Management of Mucormycosis in Post COVID-19 Patients and Its Outcome in a Tertiary Care Center: Our Experience

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Abstract To assess the common presentation and extent of disease involvement clinically and radiologically and treatment modalities, sequelae of the disease, complications and treatment response. Mucormycosis is a life-threatening infection that most commonly affects immunocompromised individuals and an exponential increase in the incidence of Rhino-orbital-cerebral mucormycosis was witnessed in the second wave of the COVID-19 pandemic, despite aggressive multimodal treatment carries a significant risk of mortality. A high index of suspicion is required in order to begin the appropriate diagnostic workup and treatment. This study is conducted to access the outcome and management of mucormycosis in post covid 19 patients. The prospective study includes 180 Patients, who are attending to E.N.T. outpatient department, Triage and patients referred from other departments who had suspected/confirmed Rhino-orbital-cerebral mucormycosis/underwent surgery and/or medical treatment or both. In our study mucormycosis predominantly affected age group between 40 and 60 years, more common in males (77.8%) than females (22.2%), 77.8% patients had post covid status. Most common risk factor was diabetes mellitus. 76% patients had undergone endoscopic/open surgery and 24% patients underwent only medical treatment. Among 138 patients operated, 40% had recurrence and mortality was 16.1% (significantly reduced). Early diagnosis and prompt intervention is paramount to reduce morbidity and mortality. Liposomal Amphotericin B is most effective antifungal with manageable side effects. Patients who underwent Radical debridement either endoscopically or open approach, had better outcome with minimal recurrence rates. Combined medical and surgical treatment has better outcome, lesser recurrence and mortality.

Keywords Mucormycosis · Liposomal Amphotericin B · FESS (Functional endoscopic sinus surgery) · ROCM (Rhino-orbital-cerebral mucormycosis)

Introduction

COVID-19 since beginning showed variation in its presentations, complications and sequelae [1]. Among various complications associated with COVID-19 that are being reported, the fungal infection mucormycosis (known as black fungus) becoming a serious issue in India due to its uncommon surge and high morbidity [2]. Mucormycosis is a fungal infection belonging to the family Mucorales [3]. Rhizopus oryzae is the most common organism isolated from mucormycosis patients and is responsible for 70% of all cases [3]. The major risk factors in patients with mucormycosis include uncontrolled diabetes mellitus with or without ketoacidosis and other forms of metabolic acidosis and immunocompromised conditions [3].

Intracranial spread of the fungus is rapid and progressive in nature, occurs either by direct extension across the bones like cribiform plate/ethmoid, walls of the frontal and sphenoid sinuses, or angioinvasion of the walls of the arteries and veins, causing microvascular thrombosis, occlusion and infarction [4].

Mucormycosis in the bone marrow may promote fungal growth by damaging the endothelial lining of vessels, resulting in vascular insufficiency and leading to bony necrosis and fungal osteomyelitis [2].
Loose teeth, gingival abscess, swelling and vague facial pain are the usual clinical presentation. Due to varied and vague clinical presentation and other post covid 19 morbidities and lack of awareness among patients and clinicians, there is usual delay in diagnosis, which leads to patient running from pillar to post. Hence patient presented with delayed complications of this disease. Earliest sign of blackening of the posterior end of the turbinate’s seen on diagnostic nasal endoscopy were followed by battery of radiological investigations, microbiological and histopathological sampling to confirm the diagnosis.

The use of high dose liposomal amphotericin B as a first-line treatment is strongly suggested, whereas intravenous Isavuconazole and intravenous or delayed-release oral tablet Posaconazole have also been advocated [2]. However, due to lack of availability and elevated cost also leads to increased morbidity and mortality in the initial phase.

This study was undertaken to assess the common presentation and extent of disease involvement clinically and radiologically and treatment modalities, sequelae of the disease, complications and treatment response.

