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## Covid 19 and opportunism of Mucormycosis

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## REVIEW

# Covid 19 and Opportunism of Mucormycosis

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### Abstract

The novel coronavirus disease (COVID-19) spread rapidly across all continents. However, data on all COVID-19 signs and symptoms are inadequate, Patients with COVID-19 may be more susceptible to fungal infections. Mucormycosis is an uncommon and often fatal fungal disease characterized via vascular invasion by hyphae leading to thrombosis and necrosis. Covid recovered patients with co morbidities like as diabetes or kidney disease, heart failure, or cancer are more likely to get black fungal infection. The signs of this infection are similar to those of Covid-19 and common flu, If the infection is neglected or mistreated, it can spread from the nose to the eyes and brain, resulting in life-threatening complications. Prompt diagnosis, therapy initiation, as well as considering the limitations of quick development COVID-19 therapeutic recommendations were already essential to increasing survival of patients. This study aimed to explain the correlation between Covid 19 & Mucormycosis.

*Keywords:* Black fungus, Covid 19, Immunosuppression, Opportunism

## 1. Introduction

According to recent data, patients infected with [SARS CoV2] might cause fungal & bacterial secondary infections [1]. Throughout the COVID-19 pandemic's second wave in May 2021, mucormycosis (Black fungus) was spread. So far, more than 31,000 instances of mucormycosis have been documented across India, with more than 2100 people died as a result of the disease. Mucormycosis cases in India have more than quadrupled in late 2020, showing a direct link between COVID-19 and the fatal black fungus viral infection that is already spread approximately to every state in the country [2]. Mucormycosis is uncommon, opportunistic, as well as highly fatal fungal infection which most commonly infects people with underlying compromising conditions like neutropenia, use of corticosteroid, diabetes, solid organ/allogeneic stem cell transplant, hematologic malignancies, immunosuppressive treatment and elementary immunodeficiency. On extremely rare cases, similar infections might be observed in otherwise immune-competent people [3]. The most frequent form of mucormycosis is (rhino orbito cerebral) mucormycosis, that is assumed to be acquired by inhalation of fungal spores to the (paranasal sinuses). Mucormycosis

associated with COVID-19 is mainly a rhino orbital cerebral infection that manifests clinically around the nose, eyes & even the brain [4]. Evidence suggests that immune-compromised individuals suffered from pulmonary mucormycosis after COVID-19. Mucormycosis, on the other hand, isn't a contagious disease in nature. Avoiding risk factors and administrating of antifungal medications, in addition to improved management, are established ways to managing mucormycosis [5].

## 2. Mucormycosis (the black fungus)

Mucormycetes, the causative agent of mucormycosis, are a kind of mold that exists in the atmosphere and releases spores that are readily aerosolized and disseminated [6]. Mucormycosis (formerly known as zygomycosis) could be exist in a number of environments, they are most commonly exist in soil & decomposing organic waste such as rotten wood,leaves, and compost piles. It can also arise as a result of a burn,wound, or another type of skin damage [7]. According to taxonomic analysis, Mucormycetes belong to the order Mucorales, and the subphylum is Mucormycotina. There are several genera in this order, but the most prevalent genera which cause diseases in human are Mucor species & Rhizopus. Mucormycosis is categorised as

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gastrointestinal, pulmonary, rhinocerebral, cutaneous, disseminated, and other pathologic conditions depending on clinical manifestations. Osteomyelitis, endocarditis, and peritonitis are some of the rare diseases associated with mucormycosis. By looking at a long pattern of disease association, it's obvious that mucormycosis is linked to a condition that causes immunosuppression. People who have had a hematological malignancy, solid organ transplant or stem cell, or who have been on long-term corticosteroid medication are at risk of developing the disease. Uncontrolled diabetes mellitus has recently been recognized as the disease's most significant global risk factor. Mucormycosis has recently been associated strongly with COVID-19, and it has become a source of intense concern in countries such as India. It might be because corticosteroids were used to treat numerous severe COVID-19 cases where cytokine storm was suspected and confirmed [8].

