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Original Research Article

Mortality, morbidity and sequelae of COVID-associated mucormycosis; 18 months follow up study

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ABSTRACT

Background: The second wave of the COVID-19 pandemic in India was associated with an increased incidence of rhino-orbital-cerebral mucormycosis. The objective of this paper was to prospectively explore the epidemiology, management, and results of 18 months follow-up of patients presenting with COVID associated mucormycosis at a tertiary referral centre in India.
Methods: Patients presenting with symptoms suggestive of COVID-associated mucormycosis over two months were included in the study. Patients were staged based on the extent of the disease. Surgery was the primary modality of treatment except in those with intracranial spread, altered sensorium, and poor prognosis. A combination of liposomal amphotericin B and posaconazole was used as adjunct medical treatment. Patients were followed up and outcomes at one year of treatment were recorded.
Results: Out of a total of 26 patients who were diagnosed with COVID associated mucormycosis, 21 patients underwent bimodality treatment (medical and surgical). The extent of surgery was based on the stage of the disease. Six eyes received retrobulbar injections of Amphotericin B to salvage vision. The overall mortality was 38.46% and 23.8% in those where the intent of treatment was curative. At the end of one year, 16 of 21 operated patients survived with mild to severe sequelae.
Conclusions: Mucormycosis is a deadly fungal infection with high mortality. Early diagnosis and prompt, aggressive treatment is paramount in preventing mortality. A multidisciplinary approach is useful for effective management. Continuous follow up is paramount to identifying and treating complications.

Keywords: COVID, Mucormycosis, Amphotericin B

INTRODUCTION

Rhino-orbital-cerebral mucormycosis (ROCM) is a rare, life-threatening invasive fungal infection that often occurs in immunocompromised individuals. The condition originates in the nose and paranasal sinuses but is often seen spreading to the orbit and brain, leading to poor prognosis.[1] The fungus destroys the surrounding bone and soft tissue through vascular thrombosis and infarction and may reach the brain with an increased risk of mortality.[2] The incidence of mucormycosis is often underestimated.[3] The incidence of all forms of mucormycosis combined is estimated to be 0.43-1.7 cases per million population with no subgrouping specific for ROCM incidence.[1,3] There is

emerging data that shows a rising trend in mucormycosis in the last decade.[1,4] This is attributed to rising populations with diabetes mellitus (DM), haematological malignancy, and transplants.[1] The second wave of COVID-19 brought an abrupt rise in opportunistic fungal infections in India. A sudden surge of COVID-associated rhino orbital cerebral mucormycosis (CAM) led to an epidemic of mucormycosis amidst the pandemic. Many hundreds of patients were treated in the Indian subcontinent with surgery and antifungal medication with significant morbidity and mortality in a resource-constrained environment.[5,6] Although the exact reason for the sudden surge of mucormycosis during the pandemic is still not established, the cause of COVID-associated mucormycosis (CAM) is thought to be multifactorial.[7] Coexisting diabetes and the use of steroids in treating COVID-19 pneumonia, and inadvertent and irrational use of zinc in COVID treatment protocols are implicated in the aetiology.[8] Furthermore, the innate immune system decline caused by COVID infection increased the risk. There is still a paucity of published data on treatment outcomes and sequelae of these patients over the medium and long term, as many require multiple interventions by way of surgeries, rescue medication, and reconstructive and rehabilitation measures. The purpose of this longitudinal study was to explore prospectively the possible causes of COVID-associated ROCM, the impact of treatment given, and evaluate morbidity, mortality, and sequelae at 1 year follow-up.

