Original Research Article

Emerging problem to health care workers in form of virus and fungus combo: a tertiary care centre experience

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ABSTRACT

Background: Rhino-orbital-cerebral mucormycosis has reached epidemic proportion during second wave of COVID-19 pandemic in India. In this study we aimed to understand the demographics, presentation, temporal sequence, risk factors and outcomes to undertake measures for prevention and treatment and benefit of administering liposomal amphotericin via retrobulbar injection in addition to systemic antifungals in the setting of rhino-orbital-mucormycosis.

Methods: Study of patients with COVID-19-associated mucormycosis managed or co-managed by ophthalmologists in our centre from April 2021 to June 2021.

Results: Male predominance and more than 75% associated with COVID-19 infection. Common risk factors associated were DM and corticosteroids use. Unilateral involvement was common (82.4%). Most common primary symptom and sign of ROCM is orbital/facial pain (68.4%) and ptosis (84.2 %) respectively. retro bulbar amphotericin B injections had slight improvement in vision (25%), ptosis (37.5%) and extra ocular movement (25%) with few complications. Surgical management were PNS debridement (42.1%), exenteration added in 17.5 % and with above procedure additional maxillectomy needed in 14%. 22.8 % cases were succumbed by disease while 40.1 % of live patients needed orbital exenteration.

Conclusions: ROCM has visible signs and symptoms, help us in early diagnosis as compared to mucormycosis at other anatomical sites and should be known to all ophthalmologists. Early diagnosis by involving root level health worker and creation of standard treatment guideline on emerging health problem is an urgent need.

Keywords: Rhino-orbital-cerebral mucormycosis, COVID-19, DKA

INTRODUCTION

Rhino-orbital-cerebral mucormycosis (ROCM) is a rare serious invasive fungal infection which often affects immune-compromised individuals, with around 70% of the cases complicating a diabetic ketoacidosis (DKA) event.^{1,2} The condition originates in the nose and paranasal sinuses but is often suspected following orbital

spread, explaining its poor prognosis.³ The incidence of mucormycosis is often underestimated.⁴ The prevalence of mucormycosis is much higher in India (0.14 per 1000) than worldwide (0.005-1.7 per million).⁵⁻⁷ India also has the second position in the world for number of patients suffering from diabetes mellitus.⁸ In COVID-19 patients, the incidence of secondary bacterial or fungal infections is 8%, with aspergillosis the most common fungal infection.^{9,10} Nevertheless, few reports states a rising

trend in mucormycosis in the this decade, which is hypothesized to reflect the rising populations with diabetes mellitus (DM), hematological malignancy, and bone marrow transplants.¹¹

Reports on ocular manifestations in patients with the novel corona virus disease 2019 (COVID-19) describe self-limiting conjunctivitis and rare neuro-ophthalmic manifestations that include optic neuritis and ocular motor cranial neuropathies.^{12,13} We are still learning about the overreaching health implications and long-term sequelae associated with the viral pandemic. Separate case reports have been emerging describing ROCM coinfection in COVID-19 positive patients.¹⁴⁻¹⁶ We have observed an increased rate of ROCM cases in our hospital during the second wave of the pandemic. To overcome this upcoming problem, we have started a separate 80bedded dedicated ward for mucormycosis patients and to fight the battle against deadly rust, there are appointed one unit each from department of ophthalmology, ENT, internal medicine, neurology and endocrinology. We evaluate the COVID-19 status, associated comorbidities, and ocular manifestations of patients in mucor ward.

Objectives

The objective of our study is to identify risk factors and proper management for mucormycosis pandemic and its relation with COVID-19. It will help to develop facilities and infrastructure for the surveillance, early diagnosis and management of mucormycosis in India as mucormycosis is here to stay with us for the next few months and probably years.

