




Is mucormycosis the end? A comprehensive management of orbit in COVID associated rhino-orbital–cerebral mucormycosis: preserving the salvageable

Amit Keshri¹ · Arulalan Mathialagan¹ · Ankita Aishwarya² · Ravisankar¹ · Govind Bhuskute¹ · Vikas Kanaujia² · A. K. Singh³ · R. K. Singh⁴ · R. K. Dhiman⁵ · Rachna Agarwal² 

Received: 2 May 2022 / Accepted: 16 August 2022 / Published online: 2 September 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

Background Rhino-orbital–cerebral mucor mycosis (ROCM) is a relatively rare opportunistic infection caused by the Mucorales species. While ROCM suggests involvement of the paranasal sinuses, orbit and brain ROM (rhino-orbital-Mucormycosis) stands for the fungal invasion in sinuses and orbit sans cerebral involvement. In India with the outbreak of the second COVID wave and the delta variant of the virus, there has been a steep increase in this opportunistic fulminant fungal infection, named COVID-associated Mucor mycosis (CAM). The most critical question in orbital management is when to go ahead with an exenteration. Our study aims to design a pertinent minimal invasive surgical protocol for surgeons to manage such cases based on our surgical experience and mitigate the need for exenteration and save the eyes wherever possible.

Methods The study is a retrospective analysis of patients of ROM with and without brain involvement, who underwent minimal surgical management between March 2021 to March 2022 along with their follow-up.

Results There were 184 eyes of 148 patients diagnosed with CAM. The mean age was 51.7 years with a male predominance of 103 (70%). All patients developed ROM following the COVID-19 infection and the duration between diagnosis of COVID-19 and ROM was 36 ± 23 days. 18 cases (12%) were bilateral. 76 eyes (41%) had no vision at the presentation. Imaging revealed paranasal sinus involvement (100%), orbital apex involvement (61%), cavernous sinus involvement (53%), and central nervous system (CNS) involvement (47%). All the patients (100%) were treated with systemic Liposomal amphotericin-B and sinus debridement. Endoscopic debridement of the orbital disease was performed in 45 (30.4%) cases, 15(8.1%) eyes underwent exenteration and were later rehabilitated with a customized ocular prosthesis, 103 (56%) eyes underwent transcutaneous retrobulbar amphotericin-B. At a mean follow-up of 13.1 months; the complete resolution was seen in 25 (17%) cases, the residual stable lesion was seen in 77(52%) of the cases and new lesions were developed in 13(9%) of the cases. Mortality was seen in 33 (22%) patients and all of them had CNS involvement.

Conclusions Systemic and protocol-based management can save the life and salvage the eyes.

Keywords Rhino-orbital–cerebral mucormycosis · COVID-associated mucormycosis · Exenteration · Orbital management

✉ Rachna Agarwal
rachna7500@yahoo.co.in

A. K. Singh
dradarshsir@gmail.com

¹ Department of Neurosurgery (Neuro-Otology Unit), Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raibareilly Road, Lucknow 226014, India

² Department of Ophthalmology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raibareilly Road, Lucknow 226014, India

³ Council of Scientific and Industrial Research, New Delhi, India

⁴ Department of Emergency Medicine, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raibareilly Road, Lucknow 226014, India

⁵ Department of Hepatology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raibareilly Road, Lucknow 226014, India

Abbreviations

CAM	COVID associated mucor mycosis
ROM	Rhino-orbital–mucormycosis
ROCM	Rhino-orbital–cerebral mucor mycosis
CRAO	Central retinal artery occlusion
TRAMB	Trans cutaneous retrobulbar amphotericin B injection
SOF	Superior orbital fissure
FESS	Functional endoscopic sinus surgery

Introduction

The second wave of COVID 19 pandemic started in the Indian subcontinent in March 2021. Within a few days of the identification of the Indian variant of COVID-19, named the “delta”, a new epidemic emerged in the Indian subcontinent, the epidemic of the opportunistic fungal infection. As of June 7, 2021, the Indian Ministry of Health had recorded 28 252 cases of black fungus [1]. The Rhino-Orbital-Mucor mycosis (ROM) is not a new disease, it is an acute fulminant form of the invasive fungal infection, caused by fungi belonging to the order Mucorales, that spreads rapidly and cause extensive tissue destruction [1–7].