METHODS

Patients

After ethical committee approval, a prospective study was conducted at a tertiary care centre (People Tree Hospitals, Bangalore) on all the patients who presented with COVID-associated ROCM in the two consecutive months of April and May 2021. All patients who were diagnosed with COVID-19 infection and presented with symptoms and signs of mucormycosis were included in the study. The diagnosis of mucormycosis was based on global guidelines published by the European federation of medical mycology.[9] Patients presenting to the ENT OPD underwent clinical examination and diagnostic nasal endoscopy. The black discoloration of turbinates was a pathognomonic sign of mucormycosis. Some patients also presented with necrosis of the nasal mucosa and mucopus in the nasal cavity. Patients were closely examined to look for other signs like proptosis, restriction of eye movements, decreased vision, palatal necrosis, and alveolar or dental sinuses. Patients were advised to have contrast-enhanced magnetic resonance imaging (MRI) of the brain and orbit and a computed tomography (CT) scan of the paranasal sinuses. Radiological evidence of bone destruction and orbital/brain infiltration was assessed. Patients underwent ophthalmological and neurological evaluations to check for eye and brain involvement. The other investigations included a complete haemogram, blood sugar panel, renal function test, and serology (Hepatitis B, C, and HIV), along with a chest X-ray and ECG for preoperative fitness. Shared decisions with patients were made with a mucormycosis information leaflet explaining the nature of the disease, treatment, and prognosis. All patients were admitted, and a treatment plan was made based on the stage of disease.[10] Disease limited to the nasal mucosa was stage 1, involvement of paranasal sinuses was indicated as stage 2, involvement of the orbit was stage 3, and intracranial spread was stage 4.

Surgery

Surgery was planned endoscopic sinus surgery (ESS), medial maxillectomy with or without infratemporal fossa clearance, palatectomy or maxillectomy, and orbital exenteration) based on the stage of the disease. All patients were offered surgery, except patients with intracranial spread with altered sensorium. A pre-anaesthetic evaluation was done to obtain fitness for surgery. Patients in stages 1 and 2 underwent extensive ESS (fronto ethmoidectomy/sphenoidotomy and middle meatal antrostomy) and, in some cases, medial maxillectomy and infratemporal fossa clearance. Patients in stage 3 underwent treatment based on vision status. Eye-preserving techniques like a retrobulbar injection of Amphotericin B and orbital decompression were done for patients who had focal orbital involvement with preserved vision. The quadrant of injection is usually based on the radiological site of involvement, and this was mostly in the medial part of the orbit. Retrobulbar injection of Amphotericin B was done under local anaesthesia. 2 % lignocaine infiltration was given for anaesthesia and 1 ml of Amphotericin B Desoxycholate was infiltrated in the retrobulbar space. Patients with no light perception and complete ophthalmoplegia underwent orbital exenteration. All the surgical tissue was sent for histopathological examination, KOH mount, and fungal cultures. KOH mount gave us the preliminary diagnosis, whereas histopathology showing vascular or tissue invasion by the fungus was confirmatory. A second stage of surgery was planned for debridement in all patients within 2 weeks of the first surgery. Additional surgeries were done based on additional imaging findings or for clinical progression of the disease.

Medical management

Medical management in the form of liposomal amphotericin B injection (3 to 5 mg per kg body weight) diluted in 500 ml of 5% dextrose was infused over 6 to 8 hours. Premedication with chlorpheniramine maleate was done to prevent a reaction to amphotericin B. When Liposomal Amphotericin was not available, Amphotericin B Desoxycholate (1 mg per kg body weight) was infused. Intravenous antibiotics were given to some patients who had purulent discharge. Amphotericin was discontinued after 2 to 3 grammes of cumulative dose or when patients developed early signs of dyselectrolytemia (4 patients required restarting of Amphotericin B later due to disease progression).Patients were clinically monitored on a

continuous basis, as well as with radiological imaging and blood indices as needed (electrolytes, blood counts, C-reactive protein, sugars, and MRI re-imaging).On discharge, patients were started on oral posaconazole-gastroresistant sustained-release tablets in the recommended dosage of 300 grams per day. All the patients were meticulously followed up for outpatient-based debridement of any necrotic tissue (douching and suction/local antifungal medication application) and laboratory evaluation of diabetes and inflammatory markers. Microsoft Excel 2013 was used for data collection, compilation, and analysis.

RESULTS

Study population

Of the 26 patients included, 5 were females and 21 were males. All patients had COVID or were recovering from COVID and all patients had one or more current symptoms suggesting ROCM (symptoms of ptosis N=8, proptosis N=8, facial pain N=22, decreased vision or vision loss N=11) at presentation. The age of patients ranged between 31 and 76, with a mean age of 50.38 years. The duration between the diagnosis of COVID and the onset of symptoms of mucormycosis ranged between 5 and 30 days. Three patients had positive RTPCR at presentation (11.54%). Twenty-four patients had diabetes mellitus (92.31%), of which 13 were detected to have diabetes during COVID infection and 11 had pre-existing diabetes. Two patients were non-diabetic, of whom one had chronic kidney disease requiring haemodialysis. 23 out of 26 patients (88%) received steroid treatment for COVID infection. 17 out of 26 patients (65.38%) required oxygen during COVID infection (Figure 1).

