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Research Paper

Surgical & medical management of ROCM (Rhino-orbito-cerebral mucormycosis) epidemic in COVID-19 era and its outcomes – a tertiary care center experience

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ABSTRACT

Objective: To evaluate the outcome of patients with ROCM (Rhino-orbito-cerebral mucormycosis) following their medical and surgical management.
Materials and methods: It is a prognostic study based in a tertiary care center in North-Western India. Patients who developed ROCM post COVID-19 infection from 1st September 2020 to 30th June 2021 were included in this study. Surgical debridement and administration of antifungal therapy was done for the post-COVID-19 ROCM patients. Disease progression and survival was studied up to 5 months of follow-up in the second wave.
Results: A total of 145 ROCM patients were included. The mean age at presentation, male: female ratio was 48.2 years and 2:1 respectively. As per our proposed new staging system and treatment strategy, the majority of patients belonged to stage II (31.72%) and stage III (31.03%). On a follow-up period of 5 months, 26 (18%) patients have lost their life and rest of the patients are on strict follow-up.
Conclusion: ROCM is an extremely aggressive fungal infection which rapidly became an epidemic following the COVID-19 pandemic. The diverse and unique presentation led us to evolve a new strategy to classify and manage these patients.

Introduction

A wide range of opportunistic bacterial and fungal infections has been associated with COVID-19 disease caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) [1]. Mucormycosis is an angioinvasive disease caused by fungi belonging to order *Mucorales* almost exclusively affecting immunocompromised population. It may affect various body systems and is thus classified as rhinocerebral, pulmonary, gastrointestinal, cutaneous, disseminated and other rare forms such as renal, osteomyelitis, endocarditis, peritonitis etc. [2].

In a recent pre-COVID era estimate (2019 and 2020), the prevalence of Mucormycosis was found to be nearly 80 times higher (0.14 per 1000) in India compared to developed countries [2–4]. It has a high mortality rate of approximately 45% in patients with diabetes mellitus and 35% in patients with no detectable underlying conditions [5]. Recently, India has seen an unprecedented epidemic of Mucormycosis, especially during the second wave of COVID-19. The medical fraternity has never experienced an epidemic of Mucormycosis of this scale that led to an acute paucity of antifungals and

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hospital beds, especially when the entire healthcare system was already overwhelmed by the COVID-19 pandemic.

It has been observed that patients with comorbidities such as diabetes mellitus, hypertension, cardiovascular disease and malignancy have a higher predisposition for developing severe SARS-CoV-2 infection [6]. Mucormycosis has also been reported in patients with diabetes mellitus, hematological malignancy, recipients of solid organ transplant and corticosteroid therapy [7]. No study has, so far, established a causal relationship between COVID-19 and Mucormycosis. Nevertheless, there has been a sudden surge of patients with ROCM (Rhino-Orbito-Cerebral Mucormycosis) during the current COVID-19 pandemic.

Patients with ROCM present with various symptoms depending on the extent of the disease. These include loss of sensation over the cheek, nasal obstruction, nasal discharge, loosening of teeth, palatal ulcers, diminution/complete loss of vision, restriction of eye movements, hemiplegia and altered sensorium. Patients can further develop sepsis and multiorgan damage leading to need for ventilatory support, prolonged hospital stay and even death [8]. Therefore, it is imperative to follow aggressive treatment strategies that combine surgical debridement, antifungal pharmacotherapy and attempted restoration of the patients' immune system [9–11].

Noticing an unprecedented rise in ROCM cases gradually during the 1st wave and rapidly during the 2nd wave of the COVID-19 pandemic, we propose a novel clinico-radiological staging to categorize the patients according to the extent of the disease to standardize their treatment during the uncertain future of the pandemic. We aim to further utilize this staging system for disease prognostication in the future. In this paper, we present our evaluation of the surgical and medical management and their outcome in patients with post COVID-19 ROCM.

Materials & methods

We conducted this study including all patients who developed ROCM after COVID-19 infection and presented to us from 1st September 2020 to 30th June 2021. The study protocol was approved by the Institute Ethics Committee and a written informed consent was obtained from all the study subjects. All procedures done for this study complied with the Helsinki Declaration of 1975 as revised in 2008.

