Pre-Operative Administration of Amphotericin B in Orbital Mucormycosis Management

Authors: Russel T. Wagner, Jacopo Berardinelli, Sammy Khalili, Neil S. Mundi, Amin B. Kassam, Stephen J. Winkler
Intent Medical Group, Endeavor Health Neurosciences Institute, Northwest Community Hospital

Introduction

- Mucormycosis is a rare, aggressive fungal infection caused by Mucorales fungi; commonly found in soil, decaying matter, and food [1,2].
- Primarily affects immunocompromised individuals, especially those with poorly controlled diabetes (DM) or diabetic ketoacidosis (DKA) [3].
- Rhino-orbito-cerebral mucormycosis (ROCM) often begins with facial pain, progressing to fever, headache, and altered mental status [3-5].
- Rapid intervention is critical for Rhino-orbito-cerebral mucormycosis (ROCM) ; standard care includes systemic amphotericin B and aggressive surgical debridement, often with orbital exenteration [2-10].
- In India, ROCM cases surged during COVID due to corticosteroid use and uncontrolled diabetes, creating a need for alternative treatments like transcutaneous retrobulbar injection of amphotericin B (TRAMB) [2,7,11].
- Studies show TRAMB preserves vision, halts disease progression, and offers an alternative to orbital exenteration [2,7-12].
- This case examines TRAMB's role in stabilizing ROCM pre-operatively, supporting less invasive surgical interventions and preserving ocular function.

Discussion

- ROCM traditionally requires aggressive debridement, often with orbital exenteration [2,6-10].
- Studies, including Sharifi et al. (2022), show TRAMB as an effective adjunct, achieving a 95% globe salvage rate with minimal side effects [2].
- Liposomal Amphotericin B enhances tissue delivery through lipid vesicles, allowing controlled release. However, its efficacy in necrotic areas is still limited due to poor blood supply [19,20].
- During the patient's reluctance to proceed with surgery, TRAMB was employed to stabilize fungal growth, improve symptoms, and prevent further orbital complications, successfully stabilizing vision and reducing orbital fungal load, though it did not affect intracranial progression (Figure 3).
- Sinus irrigation are not effective because necrosis limits drug penetration in the already poor vascularized sinuses [15-17].
- Contrarily, orbital injections are effective due to the eye's rich blood supply and orbital fat, supporting better drug distribution.
- TRAMB serves as a valuable adjunct to debridement for stabilizing orbital disease and avoiding the need for exenteration, even with intracranial progression.

Case Presentation

- A 29-year-old male with a history of DM presented with DKA, altered mental status, and dyspnea.
- CT imaging showed extensive mucosal thickening in the right ethmoid, frontal, and sphenoid sinuses, with dehiscence through the orbital wall and cribriform plate, extending into the right frontal lobe—indicative of invasive fungal sinusitis.
- Initial treatment included intravenous vancomycin, piperacillin/tazobactam, and amphotericin B.
- A bedside biopsy confirmed mucormycosis was confirmed intraoperatively.
- Upon arrival, the patient exhibited right proptosis, V2 hypoesthesia, motility deficits, and vision of 20/40 in the right eye.

Day	Dose	Vision (right Eye)	Pupils (right eye)	EOM	Treatment Notes
1	-	20/40	no APD	-2 abduction limitation, other movement intact	Initial consideration for intraorbital amphotericin B injections for preventative measures. Grade 1 orbital involvement, was likely grade 2 prior to debulking. Close monitoring.
1	-	20/30	no APD	-1 abduction limitation, otherwise full	Vision is stable in right eye, does note some double vision when looking right.
2	Dose 1	20/100	+ APD	-3 abduction, -4 infra abduction	Vision worsened drastically, new APD OD. Injection of 1 ML of 3.5 mg lipo ampho B performed.
3	Dose 2	20/100	+ APD	-3 abduction, -4 infra abduction	Vision stable, APD stable. Injection performed.
4	Dose 3	20/40	+ APD	-	Vision greatly improved. Injection performed.
6	Dose 4	20/50 -	2+ APD (improved reaction)	abduction deficit stable	Vision still stable. Injection performed.
9	-	20/50 +	2+ APD (improved reaction)	-2 abduction improved	Continued improvement in vision and motility. Decided to hold injections for now but monitor closely.
10	Dose 5	20/40-	1+ APD (improved reaction)	-2 abduction improved	Another injection performed. Vision and motility have had continued improvement.
17	-	-	-	-	Performed surgery: bicoronal craniotomy, right optic nerve decompression, right orbitotomy, intracranial resection of necrotic tissue. Intraop noted signifcantly less extension of necrotic tissue in the orbit, minimal orbital debridement required.