METHODS

We did prospective observational study of mucormycosis patients admitted in Sardar Patel medical college and associated group of PBM hospitals, Rajasthan (India) from month April 2021 to June 2021 after ethical approval from our ethics committee. Diagnosis of mucormycosis was confirmed by clinically, KOH mount, histopathologic identification and radiologically. Examination at presentation included detailed history, otorhinolaryngological, ophthalmic and neurological examination. Complete blood count, fasting blood sugar, HbA1c, urine for ketone bodies, liver function test and renal function test were done after admission. Patient having eye involvement were examined for visual acuity, periocularoedema, extraocular movement, ptosis, proptosis, pupillary reaction and fundus. Treatment was given in form of stabilization of metabolic and systemic condition, systemic antifungal drugs administration, surgical management and adjunctive treatment. Surgical treatment of patients was divided in three groups; patients who have only endoscopic sinus debridement/FESS (functional endoscopic sinus surgery), patients who have both endoscopic sinus debridement and orbital exenteration and patients who have endoscopic sinus debridement, orbital exenteration and maxillectomy

Patients having vision in eye and having radiological involvement of orbit were also tried retrobulbar liposomal amphotericin B injection in dose of 3.57 mg/ml in 5 to 10 sitting. We followed all patients in ward during admission and after discharge in OPD and telephonically till clinical and radiological remission or up to 15th July.

Statistical analysis

Descriptive analysis for the clinico-demographic and treatment characteristics using SPSS version 20.0.

RESULTS

Demographics

Total 132 patients of mucormycosis which were admitted at our mucor ward were included. There was male predominance (M:F-2.47:1) with mean age was 51.8 (range, 2-76) years. 76.5% cases came from rural background (Table 1). Most of cases were elderly (71 of 132 patients 53.7% cases had age more than 50 years) while only 7.6% cases were under age of 20.

COVID-19 relationships

In our study 73 out of 132 (55.3%) were proved cases of COVID-19 by RT-PCR test while rest of cases were RT-PCR negative. To rule out old asymptomatic cases of COVID 19, we did COVID-19 antibody titer in 26 patients who were not vaccinated, not diagnosed COVID-19 previously and now had negative RT-PCR test. 14 cases (53.8%) were found significant antibody titer (Table 1).

Risk factors for ROCM in COVID-19 cases

Corticosteroids (either oral or intravenous or both) were used in 80.8% (59 out of 73 COVID-19 test positive cases) patients, while 14 patients (19.2%) did not receive corticosteroids in any form. Intravenous corticosteroids were given to 75.3% (55 of 73) patients while only oral corticosteroids were given in 5.5% (4 of 73) patients. Mean duration of oral corticosteroid was 7.5 days and intravenous corticosteroid was 12.6 days. Need of oxygen administration was in 86.3% (63 of 73 COVID 19 positive cases) patients while 13.7% (10 of 73) did not use it. 32 patients used only mask/prongs (43.8%), 27 patients used High flow/non-invasive ventilation (36.9%) and 4 patients needed ventilator support (5.5%). Out of 132 mucormycosis patients, 83 cases (62.8%) were suffering from diabetes mellitus. 49 of 94 (52.1%) male patients and 34 of 38 (89.5%) female patients had diabetes mellitus. In our study mean duration for diabetes was 5.8 years with median fasting blood sugar was 281.5 mg%. 9 out of 83 cases (10.8%) landed at ward with diabetic ketoacidosis (DKA), 65 cases (78.3%) presented with uncontrolled blood sugar while only 9 cases (10.8%) had controlled diabetic status.

Table 1: Demographic and comorbid illness profile of the mucormycosis patients (n=132).

