



Original Article

## Rhinocerebral mucormycosis (RCM): To study the clinical spectrum and outcome of 61 cases of RCM managed at a tertiary care center in India

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### ABSTRACT

**Background:** Mucormycosis is a life-threatening infection of the paranasal sinuses and nasal cavities that can easily spread to the orbit and the brain. It is caused by fungi of the family Mucoraceae. We present a case series of 61 patients diagnosed and treated for rhinocerebral mucormycosis (RCM) at a single tertiary health care center.

**Methods:** After obtaining ethical clearance, all patient files with a final diagnosis of RCM were thoroughly analyzed in departmental records and a master chart was prepared. The study evaluated the etiology, clinical spectrum, diagnosis, management, complications, and outcome at 3 months of RCM cases.

**Results:** About 93.4% of the RCM cases were diabetic and an equal number had a past history of COVID infection. About 85.2% had received steroids for the treatment of coronavirus disease 2019 infection. The most common presentation of RCM was temporal lobe abscess (25.7%) followed by frontal lobe abscess (16.6%). At 3 months post-diagnosis, mortality in our study was 42.6%. About 26.2% of the RCM cases had no disease, 23% had a static disease, and 8.2% had progressive disease at the end of 3 months.

**Conclusion:** We report the largest single-center case series of RCM, comprising 61 patients. This case series underscores the importance of the early diagnosis and prompt treatment for a better prognosis for this dreadful disease. The three pillars of treatment for RCM cases include reversal of the immunosuppressive state, administration of antifungal drugs, and extensive surgical debridement. In spite of all this, mortality remains high.

**Keywords:** COVID-19, Diabetic, Mucormycosis, Rhinocerebral, Steroids

### INTRODUCTION

Rhinocerebral mucormycosis (RCM) is a necrotizing, angioinvasive, life-threatening infection of the paranasal sinuses, and nasal cavities that can easily spread to the orbit and the brain. It is caused by fungi of the family Mucoraceae, the principal pathogens being *Rhizopus*, *Lichtheimia*, *Apophysomyces*, and *Rhizomucor*.<sup>[1]</sup> The fungus is ubiquitous and is found in soil, decaying

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vegetation, and other organic material. RCM almost always occurs in immunocompromised patients; its diagnosis is a medical and surgical emergency. We present a case series of 61 patients diagnosed and treated for RCM at a single tertiary health-care center.

## MATERIALS AND METHODS

We conducted a prospective observational study of all patients admitted to our institute with a diagnosis of RCM after obtaining ethical clearance from the Institutional Review Board vide letter no. OW/RC/All India Institute of Medical Sciences – Raipur/2021/576 dated June 8, 2021. All patient files with a final diagnosis of RCM were thoroughly analyzed in departmental records and a master chart was prepared [Table 1]. The study evaluated the etiology, clinical spectrum, diagnosis, management, complications, and outcome at 3 months of RCM cases. The outcome at 3 months was analyzed in the form of survival or death. Patients who were alive at the end of 3 months were subjected to Magnetic Resonance Imaging Brain + Orbits + Paranasal sinuses (Plain + Contrast) and categorized into one of the following–

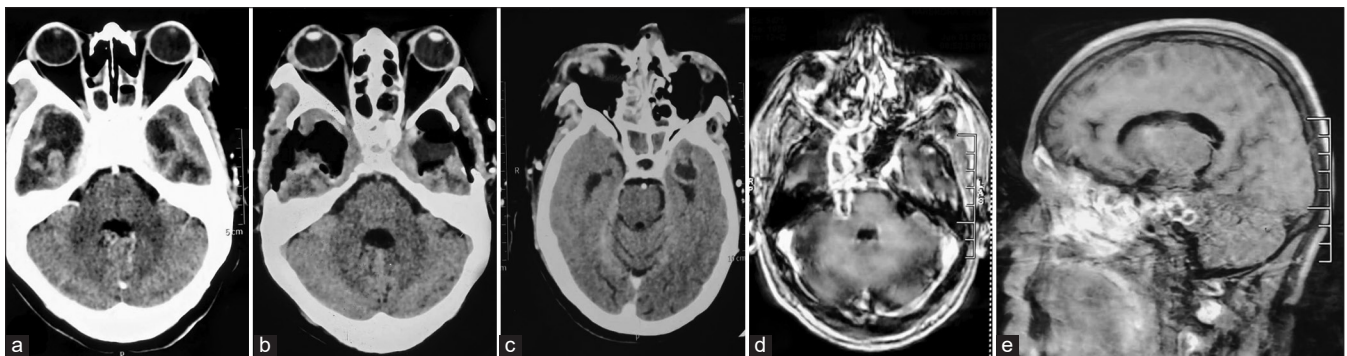
1. No disease – No contrast-enhancing lesion
2. Static disease – Contrast enhancement is present but less than in the preoperative scans
3. Progressive disease – Contrast enhancement is present which is more than in the pre-operative scans.

Data analysis was performed using the Statistical Package for the Social Sciences version 25:0 (International Business Machines Corporation, New York, United States of America).

## RESULTS

We analyzed all 251 cases of mucormycosis admitted with us to date and identified the 61 cases which had cerebral involvement. The first case of mucormycosis was presented to us on the May 2, 2021. Out of the 61 cases of RCM,

57 cases had a past history of COVID infection (93.4%). Out of these 57 cases, 52 patients had received steroids for the treatment of COVID in the past (85.2%). Fifty-seven out of the 61 cases of RCM were diabetic (93.4%). The most common presentation of RCM was temporal lobe abscess (25.7%) [Figure 1] followed by frontal lobe abscess (16.6%) [Figures 2 and 3]. Frontal bone osteomyelitis as a late complication of mucormycosis was encountered in eight cases [Figure 4]. Cavernous sinus thrombosis (CST) was present in eight cases [Figure 5]. Multiple infarcts due to the angioinvasive nature of the disease were seen in six patients [Figure 6]. Other presentations included internal carotid artery (ICA) thrombosis (3), cerebritis with hydrocephalus with fungal meningitis (1), cribriform plate osteomyelitis (2), pachymeningitis (5), extensive skull base osteomyelitis (1), and mucormycosis associated ICA bifurcation aneurysm (1) [Figures 7-11]. Temporal lobe abscess was unilateral in ten cases, bilateral in two cases, associated with midbrain lesion in one case, with CST in one case, with frontoparietal-temporal-occipital infarct in one case, and with frontal lobe involvement in two cases [Figure 12]. Frontal lobe abscess was unilateral in seven cases, bilateral in two cases, and associated with temporal lobe involvement in two cases [Figure 13]. All patients of RCM were started on conventional amphotericin B (1 mg/kg/day). The mean cumulative dose of amphotericin B was 3766 mg [Figure 14] and the mean duration of treatment was 1.45 months. Patients were discharged on oral posaconazole 300 mg twice daily on the 1<sup>st</sup> day followed by 300 mg once a day for 3 months. Thirty-one out of the 61 cases underwent neurosurgical operative intervention (50.8%). Some patients presented to us very late and were not fit for surgery. Cases of CST were managed medically. Out of the 31 neurosurgical procedures, 12 temporal craniotomies, eight frontal craniotomies, two supraorbital craniotomies, eight bilateral frontal craniectomy ± endoscopic debridement for frontal bone osteomyelitis, and one pterional craniotomy for mucormycosis associated ICA bifurcation aneurysm were



**Figure 1:** (a and b) Preoperative and postoperative computed tomography (CT) scan images of the brain showing complete excision of bilateral temporal lobe abscesses. (c) CT scan image of the brain depicting left medial temporal lobe abscess. (d and e) In a case of rhino-orbito-cerebral mucormycosis (ROCM) with radiology which is suggestive of the involvement of all sinuses (pansinusitis), in the brain, a lesion is seen involving the right cavernous sinus and right medial temporal lobe with extension into the right cerebellopontine angle.

