

Mucormycosis in COVID-19 patients

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Mucormycosis, commonly known as ‘Black Fungus’ which was then a rare fungal infection, has suddenly come to light post the COVID-19- pandemic, more so during the second wave in India. It thus becomes important not only for the medical fraternity but also the general population to build awareness about the same. The present review will focus on the pathophysiology, etiology, outcomes of some case studies, and current treatment methods of mucormycosis infection. Major focus of the current article is on rhino-orbital-cerebral mucormycosis. All the studies included in the present review article was extracted from the PubMed database.

Key words: Corticosteroids, COVID-19, diabetes, hyperglycemia, immunosuppression, ketoacidosis, mucormycosis, rhino-orbital-cerebral mucormycosis

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Mucormycetes of the order of Mucorales, cause a lethal fungal infection in humans, termed as mucormycosis. These molds are omnipresent and specifically observed in humid, decaying material as well as soil. The fatal fungal infection is instigated by mucorales and zygomycotic species, hence the infection can also be termed as Zygomycosis.^[1] The most common type of infection in humans is rhino-orbital-cerebral mucormycosis (ROCM) and other lesser common presentations are gastrointestinal, cutaneous, pulmonary, and disseminated infections.^[2]

Etiology

Mucormycosis infection mostly arises due to spore inhalation, the infection is known to affect nearly any body part, predominantly constitutes pulmonary and cerebral infections. Mucormycosis can target the gastrointestinal tract, cause dermatological infection, and also intrude on the blood vessels.^[3] This fungus is known to survive well in rich glucose medium, and thus patients with diabetes, especially with poorly controlled glucose levels become a possible host. The current COVID-19-pandemic has unfortunately, accounted for a dramatic surge in patients with hyperglycemia and ketoacidosis due to treatment with corticosteroids for treating COVID-19, simultaneously allowing the fungus to have a copious culture medium. Hyperglycemia by itself leads to a conducive environment for fungal growth-elevated expression of protein receptor (GRP 78); this increases the Mucorales binding, reduces phagocytosis in the body, and lastly contributes to hyper-glycation of iron-sequestering proteins.^[4]

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Pathogenesis

The fungi apart from being present in the environment, can also be traced in the mucosa of nasal and oral regions of a healthy human. As the spores of the fungus are inhaled, it affects the oral and nasal cavity, which is the most common type of mucormycosis, ROCM.^[2] The initial site of infection for this type of mucormycosis are the nasal turbinates, which further proliferates aggressively to involve the sinuses, palate, orbit, and brain.^[4] The mold is known to have a strong affinity for blood vessels, therefore angioinvasion further results in tissue ischemia and necrosis.^[2,4] The infection spreads either directly from the nose and sinuses or through angioinvasion. It starts multiplying along with the elastic tissues that form the outermost part of the blood vessels, as a result of which the blood supply to the organs is obstructed. The infection spreading from sinuses, gives rise to osteomyelitic bone, further the infection spreads to the orbital structures and brain following the orbital route. Cranial nerve palsies is as a result of infection spread through the sphenoid sinuses and the cavernous sinus. Ethmoid sinuses could also be the path through which infection spreads to the frontal lobes. At this stage, there can be thromboembolism observed in the carotid artery, jugular veins, and cavernous sinus.^[4] If there is no abnormality in vision, but the patient has other symptoms, it can be concluded that the infection has not yet progressed to the optic nerve. The major routes of intracranial extension are ophthalmic vessels, carotid arteries through the spaces between the nerves, bone, cartilage, and meninges.^[4,5] In a healthy

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human being, the immune system eliminates the spores with the help of phagocytic leukocytes. In contrast, in those who are immune-compromised, the spores transform to hyphae; but since the white blood cells have lower efficacy on the hyphae, the fungi proliferates with greater ease.^[5] Vision loss is due to the effect on the optic nerve. Imaging techniques such as computed tomography (CT) scan and a much recommended magnetic resonance imaging (MRI) are mandatory to detect the spread of the infection and to stage the disease. The mucormycosis infection is phenotypically confirmed by the black necrotic tissues in the infected region.

Risk Factors

Referring to the risk factors in Table 1, it could now be critically evaluated why COVID-19 patients are at a higher risk of susceptibility to mucormycosis.

