

COVID19 associated mucormycosis: A review

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ABSTRACT

Mucormycosis, a rare fungal disease has emerged as a new epidemic in India, during the CoronaVirus Disease 2019 (COVID-19) pandemic. Mucormycosis is caused by the mucormycetes group of molds. Immunocompromised states such as diabetes, chronic steroid use, and patients receiving immunosuppressant drugs are the risk factors for mucormycosis. The second wave of the COVID-19 pandemic has also invited the notorious mucormycosis in the current scenario. India has announced mucormycosis as a notifiable disease in May 2021, as the number of COVID-19-associated mucormycosis cases has increased swiftly. There are different opinions and evidence for the emergence of mucormycosis or the so-called 'black fungus'. It is proposed that the use of steroids, monoclonal antibodies, and prolonged hospitalization in the treatment of COVID-19 has substantially decreased the immunity in COVID-19-affected patients and maybe the reason for the emergence of fungal infections. The other hypothesis is that improper disinfection procedures such as using non-sterile water for humidification of oxygen can be the reason. Or, the COVID-19 infection itself produces an immunocompromised and diabetic-like state is again a question. This review mainly focuses on the discussion and identification of the most common risk factor for mucormycosis, investigations, and management of mucormycosis.

Keywords: Amphotericin B, COVID-19, fungal infection, mucormycosis, rhino cerebral

Introduction

The fungal infection mucormycosis also known as zygomycosis is caused by the molds named mucormycetes. The fungi survive throughout the environment like soil, manure, decaying plants, and leaves. The organism is widely distributed so people are exposed to its spores very frequently. The infection mainly affects the brain, sinuses, and lungs. The various forms of mucormycosis include disseminated, rhinocerebral, pulmonary and cutaneous, and renal mucormycosis.^[1] The most vulnerable population affected with fungal infections are steroid use patients, diabetic patients, immunocompromised patients, patients with hematological malignancies, and solid organ transplant patients.^[2] Recently, it was identified that there is an intertwined relationship between

COVID-19 and mucormycosis. The early identification at the primary care level and monitoring blood sugar levels can help fight the occurrence of mucormycosis. The risk factors for mucormycosis in the COVID-19 patients is the current debate in treating the COVID-19 infection. This review mainly focuses on the discussion and identification of the most common risk factor for mucormycosis, investigations, and management of mucormycosis.

Mucormycosis in India before COVID-19

The annual incidence of mucormycosis in India rose from 12.9 cases in the years 1990–1999 to 89 cases in the years 2013–2015. In Southern India alone, the number of cases was 18.4 per year in the years 2005–2015. The estimated prevalence of mucormycosis in India is 70 times ahead of the global prevalence which is 0.02–9.5 cases per 1,00,000 people.^[3]

The percentage of the contribution of the risk factors to mucormycosis in India before the beginning of COVID-19 [Table 1].

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Table 1: The percentage of the contribution of the risk factors to mucormycosis in India before the beginning of COVID 19

Risk factors	Percentage
Hematological malignancy	1-9%
Solid organ transplantation	2.6-11%
Immunocompetent host	2.6-11%
Trauma	7.5-22%
Intramuscular injection in COVID-19	-

The other underlying causes that predispose to mucormycosis are chronic kidney disease, treatment with corticosteroids, other immunosuppressant drugs, tuberculosis, Human Immunodeficiency Virus (HIV), and malnutrition.

Mucormycosis due to COVID-19: Is It Due to the Disease or the Drug or Oxygen

Impact of COVID-19 in the pathogenesis of mucormycosis

The incidence of fungal infection in severe acute respiratory syndrome (SARS) 1 in 2003 was identified to be 14.8–27% and in severely ill ones was 27–33%.^[4] COVID-19 is caused by SARS2 virus and is a major pandemic that is transmitted from person to person and has resulted in significant mortality and morbidity. Chen *et al.*^[5] identified that about 5 out of 99 COVID-19 patients were positive for the fungal infection. The fungal culture specimens showed the presence of *Aspergillus flavus*, *Candida glabrata*, and *Candida albicans*. *Aspergillus* and *Candida* are the most common fungal infections identified in COVID-19 patients. *Mucor* and *Cryptococcus* are the other uncommon fungal infections that affect the lungs in COVID-19 patients. Yang *et al.*^[6] reported that the mortality among 52 critically ill patients out of 710 patients admitted at the Wuhan Jin Yin-tan hospital from December 2019 to January 26, 2020, with SARS 2 was higher compared to the SARS and Middle East respiratory syndrome infection. The fungal co-infections like *Aspergillus flavus*, *fumigatus*, and *Candida albicans* were identified in 5% of the 52 critically ill patients.