With a sudden surge of ROCM cases post COVID 19 infections, a surgical treatment protocol has become the need of the hour. The management of the nasal and paranasal sinus Mucor mycosis has been clearly defined in the literature unlike that of orbital involvement. The traditional teaching for management of orbital Mucormycosis orbital exenteration [1, 2]. The confusion mainly arises when vision is intact. In the past, the majority of the ROCM were seen secondary to a severe long-standing Immuno-deficiency such as uncontrolled diabetes, hematological malignancies, post-organ-transplant, etc., where the ROCM was so extensive that rarely did patients present with orbital involvement had an intact vision. However, the scenario with CAM is different, the patients are in various stages of “nasal immune alterations” that the orbital involvement was not always associated with complete vision loss and also minimal orbital involvement with complete visual impairment. Does not that mean that removing the eyeball in all the patients with an orbital involvement is an over-do? What if a patient has vision loss due to thrombosis caused only by Central retinal artery occlusion (CRAO) without orbital contents being involved? Does removing it not lead to severe cosmetic deformity? Can orbit be preserved even in patients who do not have a perception of light? With so many questions and in ceasing patients with a spectrum of orbital involvement we tried to look to the literature to find answers, but the search did not answer all our queries. To date, there are no conclusive data or guidelines that give us crisp outlines or indications for orbital decompression,

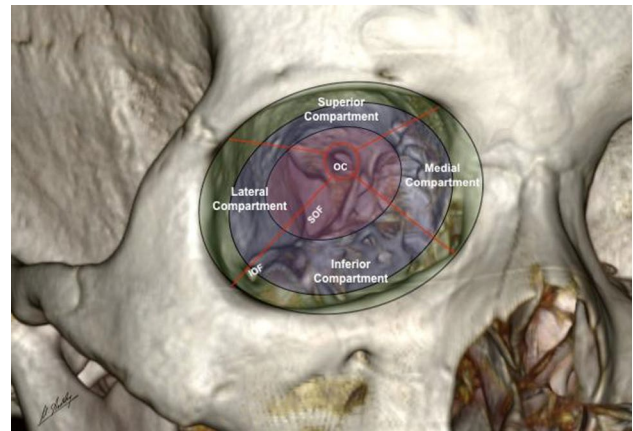


Fig. 1 Division of orbit into zones and compartments

debridement, or exenteration in Mucor mycosis of the orbit and paranasal sinuses. To address these questions we tried to make a protocol-based guideline for the treatment of orbital involvement in CAM.

Methodology

The study was performed in a tertiary referral centre in north India. All patients with ocular involvement along with proven COVID-19 infection with positive culture reports for mucormycosis were enrolled in the study group. Contrast-enhanced magnetic resonance imaging (CEMRI) and/or contrast-enhanced computed tomography (CECT) of the paranasal sinus and orbit were performed for all the patients. Bony orbit was anatomically subdivided into zones and compartments.

Orbital zone

Orbital zones are divided as subdivisions of orbit in the coronal plane.

- (1) Anterior zone—from orbit rim till the anterior margin of the inferior orbital fissure.
- (2) Mid zone—from the anterior margin of inferior orbital fissure till the junction of inferior orbital fissure with the superior orbital fissure.
- (3) Posterior zone—from the junction of the inferior orbital fissure and Superior orbital fissure to the optic canal.

Orbital compartments

The orbit was divided into four major compartments, each one had the orbital rim at its base and the apex was at the

optic canal, such as a three-sided Pyramid. Thus, we had four, three-sided pyramids encompassing the entire orbital contents (Fig. 1).

- (1) Medial compartment.
- (2) Superior compartment
- (3) Lateral Compartment.
- (4) Inferior compartment.

Surgical spaces of the orbit

The traditional surgical spaces of the orbit are

- (1) Sub-periosteal space
- (2) Extra-conal space
- (3) Intra-conal space
- (4) Sub-tenon space
- (5) Subarachnoid space

By subdividing the orbit and its contents into three zones, four compartments, and five surgical spaces the entire orbital involvement can be categorized systematically through radiology and adding the clinical evaluation which can allow a surgical team to decide the best suited surgical approach for any given case scenario. The decision on the surgical procedure was done by the CAM committee comprising of an Otorhinolaryngologist, Ophthalmologist, Neurosurgeon, Oro maxillofacial surgeon, Anesthetist, and Radiologist.

Results

A retrospective interventional study of 184 eyes of 148 mucormycosis patients from 2021 to 2022 was done at Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India. The mean age of the patients was 51.7 years with a male predominance of 103 (70%). All patients developed ROM following the COVID-19 infection and the duration between diagnosis of COVID-19 and ROM was 36 ± 23 days. 18 cases (12%) were bilateral. 121 patients (82%) had a previous history of DM and 19 (14%) had developed new-onset diabetes. 76 eyes (41%) had no vision at the presentation. Imaging revealed paranasal sinus involvement (100%), orbital apex involvement (61%), cavernous sinus involvement (53%), and central nervous system (CNS) involvement (47%). All the patients were treated with systemic Liposomal amphotericin-B and sinus debridement. All patients underwent endoscopic debridement for disease in paranasal sinuses. Endoscopic debridement of the orbital disease was performed in 45 (30.4%) patients in which the superior open approach was performed in 15 patients, the lateral open approach was performed on 3 patients and the rest were mixed. 15 eyes (8.1%) underwent exenteration. 103

