The impact of SARS-CoV-2 on the sudden onset of Mucormycosis in the Indian subcontinent-A review

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Abstract

Mucormycosis or black fungus is a rare fungal infection, but cases are rising amidst the Coronavirus pandemic. The disease mostly infects immunocompromised patients including diabetics and those receiving corticosteroid therapy. The most common etiological agent is Rhizopus arrhizus, from the Mucorales family of fungi. The fungal spores may affect the nose and sinuses, the respiratory tract, renal tract, cutaneous tissues, or may be disseminated throughout the body. Early detection can be done by PCR technique, but direct microscopy is also commonly done. Treatment is most commonly done using high-cost liposomal Amphotericin B injections. Surgical debridement of the affected tissues may sometimes be necessary. Knowledge of the disease and its management techniques is absolutely essential for healthcare professionals in the current scenario. Early diagnosis may improve prognosis. In this narrative review, we seek to provide an overview of the most essential features of Mucormycosis, especially in association with SARS-CoV-2.

Keywords: Amphotericin B, Coronavirus, corticosteroid therapy, diabetes mellitus, mucormycosis, PCR

Introduction

On 11 March 2020, WHO officially declared a global pandemic from SARS-CoV-2, one of the deadliest viruses in history.¹ As of 29 May 2021, Coronavirus had killed 3.53 million people, along with 169 million confirmed cases.¹ The virus was already deadly enough in itself, but it seems that new diseases are on a constant rise. One of these is the deadly Mucormycosis, a fungal infection that used to be a rare case before Coronavirus, but now seems to have become a common occurrence in people of the Indian subcontinent.

Mucormycosis, often known as the Black Fungus, is an invasive vascular disease characterised by tissue infarction and necrosis.² The causative agents are multiple and varied and often differ in developed and developing nations. Rhizopus arrhizus has usually been globally considered the most common pathogen.³ Apophysomyces species are the second most frequent in India, whereas Lichtheimia species are more abundant in developed countries.³ Other species may include Rhizomucor, Mucor, and Cunninghamella species. Some researchers have also discovered Thamnostylum lucknowense as a possible etiological agent.³

The infection is usually acquired by inhaling, ingesting, or direct inoculation of fungal spores in the human body.⁶ It affects the sinuses, the brain, and the lungs and can be life-threatening in diabetic or severely immunocompromised individuals, such as cancer patients or people with HIV/AIDS.⁶ Although the most common risk factor for Mucormycosis remains diabetes mellitus,⁶ several other possible causes have been recorded. In contrast to India, countries such as the USA and European nations recorded a larger number of cases having hematological malignancies and transplants as the underlying predisposing factors.⁷⁻⁹ Other factors include prolonged neutropenia, corticosteroid therapy, iron overload, trauma, illicit drug usage, premature babies, trauma, and burns.⁸ The disease may affect several organs, including the
eyes, respiratory, gastrointestinal, or renal tract, or may present as a cutaneous or disseminated disease.\textsuperscript{[10,11]}

Diagnosis of Mucormycosis from bronchoalveolar lavage (BAL), transbronchial biopsies, aspirated fluid, etc., is done by direct microscopy using H and E stain, Lactophenol cotton blue mount (LPCB), calcofluor white stain, KOH mount, and culture on Sabouraud’s dextrose agar (SDA). Polymerase chain reaction (PCR) is used for the early diagnosis of Mucormycosis.