Relevant clinical data was obtained from the medical records including the baseline blood investigations, imaging studies, histopathological reports and fungal culture reports.

Sample collection

Diagnostic nasal endoscopy was done for all suspected cases of ROCM. Nasal turbinate/palatal mucosal biopsy was sent for alkaline KOH mount. Patients proven to be having Mucormycosis on KOH mount and/or histopathological examination were included in analysis.

Imaging protocol

All suspected cases of ROCM immediately underwent Contrast Enhanced Computed Tomography (CECT) of the nose, paranasal sinuses, orbit and brain of 0.5–1 mm slice thickness in axial plane (followed by reconstruction into coronal and sagittal planes).

Gadolinium enhanced Magnetic Resonance Imaging (CEMRI) of brain, orbit and paranasal sinus was done for patients with suspected intracranial or intraorbital extension or extensive soft tissue disease or in cases with diagnostic dilemma.

A repeat CT was done on post-operative day 7 to determine whether the disease was controlled with aggressive medical and surgical management or was progressive. Serial CT/MRI scans were done every two weeks, or as per need, for patients with prolonged hospital stay and for discharged patients, for determining the disease progression.

Results

A total of a hundred and forty-five patients met the inclusion criteria from September 2020 to June 2021. There was an 11-fold increase in the number of ROCM patients in the 2nd wave (April 2021 to June 2021) as compared to the 1st wave (September 2020 to March 2021).

The mean age at presentation, male: female ratio was 48.2 years and 2:1 respectively. 53.8% patients belonged to a younger age group of 40–59 years.

All patients presenting during the first wave of the pandemic had uncontrolled diabetes at the time of presentation. However, during the second wave, 16 patients had no comorbidities except COVID-19 positive status followed by a history of steroid intake but with normoglycemia. All other patients had documented hyperglycemia and raised glycosylated hemoglobin level. Around two-thirds of these patients were newly diagnosed. The associated risk factors for developing mucormycosis among our patients is mentioned in Table 1.

Among the 145 patients included in this study from September 2020 to June 2021, the most common intracranial/intraorbital affections at the time of initial presentation were dural thickening (4.82%) and cavernous sinus thrombosis with intra-orbital involvement (4.13%). Also noted were internal carotid artery thrombosis (2.06%), cavernous sinus thrombosis without intra-orbital involvement (2.75%) and temporal lobe infarcts (3.44%). The frequency distribution of presenting clinical symptoms is depicted in Fig. 1.

Based on our proposed new staging system and treatment strategy (Table 2 and 3) which was adopted during the second wave of the pandemic and was retrospectively applied to patients who developed post COVID-19 ROCM during the first wave also, majority of patients belonged to stage II (31.72%) stage III (31.03%). On a follow-up period of 5 months, 26 (18%) patients have lost their life and rest of patients are on strict follow-up. (Table 4)

Over a follow up period of 5 months, it was found that amongst the 145 patients who developed post COVID-19 ROCM, 119 (82%) patients were under strict and regular clinical and radiological follow up and stable. Twenty six (18%) patients didn't survive, of which, mortality in 11 cases was attributed to post COVID-19 complications. The patients were followed up with a mean follow up of 2 weeks.

Additionally, we noticed certain unusual disease characteristics amongst post COVID-19 ROCM patients:

- Among the patients operated during the second wave, majority of the cases had polypoidal mucosa in the sinuses which bled profusely, in contrast to the previously established fact of finding greyish-black necrotic tissue and bone intraoperatively with minimal bleeding (Fig. 2). This may be attributed to early intervention due to the high index of suspicion in our patients who recovered from COVID-19. Furthermore, we expected a better penetration of

Table 1
Associated risk factors at the time of presentation of ROCM patients.

