Review Article

Mucormycosis "Black Fungus" New Challenge Associated with COVID 19

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Abstract

Corona virus-19 disease (COVID-19), caused by SARS-Cov-2. What was initially considered to be another worldwide flu epidemic mostly affecting the respiratory system has now emerged as a multi-organ disease, the most common extra-pulmonary involved organs include the blood vessels, eyes, heart, gastrointestinal tract, liver, skin, and kidneys. A growing number of case reports and series describe opportunistic fungal infections in COVID-19 patients. Co-morbidities such as diabetes mellitus, coupled with immune dysfunction and use of steroids, are hypothesized as the main causes. More recently, many cases of mucormycosis "black fungus" have been reported, particularly in Asian countries such as India. Mucormycosis is a rare angio-invasive illness caused by the fungi Mucorales, which is often seen in immunecompromised patients. Rhino-orbitocerebral, cutaneous, disseminated, gastrointestinal, and pulmonary forms of this unusual fungal infection exist. COVID-19 and Mucormycosis, Risks factors associated with Mucormycosis in COVID 19, Immune system response to mucormycosis, fungal pneumonias can resemble COVID-19, as well as prevention of these fungal will be discussed in this review.

Keywords: SARS-Cov-2 virus, COVID-19, Mucormycosis, black fungus, opportunistic infection

Introduction

Some opportunistic fungal infections that may be life threatening such as mucormycosis, aspergilosis, and candidiasis are more susceptible to be developed in certain viral pathogens such as COVID-19 because the immune systems are focusing fighting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. The evidence of these infections is mucormycosis appeared in India recently that affect who recovered from COVID-19.

Angioinvasion, tissue necrosis, and thrombosis are characteristics of rapid filamentous growth of an invasive fungal infection called mucormycosis with very high mortality rate more than 50% due to many reasons as the failure of the human immune system to successfully clear the infection, the aggressive nature of the infection,[1] as well as the resistance or poor therapeutics currently employed.[2-4]

Mucormycetes are several different types of fungi that have the ability to cause mucormycosis such as *Saksenaea*, *Syncephalastrum* species, *Mucor* species, *Cunninghamella bertholletiae*, *Apophysomyces*, *Absidia*, and *Rhizomucor*.[5]

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Certain prescription antifungal drugs are used for the management of the serious mucormycosis. These drugs may take through the mouth such as isavuconazole and posaconazole, whereas other drugs are given by vein as amphotericin B[6] that widely used to treat invasive fungal infection[7-9] and management of pulmonary mycotic diseases.[10]

In extreme situations, surgery to remove infected or dead tissue may be recommended to prevent the fungus from spreading. This may include removing disfiguring sections of the nose or eyes, but it is critical to treat this life-threatening infection. The most prevalent infections are rhinocerebral and pulmonary.[11] The rapid onset of tissue necrosis is a hallmark clinical indication of mucormycosis [Figure 1].[12]

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Mucormycosis and COVID-19

Mucormycosis is a fungal infection that affects the sinuses and lungs after inhaling fungal spores in the air. This infection has a low frequency in the past, with cases documented mostly in people with uncontrolled diabetes. However, numerous hospitals across the India recently are reporting an elevating in infections of COVID-19-associated mucormycosis (CAM).

Because the COVID-19 virus entered the pancreas and raised blood sugar levels, which encouraged fungal growth, CAM was also documented in individuals who had recently been diagnosed with diabetes. The virus may be able to penetrate and then destroy insulin-producing cells because the pancreas, which regulates blood sugar, is high in angiotensin-converting enzyme 2 (ACE2). The ACE2 protein (ACE2) is an enzyme involved in blood pressure regulation. It is thought to be the virus's "entry point" into the host. The journal nature describes, among other things, the story of a young 18-year-old student, infected by his parents, but asymptomatic, reached a few days later by extreme fatigue and a feeling of thirst. The diagnosis is made: it is Type 1 diabetes.[13]

Mucormycosis is an uncommon, invasive, and fungal opportunistic infection that can be life threatening. It is caused by contact with mucor mold, which can be found in soil, air, and even human noses and mucus. It erodes facial structures as it progresses through the respiratory tract.

Patients die within days of contracting the disease, and in other cases, doctors have had to remove eyes and upper jaws to prevent the life-threatening infection from spreading. The treatment of mucormycosis necessitates the collaboration of eye surgeons, ENT specialists, general surgeons, and neurosurgeons.

Rhinocerebral mucormycosis (sinus and brain) symptoms include one-sided facial edema, lesion, congestion in the nose or sinuses fever,[6] as well as black sores on the nasal bridge or upper interior of the mouth that swiftly worsen. Mucormycosis, in contrast with some other fungal infection,[14,15] cannot be transmitted from one person to another or between humans and animals.[6]

Risks factors associated with Mucormycosis in COVID-19

Mucormycosis is more common in coronavirus patients who have a weaker immune system and diabetes.[16] Mucormycosis, which is uncommon in India, has emerged as a new problem for COVID-19 patients on steroid therapy and those with diabetes. Strong steroids used to treat severe COVID-19 can reduce immunity and increase sugar levels, thereby helping the spread of "black fungus" and increasing its frequency.

