

A Brief Review on Mucormycosis

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Abstract: Across the country the COVID-19 cases continue to rise in an unproportional manner, and alarming the terror of a third wave exists. COVID-19 may not be the merely disaster we are at the risk of facing but hospitals across the country have been reported more than 200 cases of a mysterious infection called Mucormycosis (Black Fungus) affecting mostly COVID-19 patients. Mucormycosis is caused by a group of moulds called 'mucormycetes'. It is present in the air and infection occurs when immunity compromised patients inhales this impure air, which then spreads sinus cavities, lungs, and chest cavities. This review has been focused on symptoms, classification, causes and treatment therapies, diagnosis, and prevention of Mucormycosis.

Keywords: Causes, COVID-19, Mucormycosis, Prevention, Symptoms, Treatment.

1. Introduction

Mucormycosis (Black Fungus) is a typically highly deadly infection that occurs mainly in the patients with weak immunity. (Mark Tedder, 1994) The clinical manifestation usually related with mucormycosis are hematologic malignancies, renal failure, or diabetes mellitus. This disease also exist in rhinocerebral, pulmonary, disseminated, cutaneous (particularly burn wounds), and gastrointestinal mucormycosis. (Meyer RD, 1972) The increasing cases of mucormycosis in Covid-19 patients are widespread chiefly because of the increased use of steroids like dexamethasone, especially among diabetic patients. Not everyone is predisposed to the black fungus disease, but unchecked and unsupervised use of steroid therapies can often make matters worse even for non-risk patients. While it is not classified as an outbreak yet, the Indian Council for Medical Research, the government's main research organization, has released a set of guidelines to spot and treat mucormycosis.

2. Types of Mucormycosis

Rhinocerebral Mucormycosis: In these types of mucormycosis, fungi enter through the nose and first they infect the nasal sinuses after that they infect the brain. This is commonly occurs in patients with diabetes, Cancer, and patients who are recently underwent though transplantation. Rhinocerebral mucormycosis is also called zygomycosis, which is a uncommon disease caused by filamentous fungi concerning the nose, paranasal sinuses, and brain. It is caused by saprophytic fungi of the class Phycomycetes, order Mucorales, and the family Mucoraceae. These fungi include *Mucor*, *Rhizopus*, *Absidia*, *Cunninghamella* genera, and *Apophysomyces elegans*. Rhinocerebral form is the most frequent form of mucormycosis in the United State. The uncontrolled diabetes is the most common cause of mucormycosis in India.

Pulmonary Mucormycosis: In these fungi infect the lungs of host. This is commonly associated with patients having blood cancer and patients who are recently underwent though transplantation. Pulmonary mucormycosis is the

second most common type of this disease. It is an opportunistic angioinvasive fungal infection.

Cutaneous Mucormycosis: In these types of mucormycosis fungi penetrate the skin through cracks, cuts, scrapes, grazes, and various skin trauma, this happens with patients having good immunity.

Gastrointestinal Mucormycosis: In this type fungi attack GIT tract of the host and this occurs in children than adults, this is most prevalent in premature and low birth weight babies. Gastrointestinal mucormycosis is an extremely rare fungal infection caused by mold in the order Mucorales. It occurs predominantly in low birth weight infants, patients with diarrhea and malnutrition, and those receiving peritoneal dialysis; mortality is 85%. Prabudh Goe et al. reported the successful management of an immunocompetent child with gastrointestinal mucormycosis who responded to aggressive treatment with surgical debridement and antifungal agents (amphotericin B and colistin). The authos in this case study has concluded that the successful management of gastrointestinal mucormycosis requires a high index of suspicion, diagnostic evaluation and the prompt initiation of antifungal and surgical therapy. (Prabudh Goel, 2013)

Disseminated Mucormycosis: This infection spreads all over the body through systemic circulation, so, affects brain and most of the vital organs like heart, spleen, and skin also get affected, this prevalence in neutropenic patients. Disseminated cutaneous mucormycosis should be considered as a differential diagnosis in all immunocompetent patients, particularly individuals with hematologic malignancies or a history of voriconazole (VRC) use, who present with cutaneous ulcerations and eschars. (Victoria S Humphrey, 2020)

