



MUCORMYCOSIS -“THE BLACK CLOUDS ADMIST THE VIRAL STORM”

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As our country battles against an aggressive waves of covid 19 infection, the growing incidence of mucormycosis is emerging as a matter of major concern among doctors pan india. India bears the flagholder for being the diabetes ‘CAPITAL’ of the world. COVID 19 and its cocktail treatment with steroids at the helm against this background creates a perfect environment for mucormycosis.

The fungal infection clinically referred as mycormycosis also zygomycosis are common infections to human where causative agent i.e., Mucoromycotina is member of mucorales. The causative agent mucoromycotina habitats in soil and decaying organic matter.^[3] The cases of mycormycosis are not new however; a spike in such cases has been reported during COVID era. Although all the sequelae and complications of COVID-19 are yet to be documented and described, spike in secondary infections are being increasingly recognized worldwide.^[1]

The rise in cases of mycormycosis is due to COVID-19 remain associated with impaired immune system of infected patient. Patients with COVID-19 are more vulnerable to fungal infection because of the compromised immune system with decreased CD4+ and CD8+ lymphocytes, associated comorbidities such as diabetes mellitus which potentiates both the conditions, decompensated pulmonary functions, and the use of immunosuppressive therapy for the management in moderate to severe cases.^[4] The infections are also more likely in patients with severe COVID-19 disease and in those requiring intensive care unit admission or mechanical ventilation.^[2]

The cell mediated immunity such as Th1 and IFN- γ are primarily involved in offering protection during viral infections⁷. However, novel SARS-CoV-2 infection remains associated with impaired functioning of not only cellular but also humoral immunity triggers higher risk of fungal infection. Further, not only novel SARS-CoV-2 infection but also treatment associated with administration of anti-inflammatory and immunosuppressive drug further raise the risk of fungal infections. The lack of selective methods for fungal infection diagnosis, culture and treatment results in necrotic and inflammatory outcome of mucormycosis.^[5]

MODE OF TRANSMISSION

- People get mucormycosis by coming in contact with the fungal spores in the environment. For example, the lung or sinus forms of the infection can occur after someone breathes in spores. These forms of

mucormycosis usually occur in people who have health problems or take medicines that lower the body’s ability to fight germs and sickness.^[7]

- Mucormycosis can also develop on the skin after the fungus enters the skin through a cut, scrape, burn, or other type of skin trauma.^[3]

TYPES OF MUCORMYCOSIS

- 1. Rhinocerebral** (sinus and brain) mucormycosis is an infection in the sinuses that can spread to the brain. This form of mucormycosis is most common in people with uncontrolled diabetes and in people who have had a kidney transplant.^[2]

- 2. Pulmonary** (lung) mucormycosis is the most common type of mucormycosis in people with cancer and in people who have had an organ transplant or a stem cell transplant.^[1,3]

- 3. Gastrointestinal** mucormycosis is more common among young children than adults, especially premature and low birth weight infants less than 1 month of age, who have had antibiotics, surgery, or medications that lower the body’s ability to fight germs and sickness.^[1,3]

- 4 Cutaneous** (skin) mucormycosis occurs after the fungi enter the body through a break in the skin (for example, after surgery, a burn, or other type of skin trauma). This is the most common form of mucormycosis among people who do not have weakened immune systems.^[2]

- 5 Disseminated** mucormycosis occurs when the infection spreads through the bloodstream to affect another part of the body. The infection most commonly affects the brain, but also can affect other organs such as the spleen, heart, and skin.^[1]

PREDISPOSING FACTORS

- Uncontrolled diabetes mellitus
- Immunosuppression by steroids
- Prolonged ICU stay
- Co-morbidities – post transplant/malignancy
- Voriconazole therapy

WHEN AND HOW TO SUSPECT CAM

Depending upon the site involved there is varied clinical signs and symptoms. In Patients with Covid-19 illness (active/recovering/postdischarge) most commonly seen are rhino-orbito-cerebral mucormycosis (ROCM) and pulmonary mucormycosis.^[4]

1. RHINO-ORBITO-CEREBRAL MUCORMYCOSIS (ROCM)

It is the most common presentation. Initially – nasal blockage or congestion, nasal discharge (bloody or brown/ black), local pain, Facial pain or numbness or swelling III. Headache, orbital pain., Toothache, loosening of maxillary teeth, jaw involvement . Blurred or double vision with pain; paresthesia, fever, skin lesion, thrombosis & necrosis (eschar).^[3]

2. PULMONARY MUCORMYCOSIS

Fever, . cough, chest pain, . pleural effusion, hemoptysis, . worsening of respiratory symptoms.^[5]

3. CUTANEOUS (SKIN) MUCORMYCOSIS

look like blisters or ulcers, and the infected area may turn black... Other symptoms include pain, warmth, excessive redness, or swelling around a wound.^[6,7]

4. GASTROINTESTINAL MUCORMYCOSIS

Abdominal pain, Nausea and vomiting, Gastrointestinal bleeding.^[2]

5. DISSEMINATED MUCORMYCOSIS

typically occurs in people who are already sick from other medical conditions, so it can be difficult to know which symptoms are related to mucormycosis. Patients with disseminated infection in the brain can develop mental status changes or coma.^[2]

HOW TO DIAGNOSE MUCORMYCOSIS

Mucormycosis is a medical emergency even when clinically suspected. Suspected patients should undergo appropriate radio-imaging study: MRI - PNS with brain contrast study for ROCM, plain CT thorax for pulmonary mucormycosis.^[3]

RHINO-ORBITO-CEREBRAL•

Consult ENT surgeon for endoscopic collection of debrided tissue/biopsy – one portion in sterile saline for microscopy & culture, other portion in formol saline for histopathology.^[1,3]

PULMONARY

- Broncho-alveolar lavage (BAL), Mini BAL, non-bronchoscopic lavage, transbronchial biopsy, CT guided biopsy from lung – process for microscopy & culture.

