MUCORMYCOSIS

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INTRODUCTION

Mucormycosis is a serious fungal infection caused by a group of fungi known as mucormycetes (or zygomycetes). Most common fungi of this group causing mycormycosis are Rhizopus species and Mucor species. Other species like Rhizomucor species, Syncephalastrum species, Cunninghamella bertholletiae, Apophysomyces species are also responsible. This fungi habite on dead and decaying matter, soil, logs, leavs etc. and is widely spread in the environment. Humans get infection by inhalation of its spores.

Mucormycosis is an opportunistic infection. Humans come in contact with its spores very often but never develop disease owing to their strong immunity. Patients with lower immunity due to any reason are the susceptible host for this disease.

Types of mucormycosis:

1. Rhinocerebral (sinus and brain) mucormycosis-Infects the nasal sinuses and spreads to brain. Common in patients with uncontrolled diabetes mellitus and kidney transplant.

2. Pulmonary (lung) mucormycosis- common in patients with organ or stem cell transplant.

3. Gastrointestinal mucormycosis- common in premature and low birth weight infants and patients with previous surgeries and those who have had medications.

4. Cutaneous (skin) mucormycosis- infection through wound or cut in skin.

5. Disseminated mucormycosis- infection spreads in bloodstream and affects brain, heart, liver spleen, kidney etc.

Among these, the most problematic in covid-19 patients is rhino- cerebral mucormycosis.

Epidemiology of Mucormycosis

The prevalence of CAM was 0.27% in patients managed in hospital wards and 1.6% in patients managed in ICUs. We found a 2.1-fold increase in mucormycosis cases during September December 2020 than the same months of 2019; we attribute the increase to COVID19. Most CAM cases were diagnosed >8 days after COVID-19 diagnoses. Hypoxemia due to COVID-19 and inappropriate use of glucocorticoid drugs were independently associated with development of late

Figure 1. Locations of 16 healthcare centers participating in MucoCovi Network study on coronavirus disease–associated mucormycosis, India. AIIMS, All India Institute of Medical Sciences; CIMS, Care Institute of Medical Sciences; PD Hinduja, Parmanand Deepchand Hinduja; PGIMER, Post Graduate Institute of Medical Education & Research; SGPI, Sanjay Gandhi Postgraduate Institute

Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Multicenter Epidemiologic Study of Coronavirus Disease–Associated Mucormycosis, India. Emerg Infect Dis. 2021;27(9). https://doi.org/10.3201/eid2709.210934

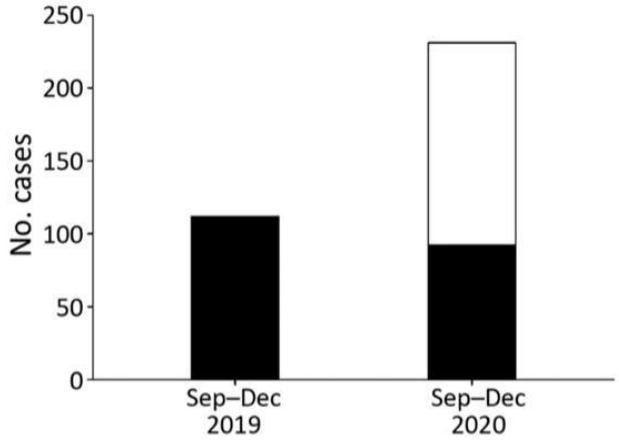

Figure 2. Cumulative number of mucormycosis cases during September–December 2019 and September–December 2020 in 10 health centers, India. White bar section indicates coronavirus disease–associated mucormycosis (CAM); black bar sections indicate non-CAM cases. During 2019, 112 cases of mucormycosis were detected, but a total of 231 cases, 92 non-CAM and 139 CAM, were detected in 2020.

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CAM. The mortality rate for CAM patients was high (44%) but was comparable to rates for non-CAM (49%) patients.

