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Mucormycosis: An Update

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Abstract

Mucormycosis is one of the rare fungal infections, which has a high rate of morbidity and mortality. Post-covid mucormycosis has emerged massively in the second wave in India. Management of the diseases depends on accurate diagnosis and prompt treatment including antifungal agents along with surgical intervention with the involved tissues. Many new agents with therapeutic effect against Mucorales are under evaluation over historical and proven first line therapy of amphotericin B-based drugs or posaconazole. The aim of this review of literature is to provide brief information about the aetiology, etiopathogenesis, symptoms of mucormycosis, along recent advances in diagnostic and treatment.

Keywords: Mucormycosis, Covid-19, Black fungus

Introduction

The corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus 2 (SARSCoV-2), first detected in Wuhan, Hubei province of China, has emerged rapidly as a health crisis that has challenged health systems and health professionals all over the world.[1] SARS-CoV-2 is a novel beta corona virus with unknown causal agent. It is primarily transmitted from human-to-human through respiratory droplets and close contact. The COVID-19 has an intubation period of

1–14 days before the onset of symptoms, and asymptomatic patients can also be a carrier of infection. Recently during the second wave of COVID-19 in India, the human infected by the COVID-19 are more prone to infected by the black fungus.[2]

'Mucormycosis -The Black fungus has emerged as a new challenge for health professionals. Covid-19 pandemic has been creating havoc among the general population and health care system of world. Post-covid mucormycosis has emerged massively in the second wave in India. A covid survivor who has already suffered the brunt of a disease which affects almost all the systems of human body has to also face the deadly fungal disease. This is like a frying pan to fire scenario for the patient. Most common type of mucormycosis being rhino-maxillary disease so, patients might report primarily to general dental practitioner for oral cavity related complains.[3] The aim of this review of literature is to provide brief information about the aetiology, symptoms of mucormycosis, along recent advances in diagnostic and treatment.

History of mucormycosis: The first reported case of Mucomycosis dates back to 1885 when the German pathologist Paltauf described the first case as Mycosis Mucorina. Rate of mucormycosis increased rapidly mostly in immunocompromised individuals consequently in 1980s and 1990s. Thus a study was carried out depending upon the prevalence rate in France which showed amplification by 7.4% per year. The supposed possibility of seasonal variation of mucorales and its occurrence all over the world was also reported.[4]

Etiopathogenesis: Some of the common predisposing risk factors associated with Mucormycosis are haematological malignancy, AIDS, uncontrolled diabetes mellitus, especially ketoacidosis, steroid use, neutropenia; especially with renal insufficiency, organ or stem cell transplantation, extremes of age, broad-spectrum antibiotics, iron overload, skin trauma, intravenous drug abuse, prophylactic voriconazole for aspergillosis and malnutrition., Mucormycosis acts as a destructive and potentially critical condition in diabetic patients due to increased availability of micronutrients and at same time compromised defence mechanism of the body.

Some of the common hypotheses include

(i) Serum inhibitory activity against Rhizopus species is low

(ii) Decreased PH level and improved availability of iron for the pathogen

(iii) Diminished facility to inhibit germination of Rhizopus species by pulmonary macrophages of persons suffering with diabetes mellitus

There is accelerated invasion of fungi in diabetes ketoacidosis, as acidic milieu produces more free iron by reducing its binding to transferrin and low level of dialyzable inhibitory factor in diabetics makes it a suitable conditions for fungal duplication. Patients that are severely neutropenic and who lack phagocytic function are more prone for mucormycosis, but this is not seen patients suffering from AIDS. Thus, it implies that only the neutrophils are significant for inhibiting fungal proliferation and not the T lymphocytes.[5-8]