Treatment of Mucormycosis mostly includes injections of Amphotericin B, surgical debridement of infected tissues, and managing the underlying disease.\textsuperscript{[2]}

The impact of SARS-CoV-2 and sudden onset of mucormycosis are rapidly increasing in India, owing to a large diabetic population, coronavirus patients who are critically immunocompromised, and corticosteroid therapy. As of 25 May 2021, 11,700 black fungus cases had been reported in India, with the maximum numbers coming from the western state of Gujarat. Other states affected were Karnataka, Uttarakhand, Telangana, Haryana, and Madhya Pradesh.\textsuperscript{[3]}

The fatality rate (31–50%) was extremely high in the second wave due to the most virulent mutant of the Coronavirus (B.1.617.2 and B.1.617.2.1).\textsuperscript{[9]}

Physicians relied on steroids to combat the severe inflammation and cytokine storm induced by the new Delta variant. Even among non-hospitalized individuals who showed no evidence of respiratory distress, corticosteroids were indiscriminately given. There were no established guidelines for the treatment of COVID-19 patients. There was a 10-fold rise in sales of dexamethasone and methylprednisolone, and one of the predominant reasons for the spurt of mucormycosis among post-COVID-19 treated patients. Another hurdle in the treatment of mucormycosis was the lack of availability of Amphotericin B and its exorbitant cost.\textsuperscript{[12,13]} Given the seriousness of the instances and the quickly rising numbers, the government should consider subsidising the drug to promote patient access and treatment.

It is critical to do quick research into better illness management and control methods, as well as to raise public awareness so that individuals can recognise symptoms early and seek treatment before drastic measures are necessary.

This systemic review highlights the impact of SARS CoV-2 and the sudden onset of mucormycosis, as well as treatment options.

**Method of Selection of Journal**

The Journal of Family Medicine and Primary Care (JFMPC) covers a broad spectrum of clinical topical catering to the academic needs of various physicians, National Health Mission (NHM) doctors, community surgeons, community health workers, and public health specialists. The impact factor of the journal is 0.60. The journal is indexed with the Directory of Open Access Journals (DOAJ), Indian Science Abstracts, PubMed Central.

The data is derived from various research articles published on epidemiology of Mucormycosis in India as well as globally and review articles published in Scopus and PubMed, including the latest updates from government websites like Indian Council of Medical Research (ICMR) and Centres for Disease Control and Prevention (CDC).

**Epidemiology**

The incidence of mucormycosis is rising globally,\textsuperscript{[12,14-19]} but the rise is very high in India and China among patients with uncontrolled diabetes mellitus.\textsuperscript{[20-23]} However, the incidence is higher in Europe than in Asia, as reported by a review of 851 cases from 2000 to 2017, as the rate was 34% in Europe, 31% in Asia, and 28% in North or South America [Figure 1].\textsuperscript{[9]}

Many cases remain undiagnosed due to difficulty in sample collection and the inadequacy of diagnostic tests. As estimated by the Leading International Fungal Education (LIFE) portal, the annual incidence of Mucormycosis is 10,000 cases globally, not including India. On including India, however, the estimate rose to 910,000 cases.\textsuperscript{[20,24]} Globally, diabetes mellitus as a risk factor varies between 17% to 88%.\textsuperscript{[3,27]}

**Etiology**

Figure 2 shows the current classification of Mucorales. The Mucoromycetes class of fungi includes Order Mucorales, as the main causal agent of Mucormycosis (previously called zygomycosis), which is a rare, opportunistic fungal infection.\textsuperscript{[19]}

Globally, 70–80% of all cases can be accounted for by Rhizopus, Mucor, and Lichtheimia (formerly Absidia or Myocladus) spp.\textsuperscript{[21,28-30]} Other rare etiological agents include Apophysomyces, Saksenaea, Rhizomucor, Cunninghamella, Cokeromyces, Actinomucor, and Syncephalastrum spp.\textsuperscript{[21,28-30]} In the Indian context, however, Apophysomyces elegans ranks second among the most common causative agents after Rhizopus oryzae.\textsuperscript{[3,21]}

Although the data indicates Mucorales as being opportunistic pathogens, Apophysomyces elegans and Saksenaea vasiformis can infect even a seemingly normal host, which may
follow severe accidental trauma in tropical and subtropical areas. Very few of these patients manifest rhino-cerebral and pulmonary infections; most others develop only cutaneous mucormycosis. It might be noted that sporulation in Apophysomyces elegans is a tedious process only attainable in the laboratory, so it is yet unclear as to how these spores manage to invade these patients from the environment. Immunocompromised individuals are also at risk of infections from Cunninghamella bertholletiae, Rhizomucor pusillus, and Rhizopus microsporus, although the incidence is rarer. Another infrequent species in India are Rhizopus homothallicus, which was first reported in patients with cavitary pulmonary mucormycosis. Mucor irregularis and Thamnostylum lucknowense have been implicated in certain recent cases.

