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Combination endoscopic surgical debridement and transcutaneous retrobulbar amphotericin B for acute rhino-orbital-cerebral aspergillosis

Kevin X. Zhang [a], David Gu [a], Christopher Puchi [b], Kevin C. Welch [b], Gary S. Lissner [a,*]

[a] Department of Ophthalmology, Northwestern University Feinberg School of Medicine, Chicago, IL, 60611, USA
[b] Department of Otolaryngology – Head and Neck Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, 60611, USA

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ABSTRACT

Purpose: To report a case of acute rhino-orbital-cerebral aspergillosis with aggressive intracranial and orbital extension co-managed medically and surgically with endoscopic sinus debridement and multiple retrobulbar injections of amphotericin B.

Observations: A 70-year-old male patient presented via external transfer with headaches and left ophthalmoplegia concerning for severe complicated sinusitis with intracranial and left orbital spread. His history is notable for a simultaneous heart-kidney transplant three years prior on chronic immunosuppression. Ophthalmologic examination revealed complete ophthalmoplegia in the left eye with no light perception concerning for a left orbital apex syndrome. The patient was taken to the operating room twice for endoscopic sinus debridement and three separate retrobulbar injections of amphotericin B. Fungal cultures from surgical specimens grew isolated *Aspergillus fumigatus*. Patient's symptoms gradually improved and repeat MRI demonstrated resolution of pansinusitis, sparing left eye exenteration.

Conclusions and importance: Multidisciplinary management of invasive fungal rhinosinusitis in the setting of profound immunosuppression poses a significant challenge. While surgical debridement remains the cornerstone approach, the achievable reduction in disease burden may be augmented by targeted retrobulbar antimicrobials.

1. Introduction

The rising prevalence of immunosuppression in the global population has led to an increase in aggressive opportunistic fungal infections. In particular, the recent era of COVID-19 has compounded the incidence of invasive fungal rhinosinusitis, which are often caused by species of *Aspergillus, Fusarium,* and *Mucorales*.[1–4] The most common underlying predisposing conditions to invasive fungal rhinosinusitis include diabetes mellitus, advanced HIV, hematologic malignancy, solid organ transplantation, systemic corticosteroid therapy, chemotherapy, and hematopoietic stem cell transplantation.[5–8] Given the proximity of the eye and brain to the sinuses, intraorbital and intracranial spread are common, and portends poorer visual and survival outcomes respectively.[9] The angioinvasive nature of the causative fungal species results in widespread tissue infarction, severely limiting systemic antifungal penetration and exacerbating necrosis.

Management of invasive fungal rhinosinusitis is therefore challenging, with no current consensus guidelines. The mainstay of therapy is debridement with endoscopic sinus surgery (ESS), which has been shown to be an independent positive predictor of survival in multiple studies.[10–12] In practice however, ESS by itself is often insufficient to substantially reduce disease burden, and in cases where the fungal rhinosinusitis is aggressive, reoperation is frequently indicated.[13] Additionally, extension of fungal infection into the periorbita has been associated with a significant increase in mortality and limits the benefit of ESS.[14] Several case series have investigated retrobulbar injections of antifungal agents (often amphotericin B) as an adjunct to ESS, with dual aims of improving survival and sparing the patient from the morbidity of a disfiguring exenteration.[15,16] Here we report a particularly aggressive case of acute invasive rhino-orbital-cerebral aspergillosis successfully managed with a combination of ESS and retrobulbar amphotericin B injections administered intra- and post-operatively, ultimately sparing the patient from exenteration.

* Corresponding author. Department of Ophthalmology, Feinberg School of Medicine at Northwestern University, 645 N Michigan Ave, Suite 440, Chicago, IL, 60611, USA.
E-mail address: gary.lissner@nm.org (G.S. Lissner).