Figure 1: Table of the Treatment Course of 1 mL of 3.5 mg liposomal amphotericin B injections performed in the supramedial orbit. Documents clinical improvements of vision from the injections.

Course of Treatment

- An expanded endonasal approach (EEA) was used to debride the fungal infection in the anterior skull base.
- In the days following, the patient's vision deteriorated to 20/100, with the development of an afferent pupillary defect (APD), indicating optic nerve compromise.
- MRI scans revealed residual disease in the extraconal and intraconal orbit with infection extending along the right anterior skull base.
- The patient received TRAMB therapy (1 mL of 3.5 mg liposomal amphotericin B injections).
- Visual acuity improved to 20/40 by the third injection, and APD and motility deficits became less pronounced. However, MRI scans showed continued intracranial disease progression despite orbital improvements.
- After five TRAMB injections, the patient consented to further surgery, which was performed one week later (Figure 1).
- Surgical procedures included bicoronal craniotomy, right optic nerve decompression, right orbitotomy, intracranial resection of necrotic tissue, and titanium mesh orbital wall reconstruction.
- Intraoperatively, minimal orbital debridement was needed due to reduced necrotic tissue and fungal load in the orbit (Figure 2).
- Post-operatively, the patient showed gradual vision improvement, stabilization of APD, and decreased proptosis as confirmed by follow-up imaging (Figure 3). Continued intravenous amphotericin B was administered for infection control.

