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Mucormycosis: Tsunami of Fungal Infection after Second Wave of COVID 19

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ABSTRACT:

Mucormycosis is a fungal infection caused by a group of molds called mucormycetes. It spreads through various modes when in contact with the its spores in the environment. It can develop on the skin after the fungus enters the skin through a cut, scrape, burn, or other types of skin trauma. It also spreads through the respiratory tract and erodes facial structures. Mucormycosis is a rare angioinvasive infection mainly recognized in immune compromised patients which occurs due to the fungi mucorales. In India, sudden surge is seen in cases of mucormycosis in post covid patients after the second wave of Covid 19. This disease seems to be lethal if not treated at early stage.

This review article aims to provide brief details regarding the etiopathogenesis, risk factors, do's and Don'ts along with recent advances in diagnostic and treatment methods of Mucormycosis.

Introduction

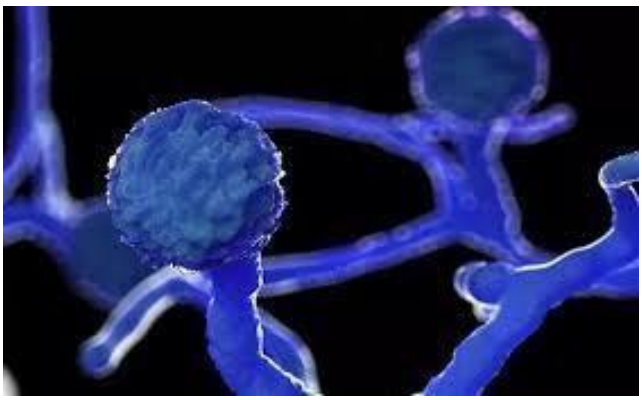
Mucormycosis, previously termed zygomycosis, is a rare fungal infection, instigated by the mucormycetemould that occurs extensively in soil, leaves, decayed wood and putrefied manure. Besides darkening of skin, inflammation, redness, ulcers, fevers, this dangerous sickness can also invade the lungs, eyes and even the brain, proving to be fatal if left unattended. The disease was first described in 1876 when Fürbinger described in Germany a patient who died of cancer and in whom the right lung showed a hemorrhagic infarct with fungal hyphae and a few

sporangia [1]. Therefore, it is highly crucial to understand the causative factors and prominent signs and symptoms associated with Mucormycosis, to quickly identify any possible warning signals arising in both, COVID-19 patients and other individuals.

Predisposing factors

Mucormycosis is a potentially lethal, angioinvasive fungal infection predisposed by diabetes mellitus [2], corticosteroids and immunosuppressive drugs, primary or secondary immunodeficiency, hematological malignancies and hematological stem cell transplantation [3], solid organ malignancies and solid organ transplantation, iron overload [4], illicit intravenous drug use, neonatal prematurity and malnourishment [5]

Risk factors for mucormycosis vary considerably by geographical area. In studies from Europe [6,7] the most common underlying disease was a hematological malignancy, while in India [8], Iran and Mexico it was diabetes mellitus. Several studies have shown that the underlying disease is correlated to the site of infection [9]. Hematological malignancies and neutropenia are associated with pulmonary mucormycosis and diabetes mellitus with sinusitis and rhinocerebral disease, while trauma usually leads to cutaneous mucormycosis. Depending on the clinical presentation it is classified as rhino orbital cerebral, pulmonary, cutaneous, gastrointestinal, disseminated or other, which includes uncommon rare forms, such as endocarditis, osteomyelitis, peritonitis, renal, etc.



PIC OF MUCORMYCOSIS (courtesy Google image).

Rhino-Orbital-cerebral mucormycosis (ROCM) most commonly being seen in India as one of the complications of SARS-COV-2. Prompt diagnosis of this disease is very essential as it proved to be lethal. There have been multiple reports of healthcare-associated mucormycosis, either as isolated cases or asoutbreaks. In a publication from India,75 cases of mucormycosis were reported during an eighteen-month period, of which 9% were nosocomial. Healthcare-associated Mucormycosis has been attributed to various exposures in the hospital environment

- The use of non-sterile products is the most commonly suspected cause of infection. Bandages, adhesives, nitro-glycerin.

