Mucormycosis in post-covid patients: An epidemic in pandemic

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ABSTRACT

Rhino-orbito-cerebral mucormycosis (ROCM) is seen as a common post-coronavirus disease (COVID-19) fungal infection in India. It is a lethal, opportunistic infection of the paranasal sinuses and brain caused by fungi of the Mucorales, most commonly with Rhizopus spp. Early diagnosis and timely management are essential. Other studies have shown high mortality up to 25–60%. However, in this study, the recovery rate is very high. We aimed to present six post-COVID mucor cases and to review the literature in terms of prevention, diagnosis, and management of this fatal infection. We carried out a retrospective case series of six patients with a confirmed diagnosis of ROCM presenting to a single tertiary-level hospital during the second wave of covid 19 pandemic. Clinical details for each case was obtained from the hospital information system. A total of six patients (five males and one female) were diagnosed with ROCM during this period. Out of six patients, four had diabetes mellitus and all were on steroid treatment during COVID-19 infection. The most common presenting features were headache (100%), facial pain (80%), orbital swelling (80%), and earache (20%). Most of the patients had sinusitis as a predominant finding in preop magnetic resonance imaging (MRI) at presentation. All patients received liposomal amphotericin B (LAmB) as the first line of treatment and subsequently shifted to posaconazole. The overall recovery rate was 100% and patients were discharged. ROCM infection is very hard to treat. The studies have shown cases with late presentation spreading beyond paranasal sinuses. Early intervention and treatment with antifungals and extensive surgical debridement resulted in the full recovery of all six cases.

Keywords: Amphotericin B, MRI-Magnetic Resonance Imaging, paranasal sinuses, rhino-orbital-cerebral mucormycosis

Introduction

One may suffer mild to moderate respiratory issues if infected with COVID-19, but in many cases, the virus is affecting different systems of the body at the same time. After months of research, it is now known that apart from attacking the respiratory tract, COVID-19 is also angiinvasive and affects our immunity also.

But of late, a number of cases have been reported of mucormycosis in COVID-recovered patients from different states of India. This post-COVID complication has mainly been seen in diabetics or those treated with steroids. Glucocorticoids are inexpensive, widely available, and have been shown to reduce mortality in hypoxicemic patients with COVID-19.[1]

The post-COVID-19 state shall be defined as four weeks from the date of being reverse transcription–polymerase chain reaction (RT-PCR) negative (or equivalent laboratory estimation, or clinical criteria constituted by three days without fever and any other symptom.[2]

The objective of this case series and review is to present patient cases who were successfully treated due to well-timed treatment.
diagnosis of infection, and identification of causative agent by KOH wet mount, lactophenol cotton blue stain (LPCB), and histopathological examination and to look for important findings for the prevention, early detection, and management of C-ROCM.

This study is of utmost importance for primary care providers and family physicians who tend to see a lot of patients with a history of diabetes and rampant uncontrolled use of steroids. Because they are the ones who first encounter such patients, a high index of suspicion and timely intervention and management is very important for the successful outcome.

**Case Series**

This study includes six-patient case record with post-COVID mucormycosis as a complication. Most of the patients are susceptible or high-risk population and belong to one of the following categories:

1. Diabetics, especially uncontrolled or with ketosis
2. Those on mechanical ventilation, especially for 2–3 weeks
3. Those on high dose steroids or on any dose for >2–3 weeks
4. High cytokines (IL6), high ferritin
5. Voriconazole therapy
6. Use of Deferoxamine or other iron overload therapies
7. Those with high computed tomography (CT) scores (higher disease severity)
8. Immunocompromised (human immunodeficiency virus (HIV), organ transplantation, etc.) or on immunosuppression medication (azathioprine, mycophenolate mofetil, etc.)
9. Neutropenic individuals (absolute neutrophil count (ANC < 1500)
10. Autoimmune disorders

**Case 1**

Patient Trilochan Singh, 65 yrs/M, known case of Type 2 diabetes mellitus (DM) (uncontrolled), hypertension, coronary artery disease turned COVID-19 positive and developed moderate COVID-19 pneumonia. CT score-17/25 (01/05), received steroids during hospitalisation (27 April–12 May), following which he developed, left-sided headache and facial pain with no history of nasal obstruction/bleed/blurring of vision, for which the patient was admitted to outside as a c/o suspected mucormycosis on 19/05. On examination, the patient was conscious, oriented with mild proptosis of left eye.

