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Review Article

Mucormycosis: the black fungus maiming COVID-19 patients in India

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ABSTRACT

The COVID-19 infection caused by the novel SARS-CoV-2 may be associated with a wide range of disease patterns, ranging from mild to life-threatening pneumonia. Mucormycosis is an emerging angioinvasive fungal infection caused by the ubiquitous filamentous fungi of the *Mucorales* order of the class of *Zygomycetes*. The prevalence of mucormycosis in India is about 80 times the prevalence in developed countries. *Mucorales* invade deep tissues via inhalation of airborne spores, percutaneous inoculation or ingestion. Rhino-orbito-cerebral form of mucormycosis is a relatively fatal infection and mortality rate rises to 50-85%. Extensive use of corticosteroids/monoclonal antibodies/broad-spectrum antibiotics may lead to the development/exacerbation of a preexisting fungal disease. Only amphotericin B and its lipid formulations and recently isavuconazole have been studied as first-line therapy for mucormycosis. On the contrary, posaconazole has been mainly studied as salvage therapy.

Keywords: COVID-19, Rhino-orbito-cerebral mucormycosis, Corticosteroids, *Mucorales*, Amphotericin B

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic, caused by SARS-CoV-2 has now affected more than 164 million people worldwide, accounting for over 3.4 million deaths till date. In India, the numbers of COVID-19 cases are rapidly increasing since last few months. Secondary fungal or bacterial infections or coinfections are important challenges increasing the patients' morbidity and mortality, probably due to immune dysregulation.[1] Candidiasis and pulmonary aspergillosis have been common fungal infections that were reported as superinfections in COVID-19 patients earlier.[2] Recently, a rare fungal disease known as mucormycosis had also emerged as one of the complications in COVID-19 patients during the treatment or recovery phase.

Mucormycosis has emerged as the third most common invasive mycosis in order of importance after candidiasis and aspergillosis in immunocompromised patients. Mucormycosis causes chronic, subacute and rapidly progressing infections.[3] Mucormycosis is an emerging angioinvasive infection caused by the ubiquitous filamentous fungi of the *Mucorales* order of the class of *Zygomycetes*. The most common agents causing mucormycosis are *Rhizopus spp*, *Mucor spp*, *Rhizomucor* and *Leichtheimia spp*. Other genera less commonly implicated in infection include *Cunninghamella*, *Saksenaea* and *Apophysomyces*.[4] Based on anatomic localization, mucormycosis can be classified as one of 6 forms: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated and uncommon presentations.[5] Rhino-cerebral forms may include rhino-orbital, rhino-orbito-cerebral, rhino-maxillary or combination of all four. Rhino-orbito-cerebral mucormycosis is a relatively fatal infection and in cases of brain involvement, mortality rises to 50-85%.[6]

The predominance of cranio-facial mucormycosis is also being diagnosed recently, probably due to increasing

number of individuals with uncontrolled diabetes and other immunocompromised conditions arise due to SARS-COV-2 infection.[7] The aim of this review article was to describe the emerging epidemiology, clinical manifestations, treatment and precautions of mucormycosis in the era of COVID-19.

Epidemiology

Mucorales species are vasotropic, causing tissue infractions. Most human infections result from inhalation of fungal sporangiospores that have been released in the air or direct inoculation of organisms into disrupted skin or mucosa. These organisms are ubiquitous in nature as they can be found in decaying organic substrates and soil. Mucorales are growing rapidly and they are releasing large numbers of airborne spores. Humans are exposed to those spores on a daily basis, but the intact immune system does not allow development of infection.[8]

In developing countries, especially in India, mucormycosis cases, although sporadic, occur mainly in patients with uncontrolled diabetes or trauma, with the prevalence of approximately 0.14 cases per 1000 population, which is about 80 times the prevalence of mucormycosis in developed countries but now in this era of COVID-19, it is very common in patients with SARS-COV-2 infections, during or after completion of treatment.[9,10] The increasing incidence of rhino-maxillary mucormycosis as post COVID-19 complication in India and elsewhere has become a matter of immediate concern.

Predisposing factors

The most important conditions that predispose to mucormycosis include diabetes mellitus (DM), with or without ketoacidosis, hematological malignancies (HM), other malignancies, transplantation, prolonged neutropenia, corticosteroids, trauma, iron overload, illicit intravenous drug use, neonatal prematurity and malnourishment. Immunocompetent patients can be affected, when the spores of the fungus are directly inoculated in the skin, as a result of trauma or burns.[3] Most of these factors are associated with COVID-19, thus increasing cases of mucormycosis in such patients are common now a days.

