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Black Fungus Mutilating COVID-19 Pandemic in India: Facts and Immunological Perspectives

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ABSTRACT

While the world is still struggling with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, an aggressive and rare fungal infection which is commonly ascribed as the black fungus has emerged as a new medical challenge in India. India had already experienced the devastating consequences of the COVID-19 and, being a rare "opportunistic" fungal infection, black fungus infection has severely complicated the post-COVID-19 recoveries. Together with the uncertain treatment modalities at the beginning of the pandemic, indiscriminate use of a plethora of medications has driven the surging cases of black fungus-associated complications. Moreover, low oxygen, high iron levels, and prolonged hospitalization with mechanical ventilators created a superlative condition for contracting black fungus infection. The disease mainly spreads through the respiratory tract and erodes facial structures. Since mucormycosis specifically attacks immunosuppressed patients, the disease started spreading rapidly, with an average mortality rate of 54 %. Common symptoms include blackening over the nose, blurred or double vision, breathing difficulties, chest pain and hemoptysis. Although not contagious, the outcome of the disease is often very frightful.

If the infection disseminates systematically, the risk of affecting the vital organs such as the spleen and heart is substantially high. We have tried to provide an epidemiological overview of black fungus infection in India. We focused on drawing a comprehensive fact check of the current situation through an immunological perspective to better understand the infection as a major co-infection in patients affected by COVID-19 and its impact on India's fight against the COVID-19 pandemic.

Keywords: Black fungus, COVID-19, Mucormycosis, Epidemiology, India

INTRODUCTION

As a rare "opportunistic" fungal disease, the black fungus infection has severely impacted the post-COVID-19 recoveries and imposed an additional burden on our medical and healthcare management system. Together with the uncertain treatment modalities at the beginning of the pandemic, the indiscriminate use of a plethora of medications, including steroids and antibiotics, have helped drive the surging cases of black fungus-associated complications. However, the persistent low oxygen level in blood with high iron levels, along with prolonged hospitalization of COVID-19 patients under the aid of mechanical ventilators, are the key contributors to contracting the black fungus infection. A black fungus is a group of molds commonly known as mucormycetes, while the resultant infection is termed mucormycosis. Mucormycosis is reported to be more prevalent among COVID-19 patients with precedent medical conditions like hyperglycemia with prescribed medications, including steroids. Mucormycosis usually spreads through the respiratory tract, predominantly erodes the facial structures, causes discoloration or blackening over the nose, and blurred or double vision. In addition to these, the infected patient often exhibits chest pain, breathing difficulties and hemoptysis (coughing up blood). Although not contagious, the outcome of the disease is often frightful as it causes gastrointestinal bleeding with severe respiratory distress. Moreover, if

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the infection disseminates systematically, the risk of affecting vital organs such as the spleen and heart is substantially high.

Considering the high population density and the high-speed dissemination rate of mucormycosis, we have tried to provide an epidemiological overview of black fungus infection in India in the first part of the review. In the second part, we have focused on drawing a comprehensive fact check of the current situation from the immunological perspectives.

EPIDEMIOLOGICAL BACKGROUND of COVID-19

Originating from Wuhan, in Hubei province, China, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus has led to the global COVID-19 pandemic. However, SARS-CoV-2 is not the first to cause a global emergency; there are six other variants of coronavirus that are known to have originated from animals. Among them, four coronaviruses are endemic in humans which include almost 10-15% of common colds. The other coronavirus variants, NL63 and 229E, probably originated from bats, whereas the sources for OC43 and HKU1 virus seem to be rodents (1). The Severe Acute Respiratory Syndrome (SARS) caused by a human coronavirus (SARS-CoV) was the first non-endemic coronavirus to be recognized, which was for the first time reported in China (November 2002) followed by Vietnam (2003) and attracted significant attention worldwide. However, the outbreak was in the same year, with the last cases reported in April 2004 from China. An estimated total of 8098 cases of SARS-CoV positive were reported worldwide, of which 774 casualties were recorded (2). The subsequent report suggested that the SARS-CoV originated from horseshoe bats and that it may be transmitted to humans through some specific kind of cats.

The next outbreak related to the SARS-CoV infection was Middle Eastern Respiratory Syndrome (MERS), first reported in Saudi Arabia in 2012 (3) which spread across 27 countries. Similar to SERS-CoV, a flu-like illness with mild to severe pneumonia and acute respiratory distress was found in MERS-CoV with symptoms varying from mild to severe pneumonia and acute respiratory distress syndrome. SARS-CoV-2 resembles the wild bat virus more than SARS-CoV or MERS-CoV. This strongly suggests that it is a novel coronavirus in humans (4). SARS-CoV-2 is one of37 members of coronaviruses in their Coronaviridae family, belonging to the order Nidovirales, and it is presently a major cause of pandemic affecting lots of people globally (5). Cell entry of the virus is mediated by binding the target receptor with the help of spike proteins. This requires six amino acids among which only one of these is with SARS-CoV (6). The spike protein regulates viral infectivity and host range which is different from SARS-CoV.