### 2.1. Mucormycosis types

Rhino cerebral Mucormycosis (infection of the brain & sinus) is a kind of infection which can be transmitted into the brain. This kind of mucormycosis is more common in diabetics and individuals who have undergone a kidney transplant. Most frequent kind of mucormycosis in cancer patients and individuals that have an organ transplant or stem cell transplant is pulmonary (lung) mucormycosis. Gastro-intestinal mucormycosis is much more common in children than in adults, especially in premature & low-birth-weight newborns under the age of approximately a month who have had surgery, undergone antibiotics, or therapies that reduce the body's ability to fight germs & disease. Cutaneous (skin) mucormycosis is caused by fungi invading the body through a skin split. This is the most frequent form of mucormycosis in persons with a healthy immune system. Disseminated mucormycosis develops when an infection spreads via the circulation from one region of the body to another. The most commonly afflicted organ is the brain, but heart, spleen, & skin may all be affected [9] (see Table 1, Figs. 1 and 2).

### 3. Reasons of suddenness outbreak

1. Although there are numerous probable explanations/hypotheses for the fast spread of Mucormycosis in India, certain aspects are important to consider in order to take the required measures to prevent similar infection in Malaysia and the entire world.

Table 1. Symptoms & signs of Mucormycosis.

	Symptoms	Signs
Face	Headache Facial pain Facial ulcers	Ulceration
Neurological problems	Decreased facial Sensation Facial deviation One sided weakness Altered sensorium	Decreased facial Sensation Altered sensorium Hemiplegia Facial palsy
Eyes and adnexa	Swollen eyes Eye pain Diminution of vision Double vision Ptosis Protrusion of eyeball	Proptosis Chemosis Visual acuity Ophthalmoplegia Ptosis Lid oedema
Oral cavity	Oral ulcers	Crusting and ulceration Discoloration
Nasal cavity	Epistaxis  Nasal discharge Nasal stuffiness	Crusting and ulceration Active epistaxis Discharge

2. Extended use of steroids reduces immunity and makes a person vulnerable to fungal infection. As a result, excess and inappropriate early initiation of steroids in COVID treatment are not advised. Steroids should be used with extreme caution and in accordance with the guidelines. Oral steroids, for example, are contraindicated in patients with normal oxygen saturation (SpO<sub>2</sub>).
3. COVID-19 patients who have been discharged from hospitals should contact their doctors if any of the following symptoms appear: swelling around the nose or eyes, stuffy or bleeding nose, nasal blockage or coloured discharge, facial pain, pain near the eyes, dental pain, loosening of teeth, blackening of the palate, and so on. Patients taking immune suppressive medications and diabetics must take extra care.
4. The indiscriminate use of anti-microbials might destroy helpful normal flora, making a person vulnerable to opportunistic infections. As a result, self-therapy without adequate medical supervision is not recommended.
5. An excessive quantity of new COVID-19 cases can force hospitals to stretch their resources, compromising the supply of hygienic ventilators, humidifiers, oxygen masks and so on, leading to Mucormycosis outbreaks. Thus, it is everyone's responsibility to rigorously follow the SOPs in order to decrease the load on the health-care system.
6. During SARS-CoV-2 infection, the risk of Mucormycosis is important in a population of a

