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COVID-19-associated mucormycosis: Preliminary report from a tertiary eye care centre

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Purpose: Mucormycosis is a life-threatening infection that has made sudden comeback in COVID-19 era. We conducted this study to determine demography, site of involvement, management, and outcome in these patients. **Methods:** All cases presenting with signs and symptoms of mucormycosis were thoroughly evaluated and confirmed diagnosis was made on demonstration of fungi in the tissue (or body fluids) either by direct microscopy and/or culture. Patients underwent computerized tomography scan for paranasal sinuses and magnetic resonance imaging scan with contrast orbit and brain to know extent of disease. **Results:** 540 proven cases of mucormycosis were included. Most common age group affected was 41–50 years with male preponderance (69%). Sinonasal was the most common site of involvement in mucormycosis (100%), followed by orbital (51.85%), cerebral (9.44%), cutaneous (1.85%), and pulmonary (0.18%). Most common presentation was periocular and facial swelling (28%). 97.96% patients had associated diabetes and 89.44% patients had history of COVID-19 with concurrent steroids use (84.85%), higher antibiotics (82.59%), oxygen therapy (52.40%), remdesivir (28.89%), and biological agents (2.56%). Duration from COVID-19 positivity to presentation of mucormycosis was 22.56 days, while 4.44% patients had coexisting COVID-19 with mucormycosis. The mortality rate was 9.25% (50/540). **Conclusion:** Timely diagnosis and appropriate management can ameliorate the consequences of mucormycosis. With the third wave of COVID-19 coming, epidemiological study to identify risk factors and possible management options can help physicians to develop the treatment strategy.

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Being a populous country, India was badly affected by the second wave of COVID-19. Due to immune system alteration by coronavirus, body becomes competent for being niche to various ubiquitous pathogens. One among them is fungus Mucormycetes, leading to mucormycosis. The disease can be transmitted by inhalation of spores or by direct inoculation of the spores into disrupted skin or mucosa. The etiologic agents can cause infections with high mortality in immunocompromised, mainly post COVID-19 and diabetic patients.[1]

Mucormycetes are characterized by the presence of broad aseptate hyphae (coenocytic mycelia) and zygospores. The order Mucorales includes several species involved in rhino-orbital -cerebral, pulmonary, cutaneous, gastrointestinal and other less frequent disseminated forms of mucormycosis.[1] The Mucorales has a unique ability of angioinvasion causing necrosis and infarction of tissues. Prompt diagnosis with tissue biopsy, local control of the disease by aggressive surgical debridement, and appropriate systemic antifungal treatment improve the prognosis and survival of the patient.[2]

Aggressive treatment of COVID-19 patients by immunosuppressants, oxygen therapy, broad spectrum antibiotics, voriconazole, etc., has also been implicated for its re-emergence in COVID-19 era.[2] Early diagnosis with appropriate antimicrobial therapy saves both sight and life. This study documents cases of mucormycosis and their management from a unique perspective.

Most of the studies done on mucormycosis are retrospective. Due to increase in number of cases, diverse risk factors, and inclusion of immunocompetent and immunocompromised patients, this study was undertaken to determine demography and associated risk factors, population at risk, presenting signs and symptoms, site of involvement, and outcome of therapy.

Methods

This is a prospective cohort study done on proven mucormycosis patients who presented at our tertiary care hospital from March to May 2021 (patients enrolled till 30 May 2021). The written informed consent was obtained from all the study subjects.

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All the cases presenting with complaints of facial pain and swelling, toothache, nasal blockage, breathlessness, fever, lethargy, ptosis, ophthalmoplegia, sudden loss of vision, black eschar over palate/lid/conjunctiva/cornea, etc., were thoroughly evaluated by a team of physician, otolaryngologist, ophthalmologist, neurosurgeon and, maxillofacial surgeon. History of COVID-19 infection, hospitalization, use of steroid use/biologicals/higher antibiotics/oxygen, diabetes mellitus, hypertension, organ transplant, etc., was recorded. All patients underwent deep nasal swab for KOH mount and diagnostic nasal endoscopy (DNE) by otolaryngologist. We defined proven mucormycosis as those patients having clinically compatible signs and symptoms and demonstration of fungi in the tissue (or body fluids) either by direct microscopy and/or culture.[3] Patients who were negative on direct microscopy and DNE were treated as nonmucor patients by respective departments and were not included in the study. Patients also underwent computerized tomography scan for paranasal sinuses (PNS) and magnetic resonance imaging (MRI) scan with contrast for orbit and brain to know the extent of disease.

