

BLACK FUNGUS: IS ANOTHER PANDEMIC PEEPING AND THREATENING THE HUMAN RACE?

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ABSTRACT

Mucormycosis is an angio-invasive fungal infection, which is associated with high morbidity and mortality. It is a life-threatening infection that occurs in patients who are immunocompromised because of suffering from low oxygen, diabetic ketoacidosis, cancer, neutropenia, organ transplantation, iron overload in patients taking deferoxamine, kidney failure, heart disease, liver disease. The overuse of steroids and other immune-suppressing medicines, and prolonged hospitalization with mechanical ventilation during the Covid-19 pandemic are also considered as instigating factor for black fungus. The current treatment procedure against severe coronavirus disease (COVID-19) is the systemic use of glucocorticoids which weakens the immune system of patients. Opportunistic fungal infections are of major concern for them. Mucormycosis is a rare infection because the immune system of a healthy person is able to prevent this infection but COVID-19 associated with mucormycosis is noticeably increased specially in patients who have been recovered from COVID-19 and are treated with glucocorticoids. This secondary fungal infection is a key factor fueling India's COVID-19 second wave. The new mutant of COVID-19 with this fungal infection, promoted the death rate which has become excessively higher than previous as India announced it as epidemic. Due to the same geographical condition and neighboring country, Bangladesh is also now at a higher risk.

KEYWORDS: Black fungus, Mucormycosis, Pandemic, COVID-19, Coronavirus, Weak immune system, Risk.

INTRODUCTION

As of 2nd June, 2021, more than 172 million people in 222 countries have been infected with SARS-CoV-2 and among them 3.5 million have suffered from fatal consequences.^[1] Being concerned with the rapid spread and severe consequences of the disease, World Health Organization (WHO) has announced COVID-19 as a pandemic on March 11, 2020.^[2]

As the COVID-19 cases continue to grow, several cases of mucormycosis or "Black Fungus" infection in COVID-19 patients after recovery or during active infection have been reported.^[3,4] Mucormycosis refers to a plethora of potentially life-threatening angioinvasive fungal infections caused by the fungi which belongs to the order "Mucorales".^[5] It is a rare form of infection and

most commonly affects individuals with compromised immune system, poorly controlled diabetes mellitus, cancer patients taking chemotherapy, neonatal prematurity, malnourishment, severe and prolonged neutropenia, iron overload treated with deferoxamine therapy though increased serum iron is not directly related to development of mucormycosis, iron chelating agent deferoxamine is responsible for growth of mucormycosis, prolonged use of corticosteroid, prolonged hospitalization with artificial ventilation. All these factors behind the black fungus lead to serious morbidity and mortality.^[6-9] The anatomic regions most commonly affected by mucormycosis are sinuses, lungs and skin; and this has also been observed in the recently reported COVID-19 associated mucormycosis as most of the cases report rhino-orbito-cerebral mucormycosis.^[10]

The unfortunate thing is that the overall morbidity rate for mucormycosis is above 50% and it is going to reach 100% among patients who have severe immunomodulatory disease and with persistent neutropenia.^[11,12]