**Table 1:** Master chart of all 61 cases of RCM.

Patient Number	COVID positive in the past	Steroids for treatment of COVID	DM	Diagnosis	Surgical treatment	Cumulative dose of Amphotericin	Duration of Posaconazole treatment	Outcome at 3 months
1	Yes	Yes	Yes	Left RCM (Left temporal lobe)	Left frontotemporal craniotomy and excision of temporal abscess with repair of dural defect	4060	3 months	Static disease
2	Yes	Yes	Yes	Right ROCM (Right temporal lobe)	Right temporal craniotomy and excision of abscess	4605	1 month	Progressive disease
3	Yes	Yes	Yes	Right RCM (Right temporal lobe)	Right frontotemporal craniotomy with excision of abscess	4160	45 days	No disease
4	Yes	Yes	Yes	ROCM (frontal bone osteomyelitis)	B/L frontal craniectomy with exteriorization of frontal sinus	5000	3 months	Static disease
5	Yes	Yes	Yes	RCM (B/L Frontal abscess)	Bifrontal craniotomy and excision of basifrontal abscess	4150	7 days	Static disease
6	Yes	Yes	Yes	RCM (Right temporal lesion)	Right frontotemporal craniotomy and excision of medial temporal lesion	3775	3 months	No disease
7	Yes	Yes	Yes	RCM (Right temporal lobe)	Right temporal craniotomy and excision of abscess	3920	3 months	Static disease
8	Yes	Yes	Yes	Recurrent RCM (frontal bone osteomyelitis with epidural abscess)	Left frontal craniectomy and excision of osteomyelitic bone	8970	6 months	Static disease
9	Yes	Yes	Yes	RCM (frontal bone osteomyelitis with patchy meningitis)	B/L frontal bone debridement craniectomy with exteriorization of frontal sinus	4350	3 months	No disease
10	Yes	Yes	Yes	RCM (Frontal bone osteomyelitis)	Bifrontal debridement craniectomy and exteriorization of frontal sinus	10240	15 days	Static disease
11	Yes	Yes	Yes	RCM (mucor aneurysms)	Right Pterional craniotomy and wrapping of Right ICA bifurcation aneurysm	17400	45 days	Aneurysm size is increasing on follow up DSA's (Progressive disease)
12	Yes	Yes	Yes	ROCM (cavernous sinus thrombosis)	No neurosurgical intervention	2825	35 days	No disease

(Contd...)

**Table 1:** (Continued).

Patient Number	COVID positive in the past	Steroids for treatment of COVID	DM	Diagnosis	Surgical treatment	Cumulative dose of Amphotericin	Duration of Posaconazole treatment	Outcome at 3 months
13	Yes	Yes	Yes	RCM (Right frontal abscess)	Bifrontal craniotomy and excision of basifrontal abscess	4710	30 days	DEATH
14	Yes	Yes	Yes	ROCM (Right temporal lobe)	Right temporal craniotomy and excision of abscess	3640	7 days	DEATH
15	Yes	Yes	Yes	ROCM (left temporal lobe lesion and midbrain lesion)	Left frontotemporal craniotomy with excision of medial temporal lobe lesion	4210	30 days	DEATH
16	Yes	Yes	Yes	RCM (cavernous sinus thrombosis)	No neurosurgical intervention	2150	7 days	DEATH
17	Yes	Yes	Yes	ROCM (Left frontal lobe abscess)	Left frontal craniotomy and excision of frontal lobe abscess	4100	Nil	DEATH
18	Yes	Yes	Yes	ROCM (left frontal lobe abscess with left orbito-frontal bone osteomyelitis)	Left Supraorbital craniectomy and excision of frontal lobe abscess	3150	15 days	DEATH
19	Yes	Yes	Yes	ROCM (Multiple infarcts in brain Right MCA/PCA, Left parietal wedge shaped infarct with B/L basifrontal hypodensities)	No neurosurgical intervention	600	Nil	DEATH
20	Yes	Yes	Yes	ROCM (right temporal lobe abscess)	Right temporal craniotomy and excision of medial temporal lobe abscess --> Right ICA infarct in post op period	850	Nil	DEATH
21	Yes	Yes	No	RCM (Ischemia along left MCA/PCA territory without midline shift - infarct)	No neurosurgical intervention	3000	60 days	Static disease
22	Yes	Yes	Yes	RCM (Frontal lobe abscess)	Right frontal craniotomy and excision of abscess	2800	3 months	Progressive disease in sinuses (plan for endoscopic debridement again)
23	Yes	Yes	No	RCM (Left cavernous sinus thrombosis plus skull base involvement)	No neurosurgical intervention	2125	30 days	Static disease
24	Yes	Yes	Yes	RCM + destruction of nasal bridge + fungal meningitis	No neurosurgical intervention	1800	10 days	DEATH

(Contd...)

**Table 1:** (Continued).

Patient Number	COVID positive in the past	Steroids for treatment of COVID	DM	Diagnosis	Surgical treatment	Cumulative dose of Amphotericin	Duration of Posaconazole treatment	Outcome at 3 months
25	No	No	Yes	Rhino-cerebro-Palatal Mucormycosis (bilateral temporal lobe abscesses)	B/L temporal craniotomy and excision of B/L abscesses	4400	2 months	No disease
26	Yes	Yes	Yes	RCM (Right basifrontal Abscess)	Bifrontal craniotomy and excision of abscess	4210	3 months	Static disease
27	Yes	Yes	Yes	ROCM (Bilateral temporal lobe abscesses [Right more than left])	No neurosurgical intervention due to poor condition of the patient	1800	7 days	DEATH
28	Yes	Yes	Yes	ROCM (altered signal intensity in left Gyri recti --> left frontal lobe and left temporal lobe)	No neurosurgical intervention	4000	30 days	DEATH
29	Yes	No	Yes	ROCM (frontal bone osteomyelitis)	Endoscopic debridement of frontal sinuses and of osteomyelitic frontal bone	4400	3 months	No disease
30	Yes	No	Yes	ROCM (Right frontal abscess/ cerebritis)	Right supraorbital craniotomy and excision of frontal abscess	4210	Nil	DEATH
31	Yes	Yes	Yes	B/L RCM (Mainly left sided disease - left temporal and left basifrontal region)	No neurosurgical intervention --> died before intervention	1050	7 days	DEATH
32	Yes	Yes	Yes	RCM (Right frontal, temporal, parietal and occipital regions and right caudate nucleus peripherally enhancing subcentric lesions)	No neurosurgical intervention	2400	15 days	DEATH
33	Yes	Yes	Yes	Disseminated mucormycosis (pulmonary + cerebral) --> Subacute infarcts involving pons, left thalamus, B/L corona radiata, centrum semiovale and B/L high parietal and right frontal lobe (Multiple infarcts)	No neurosurgical intervention	1780	10 days	DEATH

(Contd...)