On the basis of involvement, patients were staged: Stage 1–Nose and PNS; Stage 2– Nose, PNS, and orbit; Stage 3–Nose, PNS, orbit, and brain.[4]

Intravenous liposomal amphpotericin B (5 mg/kg body weight for stage 1, 2 and 10 mg/kg for stage 3) was given to all the patients with proven mucormycosis. Systemic comorbidities like diabetes and hypertension were managed concurrently. Kidney function and serum electrolytes were monitored every 48 hours. The patients were subjected to radiological imaging time to time along the course of intervention and/or DNE to know the disease activity. Repeat sinus and/or local tissue debridement was done as and when required. The resolution was confirmed by a negative sinus biopsy. Liposomal amphoterecin B was continued until 5 days of resolution of the disease, after which oral posaconazole was added in a dose of 5 mg/kg body weight/day (BD on day 1 followed by OD for 8 weeks or longer depending on condition of patient).

Stage 1: Patients were managed by otolaryngologist by functional endoscopic sinus surgery (FESS) and debridement.

Stage 2: Patients having orbital involvement were categorized as having early or extensive orbital involvement on the basis of involvement of orbit on MRI scan.

Patients having early orbital involvement received transcutaneous retrobulbar amphotericin B (TRAMB) injections in dose of 3.5 mg/ml at interval of 3–7 days depending on extent of involvement and response to treatment; patients with extensive orbital involvement without any evidence of necrosis on MRI scan with contrast received TRAMB for 7 consecutive days; patients having extensive orbital involvement with signs of necrosis on MRI Scan with contrast were planned for orbital exenteration. Tarsorrhaphy was done in patients having signs of exposure keratopathy.

Stage 3: Patients were managed in supervision of neurosurgeon with 10 mg/kg body weight liposomal amphotericin and surgical debridement.

Patients were discharged on resolution of disease and followed on weekly basis till 1 month, then fortnightly till 3 months.

Data were analyzed using the statistical package SPSS version 21.0 for MS-Windows (IBM Inc., Chicago, IL) by applying suitable statistical tests.

Results

A total of 563 patients were evaluated of which 540 were proven mucormycosis and were included in study. Results are depicted in Tables 1-5; Fig.1 and 2 shows photos of some of our patients. Age wise distribution is shown in Table 1. Most commonly affected age group was 41–50 years (range: 16–78 years), showing more predilection in males (69.07%). The mean age of study population was 48.28+/−11.40 years and median of 47.89 years. Visual acuity, stage of presentation, and risk factors are shown in Tables 2-4, respectively. Out of 529 diabetic patients, 65% were newly diagnosed diabetics. The duration

Table 1: Age distribution

Age groups (in years)	Percentage
10-20	0.37%
21-30	2.9%
31-40	20.37%
41-50	38.14%
51-60	23.70%
61-70	11.85%
>70	2.59%

Table 2: Best corrected visual acuity at presentation

Vision	Percentage
6/6-6/18	43.33%
6/24-6/60	18.14%
5/60-3/60	12.04%
2/60-PL +	6.11%
PL -	20.37%

PL=perception of light

Table 3: Stages at presentation

Stage	Percentage
1	48.14%
2	42.40%
3	9.44%

Table 4: Risk factors for COVID-19 associated mucormycosis

Risk factors	Percentage
Diabetes mellitus	97.96%
COVID-19 positivity	89.44%
Steroid use	84.85%
Higher antibiotics	82.59%
Remdesivir	28.89%
Biologicals	2.5%
Hospitalization	64.28%
Oxygen therapy	52.40%

Figure 1: (a) Palatal eschar in case of mucormycosis with concurrent COVID-19. (b) Hemifacial ischemia with eschar on lids. (c) Total ophthalmolplegia. (d) Cutaneous mucomycosis. (e) Bilateral involvement of orbits. (f) Pre and post exenteration pictures of patient

Table 5: Factors associated with death

	Death	Survived	*P*
Age (in years)			
<40	4	124	0.010271
40 and above	46	366	
Sex			
Male	28	345	0.052479
Female	22	145	
Stage			
2	6	223	0.00001
3	44	6	
Hb1AC in diabetics			
<9%	1	386	0.00001
>9.1%	49	93	
Eyes that underwent exenteration			
Stage 2	0	6	0.5552
Stage 3	5	16	

from COVID-19 positivity to presentation of mucormycosis was on an average of 22.56+/−4.78 days (range: 9–36 days). 4.44% patients had concurrent COVID19 with mucormycosis.

