COVID Associated Mucormycosis: A Study on the Spectrum of Clinical, Biochemical and Radiological Findings in A Series of Ten Patients

Pranabananda Pal1*, Nandini Chatterjee2, Soumitra Ghosh3, Biman Kanti Ray4, Pradip Mukhopadhyay5, Kaustav Bhunia6, Smiti Rani Srivastava7, Souvik Adhikari8, Debasish Barman9, Binata Banerjee10, Madhumita Mukhopadhyay11, Jyotirmoy Pal12

Abstract
Background: There is more than twofold rise in prevalence of mucormycosis cases in India during the COVID-19 pandemic which needs to be evaluated.
Aims: The study aimed to document the spectrum of cases of mucormycosis seen at our Institute during COVID-19 times.
Methods: The study is a retrospective observational study carried out at our Institute from May 2021 to mid-June 2021. All patients with biopsy-proven mucormycosis were enrolled in the study. The patients were subjected to complete history taking, ophthalmological examination, and imaging studies. The patients were treated with a multidisciplinary approach with antifungal therapy as well as surgical intervention when needed.
Results: Ten patients (n=10) were seen, with a mean age of 50.3 years. The major risk factors included recent use of steroids, uncontrolled diabetes, and CKD. The most common presentation was swelling of unilateral eye and ptosis, followed by loss of vision. Inflammatory marker (CRP) and d-dimer were raised at presentation in all cases. Imaging showed the spread of infection from paranasal sinus to orbit and brain via cavernous sinus, which was a poor prognostic factor. Intravenous Amphotericin-B was given to all patients for at least 4 weeks. Two patients were discharged after completion of treatment and mortality was seen in three patients.

Conclusion: We present an array of COVID-associated-mucormycosis (CAM) cases from Eastern India. CAM is presenting with rhino-orbito-cerebral involvement. There is poor outcome with cerebral involvement and high incidence of adverse effects with deoxylolate formulation of amphotericin-B. The causal association of COVID-19 with mucormycosis needs to be unearthed but possible preventive role of anticoagulation should be evaluated.

Introduction

Mucormycosis is an opportunistic fungal infection caused by fungi of order Mucorales which includes multiple genera including Rhizopus, Rhizomucor, Mucor, Actinomucor, and Lichtheimia (formerly Absidia), etc. This is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality. These fungi are a common commensal in healthy individuals and cause infection primarily in immunocompromised patients with uncontrolled diabetes, defects in phagocytic function (neutropenia or glucocorticoid treatment), and/or elevated free iron level (supports fungal growth). The estimated prevalence of mucormycosis is around 70 times higher in India than that in global data. However, during the second wave of COVID-19 pandemic in India, there is surge of rhino-orbito-cerebral mucormycosis (ROCM) cases which has made India the highest burden of mucormycosis cases. Multiple risk factors including overuse of steroids, poor control of hyperglycemia, ketoacidosis, increased serum-free iron (due to hyperferritinemia and acidosis), and lymphopenia (reflected in high neutrophil-lymphocyte ratio, NLR) are classical risk factors. Along with these, careless use of multiple antibiotics, overuse of zinc supplements, and poor mask hygiene are being suspected as possible risk factors but the exact cause is yet to come forward. The unique nature of COVID-associated mucormycosis (CAM) cases is a predilection to rhino-orbital involvement. Whether COVID-19 infection is an independent risk factor of ROCM is a valid research question to be answered in the future.

The progressive nature of ROCM needs to be managed promptly with great concern as delay in appropriate management leads to worse outcome. Hence early diagnosis and treatment with a multidisciplinary team are necessary consisting of experts in the diagnostic field (microbiology, pathology, radiology), medical (internal medicine, neuro-medicine, critical care), and surgical (otorhinolaryngology, ophthalmology, neurosurgery) care.

Methods

Case records, biochemical and radiological investigations of patients admitted to our institute in May and June 2021 were retrospectively analyzed and data of ten patients (n=10) of histopathologically diagnosed mucormycosis cases were obtained. A detailed history was taken and examination was done as per prefixed proforma. Figure 1 shows the institutional protocol of management of cases.

Though liposomal amphotericin-B is the standard choice of therapy, due to financial constraints deoxylolate formulation of the drug was given to the patients as per government guidelines and it was associated with high incidence of adverse effects. We took the help of descriptive statistical tools by using descriptive and inferential statistics via Microsoft Excel 2016 and SPSS version 20.0 to assess the clinical spectrum of the disease.

Results

We present clinical, biochemical, and imaging findings of ten patients with CAM after a retrospective review and detailed clinical examination. A summary of background and risk factor profile is summarized in Table 1 and clinico-radiological and biochemical findings of all the cases are summarized in Table 2.

