

Case Series

Comprehensive study on manifestation, management and outcome of post COVID rhino orbito cerebral mucormycosis in our institution

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ABSTRACT

Rhino orbital mucor mycosis in covid infected patients presented a challenge in management. We tried analysing comprehensively the manifestations and management and prognosis of post COVID rhino orbito cerebral mucormycosis (ROCM) patients in our institution. Patients with symptoms of ROCM were managed according to the guidelines issued by the directorate of medical education, Tamil Nadu, India. 30 possible ROCM patients were treated so far from May 2021. Patients underwent radiological, microbiological and pathological investigation. In stage 1, nasal cavity alone was involved in 11 patients. In stage 2, paranasal sinus extension was seen in 8 patients. In stage 3, orbital extension was seen in 10 patients. In stage 4, intra cranial extension was seen in 1 patient. 10 patients were probable ROCM without microbiological or pathological evidence. 20 patients had proven ROCM. They were treated with endoscopic debridement. Out of them 10 patients had to undergo orbital decompression and 5 of them had improvement in vision. All proven ROCM patients were treated with 3 weeks of injection liposomal amphotericin B along with oral posaconazole 300 mg for 3-6 weeks. Post-operative histopathology noted fungal invasion of blood vessels in 19 cases and thrombus in 10 cases of orbital involvement. No mortality was reported in the study group. COVID variant associated thrombosis may be the reason for increased incidence of mucor mycosis in post COVID patients. Team work, appropriate guidelines and adequate supply of medications helped in achieving desired outcome.

Keywords: ROCM, Post COVID, Mucormycosis

INTRODUCTION

COVID-19 has been a global pandemic since November 2019 and has infected close to 200 million people worldwide.¹ Mucorales of zygomycetes family of fungus causes life threatening infections in immune compromised patients.² In 2019, Cornley et al published the global guidelines for management of mucormycosis.³

Rhino orbito cerebral mucormycosis (ROCM) infection occurring in post COVID-19 patients was an unexpected challenge. From May 2021 in our institution we have seen an increase in number of mucormycosis patients

among COVID-19 recovered patients. We setup a separate ward for the treatment of these patients to enable in multidisciplinary monitoring. The team consisted of physician, otolaryngologist, ophthalmologist, microbiologist, pathologist, dentist, radiologist and anaesthesiologist.

In Tamil Nadu, India directorate of medical education published management guidelines for mucor mycosis in May 2021.⁴

According to this guidelines annexure 4, ROCM shall be staged as following.⁴

Stage 1 includes involvement of nasal mucosa alone; stage 2 includes extension to paranasal sinuses; stage 3 includes extending to orbit and stage 4 includes intracranial extension (Figure 1).

The management of ROCM was based on classifying the possible ROCM patients with further investigations as ROCM unlikely, probable ROCM or proven ROCM. We have followed this algorithm in management of our patients (Figure 2).

