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Case Series

Ophthalmology Section

A black intruder into the Pandemic: Rhino-Orbital Mucormycosis Complicating COVID-19

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ABSTRACT

There is an increased incidence of rhino orbital mucormycosis during the Coronavirus Disease-2019 (COVID-19) pandemic attributed to diabetes mellitus, corticosteroid usage and immunocompromise caused by COVID-19. In this series, seven biopsy proven cases of mucormycosis (six male patients and one female patient) are presented from a tertiary care center in Eastern India from (May 2021 to June 2021). Empirical systemic liposomal amphotericin B, radical sinus surgery with orbital decompression and irrigation of sinus and orbit with amphotericin B was performed. The mean age of the patients were 42.71±7.34 years with a male preponderance (85.7%). Five patients had orbital involvement (71.42%), and two had cerebral involvement (28.6%). All of them had elevated blood glucose levels, though only three (42.85%) were known cases of type 2 diabetes. The most common manifestations were sinus tenderness (100%), paresthesia (100%), facial swelling (71.42%) and nasal discharge (28.57%). Follow-up at two months showed zero mortality. Timely diagnosis, appropriate management with intravenous amphotericin B and endoscopic radical sinus surgery, debridement of the necrotic tissue proved to be necessary for a good outcome in rhino-orbito-cerebral mucormycosis.

Keywords: Coronavirus disease-2019, Diabetes mellitus complicating, Orbital decompression

INTRODUCTION

Mucormycosis is an opportunistic fungal infection which typically affects patients with lowered immune status like diabetes mellitus, systemic steroid therapy, patients on mechanical ventilation (invasive and non invasive) with supplemental oxygen administration, and those on immunosuppressive therapy [1-3]. This could be attributed to the increase in COVID-19 infection as well as institution of aggressive supportive treatment like systemic steroids, oxygen therapy, immunosuppressive therapy to combat the cytokine storm [2-4].

The species of fungus causing mucormycosis include *Rhizopus, Rhizomucor, Saksenaea, Absidia, Apophysomyces*, and *Mucor* [2,3]. This is a fatal infection resulting in angioinvasion, mycotic thrombosis, and ischemic necrosis of tissues [2]. The spores are inhaled through the nasal or oral cavity and enter the Paranasal Sinuses (PNS). The infection invades the orbit via lamina papyracea, infratemporal fossa, inferior orbital fissure or the orbital apex. Intracranial spread occurs through the supraorbital fissure, cribriform plate of ethmoid and perineural invasion. Complications of intracranial extension include cavernous sinus thrombosis, sagittal sinus thrombosis, carotid occlusion, cerebral infarction, intracranial aneurysm/haemorrhage and cerebral abscess [2]. Early diagnosis and prompt initiation of aggressive treatment by a multidisciplinary team is essential to improve outcomes in this rapidly progressive and devastating disease [5-7].

The present study aim at, the presenting clinical features, diagnostic criteria, management protocols, and outcome of seven cases of Rhino-Orbital Mucormycosis (ROCM) who were admitted to a tertiary care centre in Eastern India.

CASE SERIES

Seven post-COVID-19 patients were referred with signs and symptoms suggestive of mucormycosis, from May to June 2021, from various parts of eastern India. A detailed history including associated co-morbidities, details of prior COVID-19 infection and its management were recorded. An extensive clinical and radiological evaluation was performed and clinical staging of ROCM was done. A multidisciplinary team was constituted to establish and implement management protocols.

At the time of admission, patients underwent a preliminary Diagnostic Nasal Endoscopy (DNE) and the sample obtained was sent for potassium hyroxide (KOH) wet mount and fungal culture and sensitivity. To assess the extent of the disease, contrast enhanced Magnetic Resonance Imaging (MRI) of head and neck, Para Nasal Sinus(PNS), orbit and face was done. Based on initial microbiological and radiographic findings, systemic liposomal amphotericin B was started (5-7 mg/kg/day) with continuous monitoring of renal function. All patients underwent endoscopic radical sinus surgery and orbital decompression for orbital involvement (clinically and on imaging). The sinuses and orbit were irrigated with 50 mg of amphotericin B in 12.5 mL of distilled water. Biopsy specimen was sent for histopathological confirmation. Postoperatively, regular follow-up MRI, long term antifungal therapy and repeated nasal endoscopic examination and debridement, as well as ophthalmic examination whenever required were continued.

