

Black Fungus (Mucormycosis) A Rare Fungal Infection caused by Covid-19

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ABSTRACT

The coronavirus disease (COVID-19) transmission is a human-to-human transmitted disease that has been designated an emergency global pandemic that has killed more than half a billion people worldwide and created severe respiratory disasters for more than five million people. There is injury to the alveolar with significant inflammatory exudation, in addition to lower acute respiratory syndrome. COVID-19 patients had lower levels of immunosuppressive CD4+ and CD8+ T cells, and most patients in intensive care units (ICU) require mechanical breathing, resulting in a lengthier hospital stay. Fungal co-infections have been found in these individuals. Patients with COVID-19 suffer mucormycosis, a fatal black fungus illness that causes vision and hearing loss, as well as death. Mucormycosis, a black fungus produced by post-covid problems, will be the subject of this chapter.

KEYWORDS: COVID-19; Mucormycosis; Post Covid Complications; Intensive Care Units, Case report

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1. INTRODUCTION

An alarming number of infections of mucormycosis, a lethal fungal infection, have been reported in India among COVID-19 patients and those who have recently recovered. Many of these patients had diabetes and were taking steroids for their coronavirus infection, that could have put them more sensitive to the fungus attacking their tissues. Mucormycosis is an extremely uncommon infection. Mucor mould, which is widely found in soil, plants, manure, and decaying fruits and vegetables, causes it. It's everywhere, in soil and air, and even in healthy people's noses and snot. It affects the sinuses, the brain, and the lungs, and it can be fatal in diabetics or persons who are extremely immunocompromised, such as cancer patients or HIV/AIDS patients. [2] Coronavirus causes mucormycosis, a fungal infection. For a long time, black fungus, also known as mucormycosis, has been a source of sickness and death in transplant recipients, ICU patients, and viral infections.

Mucormycosis, a normally rare fungal infection, has recently become more common in India, especially affecting persons recuperating from COVID-19.

According to experts, this sort of fungal infection is highly unusual and may affect patients whose immune systems have been compromised by the coronavirus.

Experts believe that the use of steroid medicines in these patients may account for some of the increase, while the immune-compromised state of COVID-19 patients may account for others.[6]

History: The first case of mucormycosis was possibly one described by Friedrich Küchenmeister in 1855 [26]. Fürbringer first described the disease in the lungs in 1876.[27] In 1884, Lichtheim established the development of the disease in rabbits and described two species; *Mucor corymbifera* and *Mucor rhizopodiformis*, later known as *Lichtheimia* and *Rhizopus*, respectively. [26] In 1943, its association with poorly controlled diabetes was reported in three cases with severe sinus, brain and eye involvement.[26] In 1953, *Saksenaia vasiformis*, found to cause several cases, was isolated from Indian forest soil, and in 1979, P. C. Misra examined soil from an Indian mango orchard, from where they isolated *Apophysomyces*, later found to be a major cause of mucormycosis. [26] Several species of mucorales have since been described.[26] When cases were reported in the

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United States in the mid-1950s, the author thought it to be a new disease resulting from the use of antibiotics, ACTH and steroids. [27][28] Until the latter half of the 20th century, the only available treatment was potassium iodide. In a review of cases involving the lungs diagnosed following flexible bronchoscopy between 1970 and 2000, survival was found to be better in those who received combined surgery and medical treatment, mostly with amphotericin B.[28]

1.1 Symptoms of Mucormycosis:

Mucormycosis symptoms vary depending on where the fungus is developing in the body. Symptoms of a fungal infection include a stuffy and bleeding nose, eye swelling and pain, drooping eyelids, blurred vision, and lastly, vision loss. Around the nose, there could be black patches of skin. [3]

1.1.1 Symptoms of rhinocerebral (sinus and brain) mucormycosis include:[4]

- One-sided facial swelling
- Headache
- Nasal or sinus congestion
- Black lesions on nasal bridge or upper inside of mouth that quickly become more severe
- Fever

1.1.2 Symptoms of pulmonary (lung) mucormycosis include:

- Fever
- Cough
- Chest pain
- Shortness of breath

1.1.3 Cutaneous (skin) mucormycosis:

Cutaneous mucormycosis appears as blisters or ulcers on the skin, and the diseased region might turn black. Pain, warmth, extreme redness, and swelling around a wound are some of the other symptoms.