COVID-19

During 2002, in a province of China named Guangdong, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) was first introduced that resulted in 8000 reported cases and cost around 800 lives.^[13] Two novel human coronavirus were found shortly after the findings of SARS which were responsible for upper respiratory tract infections. Morbidity rate was slightly high among the elderly and immunocompromised patients.^[14] In 2012, there emerged another distinct coronavirus named Middle East Respiratory syndrome (MERS-CoV) and is circulating through the human population and animals in the Middle East. This pathogen also caused respiratory disease.^[15] In December 2019, another novel coronavirus was detected in Wuhan province of China which was responsible for acute atypical respiratory disease and soon it spread from Wuhan to other areas. That novel coronavirus was named "Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2, 2019-nCoV)" because of its similarity (~80%) with SARS-CoV.^[16] The outbreak of SARS-CoV-2 was originated through a zoonotic transmission associated with the seafood market in Wuhan, China and then the transmission between human had a great impact in the outbreak. The disease caused by this virus was designated as Coronavirus disease 19 (COVID-19). World Health Organization (WHO) declared the disease as a pandemic.^[17] The sign and symptoms of COVID-19 are homologous with SARS and MERS.^[18] Coronaviruses infect the upper GIT as well as respiratory tract of both the humans and the birds.^[19] With COVID-19, patients generally face fever, cough, dyspnea, and myalgia or fatigue. Other signs like sputum production, headache, hemoptysis and diarrhea can be present. Shortness of breath, acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), kidney failure and pneumonia were also reported due to COVID-19.^[20] The older people are at greater risk with the infection of COVID-19. Patients with health problems like heart disease, lung disease, diabetes and cancer are also in a danger zone.^[21] The supportive treatment is considered to be the most efficient treatment method till these days like treatment against symptoms such as fever, cough, asthma, dyspnea as well as fatigue etc., and administration of oxygen is the cornerstone of this supportive treatment care system and it is required approximately in 15% of cases.^[22-24] Several drugs like lopinavir-ritonavir, remdesivir, hydroxychloroquine and azithromycin are trying to be used to treat this disease. All these have been examined in clinical trials and tempted to utilize for repurposing but none of them can claim to have a definite therapeutic effect against the virus.^[25-27] However, steroids have shown some efficacy against COVID-19 and reduce mortality in hypoxic

patient with COVID-19. But because of its immunomodulatory activity, risk of secondary infection, such as bacterial and fungal infection, has been increased and black fungus (mucormycosis) is spotted into the patient recovered from COVID-19.^[28]

Black Fungus

Mucormycosis is a fungal infection which is very invasive and caused by mold fungi of the genus *Mucor*, *Rhizopus*, *Rhizomucor* and *Absidia*. They belong to the *Mucorales* order of the *Zygomycetes* class.^[29] *Rhizopus oryzae* is the most common species which caused mucormycosis and is accountable to ~70% of all cases of mucormycosis.^[30-32] Covid-19 patients, those who are diabetic, take steroids, have cancer or transplanted organs, and other comorbidities are susceptible to black fungal infection as it occurs as a secondary infection because healthy immune system can easily prevent it.^[33] These fungi are found in the environment in soil or decaying organic matter as well as heavy mould spore counts in hospital air because of hot and humid conditions in tropical climate.^[34] When someone with weakened immunity breathes in the fungal spores existing in such environment, the pathogens infiltrate into their respiratory system and affect their sinuses or lungs, as is common in all such fungal cases.

A. Morphology

The *Mucor*'s mycelium is highly branched and it is formed by a cluster of hyphae (**Figure 1**). Hyphae of *Mucor* can be filamentous, aseptate or coenocytic. In *Mucor*, there are three types of hyphae - a) **Subterranean hyphae** are the hyphae which are highly branched and possessing more penetration power. It is present horizontally to the substratum; b) **Prostrate hyphae** are the hyphae which are also present horizontally between or under the substratum. Both of these hyphae play a role of assistance in absorption of water and nutrition; c) **Aerial hyphae** are that kind of hyphae which grow vertically out from the prostrate hyphae.

Sporangiophore is long and narrow in shape. It gets swollen up to get a structure which is dome-like and called "Columella" which can show variety not only in shape but also in size. Sporangium is round shaped carrier carrying numerous spores inside it. It can be globose to spherical. It contains spores which are the reproductive structures. They are simple, flattened and show variety in shape and size. *Mucors* also possess multinucleate nuclei.^[35]

Macroscopic Morphology

Mucor is a good example of fungus which has the ability to grow rapidly. They have the ability to fill a culture plate within a few days with a woolly growth which looks like cotton candy. Fresher growth looks white but with time, growth turns a greyish-brown as a result of aging. The reverse remains a pale white.

