



A COMPREHENSIVE REVIEW ON *MUCORMYCOSIS* IN COVID-19 PATIENTS IN INDIA

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ABSTRACT

In the present scenario of COVID-19 pandemic and the second wave of COVID-19 spread in India, nearly 9,000 peoples are infected with black fungus or *Mucormycetes* in India and 200 patients lost their lives. *Mucormycosis* is a fungal infection is caused by the *Mucormycetes* found in soil and organic materials. Though it is not contagious, it is present in atmosphere. It has been observed that the reduced immunity due to COVID-19 infection and excess use of steroids in the treatment of COVID -19 are the main reason of causing black fungus and so it infects the diabetic patients. *Mucormycosis* is serious infection treat with the help of medication or by the removal of infected tissue by doing surgery. It is considered as a dangerous infection as it spreads throughout body at high-speed causing serious damages like fever, redness around the eyes, nose etc. If it is left untreated, the infection can spread to the lungs or the brain. This can cause: a brain infection, paralysis, pneumonia, seizures, death. The infection Though there are different scopes of its management like Amphotericin B, etc. better treatment medications are yet to be revised in a systematic research. In the present article a detailed highlight on the occurrence of black fungus and its pathophysiology has been elaborated along with its management prospects.

KEYWORDS: COVID- 19, black fungus, *Mucormycosis*, diabetes, Amphotericin B.

INTRODUCTION

The Corona virus Disease 2019 (COVID-19) epidemic caused by the novel corona virus (SARS-CoV-2) a worldwide outbreak in many countries and regions, currently, is a major challenge to global public health, and seriously endangering the economy and the society. SARS-CoV-2 is a novel beta corona virus with unknown causal agent. It is primarily transmitted from human-to-human through respiratory droplets and close contact. The COVID-19 has an incubation period of 1–14 days before the onset of symptoms, and asymptomatic patients can also be a carrier of infection.^[1]

Recently during the second wave of COVID-19 in India, the human infected by the COVID-19 are more prone to infected by the black fungus. First case of black fungus was seen in December 2019. Black fungus infection is also known as *Mucormycosis* or *Zygomycosis*, which is the sever fungal infection caused by *Mucormycetes* i.e, the group of moulds. They can be found in various places like soil and other organic materials (leaves, plants, and decaying fruits and vegetables, etc).^[1] It causes by inhaling fungal spores from the atmosphere and damages the lungs. It also happens because of skin injury.^[2] It has been observed that nearly 9,000 peoples are infected with black fungus or *Mucormycetes* in India and 200 patients lost their lives The moulds enter into the

body and then manifests around the nose and eye sachets, cause nasal blockage. Healthy person will fight from the fungus but it spread fast in those who have less immunity. It is prevalent in people with diabetes or those who are on immunosuppressant drugs, steroids or are undergoing chemotherapy that weakens the body's immunity and makes it unable to fight germs and viruses. The diabetics, COVID-19 patient and people on long use of steroids are at higher risk of contracting fungal infection. Doctors have also warned that delay in treatment can cause death. It has been observed that *Mucormycosis* mainly affects the face, nose eye orbit, and brain, lungs. The present review is aimed at to highlight the pathophysiology, prevention, treatment of *Mucormycosis* to update its present scenario in India. It will be beneficial for further research to get better treatment for *Mucormycosis*.

Pathophysiology of *Mucormycosis*

There are 261 species in 55 genera out of these 38 have been associated with human infection, current nomenclature of important Mucorales species is *Lichtheimia corymbifera*, *Lichtheimia ornate*, *Lichtheimia ramosa*, *Mucor ardhlaengiktus*, *Mucor griseocyanus*, *Mucor irregularis*, *Mucor janssenii*, *Mucor lusitanicus*, *Rhizopus microporus*, *Zucorale arrhizus* is most common species.^[3,4]

