20 Debates in Rhino-Orbito Cerebral Mucormycosis (ROCM): Classification Dilemmas

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Rhino-orbito-cerebral mucormycosis (ROCM) is an invasive fungal infection often found in immunocompromised individuals. The mucor is thought to inoculate the nasal cavity first and then spread to the sinuses, orbit and intracranial space [1–5]. Orbital apex allows further intracranial dissemination and cavernous sinus involvement [1]. Several classifications of ROCM have been published by various authors based on this premise [6–10]. They proposed varying degree of resection based on individual criteria. However, the recommendations lack uniformity, and the surgical management remains difficult due to frequent residual/recurrent disease that need multiple debridements. In the current outbreak, surgical debridement sessions ranged from one to seven. (More information about the pattern of the residual or recurrent disease have been provided in a separate chapter).

As a result, staging based on the anticipated route of spread has proved ineffective. Each author classified ROCM into several stages with each step being further subdivided [6–10]. The authors have provided evidence to support their classification, resulting in various classifications, and confusion among the readers.

Our recent experience with ROCM cases has shown us that different classifications lack practical utility in the management of ROCM. Because of the disease's perineural dissemination and angioinvasive nature, the staging system may not provide a clear management approach due to many paths of transmission and normal intervening areas.

There are many unanswered questions in the proposed route of spread on which the staging systems are based. The proposed route of spread does not explain why the retrobulbar space is primarily occupied with the disease with no mucor in the maxillary or ethmoid group of sinuses. It does not explain why there are acute orbital signs in the absence of any sinonasal manifestations. It fails to explain why there is facial numbness, pain and edema. This suggested route of mucor dissemination fails to explain why intensive debridement fails in some cases [1].

As a result in ROCM surgery, evidence-based decisions are more important than predetermined resections based on multiple classifications. In the patients of ROCM mapping was performed on various MRI sequences. The MRI parameters tested were consistent with what has been described in the chapter on imaging in ROCM. Pterygopalatine fossa (PPF) was found to be involved in the majority of our cases. This was consistent with the findings of Hosseni et al. who identified PPF to be the major reservoir of mucor in 100 percent of their

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cases [1]. It acts as an area for the hidden disease but has been ignored in most classifications. The involvement of PPF has its own implication that must be carefully examined. The involvement of the nasal mucosa in the form of blackish discoloration for example is considered an early sign of the disease, placing it in the lower stage. This black necrosis on the other hand does not necessarily indicate the disease inoculation at this location. It could be caused by thrombosis of the sphenopalatine artery in the pterygopalatine fossa culminating in terminal vessel necrosis [1].

These limited symptoms of nasal cavity and sinuse involvement could be the only symptoms of Isolated involvement of the pterygopalatine fossa [1]. It is possible that putting it in stage 1 and planning a limited resection may leave the residual disease that will likely progress. It highlights the importance of PPF debridement particularlly in situations involving orbits.

20.1 Prognostic Parameters in ROCM

Because ROCM is a non-classifiable angioinvasive disease, stage-based resection is not recommended. We can only have really useful prognostic parameters. These criteria are based on the areas that serve as a control point between a favourable and unfavourable prognosis in extracranial and Intracranial spread.

Extracranial Spread:

1: Orbital involvement (orbital apex spared).
2: Orbital apex involvement (one of the gateways to the intracranial space).
3: Sphenoid wing/clivus (one of the gateways to meningitis and chances of deep skull base infiltration). Extracranial areas other than those mentioned above have better prognosis provided pterygopalatine fossa is cleared wherever needed. Those areas mentioned here need to be handled meticulously to prevent spread of disease into the brain.

Intracranial spread:

1: Initial dural involvement.
2: Isolated intracranial abscess.
3: Disseminated intracranial spread.

In intracranial disseminated involvement has worst prognosis. This method of classifying the condition offers a number of advantages. It allows us to focus on the most important areas that are sometimes overlooked during primary surgery. PPF is a crucial structure that needed clearance in a majority of cases during the current outbreak. Therefore Denker's modified medial maxillectomy is a critical surgical step that every otorhinolaryngologist interested in the management of ROCM must learn [11]. A stepwise approach to PPF has been described in the chapter on the surgical management of ROCM; approach to PPF, pterygoid process, and infratemporal fossa.

The involvement of the orbital apex, sphenoid wing, and clivus marks the transition from good to guarded/bad prognosis. This is because direct invasion of the skull base and intracranial structures occurs in all of these sites. The surgeon is guided by the requirement to analyse these critical areas to perform essential radiological investigations, including various MRI sequences. In ROCM precise drilling enhances results significantly. The steps of drilling have been mentioned in the chapter on surgical management of ROCM: drilling beyond sinuses.