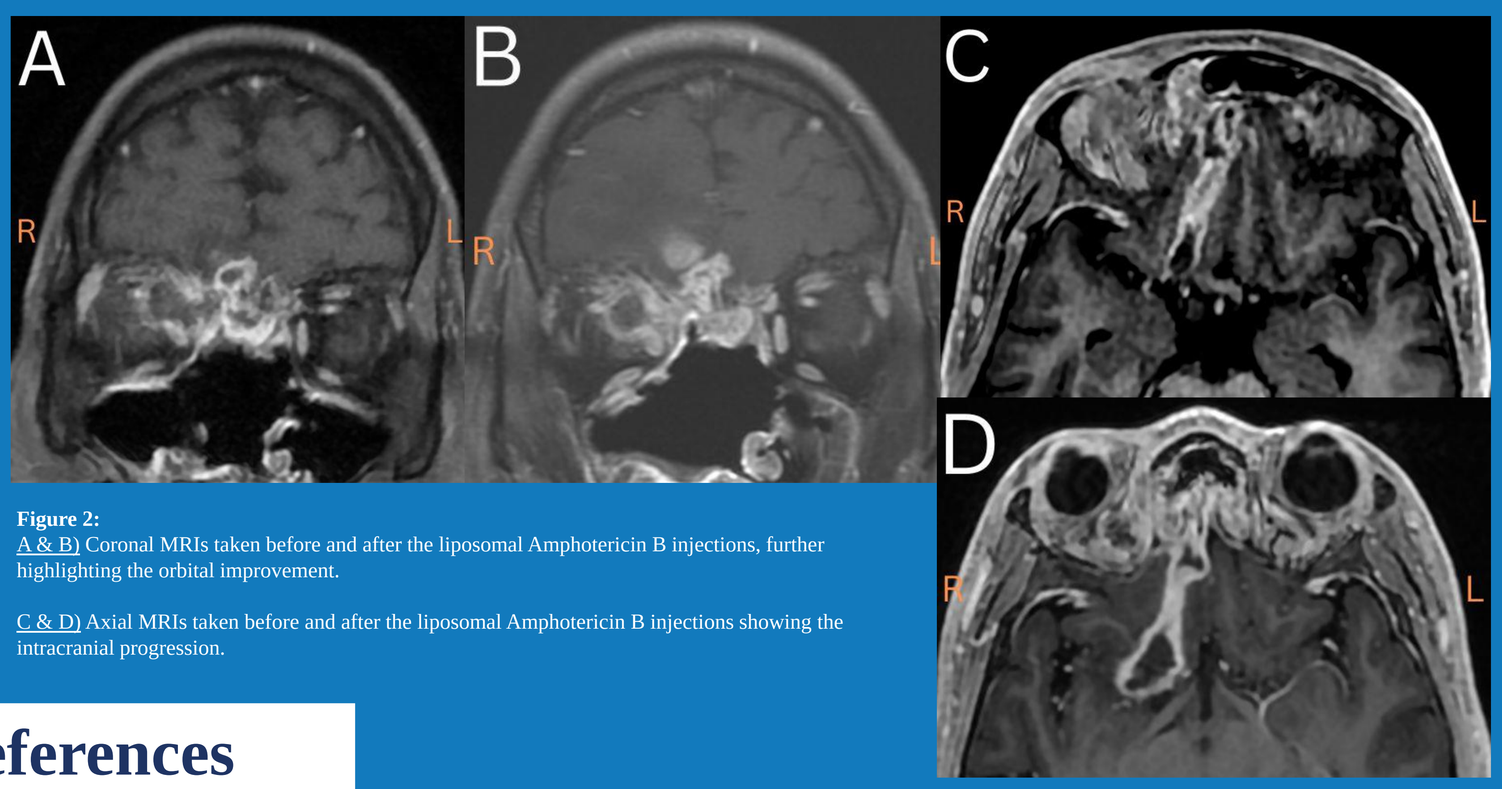

Figure 2:
A & B) Coronal MRIs taken before and after the liposomal Amphotericin B injections, further highlighting the orbital improvement.

C & D) Axial MRIs taken before and after the liposomal Amphotericin B injections showing the intracranial progression.