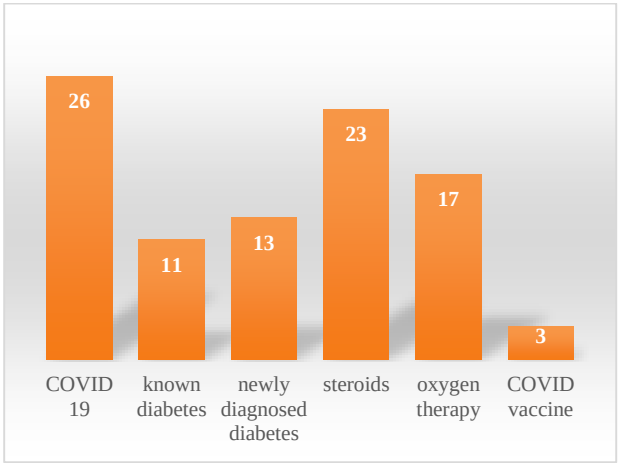

Figure 1: Risk factors for mucormycosis.

Three patients had received the first dose of the COVID vaccine, of which one had received it a month before developing SARS-CoV-2 infection, while the other two patients had received the vaccine less than one week before developing symptoms of COVID infection. Of the 26 patients, all but 6 patients had black eschar on nasal examination. The 6 patients without eschar had mucopus or polypoidal mucosa or necrotic rubbery mucosa intraoperatively. Nine patients were in stage 4, of which four were referred for palliative care after counselling patients and relatives. One patient with chronic kidney disease expired on the day of admission due to severe sepsis. The remaining 21 patients underwent bimodality treatment.

Treatment

Twenty patients had unilateral involvement, while five patients had bilateral involvement. Of 11 patients who underwent orbital exenteration, 8 had it as a part of primary surgery. Five patients (6 eyes) underwent retrobulbar injection of Amphotericin B, of which three eyes were preserved. The remaining 3 patients had some vision initially, which deteriorated later and could not be salvaged by retrobulbar injection of Amphotericin B. They eventually required orbital exenteration. Three patients underwent partial maxillectomy, and two underwent total maxillectomy as a second stage procedure. The other surgical procedures performed in indicated cases include frontal trephine (N=3), orbital decompression (N=3) and pterygopalatine fossa clearance (N=3) (Figure 2).

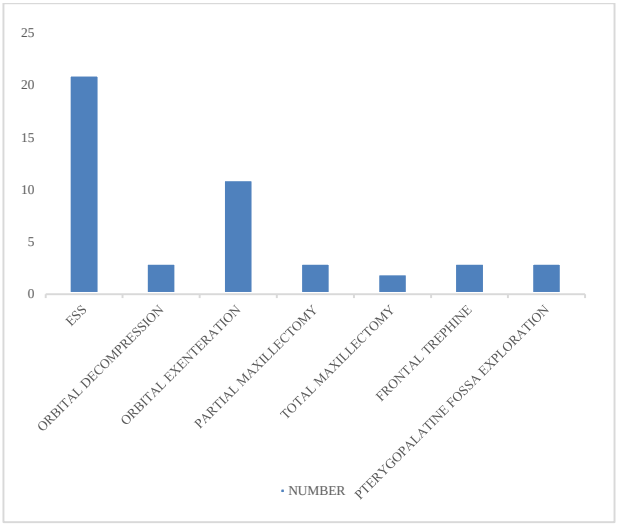

Figure 2: Chart showing numbers of different procedures.

The medical management included intravenous Amphotericin B injection, diabetic management, treatment of dyselectrolytemia, and other supportive measures. The average duration of Amphotercin B therapy was 15 days, and the average cumulative dose was about 3 grams. Three patients developed stroke (unilateral upper limb weakness in 2 patients and lower limb weakness in one patient) during treatment, which was managed conservatively. They eventually recovered completely, with minimal deficits. A total of 28 samples were processed from 21 patients. The preliminary microscopic KOH mount showed fungal hyphae suggestive of mucor in all these cases (Figure 3).