There is an alteration of innate immunity due to decreased T cells, observed in severely affected COVID-19 patients (including CD4 and CD8 cells).^[6] Conversely, higher are the levels of IL-2 R, IL-6, IL-10, and TNF- α contributing to immunosuppression of COVID-19 patients post-treatment, showing their propensity to contract the infection by mucormycetes.^[2] Another major suspected reason for compromised health of COVID-19 patients can be the liberal use of broad-spectrum antibiotics, which harshly disturbs the natural microbiota of the body, hence leading to dysregulation of first line of body's defense mechanism. It has also been noted that iron overload contributes to the pathogenesis of the mucormycosis infection. In many cases, Deferoxamine is administered in patients with diabetic ketoacidosis to diminish the iron levels, which removes iron beneficial for the fungal growth.^[7] Apart from accounting the hyperglycemia to corticosteroid therapy, studies are expected to be carried out questioning the role of the mutated COVID-19 strain B.617.2 in glucose imbalance.^[8]

Jose *et al.*^[8] mentioned additional factors that can be contributing to the surge in mucormycosis in COVID-19 pandemic. In the pathogenesis of the COVID-19 infection, virus ferritin plays an important role. Ferritin is a clinical marker of acute inflammation. At the time of active infection, the ACE2 and CD147 receptors allow the viral particle to interact with hemoglobin molecules and undergo viral endocytosis via the

spike protein on the viral surface. This results in defective hemoglobin, hemolysis, accumulation of heme, and decreased oxygen transportation. A high level of free serum iron is seen after the release of ferritin and eventually signals the liver to produce more ferritin. Thus, the disease advances to 'hyperferritinemia'. SARS-COV-2 virus manifests the hepcidin mimetic effect resulting in ferroptosis and hyperferritinemia. Hence, high ferritin and serum iron levels mediated by the virus displays the possible correlation between COVID-19 and mucormycosis. Epidemiological study done by Sen *et al.*^[9] suggested the development of COVID-19 associated ROCM mainly predisposed by corticosteroids and DM.^[10] The development of COVID-19 associated maxillofacial/ROCM was related with uncontrolled DM and usage of corticosteroids.^[11] Recent studies suggest that patients with uncontrolled blood sugar levels and those treated with corticosteroids are predisposed to the development of post-COVID-19 fungal infections.^[6,12-14] Study done by Dave *et al.*^[14] showed that the over a third of patients with ROCM following COVID-19 have an unfavorable clinical outcome.

Therefore, considering the management of the aforementioned risk factors and appropriate precautionary measures could be considered as a part of the treatment regime.

Clinical Presentations

The manifestations of mucormycosis symptoms include facial pain, headache, inflammation, swelling of periorbital and nasal region, bad odor, proptosis, eyelid drooping and edema, external and internal ophthalmoplegia, exophthalmos, nasal bleeding, facial paralysis accompanied by loss of vision, and nasal discharge consisting of some amount of reddish-black nasal turbinate. In case the disease progresses to the cranial region, the symptoms include lethargy, blindness, seizures usually followed by death if the patient remains untreated.^[1,2]

Diagnosis

The diagnosis of mucormycosis is done by performing a tissue biopsy, imaging, and microscopical examinations. CT scan, and MRI play an important role in defining the extent of involvement, which is very crucial for effective debridement of the infected tissue.^[3,15] The MRI may indicate variability in the T1 (longitudinal relaxation time) and T2 (transverse relaxation time) intensity and lack of focal enhancement in the sinus mucosal region, whereas the CT scans may show a lack of enhancement in the cavernous sinus, which can be accounted to the thrombosis caused by the fungus.^[16] The findings would depend on the infected area, abnormal tissue signalling in the orbit, abnormality in the cavernous sinus filling, meningeal signal alterations, and destroyed bones of sinus walls.^[2]

In molecular techniques, mucormycosis still does not have helpful antigen-antibody methods.^[17,18] However, 1,3 beta-D Glucan detection test is observed to be negative in infections by the mucorales, thus ruling out the possibilities of infection by *Aspergillus*.^[17] There are four reported studies of polymerase chain reaction (PCR) assay development (out of which two studies are real-time PCR based) for mucormycosis.^[18] Although there are novel molecular and serological methods developed, which are shown to have the potential to replace

