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Management of rhino-orbito-cerebral mucormycosis: a clinico-radiological study—an institutional experience

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Abstract

Background Mucormycosis in the setting of COVID-19 has given rise to the concept of "epidemic within a pandemic." Once known to be a rare fungal disease, mucormycosis has now been regrouped under emerging pathogens. It has got special affinity for the immunocompromised, which is one of the main reasons for the flare up of the fungus during the second wave of COVID. The burden of the disease was felt globally, and India is facing the major brunt owing to our population and healthcare services ratio.

Objective In our study, we have made an attempt to evaluate the clinical and radiological findings in patients of rhino-orbito-cerebral mucormycosis (ROCM) and to formulate a management protocol which will benefit such patients in forthcoming years.

Methods This is a retrospective single-center study in Northern India. A total of 350 patients, affected by ROCM, were included in the study. Medical records of these patients were reviewed. Their clinical manifestations, nasal endoscopic findings, microbiological and radiological records, extent of disease, treatment profile, surgical interventions, and outcomes were analyzed. Nasal swab which was sent for KOH mount/fungal culture revealed broad aseptate filamentous fungi branching at right angles. All patients received intravenous amphotericin B and had undergone extensive surgical debridement endoscopically. The maxillary sinus was the commonest paranasal sinus involved followed by the ethmoid sinuses. Tissue sent for histopathological examination confirmed mucormycosis, except for 3 cases.

Results The commonest presenting symptoms were cheek swelling with ophthalmoplegia, diminution of vision, and headache. The mean duration of follow-up was 8 months.

The maxillary sinus was found to be involved in around 71% of the cases followed by the ethmoids and sphenoid. Thirty percent of the cases had visual complaints including diplopia and vision loss, whereas the palate was involved in around 35%. Nine patients had no perception of light in one eye on presentation, whereas 21 patients had perception of light only; 24 patients could count fingers close to face, and the rest had ambulatory vision. Three patients presented with facial palsy. All patients had favorable outcome except six who succumbed due to cerebral involvement and uncontrolled blood glucose levels.

Conclusion A definite management protocol was formulated for ROCM which requires a multidisciplinary approach.

Keywords Rhino-orbito-cerebral mucormycosis, Nasal endoscopy, Radiological features, Surgical debridement, Management protocol

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Background

Mucormycosis, also known as zygomycosis, is life-threatening angioinvasive fungal infection caused by filamentous fungi of the order Mucorales of class Zygomycetes [1]. The predisposing factors include uncontrolled diabetes mellitus, prolonged use of steroids, and patients who are immunocompromised such as on chemotherapy, hematologic malignancies, organ transplantation, stem cell transplantation, and iron overload [2]. Mucormycosis, based on organ/s involved, can be further subclassified as pulmonary, cutaneous, gastrointestinal, renal, disseminated, and rhino-orbito-cerebral mucormycosis (ROCM) [3]. ROCM is by far known to be the most common form of all [4]. The major mode of transmission is inhalation of sporangiospores into the nasal and paranasal sinuses. The infection spreads rapidly and extensively into adjacent tissues within a period of few hours to days and may lead to cranial nerve palsies and intracranial involvement [5]. It spreads inferiorly to involve the palate, posteriorly to involve the sphenoid sinus, laterally into the orbits and cavernous sinus, and superiorly into the cranium either through the orbital apex or cribriform plate of ethmoid [1].

Earliest symptoms of ROCM have been seen to be excessive dryness of the nose with blackish discharge, numbness over and around the nose and cheek, loose teeth, blackish discoloration of the cheek and/or palate, and headache. A black eschar formation is known to be the hallmark of ROCM. In later stages, retro-orbital pain, ptosis/proptosis, ophthalmoplegia, diminution of vision, loss of vision, altered sensorium, and, in rare cases, facial palsy have been noted [3].

Early diagnosis, elimination of predisposing factors, prompt surgical intervention, and judicious use of amphotericin B are the key elements in reducing the morbidity and mortality rates [5].

Fig. 1 Mucormycosis involving the right side of the face and the orbit

Methods

This study is a single-center retrospective study carried out at a tertiary care referral-based institute, declared as the nodal center for management of COVID-19 as well as mucormycosis in Northern India. A total of 350 clinically and microbiologically confirmed cases of rhino-orbito-cerebral mucormycosis presenting between June 2021 and April 2023 were retrospectively reviewed from medical records. Their clinical presentation and laboratory investigations were analyzed. Patient complaints at the time of presentation included swelling of the cheek and peri-orbital region, headache, restricted eye movements, blackish discoloration of the palate/nose, loosening of teeth, blurring of vision, loss of vision, facial palsy, and altered sensorium, developing recently in a background of COVID-19 infection with multiple risk factors (Fig. 1).