These little viruses are extremely powerful and possess unique mechanisms to enter into the host cells. These viruses enter the host cells through the angiotensin-converting enzyme 2 (ACE2) receptor (7), which is expressed in various human organs. These receptors interact with the spike protein of SARS-CoV-2. Studies suggest that SARS-CoV spike protein and R. sinicus ACE2 might have co-evolved over time and experienced a selection pressure from each other, triggering the evolutionary arms race dynamics (8).

The first reported case of COVID-19 was in Wuhan, China, in December 2019 and the first case was reported in Kerala, India. During the first pandemic wave in April 2020, almost 5 million people in India were significantly affected, while nearly 1.57 lakh deaths were reported globally. However, a significant improvement in the early post-first wave time led pseudo confidence to push us to a riskier situation, causing the second wave's advent. The impact of the second wave was substantially high in both the number of cases and mortality, reporting many deaths (9).

COMMON MICROBIAL CO-INFECTIONS in COVID-19

Common co-infection of the SARS-CoV-2 significantly affects the diagnosis, treatment, and recovery of COVID-19 and often worsens the disease symptoms and mortality rate. Moreover, co-infection can also alter the gut homeostasis of the patients by promoting a relative abundance of opportunistic pathogens and subsequently destabilizing the host immune system. Specifically, a marked reduction in the lymphocytes count, particularly helper T-cells and cytotoxic T-cells due to COVID-19 infection, seems to make the individual highly exposed to secondary bacterial and fungal co-infections (10,11). Although not common, co-infection with other respiratory viruses such as respiratory syncytial virus (RSV) and influenza virus infection were also reported in the recent past (12). In a contemporary study, it was found that around 7% of hospitalized COVID-19 patients and around 14% of the total ICU patients in India, were affected by bacterial co-infection (12). The two most common types of COVID-19 associated bacterial co-infections are caused by *Acinetobacter baumannii* and two *Staphylococcus aureus* strains, presumably due to their acquired hypervirulence and antibiotic resistance. The source of co-infection includes bacterial infections including *Mycoplasma pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae* and *Klebsiella pneumoniae* (13,14).

BLACK FUNGUS and COVID-19

Apart from bacterial co-infections, India has also witnessed a rather daunting and terrifying epidemic outbreak of mucormycosis and other fungal co-infections, adding to India's growing COVID-19 woes during the second wave. While black fungus or mucormycosis is non-contagious in nature, a significant number of patients who at some point either suffered from COVID-19 or recovered from COVID-19 are found to be the target for black fungus infection.

Hierarchical Classification of Black Fungus

Black fungus is a disease caused by moulds known as mucormycetes (15). These moulds are abundant in natural environments with a greater percentage in soil, specifically in soil rich in decaying organic matter, which includes compost piles, leaves, and animal dung. They may cause serious fungal infections in human beings, although chances of being attacked were rare in earlier times. To know more about this disease, we have to know about the types of mucormycosis.

Position in classification:
Black fungus has the following taxonomic position: -

Order: Mucorales

Family: Mucoraceae

Genus: Mucor Fresen

Mucormycosis was previouslyknown as "zygomycosis" and was first discovered by Friedrich Küchenmeister in 1855 (16). However, Max Carl Anton Fürbringer was the first to describe the disease in the lungs (17). In 1884, Lichtheim explained the development of mucormycosis disease in rabbits and explained two species -*Mucor rhizopodiformis* and *Mucor corymbifera*, which later came to be known as *Rhizopus* and *Lichtheimia*. In 1943, the association of this disease with uncontrolled diabetes was reported in three cases with symptoms such as severe sinus, eye and brain involvement (16).

When cases of "zygomycosis" started to be reportedin the mid-1950sin the United States, it was thought to be a novel disease resulting from the extensive use of antibiotics, adrenocorticotropic hormone, corticotropin (ACTH) and steroids (18). Until the late 20th century, the only treatment that was available for treating "zygomycosis" (later named as mucormycosis) was potassium iodide (KI). Between 1970 and 2000, Amphotericin B was found to be more effective for the treatment of mucormycosis.

Common Symptoms of Mucormycosis
Until recently, the black fungus was a rare fungal ailment, with just a few cases documented around the world. However, it has now become a fresh catastrophe that requires prompt attention. Because black fungus infection has such a high mortality rate, itis critical to be aware of and warrants early diagnosis. One of the key issues associated with black fungus Infections is that of serious cosmetic problems as it affects different sections of the face. This is also known as "rhino-orbital-cerebral-mucormycosis" which is characterized by swelling and inflammation along the nasal line. In the following a brief overview of common signs are outlined:

a. **Formation of Black crust around the nose:** Swelling and black crust formation around the nasal tube are two of the most common symptoms of black fungus. If left untreated, the infection progresses to a more serious stage, resulting in nose mutilation and perhaps requiring surgery to repair the jawbone or other facial structures.

b. **Swelling and inflammation on cheeks and eyes:** Chronic swelling or inflammation around the eyes or cheeks, could also be signs of black fungus. As a result of black fungus infection patients often exhibit numbness or inflammation on one side of the face with necrosis-like symptoms, which could also be the outcome of black fungus infection.

c. **Acute headache:** Acute headaches, inflammation around the forehead, and redness are reported to be caused by black fungus when spreading to the brain. This is the most serious stage, where any lack of knowledge or inappropriate treatment modality may result in memory loss, cognitive function loss, or substantial brain injury.

d. **Partial or complete loss of vision:** If the black fungus targets the retinal nerves, it can cause partial or complete loss of vision. Any redness, irritation, or pain in one or both eyes are preliminary signs of such an outcome.