(56%) eyes underwent transcutaneous retrobulbar amphotericin-B. At a mean follow-up of 13.1 months, complete resolution was seen in 25 (17%) cases, the residual stable lesion was seen in 77 (52%) of the cases and new lesions were developed in 13 (9%) of the cases. Mortality was seen in 33 (22%) patients and all of them had CNS involvement. After performing many globe salvaging surgeries in such types of patients and following them up, we have outlined the indications of exenteration, Trans Cutaneous Retrobulbar Amphotericin B injection (TRAMB), debridement, and decompression. Moreover, we have devised an anatomy-based protocol for the management of Rhino-orbital Mucormycosis (Figs. 2, 3a, b). This protocol is based on the fact that endoscopic debridement can save the globe and eyes can be saved from exenteration. Figures 4 and 5 show self-explanatory detailing the protocol-based management of cases. For all the patients described, informed consent for publication of the cases has been taken. The study has been approved by the institutional ethics committee and abides by the WMA Declaration of Helsinki.

Discussion

With the second wave of COVID-19, The Indian Subcontinent had seen an exploding epidemic of the deadly opportunistic Rhino-orbital-Cerebral-Mucor mycosis. There had been many theories to identify the cause that seemed to be epidemic only in the Indian subcontinent. Use of high doses of steroids, oxygen, use of immunomodulator drugs, such as Tocilizumab, and others was also on the list of a possible cause, but none have been proved yet. 6,8,9 The destruction of the pancreatic cells has been linked to the delta variant of the virus, along with the use of a high dose of steroids to protect from the cytokine surge has made the host suffer from ill-controlled diabetic status and a very high serum Ferritin values, making them highly susceptible to ROCM [10, 11]. The COVID infection had destroyed the nasal mucosa, the protective cilia with a layer of mucus that acted as a conveyor belt to wash off the allergen, and inhaled pathogens were lost to a varied extent. Thus, the nasal local immunity was compromised, helping the pathogens to penetrate easily into the nasal mucosa and submucosa and eventually into the blood vessels [12, 13]. The Mucorales species are opportunistic pathogens by a vascular invasion that can reach various regions of the Paranasal sinus, orbit, and brain. Based on the site involved the clinical features develop. Thus, an immunologically 'compromised', damaged nasal cavity mucosa along with an ill-controlled diabetic state makes a deadly combination for the mucor to colonize, invade and spread, within a few minutes to a few hours [10–16]. Mucor is angio-invasive, it causes thrombi, thus making