Inclusion criteria:

- Patients with confirmed diagnosis of post-COVID rhino-orbito-cerebral mucormycosis on fungal culture and histopathology
- Patients with a history of diabetes mellitus
- Patients with history of steroid intake during hospital stay for COVID-19
- Patients who gave consent for surgery and, hence, for this study

Exclusion criteria:

- Patients of pulmonary/cutaneous/gastrointestinal mucormycosis
- Patients who did not give consent for surgery

Comprehensive work-up included detailed history, ocular examination, and neurological and otorhinolaryngological assessments to determine the extent and severity of disease. Initial investigations included complete blood counts, blood sugar, serum electrolytes, and serum urea and creatinine. This was followed by diagnostic nasal endoscopy and radiological imaging of the nose, paranasal sinuses, orbit, and brain to confirm the disease extent (Fig. 2). Contrast-enhanced computed tomography was performed. Magnetic resonance imaging including T1-weighted, T2-weighted, T1 contrast, and

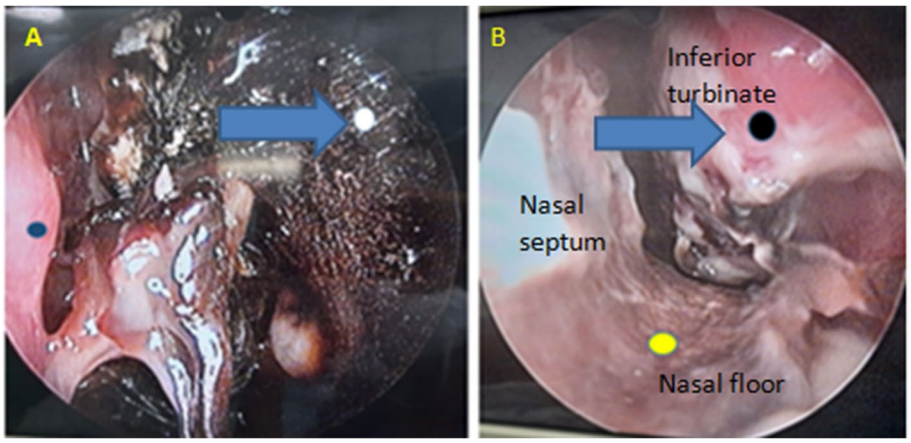


Fig. 2 **A** Black eschar over the septum. **B** Necrotic tissue at the floor of the nose

fat-suppressed T2-weighted images were acquired. The staging of ROCM that we followed was as follows [6]:

A. Stage I—involvement of nasal mucosa
B. Stage II—involvement of paranasal sinuses
C. Stage III—involvement of orbit
D. Stage IV—involvement of central nervous system

Nasal swab sent for KOH mount/fungal culture confirmed mucormycosis on the basis of demonstration of broad, aseptate hyphae branching at right angles.

All patients received systemic liposomal amphotericin B as soon as diagnosis was confirmed.

A total dose of 3–4 g in dose of 5.0 mg/kg/day was given, and in case of intracranial involvement, the dose was increased to 5–7 mg/kg/day with a total dose of 7–8 g.

As amphotericin is a nephrotoxic drug, serum urea, creatinine, and electrolytes were measured as part of premedication protocol, and injection dexamethasone and pheniramine were given as pre-medications.

A total of 3 doses of TRAMB (transcutaneous retrobulbar injection of amphotericin B) was given at alternate days in cases of orbital involvement by the ophthalmology team. One dose comprised of 3.5 g in 1 ml normal saline. Renal function and serum potassium and magnesium levels were strictly monitored. Adequate hydration was maintained. Diabetes was controlled with diet and insulin in consultation with endocrine department (Table 1).

This was followed by oral posaconazole 300 mg BD on the first day and then 300 mg OD for 6 months with regular monitoring of liver function test and monthly diagnostic nasal endoscopy.

Endoscopic extensive debridement was done under general anesthesia for all involved sinuses.

Orbital and palatal resection was done where indicated. Orbital clearance was done for patients with vision loss, and in some cases, orbital exenteration was done by the ophthalmology team in which there was impending cerebral involvement. Palatal resection was done where indicated by the oro-maxillo-facial surgery team.

Neurosurgical interventions were required in cases of raised ICP with intracranial involvement for maximal safe resection.