Demographic feature/ Comorbid condition				Male	Female	Total	
Age (years)	Mean			51.4	54.3	51.8	
	range	< 10		5	0	5	
		11-20		4	1	5	
		21- 30		11	5	16	
		31-50		26	9	35	
		>50		48	23	71	
Rural			73	28	101		
Urban			21	10	31		
COVID-19 infection (Proved by RT-PCR test) (n=73) Male-52 Female-21	Management of COVID-19	Asymptomatic		4	2	6	
		Home care		7	6	13	
		Hospitalised		41	13	54	
	Corticosteroid administration (59) (mean duration)	Yes	Only oral	2 (7.3)	2 (8.1)	4 (7.5)	
			Injectable	42 (12.3)	13 (14.2)	55 (12.6)	
		No			8	6	14
	Oxygen administration	Yes	Mask/prongs	27	5	32	
			High flow/non-invasive ventilation	17	10	27	
			Mechanical ventilation	3	1	4	
			No			5	5
Diabetic (n=83) Male-49 Female-34	Mean duration(years)		4.6	6.3	5.8		
	Mean FBS at presentation (mg%)		284.5	278.1	281.5		
	Controlled		5	4	9		
	Uncontrolled		38	27	65		
	Diabetic ketoacidosis		6	3	9		
Other immunocompromised condition	Hypertension		39	23	62		
	Bronchial asthma		7	17	24		
	Cardiovascular disorder		24	11	35		
	Cerebrovascular disease		6	0	6		
	Renal diseases		7	0	7		
	Malignancy		5	0	5		
	Obesity (BMI 25 kg/m2)		13	11	24		
	Organ transplant patients		1	2	3		
Celiac disease			1	0	1		
COVID-19 antibody test done (positive) in 26 patients*			18 (11)	8 (3)	26 (14)		

*COVID-19 antibody titer done in patients who were negative RT PCR report during admission, not positive previously and not vaccinated.

In other associated comorbid illnesses hypertension was most common in both sexes (62 of 132, 46.9%) while cardiovascular disorder found in 35 of 132 patients (26.5%), bronchial asthma and obesity were in 24 cases (18.2%), 7 cases were suffering from renal dysfunction (5.3%), 6 cases had cerebrovascular accident (4.5%) and 5 cases were suffering from malignancy, all were haematological malignancies (3.8%), Three cases were of post renal transplant and one case had celiac disease (Table 1).

Clinical presentation of ROCM

In our study most of cases had unilateral involvement (47 out of 57, 82.4%). Frequency of common primary symptoms of ROCM orbital/facial pain was most common symptom (68.4%), followed by orbital/facial oedema (59.6%). Periocular/facial discoloration (38.6%), loss of vision (35.1%), headache (29.8%), diplopia (15.8%) and facial deviation (7%). Most common sign was ptosis (84.2%) followed by conjunctival chemosis (77.2%), extraocular movement restriction (75.4%) proptosis (71.9%) and altered sensorium (28.1%) (Table 2).

Table 2: Ophthalmological manifestations in 57 patients with rhino-orbital-cerebral mucormycosis at presentation.

Manifestations		Male	Female	Total
Laterality	Unilateral	31	16	47
	Bilateral	6	4	10
Vision	PL absent	12	8	20
	<6/60	15	11	26
	≥6/60	9	2	11
Periorbital/facial pain		31	8	39
Headache		13	4	17
Periorbital oedema		26	8	34
Diplopia		8	1	9
Periocular/facial discoloration		16	6	22
Pupil	RRR	19	11	30
	RAPD	9	5	14
	Non reacting	8	5	13
Ptosis (N=48)	Mild	7	2	9
	Moderate	8	1	9
	Severe	21	9	30
Fundus	No view	6	8	14
	Normal	11	5	16
	CRAO	5	3	8
	Disc Pallor	7	4	11
	Diabetic retinopathy	15	9	24
	Hyperemic Disc	3	4	7
	Pale Retina	3	3	6
Proptosis		30	11	41
Conjunctivalchemosis		31	13	44
Altered sensorium		9	7	16
Facial deviation		3	1	4
Extraocular movement	Partially restricted	9	2	11
	Absent	23	9	32

RRR-round regular reacting, RAPD-relative afferent pupillary defect, CRAO- central retinal artery obstruction

Management of COVID-19 associated ROCM

The management of mucormycosis essentially involves control of risk factors including hyperglycemia, medical management with antifungal agents, adjunctive therapy in form of retrobulbar amphotericin B and optimal surgical debridement. In our centre all mucormycosis patients with ROCM were treated with intravenous lipid form of amphotericin B in dose of 5 mg/kg once daily with close monitoring of adverse effect especially hypokalemia, hypomagnesemia, hyperglycemia and nephrotoxicity. We did electrolytes and renal function test alternate day. Average duration of intravenous amphotericin B was 21.4 days with median of 26 days (range of 8-62 days). We used intravenous posaconazole as a salvage antifungal drug and oral delayed release tablet form as step-down

during discharge in patients who had responded on intravenous amphotericin B. Injectable posaconazole was given in dosage of 300 mg 2 doses in first 24 hours followed by 300 mg in 24 hours. It was used in 12 patients who were not responding well to liposomal amphotericin B with average for 12.8 days (median 14, 4-16 days).

