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Chronic invasive fungal sinusitis with orbital and olfactory cleft involvement secondary to indolent mucormycosis

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ABSTRACT

Purpose: Chronic invasive fungal sinusitis secondary to indolent mucormycosis is a rare clinical entity, and the ideal management is controversial. A case of indolent mucormycosis successfully managed with conservative debridement and retrobulbar amphotericin B is herein reported.

Observations: A 42-year-old man with diabetes mellitus and kidney transplant presented with chronic invasive fungal sinusitis with left orbital involvement from indolent mucormycosis. The patient was treated with aggressive systemic antifungal therapy, left retrobulbar injection of liposomal amphotericin B, reduction in immunosuppression, and conservative surgical debridement. Although the left olfactory cleft was involved, the cribriform plate was not resected due to risk of seeding the intracranial space. Given mild orbital involvement, no orbital debridement was performed and the patient had resolution of his orbital findings with systemic and retrobulbar amphotericin B. The patient had clinical and radiographic stability at 6-month follow-up.

Conclusions: Conservative resection with subsequent long-term antifungal treatment can be a successful regimen in indolent mucormycosis. Retrobulbar amphotericin B may be a prudent orbit-sparing adjuvant therapy in indolent mucormycosis.

1. Introduction

Indolent mucormycosis is an unusual cause of invasive fungal sinusitis (IFS), characterized by a chronic presentation and less aggressive behavior than fulminant mucormycosis.[1] Unlike other causes of IFS, indolent mucormycosis appears to be less strongly associated with an immunosuppressed state, and has been reported in both immunocompetent[1,2] and immunocompromised[1,3] patients. Indolent mucormycosis may also present with nonspecific symptoms or with less extensive disease. The smoldering behavior of indolent mucormycosis may allow for less aggressive management strategies in comparison to strategies used in fulminant disease.[1] Current data regarding management of indolent mucormycosis is limited due to this entity's rarity. Management of orbital involvement in IFS is also controversial due to limited comparative data amongst treatment strategies[4]; moreover, given the rarity of indolent mucormycosis, there is especially limited outcome data for its orbital involvement.

We herein report a case of indolent mucormycosis with skull base invasion and orbital involvement, which provides additional insight regarding management in this rare entity. Due to the chronic disease course, clinical stability, and potential morbidity of removing the involved skull base (resultant defect and risk of seeding the intracranial space), the patient was offered an option of observation following conservative surgical debridement. Lasting clinical stability was maintained with continued systemic antifungal therapy. Effective utilization of transcutaneous retrobulbar injection of amphotericin B (TRAMB) for orbital disease in indolent mucormycosis is also herein illustrated. TRAMB has previously been reported in fulminant mucormycosis[5–7] and

Abbreviations: IFS, Invasive Fungal Sinusitis; TRAMB, transcutaneous retrobulbar injection of amphotericin B.

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aspergillus.[4] This case report is adherent to the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Per institutional guidelines, Institutional Review Board approval was not obtained as the single case report was classified as non-research.

2. Case report

A 42-year-old man with type 2 diabetes mellitus and kidney transplant presented with 2.5 months of progressive left facial pain/pressure and rhinorrhea, and two days of painful left eye swelling. Two weeks prior to presentation the patient had undergone computed tomographic (CT) images of the sinuses (Fig. 1A and C) demonstrating primarily left paranasal sinus disease. Two courses of oral antibiotics (azithromycin followed by levofloxacin) had been prescribed without symptomatic improvement. The patient's kidney transplantation occurred 4 months prior to presentation and maintenance immunosuppression utilized tacrolimus and mycophenolate mofetil. His diabetes was poorly controlled, with recent home blood sugar measurements over 300; his hemoglobin A1c two months earlier was 8.2%.

Nasal endoscopy at presentation revealed left-sided purulent rhinorrhea and diffuse edema of nasal cavity mucosa without obvious necrosis. There was left periorbital edema involving the upper lid, mild left proptosis, and mild left conjunctival chemosis(Fig. 2A). Trigeminal sensation was bilaterally intact. Visual acuity was 20/30 in the right eye, 20/25 in the left eye. Extraocular motility examination revealed mild left eye supraduction and abduction deficits with symptomatic diplopia. Pupillary exam and intraocular pressure were normal.