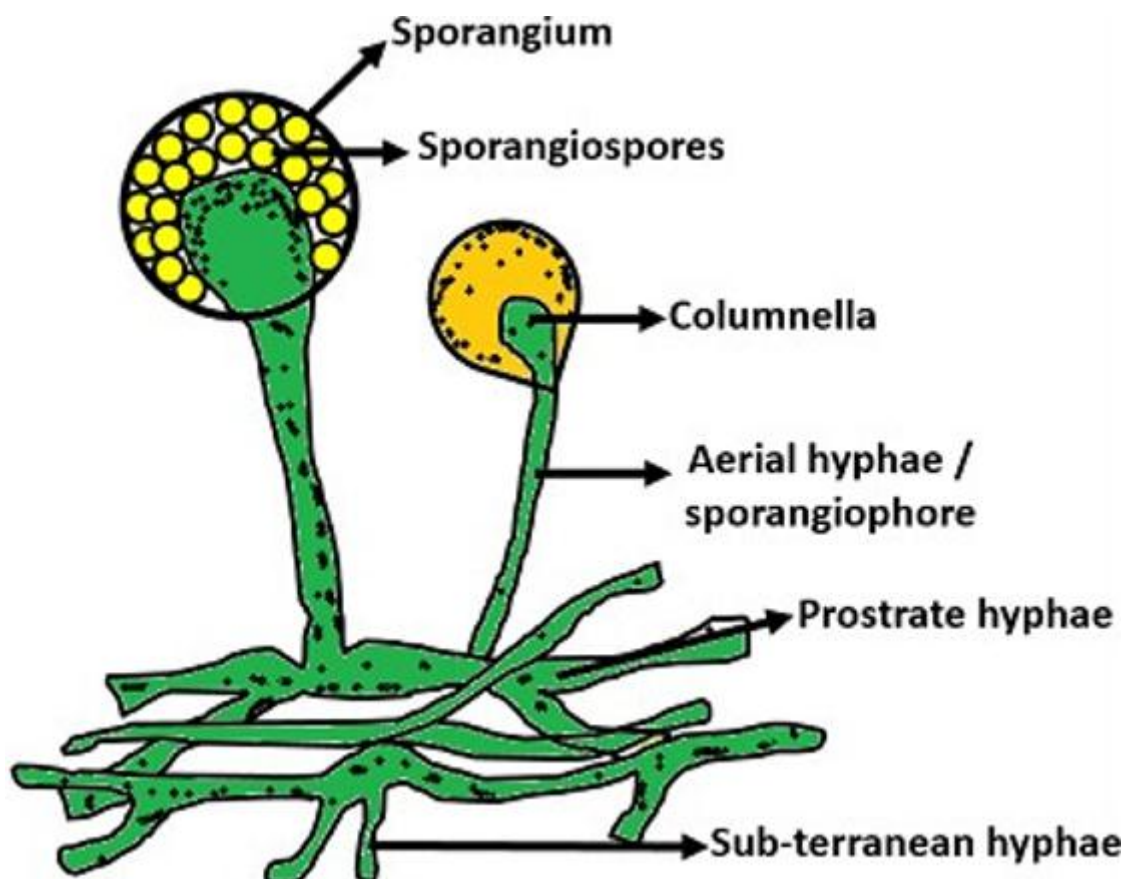


Figure 1: Structure of Mucor.^[36]

Microscopic Morphology

Mucor fungus is consisted of a broad hypha which is scarcely or non-septate. Sporangiophores are long in size, may be branched and terminate in a round spore-filled sporangia (50µm-300µm diameter). The sporangia possess a thin wall the function of which is to release round or somewhat ellipsoidal sporangiospores (4µm-8µm diameter) when sporangia become matured. With the spores scattered, the columella which carry the sporangia has become visible, sometimes leaving a collerette at the base of the sporangium.^[37]