The reason for the fungal infections in COVID-19 is due to lymphopenia and immune-mediated changes. There is an abnormality in the number of granulocytes and monocytes. COVID-19 also damages the lung tissues and makes it more susceptible to fungal infections.^[7,8]

A study compiling the case report data of 41 COVID-19-associated mucormycosis patients identified that 94% of the patients had diabetes. An alteration of iron metabolism occurs in the COVID-19 infection. Diabetic ketoacidosis may induce ferritin synthesis and increase the intracellular concentration of iron. The autopsy performed in the COVID-19 patients showed vascular endothelial injury and new vessel formation.^[9]

John *et al.*^[9] have reviewed 41 case reports of COVID-19 and mucormycosis. Twenty-nine cases were reported from India.

Among the cases reported, 33 out of 41 were diabetic and 36 out of 41 were on steroids for the treatment of COVID-19. Sixteen patients presented with COVID-19 along with mucormycosis. Some patients neither on steroids nor having diabetic also developed mucormycosis, so COVID-19 itself can be a risk factor for mucormycosis.

There are a few proposed hypotheses that the COVID-19 infection itself can pave a pathway for mucor infection. Pandiar *et al.*^[10] have suggested that angiotensin-converting enzyme (ACE) 2-mediated injuries can cause multiple organ damage and leucopenia which result in an immunosuppressive state among the COVID-19 patients. The COVID-19 infection can produce lymphocytopenia, thrombocytopenia, and insulin-like state by damaging the lymphocytes and pancreatic beta cells directly.

Pharmacological perspective of the cause of the disease: Steroids

The use of steroids in the COVID-19 patients was based on the results from the randomized evaluation of Covid-19 therapy (RECOVERY) trial conducted in the United Kingdom. In severe COVID-19 patients with invasive ventilation, the mortality at 28 days was 29.3% versus 41.4% in dexamethasone and the standard of care treated patients, respectively.^[11] Steroids cause immunosuppression by inhibiting the transcription of the cytokine genes, especially IL1 and 6 and sequestration of CD4+ lymphocytes.

In the background of an immunosuppressive state like COVID-19 and diabetes, steroids have increased the risk of mucormycosis. Singh *et al.*^[12] have done a systematic analysis on 101 reported cases of COVID-19 and mucormycosis worldwide. Among the 101 cases reported, 76.3% of the patients were on steroids [Table 2].

Relationship between oxygen delivery and mucormycosis

The use of industrial oxygen in the place of medical oxygen due to the increasing demand for oxygen cylinders in COVID-19 management is proposed as one of the causes for mucormycosis. Industrial oxygen is completely different from medical oxygen and there is a high chance that the quality and hygiene of the oxygen gets compromised. The water that is used for the humidification of the oxygen may be also the source of the fungal spores which enter the lungs through the inhalational route. The use of hyperbaric oxygen is an adjunctive treatment for mucor infection.

In 2004, Nakipoglu *et al.*^[21] assessed the fungal and bacterial contamination of the humidifiers used in their intensive care unit. Fifty-four contaminants were isolated from 32 out of 50 oxygen humidifiers' water. Among the isolated contaminants, 46% were fungus and 30% were bacteria. Mucormycetes were not isolated from the contaminated water. It was found out that

Table 2: Comparison of risk factors and outcome of COVID-19-associated mucormycosis