Several studies have shown that the underlying disease is correlated to the site of infection.[5,11] Hematological malignancies and neutropenia, DM with sinusitis and rhinocerebral disease are associated with pulmonary mucormycosis while trauma usually leads to cutaneous mucormycosis.

Diabetes mellitus

DM was the leading underlying disease in patients with mucormycosis globally. Uncontrolled type II DM, a classic risk factor for mucormycosis had been reported in 73.5% of cases in India and associated with increased morbidity and mortality in COVID-19.[12] This finding was not surprising as India had the highest burden of MCR in the world with an estimated prevalence of 140 cases per million population. Additionally, India has the second-largest number of adults aged 20-79 years with DM. In fact, DM is the single most common risk factor for mucormycosis in India, being reported in over 50% of cases of MCR.[13] In a recent nationwide multi-center study on MCR in India, 57% of patients had uncontrolled DM and 18% had diabetic ketoacidosis.[14]

Corticosteroids and other immunosuppressive agents

Chronic administration of corticosteroids and other immunosuppressive agents is an important risk factor for mucormycosis. Corticosteroids are one of the first line of drug used in COVID-19 patients. Corticosteroids impair migration, ingestion and phagolysosome fusion in macrophages. In addition they may lead to drug-induced diabetes. Prolonged (>3 weeks) high dose systemic corticosteroids are one of the risk factors for mucormycosis.[15] However, there have been reports of mucormycosis associated with short courses of corticosteroids even in well controlled diabetic patients.[16] A study disclosed that T lymphocytes (CD4 and CD8) are lower in severe COVID-19 and levels of IL-2 R, IL-6, IL-10 and TNF-α are markedly higher in these cases.[17] According to a case report, COVID-19 and the related short term corticosteroid therapy resulted in high blood sugar were the only predisposing factors conducting the patient to rhino-orbito-cerebral mucormycosis.[18] Various studies confirmed fungal superimposition or coinfection of cranio-facial region in COVID-19 patients.[19,20]

Iron overload

Increased serum iron is a risk factor for mucormycosis, as iron plays a crucial role in the pathogenesis of this infection.[21] Iron is normally attached to transferrin and ferritin and is not available to the *Mucorales* fungi. In patients with diabetic ketoacidosis or other forms of acidosis there is decreased afinity of these proteins to bind iron.[22]

History of IVDU

Patients with a history of IVDU who develop mucormycosis, most often present with isolated cerebral infection.[5] Conversely, in a review of 68 patients with isolated cerebral mucormycosis, 82% had a history of IVDU and the authors concluded that the presence of lesions in the basal ganglia, rapidly progressive symptoms and a history of IVDU should raise suspicion for mucormycosis.[23]

Healthcare associated

There have been multiple reports of healthcare-associated mucormycosis either as isolated cases or as outbreaks. In

a publication from India, 75 cases of mucormycosis were reported during an eighteen-month period, of which 9% were nosocomial.[24] Healthcare-associated mucormycosis has been attributed to various exposures in the hospital environment: (1) the use of non-sterile products is the most commonly suspected cause of infection.[25] Bandages, adhesives, nitroglycerin patches, contaminated linen, wooden tongue depressors, ostomy bags and probiotics have all been implicated;[26-28] there has even been a report of an outbreak due to allopurinol tablets and prepackaged food.[29] (2) various procedures and medical devices such as catheters, insulin pumps and finger sticks and insertion of tubes, tooth extractions and surgery are also healthcare associated.[6,30] (3) environmental factors may also be a source of infection; molds may be found in the air, dust, water or any surfaces in the hospital; construction works increase the risk of invasive fungal infections; outbreaks have been linked to defective ventilation systems and water leakage.

The rhino-maxillo-cerebral infection develops after inhalation of fungal sporangiospores into the paranasal sinuses. The infection may then rapidly extend into adjacent tissues. Upon germination, the invading fungus may spread inferiorly to invade the palate, posteriorly to invade the sphenoid sinus, laterally into the cavernous sinus to involve the orbits, or cranially to invade the brain.[31] The fungus invades the cranium through either the orbital apex or cribriform plate of the ethmoid bone and ultimately kills the host. Occasionally, cerebral vascular invasion can lead to hematogenous dissemination of the infection with or without development of mycotic aneurysms.[32]

Diagnosis

Early diagnosis of mucormycosis is of utmost importance since it may improve outcome. Studies have shown that it increases survival and it may also reduce the need for or extent of surgical resection, disfigurement and suffering. Since the disease is rare, a high index of suspicion is very important. Diagnosis consists of recognition of risk factors, assessment of clinical manifestations, early use of imaging modalities and prompt initiation of diagnostic methods based on histopathology, cultures and advanced molecular techniques.[33]

