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Review Article

Mucormycosis- A Catastrophic Challenge in COVID-19 Pandemic

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I N F O

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A B S T R A C T

Recently amidst the second wave of COVID-19, various opportunistic infections were observed globally. Amongst all, COVID-19 associated mucormycosis (CAM) was the most fatal invasive fungal infection, which was declared as an epidemic and notifiable disease in many states in India. it had caused a huge increase in mucormycosis cases which was initially considered a rare disease. As per the latest scenario, India has seen a total of 40,845 cases of black fungus until 28 June, of which 31,344 cases were rhino-cerebral, and the death toll from the infections stands at 3,129.

This article aims to provide a succinct list of warning signs to suspect Rhino-Orbital-Cerebral Mucormycosis (ROCM), to detect the disease at an early stage, use a proper diagnostic test available and follow an evidence-based management strategy and also outline various preventive measures.

Keywords: CAM (COVID-19 Associated Mucormycosis), SARSCoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), ROCM (Rhino-Orbital-Cerebral Mucormycosis), IFI (Invasive Fungal Infection), AmB (Amphotericin-B)

Introduction

Mucormycosis is an angio-invasive fungus that is usually present in the environment and grows on wet surfaces, dead and decaying vegetable matter. The term "black fungus" being used for mucormycosis is incorrect as the term "black fungus" is used for dematiaceous fungus, which is an entirely different group. Mucormycosis is a highly invasive fungal infection afflicting predominantly the immunocompromised/ high risk group patients.[1] The genera responsible for human infection are Rhizopus, Mucor and Rhizomucor; Cunninghamella, Lichtheimia and Apophysomyces. These fungi are ubiquitous in nature and human infections are rare.[2] In CoVID-19 Pandemic the whole world is facing the health emergency caused by a novel strain of severe acute respiratory syndrome coronavirus 2 (SARS CoV- 2) - which, along with severe pneumonia, is also associated with strokes, venous thrombosis, renal failure, cardiomyopathy, coronary and systemic vasculitis.[3] Till date, it has afflicted over 192.2 million people worldwide with more than 4.13 million people succumbing to the disease. In India, 31.2 million people have been afflicted with over 419,000 people succumbing to it.[4]

Predisposing Conditions

Some of the predisposing conditions for mucormycosis infection include uncontrolled diabetes mellitus with or without ketoacidosis, leukaemia, lymphoma, AIDS (Acquired Immuno Deficiency Syndrome), primary immunodeficiency, severe malnourishment, severe burns and trauma, prolonged

ICU stay, chronic kidney or liver failure, cytotoxic therapy, corticosteroid use (any dose for >3 weeks or high dose for >1 week), use of immunosuppressants like Tocilizumab or other immunomodulators, patients undergoing hematopoietic Stem cell or Solid organ transplantation, patients on itraconazole, voriconazole, posaconazole or echinocandin prophylaxis, iron chelators such as deferoxamine, exposure to contaminated adhesive bandage, wooden tongue depressors, adjacent building construction and hospital linen.[5] Concurrent or recently (<6 weeks) treated severe CoVID-19 infection is a major risk factor that has emerged in last 10-12 months.

Pathogenesis in CAM

Clinical evidence suggests that the neutrophils, monocytes, and macrophages which play a predominant role in the primary host defence against Mucorales are unaffected in CoVID-19 infection, thus eliminating their role in the pathogenesis.[7] It is hypothesised that SARS-CoV-2 infection may affect CD4+ andCD8+ T-cells, which are highly involved in the pathological process of CoVID-19 infection. It has been shown that in severe CoVID-19 cases, there is a reduction in the absolute number of lymphocytes and T-cells, which is associated with the worst outcomes. Mucorales-specific T-cells (CD4+ andCD8+) produce cytokines such as interleukin (IL) 4, IL-10, IL-17 and interferon-gamma (IFN-γ) that damage the fungal hyphae. Such specific T-cells were seen only in patients affected by invasive mucormycosis,CoVID-19 often causes endothelialitis, endothelial damage, thrombosis, lymphopenia, and reduction in CD4+ and CD8+ level and thus predisposes to secondary or opportunistic fungal infection.