In addition, other consequences of black fungus infection include gastrointestinal bleeding, hemorrhage, shortness of breath, and even blindness. If the infection spreads inside the body through the blood, then it is known as disseminated black fungus (19). In such conditions, the severity of the disease reaches its peak, and the fungus starts to attack vital organs such as the heart and spleen. It can also lead to blood clotting in the lungs and brain, and in the worst case, it may affect the nervous system and cause some unpleasant mental changes leading to coma (20) or even death.

WHAT CAUSES A BLACK FUNGUS OUTBREAK IN INDIA?

Black fungus is a rising concern for South Asian countries. However, India has reported the highest number of cases of mucormycosis over the last year. To date, there have been over 40,000 cases, of which more than 3,129 people died, were reported to be caused by black fungus across India (21). The major concern is the rapid dissemination rate of mucormycosis among COVID-19 infected patients, while a little delay, even a few hours, could cost the patient's life. When searching for predisposing factors for the incidence of mucormycosis in COVID-19 patients, it was observed that (22) prolonged hospitalization with mechanical ventilators can create a perfect environment for mucormycosis. Together with early diagnosis, retaining diabetes and other associated health issues in check, treating patients with specific intravenous antifungal medications can control the dissemination of the infection. Moreover, along with wearing masks and using sanitizers, maintenance of hygiene, if added to the already existing treatment modalities, the better management of COVID-19 associated complications can be avoided. In the following, a comprehensive discussion is presented on how COVID-19 is associated with an increase in the risk of black fungus.

HAS COVID-19 INCREASED THE RISK OF BLACK FUNGUS?

Despite its best efforts, India is still at risk in terms of vaccinating such a huge population and has inadequate health care systems for saving thousands of people from the impending threat of a future outbreak of COVID-19 and associated illness. The black fungus outbreak as a post COVID-19complication has compelled us to realize that "misfortune never comes alone". Keeping in mind that (19) with an average mortality rate of 54%, black fungus infection in COVID-19 recovered patients is indeed alarming. The association of a black fungus and COVID-19 infection is illustrated in Figure 1, explaining why covid patients may get mucormycosis. Steroids are considered a good drug for critically ill COVID-19 patients, particularly in reducing inflamma-

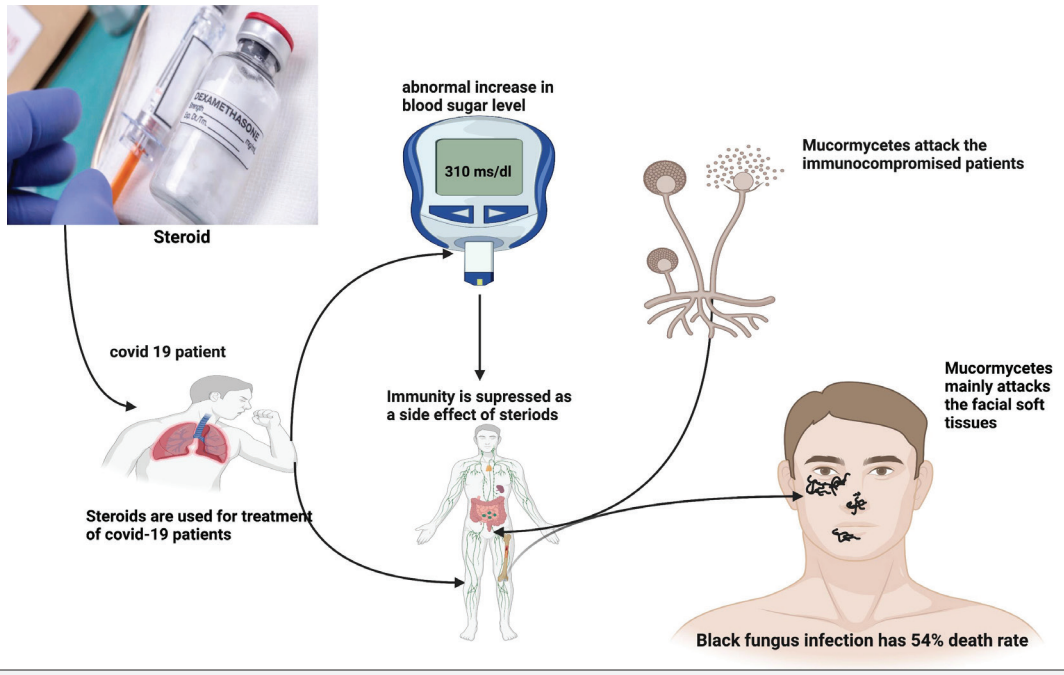

Figure 1. Illustration depicting the mechanism of attack of black fungus.