A repeat CT scan of the sinuses demonstrated interval progression of primarily left maxillary, ethmoid, and sphenoid sinus disease with potentially dehiscent cribriform plate (Fig. 1B and D) and mild left orbital post-septal fat stranding. Given the patient's poorly controlled diabetes, immunosuppression, and development of orbital disease there was concern for IFS. The history of smoldering sinus symptoms over multiple months suggested an atypical chronic process. The patient underwent emergent surgical biopsy. Intraoperatively, the left nasal mucosa was diffusely severely edematous. The left middle turbinate appeared purplish with yellow necrotic-appearing material extending inferiorly. Frozen sections from the left middle turbinate and nasal cavity revealed fungal elements and necrosis invading arterial vessels, indicating IFS; final pathologic sections from this biopsy and subsequent debridement would ultimately demonstrate mucormycosis. Empiric intravenous liposomal amphotericin B was initiated, aggressive glycemic control was pursued, and tacrolimus and mycophenolate were discontinued in favor of weaker immunosuppression utilizing cyclosporine and prednisone.

The following day, further debridement was planned. During preoperative discussions with the patient, it was decided that debridement would be terminated if there was obvious orbital or skull base involvement, as disease clearance would incur significantly greater morbidity warranting additional discussion. The patient underwent endoscopic sinus surgery with extensive surgical debridement of the involved paranasal sinuses guided by intraoperative frozen sections with middle and superior turbinate resection. Of note, the mucosa along the lamina papyracea was uninvolved. Necrotic tissue was cleared with the exception of the left posterior olfactory cleft, medial to the superior turbinate; debridement was terminated at this point. The patient had mild orbital involvement and no clinical evidence of compromised visual acuity; thus orbital debridement and exenteration were not pursued. Instead, retrobulbar injection of 1.75mL of 1.5mg/mL liposomal amphotericin B was administered to the left orbit.

MRI was obtained (Fig. 3) to better demarcate disease extent. The imaging showed dural enhancement adjacent to the left cribriform plate correlating with the left olfactory cleft mucosal findings intraoperatively. Given the patient's remarkable stability and absence of concerning neurologic features, the dural enhancement was felt to more likely represent reactive inflammation from the adjacent skull base involvement rather than frank fungal meningeal disease. Based on the chronic disease course, reassuring clinical stability, and potential morbidity of further definitive debridement (most significantly the risk of seeding the intracranial space) the patient was offered an option of