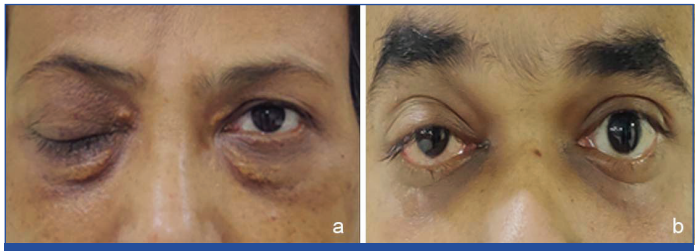
Out of the seven patients, six were males (85.71%). The mean age of presentation was 42.71±7.34 years [Table/Fig-1]. There were two patients with rhino-orbito cerebral mucormycosis, and five with rhino-orbital diseases (57.14%). The mean interval between detection of COVID-19 and development of mucormycotic symptoms was 14.43±5.59 days. The initial clinical presentation [Table/Fig-2] was similar in all patients (except for cases 4 and 6) as they presented with severe sinus tenderness (100%), paraesthesia (100%) and facial swelling along the affected side (71.42%), nasal stuffiness, black and blood-stained nasal discharge (28.57%). Five patients had orbital involvement (71.42%) at presentation which included ptosis (42.85%) [Table/Fig-3a], proptosis (42.85%) [Table/Fig-3b], ophthalmoplegia (42.85%) and diminution of vision (57.14%). Patient 4 had only diminution of vision and paraesthesia during initial presentation. Diagnostic Nasal Endoscopy (DNE) showed nasal eschar in case four [Table/Fig-4a]. Palatal eschar was seen in case five [Table/Fig-4b]. Patient 3 had lagophthalmos with exposure keratopathy.

Demographic and clinical characterstics studied		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (years)		44	37	31	42	52	55	38
Gender		Male	Male	Male	Male	Male	Female	Male
Systemic illness		Nil	Nil	Nil	*DM	*DM, †HTN, Hypothyroidism	Hypothyroidism	*DM, †HTN, ‡CKD (post transplant)
Duration of DM (Years)					2	15		3
Fasting blood sugar (mg/dL)		284	184	302	401	378	301	374
Post prandial blood sugar (mg/dL)		295	240	324	387	413	320	404
Glycated haemoglobin (HbA1c, %)		7	4	6	6	9	10.4	9.8
Mucor symptom development (days)		10	12	17	10	7	25	20
§RTPCR at time of admission		-ve	+ve	-ve	+ve	+ve	-ve	-ve
Treatment of COVID-19	Oxygen	‖NIV	‖NIV	‖NIV	Nil	‖NIV	‖NIV	‖NIV
	Steroid	** i.v. MP	†† Oral P	†† Oral P	Nil	††i.v dexa	**i.v MP + †† Oral P	††Oral P
	Remdesivir	No	No	No	No	Yes	Yes	No
	Antibiotics	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[Table/Fig-1]: Demography, clinical features, signs and symptoms and treatment of patients with Rhino orbital mucormycosis associated with or following COVID-19 infection.
*DM: Diabetes mellitus; †HTN: Hypertension; ‡CKD: Chronic kidney disease; §RTPCR: Real time polymerase chain reaction, ‖NIV: non invasive ventilation; ** i.v MP: Intravenous methyl prednisolone; ††P: Prednisolone; ‡‡i.v dexa: Intravenous dexamethasone

Clinical signs	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Facial swelling	Yes	Yes	Yes	No	Yes	No	Yes
Paresthesia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nasal discharge	No	No	Yes	No	Yes	No	No
*PNS tenderness	Yes	Yes	Yes	No	Yes	Yes	Yes
Nasal eschar	No	No	No	Yes	No	No	No
Palatal eschar	No	No	No	No	Yes	No	No
Ptosis	No	No	Moderate	No	Mild	Complete	No
Proptosis	No	No	Moderate	No	Mild	Nil	Mild
Ophthalmoplegia	No		Partial	No	Partial	Complete	No
Diminution of vision	No	No	Yes	Yes	Yes	Yes	No