High risk patient group

1. Patients with poorly controlled diabetes mellitus

2. Patients who have had kidney transplant and other organ transplant.

3. Immunocompromised patients and patients on immunosuppressive therapy.

4. Unjudicious steroid use for treatment of covid 19 patients.

5. Patients who have received immunomodulatory drugs likr tocilizumab.

6. Patients on ventilator and on long term oxygen therapy.

7. Patients with iron overload (hemochromatosis).

PATHOGENESIS

Mucormycosis is angioinvasive . It invades Blood vessels , blocks them leading to ischemia , necrosis which causes black discharge. *Three pronged assault*

COVID 19 : causes immune dysregulation, ciliary dysfunction, Thromboinflammation, leucopenia

HYPERGLYCEMIA: Polymorphonuclear neutrophils dysfunction, up regulation of GRP78 , glycation of Fe sequestrating protein

CORTICOSTEROIDS : Impairment in the neutrophil migration, ingestion and phagolysosome fusion. They also exacerbate hyperglycemia.

CLINICAL PRESENTATION

The various clinical forms of mucormycosis in India are:-

- Rhino Orbital Cerebral mucormycosis(45-74%)
- Cutaneous
- Pulmonary
- Renal
- Gastrointestinal
- Disseminated infections

Rhino-orbital-cerebral mucormycosis - Typically develops in patients with diabetes, whereas such patients very rarely develop lung infection. It has been described in haematology patients too. Rhino-orbital-cerebral infection usually originates from the paranasal sinuses, with bone destruction and

subsequent invasion of the orbit, eye, and brain. Unilateral facial oedema, proptosis, and palatal or palpebral fistula developing into necrosis may be present.

Cutaneous and soft-tissue mucormycosis are the most common forms of mucormycosis in immunocompetent patients, primarily after skin disruption due to traumatic injury (eg from natural disasters, motor vehicle accidents, improvised explosive devices in theatres of war, or iatrogenic sources), surgery, or burns. Abscesses, skin swelling, necrosis, dry ulcers, and eschars are characteristic presentations.

In immunocompromised patients, the main route of infection seems to be through inhalation of sporangiospores causing pulmonary infection. **Pulmonary mucormycosis** typically develops in patients with profound neutropenia and graft-versus-host disease. Prolonged fever is seen in most patients, although some patients might be asymptomatic.

Gastrointestinal mucormycosis accounts for 2–8% of cases from India. Primary gastrointestinal disease is a rare manifestation of mucormycosis that can present with symptoms similar to other common gastrointestinal diseases. However, gastrointestinal mucormycosis is the most common manifestation of mucormycosis in neonates, where it carries a high mortality. **Renal mucormycosis** is a unique clinical identity in India. It can affect unilateral or bilateral kidneys. CKD is a significant risk factor. Patients present with fever, flank pain, hematuria or dysuria , acute kidney injury.

When to Suspect (in COVID 19 patients , diabetics or immune compromised individuals)-

- Sinusitis: nasal blockade or congestion, nasal discharge(blackish/ bloody), local pain on the cheek bone
- One sided facial pain, numbness or swelling
- Blackish discolouration over bridge of nose/ palate
- Toothache, loosening of teeth, jaw involvement
- Blurred or double vision with pain, fever, skin lesions; thrombosis and necrosis (Eschar)
- Chest pain, pleural effusion, hemoptysis, worsening of respiratory systems.

Diagnosis

Our approach toward Mucormycosis identification, treatment and prevention:

COVID patients are screened by attending medicine department / physician for mucormycosis's sign, symptoms (Nasal-Periorbital-Facial pain, swelling and discoloration.

Headache / ophthalmoplegia/ ophthalmitis/ drooping of eyelids / restricted eye movement/vision loss/ stuffy nose/ nasal discharge (blood-tinged or black)/ dental pain, Fever, altered sensorium, paralysis, focal seizures) and risk factors.

Risk factors include uncontrolled diabetes, long term steroid and/or immunomodulators (like tocilizumab) therapy, treated with mechanical ventilation, long standing oxygen therapy and Comorbidities – post transplant/malignancy, Voriconazole therapy.

If suspected, immediately inform organized committee on Mucormycosis along with filled Annexure-1 form and send relevant investigations to pathology (blood, histopathology) and radiology (CT/ MRI).

Immediately take ENT/ Eye/ Surgery department consultancy for biopsy and surgical intervention.