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- Patches, contaminated linen wooden tongue depressors, ostomy bags and probiotics have all been implicated. There has even been a report of an outbreak due to allopurinol tablets and pre-packaged food.
- Various procedures and medical devices, such as catheters, insulin pumps and finger sticks and insertion of tubes, tooth extractions and surgery.
- 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, defective ventilation systems and water leakage increases the risk of invasive fungal infections.

Risk Factors:

Not all people who have contracted coronavirus infection and are on treatment for COVID-19 obtain mucormycosis. Certain individuals are more prone to getting infected by the fungal infection, such as:

- People with uncontrolled diabetes mellitus who are unable to maintain blood sugar levels within the normal range
- Persons with comorbid conditions taking immunosuppressant steroid medications to manage pre-existing illnesses as well as COVID-19, over an extended length of time
- Being treated in the Intensive Care Unit i.e. ICU wing of hospitals for a prolonged interval of time
- Having a vulnerable immune system that is weakened owing to comorbidities such as previous organ transplant surgeries or cancer therapy procedures
- Already taking prescription antifungal drugs to combat infections.

SIGNS AND SYMPTOMS OF MUCORMYCOSIS

- Sinusitis and clogging of the nasal tract.
- A bloody or blackish mucus discharge from the nose.
- Only one side facial pain, with numbness and bulging.
- Distinct blackish discoloration on the bridge of the nose
- Prominent aching in teeth, jawbone, degrading of tooth structures
- Sudden mobility of teeth especially in Maxillary arches.
- Hazy vision, with objects appearing blurred or in double, with eye pain

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- Abnormal blood clotting or thrombosis of tissues, along with skin injury and damage or necrosis of dermal cells
- Further deterioration of respiratory functions, with chest pain,
- Excess fluid build-up in lungs i.e. pleural effusion and coughing up blood or hemoptysis.

PRECAUTIONS:

There may be high chances of suspicion if any Covid 19 patient exhibits any one of the sign and symptom as described above. Before discharging the admitted Covidpositive patients from the hospital, doctors should explain these warning signs to patients and family members of patients. The patient should be asked to report immediately even if a single symptom or sign of mucormycosis appears. Negligence or delay may be life threatening to the patient.

DO AND DON'T IN MUCORMYCOSIS

DO's

- Control hyperglycemia post COVID-19 and also in diabetics.
- Use steroid judiciously – correct timing, dose, duration and tapering.
- Use clean, sterile/ distilled water for humidifiers during oxygen therapy.
- Use antibiotics/antifungals judiciously.
- Antibiotic sensitivity testing in the admitted patients after the stipulated period of time is recommended.

DON'T

- Do not miss warning signs and symptoms
- Do not consider all the cases with blocked nose as cases of bacterial sinusitis, particularly in the context of immunosuppression and/or COVID-19 patients on immunomodulators.
- Do not hesitate to seek aggressive investigations, as appropriate (KOH staining & microscopy, culture, MALDI TOF (Matrix-assisted laser desorption/ionization-time of flight (**MALDI-TOF**) for detecting fungal etiology.
- Do not lose crucial time to initiate treatment for mucormycosis. [11]

DIAGNOSIS OF MUCORMYCOSIS

Staging of Rhino Orbito Cerebral Mucormycosis are as follows:

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Stage 1:Involvement of nasal mucosa

1a: Limited to middle turbinate

1b: Involvement of inferior turbinate

1c: Involvement of nasal septum

Stage 2:Involvement of paranasal sinuses

2a:One sinus

2b:Twoipsilateral sinuses

2c: Two ipsilateral sinuses and or palatal or oral cavity

2d: Bilateral paranasal sinuses / zygoma/ mandible

Stage 3: Involvement of orbit

3a: Nasolacrimal duct, medial orbit, vision unaffected

3b: Diffuse orbital involvement, vision unaffected

3c: Central retinal artery/ ophthalmic artery occlusion or superior ophthalmic vein thrombosis, involvement of superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision

3d: Bilateral orbital involvement

Stage 4: **Involvement of CNS**

4a: Focal or partial cavernous involvement and or involvement of cribriform plate

4b: Diffuse cavernous sinus involvement/ cavernous sinus thrombosis

4c: 4b plus involvement of skull base, internal carotid occlusion, brain infarction