Symptoms and Causes of Mucormycosis:

Symptoms of this disease are depends on the part of the body affected due to fungus, the symptoms reported in literature are fever, cough, chest pain, shortening in breath, sinus congestion, swelling on face, headache, belly pain, nausea and vomiting, diarrhea, blood in stool, eyes infection, etc. (Pathak, 2021) Mucormycosis is caused by a group of

moulds called 'mucormycetes'. It is present in the air and infection occurs when immunity compromised patients inhales this impure air, which then spreads sinus cavities, lungs, and chest cavities. (Kanetkar, 2021)

Symptoms of rhinocerebral (sinus and brain) mucormycosis:

One-sided facial swelling, Headache, Nasal or sinus congestion, Black lesions on nasal bridge or upper inside of mouth that quickly become more severe, Fever. (Petrikos, Skiada, Lortholary, Roilides, Walsh, & Kontoyiannis, 2012)

Symptoms of pulmonary (lung) mucormycosis:

Fever, Cough, Chest pain, Shortness of breath. Cutaneous (skin) mucormycosis can look like blisters or ulcers, and the infected area may turn black. Other symptoms include pain, warmth, excessive redness, or swelling around a wound. (Lewis & Kontoyiannis, 2013)

Symptoms of gastrointestinal mucormycosis:

Abdominal pain, Nausea and vomiting, Gastrointestinal bleeding.

Disseminated mucormycosis typically occurs in people who are already sick from other medical conditions, so it can be difficult to know which symptoms are related to mucormycosis. Patients with disseminated infection in the brain can develop mental status changes or coma. (Ribes, Vanover-Sams, & Baker, 2000)

The Indian Council of Medical Research has advised the people that during or after COVID-19 treatment if anyone have the blocked nose then should not consider it as case of bacterial sinusitis but one must seek medical help for detecting fungal infection.

Diagnosis and Treatments of Mucormycosis

Rapid diagnostic methods include biopsy, KOH mount and Calcofluor stain. Mucor is difficult to routinely culture. Biopsy remains the mainstay of diagnosis and the benefits of the procedure outweigh the risk, even in a 'difficult to access' location or in the presence of coagulopathy. (Rajeev Soman, 2021)

Mucormycosis is a serious infection and needs to be treated with prescription antifungal medicine, these antifungal agent administered by orally and intravenously. Typically amphotericin B administered intravenously and posaconazole, or isavuconazole are administered both orally and intravenously. Drugs like fluconazole, voriconazole, and echinocandins, do not work against fungi that cause mucormycosis. (Bacharach, 2021) Often, mucormycosis requires surgery to cut away the infected tissue. Azithromycin which many patients still continue to receive. Surgical debridement, the earlier the better, is pivotal in the management of mucormycosis. The optimal time of surgery to reduce the operative risk to the patient with COVID-19 and the risk of transmission to the operating team is a contentious issue. Replication competent virus has not been recovered from patients with mild to moderate illness after ten days, from patients with severe illness after fifteen days or from any critically ill patient after twenty days. (Preinssl J,

2019) Adjuvant therapy with caspofungin, deferasirox, statins, aspirin, and hyperbaric oxygen may have to be considered. Mucormycosis needs to be actively managed by a team which includes members from almost all departments in the hospital. Therapy is toxic and very resource intensive. In a recent Indian study, 24.3% patients left the hospital against medical advice due to the anticipated cost, morbidity of surgery and prognosis. (Kathy H, 2020)

Amphotericin B

Amphotericin B is a polyene antifungal antibiotic produced by *Streptomyces nodosus*, with antifungal activity. Amphotericin B binds to ergosterol, an essential component of the fungal cell membrane, thereby causing depolarization of the membrane and altering cell membrane permeability. (Sneha Gurudevan, 2018) This leads to leakage of important intracellular components, cell rupture, and eventually cell death. This agent may also induce oxidative damage in fungal cells and has been reported to stimulate host immune cells. Amphotericin B is used to treat the Covid-19 patients who are now suffering from Mucormycosis, commonly known as 'black fungus'. It is usually injected into the vein of the patient suffering from Mucormycosis. The doses per day range from four to six depending on the weight of the patient. The treatment goes on for 21 days for some patients.