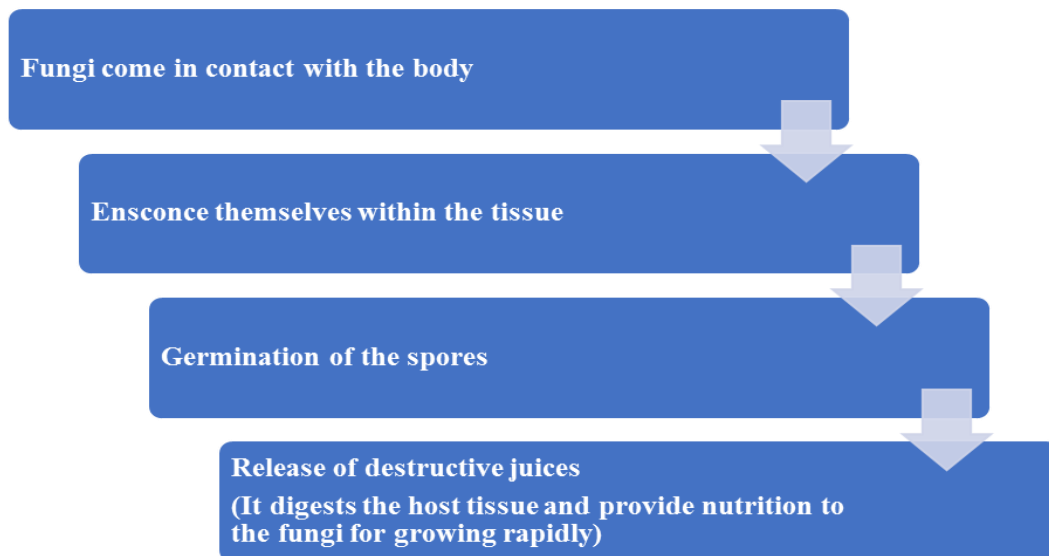


Figure 1: Pathophysiology of *Mucormycosis*.

The bones of the nasal cavity and sinuses in nasal cavity are destroyed. Gradually black masses are seen in the nasal and oral cavity. If the orbit destroys, they enter the eye socket and cause bulging of the eyes, frozen eye movement, pin and blindness. They also enter the cranial cavity by breaching, the skull base. They block arteries and veins resulting in life threatening cause brain strokes. Spores sometimes enter into the respiratory system, fungi grow rapidly, and start destroying lung tissue and then they spread into circulatory system.^[4]

Reasons behind *Mucormycosis* in COVID-19 patient

It has been observed that *Mucormycosis* can cause anytime even after COVID-19 infection. COVID-19 infection destroy the airway mucosa and blood vessels and it also increase the serum iron which helps the fungus to grow. Severe COVID-19 is currently managed with systemic glucocorticoids increase the blood sugar. Broad spectrum antibiotics not only kill the pathogenic bacteria but also the produce commensals. Antifungals like voriconazole, it inhibits the aspergillosis, but the mucor remains unharmed. The long use of ventilation reduces the immunity and therefore the fungus being

transmit from the humidifier water given along with the oxygen.^[5]

Symptoms of *Mucormycosis*

When immunity of body is weak, then it is easier for the pathogen to enter the body. Some early symptoms are: fever, redness around the eyes and nose, double vision, vomiting. The earliest sign of infection is persistent headache. One sided swelling of face is another symptom as black fungus infection can cause selling on face which is followed by localised pain. Along with these black fungi can cause the formation of black crusts on the nose and discolouration of the face which is also included as one of the most prominent symptoms of *Mucormycosis*. Nasal blockage is also one symptom which cannot be avoided as the fungus transmits along the sinus passage and nasal cavity sometimes also affects the lungs. It may also cause chest pain, cough, shortness of breath. *Mucormycosis* is particularly dangerous because it spreads quickly throughout the body. Left untreated, the infection can spread to the lungs or the brain. This can cause a brain infection, paralysis, pneumonia, seizures and even death.^[5]

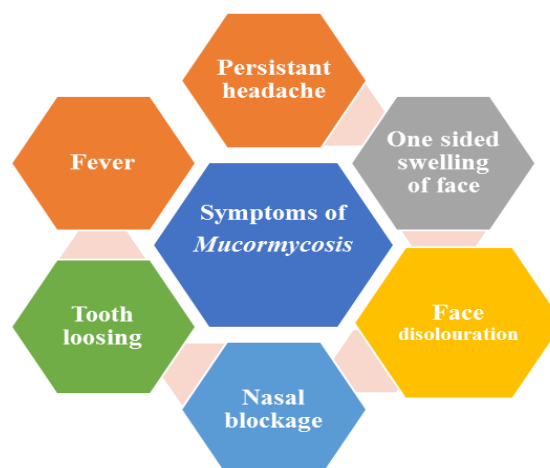


Figure 2: Symptoms of *Mucormycosis*.

Prevention of *Mucormycosis*

Mucormycosis isn't contagious, it can't be transmitted from an infected person. Self-care measures are the best way to prevent this type of infection. With weakened immune system, it's important to keep themselves safe outdoors. Wearing a mask while doing yardwork and bandaging all wounds until they heal will help prevent fungal infections. Extra precautions are to be taken during the summer and autumn months, when there's an increased amount of the fungi in the environment.^[6]

Diagnosis of *Mucormycosis*

The *Mucormycosis* diagnosis involve clinical diagnosis, routine laboratory diagnosis processes like histopathology, direct microscopy, culture applied and emerging molecular methods and serology metabolomics breath test. Histopathology: this diagnosis based on the demonstration of fungal hyphae. It is a important tool of diagnosis.^[6]