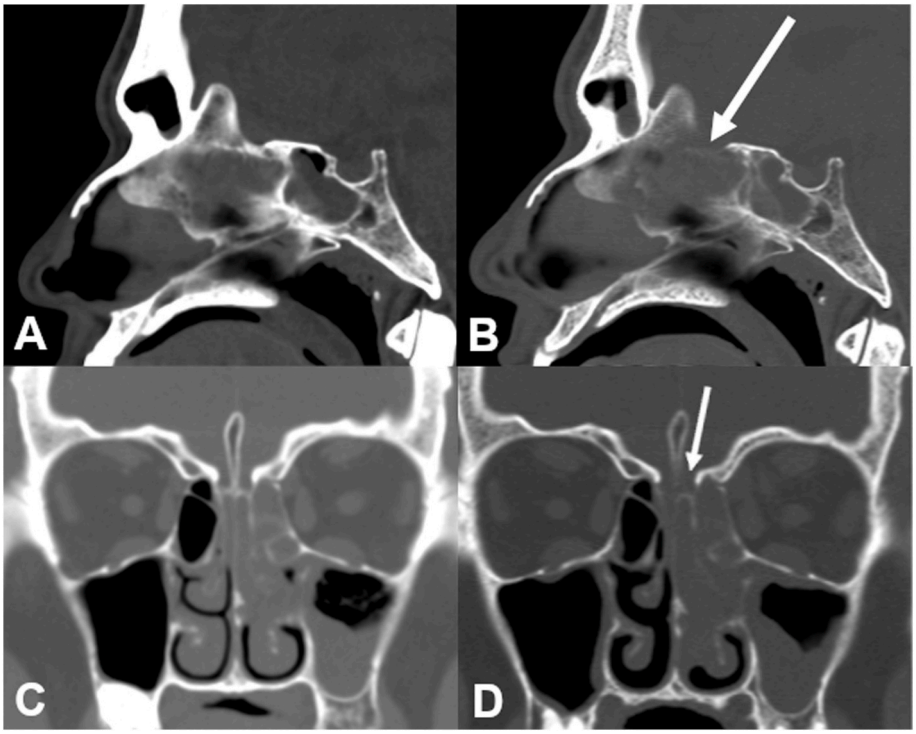

Fig. 1. CT imaging prior to diagnosis (A,C) and at time of diagnosis (B,D) showing unilateral soft tissue thickening within the left nasal cavity with new bone erosion at the anterior skull base on the follow-up imaging (white arrows).

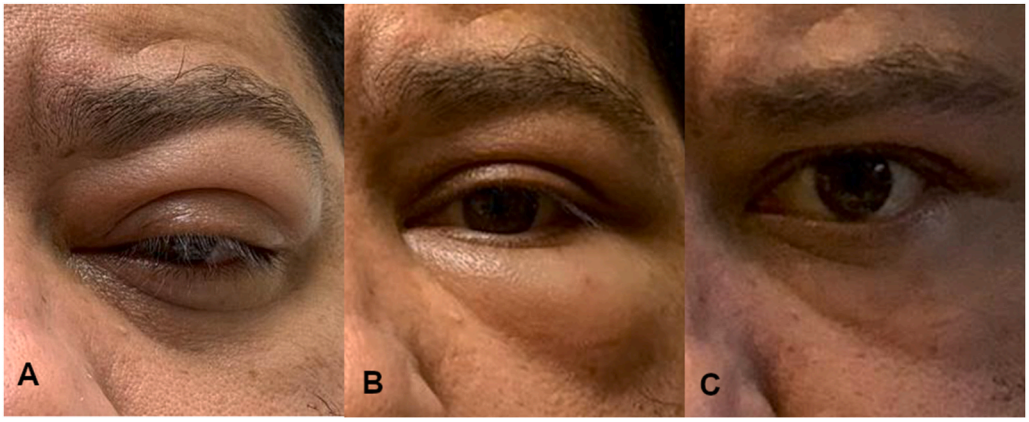

Fig. 2. A. Periorbital edema including left upper eyelid secondary to left orbital involvement by invasive fungal rhinosinusitis, prior to initiation of therapy. **B.** Two days after left transcutaneous retrobulbar injection of amphotericin B, the patient had marked improvement in his upper eyelid edema (as well as associated orbital signs), but developed a fluctuant, watery lower eyelid edema – qualitatively different from earlier edema, and likely representing local inflammatory tissue reaction to retrobulbar amphotericin B. **C.** Five days after retrobulbar amphotericin B, the watery lower eyelid edema had resolved.