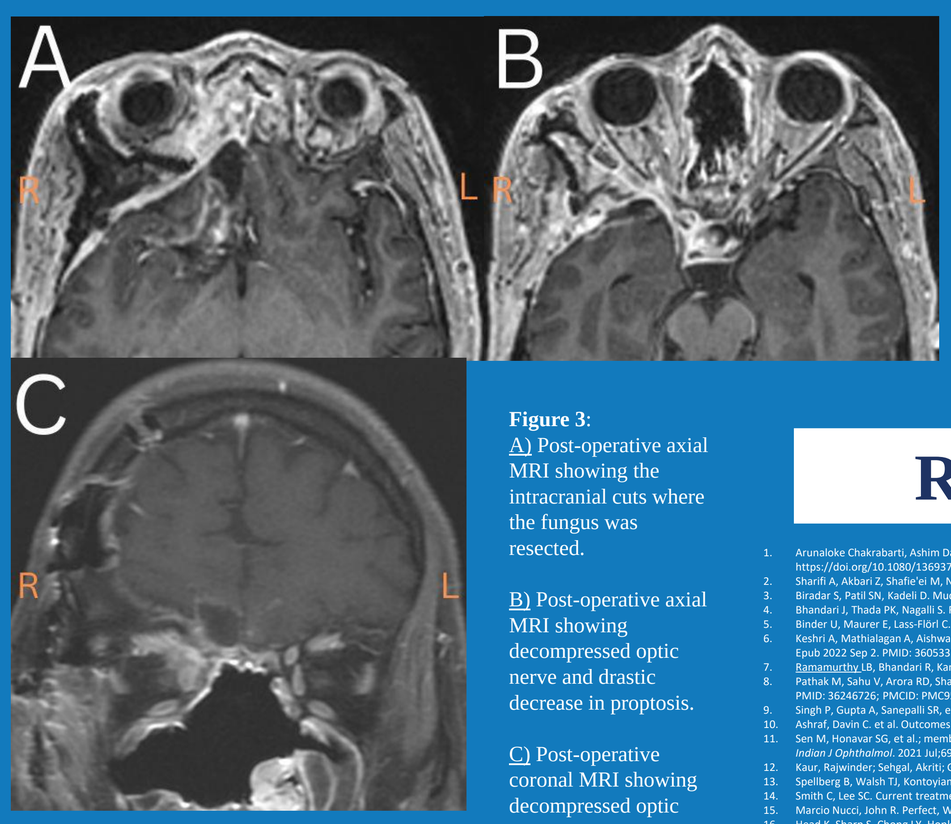

Figure 3:
A) Post-operative axial MRI showing the intracranial cuts where the fungus was resected.

B) Post-operative axial MRI showing decompressed optic nerve and drastic decrease in proptosis.

C) Post-operative coronal MRI showing decompressed optic nerve.