Table 1 Proforma for medical management of mucormycosis on a daily basis

Date	Serum Na	Serum K	Serum Mg	Dose of Ampho in mg given that day	Total dose of ampho in mg till date	Serum Urea	Serum Creatinine	Blood sugar

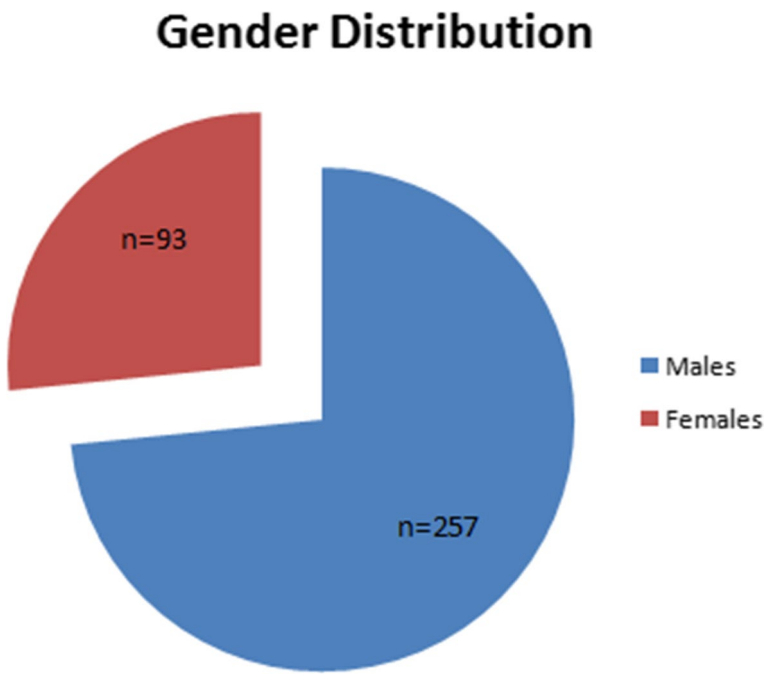


Fig. 3 Gender distribution

Table 2 Age-wise distribution of cases

Age (in years)	No. of cases	%
< 30	08	2.29
31–40	64	18.28
41–50	107	30.57
51–60	87	24.86
61–70	50	14.29
> 70	34	9.71
Total	**350**	**100**

Results

A total of 350 confirmed cases of mucormycosis were included in our study out of which 257 (73.42%) were males and 93 (26.57%) were females (Fig. 3). Out of 350 confirmed patients, 232 were proven cases of type II diabetes mellitus before contacting COVID-19 among which 76 patients had uncontrolled blood glucose levels (Hba1c of 7% and higher), whereas 118 were diagnosed as diabetics during COVID-19 treatment. One hundred seventy-eight patients had history of ICU admission and mechanical ventilation, 88 patients reported of hospital admission and need for oxygen support (via mask or HFNC) and intravenous steroids, whereas 84 reported of staying at home and being on oxygen mask and oral steroids. The age of patients ranged from less than 30 years to more than 70 years with the mean age being 51.47 + 13.13. One of the patients reportedly was 17 years old. The age-wise distribution of cases is shown in Table 2. The duration between diagnosis of COVID-19 and ROCM was 15 days to 9 months.

All the patients had undergone diagnostic nasal endoscopy (DNE) and contrast-enhanced MRI preoperatively. The classic black necrotic eschar was seen in almost all the cases in diagnostic nasal endoscopy, except three patients. The maxillary sinus was found to be involved in around 71% of the cases followed by the ethmoids and sphenoid. Thirty percent of the cases had visual complaints including diplopia and vision loss, whereas the palate was involved in around 35%. Nine patients had no perception of light in one eye on presentation, whereas 21 patients had perception of light only; 24 patients could count fingers close to face, and the rest had ambulatory vision. Peri-orbital pain and ecchymoses were seen in 78% of patients with orbital involvement, and 72% had proptosis. Almost 90% of our cases complained of headache, while 12 cases reported multiple episodes of epistaxis. One of the patients had no involvement of the nose and paranasal sinuses; rather, he presented with right abducens and hypoglossal nerve palsies only. Table 3 lists the involvement of structures in order of severity. The nasal swab sent for KOH mount/fungal culture confirmed mucormycosis on the basis of presence of broad aseptate fungal hyphae (Fig. 4).

Table 3 Involvement of structures in order of severity

Structures	No. of patients	%
Nasal cavity	346	99.0%
Maxillary sinus	249	71.33%
Sphenoid	242	69.33%
Palate	127	36.33%
Orbit	110	31.33%
Ethmoid	86	24.67%
CNS	70	20.00%
ITF	55	15.67%

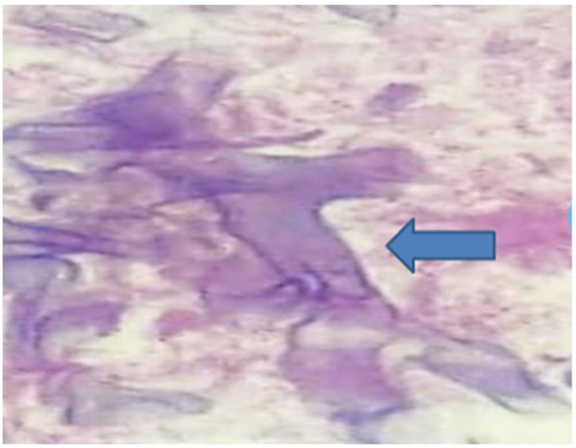


Fig. 4 Histopathological picture showing the broad aseptate obtuse angle branched fungal hyphae suggestive of mucormycosis (arrow)

Discussion

ROCM results from simultaneous occurrence of multiple risk factors and prognosis is always poor despite therapy. Prompt aggressive management is the key to reduce morbidity and mortality rates.