ROCM's recommended classifications do not work, and stage-based management may complicate the situation. The above-mentioned prognostic factors were developed based on the extensive experience with primary and revision ROCM cases during this pandemic.

The PPF and the bone of the sphenoid sinus floor were main sites left untreated during earlier procedures. During endoscopic debridement, the shenoid sinuses are frequently cleared, and at the end, a clean looking sinus cavity is left with no indication of the bone involvement.

The same patient's preoperative MRI revealed that there were subtle signs of bone erosion in this area prior to the first surgery as well.

However, the condition progressed and postoperative MRI revealed that the sphenoid wing was implicated. This became a priority region for us to search for on MRI in subsequent cases so that it could be cleared in the first sitting itself.

This prognostic classification highlights some crucial areas allowing us to look for them on various CT and MRI sequences to assist complete the debridement of necrotic areas. One may argue that there are other areas of the spread of disease to the intracranial structure; however, each one has a different dimension and has been described separately in various chapters on the area-by-area management of various case-based scenarios.

The involvement of sphenoid wing and orbital apex in extracranial spread indicates that these two locations should be cleared in the first sitting by a more experienced surgeon.

20.2 Why Doesn't a Fixed Classification Based on a Fixed spread Route Work?

The following are the reasons for this:

- Staging can lead to bias because it's a medical disease. It has angioinvasive spread and cannot be resected based on dissemination.
- It is not like malignancy which has a well defined path of spread. There are multiple pathways of spread in ROCM that are difficult to predict, so they cannot be classified.
- Consider disorders such as Juvenile nasopharyngeal angiofibroma. Its classification is useful because the disease progression follows a predictable pattern that guides the surgical planning [12]. For example, in stage 1 no Denker's medial maxillectomy is needed [11, 12], and no embolization is required (as it is Limited to the nasopharynx and nasal cavity). Stage 2, requires Denker's surgery (because the disease has spread to the pterygopalatine fossa), stage 3 requires embolization (because the disease has spread to the infratemporal fossa or orbital region with intracranial extradural involvement), and stage 4 is more extensive with Intracranial intradural spread with or without infiltration of the cavernous sinus, pituitary fossa, or optic chiasma [12, 13]. As a result neurosurgeon as well as an interventional radiologist are required. In contrast to mucormycosis angiofibroma always grows in the same direction.
- Mucor has a hematogenous spread; the outcome is determined by drug sensitivity and penetration rather than stage. Even third and fourth stage disorders will recover if drug sensitivity is present. The prognosis is excellent in cases where mucor is responsive to amphotericin B even in advanced disease. If mucor is resistant to amphotericin B, the prognosis is bad even in the early stages of disease. As a result classification-based surgical planning is not useful when it comes to selecting how to treat ROCM surgically.
- Each drug's minimal inhibitory concentration is different, which the treating surgeon is unaware of. There are 21 species of the mucor, but only three medicines are available: amphotericin, posaconazole, and isavuconazole. As described in the chapter on future directions in the management of ROCM, Amphotericin B is the most potent drug against mucormycetes, with MICs lower than 0.5 mg/L and [14]. Posaconazole is the second-line drug that has the highest activity among the azoles, with a MIC value of 0.5 mg/L [14]. However, drug resistance was noted in our cases, like reported by Drogari-Apiranthitou et al. [14].
- Drug resistance in mucormycosis leads to poor outcomes. Drogari-Apiranthitou et al. found resistance to amphotericin B in five Rhizopus species with minimum inhibitory concentrations of ≥2 mg/L (against the usual 0.5 mg/L). Resistance to posaconazole was observed in three *Rhizopus* species with minimum inhibitory concentrations ≥4 mg/L (against the usual0.5 mg/L), of which one was also resistant to amphotericin B [14]. In a series of 409 cases of ROCM, we found drug resistance in about 10% of cases.

20.3 Reason for Prognosis-Based Parameters and Ways to Improve Outcomes

- This disease can spread at anytime from Grade 1 to Grade 4.
- The disease does not always manifest in the nose and sinuses after inoculation. To begin with it can directly damage any structure, such as the eye, palate, and brain. It can strike any of these places any moment, and each patient's pattern will be unique.
- Although prognosis depends on the crucial areas affected; the species of the mucor involved and its sensitivity to amphotericin B are equally important. Therefore, based on current classifications, stage 1 may have a poorer prognosis than stage 2.
- An adequate clearance is required for better prognosis, and an expert surgeon is required to access difficult locations such as the floor of the sphenoid sinus, pterygoid process, and clivus. Because surgeons will be hesitant to clear this area for the fear of injuring the internal carotid artery, a full debridement may not be possible leading to poor prognosis.
- The difference in intracranial and extracranial spread is that the drug penetration is questionable in the brain due to the blood–brain barrier.

