

Review Article

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## An Emerging Devil, Mucormycosis alias Black Fungus : A Review

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### ABSTRACT

The SARS-CoV-2 virus has given birth to several other new diseases in that the rapidly spreading infections of post-COVID recovered cases is Mucormycosis or black fungus. Mucormycosis is a very rare infection. It is mostly found in the environment such as soil, plants, manure and decaying organic matter. Mucormycosis is more common among people who have health problems or take medicines that lower the immunity. The symptoms of mucormycosis or black fungus depend on which part of the body the fungus is growing. A classic clinical sign of mucormycosis is the rapid onset of tissue necrosis with or without fever. Early recognition, diagnosis and prompt administration of appropriate anti-fungal treatment are important for improving outcomes for patients with mucormycosis. Lipid formulations of amphotericin-B are often used as first-line treatment. The fungi that cause mucormycosis are common in the environment, so try to protect yourself from this fungus in the environment that will be the only solution and also wear a properly fitted mask or wear an N-95 respirator while working and avoid steroid drugs unnecessarily without a doctors prescription.

#### Keywords

Mucormycosis,  
COVID-19,  
Diabetes, Steroids,  
Amphotericin-B  
and Mask

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### Introduction

The SARS-CoV-2 virus has given birth to the emergence of several other new diseases. One of the rapidly spreading infections of post-COVID recovered cases is Mycromycosis or commonly as black fungus. Mucormycosis (previously called zygomycosis) is a very rare infection. It is caused by exposure to mucor mould (mucormycetes) which is mostly found

in the environment such as soil, plants, manure or dung, and decaying organic matter, such as leaves, compost piles, or rotten wood. fruits and vegetables even in the nose and mucus of the healthy people.<sup>(1,2,3)</sup> So it is ubiquitous in nature. They are mostly found in soil than in air. In summer it is more common and fall than in winter or spring. Mucormycosis particularly affects people who are having health issues or the person who are

under some medication which lower the immunity to fight germs and sickness. It mainly affects the brain, the lungs and the sinuses. It can be life-threatening in diabetic or severely immuno-compromised persons, such as cancer patients or person with HIV/AIDS. It can also affect the skin after a cut, burn, or other types of skin injury.<sup>(15,16,17)</sup>

### **Etiologic agent**

Molds are belonging to the order of Mucorales, most commonly *Rhizopus* species. Others were included in *Mucor* species, *Cunninghamella* *bertholletiae*, *Apophysomyces* species, and *Lichtheimia* (formerly *Absidia*) species.<sup>(8,15)</sup>

### **Reservoir**

Mucormycetes are thermotolerant that are found every where in the environment. Environmental sampling studies have shown that Mucormycetes are commonly found in soil, but rarely in air samples. The specific environmental niches are different among genera and species.<sup>(18,19,20,21)</sup>

### **Types of mucormycosis**

There are five major clinical forms of mucormycosis. The clinical forms are like Rhinocerebral (sinus and brain) mucormycosis, Pulmonary (lung) mucormycosis, Gastrointestinal mucormycosis, Cutaneous (skin) mucormycosis and Disseminated mucormycosis. In that rhinocerebral and pulmonary infections are the most common.<sup>(8)</sup>

Rhinocerebral mucormycosis is the most commonly found in patients with diabetes and with renal transplants. It also seen in neutropenic cancer patients and hematopoietic stem cell transplant or organ recipients. Symptoms are fever, unilateral facial swelling, headaches, nasal or sinus congestion or pain

and serosanguinous nasal discharge. As the infection spreads, ptosis, proptosis, loss of extraocular muscle function, and vision disturbance may noticed. Necrotic black lesions on the hard palate or nasal turbinate and drainage of black pus from eyes are useful signs for diagnostic purpose.<sup>(4,5)</sup>

Pulmonary (lung) mucormycosis is the most common in immuno compromised persons like person with cancer and person who had an organ transplant or a stem cell transplant. This is generally seen in patients with hematologic malignancy or profound neutropenia. The symptoms are non-specific like fever, cough, chest pain, and dyspnea. Angioinvasion leads to tissue necrosis, which may predominantly lead to cavitation and/or hemoptysis.