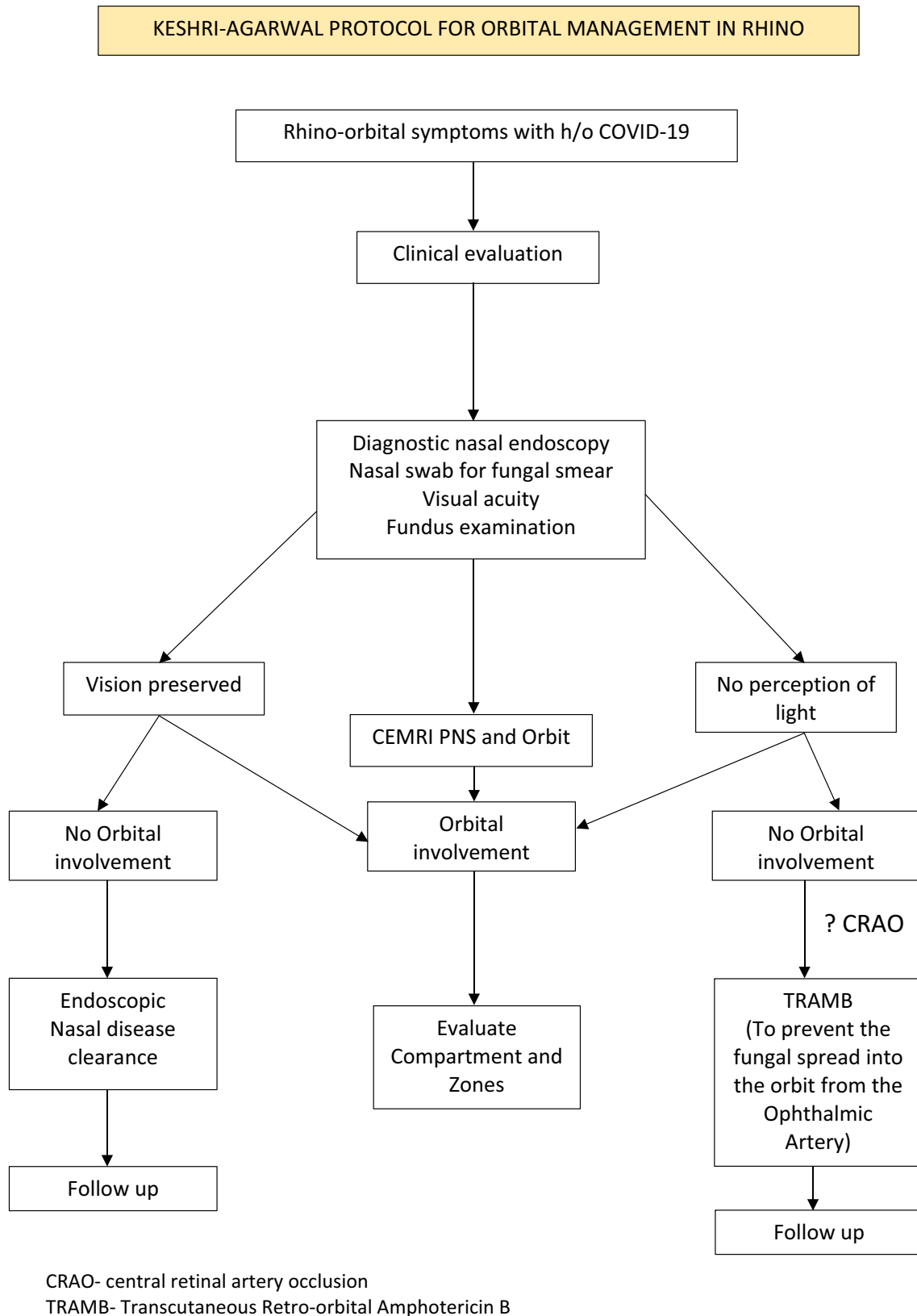


Fig. 2 Keshri–Agarwal protocol for management of ROM by minimally invasive technique