Steroids are used for the treatment of critically ill covid patients. As a result of this, the sugar level increases manifold in both diabetic and non-diabetic patients along with the suppression of immunity of those patients. The opportunistic fungus called black fungus releases its spores which if inhaled causes black coloration over the face.

tion in the lungs. Steroids are primarily used to suppress further tissue damage caused by one's immune system when it goes into overdrive response to fight against infections and can be used to control cytokine storms (23). However, while applying steroids, the other factors must be taken into account, particularly while treating high blood sugar conditions in both diabetics and non-diabetic COVID-19 patients. Since mucormycosis normally affects persons with an immunocompromised state, patients who have already recovered from COVID-19 are falling prey to such attacks by black fungus.

Types of mucormycosis

Mucormycosis can be classified as per the following types (24, 25)

a. Rhinocerebral mucormycosis: Rhinocerebral mucormycosis is also known as zygomycosis, is an infection which affects the nose, paranasal sinuses and can even spread to the brain (26). This type of mucormycosis is common in people with uncontrolled diabetes and in people who have undergone a kidney transplant. The infection starts in the nasal cavity at first and spreads towards the adjoined paranasal sinuses. Subsequently, implantation occurs in that area and grows at a faster rate in the sinuses and nasal cavity. The moist and humid environment inside the nasal cavity and paranasal sinuses are known to favor the growth and invasion of fungi.

Angioinvasion is another way through which the infection can reach the brain. In this case, the progression is very rapid and has a unique model of pathogenesis. Rhino cerebral mucormycosis symptoms include black lesions on the upper inside of the buccal cavity with induction of mild to severe fever. More serious consequences in the form of brain infarction, hematoma and orbital apex syndrome are not rare (27). Since vascular invasion is an important characteristic of this type of infection, the formation of intravascular thrombi often leads to infarction of the brain and ischemia (28). In some cases, if the aneurysmal blood vessels are ruptured, it may lead to hematoma along with intracerebral hemorrhages. Rhinocerebral mucormycosis also results in Meningitis which is a rare manifestation of this infection (27). The involvement of brain tissue leads to the formation of brain abscesses, especially in chronic cases (29). Brain abscess formation in such cases may be caused by some secondary bacterial infection (30). This infection may also affect the unilateral cranial nerves and cause hemiplegia (31). Mostly such outcome is mediated through the growth of mycelium along the invasion of leptomeningeal blood vessels (32). Diagnosis at an early stage, followed by proper treatment and surgical removal, if required, may help to save lives, and avoid permanent neurological complications.

b. Pulmonary mucormycosis: Pulmonary mucormycosis mostly attacks the lungs of individuals affected with black fungus. This is the most common type of mucormycosis in people who have had a stem cell transplant or an organ transplant which also includes cancer patients (33). Pul-

monary mucormycosis may develop due to inhalation of spores or lymphatic and hematogenous spread. The pathway of entry for *Mucorales* is primarily the respiratory tract where the fungi easily invade veins, arteries, and lymphatics and results in infarction and thrombosis which can be fatal (34). Patients suffering from haematological malignancies, diabetes mellitus, or who have received organ transplants and hematopoietic stem cell transplants are prone to invasive mucormycosis. The patients on corticosteroid-based therapy, chelation therapy and neonatal prematurity can be other reasons for infection. In addition, in low-income countries like India, malnutrition is a major issue that can play a vital role in acquiring mucormycosis infection (35). Angioinvasion and sometimes direct tissue injury of the respiratory tract, are some of the consequences of this infection which may even extend from the lungs into the great vessels (36). Clinical symptoms of the infection may include some nonspecific symptoms like fever, chest pain and dyspnea (37, 38).

In a large experimental set-up, whereof 929 cases of zygomycosis were reviewed, the overall mortality rate was found to be 44% in the diabetic patients with zygomycosis whereas there was a 76% mortality rate in the case of pulmonary zygomycosis patients. The most common species responsible for zygomycosis is *Rhizopus (39*).

c. Gastrointestinal mucormycosis: Gastrointestinal mucormycosis mostly affects the stomach and intestine and is highly prevalent among newborns, especially premature infants who are less than 1 month of age (40). There was a prevalence of gastrointestinal mucormycosis in industrialized nations. However, during the last few years, the number of cases of gastric and gastrointestinal mucormycosis has increased around the globe (41). Other rare causes of gastrointestinal mucormycosis were seen in immunocompromised patients who were suffering from AIDS, systemic lupus erythematosus and who had undergone organ transplantation (42). Some patients were seen to suffer from hepatic mucormycosis suggested an association with ingestion of herbal medications (43). A study was conducted by Morton and colleagues and they found a substantial increase in this infection in the 21st century (44). Recently, an outbreak of gastric mucormycosis occurred due to contamination of wooden applicators that had beenused to mix drugs for patients with nasogastric feeding tubes (45). These patients suffered from massive gastric bleeds.