Materials and Methods

Source of Data

180 patients who attended the department of Otorhinolaryngology OPD/triage/Causality and also referred from other departments for suspicious mucormycosis/skull base osteomyelitis with post covid status. Clinically/radiologically/microbiologically suspected mucormycosis were evaluated and treated.

Among the 180 patients, 100 patients were clinically suspected and were referred from surgical and medical departments, 50 patients from medical awareness/campaign, and 30 patients were of recurrent/incomplete treatment done elsewhere.

We devised a protocol based on the presentation and extent of involvement and were treated according to the following flow chart (Fig. 1).

On clinical suspicion a combination of CT and MRI was done. While CT helped in assessing the extent of bone involvement like orbital wall erosions, palatal erosions, sphenoid bone erosions and other sinuses wall erosions. MRI helped in assessing the soft tissue extensions into the pterygopalatine fossa, orbit, neural invasion, cavernous sinus, infratemporal fossa, orbital apex and brain.

Nasal swab for aseptate fungal spores was only for a provisional diagnosis to start antifungal therapy prior to surgery and also for radical or conservative surgical approach in addition to radiological assessment.

Antifungals mainly liposomal/Lipid complex Amphotericin B and Posaconazole were given, after a test dose and later escalation and titration of doses was done by monitoring of vitals/electrolytes/renal functions. Kidney injury was managed conservatively. Amphotericin was stopped 2–3 days prior to the surgery.

Based on CT/MRI and microbiology swab, surgical approach was planned accordingly. Depending on intraoperative extent of the disease and post operative histopathological confirmation of diagnosis, amphotericin was continued.

Antifungals were started on postoperative day 1 of surgery and were given a maximum cumulative dose up to 3–5 g and patients with CNS involvement were given up.

Fig. 1 Protocol
to 5–6 g. To complete the cumulative dose, it took approximately 30–50 days. 11.6% of patients were given retroorbital injection. 1 vial of amphotericin B (50 mg) reconstituted with 10 ml of sterile water, from this 0.8 ml containing 4 mg once daily retrobulbar injection given for 10 days.

**Results**

After the outbreak of COVID-19 from epicenter China, central city of Wuhan in 2019–2020, three waves were seen. Second wave had surge of mucormycosis, the cause for which is still being investigated but some study showed risk factors like diabetes mellitus, patients who were on aggressive steroid treatment. We being in a tertiary care center, we saw a lot of cases and operated around 138 cases, initially delay in diagnosis due to rarity and lack of education/awareness among patients, general populations and civilians. This unusual surge was investigated and diagnosed provisionally with radiological involvement of osteomyelitic changes respectively in nose / PNS / orbit / skull base and lungs. Among 180 patients, the following results were obtained.

Our study reveals that mucormycosis predominantly affected age group between 40 and 60 years, more common in males (77.8%) than females (22.2%), 77.8% patients had post covid status, KOH mount was positive for mucormycosis in 75.6% patients, type 2 diabetes mellitus is a common risk factor present in all patients (100%), Diabetic ketoacidosis (DKA) seen in 62.8% patients, Electrolyte Imbalance seen 72.2% patients, hypertension (HT) seen in 71.1%. Other risk factor includes Smoking (72.2%), Alcohol consumption (27.2%), and Anaemia (2.2%) [as showed in Table 1].

In this study patients presented with Fever (72.2%), Nasal obstruction (69.4%), Nasal discharge (71.7%), Headache (72.2%), Eye edema (71.7%), Loss of vision (70%), EOM fixed (71.7%), Proptosis (72.8%), Cheek swelling (72.2%), Palate involvement (70%), Facial nerve involvement (0.6%) and Trigeminal nerve involvement (0.6%) (Fig. 2).

180 patients received Amphotericin B, majority of patients developed adverse drug reactions (Table 2). The adverse drug reactions observed were fever (83%), chills and rigor (88%), Nausea and Vomiting (70%), Breathlessness (30%), Chest pain (20%), Electrolyte imbalance (72.2%), Anaemia (50%) and thrombophlebitis (78%) (Table 2).