[Table/Fig-2]: Clinical manifestations of the COVID-19 patients presenting with mucormycosis.
*PNS: Para nasal sinus

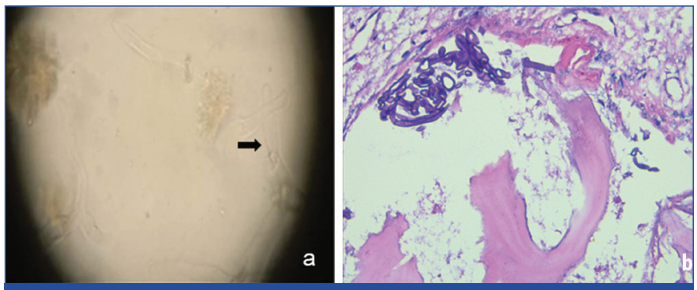


[Table/Fig-3]: a) Complete ptosis in patient 6; b) Mild proptosis, ptosis, conjunctival congestion and mild lid edema in patient 2.

[Table/Fig-4]: a) Palatal eschar in patient 5; b) Arrow shows nasal eschar removed from patient 4.

Even though all of them had hyperglycaemia, only three were known for type 2 diabetes mellitus and were under treatment (42.85%). All patients were managed with insulin, after serial monitoring of blood glucose. The mean fasting blood sugar level and glycated haemoglobin (HbA1c) at presentation was 317.71±64.49 mg/dL and 7.34±2.06, respectively. Two patients were on treatment for hypothyroidism, and one was on immunosuppressant (renal transplantation). None of the patients were vaccinated except patients 5 and 6. Both had contracted COVID-19 within one month of vaccination. Except for patient 4, who was on home isolation (14.28%), the others were hospitalised for COVID-19 treatment and were on oxygen therapy, systemic steroids and broad-spectrum antibiotic treatment. Patients 5 and 6 were on Remdesivir (28.57%) during their hospital stay.

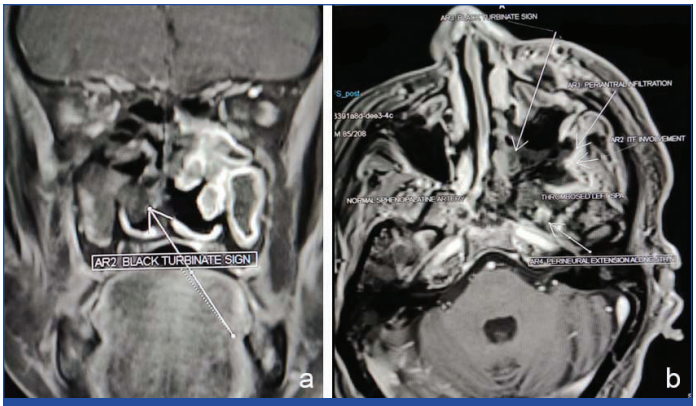
All the patients showed broad aseptate fungal hyphae with irregular branching suggestive of mucormycosis on KOH mount [Table/Fig-5a,b]. Four out of the seven cases grew whitish-brown cotton candy colonies on culture in Sabouraud's dextrose agar. Rhizopus was identified based on the rate of growth, colony morphology and microscopic features such as mycelium and sporangium. Histopathological confirmation was done for all the cases from the post-surgical biopsy specimen. All slides showed presence of thick broad aseptate hyphae of mucormycosis with surrounding inflammation and tissue necrosis [Table/Fig-5b].