- Chest X-ray and/ or HRCT – reverse halo sign, thick-walled cavity (need to differentiate from Covid associated pulmonary aspergillosis), multiple nodules, pleural effusion.^[1,3]
- galactomannan & beta-D-glucan test

TREATMENT

Team approach is required with infectious disease specialist, microbiologist, histopathologist, intensivist, neurologist, ENT specialist, ophthalmologist, dentist, surgeons, radiologists etc.^[1]

- 1...Control of diabetes & diabetic ketoacidosis
2. Reduce steroids (if patient is still on) with aim to discontinue rapidly
3. Discontinue other immunomodulating drugs if patient is taking like: Baricitinib, Tofacitinib
4. Surgical debridement: Extensive, to remove all necrotic material; if eye involved, exenteration of eye; in pulmonary, if the lesion is localized or in one lobe.
5. Medical treatment^[1,5]
 - a. Insert peripherally inserted central catheter (PICC line) or central venous catheter
 - b. Maintain adequate systemic hydration, infuse normal saline IV before amphotericin B infusion
 - c. Antifungal therapy
 - i. Liposomal amphotericin B (L-AmB) (preferred treatment) 5mg/kg/day, dilute in 200 cc 5% dextrose over 2-3 hours infusion (avoid slow escalation; higher dose 10mg/Kg/day may be given in brain involvement)^[1,3]
 - ii. Amphotericin B deoxycholate (D-AmB): only if cost and availability of L-AmB is an issue; 1mg/kg/day in 5% dextrose, slow infusion for 6-8 hours. Pre-medication may be required to avoid infusion reaction^[1,3]
 - iii. Monitor renal function & potassium level while treating with amphotericin B
 - iv. Patients who are intolerant to amphotericin B, alternative agents are posaconazole or isavuconazole (injection/tablets)^[4]
 - v. Tab posaconazole: 300mg twice a day on first day, followed by 300mg once a day. Check posaconazole trough level after 7 days of therapy & avoid interacting drugs.^[1]
 - vi. Tab isavuconazole: 200mg three time a day for two days, followed by 200 mg once a day.^[1]
6. Monitor patients clinically, with radio-imaging for response / disease progression & microbiologically.

PREVENTIVE MEASURES

As poorly controlled diabetes is the major issue, good glycemic control during management of COVID 19 patients is required. Systemic steroids should only be used in patients with hypoxemia. Oral steroids are contra indicated in patients with normal oxygen saturation on room air • If systemic steroid is used, blood sugar should be monitored. The dose and duration of steroid therapy should be limited to dexamethasone (0.1mg/kg/day) for 5-10 days.^[4] Universal masking reduce exposure to Mucorales; avoidance of construction sites. During

discharge of the patients, advice about the early symptoms or signs of mucormycosis (facial pain, nasal blockage and excessive discharge, loosening of teeth etc., chest pain, respiratory insufficiency). Wear shoes, long trousers, long sleeve shirts and gloves while handling soil (gardening), moss or manure. Maintain personal hygiene including thorough scrub bath.^[6]

DOS

1. Control hyperglycemia.
2. Monitor blood glucose level post COVID-19 discharge and also in diabetics.
3. Use steroid judiciously – correct timing, correct dose and duration.
4. Use clean, sterile water for humidifiers during oxygen therapy.
5. Use antibiotics/antifungals judiciously.

DONTS

1. Do not miss warning signs and symptoms.
2. 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.^[3]
3. Do not hesitate to seek aggressive investigations, as appropriate (KOH staining & microscopy, culture, MALDITOF), for detecting fungal etiology.^[1]
4. Do not lose crucial time to initiate treatment for mucormycosis.

MISCONCEPTIONS AND MYTHS

1. Mucorales are not black fungi. Black fungi are different category of fungi having melanin in the cell wall.^[7]
2. Mucormycosis is not contagious. It does not spread from one person to another.
3. Mucormycosis is not spread by oxygenation, humidifier, and water. The fungi remain in the indoor & outdoor environment. The spores enter the respiratory tract via air.
4. No antifungal prophylaxis is recommended as the incidence is not more than 10% in any COVID-19 cohort.^[1]

CONCLUSION

COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation.^[2] Additionally, the widespread use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of the armamentarium against COVID-19 may lead to the development/exacerbation of preexisting fungal diseases. Physicians should be aware of the possibility of invasive secondary fungal infections in patients with COVID-19 infection especially in patients with preexisting risk factors and should enable early diagnosis and treatment with the subsequent reduction of mortality and morbidity.^[7] The use of therapeutic agents should be monitored to achieve a therapeutic effect at the lowest dose and shortest durations. The use of broad-spectrum

antibiotics, especially in the absence of infection, should be re-evaluated.

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