Risk factors	Total Number	Percentage (%)
Diabetes at the time of presentation	125	86.2
Preexisting diabetes	83	57.2
New onset diabetes	42	30
HIV positive	1	0.7
Post renal transplant	1	0.7
Hematological malignancy	2	1.38
Preexisting heart disease	57	39.3
History of steroid intake	94	65

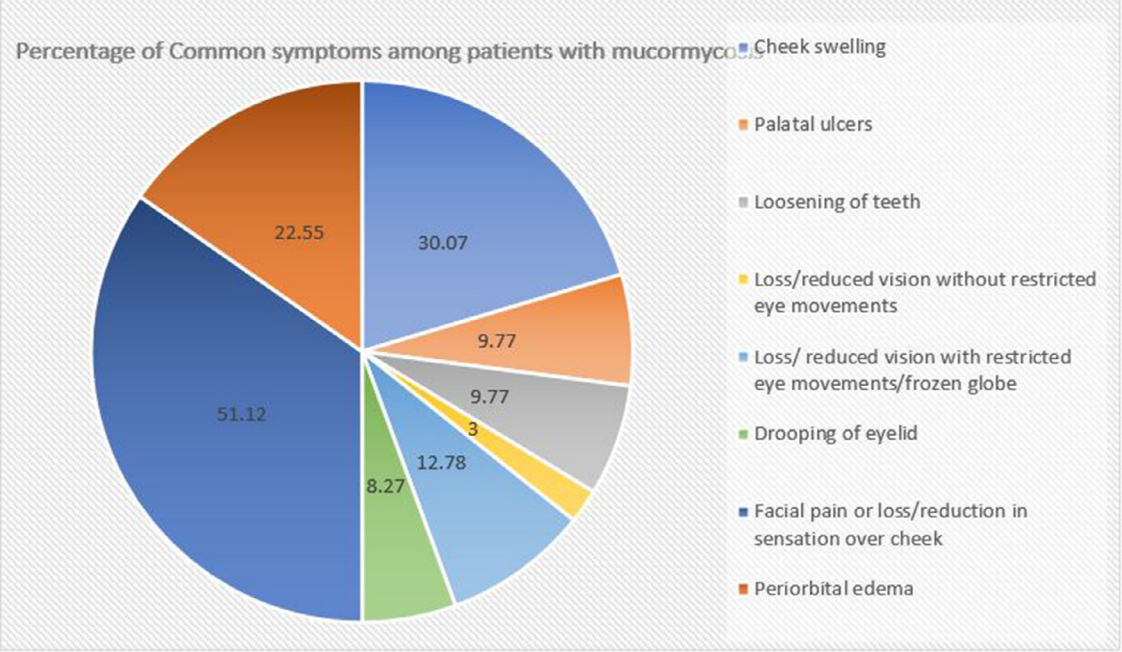

Fig. 1. Pie chart showing the various clinical presentations of patients with ROCM during the COVID-19 pandemic from September 2020 to June 2021.

Table 2
The proposed clinico-radiological classification of ROCM (AIIMS Jodhpur ROCM Staging Protocol).

Stage	Clinical profile		Radiological Findings
	Symptoms	Signs	
I	Nasal obstruction, nasal stuffiness, purulent/black tinged/ haemorrhagic nasal discharge. Cheek swelling with facial pain	Pale/blackish nasal mucosa. Blackish nasal crusts. Cellulitis/edema over the cheek.	Mucosal thickening of the nasal mucosa and/or para nasal sinuses without bony erosion/rarefaction.
II	Absent/reduced sensation over the cheek, loosening of teeth.	Hypoaesthesia/Anesthesia over the cheek or palatal mucosa	Bony involvement of septum, turbinates, Bony erosion along antero-lateral or medial wall or floor of maxillary sinus or erosion of the floor of orbit, alveolar arch and presence of sinus over alveolus. Perineural involvement of infra-orbital nerve.
III A	Restriction of eye movement in at least one quadrant but normal vision. Periorbital swelling.	Ophthalmoplegia	Erosion of posterior wall of maxillary sinus, extension of disease into the pterygomaxillary fissure/pterygopalatine fossa/sphenopalatine foramen/infratemporal fossa or extraconal intraorbital extension of disease
III B	Diminution/loss of vision, restriction of eye movements in all quadrants. Protrusion of eyeball.	Chemosis, proptosis, Complete ophthalmoplegia, Hemifacial hypoesthesia/anesthesia, Relative Afferent Pupillary Defect (RAPD)	Involvement of intraconal compartment of the orbit, erosion of pterygoid wedge, pterygoid plates, limited involvement of greater wing of sphenoid, CRAO (Central Retinal Artery Occlusion), trigeminal nerve (V1,2,3) involvement
IV A	Fever, neck rigidity, headache, vomiting, skin discoloration/ulceration, facial asymmetry, hoarseness, aspiration, trismus	Necrotic involvement of skin, facial paralysis, absent gag reflex, vocal cord palsy, deviation of tongue, positive Kernig's/Brudzinski sign.	Bony erosion of lesser wing/extensive involvement of greater wing/body of sphenoid/clivus/cribriform plate/ soft tissue neck space involvement (parapharyngeal space/ masticator space, muscles of mastication), mandible. Cavernous sinus involvement, orbital apex/superior orbital fissure involvement/skull base foramina involvement, other cranial nerves, dural involvement, skin and extensive subcutaneous tissue involvement
IV B	Altered sensorium Focal seizures Weakness/loss of power of upper and/or lower limbs, Focal neurological deficit	Hemiparesis/Hemiplegia/ Seizures	Internal carotid artery thrombosis/cerebritis/cerebral infarcts/brain abscess, direct parenchymal extension