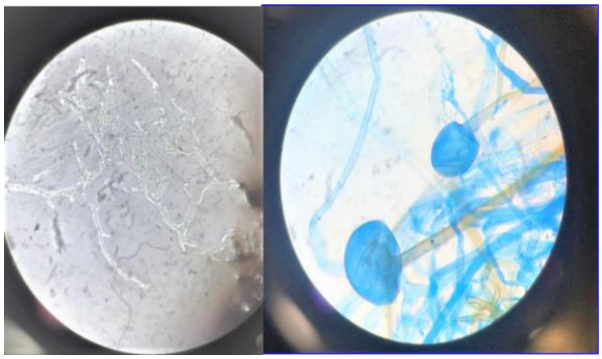

Figure 3 left: Direct KOH Microscopy from the sphenoid of one of the deceased patients shows broad, aseptate, branching hyphae of mucorale. R**ight: LPCB mount of the culture from one of the exenterated orbits showing stolons, columella, pigmented rhizoids, and sporangia of *Rhizopus Spp*.**

Mucorales grew from 15 of the samples on SDA (Sabouraud Dextrose Agar) culture at room temperature within 3-5 days-as a single isolate (N=11), mixed growth with Aspergillus species (n = 3) and with a dematiaceous fungus (N=1). The growth was plate-filling, fluffy white, and darkened over time. The culture positivity rate stood at 53.5%. The Mucorales were identified as *Rhizopus spp.* based on their microscopic morphology of aseptate hyphae, sporangia, the shape of the columella, and the presence of nodal rhizoids (Figure 3). Histopathological findings revealed classical tissue and angioinvasion by broad aseptate hyphae with an inflammatory response in PAS (Periodic acid Schiff), GMS (Grocott methenamine silver), and H & E (Hematoxylin and Eosin) stain in 14 of the examined samples, and a confirmatory diagnosis was established (Figure 4).

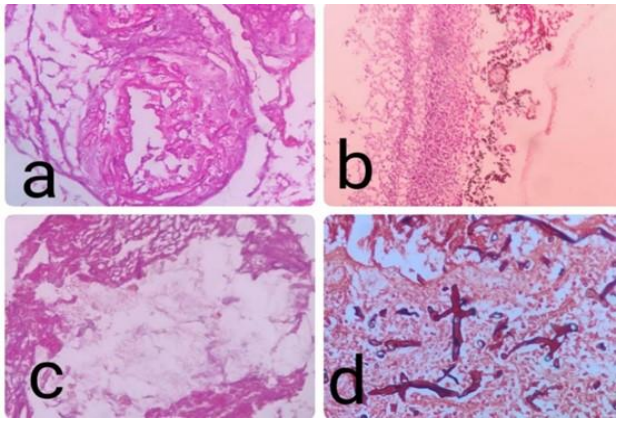

Figure 4: Histopathological images, a) angio-invasion by fungus, b) aspergillus and mucorale in the same tissue sample, c) marrow invasion, d) fungal hyphae in GMS staining.

The complications of therapy included thrombophlebitis, chills, headache, and deranged kidney function tests, which were managed conservatively. Three patients out of the 21 operated patients died, one within 10 days of surgery due to sepsis and intracranial spread of mucor, one due to acute kidney injury 15 days after surgery while on medical management, and the third died 20 days after surgery, due to cardiac causes. One patient, aged 76 years, succumbed to cardiac arrest 3 months later. The patients who were discharged were on regular follow-up with serial monitoring of CRP, blood counts, and liver function tests. The average duration of Posaconazole therapy was 3 months, some patients required longer treatment. The criteria for stopping Posaconazole in our centre are a clinical improvement, no clinical evidence of active disease elsewhere, normal mucosa on serial endoscopic examinations, normal total counts, and a CRP of less than 6. Repeat imaging was not done except in patients with persisting or worsening headaches or new symptoms. Two patients required re-admission for repeat debridement and amphotericin B injections. Both patients improved and were eventually discharged. Results are summarised in (Table 1).