Gastrointestinal mucormycosis is mainly due to ingestion of the organisms and it is less common than the other clinical forms. This clinical forms is more common in young children than adults, especially in premature children and low birth weight babies who less than 1 month of age, who had taken antibiotics, surgery, or medications that lower the immunity to protect against germs and sickness. It typically occurs in undernourished patients or premature babies. The stomach, colon, and ileum are most commonly affected in this clinical forms. The most common symptoms are non-specific abdominal pain and distension, nausea, and vomiting and also gastrointestinal bleeding can occur. It is challenging to diagnose because of its clinically similar to necrotizing enterocolitis<sup>(6,7)</sup>.

Cutaneous mucormycosis may be primary or secondary infection. The Primary infection is usually due to direct inoculation or contamination of the fungus in broken skin. It is often seen in patients with burns or other forms of local skin trauma. The primary infections can induce an acute inflammatory response with pus, abscess formation, tissue

swelling, and necrosis. The lesions are red and indurated and often progress to black eschars. The secondary cutaneous infection is commonly seen when the organism spreads hematogenously; lesions typically start with an erythematous, indurated, and painful cellulitis and then progress to an ulcer covered with a black eschar.

Disseminated mucormycosis occurs when the organisms spread through the blood circulation to affect other body parts. The most common site of spread is the brain, but the spleen, heart, skin, and other organs can also be affected.

### **Epidemiology**

The black fungal infection is rare. Before pandemic of covid-19 in this world, the incidence of black fungal cases are difficult to determine because no national surveillance system exists. The Population based incidence is roughly calculated for mucormycosis and it acquired from the laboratory surveillance in the San Francisco Bay Area during 1992–1993. That surveillance suggested a yearly rate of 1.7 cases per 1 million population.<sup>(34)</sup>

The Prospective surveillance in the number of 16,808 transplant recipients was done in 23 institutions during 2001–2006 found that mucormycosis was the third most common type of invasive fungal infection in stem cell transplant recipients and they considered that 8% of infections are invasive infections (77 mucormycete cases occurred in number of 983 stem cell transplant recipients who acquired any fungal infection).

In solid organ transplant recipients, mucormycosis was reported for 2% of all invasive fungal infections (28 mucormycete cases noticed among 1,208 solid organ transplant recipients who acquired any fungal infection).<sup>(12,35,36,37)</sup>

### **Mucormycosis outbreaks**

Mucormycosis infection is not a contagious disease. Meanwhile, it can't spread between people or between people and animals. So it is not a communicable disease too. Although most of mucormycosis infection cases are sporadic (not part of an outbreak in India), outbreaks of mucormycosis have occurred. It has a mortality rate of about 50%. Before to Covid pandemic, at least 38 countries around the world had reported cases of mucormycosis. According to the Leading International Fungal Education portal, the highest rates of black fungus cases were in India and Pakistan with around 140 cases per million annually.<sup>(39, 40)</sup>

From 28 states, around 28,252 cases of mucormycosis have been recorded till now, in India. Out of this, 86% or 24,370 cases, have a history of COVID-19 and 62.3% or 17,601, have a history of diabetes<sup>(41)</sup>. More than 300 deaths have been recorded till now.<sup>(39, 40)</sup> There is nearly 60% of the cases are from three states namely Gujarat, Maharashtra and Andhra Pradesh. Some other states like MP, Rajasthan and Karnataka are also reporting a large number of mucormycosis cases day by day. Mucormycosis is strongly related with poorly controlled diabetes and there's a lot of diabetic patients in India.<sup>(39)</sup> Around 90% - 95% of such patients in India are diabetics who were on steroids. In Tamil Nadu so far, more than 400 persons have been affected.<sup>(45)</sup>

The central government of India has now declared it as a notifiable disease<sup>(42)</sup>. Till now five states like Tamil Nadu, Odisha, Gujarat, Rajasthan and Telangana, have declared black fungus to be an epidemic.<sup>(43, 44)</sup> Mucormycosis or black fungus infection is not unknown in India, but now, with the second wave of the covid-19 pandemic continuing to rage, it has come into popular consciousness as now the country is seeing a surge in its cases.