**Table 1:** (Continued).

Patient Number	COVID positive in the past	Steroids for treatment of COVID	DM	Diagnosis	Surgical treatment	Cumulative dose of Amphotericin	Duration of Posaconazole treatment	Outcome at 3 months
34	Yes	Yes	Yes	ROCM (Cavernous sinus thrombosis with left trigeminal neuritis)	No neurosurgical intervention	2900	3 months	No disease
35	Yes	Yes	Yes	ROCM (B/L basifrontal, left high parietal and left parieto-occipital infarcts --> multiple infarcts)	No neurosurgical intervention	1240	10 days	DEATH
36	Yes	Yes	Yes	ROCM (Hemorrhagic conversion of right PCA infarct + brainstem infarct --> multiple infarcts)	No neurosurgical intervention	1640	7 days	DEATH
37	Yes	Yes	Yes	ROCM (right temporal lobe abscess)	Right temporal craniotomy and surgical debridement of right temporal lobe lesion	3450	30 days	DEATH
38	Yes	Yes	Yes	ROCM (right temporal lobe abscess)	Right temporal craniotomy and excision of abscess	3640	30 days	DEATH
39	Yes	Yes	Yes	ROCM (Altered signal in left temporal lobe --> early cerebritis/evolving abscess with meningitis)	No neurosurgical intervention	1280	15 days	DEATH
40	Yes	Yes	Yes	RCM (Right frontal abscess)	Bifrontal craniotomy with excision of right frontal abscess	1510	Nil	DEATH
41	Yes	Yes	Yes	ROCM (Left temporal infarct with hemorrhagic transformation + IVH)	Left temporal craniotomy with evacuation of hematoma	1320	10 days	DEATH
42	Yes	Yes	Yes	RCM (Right frontal abscess)	Right frontal craniotomy and excision of abscess	13400	40 days	Static disease
43	Yes	No	No	RCM (Frontal bone osteomyelitis)	Frontal bone craniectomy with removal of epidural abscess + granulation tissue	4700	3 months	No disease
44	Yes	No	Yes	RCM (Right ICA thrombosis)	No neurosurgical intervention	2150	45 days	No disease
45	Yes	Yes	Yes	RCM (Right cavernous sinus thrombosis)	No neurosurgical intervention	4460	30 days	Static disease

(Contd...)

**Table 1:** (Continued).

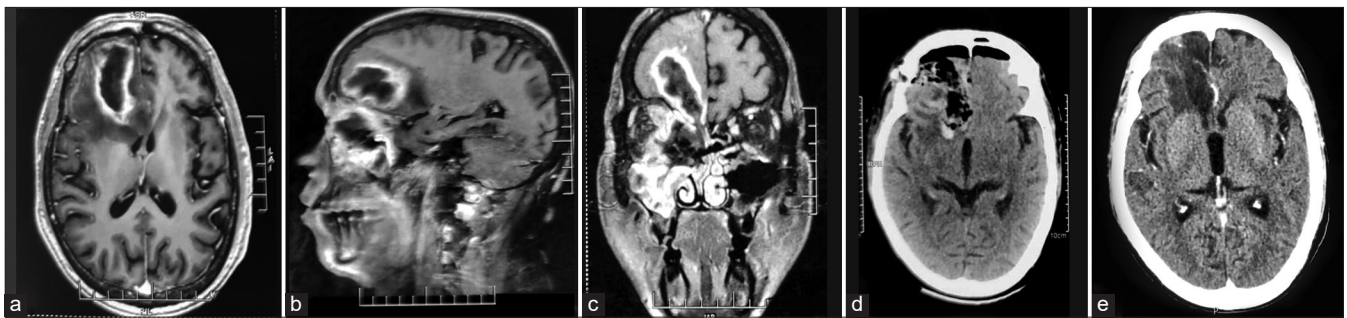
Patient Number	COVID positive in the past	Steroids for treatment of COVID	DM	Diagnosis	Surgical treatment	Cumulative dose of Amphotericin	Duration of Posaconazole treatment	Outcome at 3 months
46	Yes	Yes	Yes	ROCM (Left frontal and temporal cerebritis + hydrocephalus + fungal meningitis)	No neurosurgical intervention	780	Nil	DEATH
47	Yes	Yes	Yes	RCM (left gangliocapsular lesion + Right ICA thrombosis)	No neurosurgical intervention	4125	35 days	Static disease
48	Yes	Yes	Yes	ROCM (Pachymeningitis anterior cranial fossa + right basifrontal lobe extension with erosion of cribriform plate)	No neurosurgical intervention	4500	15 days	No disease
49	Yes	No	Yes	RCM (frontal bone osteomyelitis)	Bifrontal craniectomy with removal of osteomyelitic bone Patient took LAMA, no neurosurgical intervention	4650	2 months	No disease
50	Yes	Yes	Yes	ROCM (Left medial temporal lobe abscess + left cavernous sinus thrombosis + acute stroke leading to right hemiparesis)	Endoscopic debridement done	2120	10 days	DEATH
51	Yes	Yes	Yes	ROCM (frontal bone osteomyelitis and focal meningeal thickening)	No neurosurgical intervention	4150	3 months	No disease
52	No	No	Yes	ROCM (Left ICA thrombosis)	No neurosurgical intervention	4500	45 days	Static disease
53	Yes	Yes	Yes	ROCM (Meningeal enhancement in left basifrontal region)	No neurosurgical intervention	4010	3 months	No disease
54	Yes	Yes	Yes	RCM (Meningeal enhancement along anterior frontal convexities that is contiguous with left frontal sinus enhancement)	Bifrontal craniotomy and debridement	2500	1 month	DEATH
55	No	No	Yes	ROCM (Left medial temporal lobe lesion with Left F-P-T-O infarct)	No neurosurgical intervention	1550	10 days	DEATH
56	Yes	Yes	No	B/L Sinonasal MM (Cribriform plate osteomyelitis)	No neurosurgical intervention	1050	45 days	No disease
57	Yes	Yes	Yes	ROCM (Right ICA Thrombosis)	No neurosurgical intervention	6550	15 days	No disease
58	Yes	Yes	Yes	RCM (Right frontal pachymeningitis)	No neurosurgical intervention	4400	30 days	No disease

(Contd...)

**Table 1:** (Continued).

Patient Number	COVID positive in the past	Steroids for treatment of COVID	DM	Diagnosis	Surgical treatment	Cumulative dose of Amphotericin	Duration of Posaconazole treatment	Outcome at 3 months
59	No	No	Yes	RCM (Right cavernous sinus thrombosis)	No neurosurgical intervention	3010	30 days	Static disease
60	Yes	Yes	Yes	B/L Rhinocerebral MM (Extensive skull base osteomyelitis)	FESS done outside once, no neurosurgical intervention	On Amphotericin (1900mg till now)	Nil	Progressive disease
61	Yes	Yes	Yes	ROCM (Enhancing soft tissue involving the right cavernous sinus and extending into right pre-pontine, pre-medullary, cerebellomedullary cisterns, also involving the CP angle with probable infiltration of pons and medulla)	No neurosurgical intervention	3400 mg	60 days	Progressive disease

RCM: Rhino-cerebral mucormycosis, ROCM: Rhino-orbito-cerebral mucormycosis, ICA: Internal carotid artery, MCA: Middle cerebral artery, PCA: Posterior cerebral artery, CP: Cerebellopontine, DM: Diabetes Mellitus, B/L: Bilateral, DSA: Digital Subtraction Angiography, IVH: Intraventricular Hemorrhage, LAMA: Leave Against Medical Advice, F-P-T-O: Fronto-Parieto-Temporo- Occipital, MM: Mucormycosis, FESS: Functional Endoscopic Sinus Surgery.



