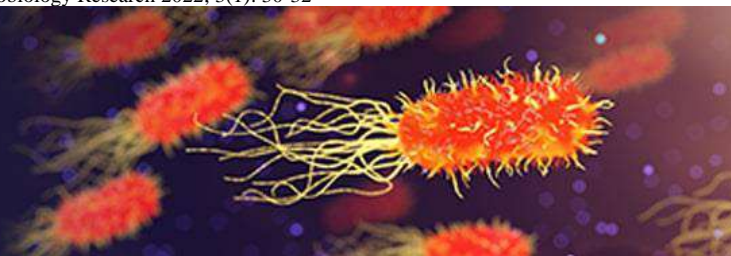


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Covid-19 associated mucormycosis in India: A review

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Abstract

Coronavirus disease Associated mucormycosis (CAM) is an emergence of opportunistic fungal infection, affecting many lives of patients suffering from COVID 19 along with other medical history. India is most suffered country as we belong to tropic and sub tropic areas where risk factor of such infections is already high. There are 6 types of mucormycosis according to the area of the body affected. This non contagious disease is mainly spread through the inhalation of spores which resides in humid areas, predominantly in hospitals and their treatment needs careful assessment of the factors like nature and effect of drugs and medical history of the patients.

Keywords: Mucormycosis, COVID 19, pandemic, India, diabetes, *Rhizopus*

Introduction

Now a days, novel coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2, also called COVID-19) has become global threat and have affected millions of people worldwide. Fungal infections, including mucormycosis, aspergillosis and invasive candidiasis, have been reported in patients with severe COVID-19 or those recovering from the disease and have been associated with severe illness and death. Mucormycosis was previously known as zygomycosis. According to WHO, mucormycosis is a serious but rare fungal infection caused by a group of molds called mucormycetes.

Mucormycosis, also known as black fungus is a filamentous fungal disease which is angioinvasive (Blood vessel infecting) caused by order Mucorales- class Zygomycetes, has become third most infective mycosis (Petrikos *et al.*, 2012; Prakash and Chakrabarti, 2021)^[10, 11]. Indian population is 80 times more affected by mucormycosis than whole world and central government has declared India as a mucormycosis pandemic on May 10, 2021. Mucorales fungi are very predominant pathogen which infects wide range of hosts, ranging from plants to invertebrates and humans. Most commonly found pathogen genus are *Rhizopus* (most common genus associated with mucormycosis), *Lichtheimia* (formerly known as *Absidia* and *Mycocladius*), and *Mucor*, zygomycetes genera (e.g. *Rhizomucor*, *Saksenaea*, *Cunninghamella*, and *Apophysomyces*). (Andrianaki *et al.*, 2013)^[1].

Based on the body parts affected, mucormycosis can be divided into 6 types-

- 1) Rhinocerebral
- 2) Pulmonary
- 3) Cutaneous
- 4) Gastrointestinal
- 5) Disseminated
- 6) Uncommon Presentations. (Petrikos *et al.*, 2012)^[10]

Patients with history of diabetes mellitus, organ transplant, kidney disease, tuberculosis, corticosteroids or immunosuppressants consumption, iron overload and trauma are at more risk of mucormycosis (Prakash and chakrabarty, 2021)^[11]. Mucormycosis majorly affect males than females and targets COVID 19 patients (Active or recovered both) along with others (Singh *et al.*, 2021)^[13].

Cam (Coronavirus disease associated Mucormycosis)

COVID-19, a global pandemic is showing significant incidence of secondary infections, bacterial and well as fungal as immune system is hampered. In regular circumstances, when we expose to the fungal spores our immune system respond in variety of ways, they doesn't allow them to settle down in our body and eradicates them, release of free oxygen radicles and phagocytosis is performed by the neutrophils, monocytes and macrophages.

In COVID-19 case, altered immune system cannot combat and this leads to the occurrence of opportunistic infections. As a treatment of variety of diseases, consumption of steroids/monoclonal antibodies/broad-spectrum antibiotics against COVID-19 may lead to the development/exacerbation of preexisting fungal diseases (Amod *et al.*, 2021; Mehta *et al.*, 2021)^[7].

Transmission of Mucormycosis

Mucormycosis is actually an opportunistic fungi, it cannot affect an individual until he is immunologically weakened. It is noncontagious, not spread from person to person. Spores of mucormycosis can be inhaled or swollen with air, food, etc. and it is more persistent in humid areas such as AC ducts, moist mask, hospital premises outbreaks are observed because of adhesive bandages, wooden tongue depressors, hospital linens, negative pressure rooms, water leaks, poor air filtration, non-sterile medical devices, and building construction, etc. They mainly colonize in nasal,

pharyngeal and oral mucosa including paranasal sinus. From paranasal sinus, it can transmit to nasolacrimal duct and medial orbit, even reaching upto skull and causes severe issues such as orbital cellulitis, chemosis, proptosis, loss of vision, ophthalmoplegia, superior orbital fissure syndrome, sagittal sinus thrombosis, epidural or subdural abscess formation. Sometimes, patient with bloody nasal discharge is diagnosed with the infection of mucormycosis to the brain via nasal turbinals causing cerebral ischemia which leads to cerebral infraction and also death. (Pagare sultan, 2021)^[8]. Zygomyces shows very high affinity to the blood vessels, shows rapid invasion and disseminate widely. (Kontoyiannis, 2012)^[6].

Rhizopus oryzae is mostly found causative agent of mucormycosis with a world-wide distribution and higher occurrence in tropical and subtropical regions. (Battaglia *et al.*, 2012)^[2].