Along with a large number of COVID-19 patients, India has millions who suffer from diabetes, which might also raise the risk of a black fungus infection. Many treatments used to treat COVID-19 decrease the body's immune system, which would typically defend the individual from a fungal infection. The fungus also has an easier time establishing itself in India due to the heat and humidity[17] as well as other countries [Table 1].[18]

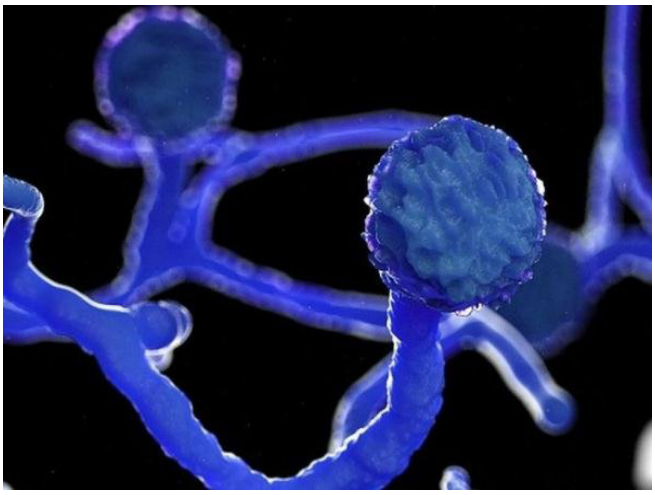

Figure 1: Hyphae of the mucormycosis [12]

Table 1: The burden of mucormycosis in different countries[18]

Countries	Total population (millions)	Total estimated fungal burden	Mucormycosis	
			Total burden	Rate/100 K
India	1300.0	NA	171,504	14
Pakistan	184.5	3,280,554	25,830	14
Nigeria	155	17,983,517	300	0.2
Japan	127.0	2,370,314	254	0.2
Brazil	194.0	3,800,000	243	0.2
Russia	142.9	3,082,907	232	0.16
Mexico	112.3	2,749,159	134	0.12
Thailand	65.1	1,254,562	130	0.2
Colombia	49.3	760,808	99	0.2
Kenya	43.6	3,186,766	80	0.2
USA	NA	NA	36	0.3

NA: Not available

Corticosteroid therapy, diabetes, organ transplant, persistent neutropenia, prolonged, skin trauma, burns, or surgical wounds, iron overload, malnourishment, and intravenous drug use are all risk factors for mucormycosis.[6]

Immune system response to mucormycosis

Immunosuppressive therapy inhibits immunological phagocytic effector activities, increasing susceptibility to invasive mold infections significantly.[1] The epithelial cells met at the early sites of infection, such as alveoli and skin epithelia, constitute the first line of defense against Mucorales.[19]

Epithelial damage extends to the basement membrane in patients at risk of invasive mucormycosis, exposing extracellular matrix proteins. The basement membrane proteins laminin and Type IV collagen have been demonstrated to attach to *Rhizopus oryzae* resting spores.[18] Mucorales spores germinate and penetrate host cells after adhering to basement

membrane proteins.[1] Mucorales sporangiospores enter a latent, resting phase during germination and expand in size as well as metabolic activity before beginning filamentous growth.[20]

When it comes to mucormycosis, the neutrophil–Mucorales interaction is fascinating, especially because of the risk factor of neutropenia.[21,22] Neutrophils are not readily recruited to resting Mucorales spores in the lungs of intranasal-infected mice under healthy immunological circumstances.[23] Intranasal injection of enlarged Rhizopus spores, on the other hand, results in a significant increase in neutrophil recruitment as well as inflammation.[22]

Resting spores are resistant to phagocytic in a healthy immunological person. Swollen spores and hyphae, on the other hand, are vulnerable to destruction by macrophages and neutrophils. The recruitment and efficacy of macrophage and neutrophil activity against mucormycetes are significantly reduced when immunological suppression is present. Mucorales come into contact with platelets after penetrating the endothelium lining. Platelets bind to both mucormycete spores and hyphae *in vitro*, suppressing germination and causing hyphal injury. Dendritic cells are activated and promote adaptive immunity only in response to Mucorales hyphae.[1]

The role of platelets in the innate immune response to Mucorales is of particular interest because thrombosis is a characteristic of mucormycosis. Platelets attach to both Mucorales spores and hyphae *in vitro*, and platelet activation and granule release are induced. Platelet contact suppresses fungal germination, lowers hyphal growth, and causes hyphal damage in Rhizopus, Mucor, Lichtheimia, and Rhizomucor.[24] Platelets' capacity to prevent Mucorales from germinating shows that these innate immune effectors are advantageous. Excessive thrombosis, on the other hand, causes thrombocytopenia, which makes surgical intervention for diagnosis and therapy unfavorable.[25]

