

Prospective Longitudinal Study on COVID-19 Associated Mucormycosis: Our Experience

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ABSTRACT

Introduction: Mucormycosis, also known as *zygomycosis*, is a serious fungal infection caused by a group of fungi known as Mucorales. In 2021–2022, there had been a significant increase in the incidence of COVID-19 associated mucormycosis (CAM) cases in India, especially among patients with comorbidities such as uncontrolled diabetes, prolonged intensive care unit (ICU) stay, and immunosuppression.

Materials and methods: Prospective longitudinal study was carried out in the Department of ENT, Bangalore Baptist hospital from a period of April 2021 to December 2022 where 39 patients diagnosed with mucormycosis by mycological/histological/radiological diagnosis were included and who were followed up to 18–20 months.

Results: Out of 39 patients, 13 were female and 26 were male (F: M ratio; 1:2). Their mean age was 51.56 years (range: 28–78 years). Patients 37 out of 39 were fit to undergo endoscopic surgical debridement, out of which 4 patients underwent orbital exenteration. During follow-up period, 23 patients underwent revision endoscopic nasal debridements, 9 underwent unilateral maxillectomy and 6 patients underwent bilateral maxillectomy. Twelve patients had lower motor neuron (LMN) facial nerve palsy, among whom 5 have recovered. Four patients had severe otitis media with conductive hearing loss who underwent myringotomy and grommet insertion. Only one patient had sudden sensorineural hearing loss (SSNHL).

Conclusion: Mucormycosis remains a serious fungal infection that requires heightened awareness and a multidisciplinary approach for optimal management. In our experience, CAM had a good prognosis in spite of inadequate medical management due to non-availability of antifungal medication at the time CAM surged. A meta-analysis of all studies published in the last 3 years may help us understand CAM better and guide us regarding management protocols in the future.

Keywords: COVID-19 associated mucormycosis, Endoscopic debridement, Maxillectomy, Mucormycosis, Otitis media with effusion, Sinusitis. *Clinical Rhinology* (2024): 10.5005/jp-journals-10013-1403

INTRODUCTION

Rhino-orbito-cerebral mucormycosis (ROCM) is a potentially lethal, fulminant fungal infection. It is caused by ubiquitous filamentous fungi belonging to the order of Mucorales. Patients with immunosuppressive states such as diabetes mellitus (DM), hematologic malignancy, hematopoietic stem cell transplantation, solid organ transplantation, immunosuppressive drugs, iron overload, chronic renal failure, metabolic acidosis, etc., are predisposed. Among the several Mucorales genera, species from the genus *Rhizopus* are the most common causes of ROCM and are detected in the majority of the cases, followed by *Lichtheimia*, *Mucor*, *Rhizomucor*, *Saksenaia*, *Apophysomyces* and *Cunninghamella*.¹ Infection is the result of inhalation of *sporangiospores*.² Further angioinvasion and thrombosis of blood vessels leads to tissue necrosis.³

The increasing incidence of COVID-19 associated mucormycosis (CAM) in India had become a matter of concern. There had been an exponential increase in its incidence in India concomitant with the second wave of COVID-19. Large numbers of cases of CAM have been reported from all over India, with many states resorting to the declaration of an epidemic as well as making it a notifiable disease. We wish to elaborate on the history, clinical presentation, comorbidities, course and prognosis of CAM in patients admitted to our hospital.

MATERIALS AND METHODS

Prospective observational study was carried out in Department of ENT, Bangalore Baptist hospital from a period of April

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2021–December 2022 and 39 patients diagnosed with mucormycosis were included. The objective of our study was to evaluate the entire course of CAM and its prognosis in patients admitted to our hospital. We included all patients with mycological evidence (KOH Smear–observation of aseptate hyphae branching at wide angle and ribbon-like hyphae associated with tissue damage suggestive of mucorales), histological evidence of mucormycosis in tissue biopsy taken either by diagnostic nasal endoscopy or endoscopic nasal debridement and radiological evidence of bone destruction, orbit or brain invasion by contrast enhanced computed tomography (CT) scan or gadolinium enhanced magnetic resonance imaging (MRI) scan of paranasal sinuses and orbit.