Case 1: A 58-year-old female, known diabetic for six years, on regular oral hypoglycemic agents (OHA), presented with right orbital swelling (Figure 1A) and diplopia for 5 days in post-COVID period (Day 30). During COVID she was prescribed multiple antibiotics, and there was history of steroid therapy and oxygen requirement. Biochemical investigation revealed increased CRP, raised neutrophil-lymphocyte ratio (NLR) and D-dimer. KOH mount microscopy was positive for broad aseptate hyphae suggestive of Mucorales. Diagnostic nasal endoscopy (DNE) showed necrotic mucosa on the right middle meatus and ophthalmological examination was normal. MRI showed involvement of nasal cavity, maxillary and ethmoid sinus along with signal changes in extraocular muscles and optic nerve on the right side [Figure 1B].

She was treated with Endoscopic debridement of the affected areas and Amphotericin-B is being continued for 4wks. Endoscopic biopsy was sent for HPE which showed non-septate hyphae with right-angle branching in H&E stain. She’s now hemodynamically stable and has a preserved vision with favorable course indicating halted progression of the disease.

Case 2: A 65 years old male, known DM for 1 year and recent use of steroid during COVID, presented with left eye ptosis and complete ophthalmoplegia for 1 week and loss of vision (LOV) in left eye for 1 day. DNE showed pale mucosa on the left middle turbinate and mycological evidence of mucor was positive in KOH mount preparation. MRI showed involvement of nose, PNS, and left orbital apex. Endoscopic debridement with orbital clearance was done.

Case 3: A 64 years old female, known diabetic for 12 years who received multiple antibiotics, steroids, and oxygen therapy during COVID developed blackish discharge from...
right nose and black discoloration of the hard palate (Fig 2A). There was bilateral complete LOV with non-reactive, dilated pupils. MRI revealed the extensive destruction of bilateral maxillary, ethmoid and frontal sinus (Figures 2E,2F). There was evidence of acute infarction at right basi-frontal lobe of forebrain (Figures 2C,2D). Biochemical parameters showed raised CRP and D-dimer. She underwent open debridement with craniotomy but succumbed to death in the postoperative period due to septic shock.

Case 4: A 38 years old male non-diabetic but history of steroid use recently developed toothache following recovery of COVID and dental extraction was done by dentist. However, following extraction, there was development of oro-antral fistula and persistent discharge from the site of extraction [Figure 3]. KOH mount microscopy from the pus was suggestive of mucor and he was started on Amphotericin-B. MRI brain showed there is evidence of disease spread to the medial wall of orbit along with maxillary and ethmoid sinus. He underwent endoscopic debridement of the diseased area and currently on antifungal therapy with favorable prognosis.

Case 5: A 36 years old non-diabetic male with recent history of steroid use developed right nasal obstruction with nasal discharge along with right eye pain. Examination of the right eye revealed right eye swelling and black discoloration of the hard palate (Fig 2A). There was bilateral complete LOV with non-reactive, dilated pupils. MRI revealed the extensive destruction of bilateral maxillary, ethmoid and frontal sinus (Figures 2E,2F). There was evidence of acute infarction at right basi-frontal lobe of forebrain (Figures 2C,2D). Biochemical parameters showed raised CRP and D-dimer. She underwent open debridement with craniotomy but succumbed to death in the postoperative period due to septic shock.
therapy during COVID developed right eye ptosis and loss of vision. MRI brain showed early involvement of cavernous sinus along with right maxillary and ethmoid sinus and orbit. He had undergone open debridement of the disease with craniotomy and is now being treated in critical care unit.

**CASE 6:** A 66 years female, known DM and CKD with severe COVID while on treatment with antibiotic, steroid, and O2 therapy developed black discoloration of palate and loss of vision in the bilateral eye. On imaging, she had involvement of bilateral orbit. She was started on Amphotericin-B but succumbed to death before any surgical intervention can be done.

**CASE 7:** A 62y non-diabetic male with a recent history of steroids presented with unilateral headache and diplopia. On examination, there was left eye ptosis with complete ophthalmoplegia and LOV. Imaging study showed disease spread from ethmoid sinus to orbital apex and destruction of lamina papyracea and he underwent endoscopic debridement with orbital clearance.

**CASE 8:** A 57 years old male with recent DM and history of multiple systemic symptoms presented with bilateral eye pain and sudden onset LOV. He had no perception of light on the right eye and on fundus examination, there was pale retina with “cherry red spot” - suggestive of CRAO (Fig. 4C). Imaging study showed destruction of right middle turbinate and ethmoid sinus and contrast enhancement in right orbital apex. The patient underwent infrastructure maxillectomy with orbital decompression and now on IV Amphotericin-B therapy.

**CASE 9:** A 28 years old female health worker, non-diabetic presented with left maxillary pain and toothache in post-COVID period. DNE showed pale discoloration of mucosa on middle turbinate with no bleeding during endoscopic punch biopsy. Mycological evidence of invasive disease was positive and she was given Amphotericin-B for 2 weeks and then shifted to oral Posaconazole therapy due to agranulocytosis following AmB therapy.

