Acute Fulminant Rhinocerebral Mucormycosis: A Case Report with Review of Management

Case Report

Farhat Q. Khan[1], Prasad T. Deshmukh[2], Sagar Gaurkar[3]

[1,2,3]Department of Otorhinolaryngology Jawahar Lal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi (Meghe), Wardha, Maharashtra, India.

ABSTRACT

Rhinocerebral mucormycosis is an uncommon, rapidly advancing, catastrophic, opportunistic fungal infection that predominantly affects metabolic and/or immunologically challenged individuals. Its frequency has increased dramatically since the SARS-COV-19 epidemic. The disease has been described as having distinct clinical categories, namely: rhinocerebral, pulmonary, cutaneous, gastrointestinal and disseminated. Extranasal dissemination has been invariably linked with an increased risk of death.

Though an aggressive disease with a substantial rate of mortality, seeking timely help, prompt investigations and diagnosis, treatment with higher antibiotics, oral or intravenous antifungals, rigorous surgical excision, and control of underlying comorbidities has resulted in effective disease management and control with a gratifying outcome and lower morbidity when compared to the pre COVID era.

We present a case of sinonasal mucormycosis with ocular, oral, pulmonary, and intracranial involvement in a young post COVID-19 immunocompromised male patient who was optimally treated with a comprehensive endoscopic surgical approach and combined with oral and systemic liposomal amphotericin B therapy.

Key Words: Amphotericin therapy, COVID-19, endoscopic sinus surgery, mucormycosis, sinonasal disease, rhinocerebral mucormycosis.

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Corresponding Author: Farhat Q Khan, Other, Department of Otorhinolaryngology Jawahar Lal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi(Meghe),Wardha, Maharashtra, India- 42004.
Tel.: 08369801364, **E-mail**: farhatqk@gmail.com

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INTRODUCTION

Mucormycosis is an aggressive and angioinvasive disease with a wide spectrum of clinical manifestations. The disease has been described as having distinct clinical categories, namely: rhinocerebral, pulmonary, cutaneous, gastrointestinal and disseminated.[1,2,5] It is an uncommon, opportunistic infection caused by fungus in the zygomycete family of the order Mucorales. These organisms are ubiquitous and are found in soil, dead and decaying organic matter.[1,2,3]

Rhinocerebral mucormycosis is the commonest form, ranging from a localized paranasal sinus disease with rhinorrhoea, nasal obstruction, intranasal or intraoral black necrotic areas, epistaxis, facial pain and oedema, orbital symptoms like Proptosis, Ptosis, chemosis, ophthalmoplegia with blindness, headache, fever and various other neurological signs and symptoms if intracranial extension occurs.[6] It mostly affects metabolic or immunologically compromised individuals. However, with the second wave of SARS-C0V-19, we saw the emergence of rhino-cerebral mucormycosis thus compounding and complicating the pandemic. Some common predisposing factors include immunocompromised with neutropenia, organ or stem cell transplantation, renal insufficiency, broad spectrum antibiotics or prophylactic voriconazole, malnutrition, iron overload, prolonged use of steroids, and diabetes with or without ketoacidosis.[4] The prognosis is substantially better if the infection has not spread beyond the sinuses prior to the surgery. In local sinonasal disease, mortality has been reported as, 10 per cent.[2] Rates of mortality increases with extra nasal involvement, and survival in cases of fungal brain disease is rare.[1,3,7]

We discuss the effective treatment of a patient with rhinocerebral mucormycosis with sinonasal, ocular, pulmonary, and intracranial infection, managed with a combination of oral and systemic antifungal therapy and appropriate surgical debridement.

Informed consent has been obtained from the patients for publication of the case report and accompanying images

CASE REPORT:

A 27-year-old male with a COVID-19 positive status and an HRCT thorax severity score of 15/25 presented