d. Cutaneous mucormycosis: This type of infection primarily affects the skin, especially in cases of skin trauma or surgery. This is one of the most common types of mucormycosis which occurs even in people with an immunocompromising history (46). Cutaneous mucormycosis is comparatively a new emerging fungal infection that is caused by fungi belonging to the phylum Glomeromycota. The clinical presentation is usually nonspecific, but a rapidly evolving necrosis indicates the presence of this infection. In view of the occurrence of cutaneous mucormycosis, the strains that are most frequently isolated are *Rhizopus oryzae, Apophysomyces elegans* and *Lichtheimia corymbifera (47*) Other isolates reported to be responsible are *Saksenaea vasiformis, Mucor* sp, *Cunninghamella bertholletiae, Rhizopus microspores* and *Rhizomucor* spp. (48). Reports are available to indicate that this type of fungus is associated with nitroglycerine patches and vascular devices (49). In a review that was done of 196 cases of healthcare-associated mucormycosis, it was found that 57% involved the skin. Among them, a predominant number of the population included surgical patients, premature infants and immunocompromised hosts (50). Cutaneous mucormycosis is classified into two types- primary and secondary type infection. In the primary type of disease, the skin is often infected by direct inoculation and in the secondary form, the infection is caused by dissemination from other locations. According to the pattern of infection, it can be categorized as localized, deep or disseminated. In a review that was conducted with 929 cases, 176 patients were found with skin involvement. The most affected areas of the skin due to this infection are the arms and legs (51). Other locations for spreading include the scalp, breast, neck and gluteal area, face, thorax, back, abdomen and perineum (52).

e. Disseminated mucormycosis: It is a type of infection that spreads via the bloodstream to affect other parts of the body. The infection commonly affects the brain. It also can affect other organs such as the heart, skin and spleen (53). Mucormycosis is a rapidly spreading infection that is associated with extensive angioinvasion, thrombosis, tissue infarction and necrosis (54). In worse cases, it leads to haematogenous dissemination of the fungi (55). Dissemination may occur in up to 40% of patients who are suffering from haematological malignancies (56). In a review about children, it was found that dissemination increases the risk of death sevenfold (57). Patients with disseminated infection in the brain can even develop stress or coma in worse cases.

HOW COMMON IS MUCORMYCOSIS?

Mucormycosis is actually a very rare infectious disease. In 1992–1993, a population-based study was performed which suggested a yearly rate of 1.7 cases per 1 million population were affected by black fungus (47). Prospective surveillance among 16,808 transplant recipients was performed during 2001–2006 and it was found that, in stem cell transplant recipients, mucormycosis was the third most common type of invasive fungal infection. It accounted for 8% of all invasive fungal infections (54). Moreover, it was also observed in the case of solid organ transplant recipients, that mucormycosis accounted for nearly 2% of all invasive fungal infections (28 mucormycetes cases among 1,208 solid organ transplant recipients who developed any fungal infection) (58). Although mucormycosis outbreaks on a global scale have not been reported yet, the risk of a mucormycosis endemic through healthcare-associated systems cannot be overruled. The risk of black fungus spread through

improper disposal adhesive bandages, wooden tongue depressors, and hospital linens is potentially high. Pathogen transmission in health care establishments via negative pressure rooms, water leakage, poor air filtration, non-sterile medical devices and hospital building construction are also found to be equally responsible (59, 60).

ORGAN WISE PATHOGENICITY OF BLACK FUNGUS INFECTION

Exposure to mucor is commonly associated with mould infestation of soil, plants, manure, and decaying vegetation. It usually spreads through the respiratory tract and erodes facial structures and in severe cases, surgical removal of the eye becomes necessary to prevent the fungus from spreading to the brain. The ethmoid sinus has proved to be a vital route of infection because mucormycosis can invade through the thin lamina papyracea and then eventually gain access to the orbit. The infection in some cases may extend posteriorly to the orbital apex, which ultimately leads to orbital apex syndrome. The optic nerve affected due to this infection results in loss of vision involving superior orbital fissure as well as the cranial nerves III, IV, and VI, and branches of V1 and V2. This altogether causes ophthalmoplegia, diplopia, and sensory loss to the areas corresponding to the cornea and face. If the infection spreads posteriorly and gains access to the cavernous sinus and the brain parenchyma, vascular thrombosis and infarction in the posterior part can also be noticed.

THE EPIDEMIOLOGICAL PERSPECTIVE OF BLACK FUNGUS

In India, an estimated 0.14 mucormycosis cases were recorded per 1000 population as per a recent report (61). Organ transplantation, diabetes and blood cancers are also common underlying problems in many developed countries (61). Even before the COVID-19 pandemic, the mucormycosis incidence in India was estimated to be around 70 times more than the rest of the world (62). In fact, the rapidly growing number of cases of mucormycosis in some parts of India declared it to be an epidemic. The mortality rate for black fungus is close to 54% which is much greater than the ongoing pandemic of COVID-19. The mortality rate of patients suffering from various types of mucormycosis is given below in Figure 2. The mortality rate varies with the type of fungus that has attacked or even with the present condition of the patient as well as the site of infection (52).