Nasal endoscopy and MRI form an integral part in management of ROCM. For a fast and appropriate diagnosis, MRI needs to be studied in detail to understand the disease extent and progression. MR imaging is a multiplanar imaging modality which has superior soft tissue resolution as compared to CECT [6]. Also, it is a better and safer imaging technique when multiple follow-up scans are planned. T1W, T2W, and T2 fat-suppressed and post-contrast T1 are the most common sequences done at our center. T1 and T2 weighted (axial and coronal) are best to delineate soft tissue and bone involvement; fat-suppressed T2 W images are more sensitive to detect pathology, and post-contrast T1W images are best to delineate the extent of disease and areas of avascular necrosis. On GAD enhancement, various patterns of enhancement include the following: intense homogenous, heterogenous, or complete non-enhancement with/without peripheral enhancement. To facilitate easy understanding of MRI, it can be remembered as the following: diseased area gives a hypointense to isointense picture on T2W scan, hyperintense image on T2 with fat suppression, and loss of uptake in post-contrast T1 scan (Fig. 5).

Sites of extra-sinus involvement commonly encountered are the orbit/orbital apex, face, masticator space, infratemporal fossa, skull base, cavernous sinus, and brain parenchyma. These changes are better appreciated on T2 fat-suppressed MRI where edema and enhancing soft tissue can be seen. In this study, the following patterns were noted:

- The classic "black turbinate sign" seen as non-enhancing dark turbinates (Fig. 6)
- Mucosal thickening was best visualized on T2W images and non-enhancement of involved mucosa/soft tissue on post-contrast T1W (Fig. 5A)
- Early orbital infection showed enlargement of medial rectus muscle with infiltration of retroorbital fat on T2 fat-suppressed. Enhancement of optic nerve is a sign of perineural invasion which was the cause of sudden onset blindness (Fig. 7)

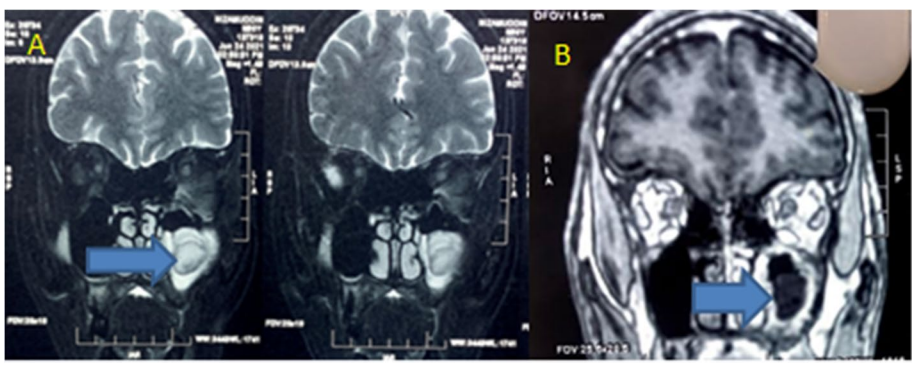


Fig. 5 **A** Fat-suppressed T2-weighted coronal section showing edema in perpheral region and loss of enhancement in the center of left maxillary sinus s/o isolated maxillary mucormycosis