Oral posaconazole was given in doses of 300 mg twice daily for 2 dose, then 300 mg once daily. In 14 patients it was used average for 18.4 (median 22, 10-28 days). Combination antifungal therapy was not used at our centre. Retrobulbar amphotericin B was used as adjunctive treatment of systemic treatment for preserve vision. It was used in 16 patients with average of 6.31 (median 5, 1-10). Dose of retrobulbar injection was 1 ml (3.57 mg/ml) once a day. Most common surgical management used at our centre was PNS debridement in 24 patients (42.1%) out of 57 ROCM patients while other surgeries used in form of PNS debridement with orbital exenteration in 10 patients (17.5 %) and PNS debridement+orbital exenteration with maxillectomy in 8 patients (14 %) (Table 3).

Outcome of retrobulbar liposomal amphotericin B injections

We tried a unique and potentially globe sparing approach i.e. retrobulbar antifungal injections in 16 ROCM patients. We completed planned sittings in all patients except one in which procedure was prematurely terminated after first sitting due to patient refusal (complaining of excessive pain and swelling after first injection). We assessed patients daily and after completion of 5 sitting, continue five more alternate days retrobulbar injections in patients who had severe involvement of orbit and again assessed after completion of all doses (after 15 days). Vision was improved in 4 patients (25 %) while stable in 9 patients (56.3%). On the other hand, it was deteriorated in 3 patients (18.7 %). Ptosis was stable in 7 cases (43.7 %) while improved in 6 cases (37.5 %) and worsened in 3 cases (18.8 %). Extraocular movement was stable in 9 cases (56.3 %), improved in 4 cases (25 %) and deteriorated in 3 cases (18.8 %). 5 cases (31.2 %) had complications in form of increased swelling, pain and conjunctival chemosis. We had no complication in form of orbital compartment syndrome (Table 4).

Prognosis of COVID-19 associated ROCM

At our centre 13 out of 57 (22.8%) were succumbed due to disease while 44 were able to survive with or without morbidity. Out of 44 survived patients, in 26 patients (59.1%) we were able to salvage eye while 18 (40.1%) were undergone for orbital exenteration. Out of 26 patients with salvage eye, 14 patients (53.8%) had visual acuity>6/60, 7 had ≤6/60 (26.9%) and 5 had PL absent (19.2 %) (Table 5).

Table 3: Rhino-orbital-cerebral mucormycosis patients: Management (out of 57 patients of ROCM).

Management	N
Amphotericin B 5 mg/ kg every 24 hours	Intravenous
	57
	Retrobulbar
	16
Posaconazole (300 mg every 12 hours on first day followed by 300mg every 24 hours)	Intravenous
	12
	Oral (step down)
	14
Number of days of intravenous amphotericin B; mean (median, range)	21.4 (26, 8-62)
Number of days of posaconazole; mean (median, range)	Intravenous
	12.8 (14, 4-16)
	Oral
	22.4 (26, 10-32)
Number of injections given retrobulbar amphotericin B mean (median, range)	6.31 (5, 1-10)
FESS/paranasal sinus debridement	24
FESS/paranasal sinus debridement+orbital exenteration	10
FESS/paranasal sinus debridement+orbital exenteration+maxillectomy	8

FESS- functional endoscopic sinus surgery

Table 4: Outcome of retrobulbar liposomal amphotericin B injections.