[Table/Fig-5]: a) KOH mount in patient 2 showing broad aseptate hyphae, b) Histopathological slide of patient 4. (40X)

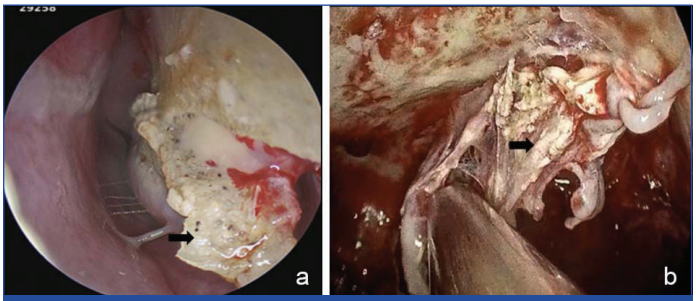
MRI [Table/Fig-6] revealed pan sinusitis with diffuse mucosal involvement in all the cases (100%). Black turbinate sign was seen in four patients (57.14%). Peri-antral involvement along with retro-maxillary space extension was seen in two cases (28.57%). Orbital involvement with optic nerve sheath enhancement was seen in cases three to six (57.14%). Intracranial spread was there in case five and six (28.57%). Patient 5 had left-sided intracranial extension along the skull base foramen with smooth dural enhancement along the left middle cranial fossa. Patient 6 had bilateral parasellar involvement extending from infratemporal fossa across foramen ovale causing encasement of cavernous segment of bilateral internal carotid artery.

Endoscopic radical sinus surgery was done in all cases [Table/Fig-7a]. For entering the maxillary sinus, endoscopic modified Denker's approach was followed. All the contents of the sinuses were radically removed. In those cases where inferior orbital nerve [Table/Fig-7b]



[Table/Fig-6]: a) Black turbinate sign; b) Perineural extension along 5th nerve and thrombosed sphenopalatine artery.

was involved, inferior orbital wall decompression was done. Medial orbital wall i.e., the lamina papyracea was removed completely by endoscopic dissection and periorbita was exposed. Multiple horizontal incisions were given in the periorbita to allow the orbital fat to prolapse into the nasal cavity and maxillary sinus and diseased or necrosed tissue was removed. Irrigation with amphotericin B irrigation was done infra-orbitally and in all the sinuses. Patient 5 had endoscopic palatal resection through transoral or transnasal approach and obturator was placed. Patient 6 had parasellar involvement, therefore bony debridement of the parasellar area was done. Repeated nasal endoscopy and minor debridement were continued after surgery daily. No patient was planned for exenteration or retrobulbar injection.



[Table/Fig-7]: a) Mucormycosis seen in the turbinate; b) Infraorbital nerve involvement in mucormycosis.

Postoperatively, anti-fungal treatment was continued, and postoperative imaging was repeated at regular intervals till discharge. Repeated ocular follow-up examinations were done and patients were followed to an average period of one and a half to two months. After discharge, the patients were given oral posaconazole 300 mg twice daily followed by 300 mg once daily for a period of 3 month while they were followed-up closely with DNE, renal and liver function tests.

DISCUSSION

The reported incidence of mucormycosis in the pre-COVID-19 era varied from 0.005 to 1.7 per million population and the global case fatality rate was as high as 46% with 80 times higher prevalence (0.14 per 1000) reported in India, as per the estimate of the year 2019-2020 [3]. In hospitalised COVID-19 patients, the reported rate of secondary infection is as high as 8% [2]. Patients in middle and later stage of the infection have a greater chance of developing secondary fungal infection [6-9]. The mortality rate is higher in patients with secondary invasive fungal infection (53%) when compared to patients without (31%) [2,6-9]. An increased risk of mortality was associated with a delay in diagnosis of mucormycosis for more than five days [10,11]. In this series, there was no mortality probably because, the disease was diagnosed in the early stages and was rigorously managed both medically and surgically. Furthermore, the follow-up period was short.