B. Pathogenesis

The skin is the main barrier to fungi causing mucormycosis because the agents of mucormycosis generally have not the ability to penetrate the intact skin. But burned or disrupted skin enables the organism to penetrate into deeper tissues and cause infection. However, the major route of entry and infection is inhalation of conidia by immunocompromised patients which leads to pulmonary mucormycosis. Once the spore germinates, neutrophil, macrophages and monocyte try to destroy the fungal hyphae.^[38] Mucormycosis develops in immunocompromised patients who lack these defense mechanisms especially due to hyperglycemia, acidosis and corticosteroid treatment.^[39] To cause disease, the agents of mucormycosis have to acquire iron from the host for their cell growth and development.^[40] In mammals, the iron is bound to the host carrier protein named transferrin, ferritin, and lactoferrin and this

sequestration prevents the toxic effect of free iron.^[41,42] But in immunocompromised hosts, iron is released from the carrier protein and is available for fungi for their growth within the host.^[43] Acidotic conditions decrease the capacity of iron binding of carrier protein probably by proton mediated displacement of ferric ion from transferrin.^[44] The agents of mucormycosis have the high affinity to iron permeases or low-molecular-weight iron chelators like deferoxamine, as a result they obtain iron from the host.^[45] This process along with the reduced number of neutrophils and phagocytes allows fungus to increase in number.^[46] Glucose regulated protein 78 (GRP78) serves as a receptor which ameliorates the ability of Mucorales to penetrate the endothelial cells.^[47]

Sign and symptoms

Sign and symptoms of mucormycosis depend on the location of the infection in the body.^[48] When the fungal infection begins in the nose or sinus and reached the brain, one sided eye pain or headache as well as pain in the face, numbness, fever, loss of smell, a blocked or runny nose can be noticed and the patient may appear to have sinusitis.^[49] The face got swollen up and with rapidly progression of "black lesions" around the nose or upper inside of mouth are happened to be observed and one eye may also look swollen and vision can be blurred.^[50-52] When lungs are infected, fever, cough, chest pain, difficulty in breathing and coughing up blood can occur. If GIT is infected nausea, vomiting and tummy ache are about to be noticed.^[53,54] Infection into

the blood vessel can lead to thrombosis and surrounding tissue can be died because of loss of blood supply.^[55]

Mental status change or coma can happen to the patient with disseminated infection.^[56-57]



Figure 2: Photograph of a patient suffering from mucormycosis.^[58]

Prevention

Preventive actions include wearing a mask in dusty areas, washing hands with soap or detergents several times, avoiding contact with water-damaged buildings and protecting skin, feet, where there is exposure for soil like gardening.^[59] Hyperglycemia needs to be controlled and in COVID-19 patients who are on steroid therapy should be on glucose monitoring all the time.^[60] Nosocomial infections should be avoided.^[61]

Treatment and Management

Treatment includes a combination of antifungal drugs having different mechanism of action (**Figure 3** and **Figure 4**) and surgically removing the infected tissues as well as treating other medical problems like diabetic ketoacidosis.^[62] When mucormycosis is diagnosed, Amphotericin B can be provided according to the body weight of the patient.^[63] Isavuconazole and Posaconazole can be used as a replacement of Amphotericin B.^[64, 65] Surgery is a drastic approach for treatment because in some cases infected brain needs to be removed and sometimes more than one operation is required.^[66, 67]