Most common initial symptoms were periocular and facial swelling (28%), periocular and facial pain (23%), headache (21%), blurred vision (14%), cheek hypoesthesia (13%), nasal blockage (12%), and others like ptosis, ophthalmoplegia, lethargy, nasal discharge, and toothache (10%). Sinonasal involvement was seen in 100% patients followed by orbital (51.85%), cerebral (9.44%), cutaneous (1.85%), and pulmonary (0.18%) cases. Orbital involvement was bilateral in 13/540 (2.40%). 21.29% had ophthalmoplegia (partial 29.17% and total 53.24%). The causes of diminution of vision were corneal haze (due to exposure keratopathy), uveitis, cataract, disc edema, exudative RD, vitreous hemorrahage, diabetic retinopathy, Central Retinal Artery Occlusion, optic atrophy, and cortical blindness. Facial palsy was seen in 16.02% patients. Average duration of intravenous liposomal amphotericin B was 18 days (10–29 days) with average stay in hospital 16 days (12–35 days). 100% of patients underwent nasal debridement with or without FESS. TRAMB was given to all patients with orbital involvement out of which 216 (40%) improved (ocular movements improved in 165, visual acuity 34, and both visual acuity and ocular movements 17 patients) and 37 (6.85%) patients were stable with no deterioration. 27 (5%) patients underwent orbital exenteration. Out of 27 patients who underwent exenteration 21 (77.78%) had stage 3 disease; among them, 5/21 (23.80%) succumbed to death within 10 days of orbital exenteration. 407 patients have been discharged and are still in close follow-up. Patients have been in our follow-up for more than 3 months. Deaths were reported in 50 cases (9.25%), out of which 92% had age more than 40 years ($P < 0.05$), 88% had cerebral involvement ($P < 0.05$), and 98.03% Hb1AC > 9.1% ($P < 0.05$).

Discussion

Mucormycosis is caused by filamentous fungi (Mucoraceae family) which is saprophytic organism and found in normal environment. It becomes pathogenic under special circumstances. The major risk factors for mucormycosis include uncontrolled diabetes mellitus with ketoacidosis, other forms of metabolic acidosis, treatment with corticosteroids, organ or bone marrow transplantation, neutropenia, trauma and burns, malignant

Figure 2: Cases who presented late with extensive necrosis and multiorgan involvement

hematologic disorders, and deferoxamine therapy in patients receiving hemodialysis.[5] A complex interplay of factors, including pre-existing diseases such as diabetes mellitus, use of immunosuppressive therapy, the risk of hospital-acquired infections, and systemic immune alterations of COVID-19 infection itself might have led to increase of mucormycosis cases post COVID-19. Its rapid pathogenesis is thought to be related to vascular invasion, leading to thrombosis and subsequent necrosis of involved tissues. This mechanism of spread is facilitated by high amounts of iron or glucose in the serum.[6,7] Mucormycosis often initially involves the maxillary and ethmoid sinuses, with subsequent spread into the orbit through the nasolacrimal duct, natural dehiscences in the papyraceous blade or through arteries and veins holes in the orbital wall.[8] Ocular symptoms may include pain, chemosis, vision loss, ophthalmoplegia, and proptosis. Ophthalmoplegia arises from inflammation of the muscles and orbital space or when the third, fourth, and sixth cranial nerves are affected.[9] Onset of signs and symptoms in the contralateral eye is an ominous sign that suggests the development of cavernous sinus thrombosis. **Cavernous sinus thrombosis**, which can present with a multitude of symptoms including ptosis, chemosis, multiple cranial nerve palsies, papilledema, headache, and nuchal rigidity, is associated with a poor prognostic outcome. **Orbital apex syndrome**, a syndrome resulting in damage to cranial nerves III, IV, VI, and the V1 branch of the trigeminal nerve in the context of optic nerve dysfunction, is another known complication of orbital mucormycosis.[10]

An early diagnosis and treatment saves life and sight of the patient. Correct diagnosis, metabolic control and antimicrobial therapy, and debridement of necrotic tissue have remained the mainstay of management of rhinoorbital mucormycosis over the years. In our study, the mean age of presentation was 48.28 years with male preponderance. The most common systemic risk factors were diabetes mellitus (97.96%), COVID-19 positivity (89.44%), and steroid therapy (84.85%). Majority of patients presented in Stage 1 (sinonasal); orbital involvement was seen in 51.85%. The age more than 40 years, presence of intracranial involvement, and Hb1AC > 9.1% were found to be significant in prediction of mortality. However, in COSMIC study, the mean age of patients was 51.9 years. Steroid therapy (87%) and DM (78%) were the most common risk factors. Orbit was involved in 72% of patients.[11]

Patel *et al*.[3] in a prospective muticentric study with 465 individuals reported 438 (96.5%) to be adults with median (IQR) age of the study population (323/465, 69.5% men) being 48 (35–58.5) years. Medical co-morbid illnesses including chronic kidney disease (93/465, 20.0%) and cardiovascular diseases (67/465, 14.4%) were noted in 37.6% (175/465) of the participants. Rhino-orbital mucormycosis (315/465, 67.7%) was the most common form followed by pulmonary (62/465, 13.3%) and cutaneous (49/465, 10.5%) mucormycosis. Uncontrolled diabetes mellitus was the most common risk factor for all forms of mucormycosis, except cutaneous and renal. The 90 day mortality rate was 52%. They also reported that disseminated and rhinoorbital (with cerebral extension) mucormycosis, shorter duration of symptoms, shorter duration of antifungal therapy, and treatment with amphotericin B deoxycholate (vs. liposomal) were independent risk factors for mortality. In our study, all patients received liposomal amphoterecin B both for intravenous and TRAMB injections.