Figure 5: Prosthetic right eye (above) and prosthetic left eye (below) 10 months after orbital exenteration.

Follow up for 18 months

At the end of one and half year, 16 patients were alive. All patients were off antifungal treatment, with the average duration of treatment ranging from 3 to 6 months. Four patients underwent rehabilitation of eye defects in terms of the prosthetic eye (Figure 5). One patient received a prosthesis for a maxillary defect. Two patients had zygomatic implants. One patient needed sinus debridement and oro antral fistula closure at 1 year. One patient developed spontaneous subdural hemorrhage, needing evacuation. The patient recovered within a week and was discharged. There were no signs of recurrence of mycormycosis radiologically or clinically.

Table 1: Epidemiology, staging, management and outcome of our patients.

Age (years)	Gender	Stage	Surgery	Medical Management	No Of Surgeries	Outcome	Sequelae/ Rehab	1 year Outcome
57	F	3	ESS+OE	AMB, PCZ	2	DS	Orbital Socket	Disease Free
47	M	4	ESS+OE, Second stage FT, PPF	AMB, PCZ	2	DS	Orbital Socket	Disease Free Intracranial Bleed after1 year, operated
44	M	3	ESS, Second Stage OE	AMB, PCZ	2	DS	Prosthetic Eye	Disease Free
62	M	4	ESS, OE, Second stage TM, PPF	AMB, PCZ	4	DS	Prosthetic Eye, Palate	Disease Free
52	M	4				Palliative Care		
44	M	3	ESS+OE	AMB, PCZ	2	DS	Prosthetic Eye	Disease Free
46	M	3	ESS, Second Stage OE	AMB, PCZ	2	DS	Prosthetic Eye	Disease Free
61	M	3	ESS+OE	AMB, PCZ	2	Death		
44	M	3	ESS, Second Stage OE	AMB, PCZ	2	DS	Orbital Socket	Disease Free
37	M	4	ESS+OE	AMB, PCZ	1	Death		
37	M	2	ESS	AMB, PCZ	3	DS		Disease Free
63	M	2	ESS	AMB, PCZ	2	DS		Disease Free
76	M	3	ESS+OE, Second stage PM, PPF	AMB, PCZ	3	DS		Death After 3 Month- Cardiac Arrest
31	F	2	ESS, OD	AMB, PCZ	2	DS	Dental Rehabilitation	Disease Free
59	F	4	ESS+OE	AMB, PCZ	2	DS	Orbital Socket	Disease Free
36	M	3	ESS, Second stage TM, FT	AMB, PCZ	3	DS, Cure	Maxilla And Palatal Defect	Disease Free
60	M	2	ESS	AMB, PCZ	1	DS		Disease Free
70	M	4				Palliative Care		
37	M	2	ESS	AMB, PCZ	2	DS		
35	M	4				Death		
52	M	3	ESS, OD, PM, Palatal surgery	AMB, PCZ	3	DS		Death After 20 days- Cardiac Arrest
32	M	2	ESS	AMB, PCZ	2	DS	Dental Rehabilitation	
45	M	3	ESS, OD, FT	AMB, PCZ	2	DS		
63	M	2	ESS, PM	AMB, PCZ	2	DS	Palatal Implant	Disease Free
62	F	4				Palliative Care		
58	F	4				Palliative Care		

M-male, F-female, ESS-endoscopic sinus surgery, OE-orbital exenteration, OD- orbital decompression, PM-partial maxillectomy, TM-total maxillectomy, FT-frontal trephine, PPF-pterygopalatine fossa clearance, AMB-amphotericin B (intravenous), PCZ-posaconazole (oral), DS-discharged.

DISCUSSION

The current study focuses on the epidemiology, clinical manifestations, treatment outcomes and associated sequelae of COVID associated mucormycosis in a tertiary care centre. The cause of the sudden surge in ROCM is clearly linked to the second wave of the COVID-19 pandemic. High sugar levels caused by the virus, use of steroids for treatment of COVID are definite cause of sudden surge in the incidence of ROCM. At 18 months follow up there was overall mortality of 38% in our center and 23% in those where the intent of treatment was curative. There was significant morbidity and sequalae during treatment with patients needing multiple surgeries and rehabilitative interventions to control disease and improve quality of life.