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to our OPD with 8 days history of progressive left-sided facial and orbital swelling, frontal headaches, foul-smelling and blood-stained nasal discharge and nasal obstruction with anosmia. He also complained of rapidly deteriorating vision in his left eye over a period of 6 days making it completely blind. The left eye had considerable chemosis and proptosis, total ophthalmoplegia, and a fixed and dilated pupil on clinical examination. Mucopus and black necrotic tissue covered the entire nasal cavity and paranasal sinuses bilaterally, revealed in diagnostic nasal endoscopy. Marked erosion and necrosis of bilateral inferior and middle turbinate with erosion of the posterior part of septum was evident. Though not a known case of diabetes, his glycaemic index was elevated at presentation (HbA1C 9.62, RBS 371). The patient was also diagnosed to be HBsAg positive. There was marked elevation of total white blood cell count which was most probably due to acute, fulminant sepsis. The haemoglobin at presentation was 13.3 g/dL. An empirical amphotericin B therapy was initiated, and a tissue biopsy from the bilateral nasal cavity was conducted under local anaesthetic. Nasal swab was also sent for microbiological examination. All of these confirmed mucormycosis. (Figure 1) The extent of the illness was determined using computed tomography (CT) and magnetic resonance imaging (MRI). The CT PNS scan showed signs of mixed density areas partially opacifying bilateral maxillary sinus (L>R), frontal, ethmoid and sphenoid sinus with obliteration and widening of bilateral maxillary ostia and infundibulum suggesting pansinusitis probably fungal. (Figure 2) Inflammatory changes were noted in left orbital cavity predominantly involving medial aspect. Medial extraconal fat showed increased attenuation and streaking suggesting orbital cellulitis. CT brain revealed evidence of non-enhancing hypodense area in the left parafalcine frontal lobe with loss of grey matter differentiation suggesting ACA infarct and oedema. (Figure 3) HRCT thorax indicated a substantial area of consodilation involving the right lower lobe with multiple internal septation and air densities with multiple satellite lesions appearing to be of infective etiology most likely mucormycosis. (Figure 4) The MRI demonstrated a profound sinonasal and left orbital disease, with direct extension into the left frontal lobe forming a 3.6 x 1.7 cm (AP x TRANS), peripherally-enhancing lesion suggesting cerebral abscess with a similar lesion in left lentiform nucleus. (Figure 5) There was e/o of bony lytic areas in the adjacent left frontal bone and underlying roof of orbit. The carotid arteries, cavernous sinus and the optic nerve were found to be devoid of any disease in the initial radiological studies. Within few days of admission, the patient underwent extensive endoscopic sinus surgery. Intra-operatively, the disease was found to be filling the paranasal sinuses, extensive erosion of the bony nasal septum with 1x1 cm necrotic patch over left side of hard palate. The skull base was intact. Radical debridement of the necrotic tissue in bilateral nasal cavity, paranasal sinuses and hard palate mucosa was carried out. The necrotic tissue was removed until healthy, bleeding area/bone was exposed. No cerebrospinal fluid leak was witnessed. In the initial post-operative period, patient responded well to the local and systemic antibiotics and antifungals. Intravenous liposomal amphotericin therapy (5-10 mg/kg) was continued according to its availability. Levetiracetam as well as broad spectrum antibiotics were added in view of the pulmonary and cerebral involvement. The left orbital cellulitis was initially managed with antibiotic drops and peribulbar amphotericin injections which showed little to no sign of improvement. A repeat MRI orbits was done which suggested post contrast enhancement at the orbital apex and supero-orbital fissure with involvement of optic nerve at apex. (Figure 6) However retro bulbar part of the optic nerve showed normal enhancement with normal intra conal fat.

Following this left orbital exenteration was done under general anaesthesia and the upper and lower eyelids were sutured together. MRI was repeated again after a week which suggested reduced frontal brain abscess to the size of 2.8 x 2.2 cm.

The patient was hospitalised for a total of 10 weeks prior to making a good recovery. The intravenous liposomal amphotericin B therapy was continued until he was discharged from the hospital. The patient was followed up on and monitored on a regular basis in the out-patient department. Diagnostic nasal endoscopy was performed every week for the first 3 weeks, thereafter every 2 weeks for the next two months, and the patient remained disease-free until the last follow-up. His nasal cavity and hard palate linings have completely re-epithelialized and is being considered for orbito-ocular prosthesis.