**CASE 10:** A 32 years old male with DM developed gum pain following recovery from COVID and underwent CT scan which revealed left maxillary sinusitis. He underwent Left FESS in outside hospital and the debrided sample showed evidence of invasive mucormycosis. He was referred to our institute and started on antifungal therapy. On review surgery endoscopy guided clearance of disease was done from the left ethmoid sinus. The patient was shifted to Posaconazole therapy after severe anaphylaxis following Amphotericin-B.

### Analysis and Discussion

The most common site of systemic mucormycosis is rhino-orbito-cerebral type in 40% cases but the COVID-associated cases are mostly rhino-orbital and rhino-orbito-cerebral type. The estimated incidence of those is 42% and 24% respectively in the systematic review by Pal R. et al.5 All of the patients included in our study had either rhino-orbital (60%) or rhino-orbito-cerebral involvement (40%).

All of them had a recent history of COVID-19 infection. The mean duration between diagnosis of COVID-19 and development of symptoms of mucor was days 22.9 days (5-40 days). Age distribution of the patients revealed a mean age of patients was 50.6 years. In this case study, recent steroid use was the most common risk factor (80%), followed by history of DM (70%), CKD (10%), and alcoholism (10%). Among the diabetic patients, 4 patients (57%) were long-term diabetic and 3 patients had recently diagnosed diabetic (43%). Overuse of steroids in dose and duration was evident as 5 patients had no history of hypoxia out of 8 patients (62.5%) who received steroids. There were use of two or more antibiotics in 7 out of 10 (70%) patients indicating there is indiscriminate use of antibiotics for viral illness.

The presenting features of ROCM are widely varied. The most commonly encountered symptom was swelling of the unilateral eye (60%). Headache and loosening of teeth with gum pain were early warning symptoms whether the involvement of extraocular muscles (ptosis and complete ophthalmoplegia) or palate (ulcer, black discoloration) was signs of advanced spread of infection. There was loss of vision (LOV) in 4 patients (40%) among them three were due to direct involvement of optic nerve and one had developed central retinal artery occlusion (CRAO). Early reporting to medical facility leading to prompt
## Table 2: Clinico-biochemical findings and summary of management of cases

<table>
<thead>
<tr>
<th>Case No</th>
<th>Presenting features</th>
<th>Biochemical findings</th>
<th>Surgical procedure</th>
<th>Medical therapy</th>
<th>Serious adverse effects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right eye swelling and Diplopia</td>
<td>CRP 121, D-DIMER 5.2, NLR 5.9</td>
<td>Endoscopic debridement + orbital clearance</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>2</td>
<td>Left eye swelling and ptosis, Total ophthalmoplegia, LOV</td>
<td>CRP 62, D-DIMER 1.6, NLR 6.5</td>
<td>Endoscopic debridement + orbital clearance</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>3</td>
<td>Right nose discharge, B/L orbital swelling</td>
<td>CRP 147, D-DIMER 3.3, NLR 8.5</td>
<td>Open debridement + Orbit exenteration</td>
<td>AmB</td>
<td>Hypokalemia, Hypomagnesemia</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>Right eye swelling and ptosis, LOV</td>
<td>CRP 80, D-DIMER 0.63, NLR 5.6</td>
<td>Endoscopic debridement</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>5</td>
<td>Black discoloration following dental extraction</td>
<td>CRP 80, D-DIMER 6.2, NLR 8.8</td>
<td>Death before surgery</td>
<td>AmB</td>
<td>AKI</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>Black discoloration of palate and LOV</td>
<td>CRP 250, D-DIMER 8.2, NLR 7.7</td>
<td>Open total maxillectomy + orbital clearance</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>7</td>
<td>Left eye swelling and ptosis, Total ophthalmoplegia, LOV</td>
<td>CRP 11, D-DIMER 6.9, NLR 7.7</td>
<td>Endoscopic medial maxillectomy</td>
<td>AmB</td>
<td>Hypokalemia</td>
<td>On therapy</td>
</tr>
<tr>
<td>8</td>
<td>Right eye swelling and ptosis, LOV</td>
<td>CRP 55, D-DIMER 2, NLR 5.5</td>
<td>Left-sided FESS + debridement</td>
<td>AmB and oral PSZ</td>
<td>Hypokalemia</td>
<td>Discharged</td>
</tr>
<tr>
<td>9</td>
<td>Headache, Maxillary pain</td>
<td>CRP 30, D-DIMER 0.3, NLR 3.2</td>
<td>Right-sided FESS + debridement</td>
<td>AmB and oral PSZ</td>
<td>Hypokalemia</td>
<td>Discharged</td>
</tr>
<tr>
<td>10</td>
<td>Headache, Looseing of teeth</td>
<td>CRP 32, D-DIMER 4.1, NLR 8</td>
<td>Extensive necrosis of bilateral PNS and orbit (right&gt;left)</td>
<td>AmB</td>
<td>Anaphylaxis</td>
<td>Discharged</td>
</tr>
</tbody>
</table>