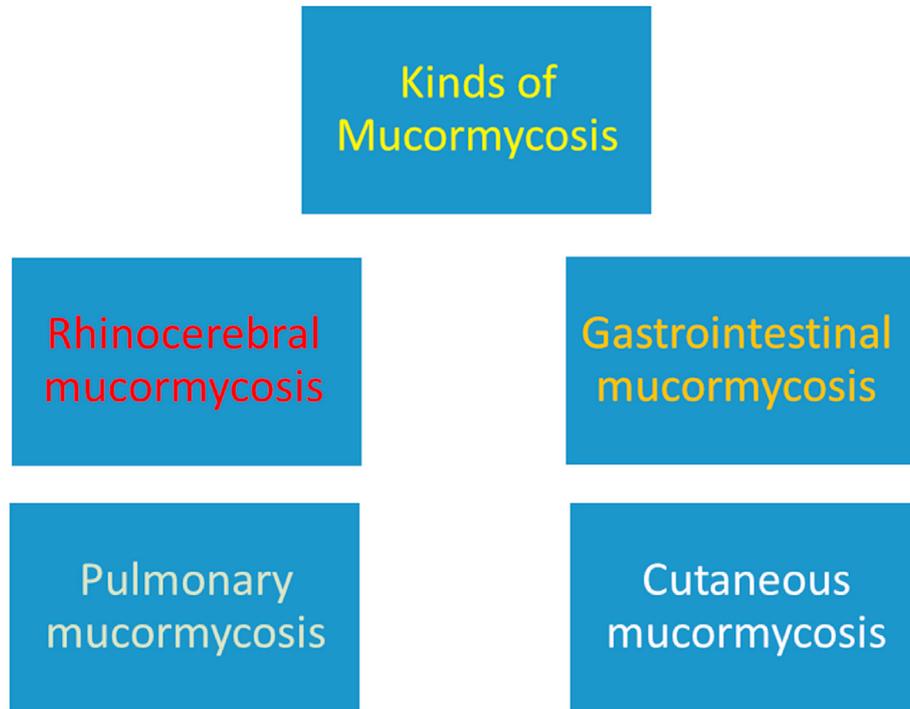


Fig. 1. Mucormycosis types.

high occurrence of diabetes and poorly controlled diabetes. Everyone has the responsibility to check on the general health and well-being of family members who may be at risk.

7. The use of zinc supplements, which are frequently used to treat COVID-19, has also been investigated in relation for Mucormycosis, with zinc supplementation resulting in more efficient energy usage by the fungi. Zinc

decreased the fungus's economic coefficient (the weight of the sugar or carbohydrate ingested divided by the fungus's growth) and caused the fungi to grow more abundantly. In addition, only in the presence of zinc did other micronutrients (copper, manganese, and molybdenum) enhance fungal growth [10]. Some researchers believe that widespread usage of stream inhalation might also facilitate such opportunistic infections [11].

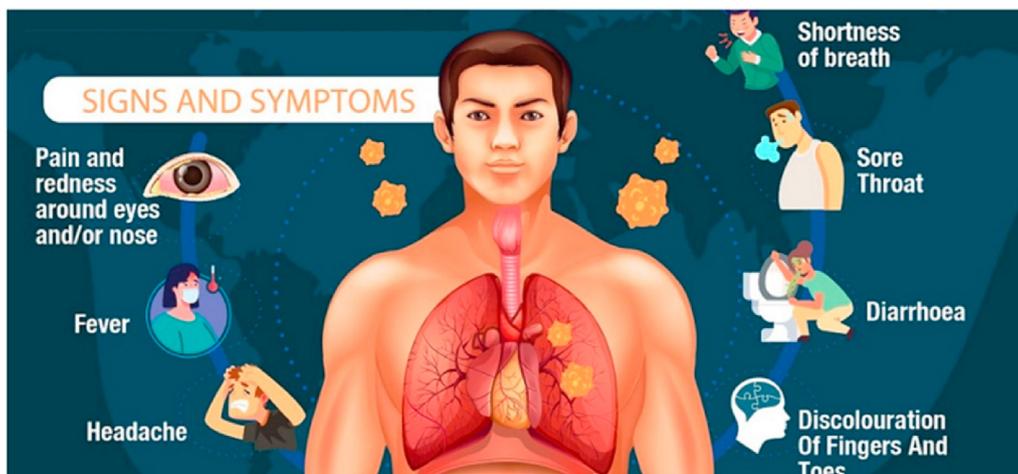


Fig. 2. Symptoms & signs of Mucormycosis.