Proposed Staging of Rhino-Orbito-Cerebral Mucormycosis (ROCM)				
Staging of Rhino-Orbito-Cerebral Mucormycosis	Symptoms	Signs	Primary Assessment	Confirmation of Diagnosis
Stage 1: Involvement of the nasal mucosa 1a: Limited to the middle turbinate 1b: Involvement of the inferior turbinate or ostium of the nasolacrimal duct 1c: Involvement of the nasal septum 1d: Bilateral nasal mucosal involvement	Nasal stuffiness, nasal discharge, foul smell, epistaxis	Foul-smelling sticky mucoid or black-tinged, or granular or haemorrhagic nasal discharge, nasal mucosal inflammation, erythema, violaceous or blue discoloration, pale ulcer, anaesthesia, ischemia, eschar	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Deep nasal swab or endoscopy-guided nasal swab or nasal mucosal biopsy for direct microscopy, culture and molecular diagnostics; nasal mucosal biopsy for rapid histopathology with special stains
Stage 2: Involvement of paranasal sinuses 2a: One sinus 2b: Two ipsilateral sinuses 2c: > Two ipsilateral sinuses and/or palate/oral cavity 2d: Bilateral paranasal sinus involvement or involvement of the zygoma or mandible	Symptoms in Stage 1 + facial pain, facial edema, dental pain, systemic symptoms (malaise, fever)	Signs in Stage 1 + unilateral or bilateral, localized or diffuse facial edema, edema localized over the sinuses, localized sinus tenderness	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 1 + sinus biopsy for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 3: Involvement of the orbit 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected 3c: Central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis; involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement	Symptoms in Stage 1 and 2 + pain in the eye, proptosis, ptosis, diplopia, loss of vision, infraorbital and facial V1 V2 nerve anesthesia	Signs in Stage 1 and 2 + conjunctival chemosis, isolated ocular motility restriction, ptosis, proptosis, infraorbital nerve anesthesia, central retinal artery occlusion, features of ophthalmic artery occlusion and superior ophthalmic vein thrombosis. V1 and V2 nerve anesthesia, and features of III, IV and VI nerve palsy indicating orbital apex/superior orbital fissure involvement.	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 2 + orbital biopsy if indicated and if feasible (if the disease is predominantly orbital) for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 4: Involvement of the CNS 4a: Focal or partial cavernous sinus involvement and/or involvement of the cribriform plate 4b: Diffuse cavernous sinus involvement and/or cavernous sinus thrombosis 4c: Involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction 4d: Multifocal or diffuse CNS disease	Symptoms in Stage 1 to 3 + bilateral proptosis, paralysis, altered consciousness, focal seizures	Signs in Stage 1-3 (some features overlap with Stage 3) + V1 and V2 nerve anesthesia, ptosis, and features of III, IV and VI nerve palsy indicate cavernous sinus involvement. Bilaterality of these signs with contralateral orbital edema with no clinico-radiological evidence of paranasal sinus or orbital involvement on the contralateral side indicate cavernous sinus thrombosis. Hemiparesis, altered consciousness and focal seizures indicate brain invasion and infarction.	Diagnostic endoscopy, Contrast-enhanced CT Scan, MRI (preferred)	Same as Stage 3

Figure 1: Proposed staging of POSTCOVID ROCM suggested by guidelines of DME, Government of Tamil Nadu, India.