For all patients, who were concurrently positive for COVID–19 and for patients on admission, a routine reverse transcription PCR (RT-PCR) test for severe acute respiratory syndrome coronavirus

2 (SARS-CoV-2) was obtained. History, clinical presentation, comorbidities, radiological findings, course, follow-up and prognosis of CAM were recorded.

RESULTS

We found 39 patients with CAM and looked at their medical history (Table 1). Out of 39 patients, 13 were female and 26 were male (F: M ratio; 1:2). Their mean age was 51.56 years (range: 28–78 years). About 41% (16) of the patients had a positive SARS-CoV-2 RT-PCR test

result at the time of diagnosis with CAM. 43% (17) tested negative for COVID-19 at the time of diagnosis but had a prior positive test record and had been admitted for treatment with symptoms of CAM. The remaining 15% (6) had negative SARS-CoV-2 RT-PCR results on diagnosis of CAM and no prior record of positive COVID-19 testing. Patients (14) concurrently positive for SARS-CoV-2 had mild to moderate disease and were treated for COVID-19. Two patients had severe COVID-19.

All patients had DM with high blood sugars at the time of occurrence of CAM. Out of 39 patients, 24 were newly diagnosed diabetic along with CAM, with a mean HbA1c of 11.16 (range: 6.8–15.5).

The most common initial presenting symptoms were facial pain and facial swelling followed by eye swelling, toothache and loss of vision. The rarer first presenting symptoms were headache, double vision, eye pain, and facial numbness.

On radiological assessment (Fig. 1), 12 patients had infratemporal fossa involvement, 17 patients had pterygopalatine fossa involvement, 19 patients had orbital involvement, and 5 patients had cerebral involvement. In the follow-up period, 9 patients had unilateral maxillary involvement and 6 patients had bilateral maxillary involvement.

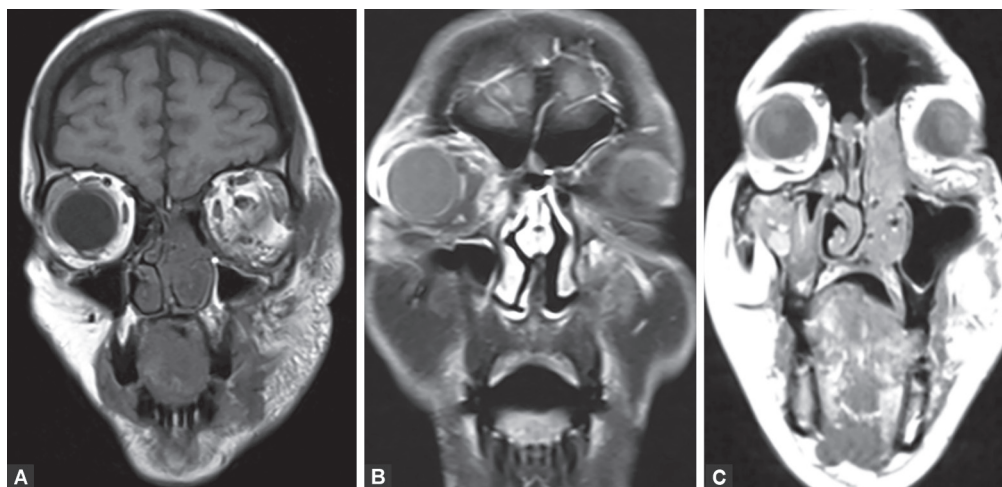
COVID-19 coinfection did not affect our management course. All cases received medical treatment (Injection Amphotericin) for CAM according to the availability, affordability and tolerability of the drug (range: 50–3 gm) along with oral posaconazole for 3 months during the postoperative period (in patients without cerebral involvement) and for 9 months postoperative period (in patients with cerebral involvement). In addition, measures to control the general health condition, underlying risk factors and complications, together with surgical management to reduce the fungal load were done.

Patients 37 out of 39 were fit to undergo endoscopic surgical debridement, out of which 4 patients underwent orbital exenteration due to orbital disease. 2 patients who had severe COVID-19 infection with other comorbidities and were in ICU on ventilator support were not fit to undergo surgery, and they expired. 37 patients are alive and on regular follow-up.