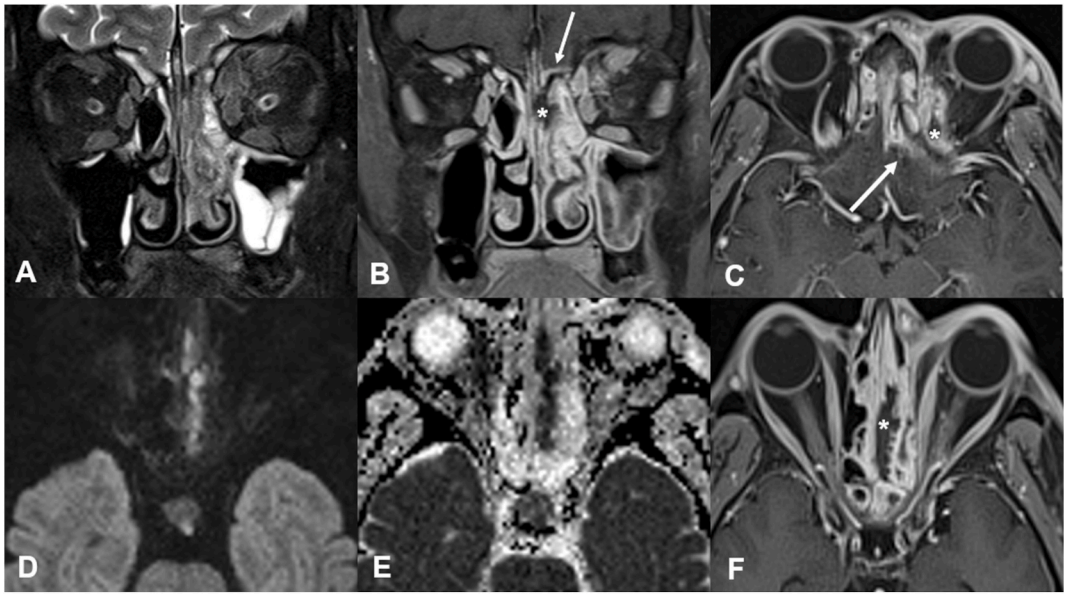

Fig. 3. MRI with contrast at time of diagnosis demonstrating T2 hypointense soft tissue thickening within the nasal cavity extending to the superomedial orbit (A,B,C F). The soft tissue thickening demonstrates "lack of enhancement" (asterisk in B,C &F) and diffusion restriction (D&E). There is accompanying dural enhancement (arrows in B&C).

medical management alone with clinical and radiographic monitoring versus definitive debridement combined with medical therapy. Following extensive discussion, the patient declined further surgical debridement, electing for medical management and monitoring.

Three days after initiating systemic antifungal therapy (two days after TRAMB), orbital signs and upper eyelid edema completely resolved but the patient developed a watery lower eyelid edema (Fig. 2B), likely representing local tissue inflammatory response to the retrobulbar amphotericin B. The lower eyelid edema resolved by day 6 of therapy (5 days after TRAMB) (Fig. 2C). The patient remained systemically stable throughout the hospitalization and transitioned to oral isovucazonium, which would be continued indefinitely upon discharge. Close multidisciplinary outpatient follow-up was coordinated.

At 6-month follow-up, the patient remained clinically stable, with mildly reduced sense of smell, but no recurrence of concerning symptoms or orbital findings. Interestingly, on nasal endoscopy, the left olfactory cleft mucosa had also normalized grossly. MRI (Fig. 4) showed marked interval improvement in sinus disease, resolution of dural enhancement, and no reoccurrence of orbital inflammation.

3. Discussion

The patient's prolonged symptoms and pathology are consistent with chronic IFS secondary to indolent mucormycosis. The chronicity of indolent mucormycosis is variably reported in the literature as symptom presence ranging from weeks to months,[8] but an accepted definition of indolent mucormycosis is pathologically confirmed sinus mucormycosis with symptom presence for at least 1 month.[1] A recent review noted only 23 published cases between 1964 and 2014,[8] which illustrates the rarity of indolent mucormycosis.

IFS is classically managed with systemic antifungal therapy and aggressive surgical debridement; however, the management of indolent mucormycosis is more controversial. Indolent mucormycosis has been successfully managed with systemic antifungal monotherapy,[2] surgical debridement alone,[9] and combined medical and surgical therapy.[1] In the current case, complete debridement of the affected tissues was deferred due to the chronic presentation (suggesting less aggressive infection behavior), the patient's clinical stability, and potential high morbidity of definitive surgical debridement. Given clinical and pathologic confirmation of cribriform involvement, a complete debridement would have required a cribriform dropout procedure. The procedure posed