Author	Year	Risk Factors	Description of Study	Type of Study	Inference
AK Singh	May 2021	Diabetes Steroids	Out of 101 cases reported, 81 people were affected in India	Systematic Review	Diabetes -80% contribution to COVID-19 mucormycosis risk Corticosteroid treatment -76.3% risk Predominant in males The triad of diabetes, steroid usage, COVID-19 increases the risk of mucormycosis ^[8]
Garg <i>et al</i>	February 2021	Diabetes CKD	A case of a 55-year-old man with COVID-19-associated pulmonary mucormycosis	Case Report	Patient was treated with liposomal amphotericin B and discharged from hospital after 54 days of admission ^[13]
Werthman-Ehrenreich A	September 2020	Diabetes (undiagnosed) Asthma Hypertension Broad-spectrum antibiotics	A 33-year-old woman presented with COVID-19 associated rhino-orbital-cerebral mucormycosis and DKA	Case Report	Patient was treated for DKA. Patient was given convalescent plasma and remdesivir for COVID-19. Sinus debridement and amphotericin B were given for mucormycosis. Patient died after 26 days of hospitalization. ^[14]
Mehta & Pandey	September 2020	Diabetes Systemic corticosteroids Broad-spectrum antibiotics Oxygen therapy and ventilator support	A 60-year-old man admitted for COVID-19, developed invasive rhino cerebral mucormycosis	Case Report	He was started with oxygen supplementation, systemic steroids, tocilizumab, meropenem, and oseltamivir. On day 10, he developed invasive rhino cerebral mucormycosis, kept on ventilator and amphotericin B. On day 16, patient died. ^[15]
do Monte Junior ES <i>et al</i>	November 2020	Hypertension Systemic corticosteroids Broad-spectrum antibiotics ventilator support	An 86-year-old male diagnosed with COVID-19 and gastrointestinal mucormycosis	Case Report	Patient was on mechanical ventilation, steroids, ceftriaxone & oseltamivir. On day 5, patient presented with abdominal tenderness and malena. Esophagogastroduodenoscopy revealed mucormycosis. Patient died on day 7 ^[16]
Mekonnen ZK	March 2021	Poorly controlled diabetes Hypertension Hyperlipidemia Asthma Systemic corticosteroids Broad-spectrum antibiotics ventilator support On home oxygen for 1 week before hospitalization	A 60-year-old man admitted for COVID-19 with invasive rhinosinusitis mucormycosis with angio invasion	Case Report	He was intubated and on systemic steroids, remdesivir, vancomycin, and cefepime, antifungal coverage with liposomal amphotericin B and caspofungin. Patient died on day 31 ^[17]
Sen M	February 2021	Diabetes Systemic steroids	COVID-19 with rhino-orbital sinusitis- mucormycosis	Case series	Out of the six cases reported, only one patient presented with COVID-19 concurrently with mucormycosis, others were patients on steroids. All received surgical debridement and liposomal AMP ^[18]
Ahmadikia <i>et al</i>	February 2021	Influenza-associated mucormycosis: Diabetes, influenza, steroids COVID-19-associated mucormycosis	Comparison of eight influenza-associated mucormycosis cases (IAM) vs. seven COVID-19-associated mucormycosis cases (CAM)	Influenza-associated mucormycosis case report followed by systematic review comparing IAM and CAM	Severity was 100% (7/7) in CAM compared to 75% (6/8) in IAM Rhino-orbito-cerebral mucormycosis is the common presentation with CAM whereas it is pulmonary-associated mucormycosis in IAM The fatality is more with COVID-19-associated mucormycosis compared to influenza-associated mucormycosis ^[19]
Revvanavar	April 2021	Diabetes	A middle-aged woman with non-ketotic diabetes presented with ophthalmoplegia COVID-19-positive was diagnosed as rhino-orbital mucormycosis. No steroid exposure	Case Report	Altered cell-mediated immunity in COVID-19 is the major reason for antifungal infection Immunosuppressive therapy should be prescribed judiciously in such patients ^[20]

the contamination occurred by adding sterile water to the water which is already present in the humidifier and also due to the use of non-sterile water. The study has recommended the use of single-use humidifiers for oxygen therapy.

In India, case overload in hospitals is one of the factors for improper disinfection of the instruments. Usage of non-sterile/tap water in humidifiers can increase the risk of mucormycosis among COVID-19 patients. Recently, the Indian Council of

Medical Research (ICMR) national task force for COVID-19 has recommended using clean, sterile water for humidifiers during oxygen therapy.^[22] The summary of the case reports published worldwide is presented in Table 2 and suggests diabetes and steroids possess the major risk factors for mucormycosis in the COVID-19 patients.

Mucormycosis –Notifiable Disease

On May 19, 2021, India announced mucormycosis as a notifiable disease under the Epidemic Diseases Act 1897. A notifiable disease is any disease that has to be informed to the government mandatorily so that government can collect, analyze the data, and formulate policies, sensitize the healthcare institute regarding the guidelines on the management and prevention of disease.^[23]

Investigations and Management

Fungal infection surveillance is preferred in critically ill patients. Investigations to identify the presence of fungal infections in severely immunocompromised individuals are the following:

- a. Microscopy and culture
- b. Serological tests
- c. Histopathology test
- d. Real-time PCR
- e. Antigen-antibody tests.