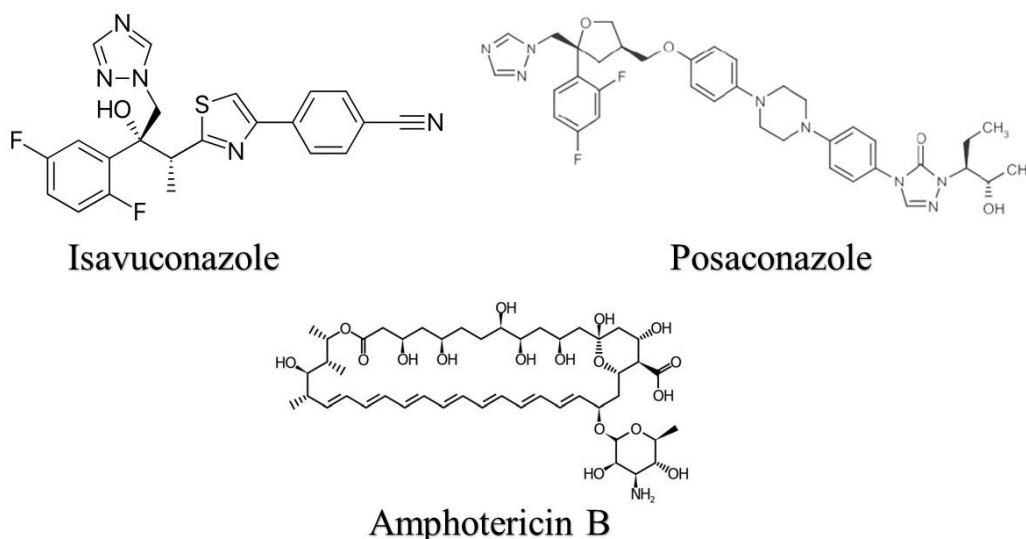


Figure 3: Chemical structure of drugs used for the treatment of black fungal infection.^[68-70]

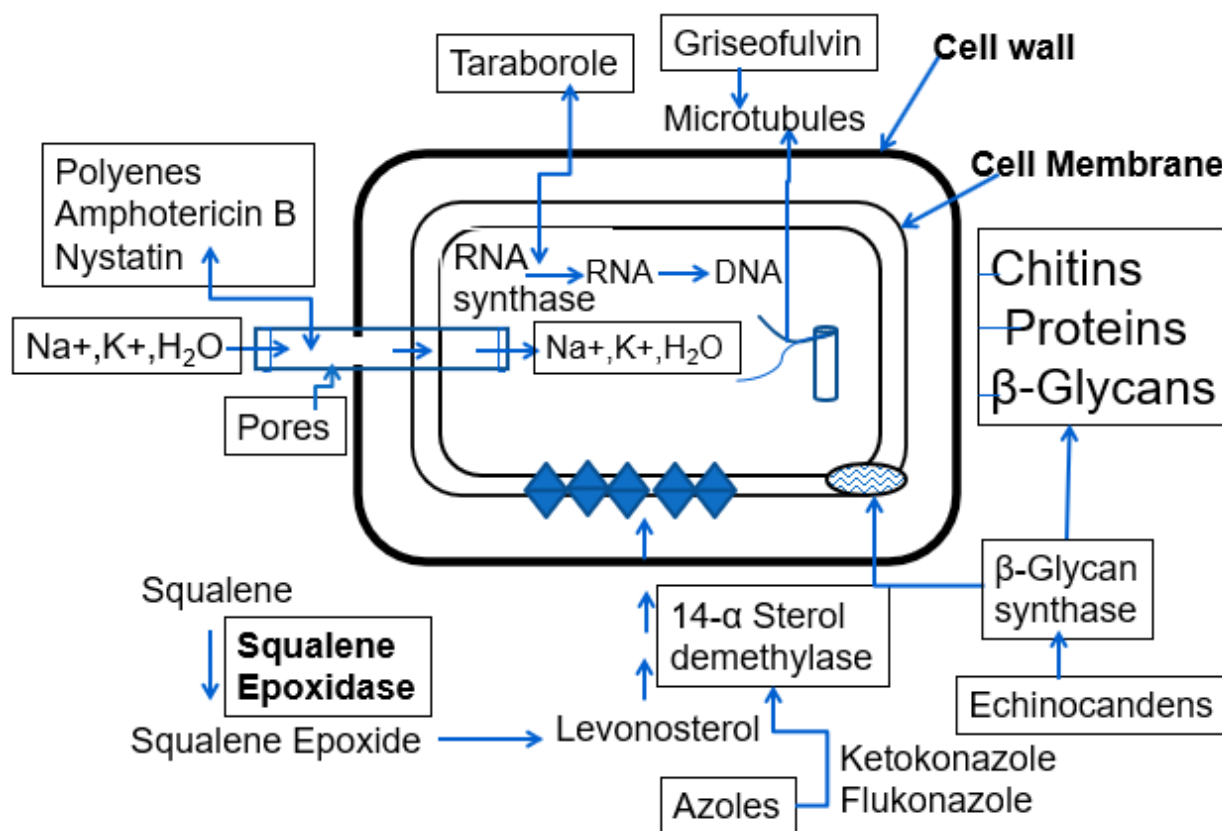


Figure 4: Schematic diagram of mechanism of action of different antifungal drugs used for the treatment of black fungal infection.