Case	Visual acuity		Ptosis	Extraocular movement	Complication
	Before	After			
1	6/60	6/36	Improved	Improved	No
2	6/60	6/60	Improved	Stable	No
3	Finger count at 3 meter	Finger count at 3 meter	Stable	Stable	Swelling increased
4	Finger count at 3 meter	Finger count at 4meter	Stable	Stable	Increase pain
5	6/60	6/60	Stable	Stable	No
6	Finger count at 4meter	Finger count at 3 meter	Stable	Stable	conjunctival chemosis
7	6/60	6/60	Improved	Improved	No
8	Finger count at 1 meter	Finger count at 2meter	Stable	Stable	No
9	Finger count at 4meter	Finger count at 1 meter	Worsened	Worsened	Sever pain and swelling*
10	Finger count at 3 meter	Finger count at 3 meters	Worsened	Worsened	conjunctival chemosis
11	6/60	6/60	Improved	Stable	No
12	6/60	6/60	Improved	Improved	
13	Finger count at one feet	Finger count at one feet	Stable	Stable	No
14	6/60	6/36	Improved	Improved	No
15	Finger count at one feet	Finger count at one feet	Stable	Stable	Swelling increased
16	6/60	Finger count at 4 meter	Worsened	Worsened	No

DISCUSSION

The second wave of COVID-19 has seen a gush of mucormycosis. COVID-19 produces a hypoxic environment with high glucose levels, high levels of ferritin, and attenuated phagocytic activity of leukocytes due to immunosuppression by the virus itself and the corticosteroids used in the management. This setting is highly conducive for the fungal spores to germinate and proliferate.⁵ Prolonged hospitalisation, use of immunosuppressants, and associated comorbidities are

other risk factors attributed to the increasing incidence of COVID-19-associated ROCM.⁵

COVID-19 relationship with ROCM

We account more rate of ROCM cases reporting at our centre during the second wave of COVID-19 in comparison to the same period in the previous year. In our study 55.3% were proved cases of COVID-19 by RT PCR test. 53.8% cases had high titer of antibody against SARS-CoV who was not vaccinated and proved COVID-

19 infection. These finding suggestive of more than 75% cases had COVID-19 infection in their life either symptomatic or asymptomatic. Same trend was found in study by Fouad et al in which half of the cases had a positive test record of SARS-CoV-2 infection.¹⁷

Table 5: Final outcome of patients with rhino -orbital-cerebral mucormycosis (ROCM) (n=57).

Outcome		Male	Female	Total
Systemic outcome	Alive with regression	9	5	14
	Alive with stable disease	7	5	12
	Alive with progression	11	7	18
	Death	9	4	13
Ocular outcome (In 44 alive patients)	Orbital exenteration	11	7	18
	Eye salvage	16	10	26
Visual acuity (26 eye salvaged patients)	>6/60	9	5	14
	≤6/60	4	3	7
	PL absent	3	2	5

Epidemiology of COVID-19 associated ROCM

In our study the mean age of patients admitted at mucor ward was 51.8 years with male predominance (71.2%). Most of cases came from rural background (76.5%). Our patient population was slightly younger than a review of global cases by European confederation of medical mycology and international society of human and animal mycoses in which they had reported to be 55 years (range 10–86 years).¹⁸ In a systematic review of cases reported worldwide and in India, the reported cases of COVID-19-associated ROCM, there was a male predilection (79%).⁵ The demographic profile in series by Sen et al was same as in our series mean age of 51.9 years and 71% male patients.¹⁹ Higher incidence in male gender may be due to greater outdoor exposure and, therefore, to fungal spores may be the possible reason for this majority.

Potential risk factors for COVID-19 associated ROCM

According to study of Kayina et al 235 patients infected with COVID 19 infection during the first wave and requiring hospitalization, out of which 77% required oxygen support in any form, 22% with high flow nasal cannula and 26% required invasive mechanical ventilation.²⁰ A study done by Sen et al found that oxygen requirement was observed in 57% and of these, masks/prongs were used in 78%, non-invasive ventilation in 15%, and mechanical ventilation was necessary in 7%.¹⁹ In our study need of oxygen administration was in 86.3% patients. 43.8 %patients used only mask/prongs,

36.9% patients used high flow/non-invasive ventilation and 5.5% needed ventilator support. Even though the recovery trial has shown the benefits of corticosteroids in reducing mortality in patients with moderate to severe COVID-19, corticosteroids have been criticized for their role in increasing the susceptibility to mucormycosis.²¹