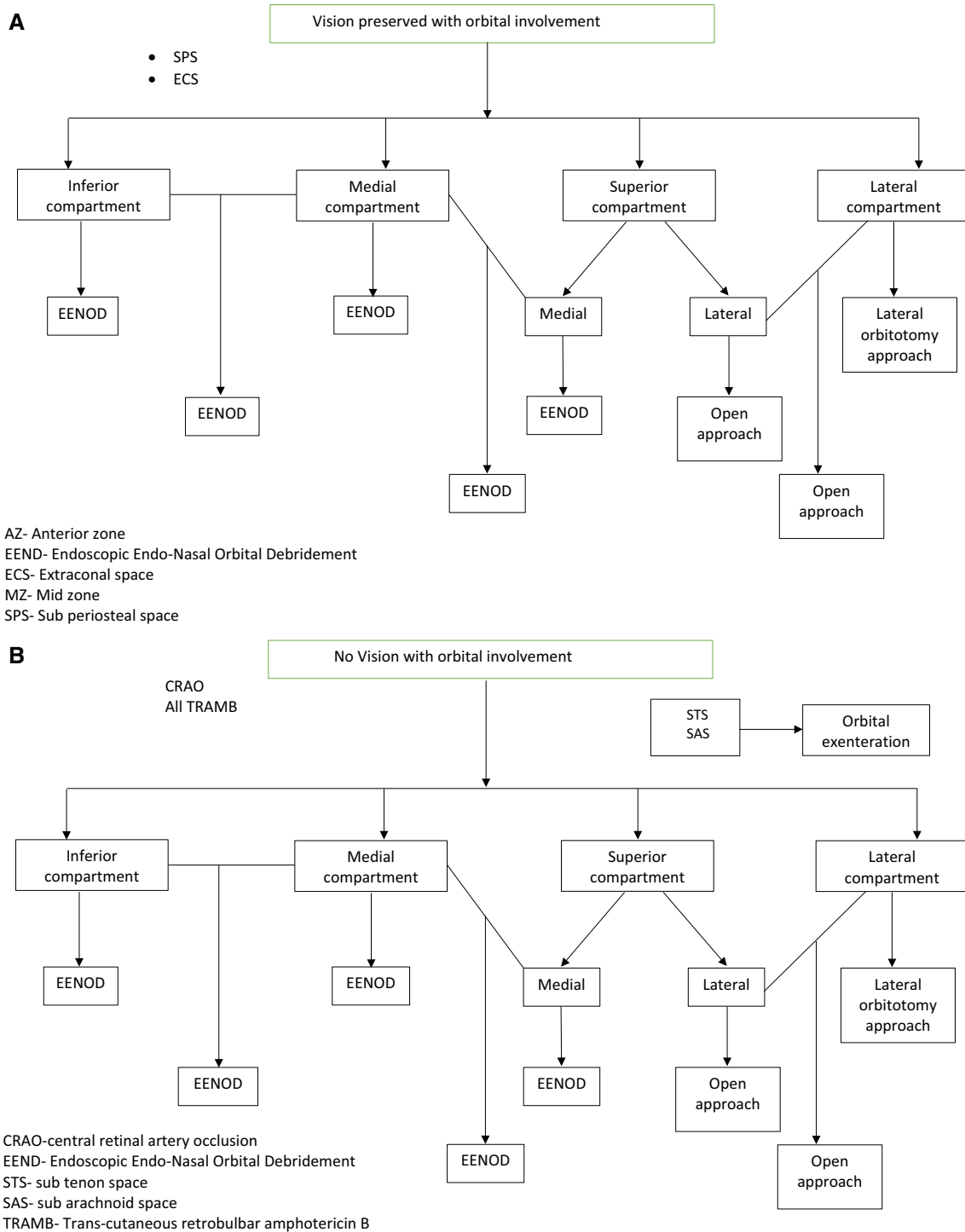


Fig. 3 **a** Management in cases of rhino-orbital mucormycosis (ROM) with vision preserved with orbital involvement. **b** Management in cases of rhino-orbital mucormycosis (ROM) with no vision with orbital involvement

the drug delivery to the affected area almost impossible as intravascular drugs cannot reach those sites. The traditional surgical principle is to debride all the involved tissue until we have a fresh bleed from the viable tissue [12–14]. The nasal mucosa and paranasal sinus are

relatively larger anatomical sites, where the principle of radical debridement can be applied. However, as far as the orbit is concerned radical debridement would almost always mean a complete exenteration of the orbital contents. There were a few research publications that spoke

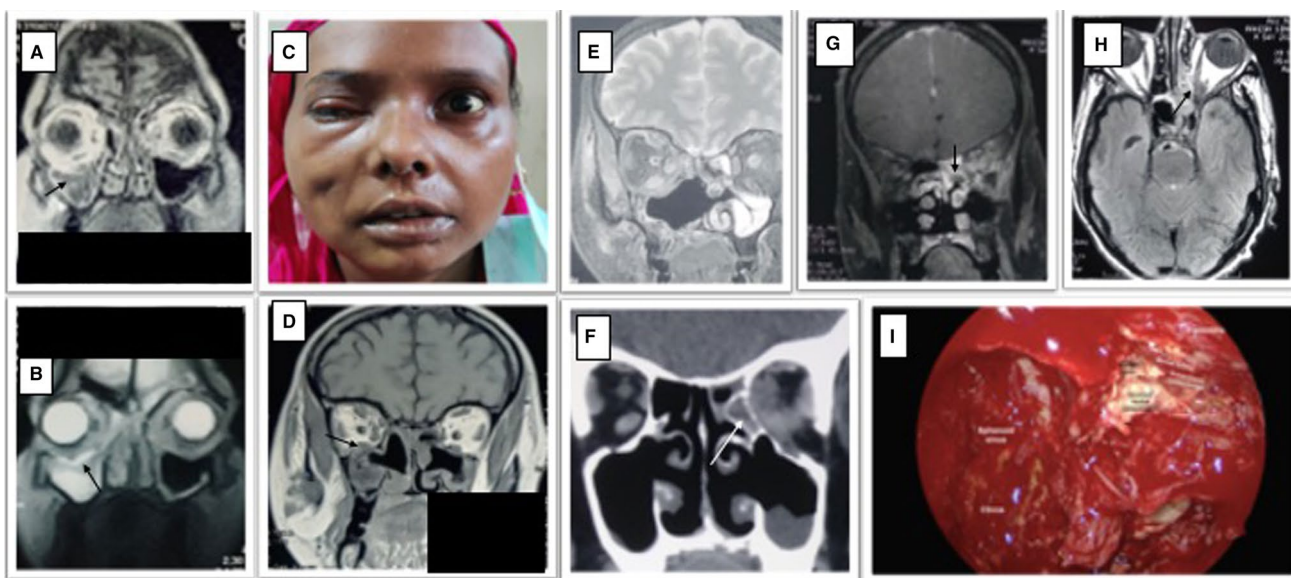


Fig. 4 Surgical management in cases of rhino-orbital mucormycosis (ROM) with inferior and medial orbital involvement