Association of Mucormycosis in COVID-19 patient: It has been observed that Mucormycosis can cause anytime even after COVID-19 infection. COVID-19 infection destroy the airway mucosa and blood vessels and it also increase the serum iron which helps the fungus to grow. Severe COVID-19 is currently managed with systemic glucocorticoids increase the blood sugar. Broad spectrum antibiotics not only kill the pathogenic bacteria but also the produce commensals. Antifungals like voriconazole, it inhibits the aspergillosis, but the mucor remains

unharmed. The long use of ventilation reduces the immunity and therefore the fungus being transmit from the humidifier water given along with the oxygen.[10]

Signs and symptoms:[11]

1. Pain in teeth, gums, sinuses and facial pains.
2. Reduced sensation or paraesthesia on affected side of face.
3. Skin over nasolabial groove/ alae nasii appears blackish in color.
4. Black or blood tinged nasal discharge and crusting.
5. Conjunctival injection or chemosis.
6. Swelling in the periorbital region.
7. Difficulty in vision including blurring of vision or diplopia.
8. Mobility in teeth with discoloration of palate or gangrenous inferior turbinates.
9. Deterioration of respiratory symptoms with hemoptysis and chest pain.

Diagnosis: The finding of any of these signs should prompt immediate further testing:

- **Nasal Endoscopic Examination-** Black Necrotic tissue
- **Blood tests-** CBC (Look for neutropenia / monocytopenia, Raised ESR), FBS, PPBS, HBA1C, LFT, RFT with electrolytes
- **Radiographic imaging-** X-Ray PNS (Para Nasal Sinuses) and OPG (Ortho-Pantomogram) – can be normal, CECT of PNS and Orbit – Erosion and thinning of hard tissues, mucosal thickening of sinuses, enlargement of masticatory muscles. Contrast MRI – Optic neuritis, intracranial involvement, CST, Infratemporal fossa involvement HRCT Chest - Reverse halo sign: nodule (≤3 cm)/ mass (>3 cm) or consolidation with surrounding groundglass opacity halo, central necrosis and air-crescent sign
- **Biopsy-** Nasal cavity for ROCM, if palatal involvement then biopsy from oral cavity, Transbronchial biopsy and BAL (for Pulmonary). CT guided FNAC can be considered in some cases of Pulmonary Mucormycosis.
- **Histopathology-** Broad ribbon-like, thin-walled, primarily aseptate or pauci septate hyphae that have irregular diameters; with non-dichotomous irregular branching and accompanying tissue necrosis and fungal angioinvasion. (Grocott Methenamine Silver GMS and Periodic Acid-Schiff PAS stains).
- **Direct microscopy -** KOH mount (or fluorescent wet mount): an inexpensive, yet invaluable method to rapidly give a presumptive diagnosis. Mucorales are seen as broad ribbon-like, thin-walled, primarily aseptate or pauci septate hyphae that have irregular diameters; with non-dichotomous irregular branching.
- **Culture and sensitivity testing –** Mucorales grow on any carbohydrate substrate. Colonies appear usually within 24–48 h and identification is based on colonial / microscopic morphology and growth temperature. Matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) can be used in equipped settings. The major concern about culture, however, is its low sensitivity, as it can be falsely negative in up to 50% of mucormycosis cases. Hence a combination of clinical and laboratory work up is essential to arrive at the actual diagnosis.
- **Molecular methods –** Molecular techniques such as PCR can be used to identify this fungus directly from the infected tissues or from bronchalveolar lavage. However, these tests require invasive sampling (biopsy, bronchalveolar lavage). Recently, Mucorales DNA detection in non-invasive specimens like serum

have been found to be effective for early diagnosis of mucormycosis. [12]

Prevention of mucormycosis in Covid patient: Mucormycosis isn't contagious, it can't be transmitted from an infected person. Self-care measures are the best way to prevent this type of infection. Prevention of COVID-associated mucormycosis needs to focus on addressing the underlying risk factors aiming for better glycemic control in those with diabetes, appropriate use of systemic corticosteroids and prevention of unnecessary use of antibiotic, antifungal and other immunomodulators.[13]

Management of mucormycosis

Do's and Don'ts For Health professionals	
Do's	Don'ts
• Steroids must be used judiciously in correct dose and for recommended duration. • Rational use of antibiotics. • Timely initiation of Amphotericin B therapy as the first sign appears. • Strict monitoring and control of blood glucose levels. • Patients with Diabetes Mellitus should be given insulin if admitted for Covid–19 treatment. • Daily examination of eyes, nose and mouth for patients with presence of risk factors, • Clean sterile water must be in humidifiers	• Early symptoms and signs must not be ignored or missed. • Blocked nose doesn't always mean bacterial sinusitis, don't overlook Mucormycosis. • Time is crucial, should initiate therapy in relevant cases even before diagnosis is made.[14,15.]