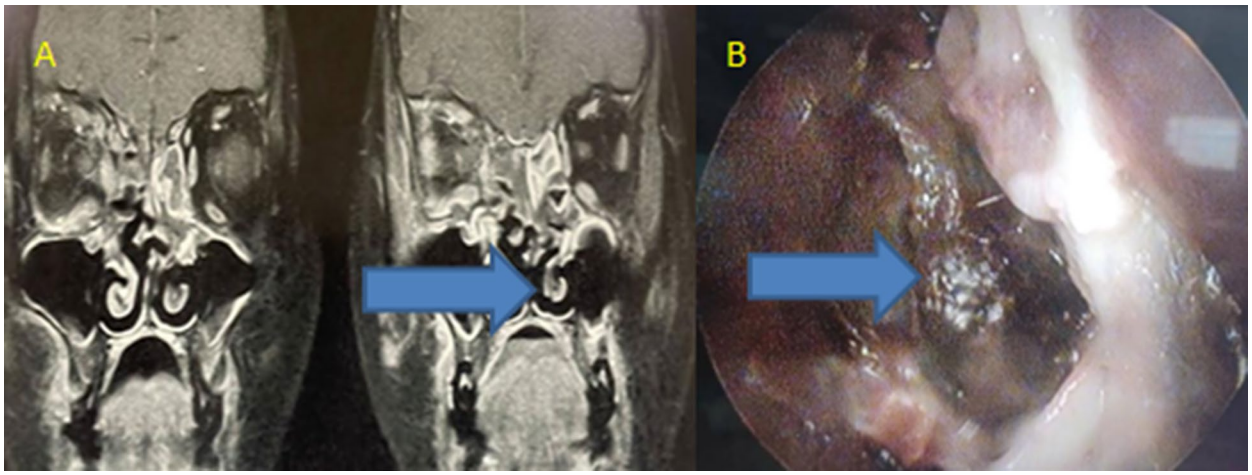


Fig. 6 **A** T1 contrast coronal image showing no uptake in the left inferior turbinate. **B** Endoscopic image showing the necrotic turbinate

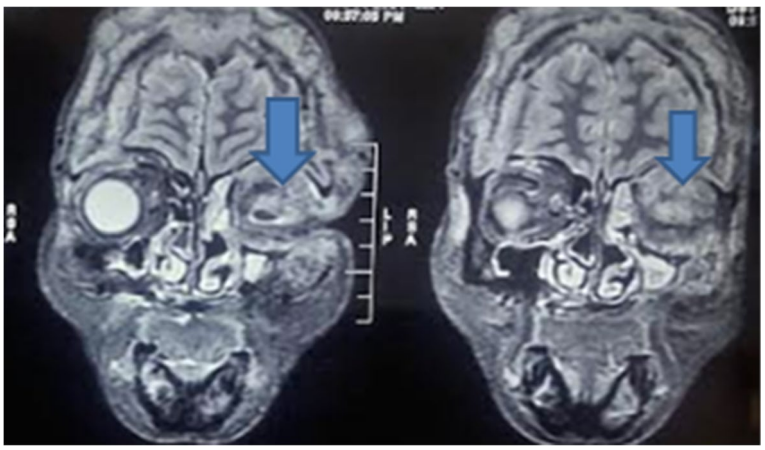


Fig. 7 T2 fat-suppressed image showing the infiltration of retroorbital fat

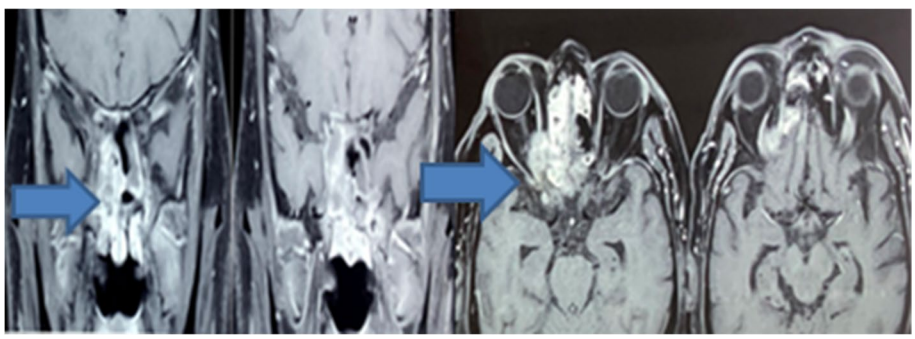


Fig. 8 Loss of concavity of the cavernous sinus on the coronal and axial sections of T2 fat-saturated images