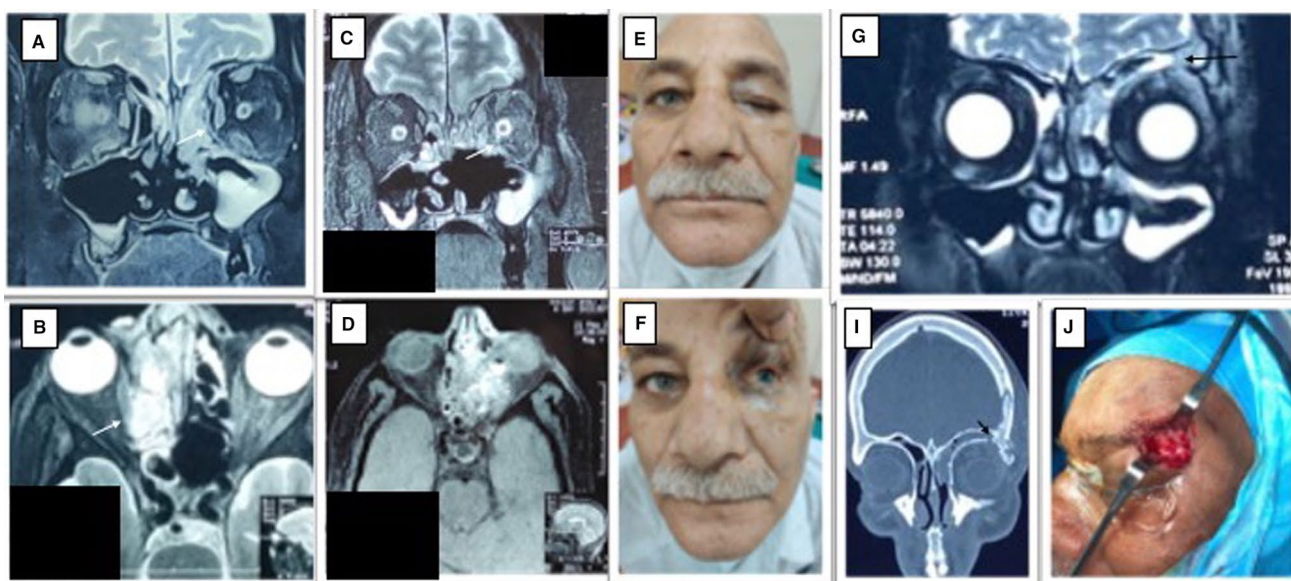


Fig. 5 Surgical management in cases of rhino-orbital mucormycosis (ROM) with superior and medial orbital involvement

about the indications of orbital exenteration but had a very complicated scoring system [11–16]. The largest series of CAM in India also showcased the spectrum of involvement but did not focus on and clarify the surgical approaches [17, 18]. With an increasing number of patients, many unanswered questions, very little information in the literature, and very little time, on one hand, Our Institutes CAM task force sat down to draft a simple, comprehensive, systematic, working surgical protocol for the management of the orbital disease in ROCM. The Surgical approach for sinonasal mucormycosis has been well-defined and with

the increasing experience with the FESS, Endoscopic debridement is the surgical approach of choice. The Extension of the endoscopic approach can be done based on the extent of the disease and the part of the Sino nasal cavity involved.

Orbital involvement in ROCM

Orbit is closely related to the paranasal sinus. Orbital involvement in PNS infections is a known complication. The involvement of the orbit can be using an extension of disease

from the PNS or through vessels and nerves [3, 4, 19]. The fungi can also reach orbit and central retinal artery via the involved and thrombosed anterior and posterior ethmoidal arteries [7, 8, 20, 21]. The disease from the maxillary sinus can reach the orbital floor and inferior compartment via the infraorbital canal and the infraorbital nerve. MRI with contrast should be undertaken before surgery to access orbital involvement to decide whether to do a debridement or exenteration. Loss of contrast enhancement in extraocular muscle if mild or moderate, debridement can be done, and if severe exenteration should be undertaken [8, 9, 11, 22].

Why is orbital mucor mycosis clearance important?

The orbit is a gateway for the spread of fungi into the intracranial cavity. The superior orbital fissure and the optic canals are direct bony openings that connect the orbit with the intracranial cavity. The Superior Orbital Fissure continues into the cavernous sinus, which is a draining area of major intracranial venous sinus, thus having a route for intracranial dissemination. Thus an effective way of orbital disease control is prudent to control the progression of Mucormycosis. Winning over the fungi after it enters the intracranial cavity is almost impossible, with literature evidence of up to 100% mortality in Cerebral Mucormycosis [4, 7–9, 20–22].

The rationale for orbital zones and compartments

The subdivision of the orbital space into zones and compartments makes the understanding of the disease involvement easier and more systematic. The anterior zone mainly contains the anterior periorbital fat with the distal lacrimal system, the lacrimal sac, and the punctum. The mid-zone has the major bulk of the eyeball and the surrounding periorbital fat. The posterior zone is the most dangerous, as it contains all the nerves, muscles, and annulus of Zinn, involvement of the posterior zone has a more likely possibility of vision loss and intracranial involvement. Compartmentalization of the orbital involvement into medial, superior, lateral and inferior helps in planning the surgical approach for the optimal resection of the involved orbit content.