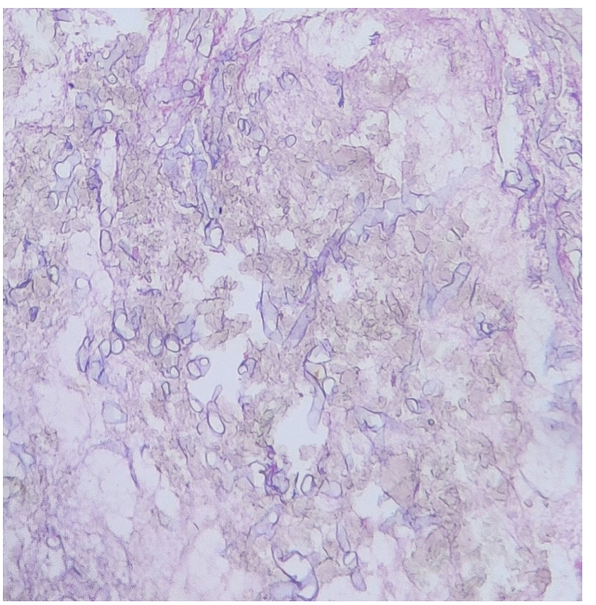

Fig. 1: Fungal hyphae (histopathological examination)

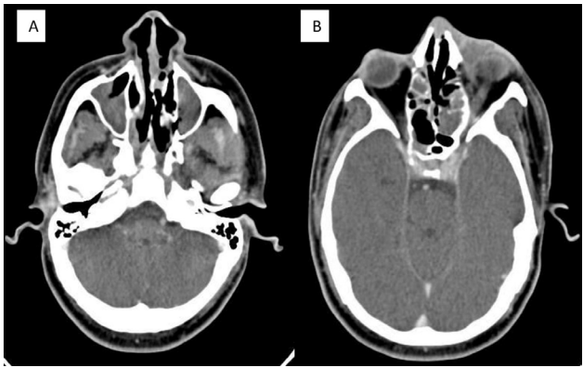

Fig. 2A and B: CT PNS revealing involvement of maxillary sinus (L>R) with obliteration and widening of bilateral maxillary ostia and infundibulum. B) Involvement of left maxillonasal region with extension to the orbital cavity s/o left orbital cellulitis.

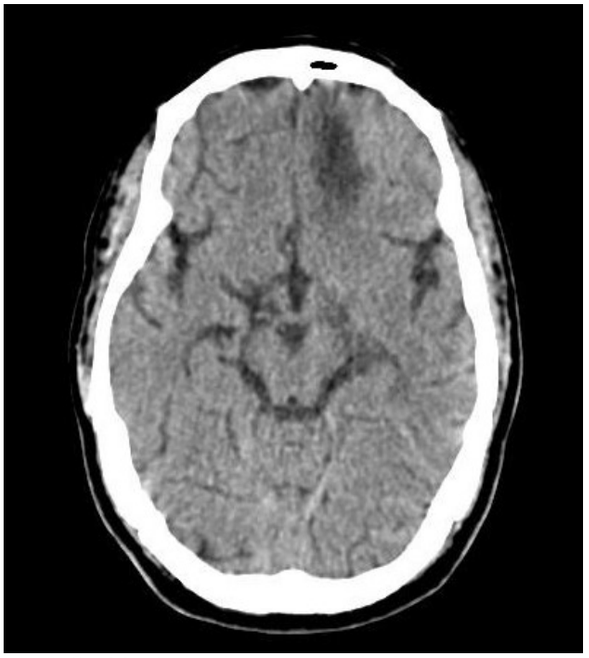

Fig. 3: CT BRAIN showing non-enhancing hypodense area in the left parafalcine frontal lobe with loss of grey matter differentiation suggesting ACA infarct and oedema.

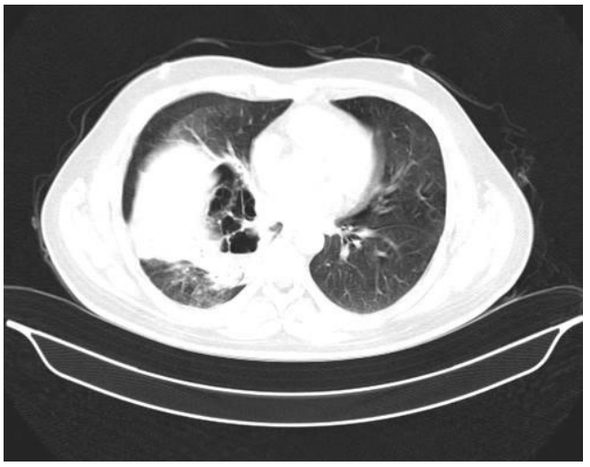

Fig. 4: HRCT THORAX revealed a large area of consodilation in the right lower lobe with multiple satellite lesions of infective etiology (mucormycosis).