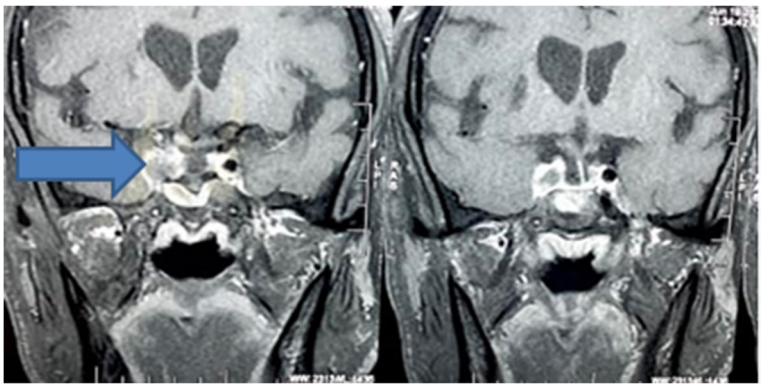


Fig. 9 Post contrast T1W images showing internal carotid narrowing

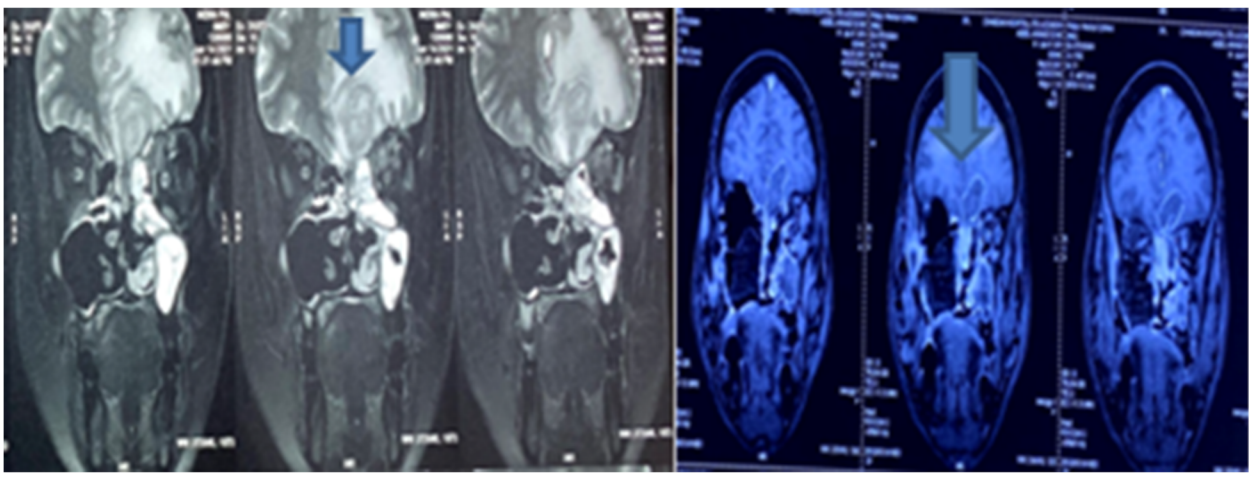


Fig. 10 T2 fat-suppresed coronal section showing (**a)** altered cerebral parenchymal changes with meningeal enhancement s/o intracranial involvement with cerebral involvement

- Loss of concavity of cavernous sinus on coronal and axial sections of T2 fat-saturated images was a sign of involvement (Fig. 8)
- For arterial wall invasion, post contrast T1W images showed internal carotid narrowing with arterial wall enhancement (Fig. 9)
- Meningeal enhancement was seen on T2W and post-contrast T1W in patients with intracranial extension (Fig. 10)
- Skull base osteomyelitis in early stage was picked up on T1W images which showed loss of normal fat signal with a hypointense marrow, whereas advanced stage was better picked up on fat-saturated T2 images which showed obliteration of fat planes with extensive heterogeneously enhanced soft tissues and bone infiltration

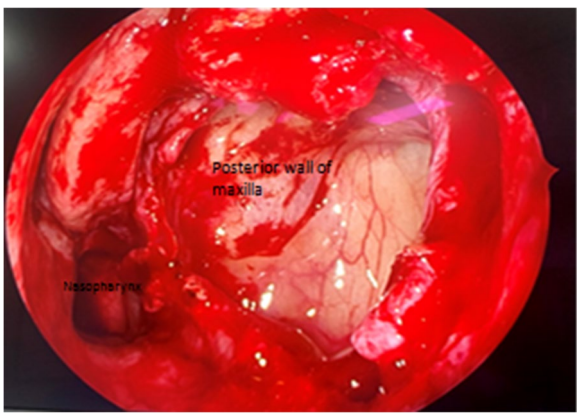


Fig. 11 Endoscopic view of the left nasal cavity showing post wall of maxilla and nasopharynx after left modified Denker's approach

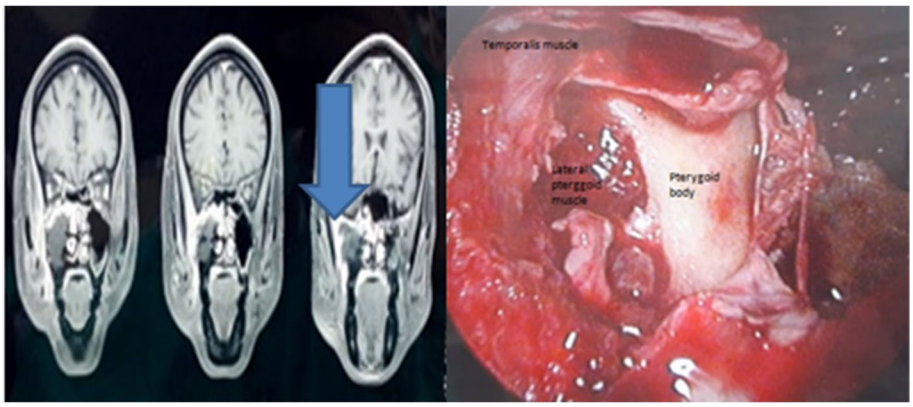


Fig. 12 **a** T1 contrast coronal section loss of uptake in the maxillary sinus and infratemporal fossa. **b** Endoscopic view of infratemporal fossa after