Link to COVID infection

Mucormycosis is a complex and multi-factorial disease, especially in the background of COVID infection. India saw a sudden surge in the cases of ROCM in April and May 2021, coincident with the second wave of the COVID pandemic. Although there were some reports of mucormycosis in the first wave, it reached an unprecedented extent in the second wave of COVID where almost 50,000 cases were recorded all over the country by November 2021.[5,6,11] The tropical climate and favourable temperature of the country contribute to the prevalence of fungi in the environment.[12] Diabetes is common in the Indian subcontinent. Studies have shown that the COVID-19 virus is also known to cause new-onset diabetes or complications of existing diabetes as it attacks the pancreatic beta cells.[12,13] Furthermore, the cytokine release in COVID can cause insulin resistance, thereby causing hyperglycaemia.[7] Impaired phagocyte function and impaired chemotaxis in a hyperglycaemic state predispose the body to fungal infections .[14] Iron metabolism plays a very important role in the pathogenesis of mucormycosis.[15,16] Both COVID infection and diabetes are associated with hyperferritinemia. The circulating ferritin in the blood can lose its iron content, leading to increased levels of free iron in the serum.[7] The fungus uses the unbound iron in the host for its cell growth and development. The use of steroids in treating and preventing COVID complications worsens hyperglycaemia and thereby predisposes to fungal infections. The use of antibiotics in treating COVID pneumonia could also impair the native protective flora and pose a risk of fungal infections.[7] Many patients required oxygen during the second wave. There was a proposed theory of the dissemination of fungal spores from oxygen humidifiers. This is, however, difficult to establish and is debatable.[17] In our series, about 35% did not receive oxygen and were in home isolation yet contracted the infection. This again reinforces the multifactorial aetiology and complex pathogenesis. However, essentially the triad of COVID, diabetes, and steroids mainly played a role in the aetiology of Mucormycosis.

Clinical presentation

Patients with ROCM present with symptoms of ptosis, proptosis, facial pain, decreased vision or vision loss in the background of an existing COVID infection or recent COVID infection.[18] The other clinical features include blood-stained nasal discharge, stuffiness, and cranial nerve palsy based on the site of involvement. In our study, eight patients had complete ophthalmoplegia at presentation, and three had facial palsy at presentation. It is, however, difficult to define active and recovered COVID infections owing to the low sensitivity of RT-PCR tests.[19] In our study, the approximate time of presentation following confirmation of COVID infection was between 5 and 30 days, with about 7 patients presenting within a week of confirmation of COVID infection. Of these, 3 patients were RT-PCR positive at presentation. A study by Hussain et al also showed that 17.57 percent of their patients had co-existing COVID and mucormycosis, while the remaining presented at an average duration of 19.24 days.[18,19] After clinical examination, the investigation of choice includes contrast-enhanced MRI of the brain and orbits with contrast and CT PNS. This helps to study the extent of disease, staging and treatment decisions.[20] Not all patients have the classical necrotic black eschar on nasal endoscopic examination. Some patients also present with mucopus and slough in the nasal cavity. Staging of disease was done based on the extent of involvement based on the proposal by Honavar et al.[10] The staging system is based on an anatomical spread from the entry point (nose). From our study it is apparent that neural involvement and orbital involvement increased mortality and morbidity. As with our study nasal swab for KOH mount for detecting the fungus may not always provide a positive result. Clinical suspicion and early intervention are paramount in the management of mucormycosis.

Management

The management strategy includes early detection, surgical debridement, antifungal therapy, and management of underlying predisposing factors.[16] The challenges in management include optimising the clinical condition of the patient and initiating early surgical treatment. Most patients are diabetic, with some in keto-acidosis needing emergency management. The initial management involves correction of hyperglycemia, hydration, and treatment of sepsis are done simultaneously with radiological tests to confirm the extent of disease. The immediate post-COVID state, poor lungs, and requirement for oxygen pose the risk of anaesthetic complications. Surgery is the mainstay of treatment for mucormycosis, followed by medical management and supportive measures.[20] The presence of vision was the single most important factor in determining the extent of surgery. In patients with orbital involvement with preserved vision, we followed eye-conserving procedures like orbital decompression and retrobulbar injection of Amphotericin B along with medical management.[22] This procedure helps to avoid disfiguring orbital exenteration in a few patients and is known to