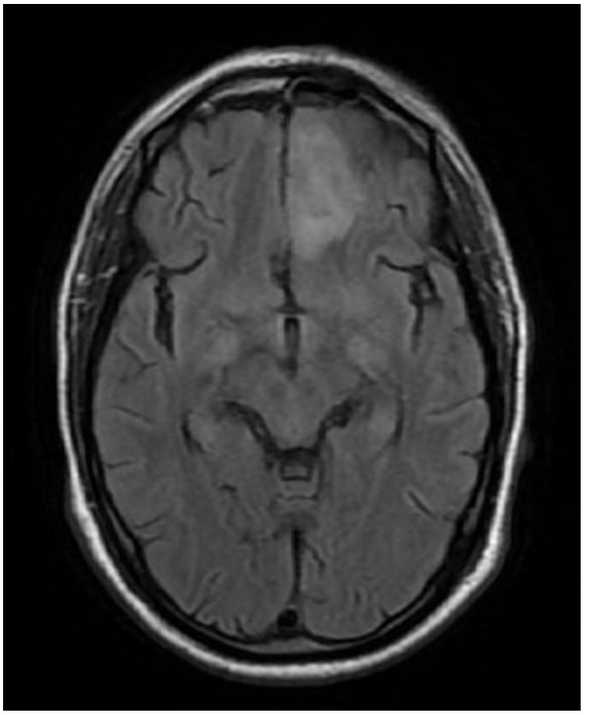

Fig. 5: MRI confirming extension into the left frontal lobe forming a 3.6 x 1.7 cm (AP x TRANS) suggesting cerebral abscess.

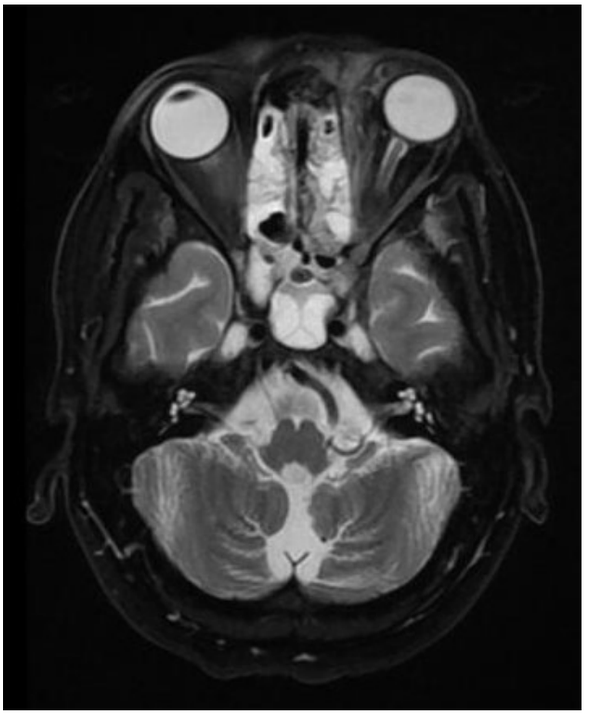

Fig. 6: MRI orbits s/o post contrast enhancement at the orbital apex and supero-orbital fissure with? involvement of optic nerve at apex.

DISCUSSION

Coronavirus disease 2019 (Covid-19) is an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The Covid-19 symptom spectrum has expanded since the detection of its first case in Wuhan, China in December 2019.[8] Mucormycosis commonly known as "the black fungus disease" is caused by a once rare and opportunistic fungus belonging to the Zygomycete family of the order Mucorales.[9] Rhino-cerebral mucormycosis is the most prevalent clinical manifestation of the infection typically developing in patients with impaired immunity due to poorly controlled diabetes status, neutropenia, on immunosuppressive agents or due to injudicious use of steroids to treat Covid-19 infection[10]. The host first line of defence involving the macrophages and neutrophils is known to be critical against the fungal infection, by damaging the fungal hyphae through phagocytosis, oxidative and non-oxidative mechanisms[11]. Chemotherapy-induced neutropenia or steroid-induced immunosuppression leads to increased risk of this opportunistic fungal infection. In patients with diabetes mellitus (DM), persistently high blood sugar level and acidosis impair both chemotactic and phagocytic neutrophil activity[12]. In addition to this, diabetic ketoacidosis creates an acidic environment that reduces the binding of iron to transferrin and thus increases free iron level that promotes fungal growth.

