



COVID-19 ASSOCIATED MUCORMYCOSIS (CAM) AND IT'S MANAGEMENT

Dental Science

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ABSTRACT

AIM - The onset of COVID-19 pandemic second wave, there have been multiple reports across the country of high incidence of MUCORMYCOSIS among the recovered patients of COVID-19, especially those who are diabetics or those who have received steroids therapy extensively. In this paper, we review about COVID-19 ASSOCIATED MUCORMYCOSIS (CAM) and its management.

DISCUSSION - COVID 19 infection may be associated with a wide range of bacterial as well as fungal infections, post-covid. These infections are result of complex interplay of factors such as pre-existing disease such as Diabetes, previous respiratory pathology, use of immune-suppressive therapy. Additionally, the wide spread use of steroids/broad spectrum antibiotics as part of the regimen against COVID-19, may exacerbate the opportunistic fungal infections. COVID-19 ASSOCIATED MUCORMYCOSIS (CAM) has been associated with high morbidity and mortality, resulting in exorbitant treatment cost and also leads to shortage of anti-fungal drugs.

RESULT - Successful management of this fatal infection requires early identification of the disease and aggressive and prompt medical and surgical interventions. Therapeutic agents should be used cautiously and closely monitored to achieve desired results.

KEYWORDS

Covid-19, mucormycosis, fungal infections, steroids

INTRODUCTION

The corona virus disease 2019 (COVID-19) infection caused by the novel severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), associated with broad spectrum of fungal and bacterial infections also. These life threatening infections are associated with pre-existing co-morbidities (diabetes or other neoplastic condition) or may develop as a nosocomial infection such as ventilator associated pneumonia. In second wave of COVID-19, there are many cases reported of life-threatening fungal infection of Mucormycosis.

Mucormycosis is an opportunistic, fulminant fungal infection. Mucormycosis (phycomycosis, zygomycosis) is a rare opportunistic fungal infection caused by fungi belonging to the Mucorales order and the Mucoraceae family. It represents the third most common angioinvasive fungal infection following candidiasis and aspergillosis. It usually affects the immunocompromised individuals and is rarely seen in apparently healthy individuals. In the compromised host, mucormycosis infection results from altered immunity in which rapid proliferation and invasion of fungal organisms ensue in deeper tissues.

Pathophysiology involves inhalation of spores through the nose or mouth or even through a skin laceration. Individuals with compromised cellular and humoral defence mechanisms may generate inadequate response. The fungus may then spread to the paranasal sinuses and consequently to the orbit, meninges, and brain by direct extension.

Mucormycosis causes 3 types of infection in human:-

- Rhino – Orbital - Cerebral
- Pulmonary
- Gastro – intestinal

PATHOGENESIS

After invasion in compromised individual, Infection by mucormycosis is caused by asexual spore formation. The tiny spores become airborne and settle on the oral and nasal mucosa of humans. In majority of immunologically competent hosts, these spores will be limited by a phagocytic action. If this response fails, germination will follow and hyphae will develop. As polymorphonuclear leukocytes are less effective in destroying hyphae, in immunocompromised individuals, the infection becomes established in these cases. It further progresses as the hyphae begin to invade arteries, wherein they propagate within the vessel walls and lumens causing thrombosis, ischemia, and infarction with dry gangrene of the affected tissues. As a result, haematogenous spread to other organs can occur (lung, gastrointestinal and brain etc.) followed by sepsis.

WHEN AND HOW TO SUSPECT CAM?

Patients with COVID-19 illness (active / recovering / post-discharge), Common presentation:

Rhino – Orbital – Cerebral – Mucormycosis (ROCM):

Signs and symptoms

- Initially, nasal blockage or congestion, nasal - discharge (bloody or brown-black) or sometimes pain.
- Black lesion on nasal bridge or upper maxillary region
- Unilateral Facial pain or numbness or swelling
- Headache or orbital pain
- Toothache or mobility in teeth or jaw involvement
- Blurred or double vision with pain, paresthesia, fever, skin lesion, thrombosis & necrosis.



Fig : 1

Pulmonary Mucormycosis:

Signs and symptoms

- Fever, cough, chest-pain, pleural-effusion, hemoptysis, worsening of respiratory symptoms
- Lung – CT scan shows COVID related shadows, suspect Mucormycosis in patients with thick-walled lung cavity (need to differentiate with COVID associated pulmonary Aspergillosis), reverse halo-sign, multiple nodules, pleural – effusion.
- Repeated negative Galactomannan & Beta-glucan tests.

Gastrointestinal Mucormycosis

Signs and symptoms

- Abdominal pain
- Nausea and vomiting
- Gastrointestinal bleeding

HOW TO DIAGNOSE MUCORMYCOSIS

Mucormycosis is medical emergency, even when clinically suspected.