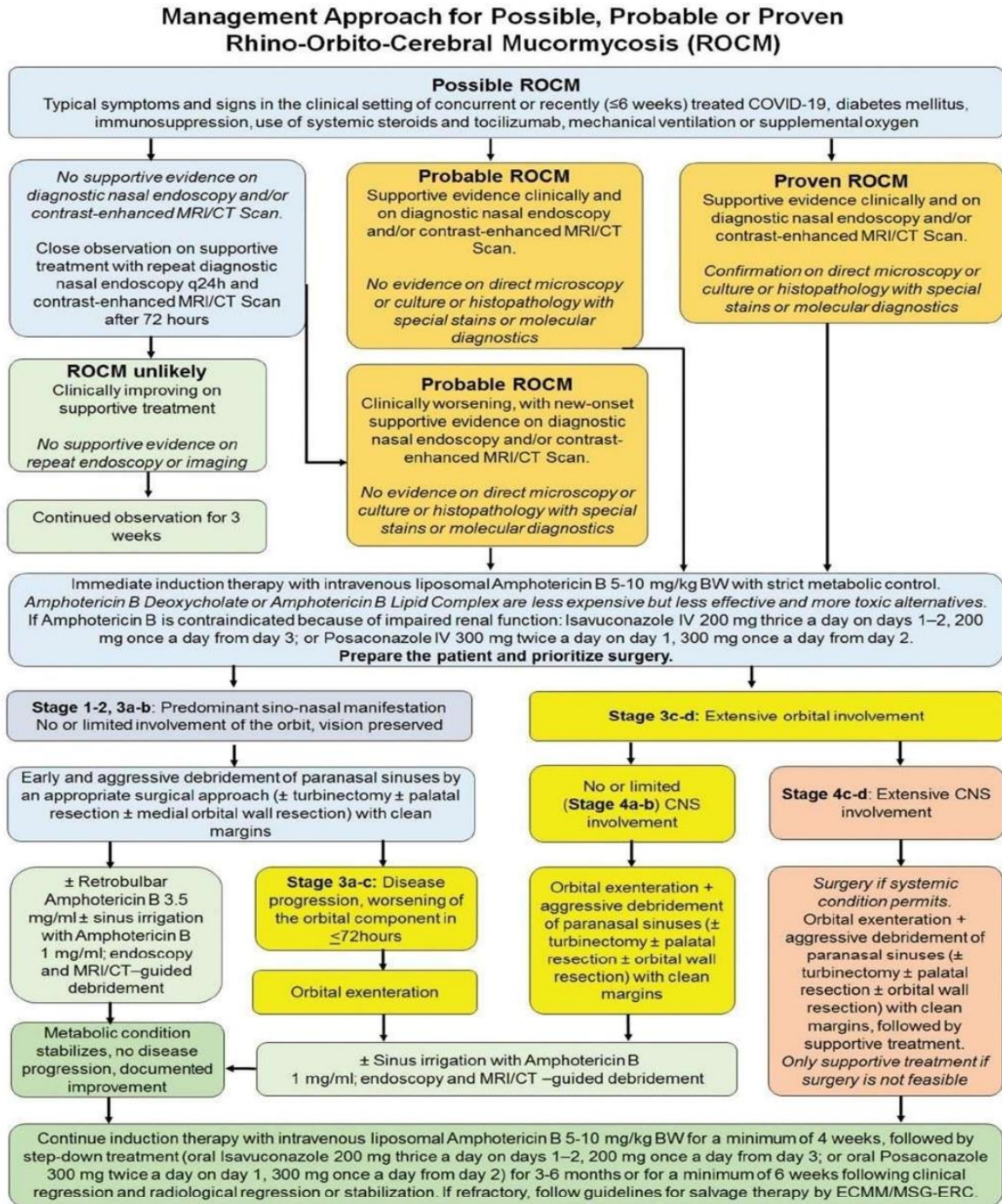


Figure 2: Management algorithm for POSTCOVID ROCM suggested by guidelines of DME, Government of Tamil Nadu, India.

CASE SERIES

All patients who presented after COVID infection treatment with suspected symptoms of ROCM like nasal obstruction, nasal discharge, visual loss, protrusion of eyeball were admitted in mucor ward.

We had 30 patients of possible ROCM in mucor ward so far from May 2021 (Table 1). There were 19 (64%) male

and 11 (36%) female patients. Age varied between 18 years to 82 years. Mean age was 56 years. 24 (80%) patients had diabetes along with other diseases, 6 (20%) patients had no predisposing factors. 21 (70%) patients were oxygen dependent during COVID treatment.

Initial assessment classifying them as possible ROCM will undergo routine investigations along with radiology, smear for microbiology and biopsy for pathology through

diagnostic nasal endoscopy (Figure 3) and started with antifungal depending on clinical suspicion of ROCM.

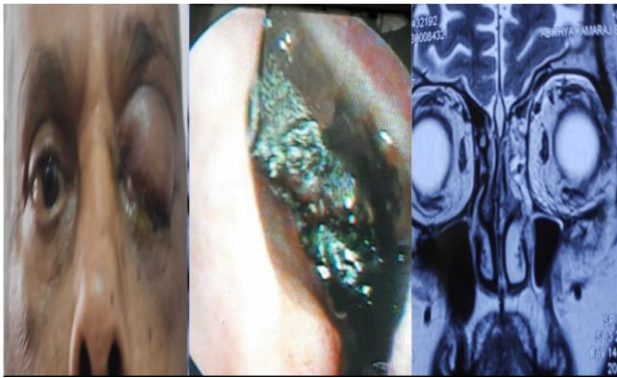


Figure 3: Patient with proptosis (a) proptosis left eye, (b) black middle turbinate, and (c) MRI sinus with orbit.

A magnetic resonance imaging (MRI) para nasal sinus with orbit is the preferred investigation of choice. Radiologists report the cases in prescribed format (Figure 4) staging ROCM. In stage 1 (36%), nasal cavity alone was involved in 11 patients. In stage 2 (28%), paranasal sinus extension was seen in 8 patients. In stage 3 (33%), orbital extension was seen in 10 patients; and in stage 4 (3%), intra cranial extension was seen in 1 patient.