A dip in immunity or a breach in the skin and/or mucosal barriers is suspected to pave way for the fungi to enter the host body. A hallmark of the disease is angioinvasion, the organisms proliferate within the internal elastic lamina, separating it away from the tunica media, infiltrating into the endothelium causes thrombotic arteritis, infarction and haemorrhage, resulting in extensive local tissue necrosis.[1,2] The angioinvasion, vessel thrombosis and tissue necrosis activates a vicious cycle as the vessel occlusion brings down tissue oxygenation, propagating further acidosis, creating an optimum environment for the fungi to propagate, triggering further angioinvasion and tissue necrosis.[3]

Association of rhinocerebral mucormycosis with the ongoing COVID 19 pandemic was studied by White *et al*. in 135 adults and reported an incidence of 26.7 per cent for invasive fungal infections.[13] Based on retrospective analysis, Song *et al*. found an association between SARS-COV-2 Virus disease and angioinvasive fungal sinusitis.[14]

India reported highest burden of mucormycotic cases worldwide sharing a load of 71% of the cases. In contrast, there are reports of sporadic occurrences of Mucormycosis cases in other regions of the world that are being ascribed to COVID-19 infections.

Pal R *et al*. revealed in his systematic review, out of the 99 published cases, 72% of them belonged to the Indian subcontinent, with 78% of all the patients being male in gender.[15] Ravani *et al*. in their study of 31 patients found most were in the fifth to seventh decades with a mean age was 56.3 years with a strong predilection for male gender (64.5%).[16] A similar study consisting of patients of COVID 19 related mucormycosis conducted by Sen *et al* , Sharma *et al* and Singh A, *et al* observed majority cases belonging to male gender.[17,18,19]

A previous study from Europe by Skiada *et al*., uncovered the most significant underlying cause of rhinocerebral mucormycosis stemming from COVID 19 to be haematological malignancies. Chakrabarti *et al*., 2009 found diabetes mellitus to be predisposing and inciting factor in Indian scenario. About 70 per cent of patients with rhinocerebral mucormycosis have been found to have diabetic ketoacidosis.[2] Ravani *et al*. concluded major risk factor to be diabetes (96.7%). 29 out of 31 cases had uncontrolled DM type II (93.54%) while one patient had uncontrolled DM type I. 6 patients (19%) had newly diagnosed diabetes at the time of presentation of mucormycosis with concurrent steroid use (61.2%).[16]

Due to its low virulence potential, it can be found as a commensal in the nasal mucosa of healthy individuals unless they are immunocompromised. Clinical manifestations of rhinocerebral mucormycosis depend on the extent and the rate of disease progression. Propagation of the hyphae from the nose and sinuses can be due direct invasion or through haematogenous dissemination facilitated by angioinvasion[1,4] wherein the fungus may germinate within the paranasal sinuses, and spread intracranially or to other nearby structures such as the orbit and hard palate. Intracranial spread via a perineural route has also been postulated.[20]

Rhinocerebral mucormycosis may initially present with symptoms consistent with either sinusitis or periorbital cellulitis.[2] These include eye or facial pain, headache, nasal blockage, blood-tinged foul smelling rhinorrhoea, facial paraesthesia, chemosis, blurry vision, orbital swelling, proptosis and ophthalmoplegia with blindness. [2,3,5] Inflammatory markers are typically raised (if the patient has functioning bone marrow) and fever is present in up to half the patients.[2] With progression, the disease spreads from the ethmoid sinus to the orbit, resulting in chemosis, ophthalmoplegia and proptosis. Reports of orbital involvement in rhinocerebral mucormycosis range from 66 to 100 per cent.[4] Blindness may result from central retinal artery occlusion or involvement of the optic nerve via direct orbital extension.[5] Orbital extension indicates not only a fulminant disease but also a direct route of possible spread along tissue planes intracranially through supra orbital fissure.[5] Cranial spread may initially be relatively asymptomatic but the stigmata of intracranial spread of the disease indicates extensive disease and a grave prognosis. First described in the 1940s, cerebral mucormycosis was

found to be invariably fatal.[3] With a considerably high mortality rate due to encasement and thrombosis of major intracranial vasculature.[2] Bilateral eye signs are more suggestive of cavernous sinus thrombosis.[2]

A high index of suspicion is required for the detection of rhinocerebral mucormycosis. The diagnosis is suggested by the aggressive clinical features of the infection in the context of an immunocompromised patient. Radiological findings dove tailed to the clinical progression of the disease; as during the advent of the infection, imaging may show very subtle or no changes. Presence of focal bony erosion on CT is strongly suggestive of the diagnosis in the appropriate clinical context[2]. An MRI enables early detection of meningeal, intraparenchymal and intracranial vascular occlusion, often before the patient develops clinical signs.[1] The initial investigation of choice is a non-contrast CT scan of the paranasal sinuses, but gadolinium-enhanced MRI is necessary if intra-orbital or cerebral extension is suspected.