Abbreviations: AKI Acute Kidney Injury, AmB Amphotericin-B, DM diabetes mellitus, CKD chronic kidney disease, PSZ Posaconazole, NLR neutrophil-lymphocyte ratio, LOV loss of vision, FESS functional endoscopic sinus surgery. D-dimer: normal value <0.5mcg/ml, CRP C-reactive protein: normal value <5mg/dl.

---

Fig. 2: (Case 3): (A,B) clinical picture showing bilateral orbital swelling and discoloration of palate. (C,D) T2 FLAIR and DWI sequence showing acute infarct at right forebrain. (E,F) Extensive necrosis of bilateral PNS and orbit (right>left)
invasive mucormycosis with infarction of the tissue around paranasal sinus is unclear and raises the question: infarction or invasion, which one is the first (‘The egg or the chick’ dilemma). Along with the focus to prevent the classical risk factors of ROCM, the role of post-COVID hyperinflammatory state causing possible venous thrombosis that can act as a nidus for growth and angio-invasion of the fungal pathogen which is a usual commensal in paranasal sinus area needs to be explored. Usage of anticoagulants in COVID-19 remains an area of research with no definite guidelines published to date to address the timing, dosage, and duration of anticoagulation.11 Most internationally published guidelines, based on consensus statements and expert opinions, rarely address the requirement of post-discharge thromboprophylaxis.12 In this context, the need for standard guidelines on anticoagulant policy to address the risk of post-discharge thrombotic events, evident from persistently high D-dimer should be evaluated in future research.

The medical management of the patients was done with deoxycholate formulation of Amphotericin-B in the dose of 1 mg/kg/day in all patients and continued for a minimum of four weeks depending on the tolerability. All recovered patients were started on additional 4 weeks to 8 weeks of oral Posaconazole therapy depending on the underlying condition of patients. There were severe adverse reactions following Amphotericin-B deoxycholate therapy, hypokalemia (90%), AKI and hypomagnesemia (30%) being most common of them. Other adverse effects include, agranulocytosis (20%) and severe anaphylaxis (10%) which lead to discontinuation of therapy in two patients. Hence effective monitoring of patients with urea, creatinine, electrolytes and blood counts is necessary to prevent therapy-related catastrophe.

Though the efficacy of liposomal and deoxycholate formulation claims to be the same, poor adverse effect profile increases morbidity of patients managed with the latter. However, in resource-poor countries like India, the deoxycholate formulation may be used with strict vigilance on the serious adverse effects.

A total of 9 patients were managed by surgical intervention, of which 7 patients were managed by endoscopic debridement (77%) and in 3 patients open debridement with orbital exenteration/clearance (23%) was done. Radical debridement was associated with high mortality (66%) due to an increased chance of postoperative complications. Hence endoscopic approach should be the choice of intervention of choice where possible as it is associated with a favorable prognosis. Overall mortality was seen in 3 out 9 patients (33.3%) managed in our setup.

Very few studies were available online for comparison of mortality rate as the entity CAM is novel and yet to be explored by the clinicians. The updated systematic review of literature by Pal R et al. reported 34% overall mortality where there was the use of liposomal formulation of Amphotericin-B as the primary drug of choice. Here we have observed similar mortality using cheaper deoxycholate formulation of the drug which is an indicator of the similar efficacy of two formulations despite poor adverse effect profile of the latter. However, management of the adverse effects were cumbersome considering the rising prevalence of the disease in Indian hospitals due to the prolonged duration of therapy.

**Conclusion**

COVID-associated mucormycosis cases have a variety of presentation which needs high levels of suspicion from clinicians. We propose that patients recovering from COVID should be screened for symptoms of ROCM during routine follow-up. Apart from control of uncontrolled DM and judicious use of steroids and antibiotics, proper anticoagulation protocol to be followed during and after COVID-19 infection.

Management of patients with deoxycholate amphotericin-B is associated with serious adverse effects which should be closely monitored. Endoscopic surgery should be done, when possible, for clearance of necrotic tissues.

The infection is associated with
high mortality, especially if cerebral involvement is there.

**Take Home Message**

1. COVID-associated-mucormycosis predominantly presents as ROCM.
2. Cerebral involvement predisposes to poor outcome.
3. Amphotericin-B deoxycholate is an effective option but adverse effects need to be monitored and managed carefully.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/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.

**References**

3. AK AK, Gupta V. Rhino-orbital Cerebral Mucormycosis. [Updated 2021 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.