Magnetic resonance imaging (MRI) paranasal sinuses (PNS) and brain suggestive of mucosal thickening of bilateral inferior and left middle turbinate with a mild mucosal thickness of left frontal sinus, fungal infection with global cortical atrophy. Patients KOH mount of left nasal cavity positive for fungal element (mucormycosis).

The patient was started with injection LAmB with broad-spectrum antibiotics. The patient underwent debridement under local anaesthesia (LA) on 26/05. Repeated MRI after surgery was suggestive of mucosal thickening of the bilateral ethmoid sinus.

The patient was taken on oral therapy (Posaconazole) and was discharged.

**Case 2**

Patient Raj Kumar, 58 yrs/M, known case of Alzheimer's disease, turned COVID-19 positive on 05 May 2021 and negative on 08 May 2021. He developed mild COVID-19 infection and was on home isolation and received seven days of steroid therapy. The patient developed swelling and redness of the left eye for five days for which he was admitted to outside on 19/05 as suspected mucormycosis. At the time of admission, the patient's vitals were stable, KOH mount of nasal crust and tissue was positive for fungal element (mucor).

MRI at the time of admission was suggestive of bilateral ethmoid sinusitis with diffuse cerebral atrophy and ischemic changes in bilateral frontal lobes.

The patient underwent debridement under LA on 26/05/21. MRI following surgery was suggestive of stage III mucormycosis. Following complete therapy, on a systemic antifungal LAmB, the patient was taken on oral therapy (posaconazole) and is now planned for discharge.

**Case 3**

Patient Santosh Yadav, 38 yrs/M with a history of COVID-19 infection for which he was hospitalised. He was on steroids and oxygen therapy given at the hospital. He is a known case of Type 2 DM, the patient presented with swelling around the left eye for seven days and itching around the left eye for seven days. These symptoms were not associated with diminished vision and nasal regurgitation. On examination, vitals were stable and pt. was conscious and oriented. Left periorbital swelling and nasal crusts were seen.

Preop MRI-suggestive of mucosal thickening involving left frontal and right maxillary sinuses with internal soft tissue thickening with an abscess in the periorbital region.

The patient was put on LAmB, retro-orbital AmB, broad-spectrum antibiotics and hyperbaric oxygen. Endoscopic debridement under LA was done on 26/05/21 [Figure 1].

**Case 4**

Patient Indrawati 62 yrs/F, a known case of Type 2 DM and hypertension had a history of COVID-19 infection. He was also on oxygen therapy and steroids for two weeks. On examination, the swelling was present over the right side of the face, periorbital region and left PNS. The patient presented with complaints of right-sided facial pain and swelling, periorbital swelling and headache for 10 days. KOH mount and HPE of nasal tissue were positive for fungal hyphae.

Preop MRI is suggestive of mild enhancing mucosal thickening in the right ethmoid and frontal sinus.
The patient underwent endoscopic debridement under LA on 20/05 and was started on injectable LAmB for 14 days and then shifted to oral antifungal posaconazole. The patient was also given hyperbaric oxygen therapy for eight sittings.

Post-op MRI is suggestive of rhino-orbital mucormycosis.

Case 5
Patient Jitendra Kumar 38 yrs/M with Type 2 DM for two years had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure and was hospitalised. He was put on intravenous (IV) steroids and oxygen therapy (CT score-11/25). The patient presented with complaints of swelling around the left eye, blurring of vision of the left eye, and left-sided headache for 18 days. On examination, drooping of the left upper eyelid (incomplete ptosis) and restricted ocular movements were present. Nasal tissue histopathology was positive for fungal elements (mucormycosis). MRI preop suggestive of mucosal thickening in the left ethmoid sinus and left frontal sinus with left-sided orbital sinusitis. LAmB, retrobulbar AmB, and hyperbaric oxygen therapy were started as treatment. Post-op MRI is suggestive of pansinusitis with left orbital cellulitis and optic neuritis (stage III).