1.1.4 Symptoms of gastrointestinal mucormycosis include:

- Abdominal pain
- Nausea and vomiting
- Gastrointestinal bleeding

1.1.5 Complication:

a) Black crusts around the nose:

The most common sign of the illness is facial malformation. If left untreated, mucormycosis can cause significant damage to a patient's nose, jaw, and other critical face structures. A unique characteristic is the development of black crusts and swelling in and around the nasal canal and eyes. In many severe cases, surgery to remove the jaw bone or the nose may be necessary. [29]

b) Headaches and swelling in/and around the forehead:

When black fungus spreads to the brain and produces nerve inflammation, one of the most serious consequences occurs. The early indications may include acute headaches, swelling, redness, and discomfort in

the forehead. Doctors also advise that the infection can affect cognitive function, and that crucial symptoms including memory loss, delirium, and mental abnormalities should be addressed as soon as possible.[29]

C) Swelling in the cheeks, eyes or parts of the face:

Swelling, localised discomfort on the cheekbone, or one-sided facial discomfort or numbness might be major indicators of infection right now. Aside from swelling, the fungal infection may have an impact on skin health, causing numerous lesions and necrosis-like signs.[29]

d) Vision loss/ partial blindness:

A black fungus infection can harm the body's essential nerves as well as cause eye impairment. Itching, redness in the eyes, eye discomfort, partial blindness, and vision loss have all been reported by some individuals. In certain circumstances, the infection might result in visual loss that is irreversible.[29]

e) Pulmonary infections:

The fungal development can move randomly throughout the respiratory tract and harm the lungs, producing severe symptoms, because the moulds can be breathed by the patient. 'Pulmonary mucormycosis' is the medical term for this condition. Nosebleeds, nasal obstruction, and a loss of face feeling are all symptoms of pulmonary problems. Mucormycosis can cause cough, fever, and chest discomfort, which are all respiratory symptoms linked with COVID-19.[29]

1.1.5 Mucormycosis that has spread throughout the body:

Because mucormycosis is most common in persons who are already sick from other medical illnesses, it can be difficult to tell which symptoms are due to it. Patients with a disseminated infection in the brain may experience changes in mental state or go into a coma.[4] [5]



Figure 1: Symptoms of Mucormycosis

1.1.6 Epidemiology of Black Fungus

During the COVID-19 epidemic in India, the illness has become a major public health concern. As of May 25, 2021, the Indian government stated that approximately 11,700 individuals were undergoing treatment for mucormycosis. Because of the black colouring of dead and dying tissue caused by the fungus, it was dubbed "black fungus" by several Indian news sites. Mucormycosis rates in India were predicted to be 70 times greater than the rest of the globe even before the COVID-19 epidemic.[30]

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Mucormycosis may have a greater actual incidence and prevalence than it seems.[31] Mucormycosis is an uncommon disease that affects less than 1.7 individuals per million in San Francisco each year.[32] [33] In India, where there are an estimated 0.14 instances per 1000 people, it is about 80 times more frequent.[34] The location of causative fungus is quite important. Asia has the largest incidence of *Apophysomyces variabilis*, whereas Europe has the highest occurrence of *Lichtheimia* spp.[35] After aspergillosis and candidiasis, it is the third most frequent severe fungal infection infecting individuals.[36] In poor and middle-income nations, diabetes is the most prevalent underlying illness, but in developed ones, blood malignancies and organ transplants are more common.[34] The statistics for mucormycosis have been shifting as new immunomodulating medications and diagnostic techniques have been discovered. Furthermore, the statistics vary when new genera and species are discovered, as well as new risk factors such as TB and renal disease. [34]

1.1.7 Case Report:

Background: Patients on steroid therapy for diabetes will have a rise in blood pressure. Some people do not have diabetes and develop it after contracting Covid, increasing their risk of contracting Mucormycosis. The fungus does not transmit from one person to another. Mucormycosis is easily contracted by someone with a weakened immune system.

Case1: After three weeks of recovery from Covid, a 60-year-old man with a history of diabetes developed mucormycosis. The patient was originally admitted to a Thane hospital, where he underwent an insufficient minor surgery, after which he was sent to us. Black crusting in the nostrils and a palate ulcer were the first indications of illness he displayed. Mild instances don't have many symptoms, but he had a severe case when he saw Dr. Milind. We used a nasal endoscopy, fungus culture, biopsy, CT scan, and MRI to make the diagnosis. For the first 1-2 months, Dr. Milind used surgery in conjunction with medicinal therapies such as antifungal medications. Currently, the patient's condition is good, and he can eat 50-60% of his food orally, but he needs a tube through his nose for 40% of the food he eats, largely due to a deformity in his palate.