HOST IMMUNE RESPONSE AGAINST BLACK FUNGUS

Exposure to fungi by inhalation, digestion, and even by traumatic inoculation of pathogens or allergens causes fungal infection in our everyday life. However, antifungal host defense protects the host either by killing the pathogen or restricting further spread in a coordinated way via both innate and adaptive immune responses. However, some Pathogenic fungi, including black fungus, use multiple strategies to subvert or exploit the host immune defense and successfully colonize and spread further. The immune evasion of black fungus is schematically represented in Figure 3.

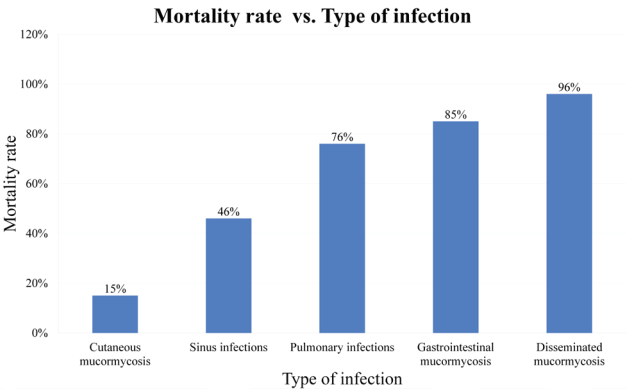

Figure 2. Representation of mortality rate of patients affected by mucormycosis.

The data for the graph was taken from a trusted journal (63). It represents the mortality rate of patients with respect to the type of mucormycosis infection.

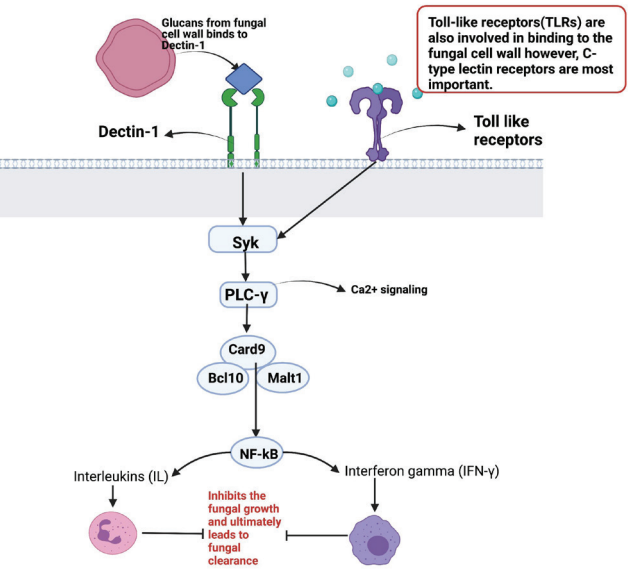

Figure 3. Host cell immune response pathway against fungal infection.

This is a schematic representation of the host immune response pathway via CARD9 molecule. When the glucans from the fungal cell wall bind to DEctin-1 receptor then a series of reactions are initiated leading to NF-kB localization which ultimately results in release of cytokines that inhibit and destroy the fungal cells.

Fungal recognition and immune activation

The cell wall of the fungi is composed of polysaccharides and lipid moieties to activate innate immune responses via binding to Toll-like receptor 4 (TLR4) expressed by major antigen-presenting cells (64). Like other prokaryotic cells, the fungal cell wall lies to the exterior of the plasma membrane and is arranged in bi-layers - the innermost layer consists of chitin. It

also consists of the adjacent layer that lies on the external side which is formed by β-(1,6) glucans and immunoreactive β-(1,3) (65). While entering the host cells, fungal cells bind to soluble pattern recognition receptors (PRRs). Subsequently, these interactions facilitate signalling responses by membrane-bound receptors to activate the antifungal effector response (66). The C-type lectin receptor (CLR) dectin-1 binds β-glucans from the fungi. The binding of β-Glucan displaces regulatory phosphatases such as CD45 and CD148 (67) and induces SRC-dependent phosphorylation of the intracellular ITAM-like motif while recruiting the SHP-2 phosphatase (68). The SYK docks to this scaffold and then transduce signals through a family of Guanine nucleotide exchange factors (GEFs) (69) to CARD9, to activate the NF-κB pathway via the subunits p65 and c-REL (70). Thus, CARD9 is considered very important for activating antifungal immune responses.

Alternatively, Dectin-1 also plays an important role in innate immunity activation primarily by triggering Th17 differentiation. IL-17 produced by Innate lymphoid, Th17 and γδ T cells at the mucosal surfaces is critical for antifungal immunity. In addition, other Dectin-1 dependent cytokines, such as IL-6, IL-23, IL-1β and TNF (71) are expressed following fungal infection. Neutrophils rapidly direct the production of reactive oxygen species (ROS) to the fungal phagosome (72). Fungal invasion of endothelial and epithelial cells promotes disease dissemination and tissue damage. In mucormycosis, the endothelial receptor glucose-regulated protein 78 (GRP78) enables the fungal hyphae to bind to endothelial cells (73) via spore coat protein surface proteins (CotH). Often metabolic changes associated with diabetic ketoacidosis (DKA) and hyperglycemia enhance the endothelial GRP78 expression and results in tissue invasion in the fungi (74).