It is feasible to take specific aspects from each classification and evaluate their advantages and disadvantages in detail. However, that is not our goal; rather, we want to provide some best practises for dealing with this disease. Based on MRI findings, the surgeons are expected to be much more aggressive with this condition. For most of us this epidemic has been a completely new experience as well as an opportunity to work as a team. The mainstay of treatment remains MRI knowledge, thorough debridement and medication susceptibility and sensitivity.

References

1. Hosseini SMS, Borghei P. Rhinocerebral mucormycosis: pathways of spread. Eur Arch Otorhinolaryngol. 2005;262:932–8. https://doi.org/10.1007/s00405-005-0919-0.
2. Hussain S, Salahuddin N, Ahmad I, Salahudin I, Jooma R. Rhinocerebral invasive mycosis: occurrence in immunocompetent individuals. Eur J Radiol. 1995;20:151–5.
3. Pelton RW, Peterson EA, Patel BC, Davis K. Successful treatment of rhino-orbital mucormycosis without exenteration: the use of multiple treatment modalities. Ophthal Plast Reconstr Surg. 2001;17:62–6.
4. Onerci M, Gursel B, Hosal S, Gulekon N, Gokoz A. Rhinocerebral mucormycosis with extension to the cavernous sinus. A case report. Rhinology. 1991;29:321–4.
5. Raj P, Vella EJ, Bickerton RC. Successful treatment of rhinocerebral mucormycosis by a combination of aggressive surgical debridement and the use of systemic liposomal amphotericin B and local therapy with nebulized amphotericin—a case report. J Laryngol Otol. 1998;112:367–70.
6. Honavar SG. Code mucor: guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. Indian J Ophthalmol. 2021;69(6):1361–5. https://doi.org/10.4103/ijo.IJO_1165_21.
7. Naik MN, Rath S. The ROC staging system for COVID-related rhino-orbital-cerebral mucormycosis. Semin Ophthalmol. 2021; https://doi.org/10.1080/08820538.2021.1946094.
8. Shah K, Dave V, Bradoo R, Shinde C, Prathibha M. Orbital exenteration in rhino-orbito-cerebral mucormycosis: a prospective analytical study with scoring system. Indian J Otolaryngol Head Neck Surg. 2019;71(2):259–65. https://doi.org/10.1007/s12070-018-1293-8.
9. Talmi YP, Goldschmied-Reouven A, Bakon M, Barshack I, Wolf M, Horowitz Z, Berkowicz M, Keller N, Kronenberg J. Rhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol Head Neck Surg. 2002;127(1):22–31. https://doi.org/10.1067/mhn.2002.126587.
10. Wali U, Balkhair A, Al-Mujaini A. Cerebro-rhino orbital mucormycosis: an update. J Infect Public Health. 2012;5(2):116–26. https://doi.org/10.1016/j.jiph.2012.01.003.
11. Upadhyay S, Dolci RL, Buohliqah L, Prevedello DM, Otto BA, Carrau RL. Endoscopic endonasal anterior maxillotomy. Laryngoscope. 2015;125(12):2668–71. https://doi.org/10.1002/lary.25205.

12. Andrews JC, Fisch U, Valavanis A, Aeppli U, Makek MS. The surgical management of extensive nasopharyngeal angiofibromas with the infratemporal fossa approach. Laryngoscope. 1989;99(04):429–37.
13. Safadi A, Schreiber A, Fliss DM, Nicolai P. Juvenile angiofibroma: current management strategies. J Neurol Surg B Skull Base. 2018;79(1):21–30. https://doi.org/10.1055/s-0037-1615810.
14. Drogari-Apiranthitou M, Mantopoulou FD, Skiada A, Kanioura L, Grammatikou M, Vrioni G, Mitroussia-Ziouva A, Tsakris A, Petrikkos G. In vitro antifungal susceptibility of filamentous fungi causing rare infections: synergy testing of amphotericin B, posaconazole and anidulafungin in pairs. J Antimicrob Chemother. 2012;67(8):1937–40. https://doi.org/10.1093/jac/dks137.