Orbital disease management

The choices in our armamentarium are orbital decompression, orbital debridement, Transcutaneous-Retro orbital Amphotericin B (TRAMB), and radical orbital exenteration. Orbital exenteration is a radical and deforming surgery that needs to be performed in case of extensive orbital involvement in ROM. It involves complete surgical removal of the eyeball along with the adnexa. The cosmetic disfigurement following exenteration is a major concern as it can have a serious psychological impact on the patient. TRAMB

(Transcutaneous Retrobulbar Amphotericin B injection) is also an option available. With only a handful of case reports available on its use in Mucor mycosis in literature, there is a need to outline its specific indications [23–25].

Surgical approaches to the orbital disease

With the advent of endoscopic sinus surgery and increasing evidence of its advantage over the open approaches, the endoscopic approach is the choice in this modern era, both for benign as well as malignant PNS pathologies. The orbital compartments can also be approached with greater clarity with the standard nasal endoscopes (4 mm, 18 cm rigid endoscope of 0° or 30°) via transnasal route. With a wide panoramic view and magnification, the endoscope can give greater clarity to the vascularity of the orbital and periorbital structures and can delineate viable tissue from non-viable and necrotic tissue in cases of ROCM. This gives the Surgeon an extra edge to adequately excise the involved tissue and at the same time preserve the viable tissue where ever possible.

The endoscopic transnasal approach can be used for orbital disease clearance. The Inferior compartment via the maxillary sinus, the medial compartment via the ethmoid Sinus, Superior compartment, along the medial aspect via the frontal Sinus. The Superior Compartment may also require an open approach if the more lateral part is involved. The lateral Compartment cannot be approached via the transnasal endoscopic route and requires an open approach.

Endoscopic orbital decompression

Indications

1. Extensive ethmoidal sinus and maxillary sinus involvement with no orbital involvement on MRI.
2. No orbital involvement with the blurring of vision, but no CRAO/fundus changes.
3. No orbital involvement with anticipated TRAMB, to prophylactically decompress the orbit.

Endoscopic debridement

Indications

1. The disease is extraconal and is responding well to medical treatment
2. If on MRI there is the involvement of inferior rectus or medial rectus only
3. Globe intact with no intraconal invasion.
4. Vision is preserved.

The extent of endoscopic debridement of the orbit depends on the extent of the disease and the orbital structures involved.

If only the medial extra conalperi-orbital fat is involved, the involved fat alone can be debrided leaving behind the healthy orbit. If the disease involves the medial and inferior recti muscle alone without intraconal or sub-tenon space involvement, the involved muscle alone can be safely debrided, leaving the rest of the viable orbital contents. With the help of the high-definition endoscope, it is possible to delineate the healthy tissues from the involved part.

Orbital exenteration

Indications

1. Significant proptosis with fulminant orbital involvement in rapidly progressive disease.
2. Globe invasion (sub-tenon space)
3. Extensive intraconal involvement in the lateral compartment, where endoscopic debridement is not possible.
4. Subarachnoid space (optic nerve sheath) involvement, to prevent intracranial extension.
5. Failure to respond to conservative surgery.

External approach exenteration

1. When the facility of endoscopic surgery is not available
2. In cases where there is globe and eyelids involvement

Transcutaneous-retro orbital amphotericin B (TRAMB)

In cases with CRAO, SOF Syndrome, and orbital apex syndrome, direct Trans-orbital Amphotericin-B can be given to act on the fungi at the orbital apex region (posterior zone) to control the disease from going into the intracranial Compartment as well as can control the spread of the disease into the orbit.

Indications

1. Residual disease after maximum debridement
2. The patient is not fit for surgery.
3. Only minimal or no involvement of the orbit with CRAO.

The Flow chart (Figs. 3 and 4a, b) shows a systematic protocol to choose the appropriate approach for the disease clearance from the orbit in cases of ROCM.

Conclusions

This document gives a detailed and systematic outline for the management of orbital disease in cases of ROCM clearly outlines the surgical approaches to be used. The key idea was to save the globe where ever possible and thus maintain the facial contour and cosmesis without leaving behind the disease. It also highlights the methods by which we can salvage the globe and alleviate the need for exenteration, which has a serious psycho-social impact.

Declarations

Conflict of interest We have no financial disclosures to make.