Note- In case of clinico-radiological discrepancy, the higher stage was considered.

antifungals in diseased tissues due to maintained vascularity, a fact which can only be established by long term results.

- The contrast enhanced CT scan of nose and paranasal sinuses showed involvement of pterygopalatine fossa (PPF) in majority of the patients in the form of fat stranding/presence of soft tissue. It was interesting to find radiological evidence of disease in the PPF with an intact maxilla and very minimal sinus disease (Fig. 3). This could be explained by the angio-invasive nature of mucorales that allows them to directly invade the sphenopalatine artery giving direct access from the nasal cavity to the PPF. Thus, we adopted the policy of removing the posterior wall of the maxilla and inspecting the pterygopalatine fossa in all patients from Stage II upwards.
- Of all the patients, 50 patients underwent at least one MRI scan during the course of treatment of which 21 (42%) revealed perineural spread of disease. The most commonly observed pattern of

Table 3
Stage-wise surgical and medical management protocol proposed for ROCM cases.

Stage	Surgical Procedure	Medical management
I	Endoscopic sinus debridement + Medial maxillectomy	Tab Posaconazole 300 mg BD on day one followed by 300 mg OD for 3–6 months
II	Stage *I* + Partial maxillectomy + Pterygopalatine fossa (PPF) and Infratemporal fossa (ITF) inspection after removal of posterior wall of maxilla	Tab Posaconazole 300 mg BD on day one followed by 300 mg OD for 3–6 months
III	A. Stage *I* + Stage II + PPF and ITF clearance B. Stage *I* + Stage II + PPF and ITF clearance + Orbital exenteration (if intraconal disease present and perception of light absent); *Transcutaneous Retrobulbar Amphotericin-B (TRAB) injections for extra/ intraconal disease, orbital apex involvement	Injection Liposomal Amphotericin-B 5 mg/kg/day of body weight for 3–6 weeks ± Tab Posaconazole 300 mg BD on day one followed by 300 mg OD for 3–6 months
IV	A. Resection of involved bone and other sites B. Resection of extracranial sites as described and neurosurgical procedure in case of: - Increased intracranial pressure - Obstructive hydrocephalus - Lesions compressing the spinal cord	Injection Liposomal Amphotericin- B 10 mg/kg/day of body weight for 3–6 weeks ± Tab Posaconazole 300 mg BD on day one followed by 300 mg OD for 3–6 months

Table 4
Stage-wise distribution of patients with post COVID-19 ROCM according to AIIMS Jodhpur ROCM Staging Protocol.

Stage	Number of patients during COVID-19 n (%)
I	13 (9%)
II	46 (31.72%)
IIIA	45 (31.03%)
IIIB	12 (8.3%)
IVA	21 (14.5%)
IVB	8 (5.5%)
Total	145

spread was along the three divisions of the trigeminal nerve (V1, V2, V3), to reach the skull base foramina, adjacent dura and subsequently the brain parenchyma (Fig. 4).