In our study, the approach was according to the above-mentioned chart (Fig. 3). Out of 180 patients, 138 patients underwent surgery, almost all patients underwent FESS with debridement (100%), Medial maxillectomy (30%), Modified Denker’s/Caldwell Luc (21.7%), orbital decompression (69.4%), Clival/Retro sphenoid clival and other skull base approach (1.3%), Infratemporal fossa/ Pterygopalatine fossa (33.3%), Infrastructure maxillectomy (30%), TOTAL maxillectomy (15%), extended maxillectomy (7.24%) and Orbital Exenteration (7.25%) (Table 3). In 138 cases, initially FESS/EXTENDED FESS was done in 3/4th of cases, remaining cases and those who had recurrence of 40% underwent open approach and debridement, which includes different types of maxillectomy and debridement of infratemporal fossa, skull base and so on.

**Discussion**

Mucormycosis is an uncommon infection, it accounts for 8.3–13% of all fungal infections [5]. Post covid 19 pandemic, prevalence of mucormycosis in India increased

### Table 1 Demographic distributions

| Sl. No. | Frequency | Percent |
|---------|-----------|---------|
| 1 Age Range | 3–82 years | Most prevalent in 40–60 years | |
| 2 Sex | Female | 40 | 22.2 |
| | Male | 140 | 77.8 |
| 3 Post COVID status | Abesnt | 40 | 22.2 |
| | Present | 140 | 77.8 |
| 4 KOH | Abesnt | 44 | 24.4 |
| | Present | 136 | 75.6 |
| 5 DM | Present | 180 | 100 |
| 6 DKA | Present | 113 | 62.8 |
| 7 Electrolyte imbalance | Present | 130 | 72.2 |
| 8 HT | Present | 128 | 71.1 |
| 9 Smoker | Present | 130 | 72.2 |
| 10 Alcoholic | Present | 49 | 27.2 |
| 11 Anaemia | Present | 4 | 2.2 |
nearly 80 times compared to that of previous that is 0.14 per 1000 population [6].

COVID-19-associated mucormycosis is characterised clinically as rhino-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, or other, and includes uncommon, rare manifestations such as endocarditis, osteomyelitis, and peritonitis. The rhino-orbito-cerebral (ROCM) variant is the most common in clinical practice around the world [7].

Depending on the extent of disease clinically, ROCM is classified into 3 stages –

Stage 1—Rhino-maxillary mucormycosis (RMM).
Stage 2—Rhino-orbital mucormycosis (ROM).
Stage 3—Rhino-orbito-cerebral mucormycosis (ROCM).

In the Rhino-maxillary stage, nasal obstruction, nasal discharge is the most common presentation followed by facial pain, paraesthesia, fever, soft tissue swelling of the face and palatal ulcerations. In the rhino-orbital stage eyelid oedema, proptosis, opthalmoplegia, blurry vision, loss of vision etc. While with intracranial spread (rhino-orbito-cerebral stage), in addition to the above symptom’s patients have opthalmoplegia, diplopia, altered sensorium, hemiplegia, loss of consciousness, fever, headache and vomiting.

Our study reveals that mucormycosis predominantly affected males (77.8%) and with mean age of 48.8 ± 5, lowest age being 3 years and maximum age of 82 years. In a study by Twinkle Choksi et al. the mean age of patients was 53.5 (12.5 [range, 32–86]) years; 48 patients (66%) were men and 25 (34%) were women. [8]

The preliminary diagnostic tools used are DNE (diagnostic nasal endoscopy) with or without biopsy followed by nasal swab for KOH mount and the radiological investigations included CT scan and MRI.

MRI is the gold standard investigation for the diagnosis of Mucormycosis. It helped us to know the complete extent of the disease, also for earliest detection of soft tissue involvement, like involvement of pterygopalatine fossa, infratemporal fossa, pterygomaxillary fissure, retroorbital area, cavernous sinus and CT was performed in order to assess bony involvement [9]. Inspite of the radiological changes being subtle and inconclusive in the early stages, evidence of retro-maxillary fat plane stranding and attenuation of the soft tissue in the CT scan and hyperintense lesion in the retro-maxillary area in an MRI, serve as early radiological pointers towards the diagnosis of mucormycosis.