T helper cells (Th) are noted to play a key role in the clearance of pathogenic fungi, which is mediated by the secretion of distinct cytokines.[26] Interferon-γ secreted by Th-1 cells is regarding protective immunity against fungi, whereas Th-2 responses elevate susceptibility to fungal invasion.[26-28] Th-17 cells are termed for their high levels of interleukin (IL)-17 production, and they have also been linked to mucosal protection against fungus.[26] Mucorales-specific T-cells belonging to both CD4+ and CD8+ subsets were detected during infection in a study on mucormycete-specific T-cells in patients with invasive mucormycosis. Furthermore, Mucorales-specific T-cell cytokine profiles revealed that the most prevalent cytokines were IL-4 (Th-2 cytokine), IFN-, and IL-10 (Th-1 cytokine), followed by IL-17.[29]

Quantitative (neutropenia) or qualitative abnormalities in phagocytic cell activity allow for uncontrolled hyphal development and invasive infection. Hyperglycemia and acidosis, in particular, are known to impede phagocytic cell chemotaxis and killing activity against Mucorales through weakening oxidative and nonoxidative processes.[30]

Lymphopenia was found to be related with disease severity and progression in COVID-19, and it is decreased significantly in severe cases,[31-33] suggesting that lymphocyte reduction decreases immunity to mucormycosis.

Fungal Pneumonias Can Resemble Covid-19

Some fungal illnesses have symptoms that are similar to COVID-19 such as fever, cough, and shortness of breath.[34] To identify if a person has a fungal infection or COVID-19, laboratory testing is required. COVID-19 and a fungal infection might occur in the same patient.[35,36]

Fever, cough, and shortness of breath are symptoms of other fungal infections such as Valley fever (coccidioidomycosis), histoplasmosis, and blastomycosis, which are comparable to COVID-19 and bacterial pneumonias.[37] These fungi can only be found in dirt. People are infected by inhaling fungi that are present in the air.

If COVID-19 testing is negative, clinicians should examine fungal pneumonias as a probable cause of respiratory disease. It is worth noting that these fungi can appear at the same time as COVID-19.[38,39]

In persons with severe COVID-19, scientists are still learning about aspergillosis (fungal infections caused by the fungus *Aspergillus*).[40] In the past, scientists believed that aspergillosis only affected those who had very damaged immune systems. However, aspergillosis is becoming more common in people who do not have a compromised immune system but have severe viral respiratory infections such as influenza. COVID-19-related pulmonary aspergillosis has been reported in several recent studies (corrective and preventive action).[41-43]

Patients admitted to the hospital with COVID-19 are at risk for healthcare-associated infections[44-46] such as candidemia or Candida-related bloodstream infections.[47,48] In individuals with severe COVID-19,[38] fungal and bacterial resistant to antimicrobial therapy have also been reported.[49]

However, outbreaks of *Candida auris* have been documented in COVID-19 units of acute care hospitals since the start of the epidemic. During the COVID-19 pandemic, modifications in normal infection control methods, such as reduced availability of gloves and gowns, or reuse of these items, and modifications in cleaning and disinfection techniques, may have contributed to these outbreaks.[50]

Among 1988 patients with COVID-19 admitted to intensive care units, 7 had fungemia (7/1988; 0.03%), among whom six had CAC. The mortality of the limited CAC cases was high and greatly exceeded that of patients with COVID-19 but without candidemia (100% (6/6) vs. 22.7% (452/1988)). Patients with fungemia were *Candida albicans*, *Candida glabrata*, and Rhodotorula mucilaginosa.[51]

Prevention of Fungal Infections in Patients with Covid-19

Mucormycosis is difficult to prevent because it is transferred by inhaling mold spores in soil, rotting vegetables or bread, or compost piles. Mucormycosis is usually not passed from person to person, but it is found in the environment.

The possibility of aspergillosis must be considered in patients with severe COVID-19 who have abnormal respiratory function, even if they do not have apparent risk factors for aspergillosis.[52]

In patients with severe COVID-19 fungal co-infections, early detection, and surveillance for Candida and antifungal resistance diseases (e.g., *C. auris*, azole-resistant Aspergillus) are critical to minimizing death from COVID-19.[50]

Conclusions

Mucormycosis is one of serious opportunistic infections and economic cost that can associated with COVID-19 infection. Much is stay unclear about the consequences of SARS-CoV-2 virus and its correlations with other diseases.

The use of steroid drugs for treating COVID-19 may partially explain the surge in these fungal infections, along with weakened immune systems from COVID-19; corticosteroids impair migration, ingestion, and engulfment activity in human macrophages. Hyperglycemia and acidosis have been shown to inhibit phagocytic cell chemotaxis and killing activity against Mucorales by weakening both oxidative and nonoxidative mechanisms.

Mucormycosis has a high mortality rate and can be seen in other parts of the worlds is possible because Mucorales are found in environment so it may be found in any part in spite of they are not contiguous from person to another. Physicians have to prescribe the right dose of cortisone. We should ensure that people who have diabetes should keep monitoring their sugar levels. As well as, we have to wear two masks, because it can be found in air, especially places like construction sites.

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Conflicts of interest

There are no conflicts of interest.

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