**Figure 2:** (a-c) A case of rhino-cerebral mucormycosis (RCM) with the right frontal lobe abscess who underwent right frontal craniotomy and excision of abscess, along with combined (open plus endoscopic) debridement of sinuses. (d) Immediate postoperative computed tomography (CT) scan images showing complete excision of the abscess. (e) Postoperative contrast-enhanced CT (CECT) scan images at 3 months follow-up showing no residual lesion.

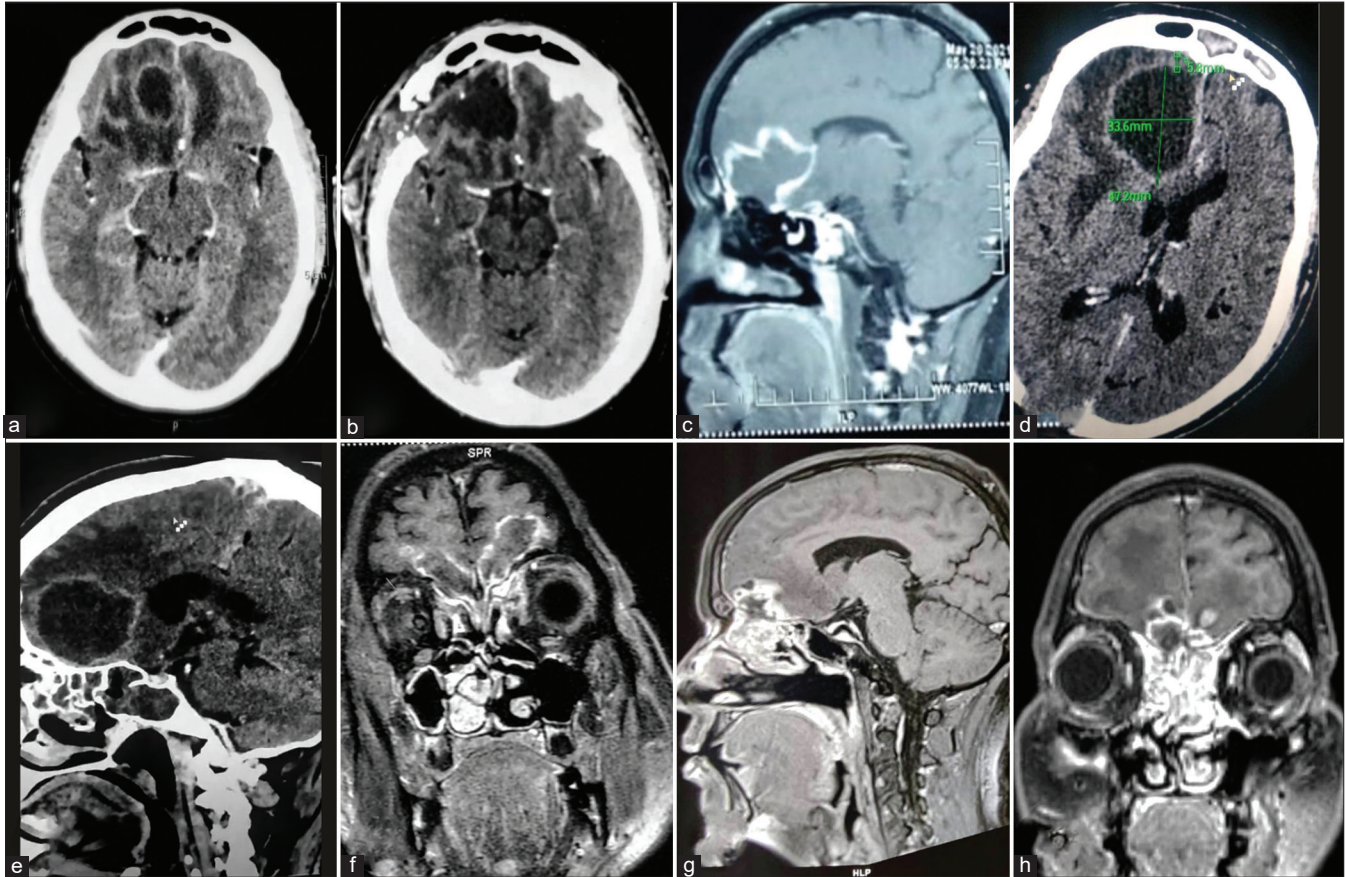
performed [Figure 15]. Out of the 31 patients who underwent neurosurgical operative intervention, 18 cases were operated on once, eight cases were operated on twice, and five cases were operated on thrice. At 3 months post-diagnosis, mortality in our study was 42.6% (The 31 cases that had neurosurgical operative intervention had a mortality rate of 38.7%). About 26.2 % of the RCM cases had no disease, 23% had a static disease, and 8.2% had progressive disease at the end of 3 months [Figure 16].

## CASE ILLUSTRATIONS

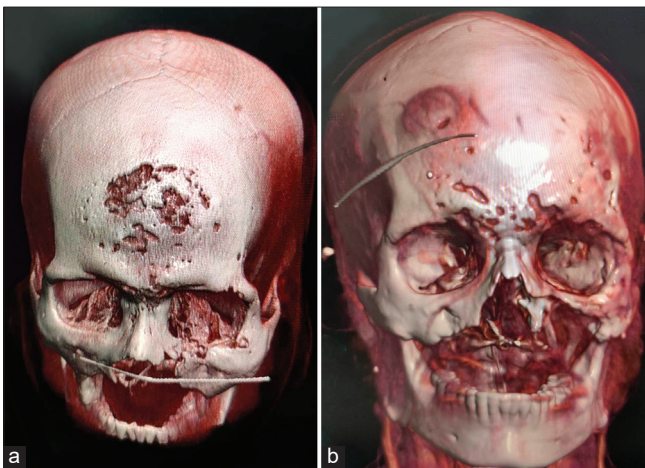
### Case 1

A 52-year-old male patient presented with bilateral multiple cranial nerve palsies. On examination, he had bilateral perception of light (PL) negative, bilateral ptosis, bilateral restriction of eyeball movements, bilateral facial palsy, bilateral corneal reflex absent, gag reduced, presence of tongue fasciculations, and left vocal cord palsy. Radiology was





**Figure 3:** (a and b) Preoperative and postoperative contrast-enhanced computed tomography (CECT) images of the brain showing complete excision of the right frontal lobe abscess. (c-e) Rhinocerebral mucormycosis (RCM) cases presented as huge unilateral frontal lobe abscesses. (f-h) Cases of RCM with bilateral basifrontal extension of the lesion through the cribriform plate.