Do's and Don'ts for Covid patients	
Do's	Don'ts
• Inform doctor about all your diseases like diabetes, hypertension, heart disease, malignancy. Inform doctor about all medicines if under medication with immuno–suppressant drugs for any immune related disorder/ disease. • Use mask and maintain personal hygiene. • Inform the doctor immediately about blocked nose with nasal discharge, unilateral facial pain/ numbness, eye swelling, difficulty in vision, any discoloration around eyes, nose or mouth	• Never self-medicate, especially steroids on your own • Never ignore warning signs detailed above. [14,15.]

Treatment of Mucormycosis

Treatment is based on multiple interventions occurring simultaneously, or with different timing and intensity. The basic principles of mucormycosis treatment include risk stratification for severity of the diseases, and intense attempts for early, clinical and laboratory diagnosis; timely initiation of an effective antifungal therapy (monotherapy or combination therapy) along with aggressive surgical debridement of necrotic lesions; reverse of immunosuppression (discontinuation of chemotherapy and increase of neutrophils), and when feasible control of the underlying medical condition. Early diagnosis and prompt therapeutic intervention may prevent progressive tissue invasion and its sequelae, may also reduce the need for extensive surgery and subsequent deformity, and may improve survival.

Rapid accurate diagnosis, administration of drugs, adjunctive application of hyperbaric oxygen, recombinant cytokines or transfusion of granulocyte, surgical debridement, and prosthetic obturator are the methods involved in successful management for mucormycosis.[16]

Medical Management

First Line Antifungal Therapy

Amphotericin B Therapy (Inj.Liposomal Amphotericin B,Inj. Amphotericin B lipid complex,Inj Amphotericin B Deoxycholate)

The recommended dose for liposomal amphotericin B (AmB) is 5 mg/kg/day and as high as 10mg/kg/day for infection involving the central nervous system. [17]

Second Line Antifungal Therapy

1. Isavuconazole (Injection/Tablet)
2. Posaconazole (Tablet)

Combined team approach of ENT Surgeon, Maxillofacial Surgeon, Ophthalmologist, Neuro surgeon and Infectious Disease Specialist is required.[18]

Surgical treatment[5,15,19]

Aim of Surgery-Aggressive clearance of pathologic tissue to make healthy tissue bed for perfusion of anti-fungal therapy.

ENT surgeon: Endoscopic sinus surgery for Sphenoid, Ethmoid and Maxillary Sinus.

Maxillofacial Surgeon: Dual role of maxillofacial surgeon in clearance surgery as well as post-mucormycosis reconstruction and dental rehabilitation. Resection of involved jaw bone by maxillectomy/Mandibulectomy. Cadwell-Luc operation for maxillary sinus debridement, resection of zygomatic bone. Use of free vascular grafts/regional soft tissue flaps for reconstruction and use of zygomatic implants for dental rehabilitation in indicated cases.

Ophthalmologist: Orbital exentration in indicated cases.

Neurosurgeon: Debridement of anterior table, posterior table of frontal bone and osteomyelitic skull bone and involved cerebral parenchyma.

Conclusion

Mucormycosis is a life-threatening and highly invasive fungal infection, particularly affecting Immunocompromised or diabetic patients. Early and prompt diagnosis, recovery from the predisposing factors and an early intervention with surgical debridement and therapeutic drugs are the only hopes to improve the condition of patient suffering from this devasting disease**.**

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