer any non-emergency invasive oral or dental procedure for at least 3 months post COVID-19 infection.

Do not miss out any of the following rules at any cost in order to get away from the ghastly effects of the mucormycosis

1. Do not miss the warning signs and symptoms
2. Do not consider all the cases with a blocked nose as bacterial sinusitis, especially in immunosuppression and/or COVID-19 patients on immunomodulators
3. Do not hesitate to seek aggressive investigations such as KOH staining and microscopy, culture, MALDI-TOF mass spectrometry for detecting fungal etiology
4. Treatment for mucormycosis should be initiated before crossing the crucial time.

CONCLUSION

The mucormycosis or the black fungus Infection that develop as one of the post-COVID – 19 opportunistic fungal infection caused by the groups of mucormycetes has been stated as a rare but potentially fatal infection that is mainly prevalent in the immunocompromised patients and in patients with diabetic ketoacidosis. It has already been declared as an epidemic in 5 states of India.

Its cataclysmic effects on human health have intensified a terrific alarm among the people as it has been costing lives of many people across the country in spite of the standard therapies.

A key to effective treatment of Mucormycosis is prompt detection, clear-cut diagnosis, and instant and bellicose treatment. Post COVID-19 recovery, the patients should maintain exemplary personal hygiene as a first-line defense to prevent Mucormycosis. Dental practitioners should beware of the warning signs and symptoms and the precautionary protocols in order to spot the oral manifestations of mucormycosis at the earlier stages.

Morbidity and mortality are high due to the invasive nature of mucormycosis. Hence, earlier and appropriate management after diagnosis by the timely dosage of antifungal therapy and surgical intervention is momentous.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Anuthama V, Gowri S, Jayakumar D. Mucormycosis and its association with coronavirus disease – 19. *J Acad Dent Educ* 2021;7:36-40.