Mucorals species produce non- pigmented, 5-20 micrometer wide, thin walled and ribbon like hyphae, right angle branching.^[7] *Aspergillus* species are 3-5 micrometer septate and shows acute angle branching. Routine hematoxylin stains shows only cell wall, having no structure. Stains used to highlight the fungal wall are Grocott- methenamine- silver (GMS) and periodic-acid-schiff. It gives better visualization than GMS.^[6]

Direct Microscopy: This method is used for the rapid determination of *Mucormycosis*. In these fluorescent brighteners are used such as blankophor and calcofluor with KOH. It increases the visualization of characteristics fungal hyphae, this is done by using fluorescent microscope. It is an expensive process.^[9]

Culture: it is an essential process of diagnosis the specimens of *Mucormycosis*. This method is used for the identification of genus and species. Mucorales are thermotolerant, they can grow early at temperature 37°C. Mucorales are grow on carbohydrate substrate, within 24- 48 hrs colonies start appearing and the identification is based on colonies and microscopic morphology.^[8] Sometimes culture method is low sensitive. It gives negative result up to 50% cases of *Mucormycosis*. This is due to the number of reasons such as grinding of tissues specimen, which lead to destroy the hyphae of *Mucormyctes*.^[9]

Molecular methods: It is a very useful method for the confirmation of infection and identification of stains. Several methods have been developed like – PCR based techniques, real – time PCR, PCR combined with RFLP^[10], PCR coupled with electrospray ionization mass spectroscopy (PCR/ESI-MS),^[11] and PCR / high resolution melt analysis (HRMA).^[12] Target gene is kept at rDNA, ITS.

Serology: There are different serology methods available for the diagnosis of *Mucormycosis*. These include Mann

and antimann IgG test, CACTA test, BDG test, ELISA test.^[12]

Treatment of *Mucormycosis*

Mucormycosis is serious infection treat with the help of medication or by the removal of infected tissue by doing surgery.^[13] Antifungal drug Amphotericin B is used in the treatment of *Mucormycosis* and some other drugs like triazoles (voriconazole, Posaconazole, itraconazole, fluconazole). Amphotericin B produced in limited quantity in the country. This drug is not used in the treatment of minor fungal infection. It is obtained from streptomyces nodosus having antifungal property.^[14]

Amphotericin B drug is normally injected into the vein and single dose of drug is given daily to the patient of *Mucormycosis*. Amphotericin B acts by bind with fungal cell membrane ergosterol. Other medicines, including fluconazole, voriconazole, and echinocandins, do not work against fungi that cause *Mucormycosis*. In recent years, numerous new options for the treatment of *mucormycosis* have become available. Lipid formulations of amphotericin are currently the preferred first-line treatment for *mucormycosis*, with a possible preference for liposomal amphotericin for CNS infection. The possibility of combination therapy with lipid amphotericin B and an echinocandins or iron-blocking strategy merits additional investigation.^[14]

Proinflammatory cytokines, such as interferon (IFN)- γ and granulocyte-macrophage colony-stimulating factor (GM-CSF), enhance the ability of granulocytes to damage the agents of *Mucormycosis*.^[15] Adjunctive immune therapy with recombinant granulocyte colony-stimulating factor (G-CSF) and GM-CSF, or with recombinant IFN- γ , has been used successfully in conjunction with lipid formulations of amphotericin B in treatment of *Mucormycosis*.^[16,18]

Often, *Mucormycosis* requires surgery to cut away the infected tissue.^[19] The extent and timing of surgical debridement necessary to maximize outcomes of *Mucormycosis* has never been defined. The use of calcofluor fluorescence microscopy has also been reported to increase the sensitivity of frozen sections for guiding extent of surgical revision.^[20]

CONCLUSION

As per the present study *Mucormycosis* is the fungal infection cause by *mucormyctes*, found to targeting mainly COVID-19 patients which may be due to the declined immunity and increased plasma sugar content due to the use of corticosteroids. After observing its main symptoms, its quick diagnosis is essential for reaching a confined treatment profile due to its severity. As the present article showed its severity that it may need surgical removal of the infected tissues though it can be treated by using medication of some antifungal drugs, like Amphotericin B, posaconazole, deferasirox and adjunctive cytokine therapy. Underlying all successful

antifungal use is the need to reverse underlying host defects predisposing to infection, surgically debride necrotic tissue whenever possible, and make an early diagnosis to facilitate rapid initiation of antifungal therapy. This study may be helpful in getting better management profile for *Mucormycosis* by profound and systematic research on this field which will be beneficial for the field of medicine and for socio-economic benefits.