Symptoms

According to WHO, different type of mucormycosis can be diagnosed by observing symptoms mentioned as follows

Sr. No.	Types of mucormycosis	Associated symptoms
1.	Rhinocerebral (sinus and brain) mucormycosis	<ul style="list-style-type: none"> • 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 • Lethargy, seizures, slurred speech, partial paralysis
2.	Pulmonary (lung) mucormycosis	<ul style="list-style-type: none"> • Fever • Cough • Chest pain • Shortness of breath • Hemoptysis
3.	Cutaneous (skin) mucormycosis	<ul style="list-style-type: none"> • Skin lesion that resembles blisters or ulcers. The infected area may turn black. Other symptoms include pain, warmth, excessive redness, or swelling around a wound.
4.	Gastrointestinal mucormycosis	<ul style="list-style-type: none"> • Abdominal pain • Nausea and vomiting • Gastrointestinal bleeding
5.	Disseminated mucormycosis	<ul style="list-style-type: none"> • Tends to occur in people who are already sick from other medical conditions, which makes it difficult to identify which symptoms are related to mucormycosis. Patients with disseminated infection in the brain may develop mental status changes or coma.

Clinical Diagnosis

Diagnosis of CAM can be done with routine laboratory diagnosis, in clinical practice, histopathology, direct examination of wet mounts and cultures, direct microscopy of culture along with non-invasive diagnostic methods such as molecular serology and metabolomics-breath test (Skiada *et al.*, 2020).

Treatment

Anti-fungal treatment along with supportive care is useful in the management of COVID-19. Glucocorticoids in combination with antiviral drugs such as Remdesivir are beneficial in COVID-19. Use of Glucocorticoids is inexpensive, easily available and reduces rate of mortality in patients. (Garg *et al.*, 2021)^[3] Treatment of mucormycosis needs an accurate and rapid diagnosis along with correction of predisposing factors, surgical resection or debridement, which will lead to effective anti-fungal therapy. Antifungal Agents such as Polyenes such as Amphotericin B deoxycholate (AmB), amphotericin B lipid complex and liposomal amphotericin B (LAmB) are useful in treatment

and Liposomal amphotericin B (LAmB) is most promising drug as it is safer, efficient alternatives to normal antifungals. Along with this, Azoles e.g. Fluconazole and voriconazole are effective against mucormycosis. Even itraconazole is also useful against *Absidia* species. Iron chelation therapy also holds promising approach in fight against mucormycosis (Jaju *et al.*, 2020; Spellberg *et al.*, 2009)^[14]. Here, physicians play an important role for the prevention of emergence of these CAM and other opportunistic pathogens and early diagnosis which can reduce mortality and morbidity rate significantly. Utilization of therapeutics with low dose for the short duration and minimum, needed use of broad-spectrum antibiotics (Mehta *et al.*, 2021)

Case Studies

Rammaert *et al.*, (2012)^[12] studied 169 cases with 29% children, 61% males. Patients were having history of solid organ transplantation (24%), diabetes mellitus (22%), and severe prematurity (21%). Most common prevalence of disease was found in skin (57%), followed by

gastrointestinal tract (15%). *Rhizopus* was the most common genus (43%) and infection portal of entry was included as surgery and presence of medical devices such as catheters or adhesive tape. Possible outbreaks can be related with use of adhesive bandages (19 cases), wooden tongue depressors (n = 5), ostomy bags (n = 2), water circuitry damage (n = 2), and adjacent building construction (n = 5). They suggest that to overcome such transmission, it is necessary to give a closer attention to avoid healthcare-associated mucormycosis, especially in neonatology, hematological, and transplantation units in hospitals.

Hosseini *et al.*, (2005)^[5] conducted a survey of ten patients with rhinocerebral mucormycosis between February 2000 to April 2004. Rhinocerebral mucormycosis along with Diabetes was the pathophysiology of nine out of ten patients. Analysis of factors such as predisposing factors, symptoms, sites of extension, number and sites of surgical debridement as well as outcome. Patients show ocular, sinonasal and facial soft tissue infection along with pterygopalatine fossa. Invasion does not occur through lamina papiracea or the maxillary sinus. Four patients lost their lives during study and causes were hypokalemia, cardiac arrhythmia and refractory pneumonia. Rhinocerebral mucormycosis was spread through the pterygopalatine fossa, and extends into the orbit and facial soft tissues. When mucor reaches to the nasal cavity, enters in pterygopalatine fossa, inferior orbital fissure and finally the retrobulbar space of the orbit, resulting in ocular signs. Other facial soft tissues, palate and infratemporal fossa can be infected through connecting pathways from the pterygopalatine fossa. Hence, debridement of the pterygopalatine fossa is a hope to minimize severity of mucormycosis.

Pal *et al.*, (2021) studied 30 case series, pooling data involving 99 patients with CAM. Maximum patients belongs to India (72%), majorly male (78%) and patients with history of diabetes mellitus (85%). History of COVID-19 was present in 37% patients with mucormycosis development after the recovery. Time period between diagnosis of COVID-19 and the evidence of mucormycosis infection (CAM) diagnosis was of 15 days, most commonly Rhino-orbital mucormycosis was most common (42%), followed by rhino-orbito-cerebral mucormycosis (24%) Pulmonary mucormycosis was observed in 10 patients (10%). Use of Glucocorticoids was found in 85% of cases and mortality rate was 34%.

Conclusion

This review mainly focuses on opportunistic nature of mucormycosis in immunocompromised patients; especially in COVID 19 infected ones. In COVID 19, due to consumption of variety of drugs, physiology of body changes and if patient has to go through the surgery or other medical utilities, these situations create higher chances of infection of mucormycosis. Early diagnosis with proper, effective and safer medication will be proven as greater help to overcome this condition.

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