In the last 20-month follow-up period of the 37 patients, 23 underwent revision endoscopic nasal debridements, 9 underwent

Table 1: Clinicopathological features

Variable	Total
Gender (n = 39)	
• Male	26
• Female	13
Age (n = 39)	
• Mean	51.56 years
• Range	28–78 years
Most common first presenting symptom	Facial pain facial swelling
COVID-19 STATUS	
• Diagnosed COVID-19	16
• Post-COVID-19	17
• No COVID-19 history	6
HbA1c (n = 24)	
• Mean	11.6
• Range	6.8–15.5
Radiological involvement	
• Pterygopalatine fossa (PPF)	17
• Infratemporal fossa (ITF)	12
• Cerebral	5
• Orbit	19
• Maxilla	
– Unilateral	9
– Bilateral	6
Follow-up period	18–20 months



Figs 1A to C: Magnetic resonance imaging of nose and paranasal sinus mucormycosis: (A) Disease in left nasal cavity and orbit; (B) Disease in right orbit; (C) Disease in right maxillary sinus and left nasal cavity and ethmoid sinus

unilateral maxillectomy and 6 patients underwent bilateral maxillectomy. 12 patients also had lower motor neuron (LMN) facial nerve palsy among which 5 have recovered. 4 patients had severe otitis media with conductive hearing loss, they underwent myringotomy and grommet insertion. 1 patient had sudden sensorineural hearing loss (SSNHL) which did not recover.

DISCUSSION

Rhino-orbital mucormycosis is an opportunistic fungal infection. Globally, the prevalence of mucormycosis varies from 0.005 to 1.7 per million populations. Pre-COVID era estimate of year 2019–2020 the reported prevalence is nearly 80 times higher (0.14 per 1,000) in India compared to developed countries.^{4–6}

The mean age of patients in our study was 51.56 years, with a male to-female ratio of 2:1. Similar results were reported by White et al.⁷ in their study of 135 adults with a median age of 57 years and a male to female ratio 2.2:1.

Many schools of thought have been put forward in relation to the etiology of CAM. Immune dysregulation, neutropenia and lymphopenia caused by COVID-19 infection, uncontrolled DM, diabetic ketoacidosis (DKA), COVID-19 associated high blood glucose levels, widespread use of steroids, and broad-spectrum antibiotics for treatment of COVID-19 may have led to a rise in mucormycosis.^{8–11} Even after the first wave in 2020, there was an increase in the number of patients and reports of CAM which remained uncertain, but there has been an exponential increase in the incidence in India with the second wave of COVID-19.¹²

The management of CAM is challenging, especially because the radiology may not correlate with the actual extent of disease. All our CAM patients underwent radiological evaluation (CT and MRI) and surgical debridement followed by medical management with Injection Amphotericin for CAM according to the availability, affordability and tolerability of the drug (cumulative dose range: 50–3 gm). In the postoperative period, oral posaconazole for 3 months without cerebral involvement and for 9 months with cerebral involvement was prescribed.

As per our observations, 5.1% (2) of the patients died. They were not fit for any active treatment as they were on ventilator support with severe COVID illness. Previous studies have reported greater fatality rates of more than 30%, but some have also found lower rates of around 9%.^{13–15}

In our study, all those who survived had to undergo repeat debridements, including maxillectomies. Patients 15 out of 37 underwent maxillectomy out of which 9 patients underwent unilateral maxillectomy and 6 patients underwent bilateral

maxillectomy compared to a study by Meher R et al.¹⁶ in which 32 out of 131 patients underwent open maxillectomy. All of our patients are still undergoing dental, prosthetic and psychosocial rehabilitation (Figs 2 to 4). Four patients underwent orbital exenteration due to orbital disease and had increased morbidity due to repeated orbital socket infections. Many healthcare professionals are still uncertain regarding orbital exenteration and duration of antifungal medication, since there are no standard guidelines for management.