Case 2: After a three-week interval after recovering Covid, a 65-year-old male with a history of diabetes and high blood pressure developed mucormycosis. The patient was from Varanasi and was flown to Mumbai in an air ambulance. A serious case of mucormycosis was discovered in the patient. The infection had already spread to the eyes, brain, and sinuses, thus the outlook was dire. He was immediately put on a ventilator and operated on and the patient was put on high doses of anti-

fungal medicine. The patient didn't survive and died within 30 hours during the treatment. He was put on a ventilator and operated on right away, and he was given heavy dosages of antifungal medication. During the therapy, the patient did not survive and died within 30 hours. [37]

1.2 Causes of Mucormycosis:

Mucormycosis, often known as black fungus, is a fungal infection consequence. Mucormycosis is obtained by coming direct interaction with fungus cells in the environment. After the fungus accesses the skin by a cut, scrape, burn, or other sort of skin trauma, it can form on the skin.

Patients who are healing or have recovered from COVID-19 have been identified to have the condition. Additionally, anyone who is diabetic and has a weakened immune system should be on the alert for this..[7] The following disorders in COVID-19 patients, according to an advisory given by the Indian Council of Medical Research, increase the risk of mucormycosis infection:

- 1) Diabetes which is uncontrolled
- 2) Immune system damage as a result of steroid use
- 3) A stay in the intensive care unit (ICU) or in the hospital after a long period of time
- 4) Co-morbidities, organ transplantation, and cancer
- 5) Treatment with voriconazole (used to treat serious fungal infections). [7]

1.3 How to prevent Mucormycosis?

- a) If you're going to a dusty construction site, wear a mask.
- b) When managing soil (gardening), moss, or dung, wear shoes, long trousers, long sleeve shirts, and gloves.
- c) Personal hygiene should be maintained, including a thorough scrub bath.
- d) According to the advise, the condition can be controlled by controlling diabetes, terminating immunomodulating medicines, lowering steroids, and performing comprehensive surgical debridement to remove all necrotic debris.

1.3.1 Do's

Control hyperglycemia

Monitor blood glucose level post-COVID-19 discharge and also in diabetics

Use steroid judiciously

Use clean, sterile water for humidifiers during oxygen therapy

Use antibiotics/antifungals judiciously

1.3.2 Don'ts

Do not miss warning signs and symptoms

In the setting of immunosuppression and/or COVID-19 patients on immunomodulators, do not consider all occurrences of blocked nose to be cases of bacterial sinusitis.

If you suspect fungal aetiology, don't be afraid to pursue rigorous investigations (KOH staining and microscopy, culture, MALDITOF).

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Don't wait until it's too late to start treating mucormycosis. [8].

2. IMPROVED MUCORMYCOSIS UNDERSTANDING

A vast variety of pathogenic organisms produce human mucormycoses. The mucorales species is associated to the site of mucormycosis; *Rhizopus arrhizus* (Figure 2) is found in 85 percent of rhino-cerebral forms, compared to



Figure 2: *Rhizopus arrhizus*

Sporangiophore branching and rhizoids (stereomicroscope); (b) grey-brownish colony on malt 2% medium; (c) melanized sporangium and sporangiospores.

The clinical manifestations of mucormycosis are frequently linked to underlying diseases. Individuals with diabetes mellitus are more likely to develop rhino-cerebral mucormycosis, whereas patients with haematological malignancies are more likely to develop pulmonary mucormycosis. In individuals with pulmonary mucormycosis, radiological findings are linked to immunological status[14]. Recently, there have been diagnoses in the gastrointestinal system, which is unusual. The stomach is the most commonly affected organ, followed by the colon. Abdominal pain and gastrointestinal bleeding are the most common symptoms[15]. Endoscopic evidence of necrotic lesions that can lead to perforation and peritonitis suggest a diagnosis. [16].

Mucorales can enter a susceptible host through inhalation, contaminated food consumption, or abraded skin. Infections of the rhino-orbito-cerebral, pulmonary, gastrointestinal, or cutaneous/wound system result from these routes. Mucormycosis is known for its angioinvasive properties, which result in vascular thromboses and, eventually, tissue necrosis. Mucormycosis is recognised to be predisposed by ketoacidosis and deferoxamine, highlighting the importance of hyperglycemia, iron, and acidifying ketone bodies in mucorales pathogenicity. The connection between a spore-coating protein family (CotH) on the surface of *Rhizopus* spp. and endothelium glucose regulator protein 78 (GRP78) expressed on the surface of endothelial cells has been linked to angioinvasion. This contact causes host cell damage, which leads to fungal hematogenous spread[17].

only 17 percent of non-rhino-cerebral forms, according to the French RetroZygo study[9]. The differential in virulence amongst Mucorales species could explain this observation. Ketoacidosis has been reported to predispose mice to *Rhizopus* spp. infection but not to *Lichtheimia* spp. infection in experimental studies[10] [11]. Corticosteroid therapy also made mice more susceptible to lung infections caused by *Lichtheimia corymbifera* or *Lichtheimia ramosa*. [10] [11].