Discussion

Rhino-orbito-cerebral Mucormycosis (ROCM) is a rare life-threatening invasive fungal infection that often occurs in immunocompromised individuals, with around 70% of the cases complicating a diabetic ketoacidosis (DKA) event [12]. India has witnessed an epidemic of Mucormycosis during the second wave of COVID-19. The reasons behind this sudden surge have been hypothesized, however, still require validation.

The SARS-CoV-2 double mutant strain B.1.617 (Delta variant), possessing the key structural mutations Glu484Gln and Leu452Arg in the spike protein, is highly infectious and less affected by our current vaccine responses, and is a central cause of the COVID-19 surge in India during its second wave [13]. Its role in causing the calamity of the ROCM epidemic especially in the second wave of COVID-19 by providing a favorable environment for fungal growth, needs to be elucidated.

There could be various factors promoting mucormycosis in patients who were affected by COVID-19. COVID-19 facilitates an environment of low oxygen (hypoxia) and reduced phagocytosis and high iron levels. Diabetes mellitus provides a state of hyperglycemia, metabolic acidosis and decreased phagocytosis causing immunosuppression. A combination of COVID-19 infection, rampant steroid treatment even in mild COVID-19 disease and comorbidities such as diabetes mellitus, hypertension and cardiovascular diseases leads to an immense immunocompromised state facilitating the germination of fungal spores [14].

In our study, we studied the patients who presented to us with post COVID-19 ROCM during the first and second waves of the COVID-19 pandemic. Twelve cases of ROCM were identified from 1st September 2020 to 31st March 2021 i.e. during the first wave of COVID-19 and 133 patients were identified from 1st April 2021 to 30th June 2021 during the second wave of COVID-19 with an increase in incidence of ROCM to epidemic proportions during the second wave of COVID-19.

In our study, there was a male preponderance (58.22 and 64.66% during the 1st and 2nd waves respectively) which is consistent with other studies in literature [15].

The mean age group of patients with post COVID-19 ROCM during the 1st wave was 55.91 years (50% patients in 60–69 years age group), while it was 47.31 years (51.8% patients in <50 years age group) during the 2nd wave. There was a significant proportion of younger patients i.e. between 30 and 49 years in the 2nd wave (46.6%) which may be due to relatively more young people being affected with COVID-19 during the second wave. The reason why the younger population is now more vulnerable to SARS-CoV-2 is not apparent and currently beyond any scientific explanation. Younger patients with ROCM are significantly affected with morbidity related to surgery as it has a huge impact on their career and life prospects.

Amongst the predisposing factors for developing Mucormycosis, diabetes mellitus has emerged as the major risk factor especially in developing countries. Other vulnerable populations include recipients of chemotherapy or other immunosuppressants, solid organ and hematopoietic stem cell transplant recipients, or steroid therapy. In a prospective multicenter study by Patel et al., around 12% of cases had no apparent risk factors, especially in those with isolated renal Mucormycosis [13].

We found that 16 patients had no comorbidities except COVID-19 positive status followed by a history of steroid intake but with normoglycemia. All other patients had documented hyperglycemia and raised glycosylated hemoglobin level. Around two-thirds of these patients were newly diagnosed. The excessive use of steroids in the treatment of COVID-19 and the amalgamation of hypoxia, immunosuppression and acidosis caused by the virus maybe the instigating factors[8].

Recently, the global guidelines for diagnosis and management of Mucormycosis were published [**16**]. According to these guidelines, in a diabetic or immunocompromised patient with facial pain or numbness, sinusitis, proptosis, ophthalmoplegia, or newly diagnosed amaurosis, radiology in the form of a CT scan or an MRI of nose, paranasal sinuses with brain and orbit, is strongly recommended. If there is any evidence of sinusitis, endoscopy is strongly recommended to diagnose ROCM. MRI is preferable when there is evidence of orbit or brain involvement over a CT scan. If ROCM is a potential diagnosis, biopsy from suspicious area in the nasal/palatal mucosa is another strong recommendation. The treatment consists of surgical debridement wherever feasible, along with prompt