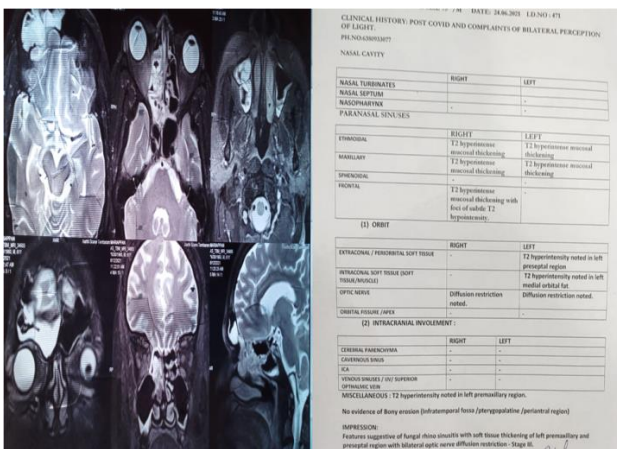


Figure 4: MRI paranasal sinuses with orbit report with staging of ROCM.

Smear for microbiology staining and culture was sent in sterile container and biopsy for histopathology was sent in formalin with clinical details.

Patients with no microbiological or histopathological evidence of mucor were grouped as probable ROCM (33%). In 8 patients of probable ROCM, only medical management with oral antifungal tablet posaconazole 300 mg once a day initially was given till confirmation of diagnosis then observed with regular nasal endoscopy for new symptoms.

Smear examination and culture proved mucor in 13 cases (43%). Histopathology examination (Figure 5A) confirmed invasive fungal infection in 19 cases and 1 non-invasive fungal infection, and they were grouped as proven ROCM was 20 patients (67%).

Upon confirmation of either or both patients will be taken up for early endoscopic debridement and orbital decompression if needed.

20 patients of proven ROCM and 2 probable ROCM underwent surgery. Endoscopic debridement alone was done in 10 patients (50%) and endoscopic orbital decompression was done in 10 patients (50%) along with debridement. 6 patients (30%) had bilateral disease. 4 patients (20%) underwent repeat debridement. 3 patients (15%) had palatal debridement. 1 patient had intracranial extension was managed with endoscopic debridement and drainage. The progress recorded and condition at the time of discharge noted.

All proven ROCM completed 3 weeks of injection liposomal amphotericin B along with oral posaconazole 300 mg for 3-6 weeks.

Post op debrided material was sent for histopathological examination. Post-operative histopathology (Figure 5B) report showed blood vessels invaded with fungus in 19 cases of proven ROCM hence termed as invasive fungal sinusitis, except 1 case which was non-invasive fungal sinusitis. In 10 cases of stage 3 proven ROCM having orbital involvement, along with angio invasion of fungus, thrombi noted in blood vessels (Figure 5C).

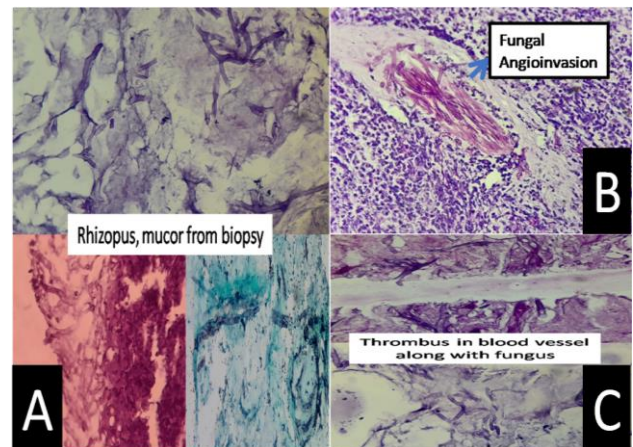


Figure 5: Histopathology picture.

21 (70%) patients had successful outcome. 8 (27%) patients had complete cure and 13 (43%) patients had improvement in symptoms. 9 (30%) patients had no worsening of symptoms or remained as same even after treatment. In 10 patients who underwent orbital decompression, vision improvement was there in 5 (50%) patients. The mean hospital stay was 14 days for ROCM.

Table 1: Master chart.