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2. Case report

A 70-year-old male patient presented as a transfer from an outside hospital with severe headaches, nausea/vomiting, total left ophthalmoplegia, and visual acuities of 20/40 in the right eye and no light perception in the left eye. He had initially presented with a two-week history of progressive headache, decreased oral intake, and weight loss. Outside neuroimaging was reviewed and revealed extensive complicated sinusitis with left intraorbital and left hemicranial extension, along with leptomeningeal and pachymeningeal enhancement along the left frontal lobe. His history was notable for a simultaneous orthotopic heart and deceased donor kidney transplant three years prior, with a chronic immunosuppressive regimen of monthly belatacept infusions and daily prednisone 5 mg. He also had stage IV chronic kidney disease, type 2 diabetes mellitus, hypertension, prior COVID-19 infection complicated by acute respiratory distress syndrome (ARDS) necessitating hospitalization, and paroxysmal atrial fibrillation on apixaban. The decision to transfer was made on the grounds of the patient likely needing urgent surgical intervention.

Upon arrival, repeat CT of the sinuses demonstrated bony destruction of the cribriform plate and lamina papyracea of the medial left orbital wall (Fig. 1A and B). MRI confirmed extensive sinus opacification and osteomyelitis of the cribriform plate (Fig. 1C and D), along with abnormal FLAIR hyperintensity representing possible phlegmon