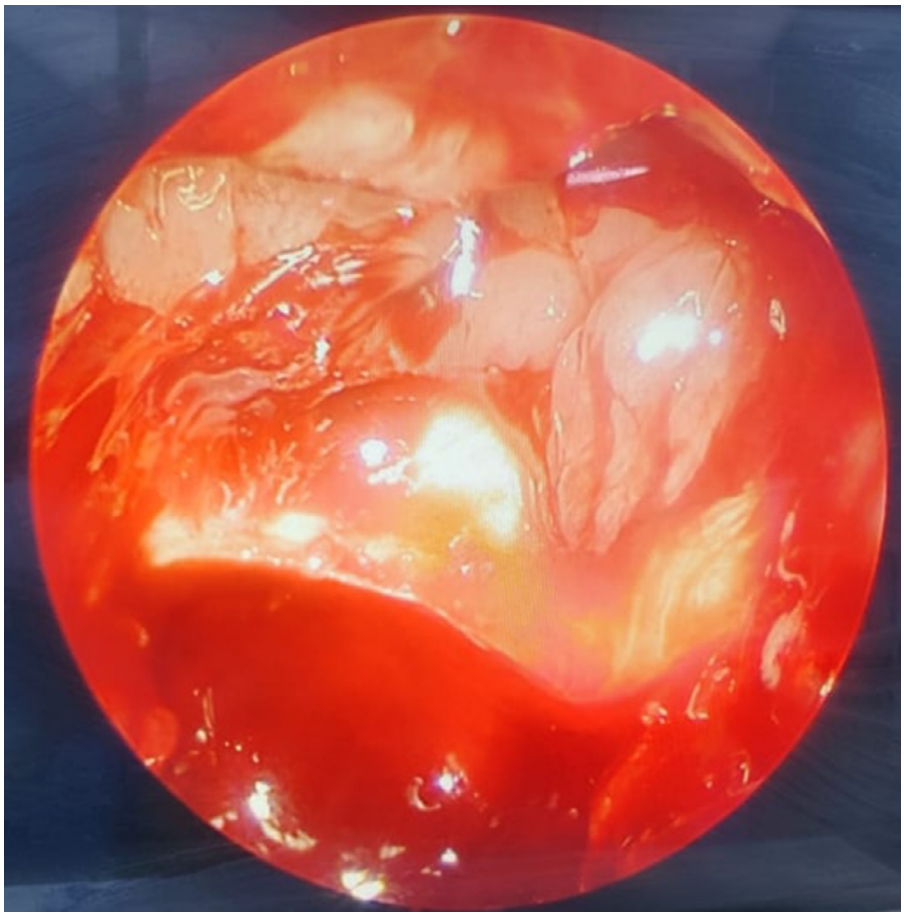

Fig. 2. Endoscopic picture of the maxillary sinus during endoscopic debridement showing bleeding polypoidal sinus mucosa, which was proven to be Mucormycosis on tissue diagnosis later.