#### 4. Mucormycosis & COVID-19: a complicated relationship

COVID-19 has sprung plenty of be widespread of conditions and complexities to the world [12]. Mucormycosis is a new milestone appeared to be a fatal infection coupled to the (COVID-19). Mucormycosis caused by COVID-19 patients is most frequent among individuals with a history of (DM), and it affects 95% of those with critical or acute COVID-19 have it [13]. Moreover, a patient of (two month old heart transplant) acquired mucormycosis (3 months) after already diagnosed with COVID 19. It was (cutaneous kind), as (older intravascular device site), and the patient died inspite of intensive treatment [14]. Because transplant patients are susceptible to mucormycosis, our research suggests that they require extra attentive care in the medical settings when being treated for COVID 19. Likewise, a patient with (AML) developed mucormycosis as a result of the COVID-19 infection [15]. Although organ transplantation, hematological variables and diabetes are frequently associated with mucormycosis, COVID-19 infections clearly functions as a cause in all of these conditions. Despite those factors like hematological factors, organ transplantation, and diabetes are frequently associated with mucormycosis. Furthermore, persons without any history of some underlying medical condition could be detected of mucormycosis after infected with COVID-19 [16]. There are several potential causes of development of mucormycosis after infection of COVID-19. COVID19 patients have different types of pulmonary complications [17], which might become a fungal initiation focal point. Additionally, COVID19 has been linked to immunological dysfunction [18], inhibiting (polymorphonuclear phagocytes) from destroying fungal spores once they have entered the body [19]. Individuals who suffer acute COVID-19 need to be hospitalized for along time as well as mechanical ventilation [20], Mucormycosis in these patients may also result from the existence of fungal spores in this equipment. Corticosteroid and Immunosuppressants drugs, which were used in COVID 19, could significantly have a key role in the development of mucormycosis [14]. COVID-19 already causes changes of iron metabolism as well as hyperglycemia. COVID-19 has high ferritin levels; elevated iron concentrations produce species of (reactive oxygen) causing damage of surrounding tissues. Released cytokines throughout COVID19 increase (intracellular iron) & iron outflows to bloodstream, providing a role in the initiation of mucormycosis [13]. Despite mucormycosis is mostly diagnosed by

detecting fungi in culturing of tissue & biopsies [21], waiting of cultures of a COVID-19 might be impracticable due to rapid development of (mucormycosis) [22]. Furthermore, alternative therapeutic approaches as well as reflection of the actual cause should be adopted, as reflection all of these conditions might not be conceivable when COVID-19 treatment is continuing. This is particularly real given the necessity for utilize high doses of steroids to treat COVID-19 [23]. Under this situation, it is obvious that the administration of steroids and antibiotics could be extremely dangerous to certain individuals since they may induce the initiation of these potentially fatal fungal diseases. It is critical significant for doctors to treat COVID-19 patients must be careful of patients who have infection and are administered immunosuppressants or steroids [24]. In spite of the enormous burden on the health care system resulting from the overwhelming increase in cases, greater attention is necessary in implementing preventative interventions for this condition [25]. It is also critical to examine the airflow in the hospital wards and the oxygen treatment apparatus of spores on a regular basis [26]. Additionally, Patients who have healed must be encouraged for staying inside for several more weeks for building up their immunity and to do follow up studies to avoid adverse effects. And it is critical for COVID-19 patients' solid waste be disposed of with care, same considerations must be followed for individuals with the infection [27]. Furthermore, there is an instant need of developing rapid diagnostic techniques to control mucormycosis in time [28]. To avoid future COVID-19-related fatalities, effective mucormycosis care must be promoted.

Epidemiology of Mucormycosis, a newly developing malignancy linked to the coronavirus (COVID-19) infection, has infected at least 7250 persons in India in (the third week of May 2021), with the number rising to over 50,000 cases at December 2021. Other continents, such as Europe (0.2 cases in Denmark to 95 cases in Portugal), the United States (3.0), Canada (1.2), and Australia (0.6), were expected to have variable case counts per million population in 2021 [29].