Clinical approach

The clinical approach to diagnosis has low sensitivity and specificity. The black necrotic eschar (tissue necrosis) is the hallmark of mucormycosis resulting from angioinvasion and thrombosis, however the absence of a necrotic eschar does not preclude the diagnosis. A patient with diabetes and sinusitis should be thoroughly examined for possible mucormycosis.[33]

Corzo-Leon et al proposed an algorithm for the diagnosis and treatment of rhino-orbito-cerebral mucormycosis in patients with DM.[34] The red flags/warning signs in this algorithm are cranial nerve palsy, diplopia, sinus pain, proptosis, periorbital swelling, orbital pain, nasal stuffiness, nasal discharge with epistaxis, black purulent discharge, erythema of nasal mucosa, facial erythema, black discoloration of affected skin, periorbital erythema and edema, fever, worsening headache, facial palsy.

Rhino-maxillary mucormycosis involvement shows following sign and symptoms depending on superficial to deep fungal involvement like mobile teeth, multiple intraoral draining sinuses, halitosis, dental pain, black palatine patches, palatine ulcers, palatal perforations, erythematic oral mucosa, burning sensation, paraguesia, and aversion of food.[35,36]

Pulmonary mucormycosis most often occurs in neutropenic patients, with prolonged fever, not responding to broad-spectrum antibiotics, non-productive cough, plueritic chest pain and dyspnea.[37]

The finding of any of these signs should prompt immediate further testing, including blood tests, imaging, ocular and/or sinus surgery or endoscopic revision and initiation of antifungal treatment.

Routine laboratory diagnosis

Microscopic examination (direct and histopathology) and culture of various clinical specimens are the cornerstones of diagnosing mucormycosis.

Microscopic examination

Direct microscopy:

Direct examination in 10% KOH wet mounts of scrapings from the upper turbinates, aspirated sinus material, sputum and biopsy material can be valuable. The presence of thick-walled, aseptate and refractile hyphae 6 to 15 μm in diameter, with some hyphae being swollen and distorted, is indicative of the presence of *Mucorales* fungi. Direct microscopy of fresh material is an inexpensive, yet invaluable method to rapidly give a presumptive diagnosis thus, it is strongly recommended, along with histopathology. These methods, however, are not able to identify a fungus to the genus or species level.[38]

Histopathology:

Histopathology is a very important diagnostic tool since it distinguishes the presence of the fungus as a pathogen in the specimen from a culture contaminant and is indispensable to define whether there is blood vessel invasion.[39] Histological sections show acute suppurative inflammation with focal areas of granulomatous inflammation. It can furthermore reveal coinfections with other molds. *Mucorales* genera produce typically non-pigmented, wide (5-20 um), thin-walled, ribbon-like hyphae with no or few septations (pauciseptate) and

right-angle branching. Routine hematoxylin and eosin (H and E) stains may show only the cell wall with no structures inside or occasionally, very degenerate hyphae. Stains that can help highlight the fungal wall include Grocott-methenamine-silver (GMS) and periodic acid-Schiff (PAS) stains, although PAS gives a better visualization of the surrounding tissue compared to GMS.[39] In patients with pulmonary mucormycosis, a definitive diagnosis is based on the demonstration of fungal hyphae typical for mucormycetes in biopsies of affected tissues or in bronchoalveolar lavage (BAL).

Tissue histopathology is dominated by inflammation which may be neutrophilic or granulomatous; inflammation seems to be absent in a few cases, particularly in immunosuppressed patients. Prominent infracts, angioinvasion and perinueral invasions are characteristics of invasive mucormycosis. Neutropenic patients display a more extensive angioinvasion when compared to non-neutropenic patients.[40]

Culture

Culture of specimens is essential for the diagnosis of mucormycosis since it allows identification to the genus and species level and eventually antifungal susceptibility testing. Most medically important *Mucorales* are thermo-tolerant and are able to grow rapidly at temperatures of 37ºC. They grow on virtually any carbohydrate substrate, colonies appearing usually within 24-48 hours and identification is based on colonial and microscopic morphology and growth temperature. The major concern about culture, however, is its low sensitivity, as it can be falsely negative in up to 50% of mucormycosis cases.[33,41]

Radiology

Radiologically, multiple (≥10) nodules and pleural effusion are reportedly more common in mucormycosis.[37] The reverse halo sign (RHS) indicates the presence of mucormycosis on computerized tomography (CT) scan, which is the strong indicator of pulmonary mucormycosis in case of pulmonary infections.[42] The positron emission tomography-computed tomography (PET/CT) with [18F]-fluorodeoxyglucose (FDG) is another emerging imaging technique in the diagnosis and management of mucormycosis is.[43]