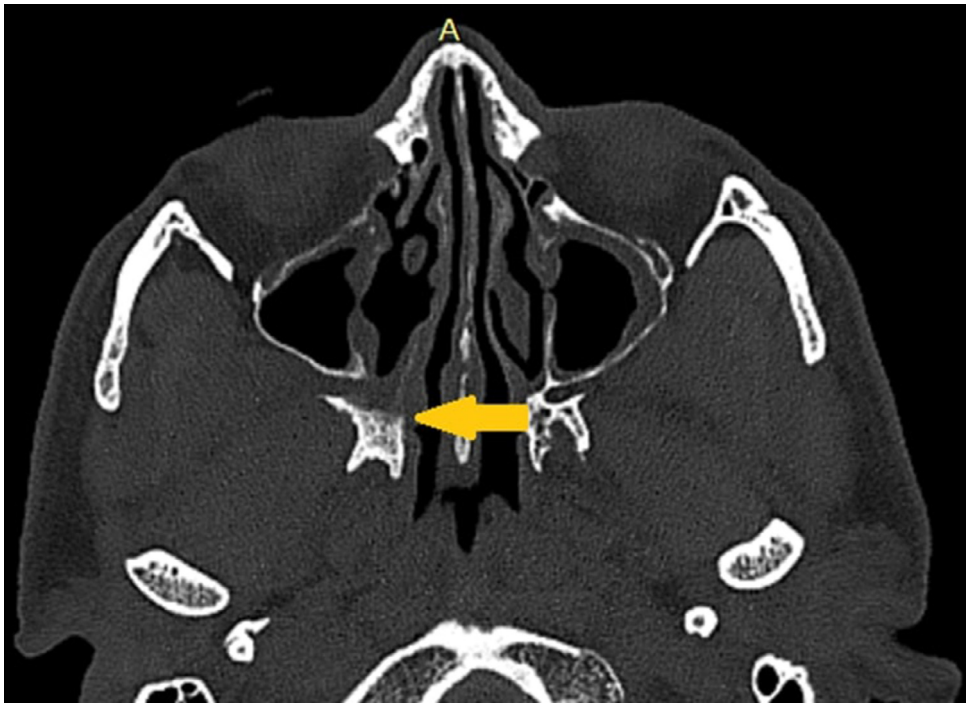

Fig. 3. NCCT showing coronal view of paranasal sinuses showing erosion of the right pterygoid wedge and widening of pterygomaxillary fissure without any obvious disease in the adjoining maxillary sinus and an intact posterior wall.

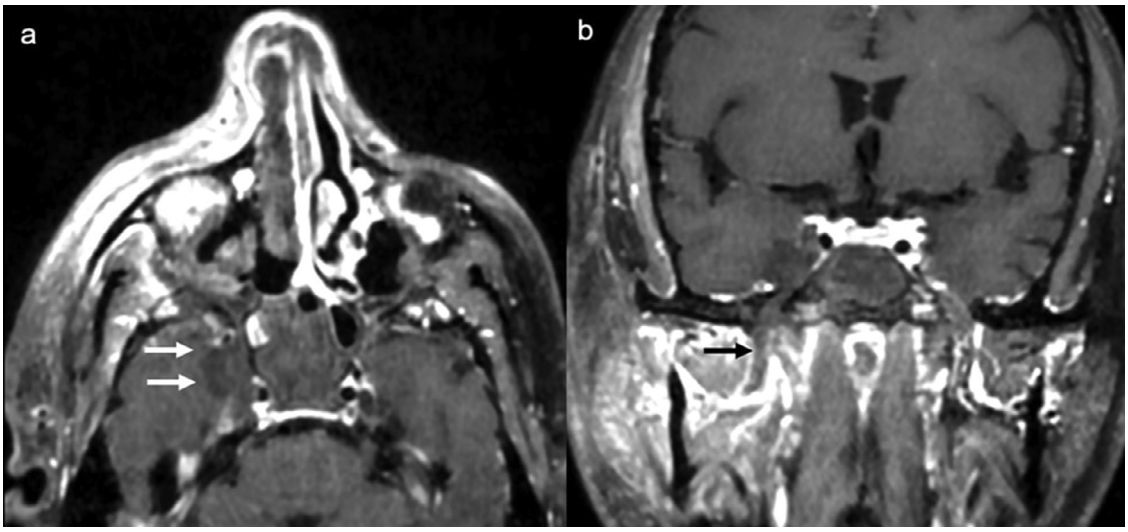

Fig. 4. Post contrast T1 weighted MRI images of a patient with Rhino-Orbito-Cerebral Mucormycosis (ROCM) (a) Axial image shows abnormal enhancement extending from right retro-maxillary region with right cavernous sinus invasion, adjacent right temporal lobe invasion (white arrows). (b) Coronal image shows cavernous sinus invasion along with perineural spread of disease along the branches of right mandibular nerve (black arrow) through foramen ovale.

antifungal therapy in the appropriate dose as per serial response assessment.

Though we followed the recommendations stated above in principle, we had to adopt alternate strategies to cope up with the huge numbers presenting over a short period of time which left us resource constrained especially with regards to availability of antifungal medication. Additionally, managing the situation included mobilization and distribution of manpower, setting protocols in place to tackle the rapid influx of patients and procuring more equipment and administrative approvals [17]. The most critical factor determining treatment outcome in ROCM is early diagnosis and urgent treatment initiation[13,18,19]. During this recent epidemic of ROCM, therefore, any patient with a previous history of COVID-19 positivity along with a history of steroid intake and presence of comorbidities was treated with a high degree of clinical suspicion of ROCM. This prompted an early recognition of cases which would have otherwise been missed due to the rarity of this condition.