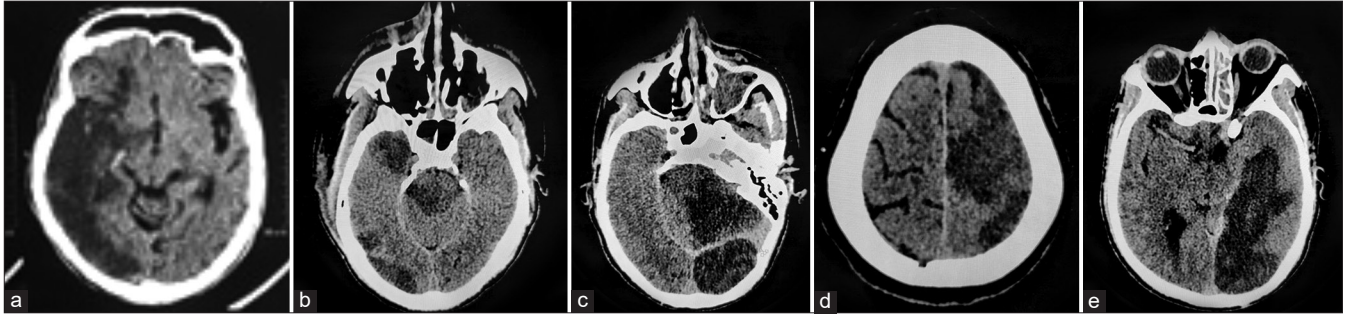
**Figure 4:** (a and b) 3D computed tomography scan images showing frontal bone osteomyelitis as a sequela of rhinocerebral mucormycosis (RCM).

suggestive of extensive skull base osteomyelitis [Figure 10]. He had suffered from a severe COVID infection in the past. He was admitted to the intensive care unit for the same and

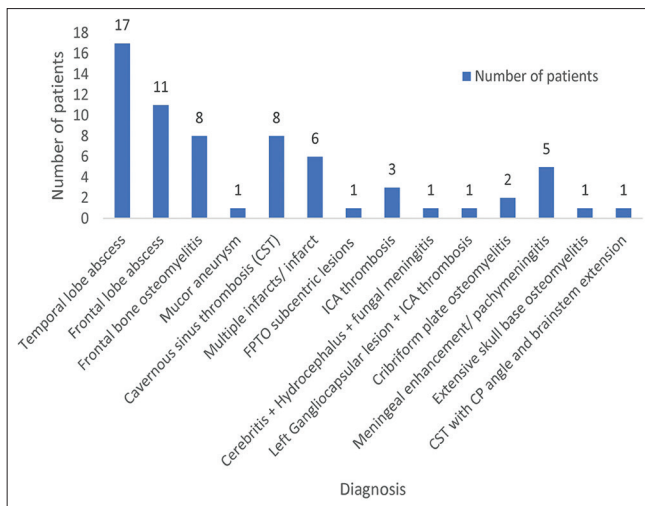


**Figure 5:** (a and b) Clinical photographs of a mucormycosis case with the left cavernous sinus thrombosis and palsies of the 3rd, 4th, and 6th cranial nerves (left complete ptosis, conjunctival chemosis, and left pupil dilated and fixed).

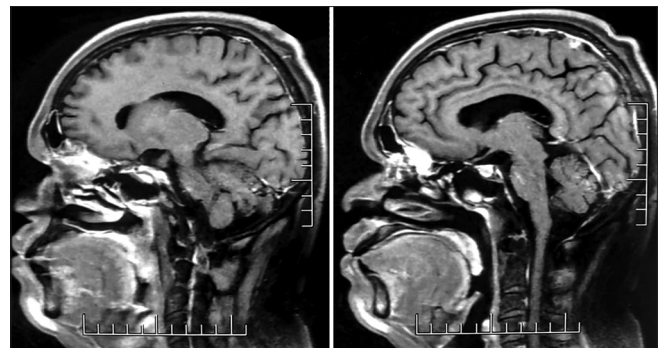
received steroids. He had undergone endoscopic debridement of bilateral sinuses in the past and now had presented with bilateral RCM with extensive skull base involvement. He was



**Figure 6:** (a-e) Cases of rhinocerebral mucormycosis which presented to us with multiple infarcts/infarct in the brain.



**Figure 7:** Bar diagram illustrating various types of presentations of rhinocerebral mucormycosis (RCM).



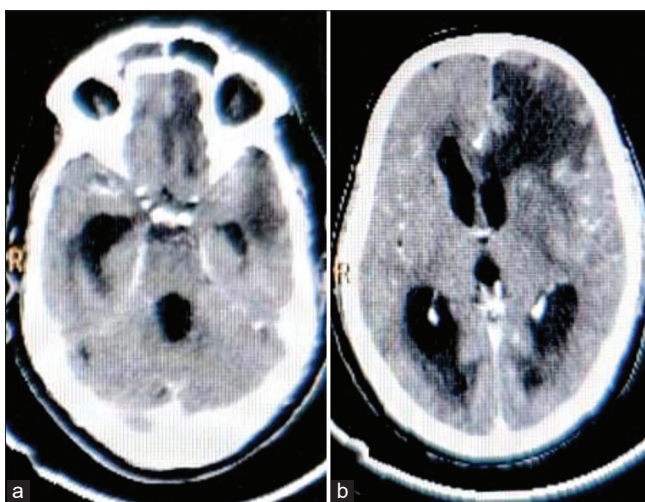
**Figure 9:** A case of rhino-cerebral mucormycosis (RCM) with cribriform plate osteomyelitis and pachymeningitis.

### Case 2

A 53-year-old male presented with sudden onset of left upper and lower limb weakness along with drowsiness. Non-contrast CT scan was suggestive of subarachnoid hemorrhage. CT angiography of the brain showed a right ICA bifurcation aneurysm [Figure 11]. He was diagnosed with mucormycosis and had undergone a right maxillectomy with obturator placement for the same. He had also received five injections of retrobulbar amphotericin B in the right eye. Right pterional craniotomy and wrapping of the aneurysm with a muscle patch was done. Intraoperatively, the entire right ICA wall was diseased and fragile with an outpouching at its bifurcation and extension of the disease into the right middle cerebral artery and right anterior cerebral artery. Postoperatively, the patient was started on intravenous amphotericin B and oral posaconazole. In spite of this, the aneurysm was increasing in size on follow-up digital subtraction angiography of the brain.

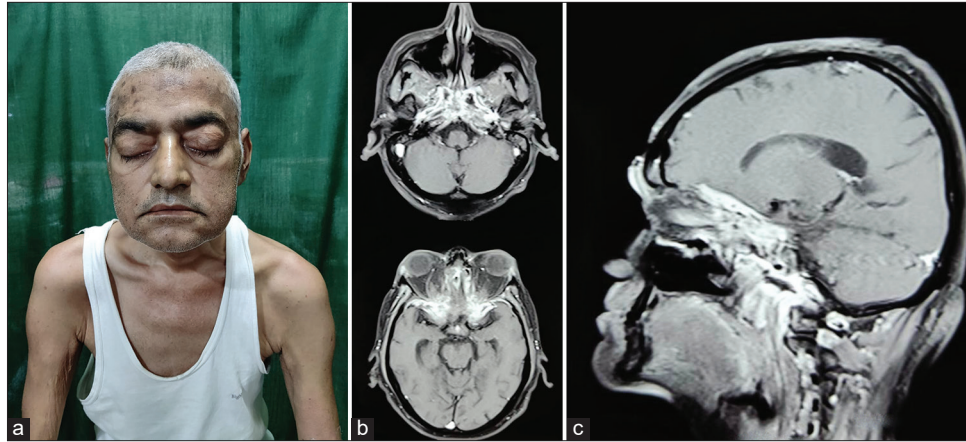
### Case 3

A 45-year-old female presented with purulent discharge from bilateral nostrils with headache and fever. She was diagnosed with post-COVID rhino-cerebro-palatal mucormycosis with bilateral temporal lobe abscesses [Figures 1a and b]. She underwent bilateral temporal craniotomies and excision of the abscesses followed by debridement of