## **Transmission**

Transmission exits through the inhalation, inoculation, or ingestion of spores from the environment. In healthcare settings, it can be difficult to consider whether mucormycosis is nosocomial infection or whether the infections were obtained from somewhere else.

Some examples for the sources in healthcare-associated mucormycosis outbreaks like adhesive bandages, wooden tongue depressors, hospital linens, negative pressure rooms, water leaks, poor air filtration, non-sterile medical devices, and building construction. Community outbreaks have been associated with damages sustained during natural disasters.<sup>(8,22,23,24,25,26,27,38)</sup>

As per the Ministry of Health in India, the infection is getting detected among the people recovering or recovered from COVID-19. People prone to the infection are undergoing oxygen therapy in ICU (where a humidifier is used) which makes people more susceptible to infection due to exposure to moisture.

The use of normal tap water in the flow meters of the oxygen cylinders is also responsible for fungal infection. There is a lot of covid-19 cases that can also be triggered by contamination of mould-tainted oxygen piper and humidifiers.

According to the observations of doctors, the usage of industrial oxygen could be one reason for the outbreak of black fungus, as there is a difference in the production of industrial and medical oxygen.

Due to the shortage of oxygen in the second wave of COVID-19, doctors had to resort to industrial oxygen. It has caused one reason behind the outbreak of this disease. While oxygen used for medical purpose is produced,

it went through many filters, and so many measures are taken to keep all the fungus away. However, no such steps are involved, in the production of Industrial oxygen. Other risks behind the industrial oxygen is more chances to leaks when transported in vans and truck.

## **Symptoms of Mucormycosis**

The symptoms of mucormycosis or black fungus depend on which part of the body the fungus is growing. A classic clinical sign of mucormycosis is the rapid onset of tissue necrosis with or without fever. Necrosis is the result of an invasion of blood vessels and subsequent thrombosis.<sup>(2,3)</sup>

Symptoms of rhinocerebral (sinus and brain) mucormycosis include Fever, One-sided facial swelling, Headache, Nasal or sinus congestion, Black lesions on nasal bridge or upper inside of the mouth that quickly become more severe, face numb, watery eyes.

Symptoms of pulmonary (lung) mucormycosis include: Fever, Cough, Chest pain, Shortness of breath

Cutaneous (skin) mucormycosis can look like blisters or ulcers, and the infected area may turn black. Other symptoms include pain, warmth, excessive redness, or swelling around a wound.

Symptoms of gastrointestinal mucormycosis include Abdominal pain, Nausea and vomiting, Gastrointestinal bleeding.

Disseminated mucormycosis typically occurs in people who are already sick from other medical conditions, so it can be difficult to know which symptoms are related to mucormycosis. Patients with disseminated infection in the brain can develop mental status changes or coma.

## **People, who get the more risk of mucormycosis**

Mucormycosis is rare, but it's more common among people who have health problems or take medicines that lower the body's ability to fight germs and sickness. Certain groups of people are more likely to get mucormycosis, including people with Diabetes, especially with diabetic ketoacidosis, Cancer, Organ transplant, Hematopoietic Stem cell transplant, Persistent Neutropenia (low number of white blood cells), Long-term corticosteroid usage, Too much iron in the body (iron overload or hemochromatosis), Skin injury due to surgery, burns or wounds, malnourishment and Prematurity and low birth weight (for neonatal gastrointestinal mucormycosis).<sup>(2,8,9)</sup>

## **Diagnosis and testing for Mucormycosis**

Medical history, symptoms, physical examinations, and laboratory tests are used to diagnose mucormycosis. Sample of fluid or sputum from the respiratory system, tissue biopsy for histopathological evidence (definitive diagnosis method) and also for fungal culture and imaging tests such as a CT scan of your lungs, sinuses, or other parts of your body, depending on the location of the suspected infection.<sup>(9,28)</sup>

No routine serologic tests for mucormycosis are currently available, and blood tests such as beta-D-glucan or Aspergillus galactomannan do not detect mucormycetes. DNA-based techniques for detection are promising but are not yet fully standardized or commercially available.<sup>(29)</sup>

## **Treatment**

Early recognition, diagnosis, and prompt administration of appropriate antifungal treatment are important for improving outcomes for patients with mucormycosis.<sup>(30)</sup>