Case 6
Patient Mahmood Ahmad 47 yrs/M with a history of COVID-19 pneumonia, steroid therapy and oxygen therapy for 12 days presented with complaints of earache and headache for 1.5 months. On examination, right-sided facial swelling and right nasal crusts were present. Nasal tissue histopathological examination (HPE) was positive for the fungal element (mucormycosis). MRI preop showed invasive fungal sinusitis with cavernous sinus and apex involvement and thrombosis of right internal carotid artery (RICA) [Figure 2].

For treatment, LAmB, endoscopic nasal debridement, and otorhinoplasty surgery (OMFS) surgery were done.

Discussion
Mucormycosis infection has a high mortality rate. Nonetheless, all cases of this study were treated in consequence of good management of the infection. Mohammadi R et al. introduced 22 patients who were treated with AmB. Javadi et al. reported nine mucormycosis cases among diabetic patients in Tehran. The mortality rate was 75% in their study. These findings highlighted the role of posaconazole in the treatment of mucormycosis. Fortunately, LAmB was accessible and so patients were treated with LAmB.

This study demonstrates six cases with different presentations but the root cause is the same, uncontrolled diabetes and unregulated use of steroids to control cytokine storm during COVID-19 infection. Therefore, it gives a valuable clue to all primary care providers and family physicians for a high index of suspicion and aggressive management to ensure a successful outcome.

Review of literature
The orders Mucorales and Entomophthorales belong to class Zygomycetes. The Entomophthorales are rare causes of subcutaneous and mucocutaneous infections known as entomophthoromycosis, which largely afflict immunocompetent hosts in developing countries. Fungi of the order Mucorales are causes of mucormycosis, a severe devastating fungal infection affecting both immunocompetent and immunocompromised hosts in either developing or industrialized countries.

Diagnosis of mucormycosis

Laboratory aspects
Confirmation on direct microscopy (KOH mount) or culture or histopathology with special stains or molecular diagnostics.

Test requisition label
KOH microscopy and SDA culture (C-ROCM).

Transportation of sample: All specimens should be transported to the lab preferably within 2 hrs of sample collection.
- DO NOT FREEZE the sample
- DO NOT CRUSH/HOMOGENISE the biopsied material
Turnaround time KOH Microscopy: 4 hrs

Fungal culture report: 2–21 days

Serology: Non-contributory-Galactomannan, 1,3 β-D-glucan may be done to rule out concomitant or disguised Aspergillosis.

Diagnosis of mucormycosis

Imaging preference
CT of the paranasal sinuses and orbits with contrast: Best used to look for bony erosion.

MRI of the brain and orbit with Gadolinium contrast: Best to look for soft tissue and the extent of involvement.

Treatment
1. Role of Surgery:
Mucormycosis is angioinvasive infection that progresses fast to fatal infection, and antifungal therapy alone is often inadequate to control the infection. Surgical debridement of infected and necrotic tissue should be performed on an urgent basis.

2. Antifungal agents:
   a. Amphotericin B: Preparations available:
      • Lipid-complex Amphotericin B (AMB-LC): Most preferred AMB due to a lower incidence of nephrotoxicity, higher tissue penetrability and higher tissue concentration. 5 mg/kg/day, dilute in 200 cc 5% dextrose over 2–3 hrs infusion. First-line AMB provided the supply logistics are favourable.
      • Amphotericin B deoxycholate (AMB-D): Only if cost and availability of L-AmB is an issue; 1 mg/kg/day in 5% dextrose, slow infusion over 6–8 hrs.
   b. Posaconazole: 300 mg twice a day on the first day, followed by 300 mg once a day.
   c. Isavuconazole: 200 mg three times a day for two days, followed by 200 mg once a day.

3. Novel iron chelators:
As iron is needed for the growth of mucor, iron chelators can also be helpful in the management of mucor patients (except for deferoxamine).

4. Other adjunctive therapies:
Hyperbaric oxygen therapy has the advantage to improve the ability of neutrophils to kill the organism.

Conclusion and Key Messages
As compared to mucor infection at other sites, ROCM has higher survival rates because patients are frequently diagnosed earlier. Also, the underlying causes such as overuse of steroids and uncontrolled DM can be corrected. In patients with mucormycosis, timely detection, surgical management and appropriate debridement, right antifungal therapy, and control of risk factors like DM and judicious use of steroids are the main parameters of successful management of this fatal infection.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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