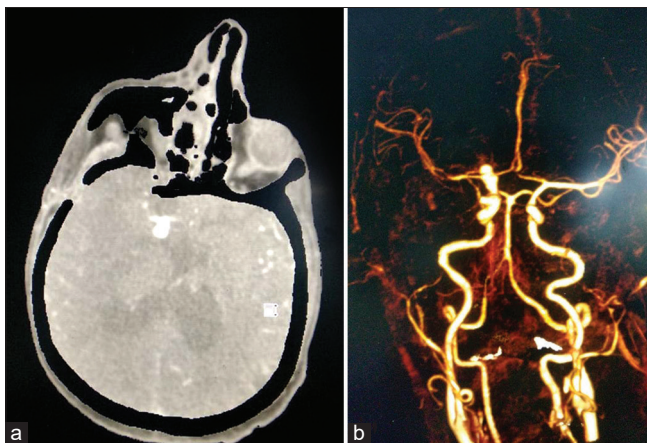


**Figure 8:** (a and b) Contrast-enhanced computed tomography (CECT) scans of the brain demonstrate left frontal and temporal early cerebritis with hydrocephalus in a case of rhino-orbito-cerebral mucormycosis (ROCM) with fungal meningitis.

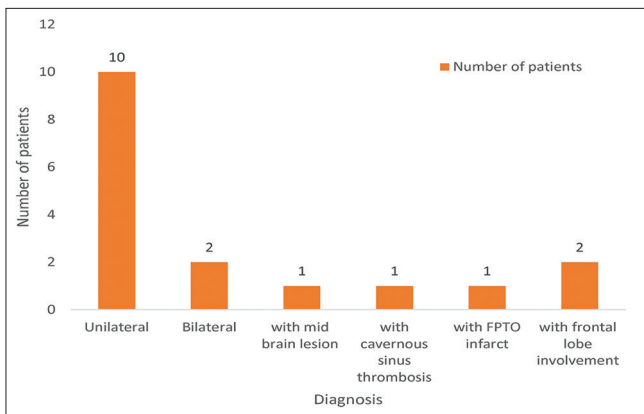
started on a medical line of management as the disease was inoperable.



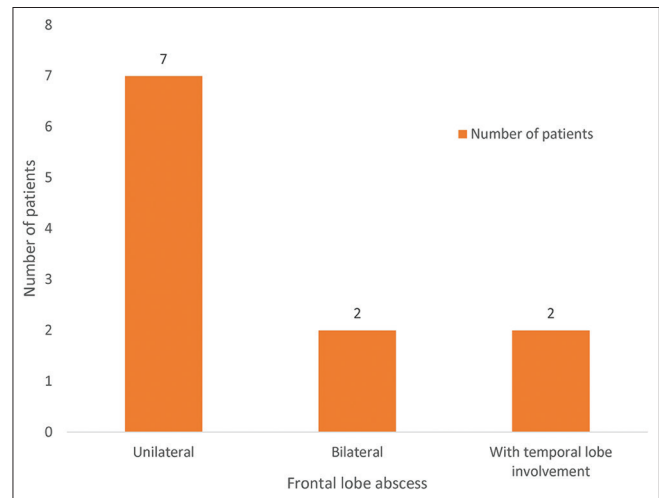
**Figure 10:** (a) Clinical photograph of a patient with bilateral Rhino-orbito-cerebral mucormycosis (ROCM) with extensive skull base osteomyelitis with multiple cranial nerve palsies bilaterally. (b and c) Radiology was suggestive of bilateral ethmoid sinusitis with involvement of bilateral infratemporal fossae, pterygopalatine fossae, inferior orbital fissure, superior orbital fissure, orbital apex, and bilateral cavernous sinuses with pachymeningitis. There was an erosion of the clivus, occipital condyles, basisphenoid, and anterior skull base.



**Figure 11:** (a and b) Radiology in a case of rhino-orbito-cerebral mucormycosis (ROCM) suggestive of mucormycosis associated with the right internal carotid artery bifurcation aneurysm.



**Figure 12:** Bar diagram showing the clinical spectrum of rhino-cerebral mucormycosis (RCM) cases with temporal lobe abscess.

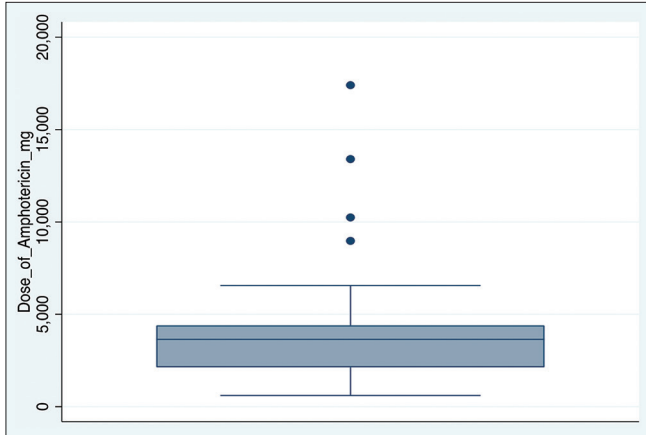


**Figure 13:** Bar diagram showing the clinical spectrum of rhinocerebral mucormycosis (RCM) cases with frontal lobe abscess.

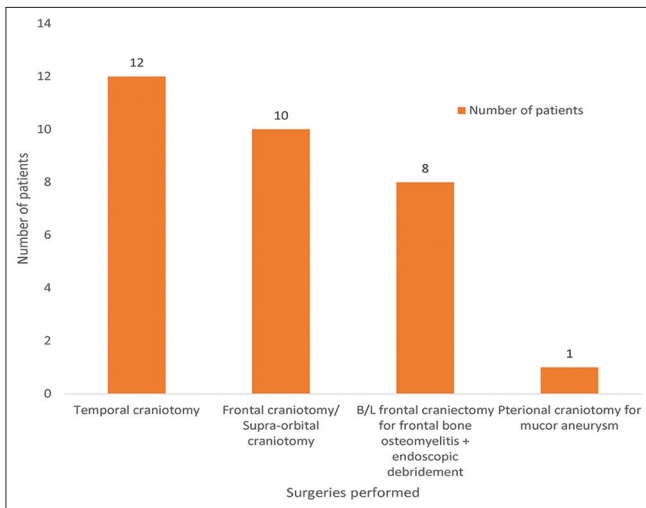
the sinuses through a combined approach (endoscopic and open). In the postoperative period, she received a cumulative amphotericin B dose of 4400 mg and also took oral posaconazole for 2 months. At 3 months follow-up, she had no fresh complaints and radiology was suggestive of no residual or recurrent disease.