Bala *et al.* in a prospective study on 38 patients in North India reported that rhino-orbital type (61.5%) was the most common presentation followed by cutaneous (31%), gastrointestinal (5%), and pulmonary (2.5%) mucormycosis. Out of 38 patients, only 12 were immunocompetent, and 26 patients were immunocompromised due to underlying factors such as diabetes mellitus, diabetic ketoacidosis, chronic renal disease, and operative procedures such as exploratory laparotomy and trauma. None of their patients had undergone transplantation, chemotherapy, steroid use, severe burns, or HIV,[1] while we found 84.85% of our patients had history of steroid use during COVID-19 treatment.

In our study, all patients underwent nasal debridement surgery with or without FESS depending upon the extent of disease by otolaryngologist. Nithyanandam *et al*.[12] in their study on the clinical features and treatment outcomes of rhinoorbital cerebral mucormycosis have reported that debridement of sinuses is necessary in all cases of rhinoorbital cerebral mucormycosis. Majority of our patients who had orbital involvement without any signs of necrosis on MRI with contrast responded well to TRAMB. Ashraf *et al*.[13] in their study have assessed that TRAMB injections can reduce the risk of exenteration without compromising survival. Our study is also in favor of this outcome. Not a single patient had suffered from ocular compartment syndrome after TRAMB in our study. Brodie *et al*.[10] in a case reported that after the fifth TRAMB, patient developed acute orbital compartment syndrome with intraocular pressures ranging from 47 to 86 mmHg and vision declined to 20/200, requiring emergent lateral canthotomy

and superior and inferior cantholysis. Ashraf *et al*.[13] also reported orbital compartment syndrome in one eye out of 69 eyes receiving 1 ml of TRAMB, although they used amphoterecin B deoxycholate in their patients. 5% of our patients underwent orbital exenteration out of which 77.78% had stage 3 disease; among them, 23.80% succumbed to death within 10 days of orbital exenteration. Songu *et al*.[14] in their study found no survival benefits after exenteration surgery, which is consistent with our findings. However, COSMIC study reported patients with stage >3b had poorer prognosis and paranasal sinus debridement and orbital exenteration reduced the mortality rate from 52% to 39% in patients with stage 4 disease with intracranial extension.[11]

We found that duration from COVID19 positivity to presentation of mucormycosis was on an average of 22.56 days and 4.44% patients had concurrent COVID19 with mucormycosis while Ravani *et al*.[15] in their study of 31 patients of mucormycosis reported duration from COVID-19 positivity to presentation of mucormycosis was average of 2 months; however, they did not report any concurrent ongoing COVID-19 with rhino-orbital mucormycosis. Mehta,[16] Mekonnen *et al*.,[17] and Werthman-Ehrenreich[18] have documented single case reports of concurrent COVID-19 infection with invasive rhino-orbital mucormycosis. COSMIC study iterated symptoms of ROCM were evident between 10 and 15 days from the diagnosis of COVID-19.[11]

Ours is a multispecialty government hospital with a dedicated COVID-19 facility. Patients were seen as a team with Medicine, Otorhinolaryngology, Maxillofacial, Ophthalmology, Neurosurgery, Pathology, Microbiology, and Radiodiagnosis, coordinating with each other at every level of patient management. Average duration of intravenous liposomal amphotericin B was 18 days. Average stay in hospital was 16 days. Petrikkos in his review article reported that although the optimal dose and duration of treatment with liposomal amphoterin B has not been established and the recommended dose for other invasive fungal infections is 3 mg/kg, in most cases it has been used in doses of 5–15 mg/kg/day and for a duration of ≤6 months.[19] Smaller duration of hospital stay and course of systemic liposomal amphoterin B could be because of early presentation, timely appropriate management of disease, and concurrent use of TRAMB in patients with orbital involvement.

Conclusion

COVID-19 associated mucormycosis is a disease of great public health concern. Timely diagnosis and appropriate management can ameliorate the devastating consequences of this disease. With the third wave of COVID-19 coming, epidemiological study to identify the risk factors and possible management options can help physicians to develop the treatment strategy.

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 initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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