It has been observed that nasal mucociliary clearance was profoundly delayed throughout the course of infection and may persist even after.[8] The nasal mucosa, sinus, skin and endothelium constitute the fundamental barriers against fungal invasion. Any injury, chronic irritation, or breach in continuity (nasal prongs, swab stick injury) of nasal or sinus mucosa would result in the adherence of fungus to the laminin and type IV collagen on the basal cell layer of epithelium.[9] Hyperglycaemia directly contributes to Mucormycosis by following mechanisms: (1) Hyperglycation of iron-sequestering proteins, disrupting normal iron sequestration, (2) Upregulation of mammalian cell receptor GRP78 (Glucose Regulating Protein-78) that binds to mucorales and enable tissue penetration, (3) Induction of phagocytic defects, (4) Enhanced expression of CotH that mediates host cell invasion by binding to GRP78. (5) Ketoacid Beta Hydroxy-Butyrate increases expression of the host and fungal receptors that result in fungal adherence and penetration into tissues.[6] Free available iron is an ideal resource for mucormycosis. Hyperglycaemia causes glycosylation of transferrin and ferritin, and reduces iron binding allowing increased free iron. Moreover, increase in cytokines in patients with CoVID-19 especially interleukin-6, increases free iron by increasing ferritin levels due to increased synthesis and decreased iron transport. Furthermore, concomitant acidosis increases free iron by the same mechanism and additionally by reducing the ability of transferrin to chelate iron. SARS-CoV-2 regulates ferritin, and causes extensive endothelitis, although it has not been studied well in CoVID-19-associated Mucormycosis. It is also likely that we have higher load of mucor spores in the indoor and outdoor air in India due to tropical and humid climate.

Clinical Manifestations: Rhino-Orbital-Cerebral Mucormycosis

Being most common form of the disease, mostly associated with DM/ DKA. Symptoms according to the recent ICMR advisory[10] are nasal stuffiness, foul smelling nasal discharge, bleeding from nose, facial edema (unilateral), facial paraesthesia, anaesthesia, eye pain, conjunctival suffusion or sudden blurring of vision. There can also be black scar over nasal bridge or palate. Patients may also complain of fever, headache, loosening of teeth, jaw involvement or alteration in mental status. Onset of bilateral proptosis, chemosis, loss of vision and ophthalmoplegia are ominous suggesting development of cavernous sinus thrombosis.[6] Fever may be absent in most of patients in progression of the disease.

Pulmonary Mucormycosis

It is the second most common manifestation. Most common symptoms include dyspnoea, cough, haemoptysis, chest pain and fever. Fall in oxygen saturation can be seen frequently. It should be differentiated from pulmonary infiltrates that are also seen in Covid pneumonia. Contrast enhanced CT scan (CECT) of thorax remains the investigation of choice.

Cutaneous Disease

Can occur from external implantation (soil exposure from trauma, thorn prick or contaminated dressing) or hematogenous dissemination. Patient can have erythema, induration, black eschar at trauma or puncture site. Severe form termed as necrotising fasciitis that can penetrate into muscle, fascia and even bones.[6] This type of disease most commonly observed in leukaemia or patients receiving chemotherapy/ Hematopoietic Stem Cell Transplant.

Gastrointestinal Disease

Occurs primarily in premature neonates in association with disseminated disease and necrotising enterocolitis or in adults with neutropenia, glucocorticoid use and other immunosuppressed conditions. Patients may have nonspecific abdominal pain and distension, gastrointestinal bleeding, fungating stomach mass on endoscopy or gut perforation.[6] Some cases have been reported in ongoing Covid pandemic.

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Disseminated and Miscellaneous forms

Most common site of dissemination is brain; metastatic lesions can be found anywhere in the body including bones, mediastinum, trachea, kidneys, peritoneum or teeth. It carries high mortality rates exceed 90%.[6] Among all clinical types, ROCM is easily diagnosed, but mortality may go high due to delay in seeking medical care and surgical intervention.

Diagnosis

Rapid diagnosis and initiation of therapy is critical due to the acute, fulminate nature of the infection. Diagnosis of mucormycosis requires the presence of predisposing conditions, clinical and radiological evidence, observation of fungal elements of specific morphology in histological sections, and direct smears of material, and to a lesser extent by culture.[11]

KOH Mount

Direct examination in 10% KOH of scrapings from the upper turbinates, aspirated sinus material, sputum, and biopsy material can be valuable. This is a rapid method to diagnose the disease. 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.[11]

Staining and Microscopy

Mucorales are visualized best with Grocott-Gomori-methenamine stain but silver Periodic Acid-Schiff or Haematoxylin and Eosin are also effective. Methenamine silver may not result in optimum staining. Sample is to be collected in saline.