reduce the risk of cerebritis.[23] The risks of the procedure include orbital inflammation and orbital compartment syndrome.[24] In our series, this procedure was done in five patients, one with bilateral involvement (6 eyes). Three patients eventually lost their vision and underwent orbital exenteration, but two patients' vision could be saved. We noticed that in the 3 patients who underwent exenteration after retrobulbar injection of Amphotericin B, the tissue inflammation and oedema were relatively less. A study conducted by Sen et al which studied 2826 patients with ROCM across India showed that 78 per cent had diabetes, 72% had orbital involvement, and intra-orbital injection was given to 22 percent of patients. In patients with stage 4 disease, the decision to operate was based on their general condition and GCS (Glasgow coma scale) level.[17] Those with poor GCS were referred for palliative care. The others underwent bimodality treatment after explaining the prognosis to patients and relatives. In patients who underwent surgery, the black tissue, which is pathognomonic of mucormycosis, was seen in 14 patients, but some had necrotic, rubbery mucosa with purulence. One patient had a combination of both findings. This made us speculate on a possible spectrum of sinus findings, from classical black eschar to necrotic sinusitis with pus. Direct microscopy of KOH wet mounts gives a rapid presumptive diagnosis of mucormycosis. It is inexpensive yet very useful in initial diagnosis. Cultures help to diagnose the specific organism, but the sensitivity is low and cultures are not always positive.[25] Zygomycetes exhibit broad, pauci-septate or aseptate hyphae with wide-angle branching on microscopy. Histopathology showing angio-invasion is pathognomonic for diagnosis.[26] The mortality rate of this disease varied between 33% and 50 %.[27] In our series, the survival rate was 76.19% in patients who underwent bimodality treatment at the end of one year, and the overall mortality at the end of one year was 38.46%. This includes four patients who were referred for palliative care and one who expired on the day of admission. Early surgical debridement and initiation of therapy with Amphotericin B are known to reduce the mortality rate. A very strong multidisciplinary team consisting of an ENT surgeon, ophthalmologist, diabetologist, anaesthetist, intensivist, nephrologist, neurologist, and microbiologist was involved in the management of patients. This team approach resulted in better outcomes for the patient. Although our orbital exenteration rates are high, this probably reflects a strong referral base from a regional eye centre. Constant follow-up is paramount to avoid disease progression and complications of treatment. A further focus is on rehabilitation, as most of these patients have undergone morbid procedures, leaving them with deformities for life. Before considering rehabilitation procedures, one needs to ensure a complete disease cure. It is important to understand patients' needs and preferences. Proper counselling plays a vital role as all these procedures have financial implications in a society where major treatment care is self-funded. A qualified technical team of ocularists and maxillofacial surgeons, along with the treating surgeons, plans the best form of rehabilitation for the patients. All four of our patients who received prosthetic eyes, and one who received a prosthetic palate and maxilla, are doing well. The strength of the study is the prospective nature and follow-up of patients over 18 months. There is a scarcity of data on the sequelae and medium-to long-term outcomes of such patients. Further research is needed to establish the exact mechanism of diabetes and mucormycosis in COVID patients. The limitations of our study are its relatively small sample size compared with earlier published data. Regardless, mucormycosis is a rare disease. This study represents a good sample from a tertiary referral center and has consistency with regard to patient treatment methods and a longitudinal follow up.

CONCLUSION

Mucormycosis is a deadly fungal infection with high morbidity and mortality. Early diagnosis and treatment are paramount in preventing mortality. A multidisciplinary approach is useful for effective management. Continuous follow-up is paramount to identify and treat complications and sequelae.