For diagnosis of CAM, Histopathology or culture-based tests often identify CAM as wide, irregular, pauci septate hyphae, whereas cryptococcosis and endemic mycoses, such as fungal infections, are distinguished by encapsulated yeast cells and budding spherules, respectively. CAM, on the other hand, may be detected in both blood and BAL samples, contrasting to aspergillosis and candidiasis. Other than mass spectrometry, molecular tests

such as Genus-NAAT (Nucleic Acid Amplification Test) and pan fungal PCR are indicated for CAM identification. However, like with other non-CAM fungal species, neither enzyme immunoassays nor antigen detection methods are highly effective [30].

Conventional amphotericin B at 1 mg (/kg/d) is advised for the treatment of Mucormycosis, while a dosage of 1.5 mg (/kg/d) may be necessary for the treatment of individuals with severe and fast progressing infections [69]. The patient's response, the underlying disease, and the nature and degree of amphotericin B-related toxicity are all aspects to consider when determining the success rate of any treatment approach. Some of the untested techniques include combining rifampin or tetracycline with amphotericin B to boost antifungal effectiveness and administering hyperbaric oxygen therapy [31].

## 5. Pathophysiological mechanisms & administration of CAM

COVID19 could induce mucormycosis in susceptible individuals via altering cell mediated immunity for example (phagocytosis), secretion of cytokine and chemotaxis [32]. Mucormycosis is much more common in individuals that have uncontrolled diabetes either with or without (diabetic ketoacidosis), organ transplantation, hematological malignancies, corticosteroid treatment, persistent neutropenia, iron overload, and immunosuppressive drugs [33]. In a retrospective analysis, Song et al. [34] suspected that fungal co-infection in relationship with pandemic COVID19, particularly in severely ill or immunocompromised patients, and supplied a diagnostic/therapeutic course of administration of COVID-19 patients with mucormycosis, cryptococcosis, aspergillosis, or candidiasis. SARS-CoV-2, according to Pandiar et al., [35], creates a favorable micro-environment to (opportunistic infections) such as mucormycosis via dysregulating [ACE2] expression that is not limited to the (lungs) but also in the pancreas, esophagus, ileum, renal tissues, cardiovascular, and colon. COVID19 causes hyperglycemia and induces severe diabetic condition due to its impacts on [ACE2]  $\beta$  cells of pancreas [36]. Lactic acidosis caused by type II alveolar cell injury, which causes cell to switch to anaerobic glycolysis, that is a recognized risk factor of mucormycosis. Endothelial damage and vascular thrombosis are caused by [ACE2] dysregulation of vascular endothelium. The increase in serum iron & serum ferritin levels as a result of each hemolysis & acidosis, offers a source of nourishment for Mucorales [37]. Another character of COVID-19

disease include lymphopenia [38]. Furthermore, *Rhizopus oryzae* is rapidly growing organism that grows at (3 mm/h at 36 °C), allowing Mucor to develop quickly when optimum circumstances are found. Mucor species generally thermotolerant, that can effectively tolerate the elevated temperature accompanied with Covid19 disease [35]. There have been no similar mucor outbreaks among immunocompromised patient populations like those with cancer, chemotherapy undergoing, diabetes, or steroids, pointing to COVID-19's specific cascade being the major cause of CAM. Furthermore, presence of mucor cases among individuals who did not use oxygen adds credence to an alternative explanation of the outbreak rather than use of industrial oxygen. Based on our findings, we think that COVID19 causes immunosuppression, resistance of insulin, and is an independent risk factor of mucormycosis. The diagnosis by utilizing direct microscopy, histology utilizing H and E stains, and culture [39]. Clinical specimens including paranasal sinus secretions, sputum, skin lesions & bronchoalveolar lavage, particularly with optical brighteners are examined directly under the microscope raises the possibility of mucormycosis. The hyphae of these fungi are broad and non-septate. Specimens culture is generally advised for confirm diagnosis. The first line medication is high dose of (liposomal amphotericin B), whereas the novel oral antifungal posaconazole is recommendable to step down or salvage therapy after initial treatment by amphotericin B [40]. Postpone treatment by (amphotericin B) significantly raises mortality [41]. Fast surgical debridement is still the cornerstone of improved survival chances [40,41]. Just few studies have shown that nutraceuticals may be useful in treatment of COVID19. Natural compounds curcumin, nimbin, berberine, andrographolide, withaferin A, gallic acid, mangiferin, piperine, theaflavin, zingiberene, luteolin, quercetin, resveratrol, and naringenin bind to the ACE-2 receptors and block [SARS CoV2] viral attachment to the host cell [42]. The spices' anti-inflammatory activities could be used for decrease storm of cytokine in COVID19 patients. Diet might be able to reduce inflammation, while nutraceuticals might be able to prevent viral invasion. Dietary nutraceuticals can be used as an extra measure in the administration of CAM [42].