Biopsy and Histopathology

It remains the most specific modality for definitive diagnosis. Biopsy reveals wide (>6 to 30 micrometre) thick walled, ribbon like, aseptate hyphal elements that branch at right angles. There can be associated findings of haemorrhagic infarction, coagulation necrosis, angioinvasion, infiltration by neutrophils, perineural invasion. Distinguishing with other fungi *Aspergillus, Fusarium* and *Scedosporium* is necessary which can be identified as septate, thinner, and branched at acute angle. Sample for histopathology is to be collected in 10% Formalin.[6]

Fungal Culture

Routine culture media can be used for species identification, but it has low sensitivity caused by damage of mucorales on homogenization in laboratory. Mucorales can form cotton white or greyish black colony.

Diagnostic Nasal Endoscopy

Endoscopy guided biopsy can be done in high-risk patients, and it shows crusting, debris, scabbing, granulation or discoloured mucosa.

Imaging

CECT and MRI (Magnetic Resonance Imaging)Orbit, PNS (paranasal sinuses) and brain is done to analyse the extent and further staging of the disease and also required for follow up after surgical debridement to see the residual disease in ROCM. Chest X-ray might reveal lobar consolidation, isolated masses, nodular disease, cavities or wedge-shaped infarcts. CECT is the best diagnostic method for early detection of the disease. Presence of >10 nodules, Pleural effusion, concomitant sinusitis differentiates Mucormycosis from Aspergillosis in the setting of cancer.[6] However BAL, CT guided biopsy and CT Angiography are done for pulmonary mucormycosis.[12]

Recent Advances

Developing a culture-independent biomarker for the early diagnosis of mucormycosis is a major unmet need in modern mycology. Several approaches have been developed, such as immunohistochemistry (IHC) that can confirm the histopathologic diagnosis of the invasive mold infection, polymerase chain reaction (PCR) on formalin-fixed paraffin-embedded (FFPE) or fresh tissue, body fluids such as bronchoalveolar fluid (BAL), and detection directly from serum/blood. Serologic tests, matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS), metabolomics, and metagenomic shotgun sequencing are other evolving technologies.[13]

Treatment

A high index of suspicion for patients at risk for mucormycosis is critical so that early initiation of therapy can be started while the confirmation of the diagnosis is awaited.

Preventive strategies and General Management[6,10]

- Maintenance of euglycemia
- Correction of ketoacidosis by administration of sodium bicarbonate
- Avoidance of glucocorticoids and other immuno-modulators
- Iron transfusion in active mucormycosis should be avoided
- Exposure to decaying organic matter should be avoided
- Clean distilled water for humidifiers should be used during oxygen therapy
- Rational use of antibiotics

Anti-fungal Therapy[6]

Primary therapy of mucormycosis is based on Polyene antifungal agent. Non-polyene based regimens may be appropriate for patients who refuse polyene therapy or for relatively immunocompetent with mild disease (e.g., isolated suprafacial cutaneous infection).

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First -line Antifungal Therapy	Recommended Dosage	Advantages	Disadvantages
AmB deoxycholate	1.5 mg/kg/day for 3-6 weeks	>5 decades of clinical experience Inexpensive FDA approved for treatment of mucormycosis	Highly toxic Poor CNS penetration
LAmB	5-10 mg/kg/day for 3-6 weeks	Less nephrotoxic than AmB deoxycholate Better CNS penetration than AmB deoxycholate or ABLC Better outcome than AmB deoxycholate in murine models and retrospective clinical review	Expensive
ABLC	5mg/kg/day for 3-6 weeks	Less nephrotoxic than AmB deoxycholate Murine models and retrospective clinical data suggest benefit of combination therapy with echinocandins	Expensive Possible less efficacious than LAmB for CNS penetration
Second- line/ salvage option			
Ivasuconazole	200mg load q8h×6 followed by once daily dosing for 3-6 weeks.	Efficacy similar to that of LAmB in mouse models FDA approved for treatment of mucormycosis May be a rational empirical option when septate mold vs. mucormycosis is not yet established	Much less clinical experience; concern about a more slowly cidal agent than lipid polyenes Clinical study supporting approval was small and historically controlled.
Posaconazole	200mg four times per day for 3-6 weeks.	In-vitro activity against the mucorales, with lower MIC than ivasuconazole Retrospective data for salvage therapy in mucormycosis	Substantially lower blood levels than ivasuconazole No data on initial therapy for mucormycosis. and no evidence for combination therapy Experience limited, potential use for salvage therapy
Combination therapy			
Echinocandin plus lipid polyene	Standard echinocandin doses	Favourable toxic profile Synergistic in murine disseminated mucormycosis Retrospective clinical data suggest superior outcomes for ROCM	Limited clinical data on combination therapy
Lipid polyene plus azole	Standard doses	Favourable toxic profile	Limited efficacy data, with no available evidence of superiority vs monotherapy
Triple therapy (lipidpolyene plus echinocandin plus azole)	Standard doses	Maximal aggressiveness	Limited efficacy data, with no available evidence of superiority vs monotherapy