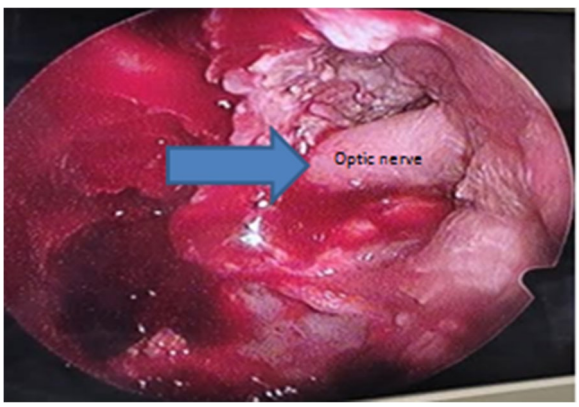


Fig. 13 Endoscopic view of the left orbit showing the left optic nerve after orbital clearance of necrotic material

At our center, endoscopic surgical debridement was performed in all patients as soon as possible after taking proper written informed consent from patient attendants explaining the need for immediate surgery and possible complications. Modified Denker's approach was used in majority of the cases for exposure and debridement (Fig. 11). The Caldwell-Luc procedure was done in cases of intractable maxillary sinus disease.

In cases with infratemporal fossa disease, meticulous care was taken not to leave behind any residual disease (Fig. 12).

Orbital decompression was performed in patients who presented with only diplopia.

In 10% of patients who had complete vision loss, endoscopic orbital clearance had to be done in consultation with the ophthalmology team of surgeons (Fig. 13).

For all cases of palatal involvement, maxillo-facial team performed maxillectomy along with palatoplasty.

For intracranial disease, most of the patients were declared as non-operative from the neurosurgery point of view and were kept under rigorous monitoring. A total of 3 doses of TRAMB (transcutaneous retrobulbar injection of amphotericin B) were given in cases of orbital involvement by the ophthalmology team.

Following surgery, induction therapy was started with intravenous liposomal amphotericin B (drug of choice) in a dose of 5 mg/kg/day and, for CNS involvement, in a dose of 5–7 mg/kg/day along with systemic antibiotics.

Continuous monitoring of serum electrolytes, creatinine, and blood sugar was done.

Thirty-six patients (12%) developed intolerance to amphotericin in view of systemic complications and hence were shifted to posaconazole. A total dose of 3–5 g was administered for patients without intracranial extension, and for those with intracranial disease, a total dose of 7–8 g was given following appropriate neurosurgical consultation. This was followed by maintenance therapy with oral posaconazole 300 mg BD on day 1 followed by 300 mg OD thereafter for a period of 6 months along with antibiotic roxithromycin 150 mg BD.