Some studies states PET-CT is an effective tool for detecting and assessing treatment response [10]. However owing to its false positivity due to inflammation in post operative

### Table 2: Adverse reactions to Amphotericin-B

| Sl.no | Reactions               | Percentage (%) |
|-------|-------------------------|----------------|
| 1     | Fever                   | 83             |
| 2     | Chills and rigor         | 88             |
| 3     | Nausea and vomiting     | 70             |
| 4     | Breathlessness           | 30             |
| 5     | Chest pain               | 20             |
| 6     | Electrolyte imbalance    | 72.2           |
| 7     | Anaemia                  | 50             |
| 8     | Thrombophlebitis         | 78             |
period in patients and also not a cost-effective tool, it is not considered in our study. Thus, we have considered Diagnostic nasal endoscopy, biopsy, CT and MRI for most of our cases.

In our study maxillary sinus (90.7%) is commonly involved followed by sphenoid sinus (84%) ethmoid sinus (70.3%) and Frontal sinus (60%). Orbital involvement (minimal to gross) was present in 70% cases. Multiple cranial nerve involvement is seen in 4 patients.

The treatment protocol included medical, surgical and combined approaches.

Medical Management

The drug of choice for mucormycosis has always been liposomal amphotericin B but due to sudden surge of cases during the 2nd wave of covid 19 an acute scarcity in the
supplies was noted. Liposomal form being safest among all other forms, due to lack of availability, lipid complex and
conventional forms were used initially and with subsequent adequate availability of liposomal form it was switched over
to the same.

Antifungals was given after test dose. The escalation dose
of antifungals was preferred. It was observed that Injection
liposomal Amphotericin B was tolerated up to 300 mg/day
in most of the cases, while other forms of Amphotericin B
needed titration and intermittent treatment due to its sys-
temic side effects mainly acute kidney injury, electrolyte
imbalance and other constitutional symptoms like fever,
chills, rigor and breathing difficulty.

Antifungals were started on postoperative day 1 of sur-
gery and were given a maximum cumulative dose up to
3–5 g and patients with CNS involvement were given up
to 5–6 g. To complete the cumulative dose, it took approxi-
mately 30–50 days.

A study by Laniado-Laborín et al. patients who required
higher dose of Amphotericin-B had to undergo dialysis for
kidney injury [11]. While in our setup, none of the patients
who received high dose of Amphotericin and who had acute
kidney injury needed dialysis. They were managed conserva-
tively by titrating the dose and intermittent treatment.

Patients who were intolerant to Inj.Amphotericin-B were
treated with Inj.Posaconazole. Some patients who were
intolerant to both and postoperative patients who completed
cumulative dose of Inj.Amphotericin B, were given Tab
Posaconazole 300 mg for up to 3 months.

A study by Safi et al. on effectiveness of retrobulbar injec-
tions, showed favorable results 10 while in our study none of
the patients showed any signs of improvement [10].

Surgery

The main aim of surgery is radical debridement of Rhino-
Orbital-Cerebral mucormycosis (ROCM). But no clear
guidelines are present with regard to this.

In our institute, depending on CT/MRI/microbiology
swab and involvement of medial and posterior wall of max-
illa, palate, orbital walls,sphenoid bone, orbital apex/cavern-
ous sinus, extended FESS via modified denkers approach
was done. Thoses patient with gross palatal involvement,
masticator space, malar bone, infratemporal fossa, orbital
apex, greater wing of sphenoid, debride-
ment and drilling of the same were done. Foramen rotundum
and ptgeyoid canal was drilled till healthy tissue appeared.
Necrotic maxillary nerve and nerve to ptgyoid canal was
noted. In our study, we opened cavernous sinus in two
patients and fungal debris was evacuated.