## 6. Potential mucormycosis action among patients of COVID-19

COVID-19 is characterized by an increase of body temperature, hypoxia breathlessness and osmolarity [43]. Recently, COVID-19 healed individuals were

already afflicted with a novel disease known as (mucormycosis). It is fungal disease might readily infect lungs & sinuses before spreading to the intracranial and intra-orbital regions of the body [44]. The major clinical manifestations of COVID19 provide an ideal environment allowing Mucorales to grow & develop within the human body. Patients with neutropenia, Diabetics, hematologic malignancies, people on systemic corticosteroids use, hematologic malignancies, immunocompromised persons and stem cell transplant patients, are all susceptible to mucormycosis [45]. According to reports, patients with diabetes seem to be more likely to get COVID-19 and become infected with mucormycosis [46]. Diabetes may increase COVID-19 morbidity and mortality by the following mechanisms: 1- reduction in T-cell activity, 2- decreased viral clearance 3- immune-suppression, and 4- increased storm of cytokine [20]. With COVID19 patients, hyperglycemia exacerbates cytokine storm via deactivating (endothelial cells), resulting in multi organ damages. The acidic environment and increased amounts of unbound (free) ferric ions promote development of (Mucorales) during diabetic ketoacidosis. These conditions encourage the invasion & effective attachment of hyphae of Mucorales within the body. People suffering from (chronic diabetes) who have ulcers of foot be predisposed to this disease because anything damaged tissue of skin provides easy entrance point of these fungi. Furthermore, COVID19 treatments are now in its early stages [47], so to reduce the impact of (SARS-CoV 2) disease, patients must given high doses of corticosteroids, which decreases inflammation of lungs and may minimize the effects caused by the storm of cytokine. In the meantime, individuals infected by novel strains of COVID19 are typically treated by high doses of (steroids), as well as extensive utilize of ventilators & oxygen masks, making them most susceptible for mucormycosis. (Steroids) decrease immune system activity & inflammation, in which generation of T-helper cells & WBCs is reduced, allowing harmful material to invade that totally destroy immune system of host cells. Furthermore, steroids may cause an unregulated release of sugar, allowing Mucorales for growth, multiply, and invading at a faster rate. Only a few case studies on the impact of (mucormycosis) on COVID19 patients have been reported. As a consequence, these probable mechanisms have been identified based on the points and information supplied via many scientists, where the reasons mentioned above may be prospective causes of Mucormycosis development in COVID 19 healed or affected individuals [32].

## 7. Conclusion

This fungal infection seems to be life threatening because it arises in people with diabetic ketoacidosis, immuno-suppression, elevated serum iron levels, neutropenia, and excess sugar release due to steroid overuse, which leads to a reduction in T-cells, white blood cells as well as immuno-modulatory cells and stimulates the cytokine storm which destroy the organ systems. As a result, healthcare practitioners & scientists must act quickly to manage the mucormycosis disease via studying its own impact and severity spectrum, particularly in COVID-19 patient populations.

## List of abbreviation

CAM	COVID19 associated Mucormycosis
DM	Diabetes mellitus
ACE2	Angiotensin Converting Enzyme 2
Spo2	Blood Oxygen Saturation
AML	Acute myeloid leukemia

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