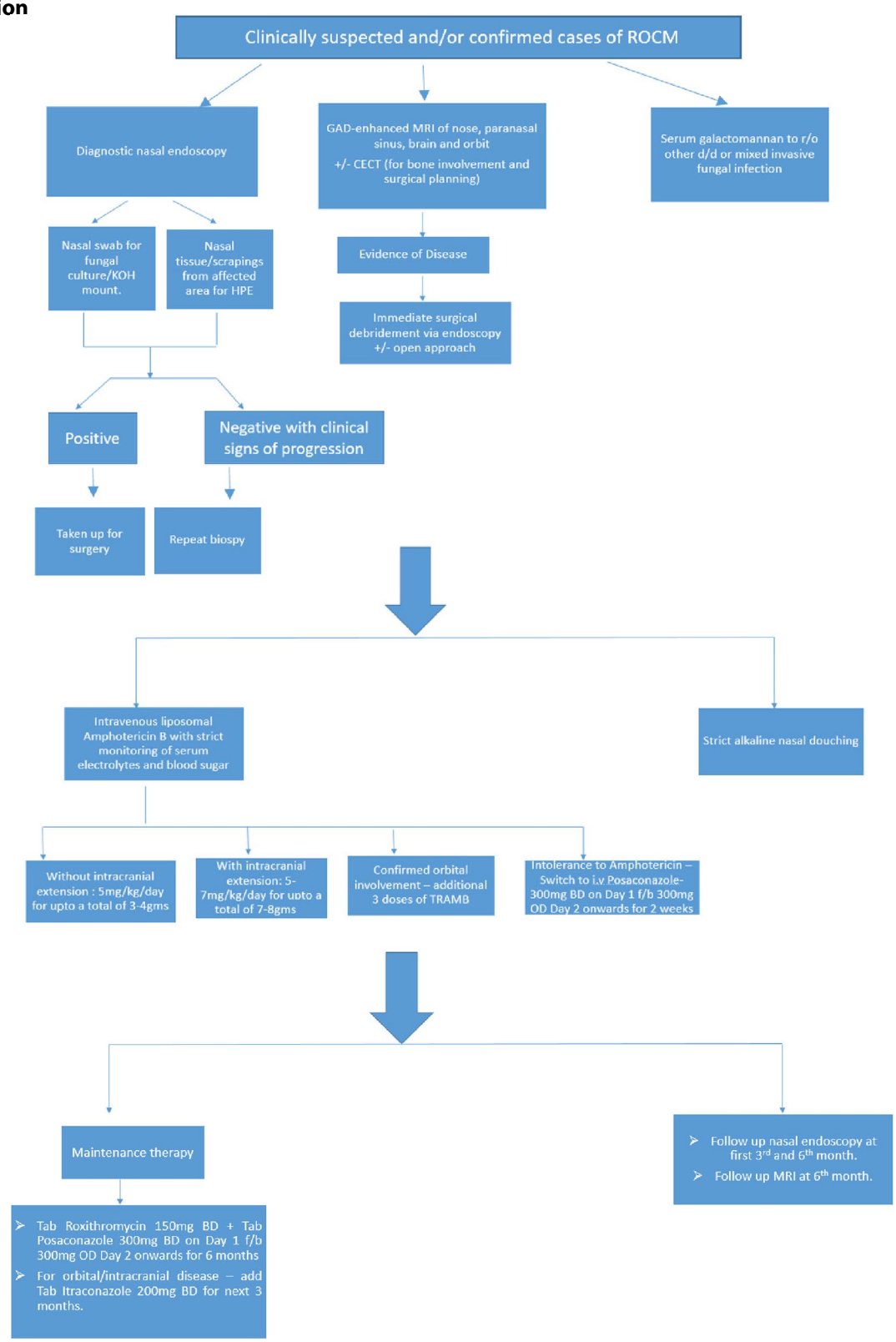
In patients who had orbital and CNS involvement, oral itraconazole was given for another 3 months in a dose of 200 mg BD.

Alkaline nasal douching thrice daily was advised strictly for 9 months.

Follow-up nasal endoscopy was done at the first, third, and sixth months. A healed cavity, presence of granulations, and osteoneogenesis were all signs of a favorable outcome. Restoration of eye movements, ability to take feeds, and overall general well-being were positive signs for an improved quality of life. A follow-up MRI was done at the sixth month for all patients and compared with pre-op MRI scans. Complete clearance was noted in all except 7, who had recurrence due to poor glycemic control and underwent revision surgery. Mortality was seen in 16 patients during the course of follow-up owing to intracranial disease, non-compliance to treatment regime, uncontrolled diabetes, and recurrence of disease.

Algorithm for management of ROCM

Conclusion



A suitable algorithm for efficient management of ROCM providing an improved quality of life to patients would include early detection of disease, prompt and aggressive surgical debridement, administration of liposomal amphotericin B, and long-term follow-up of patients for at least 9–12 months. It thus becomes imperative for every member involved in the management of patients of ROCM to be familiar with the interpretation of MRI. This would go a long way in deciding the surgical approach and predicting a prognosis for such patients. Through this study, we have made an attempt to guide fellow otolaryngologists and doctors in effective management of patients of ROCM.

That being said, empirical antifungal therapy can still be started in patients with clinical suspicion and imaging evidence of ROCM even before microbiological/histopathological confirmation.

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Authors' contributions
1st author—MP: concepts, design, literature search, clinical studies, data acquisition, manuscript preparation, manuscript editing, manuscript review, guarantor. 2nd author and corresponding author—RJ: concepts, design, literature search, clinical studies, data acquisition, manuscript preparation, manuscript editing, manuscript review, guarantor. 3rd author—ABS: concepts, design, literature search, clinical studies, data acquisition, manuscript preparation, manuscript editing, manuscript review, guarantor. 4th author—SK: literature search, manuscript preparation, manuscript editing, manuscript review, guarantor. 5th author—VV: literature search, manuscript preparation, manuscript editing, manuscript review, guarantor.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval Issued by King Georges Medical University U.P, Institutional Ethics Committee No-116th ECM IIA/P26. Written Consent was taken from the participants to participate.

Consent for publication
Written consent was taken for publication.

Competing interests
The authors declare that they have no competing interests.

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