4d: Multifocal / diffuse CNS disease

The major factor that increases the efficacy of mucormycosis treatment is an accurate immediate diagnosis in providing urgent medical care by a team of specialists. This guarantees reduced damage to bodily organs, thwarts fungal infection completely, thereby averting grave complications and fatal outcomes. Optimizing the outcome, minimizing the morbidity, and improving the survival in RCOM needs concerted action and rapid response by a multi-disciplinary team comprising of experts in

A. Diagnosis (radiology, microbiology,pathology, molecular biology),

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B. Medical (infectious disease,neurology, critical care) and

C. Surgical (otorhinolaryngology, ophthalmology, neurosurgery.Oral and Maxillofacial Surgery.

TEAM APPROACH

- Microbiologist
- Internal Medicine Specialist
- Intensivist
- Neurologist
- ENT Specialist
- Ophthalmologist
- Maxillofacial Surgeon
- Plastic Surgeon
- Biochemist

Management Approach for Rhino Orbito Cerebral Mucormycosis (ROCM)

1. POSSIBLE MUCORMYCOSIS –

Diagnosis: A patient who has symptoms and signs of concurrent or recently (<6 weeks) treated COVID-19, diabetes mellitus, use of systemic steroids and tocilizumab, mechanical ventilation, or supplemental oxygen is considered as Possible ROCM

ROCM is unlikely in cases of no Supportive evidence on diagnostic nasal endoscopy and or contrast / enhanced MRI / CT Scan and no evidence on direct microscopy or culture or histopathology with special stains or molecular diagnostics.

Management: Continued observation for 3 weeks.

2. PROBABLE MUCORMYCOSIS

Diagnosis: When the clinical symptoms and signs are supported by diagnostic nasal endoscopy findings or contrast-enhanced MRI or CT Scan, but evidence on direct microscopy or culture or histopathology with special stains or molecular diagnostics , the patient is considered as Probable ROCM.

Management: Immediate induction therapy with intravenous liposomal amphotericin B 5-10 mg / kg body weight with strict metabolic control. If Amphotericin B is contraindicated because of

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impaired renal function Isavuconazole IV 200 mg thrice a day on 1 and 2 and 200 mg once on day 3 or Posaconazole IV 300mg twice a day on day 1 , 300 mg once a day from day 2 . Surgery should be prioritized in such a stage. [10,11]

3. PROVEN MUCORMYCOSIS

Diagnosis: When the clinical symptoms and signs are supported by diagnostic nasal endoscopy findings, or contrast-enhanced MRI or CT scan, Confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics, the patient is considered as Proven ROCM.

Management: Immediate induction therapy with intravenous liposomal amphotericin B 5-10 mg / kg body weight with strict metabolic control. If Amphotericin B is contraindicated because of impaired renal function Isavuconazole IV 200 mg thrice a day on 1 and 2 and 200 mg once on day 3 or Posaconazole IV 300mg twice a day on day 1 , 300 mg once a day from day 2 . Surgery should be prioritized in such a stage.

HOW TO PREVENT

Additionally, simple preventive measures go a long way in lowering the chances of acquiring mucormycosis post COVID-19 recovery, such as:

- Ensuring personal hygiene by bathing and scrubbing the body thoroughly, particularly after returning home from work, working out or visiting neighbours, relatives, friends
- Wearing face masks and face shields when going to dirty polluted environments such as construction sites
- Making sure to don fully covered clothing of concealed shoes, long pants, long-sleeved shirts and gloves while coming in contact with soil, moss, manure, like in gardening activities

Summary and Conclusion:

Mucormycosis is a difficult to diagnose rare disease with high morbidity and mortality. Diagnosis is often delayed, and disease tends to progress rapidly. Urgent surgical and medical intervention is lifesaving. Guidance on the complex multidisciplinary management has potential to improve prognosis, but approaches differ between health-care settings..

Upon suspicion of mucormycosis appropriate imaging is strongly recommended to document extent of disease and is followed by strongly recommended surgical intervention. First-line treatment with high-dose liposomal amphotericin B is strongly recommended, while intravenous isavuconazole and intravenous or delayed release tablet posaconazole are recommended with moderate strength. Both triazoles are strongly recommended salvage treatments. Amphotericin B deoxycholate is recommended against, because of substantial

toxicity, but may be the only option in resource limited settings. Management of mucormycosis depends on recognizing disease patterns and on early diagnosis.

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