Table 1: Factors leading to higher risk of development of mucormycosis^[2,7]

1. Diabetes
2. Chronic Sinusitis
3. Hematological Malignancies
4. Renal Insufficiency
5. Stem Cell Transplant
6. Skin Trauma
7. Malnutrition
8. Ketoacidosis
9. Neutropenia
10. HIV Infection
11. Organ Transplant
12. Previous Steroid treatment
13. Broad spectrum antibiotics
14. Drug Abuse

the traditional methods due to the inconsistencies in those approaches, the reproducibility to large-scale clinical implementation is delayed. Thus, those procedures require standardization.^[18]

As mentioned above, there are not enough molecular techniques for larger clinical application, hence microscopic and microbiological evaluation of the site-specific biological specimen becomes inescapable for the diagnosis. Following specimens can be used for histopathology and examining the culture: tissue biopsies, sinus biopsies, and orbital tissue biopsies for direct examination.^[3,17,19]

Another method is to microscopically study the fungal hyphae, this would be a simple method for diagnosis.^[19] Potassium hydroxide (KOH) and calcofluor white mounts are used for microscopy.^[17] The morphology of the hyphae shows 5–25 µm diameter of a ribbon-like structure with irregular width and right-angled branches. In case of fragmented hyphae, mucormycosis is difficult to diagnose; hence the infection should be confirmed by the culture.^[17]

Treatment

Standard therapies

Therapy regime

Mucormycosis involves the orbit. Hence, an ophthalmologist is among the first clinicians to be visited, and detection at this stage would be vital. The standard therapy is initiated by obliteration of predisposing factors like immunosuppressors, deferoxamine, hyperglycemia, neutropenia, and metabolic acidemia. While the predisposing factors are being controlled, surgical debridement of the infected site and antifungal therapy can be followed. In case of further progression of the disease to the orbit, orbital exenteration is considered. In the process of surgical treatment, the administration of liposomal Amphotericin is continued.^[2,20-22]

The first line of treatment

Initiation of antifungal drugs is the preliminary treatment, and early initiation of the same improves the outcome. The first choice of antifungal drug is a liposomal Amphotericin B. Mechanistically it is known to destroy the fungal cell wall and is usually prescribed in higher doses (5–10 mg/kg); administering the liposomal formulation reduces the risk of nephrotoxicity. An adjunctive to this drug is a fungal growth-inhibitor drug, Posaconazole that is suggested as a step-down. The delayed-release tablets of Posaconazole are recommended to be consumed with food (first day 400 mg after every 12 hours later continued by 400 mg once daily). There is a need for further studies to establish the role of Posaconazole for primary treatment, hence currently it is only recommended as an alternative therapy.

The monotherapy of drugs showcased a high mortality rate, hence a combination therapy is proposed. The secondary treatment prescribed in case of failure is a combination of caspofungin and liposomal Amphotericin B a combination of or Posaconazole.

Recent case reports suggest a potential alternative to halt the orbital progression and thus a possible scope to avoid exenteration in the form of administration of retrobulbar Amphotericin B deoxycholate (1 ml of 3.5 mg/ml)^[23] in ROCM.

However, it was also reported that following the injection, the increased cytokine expression may lead to pro-inflammatory state and orbital compartment syndrome (OCS) owing to edema. Management of OCS can be done by use of IL-6 inhibitors (eg: Tocilizumab) or by surgical bony decompression in severe conditions.^[24] The cases that had intraocular involvement were treated with Intravitreal Liposomal amphotericin B injections (5 µg/0.1 ml).^[23] The duration between both intravitreal and retrobulbar injections range from 2 to 8 days, and 6 weeks is the maximum that the therapy can be continued for, as mentioned in the study by Bayram N, *et al.*^[23]

Duration of therapy

Once the desired clinical response is obtained, patients are generally switched from the liposomal Amphotericin B to oral Posaconazole as a step-down therapy. To achieve this stage usually it takes several weeks. The therapy is continued until there is a clinical resolution of both signs and symptoms of mucormycosis and radiological resolution of the disease. The treatment goes on up to several months depending on individual response to treatment.^[25] Maintenance therapy and follow-up are highly recommended.^[17] Even after optimal medical therapy, surgery needs to be performed because the medications do not reach the infected tissues because of the occlusion in blood vessels.