The considerable risk factors for mucormycosis involve factors such as uncontrolled diabetes mellitus in ketoacidosis, other forms of metabolic acidosis, corticosteroids therapy, organ or bone marrow transplantation, neutropenia, trauma and burns, malignant hematologic disorders, illicit intravenous drug use, neonatal prematurity, and malnourishment and deferoxamine therapy in patients receiving hemodialysis. Patients on Immunosuppressive therapy and high steroid doses (≥ 600 mg of prednisone) are susceptible to mucormycosis. Corticosteroid impairs the macrophage and neutrophil function and makes the patient susceptible.

However, since all these factors were also present in the first wave but did not lead to Mucormycosis, the question arises—what changed in the second wave of Covid-19? The answer may lie in the fact that since the second wave was much more widespread and the patient numbers had increased drastically, it led to a rapid shortage of medical supplies, the most important being oxygen cylinders. Due to the lack of medical-grade oxygen, over 130 Indian cities reported massive deaths of COVID-19 patients in intensive care units. Oxygen, crucial for several biochemical processes, makes survival under hypoxic conditions and aspect of increased virulence for some human pathogenic fungi. The endocytosis mechanism of some Mucorales species is enhanced by hypoxia, which further shifts fungi energy metabolism from carbohydrates to fatty acid, thus enabling lipid uptake from host serum to function, which serves as an extracellular nutrient source during the infection, therefore portraying a specific pathogenicity pattern. This might explain the destructive lesions with widespread necrosis, most commonly seen in the central face area, where the sebaceous glands are profusely found. Hypoxia-Inducible Factors (HIFs) also play a notable regulatory role in immunometabolism, which follows inadequate tissue oxygenation, thus favouring tissue damage and immune cell dysfunction under hypoxic conditions.

Moreover, the possibility that some of the SARS-CoV-2 variants enhance the mycoviral properties can also be considered. In fact, double and single-stranded RNA viral elements have been found in Mucorales species, raising clinical interest over how mycoviruses may increase or decrease fungal virulence, leading to a killer phenotype.

**Pathogenesis**

Iron is an essential element for cell growth and development, thus, successful pathogens use varied techniques to get iron from the host.

Recent data is indicative of the fact that the level of available, unbound iron in serum plays a key role in uniquely predisposing patients with Diabetic ketoacidosis (DKA) to mucormycosis. Such patients have elevated levels of free iron in their serum.
which is suitable for the growth of R. oryzae at acidic pH (7.3–6.88) only, not at alkaline pH (7.78–8.38).66

Patients undergoing dialysis who are treated with deferoxamine, an iron chelator, are also uniquely susceptible to a deadly form of mucormycosis.62–65 Cases of transplantation that include an underlying myelodysplastic syndrome are at a major risk of developing mucormycosis probably because of the iron load resulting from repeated blood transfusions.66

Rhizopus secretes a siderophore rhizoferrin that belongs to the polycarboxylate family.67 In a receptor-mediated, energy-dependent process, Rhizopus is supplied with Iron by Rhizoferrin.67,68

The fungi can even fulfill their need for iron from the host by heme.69,70 The Rhizopus genome project revealed two homologs of heme oxygenase,71 and these enable R. oryzae to obtain iron from the haemoglobin of the host, which might be the reason for its angioinvasive nature.72

Pathological Changes in Mucormycosis

Mucormycosis frequently affects sinuses, the brain, or the lungs. It can also impact the oral cavity, gastrointestinal tract, skin as well as other organs.72 The outcomes of mucormycosis on different organs are as under:

Sinuses: Blocks the nasal septum and leads to blackish or bloody discharge.