Ravani *et al*. found orbital cellulitis (61.29%), pansinusitis (77.41%) and Intracranial extension in the form of cerebral involvement (22.58%) in the patients of mucormycosis.[16]

The tissue infarction can also extend downwards into the oral cavity through the floor of nose and paranasal sinuses producing painful, necrotic ulceration of the hard palate.[2] Sharma *et al* discovered that the ethmoidal sinuses were infected in 100% of the cases, whereas the maxillary sinus was afflicted in 12 (52.17%) of the 23 cases. Of the 23 patients, 10 (43.47%) had involvement of the eye at the time of presentation, 9 (39.13%) had palate involvement with intra cranial extension in 2 (8.69%).[18] Sen *et al* observed that 5 out of 6 cases had orbital as well as intra cranial involvement,[17]

It is rewarding to be aware that if clinical suspicion is high, a negative imaging study does not provide a rationale for delaying an invasive diagnostic technique.[2] Presence of necrotic black eschar during Diagnostic nasal endoscopy is suspicious of the disease, which is confirmed histologically by demonstrating angioinvasion by irregular, broad, non-septate hyphae that branch at right angles. The presence of angioinvasion is essential for diagnosis, as the organism can be present as a colonizer or contaminant in the biopsy specimen.[1]

In case of suspicion of mucormycosis, initial empirical therapy with antifungals initiated while the diagnosis is being confirmed with a protracted series of diagnostic investigations has been reported to be associated with improved outcome.[2] The treatment of mucormycosis is multidisciplinary and multilayerd. The approach begins with reversal of the underlying metabolic factors like hyperglycaemia or acidosis in diabetic patients contributing to an improved prognosis. Early diagnosis is imperative and offers scope for a complete surgical excision of smaller foci of infection, before the disease progresses and disseminates.[2] Delayed diagnosis and treatment has been shown to be associated with higher mortality rate.[4] As the fungus thrives in the necrotic tissue making it difficult for chemotherapeutic agents to penetrate, prompt and aggressive surgical debridement thus is considered an essential component of an optimal treatment regimen. A fulminant orbital invasion, may necessitate immediate exenteration to maximize the patient's chance of survival in the backdrop of rapidly progressive disease.[17] 30 out of 32 (93.3%) patients studied by Mishra *et al* benefited from endoscopic debridement of sinuses[18]. All the 6 (100%) cases had endoscopic sinus surgery and 2 (30%) underwent orbital exenteration in a small series by Sen *et al*.[17]

Although most reports pleads for surgical debridement, other authors have questioned the value of aggressive surgical pursuit in the presence of intracranial disease.[4,6,7] Intracranial extension has been shown to be the cause of death in 80 % of cases and the infection was considered to be almost invariably fatal in the presence of intracranial extension.[4,6]

Medical therapy in tandem with surgical debridement has proven to increase survival rate (78%) when compared with medical management alone (57.5%).[1] The mainstay of medical treatment of mucormycosis are amphotericin B deoxycholate and liposomal amphotericin B (a lipid derivative of amphotericin B deoxycholate).

The overall mortality was reported to be 30.7% in Singh A *et al*.'s study of 101 cases of rhinocerebral mucormycosis.[19] While in the systematic review by Pal R *et al*, among 96 cases, 33 (34%) succumbed to the illness and 63 (66%) were alive.[15] 12.5% patients of COVID associated mucormycosis did not survive in Mishra *et al* study.[18] and 28 patients (90.32%) recovered and were alive on the last follow up during the study period in case series of Ravani *et al*.[16]

CONCLUSION

Rhinocerebral mucormycosis is an aggressive disease with a substantial mortality rate but seeking timely help, prompt investigations and diagnosis, treatment with higher antibiotics, oral or systemic antifungal agents, wide surgical debridement and control of underlying predisposing factors has led to optimum management and control of the infection with gratifying outcome and lower morbidity as compared to pre COVID era. This is applicable to all forms of the disease, including cases with extensive disease.

CONFLICT OF INTEREST

There are no conflicts of interest.

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