Posaconazole

Posaconazole (Noxafil®) is a systemic triazole antifungal drug derived from itraconazole and exerts the same antifungal mechanism of action as other azole derivatives. (H, 2006) It is available in oral suspension (40 mg/mL), a delayed-release tablet (100 mg), and an intravenous formulation (18 mg/mL).

Apart from the promising in vitro activity against Mucorales species, posaconazole also showed potential for preventing neutropenic mice from pulmonary mucormycosis by *Rhizopus delemar*, (Barchiesi F, 2007) and disseminated mucormycosis by *Lichtheimia corymbifera* or *R. arrhizus*. When posaconazole is used for treatment of mucormycosis, an AUC₀₋₂₄/MIC ratio of 63 proved to be the target that was associated with half-maximal effect of lung fungal burden based on a neutropenic murine model of pulmonary mucormycosis infected with *R. arrhizus*. Unfortunately, no controlled, adequately powered clinical efficacy trial is available to confirm this finding in humans. In clinical practice, the posaconazole suspension has been used as salvage therapy of mucormycosis and showed satisfactory efficacy in many cases, (van Burik JA, 2006)

Isavuconazole

Isavuconazole is the newest azole antifungal approved that comes as the salt formulation isavuconazonium. The United States Food and Drug Administration approved isavuconazole in March of 2015 for the treatment of invasive aspergillosis and invasive mucormycosis. Isavuconazole is available as an oral and intravenous formulation. (Ruth Van Daele, 2019) The intravenous formulation is available without a cyclodextrin-solvent ingredient, which may be more favorable compared to voriconazole and posaconazole intravenous, which do contain this ingredient. Not having this solvent is an

advantage because although the clinical data do not suggest accumulation of cyclodextrin-solvent results in acute kidney injury caution is advised in patients with decreased renal function. Isavuconazole has a broad spectrum of activity including most yeast species, *Aspergillus* species, and mucormycosis. Oral bioavailability is good at approximately 98%. The drug is mostly metabolized via the liver and is a substrate of and mild to moderate inhibitor of CYP3A4 which does result in some drug–drug interactions, similar to the other azole antifungals. (Matt Shirley, 2016)

COVID-19 and Fungal Infections

Patients hospitalized for COVID-19 are at risk for healthcare-associated infections (HAIs), including candidemia, or bloodstream infections caused by *Candida*. (Hughes S, 2020) Fungal infections resistant to antifungal treatment have also been described in patients with severe COVID-19. (Meijer EFJ, 2020) Early diagnosis and monitoring for *Candida* infections and antifungal resistant infections (e.g., *C. auris*, azole-resistant *Aspergillus*) are key to reducing death from COVID-19 in patients with severe COVID-19 fungal coinfections. Other fungal diseases, such as Valley fever (coccidioidomycosis), histoplasmosis, and blastomycosis, can cause fever, cough, and shortness of breath, similar to COVID-19 and bacterial pneumonias. (Benedict K, 2020) These fungi live in soil. People become infected by breathing in fungi present in the air. Clinicians should consider fungal pneumonias as a possible cause of respiratory illness, particularly if COVID-19 testing is negative. It is important to note that these fungal diseases can occur at the same time as COVID-19.

3. Conclusion

Mucormycosis is an increasingly widespread infection in immunocompromised patients. At present current therapy for mucormycosis includes combination lipid-based amphotericin plus either an echinocandin or itraconazole or both. As well, compassionate-use posaconazole is currently available, and its potential for combination therapy with a polyene, caspofungin, or both is meritorious for study. In the future, novel drug therapy may be discovered as an adjunct to standard antifungal therapy. Finally, prompt diagnosis, reversal of predisposing conditions, and aggressive surgical debridement remain cornerstones of therapy for this deadly disease.

4. Conflict of Interest

The authors have reported no conflict of interest

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