Increased levels of serum glucose, iron, and ketone bodies promote fungal growth and enhance the expression of GRP78 and CotH, allowing *Rhizopus* to infiltrate host tissues more easily and explaining why diabetic and deferoxamine-treated individuals are more susceptible to mucormycosis. It should be highlighted, however, that the majority of research on virulence and the advisory board [18]. Monocytes and neutrophils have been shown to limit Mucorales spore development, hence their numbers and function are major mucormycosis risk factors. Patients with haematological diseases, AIDS, or liver cirrhosis, as well as those who have had a solid organ transplant or are on high-dose steroids, fall into this category[19] [20]. Finally, natural disaster victims are at risk[21]. owing to water, mud, or debris-contaminated wounds[22], such as those sustained following the 2004 Indian Ocean tsunami[23] or the 2011 Missouri tornado[24].

3. TREATMENT FOR MUCORMYCOSIS:

Mucormycosis is a dangerous infection that requires treatment with antifungal medications such as amphotericin B, posaconazole, or isavuconazole. Amphotericin B, posaconazole, and isavuconazole are given intravenously (amphotericin B, posaconazole, and isavuconazole) or orally (posaconazole, isavuconazole) (posaconazole, isavuconazole).

3.1 Amphotericin B

Antifungal amphotericin B is used to treat fungal infections in neutropenic patients, cryptococcal meningitis, fungal infections, and leishmaniasis.

Abelcet, Ambisome, Amphotec, and Fungizone are examples of brand names.

Generic Name: Amphotericin B

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Background: In vitro, amphotericin B has a high level of action against a wide range of fungi. In vitro, doses of amphotericin B ranging from 0.03 to 1.0 mcg/mL inhibit *Histoplasma capsulatum*, *Coccidioides immitis*, *Candida* species, *Blastomyces dermatitidis*, *Rhodotorula*, *Cryptococcus neoformans*, *Sporothrix schenckii*, *Mucor mucedo*, and *Aspergillus fumigatus*. While *Candida albicans* is often responsive to amphotericin B, other *Candida* species may be less so. Amphotericin B resistance is common in *Pseudallescheria boydii* and *Fusarium* sp. Bacteria, rickettsiae, and viruses are unaffected by the antibiotic.

Indication: It is used to treat fungal infection.

Mechanism of Action: Depending on the dosage found in body fluids and the fungus' susceptibility, amphotericin B is either fungistatic or fungicidal. The medicine works by binding to sterols (ergosterol) in susceptible fungi's cell membrane. This results in the formation of a transmembrane channel and a change in membrane permeability, allowing intracellular components to flow out. The main sterol in the fungal cytoplasmic membrane is ergosterol, which is where amphotericin B and the azoles act. Amphotericin B, a polyene, binds irreversibly to ergosterol, causing membrane rupture and, eventually, cell death.

Absorption: Bioavailability is 100% for intravenous infusion.

Protein Binding: Highly bound (>90%) to plasma proteins.

Metabolism: Exclusively renal.

Half Life: An elimination half-life of approximately 15 days follows an initial plasma half-life of about 24 hours.

Adverse Effect: Amphotericin B overdoses can result in cardio-respiratory arrest.

There is no food interaction found. [25]

FORMULATION STUDIES

Recent Novel Researches on Black Fungus: On May 13, 2021 Lundquist Institute announced that one of its spinoff start-up companies, Vitalex Biosciences, is producing an antibody that stems the spread of mucormycosis, a deadly fungal infection with an overall mortality rate of 50% and higher. Laboratory has discovered a molecule that allows the fungus to invade human cells. The preclinical studies indicated that a mouse antibody targeting this molecule is highly protective against mucormycosis especially when given combined with antifungal drugs. A humanized version of this antibody is currently in manufacturing by Vitalex Biosciences. It is hoped that this antibody will improve the outcome of the disease and save lives from mucormycosis including those with COVID-19. [38]

CONCLUSION

Since the initial wave in 2020, it has been established that Covid-19 causes a variety of issues as a result of the virus and the body's immunological response. Long Covid is a well-known and well-documented condition characterised by lethargy, exhaustion, and shortness of breath over an extended period of time. Treatment has a number of noticeable adverse effects. Mucormycosis, or black fungus, is one example of this, which affects persons recuperating from Covid-19. So, what do we know about these side effects of the treatments individuals receive, what are the lessons we can learn from them, and how can individuals be more aware of the risks they may encounter as a result of the medications they take?

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