In our study, we have done 30% infra-maxillectomy, 15%
total maxillectomy, 7.24% extended maxillectomy. In open
approach during maxillectomy, the necrotic bone was easily
removed as it was already devitalized and thinned. Preop-
eratively, a dental impression was taken by dental (Prostho-
dontist) department for fabricating a temporary obturator,
the same was placed during surgery/immediate postopera-
tive day. At the time of discharge, temporary obturator was
replaced by permanent obturator.

In our study, histopathological positivity for mucormy-
cosis was seen in 70% of the tissue samples, 20% showed
mixed infections (mucormycosis and aspergillosis), 10%
showed chronic inflammatory disease.

Follow-up

For Post operative cases weekly post diagnostic nasal
endoscopy was done till they were discharged. Once the
patients achieved complete mucosalisation of the cavity and attained a cumulative dose of antifungals, they were discharged. Later patients were reviewed, once a week for 3 weeks, once in 2 weeks for 3 months, later once in a month for 6 months.

During follow up we noticed no recurrence in first 1 month, 40% of patients had recurrence within 3 months. In 60% cases, follow up diagnostic nasal endoscopy showed healthy mucosa, no discharge/necrotic bone/tissue with no orbital involvement whereas in recurrent cases showed necrotic tissue/bone/purulent discharge in the nasal cavity, along with orbital symptoms like gradual loss of vision, ophthalmoplegia, headache and fever. In suspicious of recurrence/residual disease radiological investigation MRI was done. Among these 10.86% patients underwent infrastructure maxillectomy/Palatectomy, Orbital Exenteration (12.31%), total/extended maxillectomy (8%) and Infratemporal fossa/Pterygopalatine fossa (8.69%).

### Outcome

| Sl. No. | Frequency | Percentage |
|---------|-----------|------------|
| 1       | Follow up at 1 month | No recurrence | 0 | 0 |
| 2       | Follow up at 3 months | Recurrence | 55 | 40 |
| 3       | Follow up at 6 months | No recurrence | 0 | 0 |
|         | Recurrence treatment | infrastructure maxillectomy/Palatectomy | 15 | 10.86 |
|         | Orbital Exenteration | 17 | 12.31 |
|         | Total/extended maxillectomy | 11 | 8 |
|         | Infratemporal fossa/Pterygopalatine fossa | 12 | 8.69 |
| 4       | Outcome | Death | 29 | 16.1 |
|         |         | Good | 151 | 83.9 |

### Mortality

Prior to Amphotericin, mucor mycosis was uniformly fatal [12]. Presently, with early diagnosis and prompt aggressive intervention the mortality decreased to 50%. With extensive surgical debridement and complete course of injection Amphotericin-B (antifungal treatment), the mortality was around 16.1% in our study, which is quite low.

Most of the patients who succumbed were due to gross involvement of brain and those who had electrolyte imbalance, acute cardiac events, poor cardiac status and one patient had rupture of internal carotid artery intraoperatively and died on 2nd post operative day.

In a study by Mrittika Sen et al. [10] Santosh G Honavar et al., a retrospective study in 2826 patients, ROCM is a rapidly progressive disease, with 30–90% mortality rate in cases with cerebral involvement. For cases associated with COVID-19, the overall mortality has been estimated to be 31% [10].

Jeong et al. [13] study showed overall mortality of 46%, out of which the highest was in disseminated mucormycosis (68%) and least in cutaneous mucormycosis (31%) [13].

Study by Hong et al. [14] Mortality in ROCM (43%) ranged from 34 to 75% with Sino-cerebral having the worst mortality (75%) [14].

### Conclusion

In our study, the most common risk factors were post covid status, diabetes mellitus and underlying systemic conditions. The most common type was Rhino-orbital mucormycosis, presented with facial swelling, pain, orbital oedema and nasal discharge. MRI is the gold standard to know the extent of disease and to know the recurrence; CT was done to check for bony involvement. Liposomal Amphotericin B is the most effective antifungal with minimal side effects. Extended FESS with Maxillectomies and thorough debridement had better outcome with minimal recurrence rate. Most of the cases had histopathological confirmation of chronic fungal infection, with aseptate hyphae suggestive of mucormycosis. Combined medical and surgical treatment has better outcome, lesser recurrence and mortality. The main emphasis should be on the prolonged postoperative care and on regular follow up.