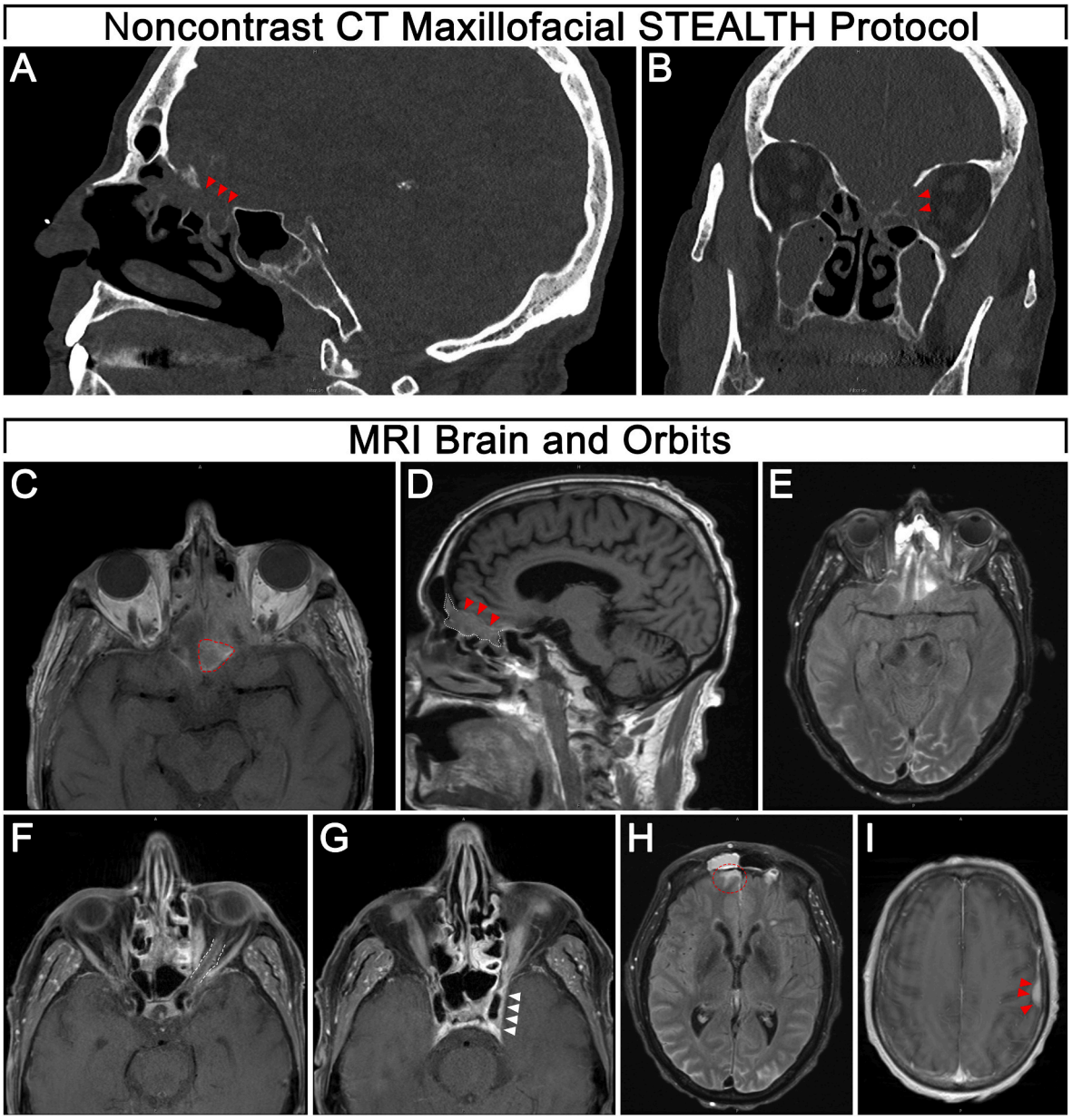

Fig. 1. Neuroimaging studies with CT of the face, orbits and paranasal sinuses demonstrating (A) bony erosion of the cribriform plate (red arrows) and (B) soft tissue extension from the left ethmoid complex into the medial left orbit through a defect in the lamina papyracea (red arrows). (C) T1-weighted transverse MRI showing extensive opacification of the paranasal sinuses and irregular posterior enhancement (dashed red line) and (D) extension with bony destruction of the cribriform plate (red arrows). (E) Diffuse FLAIR hyperintensity throughout paranasal sinuses contiguous with medial left orbit and involvement of left orbital apex. T1 fat-saturated images showing (F) patchy enhancement along left optic nerve sheath (dashed white lines) and (G) localized lateral asymmetric thickening of the left cavernous sinus (white arrows). (H) Right inferomedial frontal lobe enhancement on FLAIR (dashed red circle). (I) Asymmetric dural enhancement with focal lenticular shaped area of collection (red arrows) that could represent dural phlegmon. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

extending from the left ethmoid complex into the left superomedial orbit and apex (Fig. 1E). Additional MRI of the orbits demonstrated patchy enhancement of the left optic nerve sheath (Fig. 1F) and lateral asymmetric thickening of the enhancing left cavernous sinus (Fig. 1G) consistent with spread of inflammation. Additional extranasal findings included FLAIR hyperintensity of the inferomedial right frontal lobe (Fig. 1H) and a focal lenticular left dural enhancement temporally (Fig. 1I). Ophthalmic examination at this time revealed an uncorrected visual acuity of 20/70 OD and no light perception OS, with a fixed left pupil and complete limitations in all positions of gaze OS consistent with orbital apex syndrome (Fig. 2). Intraocular pressures were 15 and 18 mmHg for the right and left eye respectively. The anterior exam was notable for mild proptosis but was otherwise unremarkable, with non-injected conjunctivae. The posterior exam was initially deferred due to urgent surgery. Empiric therapy was continued with IV liposomal amphotericin B, ceftazidime, metronidazole, and vancomycin. The patient's next belatacept infusion was held but his prednisone was continued.

Given the extent of pansinusitis with abscess formation and destruction of the left skull base with evidence of intracranial spread, wide debridement via endoscopic sinus surgery (ESS) and left orbital decompression was jointly performed by otolaryngology and neurosurgery. Multiple pockets of purulence were encountered along the skull base. These were surgically addressed and grew isolated *Aspergillus fumigatus* on fungal cultures. The periorbita around the apex was noted to be necrotic and purulent in appearance and was carefully debrided, followed by bony decompression via partial removal of the turbinates and soft-tissue decompression of the orbit back to the anterior orbital apex. The operation terminated without complication, but the patient continued to note headaches as well as a new-onset periorbital burning sensation in both eyes. Repeat neuroimaging on hospital day 3 found residual airspace opacification and left skull base enhancement (Fig. 3A), along with multiple fluid pockets concerning for empyemas extending through the left orbital apex (Fig. 3B). Enhancing soft tissue encasement of left medial orbital wall structures (Fig. 3C) and a subdural empyema along the left anterior falx (Fig. 3D) also supported the diagnosis of persistent rhino-orbital-cerebral sinusitis with continued intracranial and intraorbital involvement. The patient was taken back to the operating room for repeat sinus debridement on hospital day 4. Pathologic examination of debrided periorbital tissue revealed tissue-invasive fungal hyphae consistent with *Aspergillus*. Given the extensive and aggressive reinfection noted after the initial ESS, the decision was made to perform a retrobulbar injection of liposomal amphotericin B (AmBisome, 3.5 mg/mL, 1 cc volume) intraoperatively.