REFERENCES

- Richardson M. The ecology of the Zygomycetes and its impact on environmental exposure. *Clin microbial infect*, 2009; 15Suppl(5): 2-9.
- Kanamori H, Rutala WA, Sickbert- Bennett EE, et al. Review of fungal outbreaks and infection prevention in healthcare settings during construction and renovation. *Clin Infect dis.*, 2015; 61(3): 433-444.
- <https://indianexpress.com/article/lifestyle/health/mucormycosis-why-are-covid-19-patients-being-affected-by-black-fungus-7321627/lite/>.
- Walther, G.; Wagner, L.; Kurzai, O. Updates on the taxonomy of Mucorales with an Emphasis on Clinically Important Taxa. *J. Fungi*, 2019; 5: 106.
- <https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/black-fungus-recovering-from-covid-19-watch-out-for-these-signs-of-mucormycosis/photostory/82944896.cms>.
- Guarner, J.; Brandt, M.E. Histopathologic Diagnosis of Fungal Infections In the 21st Century. *Clin. Microbiol. rev.*, 2011; 24: 247-280.
- Ribes, J.A.; Vanover-Sams, C.L.; Baker, D.J. Zygomycetes in human disease. *Clin. Microbiol. Rev.*, 2000; 13: 236-301.
- Walsh, T.J.; Gamaletsou, M.N.; McGinnis, M.R.; Hayden, R.T.; Kontoyiannis, D.P. Early Clinical and Laboratory Diagnosis of Invasive Pulmonary, Extrapulmonary, and Disseminated Mucormycosis (Zygomycosis). *Clin. Infect. Dis.*, 2012; 54: S55-S60.
- Cornely, O.A.; Alastruey-Izquierdo, A.; Arenz, D.; Chen, S.C.A.; Dannaoui, E.; Hochhegger, B.; Hoenigl, M.; Jensen, H.E.; Lagrou, K.; Mucormycosis: An initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect. Dis.*, 2019; 19: e405-e421.
- Zaman, K.; Rudramurthy, S.M.; Das, A.; Panda, N.; Honnavar, P.; Kaur, H.; Chakrabarti, A. Molecular diagnosis of rhino-orbito-cerebral mucormycosis from fresh tissue samples. *J. Med. Microbiol.*, 2017; 66: 1124-1129.
- Alanio, A.; Garcia-Hermoso, D.; Mercier-Delarue, S.; Lanternier, F.; Gits-Muselli, M.; Menotti, J.; Denis, B.; Bergeron, A.; Legrand, M.; Lortholary, O.; et al. Molecular identification of *Mucor* in human tissues: Contribution of PCR electro-spray-ionization mass spectrometry. *Clin. Microbiol. Infect.*, 2015; 21: 594.e1-594.e
- Lengerova, M.; Racil, Z.; Hrnčirova, K.; Kocmanova, I.; Volfova, P.; Ricna, D.; Bejdak, P.; Moulis, M.; Pavlovsky, Z.; Winbergerova, B.; et al. Rapid detection and identification of Mucormycetes and bronchoalveolar lavage samples from immunocompromised patients with pulmonary infiltrates by use of high-resolution melt analysis. *J. Clin. Microbiol.*, 2014; 52: 2824-2828.
- <https://www.financialexpress.com/lifestyle/health/mucormycosis-or-black-fungus-doctors-explain-causes-symptoms-treatment-and-precautionary-measures/2259892/>
- Brad, S.; Ashraf S. I. Recent Advances in the Treatment of Mucormycosis. *Curr. Infect. Dis. Rep.*, 2010; 12: 423-429.
- Gil-Lamaignere C.; Simitopoulou M.; Roilides E.; et al. Interferon- gamma and granulocyte-macrophage colony-stimulating factor augment the activity of polymorphonuclear leukocytes against medically important zygomycetes. *J. Infect. Dis.*, 2005; 191: 1180-1187.
- Abzug M.J.; Walsh T.J.; Interferon-gamma and colony-stimulating factors as adjuvant therapy for refractory fungal infections in children. *Pediatr. Infect. Dis. J.*, 2004; 23: 769-773.
- Gonzalez C.E.; Couriel D.R.; Walsh T.J.; Disseminated zygomycosis in a neutropenic patient: successful treatment with amphotericin B lipid complex and granulocyte colony-stimulating factor. *Clin Infect Dis.*, 1997; 24: 192-196.
- Kullberg B.J.; Anaissie E.J.; Cytokines as therapy for opportunistic fungal infections. *Res Immunol.*, 1998; 149,478-488: discussion 515.
- Roden M.M.; Zaoutis T.E.; Buchanan W.L.; et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin. Infect. Dis.*, 2005; 41: 634-653.
- McDermott N.E.; Barrett J.; Hipp J.; et al. Successful treatment of periodontal mucormycosis: report of a case and literature review. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.*, 2010; 109,e64-e69.