S. no.	Age	Sex	Predisposing factors	COVID severity	Symptoms	Staging	Micro	Biopsy	Surgical extent	Final diagnosis	Antifungals	Condition on discharge	Duration of stay (days)
1	47	M	DM/SHT	Oxygen dependent	Proptosis, vision loss, nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit, decompression	Proven ROCM	Ampho, Posco	Vision improved	16
2	68	F	DM/IHD	Oxygen dependent	Proptosis, vision loss, palate, nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit, decompression, repeat palate, debridement	Proven ROCM	Ampho, Posco	No worsening of symptoms	30
3	82	M	DM/SHT/IHD	Oxygen dependent	Proptosis, vision loss, nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit, decompression	Proven ROCM	Ampho, Posco	Vision improved	25
4	56	M	DM	COVID care centre	Nasal discharge, left cheek pain	2	Mucor	Invasive fungal	Endoscopic orbit, decompression	Proven ROCM	Ampho, Posco	Cured	14
5	56	M	DM	Oxygen dependent	Proptosis, vision loss, nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit, decompression	Proven ROCM	Ampho, Posco	Vision improved	12
6	44	F	DM	Oxygen dependent	Nasal discharge	1	Nil	Nil	Not done	Probable ROCM	Posco	Improved	10
7	65	F	DM /SHT	Oxygen dependent	Proptosis, vision loss, palate, nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit Decompression	Proven ROCM	Ampho Posco	No worsening of symptoms	16
8	31	F	Nil	Home isolation	Nasal discharge, left cheek pain	2	Nil	Non-invasive fungal	Endoscopic debridement	Probable ROCM	Posco	Cured	10
9	37	F	DM	Oxygen dependent	Nasal discharge	1	Nil	Nil	Endoscopic debridement	Probable ROCM	Posco	Status same	14
10	48	F	DM	Oxygen dependent	Nasal discharge	1	Nil	Nil	Not done	Probable ROCM	Posco	Improved	14
11	63	M	DM	Oxygen dependent	Proptosis Vision loss Nasal discharge Seizures	4	Mucor	Invasive fungal	Endoscopic orbit, decompression, repeat debridement	Proven ROCM	Ampho Posco	Vision improved, seizures stopped	25
12	57	M	DM/SHT	Oxygen dependent	Proptosis Vision loss Nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit, decompression	Proven ROCM	Ampho Posco	No worsening of symptoms	16
13	55	M	Nil	Ward	Nasal discharge	1	Nil	Nil	Not done	Probable ROCM	Posco	Improved	7
14	37	F	DM	Oxygen dependent	Nasal discharge	1	Nil	Nil	Endoscopic debridement	Probable ROCM	Posco	Status same	14
15	53	F	Nil	Ward	Nasal discharge	1	Nil	Nil	Not done	Probable ROCM	Posco	Improved	7
16	82	M	DM/SHT/IHD	Oxygen dependent	Proptosis, vision loss, nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit, decompression	Proven ROCM	Ampho, Posco	Vision improved	25

Continued.

S. no.	Age	Sex	Predisposing factors	COVID severity	Symptoms	Staging	Micro	Biopsy	Surgical extent	Final diagnosis	Antifungals	Condition on discharge	Duration of stay (days)
17	61	M	Dm/sht	Oxygen dependent	Proptosis, vision loss, nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit, decompression	Proven ROCM	Ampho, Posco	No worsening of symptoms	16
18	45	M	DM	Ward	Nasal discharge	1	Nil	Nil	Not done	Probable ROCM	Posco	Improved	14
19	75	M	DM/IHD	Oxygen dependent	Proptosis, vision loss, nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit, decompression	Proven ROCM	Ampho, Posco	No worsening of symptoms	16
20	54	M	DM	COVID care centre	Cheek pain, nasal discharge	2	Nil	Invasive fungal	Endoscopic debridement	Proven ROCM	Ampho, Posco	Cured	16
21	32	M	DM	Oxygen dependent	Cheek pain, nasal discharge	2	Nil	Invasive fungal	Endoscopic debridement	Proven ROCM	Ampho, Posco	Cured	14
22	45	M	Nil	Ward	Nasal discharge	1	Nil	Nil	Not done	Probable ROCM	Posco	Improved	7
23	35	M	Nil	Oxygen dependent	Cheek pain, nasal discharge	2	Nil	Invasive fungal	Endoscopic debridement	Proven ROCM	Ampho, Posco	Cured	14
24	53	M	DM	Oxygen dependent	Cheek pain, nasal discharge	2	Nil	Invasive fungal	Endoscopic debridement	Proven ROCM	Ampho, Posco	Cured	14
25	57	M	DM	Oxygen dependent	Cheek pain, nasal discharge	2	Nil	Invasive fungal	Endoscopic debridement	Proven ROCM	Ampho, Posco	Cured	14
26	37	F	DM	Oxygen dependent	Nasal discharge	1	Nil	Nil	Endoscopic debridement	Probable ROCM	Posco	Status same	14
27	54	M	DM	Ward	Nasal discharge	1	Nil	Nil	Not done	Probable ROCM	Posco	Improved	7
28	65	F	DM	Ward	Nasal discharge	1	Nil	Nil	Not done	Probable ROCM	Posco	Improved	7
29	48	F	Nil	Oxygen dependent	Cheek pain, nasal discharge	2	Nil	Invasive fungal	Endoscopic debridement	Proven ROCM	Ampho, Posco	Cured	14
30	18	M	DM	Oxygen dependent	Proptosis, vision loss, nasal discharge	3	Mucor	Invasive fungal	Endoscopic orbit Decompression	Proven ROCM	Ampho, Posco	No worsening of symptoms	16