The patient was given two additional retrobulbar injections (AmBisome, 3.5 mg/mL, 1 cc volume) of liposomal amphotericin B on hospital days 5 and 9. He endorsed improvements in headache and periorbital burning symptoms on hospital day 5 with complete resolution on hospital day 10. Final visual acuities were 20/50 in the right eye and no light perception in the left eye. Discussion commenced with his original transplant team and the decision was made to transition him from belatacept to tacrolimus while inpatient and to continue his daily 5 mg of prednisone. His preexisting pancytopenia worsened on hospital day 10, necessitating transfusions, and further retrobulbar injections were withheld. His ophthalmic exam remained stable and unchanged for the remainder of his admission, with no development of new ocular symptoms or neurologic deficits. He continued to improve on systemic antimicrobials with repeat MRI on hospital day 13 demonstrating resolution of his pansinusitis and postsurgical soft tissue changes along the left medial orbital wall (Fig. 4A and B). Stable to improved FLAIR hyperintensity was also noted along the left orbital apex and the left inferomedial frontal lobe (Fig. 4C and D). The patient was eventually discharged on hospital day 22 in stable condition with systemic antimicrobial therapy and close follow-up care near his home.

3. Discussion

In this report, we described a case of aggressive acute rhino-orbital-cerebral aspergillosis manifesting in a 70-year-old immunosuppressed patient. In addition to his documented leukopenia, his other risk factors included recent severe COVID-19 infection and a history of diabetes mellitus, although the latter shares a stronger association with fungal rhinosinusitis caused by *mucor* species. Prior comparative studies largely support no statistical difference in overall morbidity-mortality rate between invasive fungal rhinosinusitis caused by *aspergillus* or *mucor* species with Valera et al.[11] reporting a 46.2% (6/13) and 58.3% (7/12) mortality rate with *mucor* and *aspergillus* associated rhinosinusitis respectively. This shows good agreement with the mortality rate reported by Kasapoglu et al.[17] of 61.5% (8/13) and 38.5% (5/13) from *mucor* and *aspergillus* associated invasive rhinosinusitis respectively. A larger comprehensive meta-analysis of 807 patients diagnosed with acute invasive fungal sinusitis revealed that 49.6% (264/532) had