Serology

Enzyme-linked immunosorbent assays, immunoblots and immunodiffusion tests have been evaluated with variable success.[44-46] Mucorales specific T cells were detected by an enzyme-linked immunospot (ELISpot) assay in three hematological patients who developed invasive mucormycosis.[47]

Molecular assays

Molecular based assays include conventional polymerase chain reaction (PCR), restriction fragment length polymorphism analyses (RFLP), DNA sequencing of defined gene regions and melt curve analysis of PCR products.[48-51] All assays described above can be used either for detection or identification of *Mucorales*. The majority of the molecular assays target either the internal transcribed spacer or the 18S rRNA genes.[52]

Applied and emerging molecular methods

Molecular methods have evolved as a useful tool that not only detect the mucormycetes in tissues but also accurately identify the strains to species level. Applied and emerging molecular methods to be used are ITS sequencing, PCR based techniques, PCR coupled with electrospray ionization mass spectrometry (PCR/ESI-MS) and PCR/high-resolution melt analysis (HRMA).[53,54]

Treatment modalities

Successful management of mucormycosis is based on a multimodal approach including reversal or discontinuation of underlying predisposing factors, early administration of active antifungal agents at the optimal dose, complete removal of all infected tissues and the use of various adjunctive therapies. Rapid correction of metabolic abnormalities is mandatory in patients with uncontrolled diabetes and suspected of mucormycosis. Experimental evidence suggests that the use of sodium bicarbonate (with insulin) to reverse ketoacidosis.[55]

Antifungal agents for mucormycosis

Only amphotericin B (AMB) and its lipid formulations, and recently isavuconazole have been studied as first-line therapy for mucormycosis. On the contrary, posaconazole has been mainly studied as salvage therapy.

Lipid formulations of AMB

AMB is considered the drug of choice for primary treatment of mucormycosis. Lipid formulations of AMB (liposomal AMB, LAMB and AMB lipid complex, ABLC) have better therapeutic index than the conventional AMB deoxycholate and are considered as the first-line therapy of mucormycosis.[56] The standard daily dose of LAMB and ABLC suggested by current guidelines is 5 mg/kg/day.[57] Indeed, in a neutropenic murine model of pulmonary mucormycosis, the efficacy of liposomal AMB was dose-dependent: a dose of 10 mg/kg/day has been proved to be more effective in reducing fungal burden compared to 5 or 1 mg/kg/day.[58] High dose LAMB was associated with increased nephrotoxicity and electrolyte derangements. Characteristically, doubling of the baseline serum creatinine levels has been observed in 40% of the patients, dictating dose reduction.[59] Although dosages

beyond 5 mg/kg/day have not been proved to be more efficacious for mucormycosis, they may be considered on an individual basis, especially when there is CNS or osteoarticular involvement.[60]

New triazoles

Triazoles act by depleting ergosterol from the fungal cell membrane. Among triazole antifungals, fluconazole, itraconazole and voriconazole have little or no activity against *Mucorales*. Newer triazoles namely posaconazole and isavuconazole have better in vitro activity against *Mucorales* and clinical data supporting their use in mucormycosis in the current standard dose of 300 mg/day of extended release tablets.[61,62]

Posaconazole

Clinical studies on the efficacy of posaconazole for mucormycosis are scarce. Early case reports and case series reported that posaconazole could be an option as salvage therapy in patients unresponsive or intolerant to LAMB.[63] Currently, posaconazole (oral suspension 400 mg×2 /day when taken with meals, or 200 mg×4 /day if not taken with meals) may be considered as salvage treatment of mucormycosis. First-line treatment with posaconazole is considered only in cases when treatment with AMB is absolutely contraindicated, although isavuconazole might be a better option in this situation, as primary treatment data exist only for this newer azole.[60,61]

Isavuconazole

Isavuconazole is a new broad-spectrum triazole and is the biologically active agent of the prodrug isavuconazonium sulfate. It is approved in the United States for the treatment of mucormycosis and in Europe when AMB is not feasible. It is available in both intravenous and oral formulations and it is administered with a loading dose of 200 mg three times a day for two days and 200 mg daily thereafter.[61]

Combination therapy

Despite the lack of solid clinical data therapy of mucormycosis in heavily immunosuppressed patients with a combination of antifungals has become an increasingly common practice. The modest existing pre-clinical and clinical data do not support the use of combination therapy, with the possible exception of CNS mucormycosis, where a combination of high-dose LAMB and posaconazole or isavuconazole might be considered.[64]