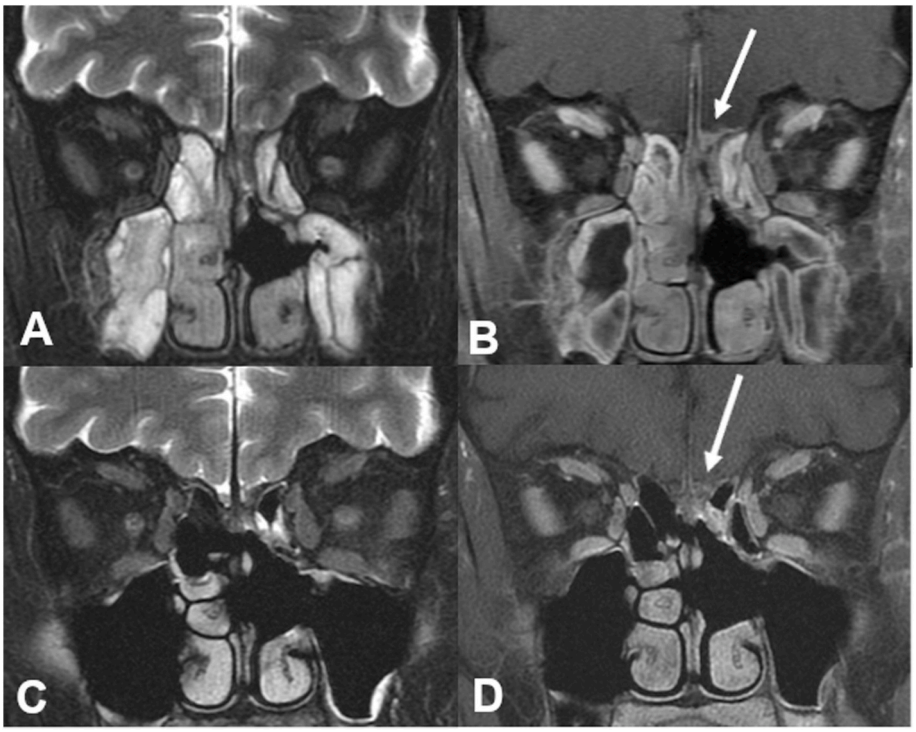

Fig. 4. MRI from follow-up at one month (A,B) and five months (C,D). Images show progressive resolution of T2 hypointense soft tissue thickening (A, C). Post-contrast images (B, D) show resolution of dural enhancement (arrows).

significant risk of removal of a physical barrier to spread and possible contamination of the intracranial space with consequent fungal meningitis. Alternatively, the benefit of further debridement would be reduction of known disease burden. Thus, further definitive debridement was weighed against continued medical management alone. The patient ultimately elected to forego additional surgery and definite cribriform plate involvement was not addressed surgically, but the patient had lasting clinical stability and continued radiographic improvement in his disease on reduced immunosuppression with continued systemic antifungal therapy. Dooley et al. reported a similar case of chronic IFS from indolent mucormycosis with cavernous sinus involvement in which family refused additional recommended surgical debridement, yet clinical stability was maintained at 4 years.[10] These cases of incomplete surgical debridement challenge the classic teaching in management of IFS, that complete removal of diseased tissue is mandatory. Moreover, the cases illustrate that in some IFS patients such as those with indolent mucormycosis, less aggressive approaches may be appropriate. It is important to note that the current case's dural enhancement on MRI was likely reactive inflammation rather than meningeal involvement by the fungus; in cases of true meningeal or cerebral involvement by mucormycosis, a conservative approach is unlikely to be feasible. In addition, a more conservative approach may increase reliance on long-term systemic antifungal therapy, and thus the consequences of prolonged courses of systemic antifungal therapy including medication toxicity must also be considered in the clinical decision-making process.