#### Case 4

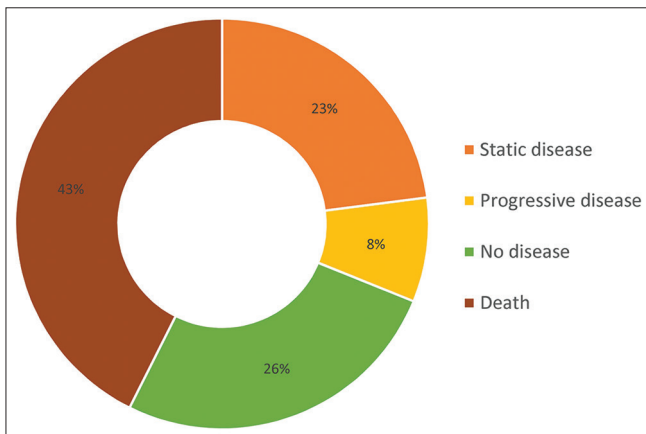
A 41-year-old male presented with right hemifacial pain, right eye swelling, and right-sided headache. He was diagnosed with post-COVID rhino-orbito-cerebral mucormycosis (ROCM) with a huge right frontal abscess. He underwent right frontal craniotomy and excision of abscess followed



**Figure 14:** Box plot for a cumulative dose of amphotericin B (Median - 3766 mg).



**Figure 15:** Bar diagram depicting various types of neurosurgical procedures performed on rhino-cerebral mucormycosis (RCM) cases.



**Figure 16:** Donut variant of pie chart portraying outcome at 3 months post-diagnosis in 61 cases of rhinocerebral mucormycosis (RCM).

by debridement of the sinuses through combined approach (endoscopic and open). In the postoperative period, he received a cumulative amphotericin B dose of 8400 mg and also took oral posaconazole for 3 months. At 3 months follow-up, he had no fresh complaints and radiology was suggestive of no residual or recurrent disease [Figure 2].

#### Case 5

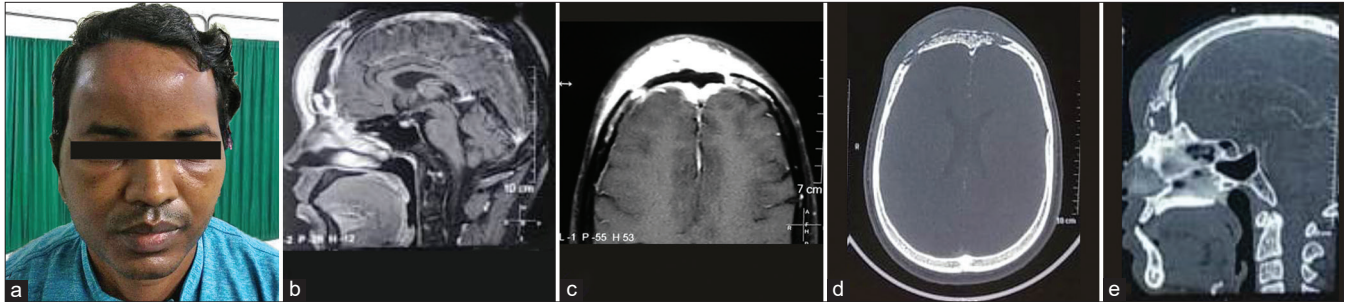
A 33-year-old male patient presented to us with swelling over the forehead and periorbital region. He was diagnosed case of post-COVID mucormycosis. He had undergone endoscopic debridement of sinuses for the same. His radiology was suggestive of frontal bone osteomyelitis with pachymeningitis with epidural and subgaleal abscesses [Figure 17]. He underwent bilateral frontal bone debridement craniectomy with exteriorization of the frontal sinus and drainage of abscesses. In the postoperative period, he received a cumulative amphotericin B dose of 4350 mg and also took oral posaconazole for 3 months. He had no fresh complaints at 3 months follow-up, and imaging revealed no residual or recurrent disease.

#### Case 6

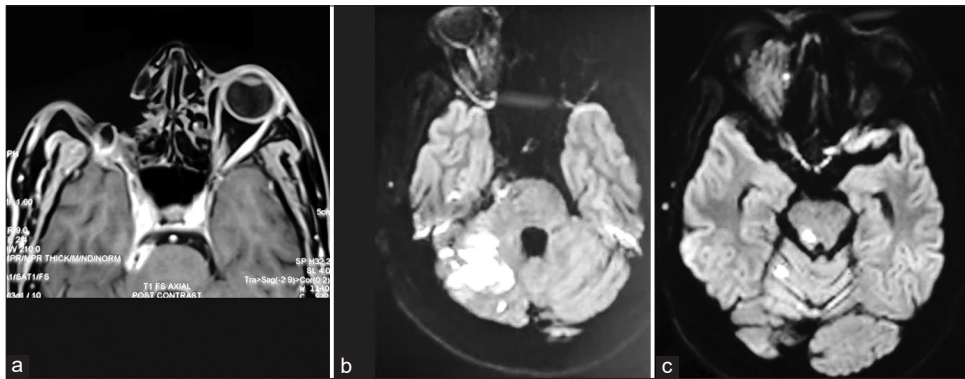
A 44-year-old male patient presented to us with pus discharge from the right eye exenterated site. He was diagnosed case of post-COVID mucormycosis, for which he had undergone debridement of sinuses through combined approach (open + endoscopic), along with right orbital exenteration (right eye perception of light negative). He received a total dose of 3400 mg of amphotericin B and also took oral posaconazole for 2 months. At 3 months follow-up, his radiology was suggestive of progressive disease in the right cavernous sinus with extension into right pre-pontine, pre-medullary, and cerebellopontine angle cisterns. Diffusion-weighted images showed increased signal intensity in the right hemicerebellum, right brachium pontis, and the right lateral aspect of pons suggestive of an infarct. We have started him on a medical line of management (Amphotericin B and posaconazole) [Figure 18].

#### Case 7

A 56-year-old male patient presented to us with the left-sided headache, left eye proptosis, restriction of all left eyeball movements, left eye ptosis, conjunctival chemosis, double vision, and cough with expectoration. He was diagnosed with ROCM with pulmonary involvement. He had no past history of Coronavirus Disease 2019 (COVID-19) infection. He had also received the first dose of COVID vaccination (Covishield). His radiology was suggestive of pansinusitis



**Figure 17:** (a-e) Clinical Photograph and radiology suggestive of frontal bone osteomyelitis with pachymeningitis with epidural and subgaleal abscesses in a known case of mucormycosis.



**Figure 18:** (a) An operated case of right rhino-orbito-cerebral mucormycosis (ROCM) with progressive disease in the right cavernous sinus with extension into right pre-pontine, pre-medullary, and cerebellopontine angle cisterns as seen on magnetic resonance images of the brain taken 3 months post-surgery. (b and c) Diffusion-weighted images (DWI) of the same patient showed increased signal intensity in the right hemiserebellum, right brachium pontis, and the right lateral aspect of pons suggestive of an infarct.

with the left orbital cellulitis and left CST. He also had multiple nodular lesions in both lungs, predominantly in the upper lobes with cavitory changes and halo sign, likely pulmonary mucormycosis. He underwent debridement of sinuses through a combined approach (open plus endoscopic) and medial orbitotomy. He had received a cumulative dose of amphotericin B of 1050 mg but succumbed to his illness and died on postoperative day 3.

#### Case 8

A 67-year-old female presented to us with complaints of headache, swelling of the left eye, decreased vision in both eyes (the left eye was affected first followed by the right eye), left conjunctival chemosis, and restriction of all movements of the left eye. She was diagnosed with post-COVID bilateral ROCM [Figure 19]. The patient was a known diabetic, hypertensive, hypothyroid, and had coronary artery disease which required coronary angioplasty 5 years back. Her radiology was suggestive of pansinusitis, left orbital cellulitis, lobulated soft-tissue density lesion in the right pre-maxillary region, and involvement of the left temporal and left basifrontal lobes. She was planned for a two-staged

surgery. In the first operation, she underwent endoscopic debridement of sinuses and left orbital exenteration. In the postoperative period, the patient developed acute kidney injury, for which dialysis was done. She succumbed to her illness and died on postoperative day 8.