Surgery

Surgical resection of necrotic tissues is the core of mucormycosis therapy. In pulmonary mucormycosis, surgical treatment along with appropriate systemic antifungal therapy has been shown to significantly improve survival compared to antifungal therapy alone.[65] Bouts of hemoptysis due to cavitation of lesions near hilar vessels is an indication for urgent resection of the lesion.[66] In certain cases of localised disease surgery might be curative. Similarly, surgical removal of infected tissues is of paramount importance in the treatment of rhino-orbital-cerebral disease.[67]

An endoscopic approach is preferred over the open surgery in patients with early, limited disease or with significant medical co-morbidities.[68] Open surgeries are preferred for extensive disease and include maxillectomy, orbital exenteration and/or craniofacial resection; yet no survival benefit has been proved for such radical approach, especially in patients with limited life expectancy.[69] Local control of the disease with wide and repeated surgical debridement was associated with improved outcomes. Local control was obtained in 90% of the patients after radical surgery versus 41.6% in patients who had limited surgery.[70]

Adjunctive therapy

The increased oxygen pressure achieved with hyperbaric oxygen (HBO) treatment improves the functionality of neutrophils. Furthermore, HBO promotes the AMB action by reversing acidosis. Finally, high oxygen pressure inhibits fungal growth and improves the rate of wound healing. Thus, treatment with HBO has been proposed as adjunct to surgical and antifungal therapy for mucormycosis, particularly in diabetic patients who have sinusitis, or in cutaneous mucormycosis.[71]

Finally, the investigational drug VT-1161, an inhibitor with selective activity against the fungal CYP51, has in vitro activity against *Mucorales* including *R. oryzae*, *Lichtheimia* and *Cunninghamella*. VT-1161 was shown to prolong survival of neutropenic mice with mucormycosis due to *R. oryzae* when given therapeutically or prophylactically. Although additional studies are required to establish the efficacy of VT-1161 against other *Mucorales* (higher MIC values were noticed versus *R. delemar*), this ergosterol synthesis inhibitor might prove to be an additional asset in our armamentarium against mucormycosis.[72]

Treatment duration

There is no standard duration of treatment for mucormycosis. Decisions are made on an individual basis, and as a principle, antifungal therapy of mucormycosis is continued until resolution of all clinical, laboratory and imaging signs and symptoms of infection and reversal of immunosuppression. Oral formulations of newer azoles with activity against *Mucorales* such as posaconazole and isovuconazole have an important role in bridging the initial IV treatment of mucormycosis to long-term treatment.[57] In selected patients, PET/CT scan might have a role in making the distinction between radiographic signs of active disease and inactive scars,

thus facilitating treatment discontinuation. Debridement of necrotic tissues was continued until the necrotic tissues were not detectable in three consecutive days. Regular daily debridement of necrotic tissues from paranasal sinuses is necessary to prevent the propagation of mucormycosis. Also, irrigation of the sinuses and the involved regions with diluted AMB is recommended.

Prognosis

The survival rate in patients with uncontrolled DM suffering from the rhinocerebral form is very rare. The overall mortality is high, usually 30% to 70%. Death usually results in 2 weeks if untreated or unsuccessfully treated. The survival rate lowers as the diagnosis to treatment interval increases. 70% of survivors have permanent residual effects including blindness, cranial nerve defects and surgical disfigurement. Early diagnosis is crucial in order to promptly initiate therapeutic interventions necessary for preventing progressive tissue invasion and its devastating sequelae, minimizing the effect of disfiguring corrective surgery and improving outcome and survival.

CONCLUSION

The diagnosis and treatment of mucormycosis remains a challenge. COVID-19 patients undergoing corticosteroid therapy have a risk of rhino-orbital, rhino-maxillary and/or rhino-orbito- cerebral mucormycosis, particularly when another risk factor such as DM is present. The clinical presentation is nonspecific, and, when it becomes apparent that the patient most probably has mucormycosis, it is often too late to administer effective treatment. Early diagnosis is thus crucial and is the main target of current research. Direct examination, culture and histopathology are the cornerstones of diagnosing mucormycosis, but they are time consuming and lack sensitivity. Newer molecular diagnostic techniques such as *in situ* hybridization and PCR, offer an alternative which may lead to earlier diagnosis and prompt initiation of treatment. The management of mucormycosis is multimodal including reversal of underlying risk factors, administration of antifungal agents, surgical intervention and various adjunctive therapies. Timely and adequately dosed antifungal therapy is necessary. Immunologic and metabolic profiling of the host, targeted immunotherapy and reversal of tissue hypoxia, may evolve in the future, leading to a better treatment of this devastating disease.

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