Singh AK et al., studied 28 publications involving a total of 101 patients and concluded that 81.2% cases of post-COVID-19 mucormycosis were from India. There was a male preponderance (78.9%) and no age group was spared. A 59.4% presented during the active stage of COVID-19 infection and 40.6% presented in the recovered stage; 83.3% (75) had hyperglycaemia at the time of presentation. A 14.9% presented with diabetic keto acidosis; 76.3% were on steroids; 4.1% were on tocilizumab; 20.6% were on remdesivir. There was a total of 94.1% proven cases (confirmed by both Histopathological Examination (HPE) and microbiological examination). The most common presentation in this case review was naso-sinus involvement (88.9%) followed by rhino-orbital (56.7%) with quite a bit of overlap between the two [3]. The index series also showed a clear male preponderance (85.71%). All patients were hyperglycaemic; 85.71% were on systemic steroids; 85.71% were on oxygen therapy with non invasive ventilation; and 28.57% on remdesivir. The clinical presentation, response to therapy as well as the predisposing risk factors were similar to the published reports. The only difference that we observed was an earlier onset of mucormycosis (as early as seven days) within 14.43±5.97 days of possible infection with Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). It is seen that ROCM develops as late as 30-42 days post-diagnosis of COVID-19 [2]. The cases were classified into proven and probable based on European Organisation for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) criteria [12]. Accordingly, all the patients were proven cases of mucormycosis.

It is being gradually recognised that there is a complex interplay of various factors that increasingly impact the morbidity and mortality in COVID-19. Predominantly, these factors include pre-existing diseases like type 2 diabetes mellitus, use of immunosuppressive therapy and systemic immune alterations of COVID-19 infection itself [5,6]. In this case series, all patients presented with uncontrolled diabetes, even though only three were known cases of pre-existing diabetics. The increase in incidence of uncontrolled diabetic status seems to be bidirectional with COVID-19. The strong association between SARS-CoV-2 and diabetes could be attributed to the pleiotropic alterations of glucose metabolism caused by the virus as well as binding of the virus to Angiotensin-Converting Enzyme 2 (ACE-2) receptors that are expressed in key metabolic organs and tissues that causes raised blood glucose levels [4]. Almost all studies also showed a diabetic preponderance [1,3,5,7]. COVID-19 infection induces an immunocompromised state by decreasing the T-lymphocytes i.e., CD4+T and CD8+T [4]. Major damage is caused by increased expression of Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)-α which causes the cytokine storm. The additional risk factors for the sudden increase in invasive fungal sinusitis during the COVID-19 era could be the increase in the use of steroids, monoclonal antibodies, and broad-spectrum antibiotics [8]. The analysis of these seven cases showed that all the patients had uncontrolled sugars. They were all managed with insulin. Prognosis remains poor even with aggressive surgery and intravenous anti-fungal therapy, with reported mortality rates of 33.3%-80%, increasing up to 100 per cent in disseminated infections [8].

A total of eight genus (24 species) of mucorales organism have been identified in a meta-analysis of 851 cases, out of which Rhizopus species was found to be most common. It was also found to be the most often isolated species from cases with ROCM all four culture positive cases [13]. However, an antifungal drug sensitivity was not done before starting antifungals in the patients.

Aggressive surgical debridement along with intravenous amphotericin B is the standard of care for rhino orbito-cerebral mucormycosis. Extensive and multiple debridement may be necessary. Availability of endoscopic surgery improves visibility, offers better access to the sphenoid, ethmoid and maxillary sinuses, and ensures complete debridement of the diseased tissue with relative sparing of normal tissue [14]. Very little bleeding is usually encountered due to the

vaso-occlusive effect of the fungal infection and hence the principle of surgical debridement is to debride until one encounters normal bleeding tissue [15]. Traditional surgical options depend on the extent of the disease and may vary from debridement with Cadwel Luc, medial maxillectomy, ethmoidectomies, sphenoidotomies, and in extensive cases, radical maxillectomy with orbital exenteration [16]. In an acutely ill patient, it is best to consider an endoscopic sinus surgery because of its minimal invasiveness and low operative morbidity. In this series, all patients underwent endoscopic radical sinus surgery and orbital wall decompression. It is also mandatory that the extent of the disease be accessed, and pre-operative staging performed to decide on the type of adjunctive procedures that will be necessary to eradicate fungal infection [14-16].

CONCLUSION(S)

Prevention of rhino-orbito-cerebral mucormycosis in COVID-19 patients should involve judicious use of corticosteroids, proactive and rigid control of diabetes and adoption of strict aseptic precautions to minimise exposure to any potential source of infection. Daily change of the sterilised humidifier and the sterile water of the humidifier while administering oxygen in high-risk patients. Quick and aggressive medical management as well as endoscopic sinus surgery is essential for salvaging life of patients.

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