COVID-19 ASSOCIATED MUCORMYCOSIS: WHY IT IS MORE IMPORTANT THAN OTHER FUNGAL DISEASES

Low oxygen, diabetes, high iron levels, and immunosuppression are predisposing conditions that make the COVID-19 affected person more vulnerable to black fungus infection. Various other factors, including prolonged hospitalization under mechanical ventilation, can create an ideal milieu for contracting mucormycosis. Similar to cryptococcosis or oral candidiasis (oral thrush) in HIV-infected patients, COVID-19 patients are also vulnerable to opportunistic pathogens such as black fungus which suggests some similarity between SARS-COV-2 and HIV infection where the patient's immunity is compromised (75). In contrast, since opportunistic infections breach the host defenses due to weakened host immunity (76), any viral attack that doesn't weaken the immune system won't attract further attacks by opportunistic fungi such as the influenza virus.

HOST SUSCEPTIBILITY TO MUCORMYCOSIS

For the current scenario, in the following section, we discuss the predisposing factor that makes the COVID-19 patient more vulnerable to black fungus infection:

A pre-existing condition such as diabetes, specifically diabetic ketoacidosis, organ transplant, and Cancer. Injection drug use, excessive iron in the body (commonly known as hemochromatosis), skin injury which may occur as a result of surgery, burns, or wounds and prematurity due to low birthweight, stem cell transplant, long-term corticosteroid use and low number of white blood cells and neutropenia (77).

MUCORMYCOSIS: A THERAPEUTIC CHALLENGE/TREATMENT OPTIONS

The ray of hope for us to battle this dangerous disease is our dedicated doctors and researchers who have put all their efforts into identifying a suitable drug of choice. If treatment is initiated in a timely manner, it reduces the mortality rate. Treatment of Mucormycosis involves a combination of surgical removal and antifungal therapy. The appropriate treatment and medications suggested are as follows (Table 1).

This treatment protocol has to be followed until clinical signs of infection are resolved with the elimination of predisposing risk factors such as hyperglycemia, immunosuppression etc. For the treatment of mucormycosis, it is vital to understand the mechanism of drug action for mucormycosis. Amphoter-

Table 1. Treatment modalities.

1.	Amphotericin B deoxycholate (D-AmB)- should be given for 1.0-1.5 mg/kg/day
2.	Liposomal amphotericin B (L-AmB) is the preferred treatment- 5- 10mg/kg/day that has to be continued till an appropriate response is achieved and the disease reachesa stabilized condition. It may even take several weeks, following which,step down to oral Posaconazole of 300 mg dose del tablets twice a day for 1 day which is then followed by 300 mg daily or Isavuconazole of 200 mg 1 tablet 3 times daily for 2 days followed by 200 mg dose of a tablet daily would be a good drug of choice.
3.	Injection of Amphotericin B Lipid Complex may also be given as a drug of choice for - 5mg/kg/day
4.	We need to reduce the dose of steroids if the patient is still taking it and discontinue it rapidly.
5.	Discontinue other immunomodulating drugs. The earlier the Surgical debridement is performed, the better, is pivotal in the management of mucormycosis.
6.	Surgical debridement involves an extensive process to remove all necrotic material
7.	Exenteration of eye can be performed if there is involvement of the eyes
8.	Immediate management has to be done to control diabetes & diabetic ketoacidosis.

icin B is currently considered the best drug of choice for the treatment of mucormycosis. The mechanism of drug action is given in Figure 4. Along with traditional antifungal agents and surgery methods, some other therapies include reversing immunosuppression and correcting metabolic deficits and involve strategies of immune augmentation for controlling mucormycosis beneficially (78). Some popular adjunctive therapies include immunomodulation strategies, iron chelation and hyperbaric oxygen (79). Hyperbaric oxygen is known to be an effective treatment for diabetic patients who have rhino cerebral or severe cutaneous mucormycosis (80). High concentrations of oxygen may also improve wound healing by releasing enhanced tissue growth factors (81). Other techniques, such as immune augmentation strategies, which include interferon-γ and granulocyte colony-stimulating factor (G-CSF), have been stated as adjunctive therapies for improving host response (82).

FUTURE PERSPECTIVE

Although fungi evolved 400 million years ago and played an important role on Earth, some of them have evolved to become pathogenic (83). The great Irish famine of 1845 that affected millions of people resulted from the fungus *Phytophthora infestans*, which wiped out the country's staple potato crop. Although fungal diseases are common among plants, only a tiny fraction of them tends to attack humans and animals. However, our immune system gets compromised due to other illnesses, and fungi, which are otherwise harmless, immediately take advantage to invade the hosts (84). This opportunistic nature of fungi has often hindered COVID-19 recovery of affected patients and makes them more vulnerable to several other secondary bacterial and fungal infections. There are three main ways humans can contract fungal infection: inhaling spores, swallowing fungal spores in food or medicines, or when spores contaminate wounds. Specifically, in the case of black fungus, mucor spores, when they attack the sinuses, spread to the lungs and brain, and then finally affect the central nervous system. Though many other secondary bacterial and fungal infections may attack Covid patients, the black fungus remains a fatal fungal infection. Although mucormycosis is not contagious, it spreads from fungal spores circulating in the air or the environment, hence, it is almost impossible to avoid. However, in addition to maintaining personal hygiene, basic precautions such as avoiding contact with soil, moss, and dusty construction sites along with wearing shoes, long trousers, and long-sleeved shirts while doing professional activi-