DM-Diabetes mellitus, IHD, ischemic heart disease, SHT-systemic hypertension, ROCM-rhinorbitocerebral mucormycosis, AMPHO-amphotericin B, POSCO-posaconazole

Table 2: Manifestation and management of ROCM.

Possible ROCM=30			
Stage 1=11; stage 2=8; stage 3=10; stage 4=1			
Probable ROCM=10		Proven ROCM=20	
Medical management	8	Endoscopic debridement	10
Fess	2	Endoscopic debridement with orbital decompression	10
Successful outcome=21		Unsuccessful outcome=9	
Complete cure=8	Symptoms improved=13		No worsening=6
Mortality - nil		Symptoms same=3	

DISCUSSION

Mucorales cause invasive fungal sinusitis in immunosuppressed individuals.⁵ In India among general population mucor mycosis incidence was 0.14 cases per 1000 according to Skiada et al.⁶ In 2020, White et al reported 26.7% of invasive fungal infection in COVID-19 patients.⁷

The reason for increased incidence of mucor mycosis in COVID infected individuals has been the topic of interest not answered so far.

In China, Song et al concluded impaired T cell immunity as pathogenic factor.⁸ Steroids usage was hinted as cause for ROCM by Mehta et al and Chaudhary et al.^{9,10} Neha et al published a case series of 10 patients with invasive mucormycosis in patients with COVID infection and concluded that impairment of barrier defense with steroids and tocilizumab make COVID patients susceptible for mucormycosis.¹¹ Ahmadikia et al cited corticosteroid administration may be the reason for ROCM in COVID 19 patients.¹² Moorthy et al postulated possible peripheral microthrombi as a cause.¹³ Peman et al stated that the COVID virus itself may be a cause.¹⁴

In past 6 months there have been publications on post COVID ROCM like Sarkar et al, Alekseyev et al, Maini et al and Krishna et al.¹⁵⁻¹⁸ Mitra et al published 32 documented post ROCM patients and had similar results.¹⁹ They concluded that judicious COVID treatment protocol, high index of suspicion, close monitoring of high-risk patients and early institution of treatment can prevent case severity and reduce mortality. Sharma et al published case series of 23 patients with post COVID mucormycosis and concluded that uncontrolled diabetes and over-zealous use of steroids are two main factors aggravating the illness, and both of these must be properly checked.²⁰

In our study 20% patients had no predisposing factor like diabetes before contacting COVID infection. 30% of patients had only mild COVID and was not treated with steroids or oxygen supplement. Blood vessels filled with thrombus is noted in 10 cases of stage 3 orbital ROCM along with fungus. This may hint upon COVID virus itself may be the reason for ROCM possible due to peripheral thrombosis as mentioned in Moorthy et al and Peman et al.^{13,14}

In our study (Table 2) high vigilance and team work helped in identifying cases early. Out of 30 possible ROCM with stage 1 radiology findings, 10 cases had negative finding in microbiology and pathology. They were treated as probable ROCM and followed up regularly.

Surgical debridement was done early in proven ROCM 20 cases. In 10 cases with orbital involvement, surgical decompression and antifungals brought back vision in

50% of cases. Mortality was nil in our study group. 70% patients had satisfactory outcome.

CONCLUSION

Post COVID ROCM is different from invasive fungal sinusitis occurring in other immune compromised patients. COVID variant associated thrombosis may be the reason for increased incidence of mucor mycosis in post COVID patients. A good team work, appropriate guidelines issued by authorities and adequate supply of antifungal medications have helped us to achieve desired outcome so far in the management of post COVID ROCM in our institution.

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