If ENT/ Eye/ Surgery department have clinical suspicion. Then consult Microbiology (Infectious disease) department to assess the patient and process the biopsy (nasal, endoscopic guided) sample for KOH, Culture and sensitivity. Microbiological evidence is also evaluated on Histopathological slide for proven/confirm Mucormycosis diagnosis by clinical microbiologist. Start empirical anti-fungal therapy immediately.. Further continuation of anti-fungal therapy should be according to antimicrobial stewardship under Microbiology department

Treatment

1.Diabetes control

2.Reduce steroids

3.Discontinue immunomodulaters

Extensive surgical debridement (If eye involved, exenteration of eye; in lung, if localized or one lobe involved)

Medical therapy (maintain adequate hydration; put PICC or CVC)

<u>Drugs treatment according to availability</u>

Liposomal/lipid amphotericin B

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5mg/kg/d for 3-6 weeks

1. In 200ml 5% dextrose over 2-3h
2. No slow escalation

3. In CNS infection, dose can increase to 10mg/kg/d

4. Monitor RFT, potassium & magnesium level

Lipid amphotericin B not available

Amphotericin B deoxycholate

– 1-1.5mg/kg/d for 3-6 weeks

1.In 5% dextrose slow infusion for 6-8 hours

2.Pre-medication to avoid infusion reaction

3.No slow escalation

4.Monitor RFT, potassium & magnesium level

Polyene not available or intolerant to polyene

Isavuconazole inj – 200mg tid on day 1-2 & 200mg/d from day 3 for

3-6 weeks

OR

Posaconazole inj. – 300mg on day 1 & then 300mg/d for 3-6 weeks

(Monitor trough level after 3-5 days)

Polyene /isavuconazole/posaconazole not available

Itraconazole – 200mg tid for 3-6 weeks (Monitor LFT every week)

• Injection preferable, suspension is the next choice before tablet

• Stop proton-pump inhibitor, H2 blockers when tablet used

• Consume along with food

• TDM after 5 days is recommended

For stable disease

Isavuconazole tab – 200mg tid on day 1-2 & then 200mg/d for 3-6 months

OR

Posaconazole tab – 300mg on day 1 & then 300mg/d for 3-6 months (Posaconazole trough level after 3-5 days recommended)

For Progressive disease

If on amphotericin B

Raise the dose of amphotericin B OR Isavuconazole tab – 200mg tid on day 1-2& then 200mg/d for 3-6 months OR Posaconazole tab – 300mg on day 1 &then 300mg/d for 3-6 months (Monitor Posaconazole trough level after 3-5 days)

If on azole

Consider adding polyene; TDM, dose adjustment, drug-drug interaction with azole

If Toxicity

1.Shift to azoles, if the patient is on polyene

2.Shift to Isavuconazole, if drug interaction with Posaconazole.

Prevention of Mucormycosis

Currently, there are no proven feasible measures for prevention and early detection is the best policy in treatmentar. Some basic points to remember are:

Proper control of DM/Sugar

Judicious use of Steroids.

Strict diabetic control during steroid therapy and after recovery

Low threshold for Antifungals in at risk patients ,local wash or systemic therapy

Tubing of oxygen should be changed frequently and not to be reused

Humidification of Oxygen and frequent changing of humidifier solution

Regular gargle by Saline and douching with Betadine solution

Frequent post recovery evaluation and patient education for the disease for early diagnosis

Avoid water-damaged areas, foods that have spoiled and construction or excavation sites.

Wear a mask. Fungi may be present in the environment but wearing a mask can keep you from inhaling spores.

Keep your home environment fungus and spore-free. Clean your refrigerator and pantry regularly and dispose of spoiling foods without delay.

Boost your immune system and don't take unnecessary risks if you are •immunocompromised, have an underlying disease or have had a surgery or •transplant recently.

Keep a track of your health and focus on keeping your blood sugar, blood •pressure, weight and cholesterol under control.

Note: Currently there are no recommendations to use prophylactic antifungal therapy for preventing Mucormycosis.

Prevention of black fungus disease

Avoid going to the dusty area or construction sites, wear N95 mask if not able to avoid going to area with a lot of dust.

Clean the skin injuries with warm water and antiseptic liquid to avoid having skin infection. Maintain personal hygiene including thorough scrub bath.

If you have had a stem cell transplant or organ transplant talk to your doctor for antifungal medication to prevent fungal infections.

Avoid activities that has direct contact with dust or soil. Wear shoes, long trousers, long sleeve shirts, gloves while handling soil (gardening), moss or manure.