Oral cavity: Appearance of necrotic lesions in the form of pressure sores in the naso-orbital region, palate, the floor of the mouth.73

Eye: Blurred vision or vision loss. Lesions in the eye occur due to the angioinvasive nature of the germinated hyphae, which results in dry gangrene.74

Skin: Thrombosis or necrotic lesions.

Brain: Vascular occlusion due to intravascular thrombosis leads to cerebral infarction and haemorrhagic necrosis even before the fungal hyphae invades the brain tissue.75 In advanced CNS mucormycosis hyphal invasion of the necrotic brain parenchyma might lead to death.76

Clinical Forms of Mucormycosis

The most common form is rhino-orbito-cerebral mucormycosis (ROCM), often seen in diabetic ketoacidosis patients or those with uncontrolled diabetes mellitus. It was concluded from a study in India that 88% of the patients with ROCM had diabetes mellitus.78 Similarly, other factors pose an equal risk in ROCM cases [Figure 4].79,80

The second most common site is the lungs, leading to pulmonary form, often seen in patients with blood dyscrasias or transplant recipients [Figure 4].11,25 Risk factors include haematological malignancy (32–40%), diabetes mellitus (32–56%), renal disease (13–18%), solid organ transplant (6.5–9%), and haematopoietic stem cell transplant (1–9.8%).79,81

Penetrating trauma or skin breach is most often the cause of Cutaneous mucormycosis, especially in an immunocompetent host. The major predisposing factor is penetrating trauma (23–88%).82

Ante-mortem diagnosis of Gastrointestinal (GI) mucormycosis is very difficult. It is common in premature or low birth weight infants, in patients with malnutrition, or on renal dialysis [Figure 4].10,77

A rise in patients with isolated renal mucormycosis from 5.4% to 14% has been recently observed by various researchers.12,20,21,23

Dissemination of Mucorales occurs through haematogenous routes. 13% of cases were present with disseminated disease, as reported by a meta-analysis. Lung (91.2%), CNS (53%), sinus (32.4%), liver (17.6%), and kidney (14.7%) describe the decreasing order of frequency of sites of dissemination.83

Clinical Symptoms

As stated above, Mucormycosis presents with various symptoms depending on the tissue or organ which is primarily affected. Symptoms of rhino cerebral mucormycosis include unilateral facial oedema, headache, nasal or sinus congestion, black lesions on the nasal bridge or upper inside of the mouth that rapidly increase in severity, and fever. Pulmonary symptoms may include fever, cough, chest pain, or shortness of breath.80,83–86 Blisters or ulcers are present in cutaneous manifestations, and the infected area may turn black. Other symptoms are pain, warmth, excessive redness, or swelling around a wound. Symptoms of gastrointestinal mucormycosis include abdominal pain, nausea and vomiting, and gastrointestinal bleeding. Disseminated mucormycosis usually occurs in people already sick from other medical conditions, so the patient's symptoms cannot be attributed to any one disease. Neural manifestations might be mental status changes or coma.50,61,74

Laboratory Diagnosis

Studies suggest that there is an increased survival and even reduced need for surgical resection, disfigurement, and suffering in cases of early diagnosis of mucormycosis.87–89
Clinical diagnosis: During initial CT scans of immunocompromised patients having pulmonary mucormycosis, a nodule (≤3 cm)/mass (>3 cm) or consolidation with surrounding ground-glass opacity halo (18/20, 90%) was observed. In follow-up CT scans, morphologic changes were observed in 87%, which included RFS, central necrosis, and air-crescent sign. In 13 out of 15 patients, sequential morphologic changes were related to the absolute neutrophil count. Another imaging technique that can be used is the Positron emission tomography-computed tomography (PET/CT) with [18F]-fluorodeoxyglucose (FDG).

Specimens: Can be collected from scrapings of lesions, pus, sputum, nasal discharge.