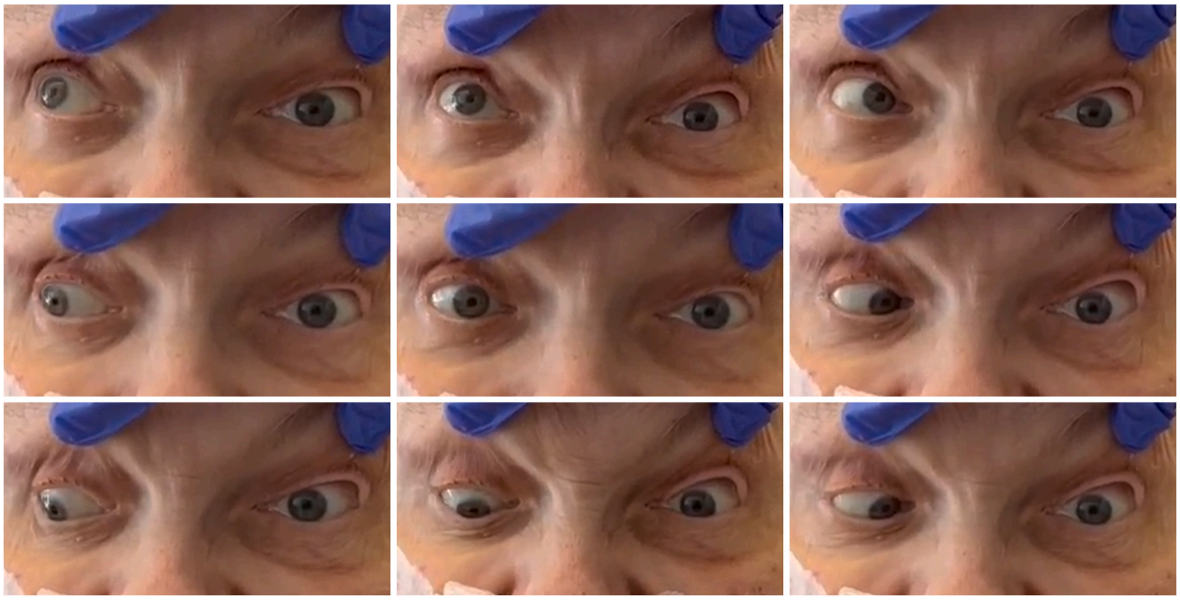

Fig. 2. Photographs of nine gaze positions of the patient at initial presentation.