References

1. Tay MZ, Poh CM, Rénia L, Macary PA, Ng LFP (2021) The trinity of COVID-19: immunity, inflammation and intervention the unseen “fungal infections”—an extra thrust aggravating COVID second wave in India. May 24, 2021
2. Soare AY, Watkins TN, Bruno VM, Bruno VM (2020) Understanding mucormycosis in the age of “omics.” *Front Genet* 11:1–11
3. Stanford FA, Matthies N, Figge MT, Hassan MIA, Voigt K (2021) Expression patterns in reductive iron assimilation and functional consequences during phagocytosis of lichtheimiacorymbifera, an emerging cause of mucormycosis. *J Fungi* 7(4):272
4. Khunti K, Davies MJ, Kosiborod MN, Nauck MA (2021) Long COVID — metabolic risk factors and novel therapeutic management. *Nat Rev Endocrinol* 0123456789
5. Lax C, Carlos P, Tahiri G, Antonio P, Osorio-concepci M, Murcia-flores L et al (2020) Genes, pathways, and mechanisms involved in the virulence of mucorales. *Genes* 11(3):317
6. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T (2021) Post coronavirus disease mucormycosis : a deadly addition to the pandemic spectrum. *J Laryngol Otol* 135:442–447
7. Prakash H, Chakrabarti A (2019) Global epidemiology of mucormycosis. *J Fungi* 5:26
8. Prakash H, Skiada A, Paul RA, Chakrabarti A, Rudramurthy SM (2021) Connecting the dots : interplay of pathogenic mechanisms between COVID-19 disease and mucormycosis. *J Fungi* 7:616
9. Bonaventura A, Vecchié A, Dagna L, Martinod K, Dixon DL, Van Tassell BW et al (2021) Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat Rev Immunol* 21:319–329
10. Mohta S, Agarwal A, Makharia GK (2020) Exploring COVID-19 therapies: an extraordinary global challenge. *J Digestive Endosc* 8:73–75
11. Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J et al (2018) A prospective multicenter study on mucormycosis in India : Epidemiology, diagnosis, and treatment. *Med Mycol* 57(4):395–402
12. Id NVS, Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP (2018) Therapy of mucormycosis, 117
13. John TM, Jacob CN, Kontoyiannis DP (2021) When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. *J Fungi* 7:298

14. Montaña DE (2020) Host immune defense upon fungal infections with mucorales: pathogen-immune cell interactions as drivers of inflammatory responses. *J Fungi* 6:173
15. Ahmadikia K, Jamal S, Sadegh H, Ibrahim M, Neda G, Hamid A et al (2021) The double-edged sword of systemic corticosteroid therapy in viral pneumonia: a case report and comparative review of influenza-associated mucormycosis versus COVID-associated mucormycosis. *Indian J Ophthalmol* 69:1670
16. Tay MZ, Poh CM, Rénia L, Macary PA, Ng LFP (2020) The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 20(6):363–374
17. Sen M, Honavar SG, Bansal R et al (2021) Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India-Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. *Indian J Ophthalmol* 69(7):1670–1692. https://doi.org/10.4103/ijo.IJO_1565_21
18. Shah K, Dave V, Bradoo R, Shinde C, Prathibha M (2019) Orbital exenteration in rhino-orbito-cerebral mucormycosis: a prospective analytical study with scoring system. *Indian J Otolaryngol Head Neck Surg* 71(2):259–265. <https://doi.org/10.1007/s12070-018-1293-8> (Epub 2018 Mar 13)
19. Soare AY, Watkins TN, Bruno VM, Bruno VM (2020) Understanding mucormycoses in the age of “omic.” *Front Genet* 11:1–11
20. Lax C, Carlos P, Tahiri G, Antonio P, Osorio-Concepci M, Murcia-flores L et al (2020) Genes, pathways, and mechanisms involved in the virulence of mucorales. *Genes* 11:317
21. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T (2021) Post coronavirus disease mucormycosis : a deadly addition to the pandemic spectrum. *J Laryngol. Otol* 135:442–447
22. Mohta S, Agarwal A, Makharia GK (2020) Exploring COVID-19 therapies : an extraordinary global challenge. *J Digestive Endosc* 11:73–75
23. Hirabayashi KE, Kalin-Hajdu E, Brodie FL, Kersten RC, Russell MS, Vagefi MR (2017) Retrobulbar injection of amphotericin B for orbital mucormycosis. *Ophthal Plast Reconstr Surg* 33(4):e94–e97
24. Safi M, Ang MJ, Patel P, Silkiss RZ (2020) Rhino-orbital-cerebral mucormycosis (ROCM) and associated cerebritis treated with adjuvant retrobulbar amphotericin B. *Am J Ophthalmol Case Rep.* 19:100771
25. Brodie FL, Kalin-Hajdu E, Kuo DS, Hirabayashi KE, Vagefi R, Kersten RC (2016) Orbital compartment syndrome following retrobulbar injection of amphotericin B for invasive fungal disease. *Am J Ophthalmol Case Rep* 1:8–10

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.