A cumulative dose greater than 600 mg for prednisone and 2-7 g of methylprednisolone has been found to predispose immunocompromised patients to mucormycosis.²² Greater than 3 weeks of high-dose systemic corticosteroid has been concerned as a risk factor for mucormycosis in non-COVID-19 patients.²³ A systematic review by Singh et al for cases reported worldwide and in India 76% of the patients with COVID-19-associated ROCM gave history of systemic corticosteroids.⁵ Data of study done by Sen et al systemic corticosteroids had been used in 87% of the patients, 21% patients received systemic corticosteroids for more than ten days. 73% of patients treated at home were also used corticosteroids.¹⁹

We observe that corticosteroids were used in 80.8% patients. Intravenous corticosteroids were given to 75.3% patients. Mean duration of oral corticosteroids was 7.5 days and Intravenous corticosteroids was 12.6 days. According to some theories SARS-CoV may damage islets and cause acute insulin dependent diabetes mellitus, worsening of pre-existing DM and cytokine storm indirectly fuels this by resulting in resistance.^{24,25} Corticosteroids add fuel to the fire by increasing hyperglycemia and DKA. Hyperglycemia causes glycosylation of transferrin and ferritin and reduces iron binding. By reducing the ability of transferrin to chelate iron, acidosis presents an additive effect causing an overall increase in free iron levels, allowing mucor to thrive. DM has been identified as an independent risk factor for mucormycosis.²⁶ According to multicentre observational study by Patel et al 74% of mucormycosis patients were diabetic in pre-COVID-19 era.¹⁰ The risk is 7.5 times higher in diabetics than the general population.²⁷

In a series of 41 cases by John et al 93% of cases of COVID-19 associated ROCM were diabetics. According to Hoenigl et al showed that diabetics account for 82.5% of the cases with predominantly type II (89.4 %) and most of patients presented with uncontrolled or poorly controlled diabetics (80.3%) concomitant DKA was found in 40.9% of the patients.^{28,29}

We found slightly lower trend of diabetes mellitus than above mention studies. In our study 62.8 % were suffered from diabetes mellitus higher incidence in females than males (89.5% versus 52.1%). Patients with diabetes landed in ward in uncontrolled blood sugar were 89.1% out of which 10.8% in DKA. Most of patients associated with ROCM were also associated with other comorbid illness. In our series of 132, hypertension was most common in both sexes (46.9%) followed by

cardiovascular disorder (26.5%), bronchial asthma and obesity (18.2%), renal diseases (5.3%), cerebrovascular (4.5%), haematological malignancies (3.8%), Post renal transplant (2.27%) and one case of celiac disease. In Sen et al study 24% had hypertension and 3% renal disease.³⁰ With these observations we took lesson that patients of ROCM in the background of COVID-19, should be investigated thoroughly with high index of suspicion even in the absence of an underlying comorbidity. Out of 19 asymptomatic or less symptomatic patients who were not hospitalised for COVID 19 treatment 14 did not exposed with corticosteroids. Out of these 11 patients also did not have any known risk factors. This indicates that we need further studies on virus host interactions and search for other potential risk factors.

Figure 1: Clinical picture showing ptosis, proptosis, conjunctival chemosis, periocular oedema and complete restriction of movement in left eye in all direction of gaze.

Symptoms and signs of COVID-19 associated ROCM

In our study bilateral involvement of disease was 15.8%. Common symptoms observed were orbital/facial pain, orbital/facial oedema, periocular/facial discoloration, loss of vision, headache, diplopia and facial deviation. Most common sign was ptosis followed by conjunctival chemosis, extraocular movement restriction, proptosis and altered sensorium. Our study had same trend as observed in other studies.^{18,19}