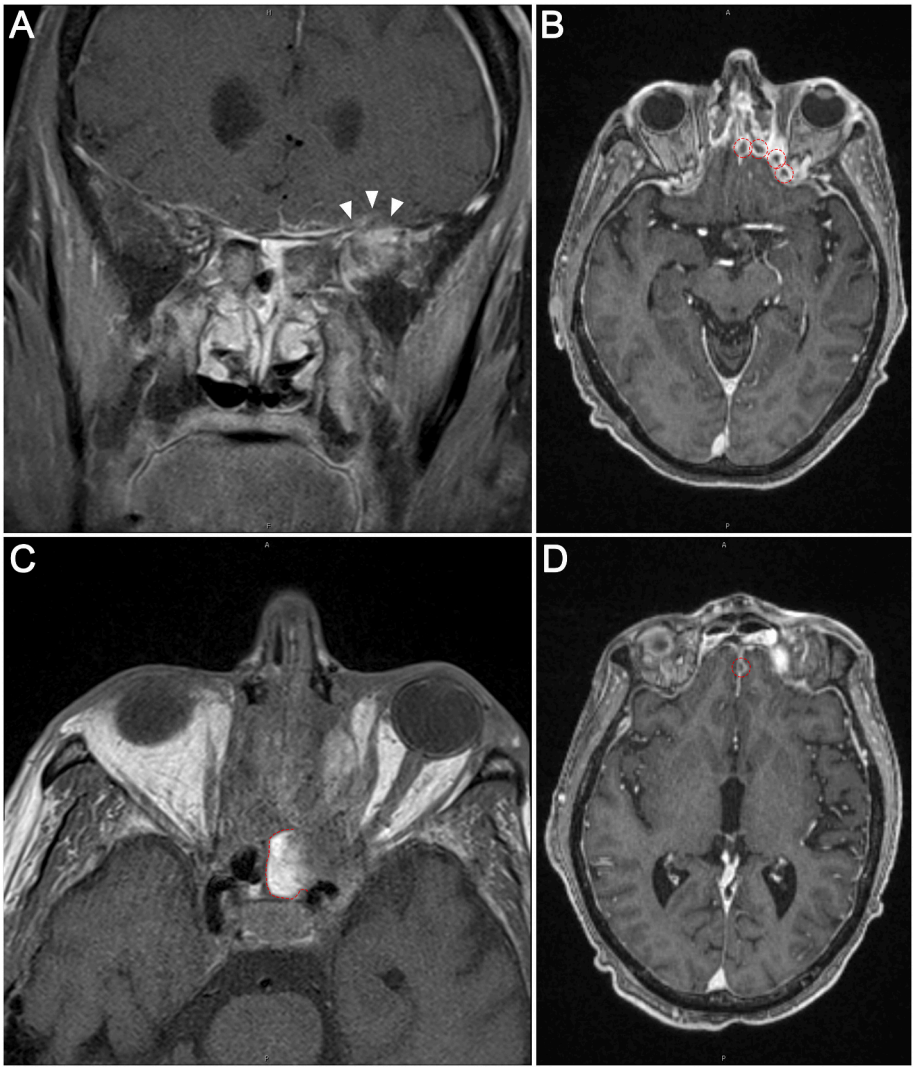

Fig. 3. T1-weighted MRI images following the first round of endoscopic sinus surgery (ESS) with left orbital decompression. (A) Postsurgical changes difficult to appreciate given persistent extensive disease and pansinusitis with diffuse T1 hyperintensity throughout indicating residual soft tissue filling of ethmoidal air cell complex and enhancement of left anterior skull base (white arrows). (B) Multiple pockets of pus consistent with additional empyemas (dashed red circles) are visualized along left paranasal sinuses extending to the orbital apex. (C) Abnormal enhancement of left medial rectus and superior oblique muscles, along with posterior fullness and enhancement beyond left orbital apex (dashed red line). (D) Small subdural empyema is visualized along the left anterior falx (dashed red circle). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

orbital extension of disease and 21.2% (105/496) had intracranial extension, with the latter being significantly associated with mortality ($P = 0.0005$, OR 2.77).[10] Ultimately, of all 807 patients in the analysis, 406 died, for an overall mortality of 50.3%.

Endoscopic surgical debridement via ESS still remains the mainstay of therapy for acute invasive fungal rhinosinusitis, and derives its benefit primarily from decreasing total fungal burden. However, extension of the infection into the orbit often limits the utility of ESS due to challenging access and limited debridement without severely compromising delicate orbital structures in the apex. Traditionally, extensive orbital involvement beyond the capabilities of surgical extirpation often necessitated exenteration, with studies later showing that it did not improve overall survival.[10,18] More recently, retrobulbar injection of antifungals have been studied as a globe-sparing alternative to exenteration.[19] Several published cases report the successful management of acute invasive fungal rhinosinusitis from *aspergillus* and *mucor* species by retrobulbar amphotericin B.[20–22] Ashraf et al. showed that incorporating retrobulbar amphotericin into the treatment algorithm for invasive fungal rhinosinusitis lowered the risk of exenteration without an increase in the risk of mortality.[23] However, only *mucor*-associated invasive rhinosinusitis feature larger systematic and prospective studies. In a systematic review of 647 cases with retrobulbar injections of amphotericin B for COVID-19 associated rhino-orbito-cerebral infection with mucormycosis as the sole causative pathogen, Sharifi et al. reported a globe salvage rate of 95%.[24] A prospective study of 82 eyes with COVID-19 associated rhino-orbito-cerebral mucormycosis also found statistically significant symptomatic improvement in 72% (59/82) of patients, with the most improvement found in mild and moderate cases, while severe cases benefitted less and often necessitated repeat surgery or eventual exenteration.[25] The reported side effects were rarely serious and often self-limited, and mostly included transient symptoms such as injection site swelling, ocular motility restriction, and mild orbital inflammation, of which our patient did not experience.[24] While further studies are required to define firm guidelines and indications for retrobulbar amphotericin B, our case and others illustrate effective resolution of disease and sparing of orbital exenteration when used in conjunction with surgical debridement.

Another point of discussion in our case involves the decision to continue the patient's immunosuppressive regimen in the setting of active invasive fungal infection. Preferred practice patterns in infectious disease management advocate for the restoration of immune function by prompt withdrawal of immunosuppressive medications. However, heart transplant recipients typically require more aggressive immunosuppression than do recipients of other solid organ transplants, and our patient was receiving monthly belatacept infusions as part of a renoprotective calcineurin inhibitor-sparing regimen given past kidney transplantation. Given the concern for allosensitization if total cessation of immunosuppression was enacted, the decision was made to delay the patient's belatacept infusion while continuing his systemic prednisone. This decision was also made in part due to the patient receiving two