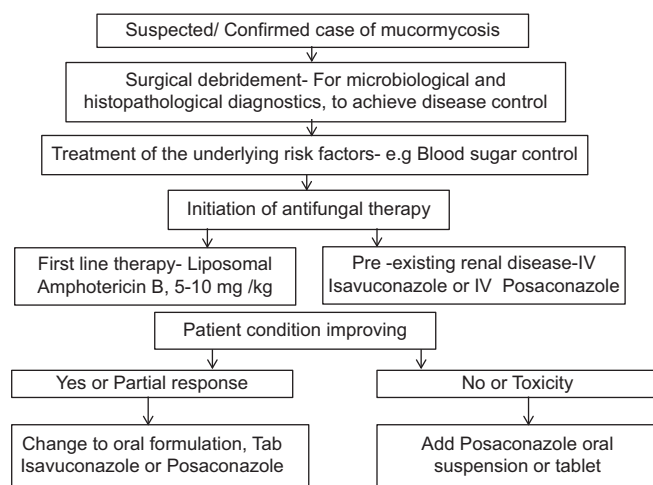


Figure 1: Management of mucormycosis according to ECMM/ MSG-ERC

Management: The European Confederation of Medical Mycology (ECMM) with the Mycoses Study Group Education & Research Consortium (MSG ERC) had developed comprehensive guidelines for the diagnosis and treatment of mucormycosis in 2019^[24] [Figure 1].

Polyenes and the azole group of drugs are the most preferred drug groups for the management of mucormycosis. The total duration of the antifungal therapy is customized for each patient [Table 3]. The antifungal therapy should be continued until a certain time point and that includes the following:

- The patient is relieved from the signs and symptoms of the disease
- The disappearance of residual radiological symptoms
- The underlying immunodeficiency is improved.

A UK-based study reported by Bagshaw *et al.* identified that the per-patient cost of mucormycosis treatment including hospital stay is costlier with the administration of drugs liposomal amphotericin + posaconazole when compared with isavuconazole.^[27]

Prevention and Care

ICMR has issued an evidence-based advisory for the screening and management of mucormycosis along with COVID-19. The preventive measures suggested by ICMR include

At the primary care level

- Look for the warning signs and symptoms of mucormycosis
- Suspect mucormycosis in cases of blocked nose or sinusitis in the context of immunosuppressive conditions and/or COVID-19 patients
- Blood sugar monitoring in patients with COVID-19 and diabetes mellitus, steroid therapy
- Taper steroids in post-COVID-19 patients on long-term steroid therapy
- Refer for appropriate investigation (Potassium hydroxide staining and culture)

For mucormycosis management,

- Do appropriate investigations as early as possible, as (KOH staining and microscopy, culture, MALDITOF), for the detection of fungal infection

Table 3: Comparison of antifungal drugs used in the treatment of mucormycosis:

Antifungal drug	Cost (in INR)	Safety	Efficacy
Amphotericin B	263.50-452.95 Cheaper	Highly nephrotoxic	Good efficacy but increased adverse effects
Liposomal amphotericin B	2847.61-7900.00 Costlier	Targeted drug delivery Safe compared to amphotericin B Minimal nephrotoxicity	Efficacy similar to amphotericin B
Isavuconazole	200 g vial 8500	Less adverse effect profile compared to amphotericin B Isavuconazole can be administered to patients with reduced renal function ^[25]	Efficacy similar to Amphotericin B Good tolerability and bioavailability
Posaconazole	300 mg/16.7 mL injection 5500-6500	Adverse effects are significantly less compared to amphotericin B lipid complex ^[26]	Erratic absorption Efficacy comparable to amphotericin B

- Initiate treatment for mucormycosis in appropriate time, do not delay the treatment

Out of the 116 cases analyzed [Table 2], 81.6% had diabetes and 86.6% had steroid treatment. It is important to look for signs and symptoms of mucormycosis in COVID-19 patients with these risk factors. But other than the two mentioned, oxygen therapy or the COVID infection itself can be a risk factor. Treating mucormycosis is far difficult than preventing it, so the physician should create awareness of mucormycosis in patients with the COVID-19 infection as well as the other health professionals.

Conclusion

The most common risk factors of the COVID-19-associated mucormycosis are diabetes followed by steroid usage and contaminated oxygen. Rhinocerebral mucormycosis is the most commonly manifested among diabetic COVID-19 patients rather than the pulmonary and gastrointestinal types. It is essential to look for any signs and symptoms of rhinocerebral mucormycosis in middle-aged diabetic patients who are diagnosed with COVID-19, because an early diagnosis may improve the prognosis. Steroid therapy should be used judiciously and the blood sugar levels should be kept under control in diabetic patients while treating the COVID-19 symptoms. The prevention of mucormycosis is easier compared to the treatment of the same.

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Conflicts of interest

There are no conflicts of interest.

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