### Author Contributions

All authors contributed to the study conception and design. Material preparation and analysis were performed by Dr. KMR and Dr. PN. Data collection was done by Dr. PN. The first draft of manuscript was done by Dr. PN and all authors commented on previous version of manuscript. All authors read and approved the final manuscript.

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### Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.
Declarations

Conflict of interest The authors declare that they have no conflicts of interest to declare that are relevant to the contents of this article.

Ethical Approval Ethical approval was waived by the Institutional Research Committee VIMS in view of retrospective nature of study and all procedures being performed were part of routine care.

References

1. Bhandari S, Bhargava S, Samdhani S, Singh SN, Sharma BB, Agarwal S, Sharma MP, Sharma S, Sharma V, Kakkar S, Dube A (2021) COVID-19, diabetes and steroids: the demonic trident for mucormycosis. Indian J Otolaryngol Head Neck Surg 4:1–4
2. Rao VU, Arakeri G, Madikeri G, Shah A, Oeppen RS, Brennan PA (2021) COVID-19 associated mucormycosis (CAM) in India: a formidable challenge. Br J Oral Maxillofac Surg 59(9):1095–1098
3. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP (2012) Pathogenesis of mucormycosis. Clin Infect Dis 54(Suppl_1):16–22
4. Kaushik KS, Ananthasivan R, Acharya UV, Rawat S, Patil UD, Shankar B, Jose A (2021) Spectrum of intracranial complications of rhino-orbito-cerebral mucormycosis resurgence in the era of COVID-19 pandemic: a pictorial essay. Emerg Radiol 28(6):1097–1106
5. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP (2012) Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis 54(Suppl_1):23–34
6. Singh AK, Singh R, Joshi SR, Misra A (2021) Mucormycosis in COVID-19: a systematic review of case reports worldwide and in India. Diabetes Metab Syndr 15(4):102146
7. Alloush TK, Mansour O, Alloush AT, Roushdy T, Hamid E, El-Shamy M, Shokri HM (2022) Rhino-orbito-cerebral mucormycosis during the COVID-19 third wave in 2021: an Egyptian preliminary report from a single tertiary hospital. Neurol Sci 43(2):799–809
8. Choksi T, Agrawal A, Date P, Rathod D, Gharat A, Ingole A, Chaudhari B, Pawar N (2021) Cumulative mortality and factors associated with outcomes of mucormycosis after COVID-19 at a multispecialty tertiary care center in India. JAMA ophthalmol 140:66
9. Kanduri Sreshtha TV, Varma DR, Nair AG, Bothra N, Naik MN, Sistla SK (2021) Magnetic resonance imaging in rhino-orbital-cerebral mucormycosis. Indian J Ophthalmol 69(7):1915
10. Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, Sharma M, Sachdev M, Grover AK, Surve A, Budharapu A (2021) Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India-Collaborative OPAI-JO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. Indian J Ophthalmol 69(7):1670
11. Laniado-Laborín R, Cabrales-Vargas MN (2009) Amphotericin B: side effects and toxicity. Revistaiberoamericana de Micol 26(4):223–227
12. Yohai RA, Bullock JD, Aziz AA, Markert RJ (1994) Survival factors in rhino-orbital-cerebral mucormycosis. Survey Ophthalmol 39(1):3–22
13. Jeong W, Keighley C, Wolfe R et al (2019) The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect 25(1):26–34.
https://doi.org/10.1016/j.cmi.2018.07.011
14. Hong H-L, Lee Y-M, Kim T, Lee J-Y, Chung Y-S, Kim M-N et al (2013) Risk factors for mortality in patients with invasive mucormycosis. Infect Chemother 45(3):292

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