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REFERENCES

1. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi. 2019;5:26.
2. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis. 2012; 54 (1):S16-22.
3. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and Clinical Manifestations of Mucormycosis. Clin Infect Dis. 2012;54:S23-34.
4. Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B, et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med Mycol. 2006;44:335-42.
5. Singh Y, Ganesh V, Kumar S. Coronavirus disease-associated mucormycosis from a tertiary care hospital in India: a case series. Cureus. 2021.
6. Muraleedharan M, Panda NK, Angrish P. As the virus sowed, the fungus reaped! A comparative analysis of the clinico-epidemiological characteristics of rhino-orbital mucormycosis before and during COVID-19 pandemic. Mycoses. 2022;65(5):567-76.
7. Pal R, Singh B, Bhadada SK. COVID-19-associated mucormycosis: An updated systematic review of literature. Mycoses. 2021.
8. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. J Laryngol Otol. 2021;135(5):442-7.
9. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global

guideline for the diagnosis and management of mucormycosis: an initiative of the European confederation of medical mycology in cooperation with the mycoses study group education and research consortium. Lancet Infect Dis. 2019;19:e405-21.
10. Honavar SG. Code Mucor: Guidelines for the Diagnosis, Staging and Management of Rhino-Orbito-Cerebral Mucormycosis in the Setting of COVID-19. Indian J Ophthalmol. 2021;69:1361-5.
11. Mucormycosis. Available at: https://www.indiatoday.in/india/story/mucormycosis-cases-india-health-minister-mansukh-mandaviya-1883980-2021-12-04. Accessed on 20 December 2021.
12. Dilek A, Ozaras R, Ozkaya S, Sunbul M, Sen EI, Leblebicioglu H. COVID-19-associated mucormycosis: Case report and systematic review. Travel Med Infect Dis. 2021;44:102148.
13. Rubino F, Amiel SA, Zimmet P. New-onset diabetes in COVID-19. N Engl J Med. 2020;383(8):789-90.
14. Revannavar SM, Samaga L. COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world?. BMJ Case Rep. 2021;14(4):e241663.
15. Banchini F, Cattaneo GM, Capelli P. Serum ferritin levels in inflammation: a retrospective comparative analysis between COVID-19 and emergency surgical non-COVID-19 patients. World J Emerg Surg. 2021; 16(1):9.
16. Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005;18(3):556-69.
17. Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. Indian J Ophthalmol. 2021;69(7):1670-92.
18. Hussain S, Baxi H, Riad A. COVID-19-Associated Mucormycosis (CAM): An Updated Evidence Mapping. Int J Environ Res Public Health. 2021;18(19):10340.
19. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021; 15(4):102146.
20. Kaushik KS, Ananthasivan R, Acharya UV, Rawat S, Patil UD, Shankar B, Jose A. Spectrum of intracranial complications of rhino-orbito-cerebral mucormycosis - resurgence in the era of COVID-19 pandemic: a pictorial essay. Emerg Radiol. 2021;28(6):1097-106.
21. Claustre J, Larcher R, Jouve T, Truche AS, Nseir S, Cadiet J, et al. Mucormycosis in intensive care unit: surgery is a major prognostic factor in patients with hematological malignancy. Ann Intensive Care. 2020; 10(1):74.
22. Ashraf DC, Idowu OO, Hirabayashi KE, Kalin-Hajdu E, Grob SR, Winn BJ, et al. Outcomes of a modified treatment ladder algorithm using retrobulbar amphotericin B for invasive fungal rhino-orbital sinusitis. Am J Ophthalmol. 2022;237:299-309.
23. Safi M, Ang MJ, Patel P, Silkiss RZ. Rhino-orbital-cerebral mucormycosis (Rocm) and associated cerebritis treated with adjuvant retrobulbar amphotericin B. American J Ophthalmol Case Rep. 2020;19:100771.
24. Brodie FL, Kalin-Hajdu E, Kuo DS, Hirabayashi KE, Vagefi R, Kersten RC. Orbital compartment syndrome following retrobulbar injection of amphotericin B for invasive fungal disease. Am J Ophthalmol Case Rep. 2016;1:8-10.
25. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: an update. JoF. 2020;6(4):265.
26. Challa S. Mucormycosis: pathogenesis and pathology. Curr Fungal Infect Rep. 2019;13(1):11-20.
27. Bhattacharyya A, Sarma P, Sharma DJ, Das KK, Kaur H, Prajapat M, et al. Rhino-orbital-cerebral-mucormycosis in COVID-19: A systematic review. Indian J Pharmacol. 2021;53:317-27.

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