Surgery

An aggressive surgical debridement should be the first and most important surgical step following the diagnosis for successful infection management and improved survival rates. It can be performed both by open approach and endoscopically. The procedure involves the removal of all the necrotic tissue, until the surgeon encounters the perfused tissue. This surgical intervention might be required to be repeated until the improvement is observed. In severe cases, orbital exenteration may be inevitable. In severe cases of ROCM, excision of the nasal cartilage and the palate may also be required. Several severely infected patients do not agree to the resection and reject the recommended surgery; in such sensitive cases other measures such as optimizing the predisposing factors, immunosuppression reversal, and antifungals are the only sincere efforts that can be made.^[2,5,22,25-27]

Prognosis

Due to the fast-spreading nature of this fungus, urgent and aggressive intervention is crucial in suspected or confirmed cases of mucormycosis for a satisfactory prognosis. The prognosis of the infection depends upon multiple factors including early detection, the general health of the patient during the diagnosis of the infection, and the site of infection. The mean duration between the diagnosis of COVID-19 and the development of symptoms of mucormycosis is seen to be 15.6 ± 9.6 days.^[12] Hence, COVID-19 patients with risk factors for mucormycosis should be monitored vigilantly and proper follow-up should be encouraged. A delay of even 6 days in initiating treatment doubles mortality from 35% to 66%.^[12] The overall mortality of patients with ROCM ranges from 25% to 62% and the best prognosis is observed in patients with infection restricted to the sinuses.^[20] The prognosis is poor for patients with late detection and initiation of treatment and administration solely with Amphotericin B.

ROCM with Concurrent COVID-19 Infection

There are several thousand mucormycosis cases during the COVID-19 pandemic, which may not have been reported. The following are a few studies in the Indian population of COVID-19 patients. Maini *et al.*^[5] in their study reported a case diagnosed with COVID-19 infection and during admission was infected with mucormycosis infection. Amphotericin B and debridement resulted in normal eye movement and minimal residual deformity. Sarkar *et al.*^[6] reported a series of 10 cases of clinically diagnosed orbital mucormycosis along with coexisting COVID-19 illness. Liposomal Amphotericin B was received by all the patients for mucormycosis treatment. Surgical debridement was carried out for all 10 patients. Four patients succumbed and five had vision loss. Satisfactory ocular and systemic outcomes were seen in one patient. Mehta *et al.* in a case study reported a COVID-19 patient who developed bilateral eyelid edema. On ophthalmic evaluation, the right eye was congested and the left eye had a dilated non-reactive pupil. The patient to mucormycosis.^[28]

Updates on Clinical Trials

All ongoing clinical trials are listed in the Table 2. Clinical trials on new antifungal agents and combinations of existing agents are very important in order to address the current treatment challenges. Definitive clinical data from prospective randomized studies and observational studies will be helpful for better therapeutic recommendations.

Clinical trials data suggest that isavuconazole showed similar efficacy and improved safety compared to voriconazole for the treatment of invasive molds and mucormycosis. The clinical data obtained from AmBizygo study provide evidence that high-dose liposomal Amphotericin B, in combination with surgery was associated with an overall response rate of 36% at week 4 and 45% at week 12 and creatinine level doubling in 40% of patients (transient in 63%) (NCT00467883). A DEFEAT Mucor study failed to demonstrate any benefit from combination therapy (liposomal Amphotericin B and deferasirox iron chelation therapy) NCT00419770.