Despite the aggressive and potentially fatal nature of the disease, clear cut guidelines for management especially in terms of staging and prognostication of disease, dose and duration of antifungal therapy, follow up protocol, are not available in existing literature. Recently, a clinico-radiological staging system and stage-wise treatment protocol has been proposed by Honavar for which results of clinical application are not yet available [20]. Therefore, based on our experience with more than 100 patients, we propose a new staging system to stage ROCM patients. The study of the clinico-radiologic progression of the disease was a constantly evolving process and we continued to modify our approach and treatment strategy accordingly. The following disease characteristics prompted us to propose this staging protocol:

- The mucosa of nose and paranasal sinuses is continuous and contiguous. Hence the two should be considered as a single entity while staging the disease.
- Bony involvement has a worse prognosis than mucosal involvement alone. Hence, isolated involvement of sinonasal mucosa should be placed in a lower stage compared to bony involvement.
- Compared to the anterior wall, bony involvement of the posterolateral wall of the maxilla suggests a worse prognosis as the pterygopalatine fossa and sphenopalatine foramen offer a pathway for early spread of disease.
- Perineural spread of disease was commonly observed and played a role in spread of disease especially intracranially, as discussed later. Involvement of peripheral branches such as the infraorbital nerve was thus placed in a lower stage relative to the main nerve trunk and roots.
- Soft tissue infiltration in ROCM (eg. skin and subcutaneous tissue, masticator space, parapharyngeal space) due to direct spread through destruction of maxillary bone poses a real challenge and worsens the prognosis. Hence, it should be addressed in staging systems and that too, as a higher stage.
- Mandibular involvement per se is uncommon with ROCM. Perineural spread to the mandible along V3 was observed and should be considered as a poor prognostic factor.
- Laterality of disease was not found to affect principles of treatment and prognosis except in certain cases such as bilateral orbital involvement wherein visual prognosis needs to be considered.

This staging system was formulated with the intention of triaging the patients, forming an effective uniform treatment strategy, stringent follow-up regime and evaluating the short and long-term prognosis. We found this approach to be satisfactory for directing patient management especially under the trying circumstances. Due to an increased awareness in the public and our strategy of having a high index of suspicion in all cases, we were able to detect 41.3% patients in early stages (Stage I and II) with an additional 30.82% in Stage IIIA of ROCM during COVID-19.

Significant proportion of patient's revealed perineural spread on MRI. Perineural spread of the disease has been described in the past, especially with regards to the trigeminal nerve [11]. Retrograde spread from the infraorbital nerve to the V2 root, spreading to the pterygopalatine fossa via the inferior orbital fissure and further to the middle cranial fossa via the foramen rotundum has been described by Parsi et al. [21].

Liposomal amphotericin B is the first choice for patients with ROCM [22]. We faced an acute shortage of Amphotericin B both conventional and liposomal due to epidemic of Mucormycosis all across the country. So we devised our own treatment strategy with elaborate surgical and medical strategy as depicted in Table 2.

Strengths and limitations

The strength of this study is that it provides a guideline for staging, treating and assessing disease progression for ROCM along with the preliminary outcomes. However, involvement of a single center

only and lack of long-term follow-up of patients are the limitations of the present work.

Conclusion

High index of suspicion, prompt initiation of optimum antifungal therapy, early and repeated surgical debridement to decrease the fungal load and restoration of the immune status of the patient play a key role in management of ROCM.

Even though long-term follow-up is essential to establish the prognostic significance of our proposed system, we believe this system of staging and decision-making regarding treatment strategy might help other institutes facing a similar crisis in the wake of the spread of the Delta variant of SARS-CoV-2 across the world and the consequent Mucormycosis epidemic in a resource constrained setting.

Declaration of Competing Interest

There are no conflicts of interest among the authors.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.mycmed.2021.101238.

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