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Surgical Management

Early aggressive surgical debridement and resection of involved structures should be done in case of involvement of nose and sinus, maxilla involvement, zygomatic and orbital involvement through endoscopy or open approach. Debridement of paranasal sinuses (± turbinectomy± palatal resection± medial orbital wall resection) with clean margins with endoscopic approach or CT/MRI guided. Retrobulbar injection of AmB 3.5mg/ml± sinus irrigation with AmB 1mg/ml is given in limited or no involvement of orbits with preserved vision. Exenteration of eye should be done in case of vision loss, total ophthalmoplegia, chemosis and necrosis of orbital tissues. In case of CNS involvement if systemic condition permits orbital exenteration with aggressive paranasal sinus debridement with clean margins is done. Fontal bone and skull involvement debridement of anterior table of skull, cranialization of posterior table of skull and debridement of osteomyelitis skull bone should be done. Only supportive treatment is done if surgery is not feasible. Induction with anti-fungal therapy is to be continued. Daily repeat debridement may be needed until clinical improvement is established.[14]

Subsequent Treatment

In case of stable disease, oral Isuvaconazole and Posaconazole in their usual doses should be given for 3 to 6 months. In case of progressive disease, for patients already on Amphotericin B, the dose is to be increased and, if on Azole, a Polyene is to be added. In case of improvement (clinical and radiological) step down therapy with oral Posaconazole 300 mg B.D. maintaining a trough level of 1 mcg/dL should be considered.[6]

Discussion

Mucormycosis is a potentially lethal, angio-invasive fungal infection predisposed by diabetes mellitus, corticosteroids and immunosuppressive drugs, primary or secondary immunodeficiency, haematological malignancies and haematological stem cell transplantation, solid organ malignancies and solid organ transplantation, iron overload, etc.[15] It is considered a rare disease until the soaring 2nd wave of Covid hit the entire world, more severely the developing nations, and India has reported the maximum cases of mucormycosis.

As we have seen that a large number of patients were on home isolation and taking steroids with or without the physician opinion, their hyperglycaemic state and prolonged immunosuppression remained undiagnosed, and they acquired these invasive fungal infections promptly, hence, caused mucormycosis as an emerging epidemic in many states in India including its capital, Delhi. Ignorance of symptoms by the patients and their undiagnosed diabetic status due to lack of health check-ups during lockdown which could possibly be the factor for delay in diagnosis. Another crisis that we have faced is that of shortage of amphotericin-B availability and its cost that has further delayed the effective treatment in many states.

Even though no official figures about mucormycosis in CoVID-19 cases were released by the Union Health Ministry during the first wave of CoVID-19, India contributed to approximately 71% of the global cases of mucormycosis in patients with CoVID-19 based on published literature from December, 2019, to the start of April, 2021.[16] Patients receiving antifungal prophylaxis with either itraconazole or voriconazole predispose them for disseminated mucormycosis. Even breakthrough mucormycosis has been reported in patients receiving Posaconazole/ echinocandins prophylaxis. Anti-fungal prophylaxis and combined anti-fungal therapy is not recommended as per the recent guidelines.[10]

Conclusion

An unholy combination of diabetes, rampant use of corticosteroid and a dysfunctional immune system due to SARS-COV-2 are largely responsible for this malady, the invasive-mucormycosis. Physician must have high index of suspicion for early diagnosis and treatment of mucormycosis that involve antifungal therapy and surgical debridement. Hence, control of glycaemic index, judicial use of steroids, and regular health check-ups for early detection of warning signs are the keys to prevent CAM. Aggressive multidisciplinary approach which involves an internist, an infectious disease specialist and surgical specialist are required for the management of this fatal mucormycosis, especially in those with comorbidities and on any immunosuppressive therapy.

Conflict of Interest: None

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