Discussion

Among all the mucormycosis, ROCM is most commonly observed in COVID-19 patients during or following COVID-19 treatment. In severe cases where the infection has progressed to the brain, the mortality rate is known to be in the range of 50%–80%^[2] The survival rate in this fatal fungal infection depends on several of factors like early detection, elimination of predisposing factors and immunosuppressive agents like the corticosteroids, surgical debridement of the necrotic tissue, and antifungal therapy.^[2] Liposomal Amphotericin B is the first drug choice prescribed in the current treatment regime; once the infection is under control, oral antifungal drug Posaconazole is initiated. According to recent advancements in management of the condition, retrobulbar injection of Amphotericin B is recommended to minimise the need for orbital exenteration, and intravitreal amphotericin B can be recommended for treatment of mucormycosis endophthalmitis.^[23]

The mucormycosis outbreak control is definitely an interdisciplinary approach. The outbreak requires effective communication, awareness, and close coordination within the following fraternities: clinicians (dentists, ophthalmologists, ENT specialists infectious disease specialists), research team, environmentalists, media personnel, and hospital administration.^[3]

It should also be noted that according to one of the previous studies, the risk factors of mucormycosis have shown to differ geographically. In Europe, the hematological malignancy patients were highly prone to the infection whereas in countries like India, Iran, Mexico, North Africa, and the Middle East, the underlying condition was diabetes.^[29] A variety of studies also indicate that there is a correlation between site of infection and underlying disease (for example diabetes mellitus with sinusitis is associated with rhino-cerebral disease, whereas trauma leads to cutaneous mucormycosis)^[29] Such observations can help the clinicians build a pre-diagnosis judgment.

The physicians could involve and encourage patients to take special care of personal hygiene following COVID-19 recovery and monitor the intake of carbohydrates. If the physicians could rationalize the use of corticosteroids that may bring about a change in the incidence of ROCM. Simpler tests like vision, pupil, ocular motility, and tenderness of sinuses could be a part of examination of patients with severe COVID-19 infections, specifically in patients with uncontrolled blood sugar levels and those who are administered systemic corticosteroids. Depending on the above examinations, suspected patients can be evaluated with immediate imaging studies.^[30]

Basic precautionary measures could be followed to control the mortality rates by mucormycosis: Mass awareness could be practised for visiting the respective clinicians as soon as the initial signs of the disease is encountered by the patients (for example: immediately reporting to a dentist is there is tooth loosening without known reason, visiting an ophthalmologist for sudden blurred vision or ptosis, etc.), strict maintenance of blood glucose levels following the treatment of COVID-19 can be a key in prevention of mucormycosis. All the above actions cumulatively can improve prevention, early detection and outcome.

Conclusion

Early diagnosis and aggressive debridement can play a key role in successful treatment of mucormycosis. Apart from systemic anti-fungal treatments, retrobulbar Amphotericin B injections can help eye and vision salvage.

An interesting probable future perspective would be the understanding of the association between COVID-19 vaccinated patients and development of COVID-19-associated mucormycosis. Clinical trials on new antifungal agents and combinations of existing agents are very important in order to address the current challenges due to this infection. Definitive clinical data from prospective randomized studies, observation studies will be helpful for better therapeutic recommendations.

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Table 2: Summary of Clinical Trials related to mucormycosis^[25]

ClinicalTrials.gov Identifier	Sponsor	Condition	Phase	Study Type	Intervention/Treatment
NCT03816176	Astellas Pharma Inc	Invasive Mucormycosis Invasive Aspergillosis	Phase 2	Intervention	Isavuconazonium sulfate
NCT03387696	University Hospital, Grenoble	Mucormycosis	Not Applicable	Observational	Not Applicable
NCT02226705	Assistance Publique - Hôpitaux de Paris	Rhinocerebral Mucormycosis	Not Applicable	Interventional	Procedure: Multiple transnasal endoscopic surgeries
NCT04502381	Postgraduate Institute of Medical Education and Research	Pulmonary Mucormycosis	Phase 2	Interventional	Drug: Inhaled amp B deoxycholate + intravenous liposomal amp B Drug: Intravenous liposomal amphotericin B alone
NCT00419770	Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center	Mucormycosis	Phase 2	Interventional	Drug: deferasirox Drug: Placebo Drug: Liposomal amphotericin B
NCT04550936	Pfizer	Invasive Aspergillosis Mucormycosis	Not Applicable	Observational	Drug: Isavuconazole
NCT04744454	Pfizer	Aspergillosis	Post Marketing Surveillance (PMS) Study	Observational	Drug: Isavuconazole group
NCT00467883		Mucormycosis			

Conflicts of interest

There are no conflicts of interest.

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