While it is treated with antifungals, mucormycosis may eventually require surgery. If patients are highly prone for developing mucormycosis For example, if they had an organ transplant or a stem cell transplant, physicians may prescribe medication to prevent mucormycosis and other mold infections.<sup>(13,14)</sup>

Amphotericin B, posaconazole, and isavuconazole are more sensitive against most mucormycetes. Lipid formulations of amphotericin B are often used as first-line treatment.<sup>(30)</sup> To maintain adequate systemic hydration, the treatment includes an infusion of normal saline (IV) before infusion of amphotericin B and antifungal therapy, for at least 4-6 weeks. Meanwhile, it needs to control hyperglycemia, and monitor blood glucose level after discharge following Covid-19 treatment, and also in diabetics.

Aspergillus is sensitive to some anti fungal medicine such as voriconazole are not active against mucormycetes. Some evidence suggest that pre-exposure to voriconazole may be associated with increased incidence of mucormycosis in some patients.<sup>(31,32)</sup>

In addition, surgical resection of infected tissue is often necessary, particularly for rhinocerebral, cutaneous, and gastrointestinal infections.<sup>(4,30)</sup> Control of the underlying immuno-compromising condition should be attempted when possible. The efficacy of other treatments such as hyperbaric oxygen therapy is uncertain but have been useful in certain situations.<sup>(33)</sup>

## **Sequelae**

The overall prognosis depends on several factors, including the rapidity of diagnosis and treatment, the site of infection, and the patient's underlying conditions and the degree of immunosuppression.<sup>(8)</sup>

Although early identification and treatment can lead to better outcomes mucormycosis is frequently a life-threatening infection. According to the findings of mucormycosis cases have an overall all-cause mortality rate of around 50 % - 54%. The mortality rate varied depending on underlying patient condition, type of fungus, and body site affected (for example, the mortality rate was 46% among people with sinus infections, 76% for pulmonary infections, and 96% for disseminated mucormycosis). it may be being triggered by the use of steroids, a life-saving treatment for severe and critically ill Covid-19 patients.<sup>(33)</sup>

Steroids reduce inflammation in the lungs for Covid-19 and appear to help stop some of the damage that can happen when the body's immune system goes into overdrive to fight off coronavirus. But they also reduce immunity and push up blood sugar levels in both diabetic and non-diabetic Covid-19 patients. It's lead to drop in immunity could be triggering these cases of mucormycosis.

### **Protective ways from the risk of mucormycosis**

The fungi that cause mucormycosis are common in the environment so it's very difficult to avoid breathing in fungal spores. There is no vaccine to prevent mucormycosis. To protect yourself from this fungus in the environment will be the only solution for people who have weakened immune systems, there may be some ways to lower the chances of developing mucormycosis. It's important to note that although these actions are recommended they haven't been proven to prevent mucormycosis.<sup>(10,11)</sup>

Try to avoid dusty areas like construction or excavation sites. If you can't avoid these areas, wear a properly fitted mask or wear an N95 respirator while working.

Try to avoid direct contact with water-damaged buildings and flood water after hurricanes and natural disasters.

Avoid activities which are closely contact with soil or dust, such as yard work or gardening. Try to wear shoes, long pants, and a long-sleeved shirt when doing outdoor activities such as gardening, yard work, or visiting wooded areas. Wear gloves when handling materials such as soil, moss, or manure.

To reduce the chances of developing a skin infection, clean skin injuries well with soap and water, especially if they have been exposed to soil or dust.<sup>(16)</sup>

There is "no big outbreak". Since it is difficult to say that how the number of cases of mucormycosis are rising from all over the country. The strain of the corona virus appears to be more virulent day by day. And strangely, the fungal infection is affecting a lot of young peoples. The only possibility of the fungal infection was to make sure that Covid-19 patients both in treatment and after recovery - were being administered the right dose of anti-fungal drugs and duration of steroids. Finally, the occasion of diagnosis, course of action of predisposing conditions, and aggressive surgical debridement remain key steps of therapy for this deadly disease. The fungi that cause mucormycosis are common in the environment so try to protect yourself from this fungus in the environment that will be the only solution and also wear a properly fitted mask or wear an N95 respirator while working and avoid steroid drugs unnecessarily without doctors prescription.

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