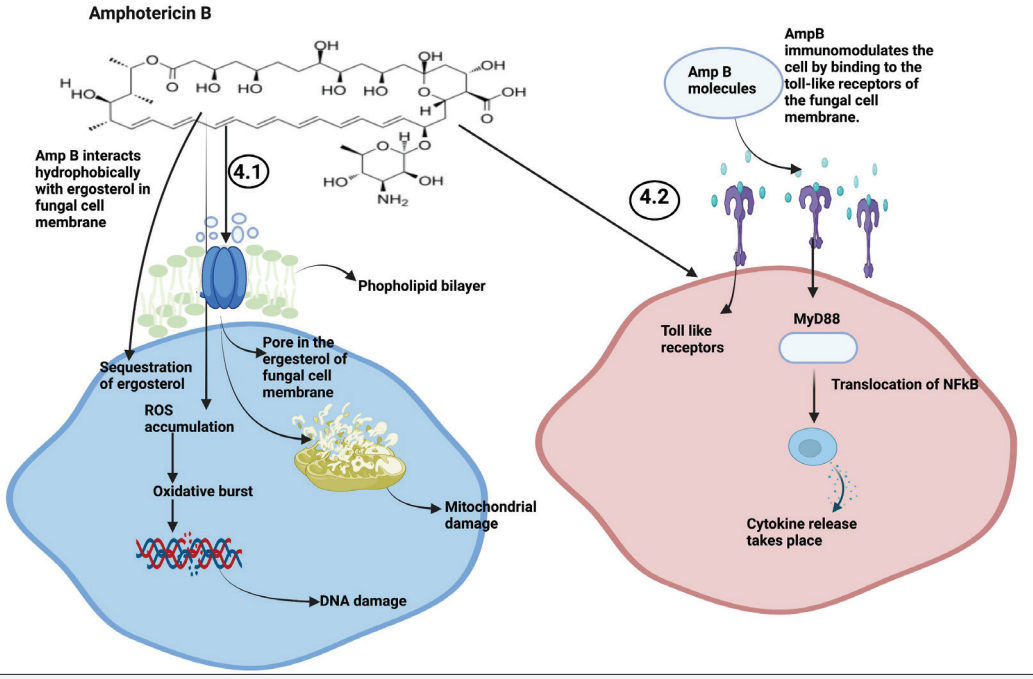

Figure 4. Mechanism of drug of choice.

We can see 2 pathways through which Amphotericin B can damage the fungal cell. In the pathway marked in Figure 4.1. we can see that Amphotericin B interacts hydrophobically with the ergosterol present in the fungal cell membrane and leads to the formation of pores. As soon as it forms pores, the molecules inside the fungal cell start to leak out through the pores. Figure 4.1. also demonstrates that Amphotericin B leads to Reactive Oxygen Species accumulation which leads to oxidative burst ultimately resulting in mitochondrial damage and DNA damage. In the pathway marked in Figure 4.2., it is demonstrated that Amphotericin B molecules bind to the toll-like receptors, specifically TLR-2, TLR-4 and CD-14 on the fungal cell membrane. The adapter protein or MyD88 gets activated and helps to translocate NF-KB to the nucleus which leads to cytokine release in the end step. Cytokines modulates the fungal cell immunologically and help in damaging the cell.

ties may provide us with enough protection to stop us getting affected by black fungus (85). Regular steam inhalation and maintaining nasal and oral hygiene also contribute to avoiding infections, especially from those suffering from COVID-19. Patients, especially those with diabetes or taking steroids because of COVID-19 or any condition that affects the immune system, need to control high blood sugar levels, and regularly monitor blood sugar levels. Other preventive measures to be followed are to regularly clean and replace humidifiers for those using oxygen concentrators and to change masks daily. Further progress in research and exploring novel methods of diagnosis and antifungal treatment modality should continue for better therapeutic and preventive measures against black fungus (86).

CONCLUSION

Educating patients about the symptoms will act as a very helpful armament in the early detection of the condition. Although it is a life-threatening disease, we shouldn't lose hope as early diagnosis and rigorous treatment may control the situation to a great extent. Liposomal amphotericin B is the best quality antifungal to be used for the treatment of this infection.

In this review article, we have mainly tried to highlight all the necessary points we all need to know about this deadly disease. Our main aim through this article is to create awareness among people instead of creating panic. We all need to understand that while biological systems are definitely unpredictable, we can prevent them by taking a few simple precautions and that is true for both covid and black fungus infections. Let's try to win this evolutionary arms race by bravely fighting this battle with covid and the deadly fungal disease "The black fungus".

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