Patients should undergo for appropriate radio-imaging study and histopathology study, advised by medical practitioner:-

Rhino –orbital - Cerebral Mucormycosis:

- MRI - PNS with brain contrast study for ROCM

Consult ENT surgeon or maxillofacial surgeon for collection of debrided tissue / nasal biopsy –

- One part in sterile saline for microscopy & culture
- Other part in formalin for histopathology

Direct Microscopy

- Optical brighteners like Calcofluor white and KOH
- Hyphae are of variable width, non-septate, irregular ribbon like with wide angle bifurcation (90 degree)
- Grocott Gomori's Methenamine silver staining and Periodic Acid Schiff staining for highlight fungal hyphae (Fig.2)

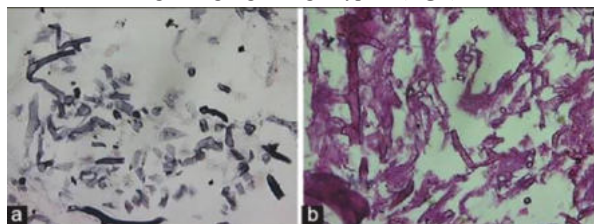


Fig. 2 : Fungal organism identified by Gomori's methenamine stain (a) & Periodic Acid Schiff stain

Culture:

- Tissue swab culture or BAL cultures are not confirmatory diagnosis
- Direct microscopy of BAL and trans-bronchial biopsy may increase the yield.
- Rapid growth (3-7 days) on Sabouraud's Agar at 25°C to 37°C.
- Aggressive vertical growth towards the lid of petri-dish Lid lifters. (Fig.3)



Fig. 3: Culture

Histopathology:

- Hyphae will be seen
- Neutrophilic or granulomatous inflammation
- Perineural invasion may be present

Pulmonary Mucormycosis:

- Broncho - Alveolar Lavage (BAL), mini BAL, non-bronchoscopic lavage, trans-bronchial biopsy, CT-guided biopsy from lungs
- Process for microscopy & culture
- Chest X-ray and HR-CT- chest shows reverse halo-sign, thick-walled cavity, multiple nodules, pleural - effusion
- Repeated negative galactomannan and beta-D glucan test

Gastrointestinal Mucormycosis

- Histological examination
- Culture
- Biopsy
- PCR of Biopsy specimen

MANAGEMENT OF MUCORMYCOSIS

Team approach is required with Physicians, Microbiologists, Pathologists, Intensivist, Neurosurgeons, ENT specialist, Ophthalmologist, Radiologists, Plastic-surgeons, Surgeons and Maxillofacial surgeons.

Preventive Measures

1. Control of diabetes and diabetic-ketoacidosis
2. Avoid steroids, if possible
3. Discontinue other immuno-modulating drugs, if patient is taking them e.g., Baricitinib, Tofacitinib etc.

Medical Management

1. Insert peripherally inserted central catheter (PICC) or central venous catheter
2. Maintaining adequate systemic hydration, infuse normal saline i.e. before Amphotericin B infusion
3. Antifungal therapy

- Liposomal Amphotericin-B 9 (L-Amb) - most preferred - 5mg/kg/day, diluted in 200 cc 5 % dextrose over 2-3 hours infusion (avoid slow escalation; higher dose 10mg/kg/day may be given, if brain involvements)
- Amphotericin B deoxycholate (D-Amb) - only if cost and availability of L-Amb is an issue; 1 % dextrose over 6-8 hours slow infusion
- Monitor renal function & Potassium level, while treating with Amphotericin
- If patient is allergic to Amphotericin, then alternative are posaconazole or isavuconazole
- Monitor patient clinically, with radio-imaging for response or disease progression
- After 3-6 weeks of Amphotericin B therapy, consolidation therapy with posaconazole or isavuconazole for 3-6 months.

Surgical Management

- Surgical debridement: Extensive, All necrotic tissue along with surrounding healthy looking tissue should be removed. It facilitates-increase penetration of anti fungals.
- If eye involved then, exenteration of eye.
- In pulmonary, if the lesion is localized or in one lobe - Lobectomy, Pneumonectomy or wedge resection
- If nasal and sinus involvement without bony erosion of maxilla/zygoma - Erosion of maxilla/zygoma and orbital floor
- Maxilla involvement without involvement of intraoral soft tissue - maxillectomy & surgical debridement by Maxillofacial surgeon/Plastic surgeon
- If Maxilla involvement with involvement of intraoral soft tissue - Maxillectomy & surgical debridement
- If Maxilla, zygoma and orbit involved - Maxillectomy, debridement and exenteration by
- Occuloplastic surgeon

Prosthetic obturators can be given to patient after recovery within 4-6 weeks.

HOW TO PREVENT THIS INFECTION

- If poorly controlled diabetes is a major issue, then good glycemic control during management of COVID-19 is required
- Systemic steroids should only be used in the condition of hypoxemia only
- If steroids are being used, then close monitoring of glucose level is essential
- The dose and duration of steroid should be limited to Dexamethasone only (0.1mg/kg/day) for 5-10 days
- During discharge of the patients, advice about the early signs and symptoms of Mucormycosis (nasal blockage or congestion, nasal-discharge, Facial pain or numbness or swelling, Headache or orbital pain, Toothache or mobility in teeth or jaw involvement)

MISINFORMATION & MISLEADING

- Mucormycosis is not contagious. It does not spread from one person to another.
- Mucormycosis does not spread by oxygenation, humidifier or water. The fungi remain in outdoor and indoor environment.
- No anti-fungal prophylaxis is recommended in all COVID-19 patients, as incidence is not more than 10% in any COVID- Cohort study.

CONCLUSION

Mucormycosis is more common in immune-compromised patients. Early diagnosis of Mucormycosis, especially RCOM, leading to early treatment and less mortality and morbidity with good prognosis and reversal of underlying factors. Liposomal Amphotericin-B and surgery are main treatment options.

DECLARATION OF CONFLICTING INTERESTS

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