#### Case 9

A 48-year-old male presented to us with the right nasal discharge, right nasal stuffiness, and right visual loss. He was diagnosed as a case of post-COVID ROCM with cribriform plate osteomyelitis. Radiology was suggestive of pansinusitis, right orbital cellulitis (right eye perception of light negative) and pachymeningitis in the anterior cranial fossa with an erosion of the right cribriform plate [Figure 9]. He underwent debridement of sinuses through a combined approach (open + endoscopic) and right orbital exenteration. In the postoperative period, he received a cumulative dose of amphotericin B of 4000 mg. He also took oral posaconazole for a month. He had no fresh complaints at 3 months follow-up and imaging revealed static disease (mild enhancement in the cribriform plate region).



**Figure 19:** (a-c) A case of bilateral rhino-orbito-cerebral mucormycosis (ROCM) with peri-orbital skin changes (ecchymotic patch, skin induration with eschar).

### Case 10

A 44-year-old male patient presented to us in a comatose state (M2 motor response according to Glasgow Coma Scale). He was diagnosed case of post-COVID disseminated mucormycosis. Non-contrast CT scan of the brain was suggestive of multiple infarcts involving the right side of the pons, left thalamus, centrum semiovale, bilateral high parietal lobes, and right frontal lobe. He was started on a medical line of management but succumbed to his illness.

### DISCUSSION

Mucormycosis is a rapidly progressing infection caused by the angioinvasive fungi in the order of Mucorales.<sup>[4]</sup> Predisposing conditions include uncontrolled diabetes mellitus especially with diabetic ketoacidosis (hyperglycemia favors fungal growth due to enhanced expression of Glucose Regulated Protein 78, a mammalian protein receptor, which increases binding to Mucorales, decreased phagocytosis and impaired iron sequestration), steroid therapy, solid organ or hematopoietic stem cell transplant recipients, chemotherapy, blood dyscrasias, severe burns, and patients on deferoxamine therapy.<sup>[1]</sup> The initial site of infection in RCM is the nasal turbinates. The pterygopalatine fossa is believed to be the largest reservoir of infection.<sup>[1]</sup> Patients may present with nasal discharge (purulent/blood stained), nasal stuffiness, blurring of vision or visual loss, inflammation around the orbit (periorbital cellulitis), double vision, proptosis, or even ophthalmoplegia, facial pain or numbness, swelling of the cheek, discoloration of the facial skin, loosening of teeth, dental pain, blackening/perforation of the palate, headache, fever, irritability, and altered sensorium. An acute episode of sinusitis can progress to involve all the sinuses (pansinusitis) followed by contiguous spread to the orbit, palate, and brain

resulting in severe tissue ischemia and necrosis due to the angioinvasive nature of the fungus. Nasal, palatine, facial, or orbital black eschars can develop due to tissue necrosis which is highly suggestive of the disease but occurs in only 40–50% of the cases.<sup>[2]</sup> Spread of the infection to the frontal lobes can occur through the cribriform plate, ethmoid, or frontal sinuses.<sup>[5]</sup> Spread of the infection to the temporal lobes can occur through the maxillary sinuses through the infratemporal fossa to the temporal lobe or through hematogenous spread.<sup>[5]</sup> Infection can also spread through the sphenoid sinuses or orbital apex to the cavernous sinus resulting in CST.<sup>[7]</sup> Internal carotid artery thrombosis is also well-documented in cases of RCM. CST with loss of vision is a characteristic feature of mucormycosis, whereas CST without loss of vision is observed in bacterial infections.<sup>[1]</sup> Patients with RCM can also present with ophthalmoplegia (internal and/or external), superior orbital fissure syndrome, orbital apex syndrome, central retinal artery occlusion, and superior ophthalmic vein thrombosis resulting in varying involvement of II, III, IV, V, and VI cranial nerves. Definitive diagnosis can be reached by demonstrating ribbon-shaped, non-septate, or pauci-septate, irregularly branching hyphae in the tissue specimens, but tissue cultures are rarely positive. Smears can be examined under a potassium hydroxide wet mount to demonstrate the fungi. Treatment includes a three-pronged strategy of reversal of immunosuppressive state (correction of hyperglycemia, tapering steroids if feasible), administration of anti-fungal drugs (IV amphotericin B [Conventional/Liposomal/Emulsion] and/or oral posaconazole/isavuconazole) and extensive surgical debridement. In spite of all this, RCM has a mortality rate of 40–50% and 70% of survivors are left with residual deficits.<sup>[6]</sup>

Mohindra *et al.*, in his paper, reported ten cases of mucormycosis with intracranial extension in the form of CST (3), intracranial masses (3), brain abscesses (2), and ischemic

infarcts (2).<sup>[8]</sup> Mortality in these ten cases with intracranial extension was 60%.<sup>[8]</sup> Mehta *et al.*, in their paper, reported 33 cases of mucormycosis with cerebral involvement.<sup>[7]</sup> Cases with sino-naso-orbito-palato-cerebral involvement had an overall mortality of 80% and disease-specific mortality of 60%, followed by cases of sino-naso-orbito-cerebral and sino-naso-cerebral involvement having an overall mortality of 37.5% and 41.7%, respectively, and disease-specific mortality of 18.7% and 25%, respectively.<sup>[7]</sup> Balai *et al.*, in their paper, have reported nine patients with mucormycosis, out of which four patients had intracranial involvement (two had a cerebral abscess and two had skull base involvement with cranial nerve palsies).<sup>[3]</sup> All patients had diabetes mellitus (100%) and overall mortality in this study was 78%.<sup>[3]</sup> Roushdy and Hamid, in their paper, reported four cases of post-COVID-19 mucormycosis – all had diabetes mellitus and had received steroids for the treatment of COVID-19. Three out of the four cases had total ophthalmoplegia and in hospital, mortality was 25% in this study.<sup>[10]</sup>

Patel *et al.*, in their paper, have reported 187 cases of COVID-19 associated mucormycosis (CAM) of which 44 patients had rhino-orbito-cerebral involvement.<sup>[9]</sup> Overall, 78.1% had received steroids for the treatment of COVID-19 and 60.4% had diabetes mellitus.<sup>[9]</sup> In this study, mortality at 12 weeks in the 187 CAM patients was 44.1%.<sup>[9]</sup> The study also concluded that sequential use of antifungal drugs (Amphotericin B then posaconazole or isavuconazole) was independently associated with improved survival among mucormycosis patients than concurrent use.<sup>[9]</sup>

In our study also, 93.4% of the RCM cases had a past history of COVID infection and were diabetic and 85.2% of cases had received steroids for the treatment of COVID-19 infection in the past. The overall mortality in our study was 42.6%.

## CONCLUSION

We report the largest single-center case series of RCM, comprising 61 patients. This case series underscores the importance of the early diagnosis and prompt treatment for a better prognosis for this dreadful disease. The three pillars of treatment for RCM cases include reversal of the immunosuppressive state, administration of antifungal drugs, and extensive surgical debridement. In spite of all this, mortality remains high.

## Declaration of patient consent

The Institutional Review Board (IRB) permission obtained for the study.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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