Given that immunosuppression is a risk factor for the development of IFS, reversal or reduction in immune compromise is an important component of the multimodal approach to these patients.[9,11] In the current case, the patient's immunosuppression was unable to be completely discontinued due to concern for precipitating a fulminant failure or rejection of his transplant. However, transition to a less potent immunosuppressive regimen was feasible. Aggressive control of diabetic derangement is also essential, not only for immune implications but also insofar as ketoacidosis may be conducive to the fungal organism.[11]

Management of orbital involvement in IFS has shifted toward less aggressive strategies. Exenteration (removal of all orbital contents) has increasingly fallen out of favor as an initial intervention for orbital involvement since it does not improve mortality.[4,12] Alternate strategies of increasing interest include conservative orbital debridement with irrigation of amphotericin B, and TRAMB.[13] TRAMB offers advantages of globe sparing, possible injection at the bedside, and ability for repeating injections based on response.[4,13] Presently, there is relatively limited comparative data regarding these techniques.[4] However, a recent large retrospective study by Ashraf et al. examined outcomes for treatment strategies before and after TRAMB was incorporated into an institutional stepladder treatment algorithm for IFS. The study found that following incorporation of TRAMB into the algorithm, rates of exenteration were lower and mortality was similar.[14]

An optimal management strategy for orbital involvement in indolent mucormycosis has similarly not been determined due to the rarity of this clinical entity. Orbital exenteration has been utilized in indolent mucormycosis and may be useful when there is progressive orbital disease in spite of sinus debridement and/or systemic antifungal therapy.[1] Long-term clinical stability with orbit preservation has been achieved with combined sinus debridement and systemic antifungal therapy[3] and antifungal therapy alone.[2]

TRAMB may be especially well suited to indolent mucormycosis. The smoldering behavior of indolent mucormycosis lessens urgency for debriding tissue, including of the orbit. Moreover, given successful treatment of indolent mucormycosis with systemic antifungal monotherapy,[2] adjuvant bedside treatment with TRAMB can be easily added. Multiple reports have described successful use of TRAMB in fulminant mucormycosis.[5–7] In the current case, TRAMB resulted in rapid resolution of the patient's clinical orbital signs after a single injection, and he had long-term clinical resolution of orbital involvement. Orbital involvement by mucormycosis in the current case was relatively mild, which may have been especially amenable to medical therapy. It must be noted that the precise contribution of TRAMB cannot be extricated from that of the systemic antifungal therapy nor the extensive adjacent sinus debridement. Post-injection, the patient developed self-limited lower eyelid watery edema. Local reaction after TRAMB has been

previously reported and may be more severe for amphotericin B with deoxycholate than for the liposomal form.[6]

Imaging plays an important role in the evaluation and management of patients with IFS. CT has superior resolution of characteristic erosions in bone, while MRI provides better and earlier visualization of soft tissue changes. Because soft tissue findings in IFS precede radiographically appreciable bony changes, MRI is the modality of choice in establishing diagnosis of IFS. Moreover, the superior resolution of soft tissue also makes MRI preferrable to CT for demarcating the severity and extent of disease. In particular, MRI may be of utility in distinguishing between devitalized tissue from angioinvasion versus surrounding edema.[15,16] In the current case, CT was initially utilized in the evaluation of the patient due to this imaging modality being more readily available, and it demonstrated characteristic findings including bony erosions to support the diagnosis of IFS (Fig. 1). MRI was subsequently utilized to determine the extent of the disease (Fig. 3) and in longitudinal surveillance (Fig. 4).

Further studies of indolent mucormycosis with a larger number of patients, varying orbital disease severity, and different co-occurring sinonasal disease management strategies may help clarify the role for TRAMB in indolent mucormycosis. While its use as an adjuvant therapy seems promising, TRAMB might not offer significant benefit beyond systemic antifungal therapy and/or sinonasal debridement, and the risks of retrobulbar injection strategy (including optic nerve direct injury, retrobulbar hemorrhage, orbital compartment syndrome) may outweigh theoretical benefit. Although data is preliminary, TRAMB may be a prudent strategy for indolent mucormycosis.

4. Conclusions

Conservative surgical debridement may allow lasting clinical stability in chronic IFS from indolent mucormycosis. TRAMB, a non-invasive globe-sparing intervention, may be well suited to the smoldering course of indolent mucormycosis.

Patient consent

This case report was a retrospective chart review and all unique patient identifiers were eliminated; accordingly patient consent was neither required nor obtained. The external photographs of the patient have been adequately cropped so that the patient is not identifiable from these images.

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Authorship

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

Declaration of competing interest

The authors have no relevant financial disclosures.

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