Epidemiology

Most of the data about the epidemiology of mucormycosis have been collected from case reports and case series.^[71] The incidence of mucormycosis is rapidly increasing day by day. The exact prevalence is not known due to lack of population-based studies and they vary in periods, populations and definition or diagnostic procedures. In a study in the area of San Francisco Bay, in the year of 1992 to 1993, 1.7 cases were found per 1 million individuals. The incidence of mucormycosis-related hospitalizations was estimated as 0.12 per 10,000 discharges during January 2005-June 2015 in the study published by Kontoyiannis *et al.*, in 2016. In the population-based study in France, the record showed the prevalence of mucormycosis as 0.7 cases per million in 1997 and then jumped to 1.2 per million in 2006. A study in Belgium showed the rise from 0.019 cases per 10,000 patients during 2000 to 0.148 cases per 1000 population.^[72]

On May 20, 2021, India declared “Black Fungus” (Mucormycosis), a complication commonly associated with Covid-19, as an epidemic.^[73] Black fungus or mucormycosis, a disease that has an alarming and fearful mortality rate of about 50% and is rapidly being noticed in recovering Covid-19 patients in the country, has grown over 150 percent over the last three weeks. There are 31,216 reported cases and 2109 deaths because of black fungus in the last three weeks. Out of this, 86%

cases had a history of COVID-19 and 62.3% cases had a history of diabetes.^[69]

In May 2021, Maharashtra topped the list of worst affected states with 7057 cases and 609 deaths. Gujarat is in the second worst state with 5418 cases and 323 deaths. 2976 cases have been reported in Rajasthan. 276 cases of black fungus have been reported in Chhattisgarh so far and also 17 deaths. Uttar Pradesh has reported 1,744 cases and 142 deaths and 1200 cases have been reported in national capital and 125 deaths.^[74, 75]

Risk about Bangladesh

Bangladesh is at a higher risk in terms of mucormycosis infection. As it has been seen as an epidemic in our neighboring country, we are also in a great threat. The geographic, edaphic and environmental conditions of Bangladesh are almost similar with that of India. It is, therefore, assumed that Indian black fungus could persist in our environment and may pose a great threat if it enters our country. There is a possibility that the Indian (delta) variant of corona and black fungus may easily enter into Bangladesh as this country shares a more than 4,000-kilometer (2,485-mile) land border with India, which is the longest common border of the country. Nearly 10,000 people in India have already been infected with black fungus with over 200 deaths while the country’s health authorities have warned that the rare fungal disease with a 50% mortality rate is linked to the global coronavirus pandemic. Furthermore, it affects

mostly the patients who have recovered from COVID-19 and suffering from diabetes mellitus as well as using steroids. In our country, people are not aware of this problem and are also unaware about using drugs properly. As the pathogen travels through air, our people must use masks, maintain social distance, wash hands with soap or use hand sanitizers, should wear shoes which they are not obeying. Our health sector should build the capability of treating black fungus immediately as it has already entered Bangladesh. Otherwise, we are going to face the same scenario as India is facing. Till date, a total of three, including the one who expired, have so far been identified with black fungus at BIRDEM Hospital, Dhaka, and few patients in Dhaka Medical College Hospital, Dhaka, Bangladesh in patients who have recovered from Covid-19. Except the deceased person, one of the patients, aged 45, was detected with black fungus on May 8 and the other, aged 60, was detected on May 23.^[76]

CONCLUSION

Mucormycosis is a rare but emerging fungal infection which has a high mortality rate. The second wave of COVID-19 makes this world more dangerous for us to survive. A coronavirus patient sometimes uses steroids out of panic and this compromises the patient's immune system and puts the patient at risk of a black fungus infection. So, patients recovered from COVID-19, using steroid and suffering from diabetes mellitus are the most susceptible to this fungal infection. In developing countries, uncontrolled diabetes, trauma and ignorance of obeying health guidelines are the most common reasons behind the spreading of this infection. Social awareness, clinical suspicion and early proper diagnosis and treatment are key points to prevent mortality and morbidity of mucormycosis.

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