We also observed that in different groups of CAM patients, the same fungal disease had varied presentation either with:

- Acute-onset fatal CAM with rapid progression.
- Loss of vision due to central retinal artery occlusion (CRAO)/ central retinal vein occlusion (CRVO) and not due to fungal disease with direct invasion of orbit.
- Delayed subacute presentation of nasal symptoms lasting weeks to months.
- Isolated involvement of the palate (osteomyelitis) without involvement of the nose or sinuses, where postoperative histopathological and microbiological examination confirmed invasive fungal etiology.

Following surgery and medical management, only a small set of patients succumbed to the disease with a reported death rate of about 1.15% in CAM whereas mucormycosis in pre COVID-19 times had a much higher case-fatality rate of about 50% or more.¹⁷ Though all these CAM patients had high HbA1c and high blood glucose



Fig. 2: Patient rehabilitated with temporary denture



Fig. 3: Patient rehabilitated with temporary denture

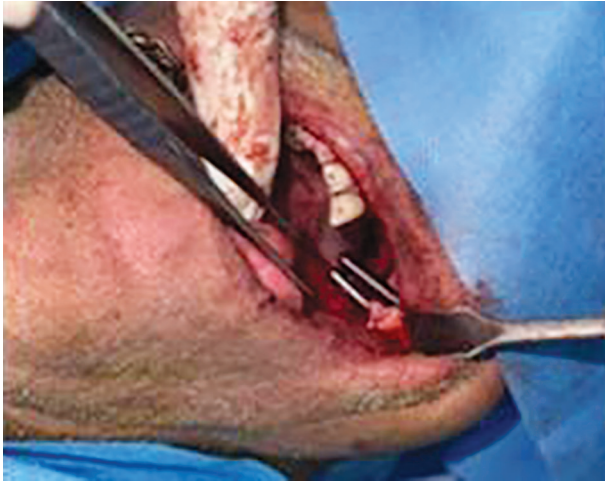


Fig. 4: Zygomatic implant for permanent denture fixation

levels at presentation, in those newly diagnosed diabetics, blood glucose values and HbA1c have normalized and medication has been discontinued. Hence, we can assume it as a transient COVID-19 induced hyperglycemia.

The majority of patients with stable radiological intracranial disease with or without retro-orbital involvement, who have not undergone orbital exenteration/neurosurgical intervention, are asymptomatic and survive without any progression of disease or adverse events. So it is still not clear when to stop the antifungal medication posaconazole. It was also observed that few patients with ophthalmoplegia regained eye movements in the follow-up period. Although 19 patients had orbital involvement of CAM, only 4 underwent exenteration and 15 were observed. All 15 patients have no progression of disease during the 20-month follow-up period. Hence, it remains unexplained whether all patients with vision loss and orbital involvement require exenteration or can be observed and planned for repeat debridement if required.

Twelve patients also had LMN facial nerve palsy, of these, 5 have recovered completely. As per the study by Das SK et al.¹⁸ skull base involvement can be hypothesized to be the predominant route of facial nerve involvement causing palsy by concomitant hypoxic neural damage due to involvement of the vasa nervosum as CAM is angioinvasive. There are studies that suggest that COVID-19 infection as such might have triggered facial nerve palsy, leaving us with a knowledge gap regarding the cause of LMN facial palsy.^{19,20}

With these observations, we have more unanswered questions on the possibility of different presentation types of CAM or are we looking at different stages of progression of the same disease, i.e,

- Rapidly progressive fatal CAM with intracranial complications requiring immediate aggressive surgical and medical management for a better prognosis.
- Acute inflammatory CAM with rhino orbital disease.
- Chronic stable inflammatory CAM with delayed presentation.
- Limited invasive fungal disease where adequate surgical debridement would suffice with limited need for expensive antifungal medication.

CONCLUSION

In our experience, CAM had a good prognosis in spite of inadequate medical management due to non-availability of antifungal

medication at the time of CAM surge. Long-term follow-up and surveillance of patients with mucormycosis is essential to assess the efficacy of treatment and management of complicated sequelae. Research efforts are needed to develop more effective therapies and preventive strategies for mucormycosis related complications. There have been many studies on CAM from all over India with varied results; a meta-analysis of all those prospective studies may help us in understanding CAM better and guide regarding management protocols in the future.

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