Management of COVID-19 associated ROCM

The management of mucormycosis essentially involves treatment of underlying risk factors, judicious use of antifungal agents, adjunctive Therapy in form of retrobulbar amphotericin B and last but not most important was optimal surgical debridement. Antifungals; amphotericin B is the drug of choice for initial therapy but total dosage of lipid amphotericin B has not been studied. Therapy should continue until there is clinical resolution of sign and symptoms of infection, as well as resolution of radiographic signs of active disease; also continue until reversal of underlying immunosuppression has been achieved. Although there are anecdotal reports of using combination therapy with amphotericin B and

either posaconazole or an echinocandin but no convincing data found to support any combination therapy and not recommended in the major treatment guidelines. Posaconazole and isavuconazole broad-spectrum azoles are available for patients who have responded to a lipid amphotericin B for oral step down therapy.^{29,30} Most of centre prefers delayed-release tablets over suspension since suspension requires fatty food for absorption. Intravenous posaconazole or isavuconazole used as salvage therapy for patients who do not respond to or cannot tolerate amphotericin B. Posaconazole led to complete or partial response in 60% of patients; 21% had stable disease.³¹ In our centre all mucormycosis patients with ROCM were treated with intravenous amphotericin B with close monitoring. We use intravenous Posaconazole in 21 % cases as a salvage antifungal drug and oral delayed release tablet form as step-down in 6 % case. Combination antifungal therapy was not used at our centre.

Figure 2: Clinical picture of 2 yr old child.

Figure 3: Axial MR image (T2/T2ES sequences) shows thickening of lateral and medial rectus muscles with extensive fat stranding in intra and extraconal region with muscle oedema resulting in distortion of right globe (guitar pick sign) with ptosis.

Retrobulbar liposomal amphotericin B injections

Amphotericin Intraorbital injection of amphotericin B deoxycholate has shown to be effective for life and eye salvage in certain case reports.³²⁻³⁴ There is paucity of data with regard to its safety and potential for vision salvage. In our study, vision, ptosis and extraocular movement were improved in 25%, 37.5% and 25% respectively. Complications were found in 31.5% cases while we were able to avoid most serious complication, orbital compartment syndrome. Most common surgical management used in our centre was PNS debridement (42.1%) while others were PNS debridement with orbital

exenteration (17.5%) and PNS debridement +orbital exenteration with maxillectomy (14%). In our centre orbital exenteration was done in patients of radiological orbital involvement with loss of vision without CNS involvement. In Sen et al, PNS debridement was performed in 67%, orbital exenteration in 15%, and simultaneous PNS debridement and orbital exenteration was performed in 17%.¹⁹ In a review of 80 published cases of ROCM in COVID-19, 37% required an orbital exenteration.^{35,36} Literature has shown that ROCM patients without CNS involvement had better outcome with surgical intervention than with medical management alone (mortality 14% vs. 63%, $p=0.01$). Surgery did not have an impact on the survival of patients with CNS involvement (mortality 71% vs. 57%, $p=0.66$).¹⁸

Figure 4: X-ray.

Figure 5: Clinical picture of 4 yr old child.

Prognosis of COVID-19 associated ROCM

At our centre mortality was 22.8% and loss of eye tissue was 40.1% in live patients. Patients with eye salvage had loss of PL in 19.2%, visual acuity $\leq 6/60$ in 26.9% and $>6/60$ in 53.8%. In other series for COVID-19 associated ROCM, the overall mortality has been estimated to be 31%.⁵ Results from Sen et al show that overall, the mortality with COVID-19-associated ROCM is 14% and disease progression is seen in 13% of the cases. Results may change on long term follow up so long term large study required for validate results.

Limitations

Limitations of current study were; data from one centre, may not representative of the actual picture of India, follow up was limited so validation of results cannot be

done and proper guideline for management not still available.

CONCLUSION

We report a higher rate of ROCM cases presenting to our centre during the second wave COVID-19 pandemic in comparison to the first wave and previous years. More than three fourth cases had COVID-19 infection proved by RT-PCR test or by antibody titer in their blood. COVID-19 associated ROCM was further complicated with comorbid illness especially diabetes mellitus and late presentation due to lockdown and rural background. ROCM has visible signs and symptoms help us in early diagnosis as compared to mucormycosis at other anatomical sites and should be known to all ophthalmologists. This Giant causes either loss of life or loss of organ and tissue causing functional impairment in more than half of patients. We need more education and awareness for strict social distancing, good hygiene and public education regarding early sign and symptoms for prevention and more studies for development of standard treatment guideline.

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