References

1. Arunaloke Chakrabarti, Ashim Das, Jharna Mandal, M. R. Shivaprakash, Varghese K. George, Bansidhar Tarai, Pooja Rao, Naresh Panda, Subhash C. Verma, Vinay Sakhuja, The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus, *Medical Mycology*, Volume 44, Issue 4, June 2006, Pages 335–342, https://doi.org/10.1080/13693780500464930
2. Sharifi A, Akbari Z, Shafie'ei M, Nasiri N, Sharifi M, Shafiei M, Zand A. Retrobulbar Injection of Amphotericin B in Patients With COVID-19 Associated Orbital Mucormycosis: A Systematic Review. *Ophthalmic Plast Reconstr Surg*. 2022 Sep-Oct 01;38(5):425-432. doi: 10.1097/IOP.0000000000002256. Epub 2022 Aug 8. PMID: 35943425; PMCID: PMC9451608.
3. Biradar S, Patil SN, Kadeli D. Mucormycosis in a Diabetic Ketoacidosis Patient: A Case Report. *J Clin Diagn Res*. 2016 May;10(5):OD09-10. doi: 10.7860/JCDR/2016/16241.7734. Epub 2016 May 1. PMID: 27437278; PMCID: PMC4948454.
4. Bhandari J, Thada PK, Nagalli S. Rhinocerebral Mucormycosis. [Updated 2023 Sep 15]. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing*; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526068/
5. Binder U, Maurer E, Lass-Flörl C. Mucormycosis–from the pathogens to the disease. *Clin Microbiol Infect*. 2014 Jun;20 Suppl 6:60-6. doi: 10.1111/1469-0691.12566. Epub 2014 Feb 24. PMID: 24476149.
6. Keshri A, Mathialagan A, Aishwarya A, Ravisankar, Bhuskute G, Kanaujia V, Singh AK, Singh RK, Dhiman RK, Agarwal R. Is mucormycosis the end? A comprehensive management of orbit in COVID associated rhino-orbital-cerebral mucormycosis: preserving the salvageable. *Eur Arch Otorhinolaryngol*. 2023 Feb;280(2):819-827. doi: 10.1007/s00405-022-07620-3. Epub 2022 Sep 2. PMID: 36053359; PMCID: PMC9438883.
7. Ramamurthy LB, Bhandari R, Kanakpur S, Thejaswini P. Outcome of transcutaneous retrobulbar injection of liposomal amphotericin B in post-COVID-19 rhino-orbito-cerebral mucormycosis: Our experience. *Indian J Ophthalmol*. 2022 Mar;70(3):1019-1024. doi: 10.4103/ijo.IJO_2356_21. PMID: 35225564; PMCID: PMC9114606.
8. Pathak M, Sahu V, Arora RD, Shambharkar MM, Naveen P, Pati SK, Nagarkar NM. Retrobulbar Amphotericin B Injection in Curbing the Progression of COVID Associated Rhino-orbital Cerebral Mucormycosis: A Retrospective Case Series. *Indian J Otolaryngol Head Neck Surg*. 2022 Oct;74(Suppl 2):3352-3358. doi: 10.1007/s12070-022-03199-7. Epub 2022 Oct 9. PMID: 36246726; PMCID: PMC9547996.
9. Singh P, Gupta A, Sanepalli SR, et al. Transcutaneous retrobulbar amphotericin-B (TRAMB) injection in orbital mucormycosis. *BMJ Case Reports CP*. 2022;15:e246307.
10. Ashraf, Davin C. et al. Outcomes of a Modified Treatment Ladder Algorithm Using Retrobulbar Amphotericin B for Invasive Fungal Rhino-Orbital Sinusitis. *American Journal of Ophthalmology*. Volume 237, 299 – 309.
11. Sen M, Honavar SG, et al.; members of the Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC) Study Group. 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*. 2021 Jul;69(7):1670-1692. doi: 10.4103/ijo.IJO_1565_21. PMID: 34156034; PMCID: PMC8374756.
12. Kaur, Rajwinder; Sehgal, Akriti; Gupta, Priyanka; Budhiraja, Grace; Sharma, Vandana; Aggarwal, Anupriya. To determine the role of transcutaneous retrobulbar amphotericin B in COVID-19-related rhino-orbital-cerebral mucormycosis. *Oman Journal of Ophthalmology* 17(2):p 198-204, May–Aug 2024. | DOI: 10.4103/ojo.ojo_19_23
13. Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J Jr, Ibrahim AS. Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis. 2009 Jun 15;48(12):1743-51. doi: 10.1086/599105. PMID: 19435437; PMCID: PMC2809216.
14. Smith C, Lee SC. Current treatments against mucormycosis and future directions. PLoS Pathog. 2022 Oct 13;18(10):e1010858. doi: 10.1371/journal.ppat.1010858. PMID: 36227854; PMCID: PMC9560507.
15. Marcio Nucci, John R. Perfect, When Primary Antifungal Therapy Fails, *Clinical Infectious Diseases*, Volume 46, Issue 9, 1 May 2008, Pages 1426–1433, https://doi.org/10.1086/587101
16. Head K, Sharp S, Chong LY, Hopkins C, Philpott C. Topical and systemic antifungal therapy for chronic rhinosinusitis. *Cochrane Database of Systematic Reviews 2018*, Issue 9. Art. No.: CD012453. DOI: 10.1002/14651858.CD012453.pub2.
17. Ebbens, F. A., Scadding, G. K., Badia, L., Hellings, P. W., Jorissen, M., Mullol, J., Cardesin, A., Bachert, C., van Zele, T. P. J., Dijkgraaf, M. G. W., Lund, V., & Fokkens, W. J. (2006). Amphotericin B nasal lavages: Not a solution for patients with chronic rhinosinusitis. *Journal of Allergy and Clinical Immunology, 118*(5), 1149–1156. https://doi.org/10.1016/j.jaci.2006.08.043.
18. Soler ZM, Schlosser RJ. The role of fungi in diseases of the nose and sinuses. *Am J Rhinol Allergy*. 2012 Sep-Oct;26(5):351-8. doi: 10.2500/ajra.2012.26.3807. PMID: 23168148; PMCID: PMC3904040.
19. Andreas H Groll, Bart J A Rijnders, Thomas J Walsh, Jill Adler-Moore, Russell E Lewis, Roger J M Brüggemann, Clinical Pharmacokinetics, Pharmacodynamics, Safety and Efficacy of Liposomal Amphotericin B, *Clinical Infectious Diseases*, Volume 68, Issue Supplement_4, 15 May 2019, Pages S260–S274, https://doi.org/10.1093/cid/ciz076
20. Thomas J Walsh, Russell E Lewis, Jill Adler-Moore, Pharmacology of Liposomal Amphotericin B: An Introduction to Preclinical and Clinical Advances for Treatment of Life-threatening Invasive Fungal Infections, *Clinical Infectious Diseases*, Volume 68, Issue Supplement_4, 15 May 2019, Pages S241–S243, https://doi.org/10.1093/cid/ciz091