Routine laboratory diagnosis: As routine haematoxylin and eosin (H&E) might show only the cell wall with no structures inside or very degenerate hyphae. Mucorales genera produce non-pigmented, wide (5–20 μm), thin-walled, ribbon-like hyphae with no or few septations and right-angle branching. Fungal walls can be viewed easily through Grocott’s methenamine-silver (GMS) and periodic acid-Schiff (PAS) stains. PAS gives a better visualization of surrounding tissue when compared with GMS. Direct microscopy of KOH and calcofluor white wet mounts shows non-septate hyphae, which can be used for presumptive diagnosis of mucormycosis. Immunohistochemistry using monoclonal antibodies against R. arrhizus can prove to be of significant help in the diagnosis where cultures are negative; it has also been proven useful for differentiating between aspergillosis and mucormycosis (sensitivity 100%, specificity 100% for mucormycosis).

Culture of specimens helps in the identification of the genus and species and can also be used for antifungal susceptibility testing. Fungi can be readily grown on Sabouraud’s dextrose agar (SDA) without cycloheximide at 37°C. Lactophenol cotton blue preparation of colonies shows branched sporangiospores arising across aerial mycelium.

Applied and emerging molecular methods: For the detection of mucormycosis in tissues, numerous methods have been developed, which includes PCR based techniques like nested PCR, real-time PCR (qPCR), nested PCR combined with RFLP, PCR coupled with electrospray ionization mass spectrometry (PCR/ESI-MS), and PCR/high-resolution melt analysis (HRMA). Studies done recently have stated that qPCR in BAL concerning cases of pulmonary mucormycosis leads to early diagnosis and even better outcomes.

Treatment

Early discovery, surgical debridement of infected tissue, antifungal medicines, and addressing the underlying cause are all effective treatments for mucormycosis. The first-line treatment is amphotericin B (AmB), followed by posaconazole and isavuconazole. Isavuconazole is a novel antifungal medicine with similar potency to AmB; however, it was only recently introduced in the Indian market thus its efficacy has yet to be determined.

Discussion & Conclusion

Mucormycosis epidemiology is changing all the time. The difficult component is detecting mucormycosis in COVID-19 patients. Histopathology, direct examination, and culture are all important techniques for identification, as are substantial developments in molecular approaches. Reports state a total of 45,432 cases of mucormycosis till 15 July 2021 of which 4,252 were fatal. Of all these cases, 84.4% of patients had a history of Covid-19, mostly of rhino cerebral type (77.6%). Males were found to be more impacted (78.9%) than females in a study of 101 Mucormycosis individuals (21.1%). HCWs should try to deescalate the underlying systemic disease while managing Mucormycosis. Sinusitis is not necessarily caused by bacteria; it can also be caused by Mucormycosis, so caution should be used while treating Covid or immunocompromised people. It is prudent to conduct a thorough investigation into such patients in order to rule out a fungal cause. Surgical debridement of necrosed tissues should be performed, followed by antifungal medication for 4–6 weeks.

Summary

Mucormycosis is a potentially fatal fungal infection. It is an opportunistic infection associated with immunosuppression and can manifest in a variety of ways. The Rhinocerebral type displays obvious signs on the oral cavity’s hard palate or swelling in one portion of the face. CT scans help confirm the diagnosis. After aspiration of fluid from the lungs or a tissue biopsy, pulmonary type can be determined. Following surgical debridement of diseased tissue, antifungals such as isavuconazole and amphotericin B can help to restrict dissemination. The ICMR and the CDC have published guidelines on Mucormycosis prevention, diagnosis, and treatment. The treatment guidelines, as well as the medicine of choice and the drugs to be discontinued, should be updated on a regular basis and made available to doctors as soon as possible. Innovative approaches to lessen the hardship of wearing PPE kits for longer periods methods to improve PPE donning and doffing off to reduce the risk of infection and reduce the excessive demand on doctors should also be investigated.

Conflicts of interest

There are no conflicts of interest.
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