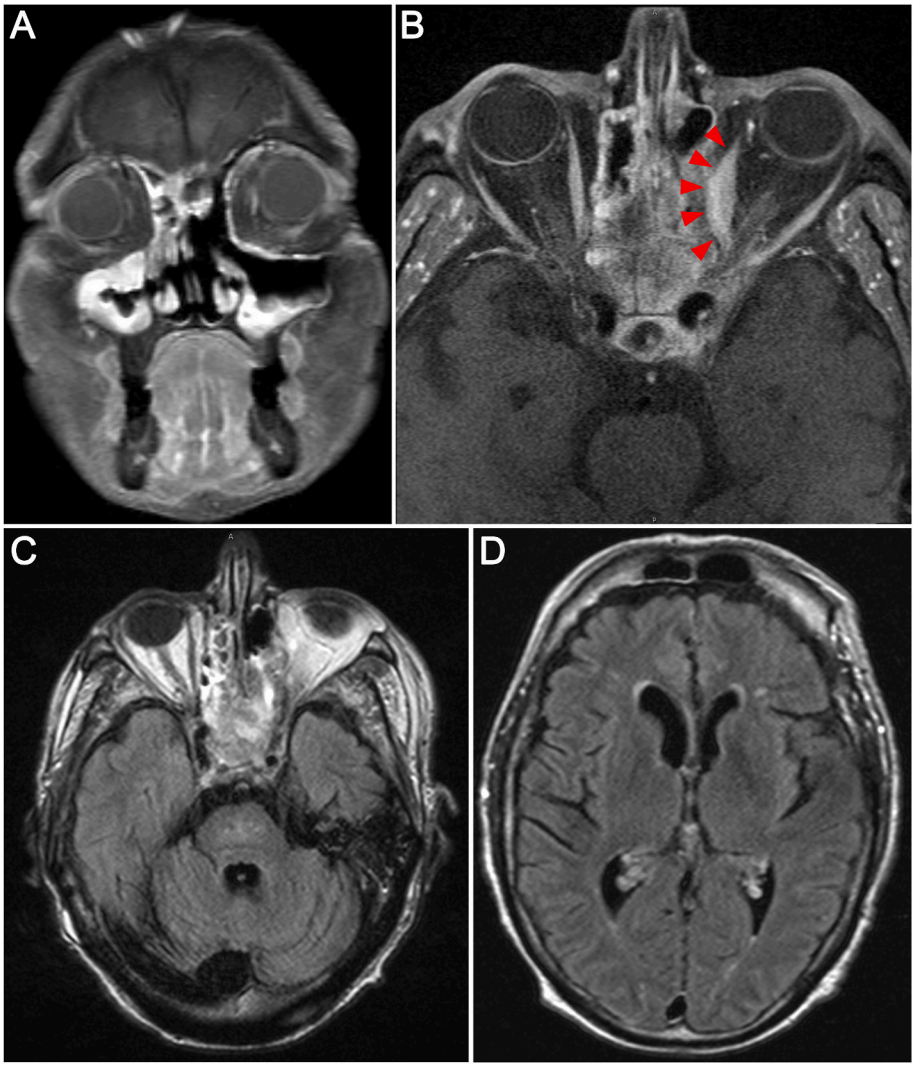

Fig. 4. MRI brain and orbits following two rounds of orbital decompression surgery and three retrobulbar injections of amphotericin B. (A) T1-weighted images demonstrating extensive postsurgical changes including bilateral ethmoidectomy. (B) Persistent enhancement of soft tissue contiguous with the left medial rectus (red arrows). (C) FLAIR images demonstrating stable to slightly decreased hyperintensity in the left orbital apex. (D) Resolved abnormal FLAIR signal through the cortical sulci and inferomedial frontal lobes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

separate local interventions for his rhinosinusitis, namely, the combination of endoscopic debridement and retrobulbar antifungals.

In conclusion, retrobulbar injection of amphotericin B for invasive fungal rhinosinusitis is a relatively safe alternative to exenteration in the management of infectious extension into the orbit. The complications are often mild, and are often outweighed by the benefit of potential globe salvage. However, additional studies are needed to quantify the efficacy in improving vision and to establish objective indications for its use in complex cases where surgical debridement alone may be insufficient.

Patient consent

Consent to publish this case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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