Orbital compartment syndrome following retrobulbar injection of amphotericin B for invasive fungal disease

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ARTICLE INFO

Article history:
Received 24 November 2015
Received in revised form
12 January 2016
Accepted 14 January 2016
Available online 10 February 2016

Keywords:
Aspergillus
Amphotericin B
Compartment syndrome
Retrobulbar

ABSTRACT

Purpose: To describe a complication of retrobulbar amphotericin B injections in the treatment of invasive rhino-orbital aspergillosis.
Observations: 27 year-old renal transplant recipient presented with a two-week history of headache, binocular diplopia and proptosis of the left eye. Endonasal biopsy on hospital day 3 confirmed the diagnosis of rhino-orbital invasive Aspergillus fumigatus involving the left orbital apex. In addition to systemic antifungal treatment and cessation of immunosuppression, retrobulbar amphotericin B injections (3.5 mg/1 ml) combined with endoscopic local debridement were initiated when the patient developed progressive visual loss. Retrobulbar injections were administered on hospital days 8, 10, 14, 17, and 20. Endoscopic debridement occurred on hospital days 10 and 16. After the fifth retrobulbar amphotericin B injection, the patient developed acute orbital compartment syndrome with intraocular pressures ranging from 47 to 86 mmHg and vision declined to 20/200, requiring emergent lateral canthotomy and superior and inferior cantholysis. Close observation without further intervention resulted in return of vision to 20/20 and normalization of intraocular pressure.

Conclusion and importance: Retrobulbar amphotericin B in combination with local debridement may be considered an alternative to exenteration for invasive aspergillosis secondary to reversible immunosuppression. To the authors’ knowledge, orbital compartment syndrome secondary to retrobulbar amphotericin B administration has not previously been reported. Patients should be counseled on the risk of severe local inflammation due to amphotericin B. More research is needed to establish the most appropriate dosing, frequency, and duration of retrobulbar amphotericin B injections in the treatment of life-threatening Aspergillus infections.

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1. Introduction

Considerable debate surrounds the management of invasive sino-orbital fungal infections: when orbital tissue is involved certain authors advocate exenteration, where as others report positive outcomes following globe-sparing procedures [1–3]. Although rarely published, retrobulbar amphotericin B injection has been described as a viable globe-sparing technique in the management of orbital aspergillosis [3–6]. Herein, the authors report a case of an immunocompromised patient who received repeat amphotericin B retrobulbar injections for sino-orbital aspergillosis. Despite a successful long-term outcome, retrobulbar amphotericin B induced an acute orbital compartment syndrome, requiring urgent intervention. To the authors’ knowledge, this is the first documented case of orbital compartment syndrome subsequent to retrobulbar amphotericin B.

The Review Board at our institution ruled that approval was not required for this study. All patient information was handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and research adhered to the tenets of the Declaration of Helsinki. Additionally patient consent for publication was obtained per University of California San Francisco guidelines.

2. Case report

A 27 year-old African American male was admitted for severe left-sided headache and diplopia. The patient’s past medical history
included cadaveric renal transplant for end-stage focal segmental glomerulosclerosis, for which he was on prednisone, mycophenolate mofetil and belatacept.

Ophthalmologic examination revealed visual acuity (VA) of 20/20 in both eyes, left upper lid ptosis and severe generalized restriction of extraocular movements in the left eye (Fig. 1A). Pupillary reflexes, intraocular pressure (IOP), corneal sensation, slit lamp exam and fundus exam including optic disks were normal in both eyes. Although rigid nasal endoscopy was normal at the time of admission, Brain MRI with contrast revealed focal soft tissue enhancement at the left orbital apex with a low diffusion coefficient (Fig. 1B). Presuming a diagnosis of invasive fungal infection, immunosuppression was discontinued and the patient was empirically placed on intravenous antifungal therapy.

On hospital day 2 the patient underwent left maxillary antrostomy, total ethmoidectomy, concha bullosa resection and sphenoidotomy with necrotic tissue and hyphae removed from the sphenoid sinus. Pathology specimens from the procedure were consistent with *Aspergillus* and therapy was narrowed to intravenous Voriconazole and Caspofungin.

VA remained stable at 20/25 OU, however the patient gradually developed increased proptosis of the left eye with an associated afferent pupillary defect. Repeat MRI revealed disease progression at the orbital apex. Out of reluctance to undergo aggressive orbital debridement in a patient with normal VA, it was elected on day 8 to proceed with a retrobulbar injection of amphotericin B for the left eye. One milliliter (ml) of 3 mg/ml (mg/ml) amphotericin B with antecedent retrobulbar injection of 1:1 2% lidocaine, 0.5% Marcaine was performed without incident. On hospital day 10, the patient underwent endoscopic orbital decompression with resection of necrotic material at the orbital apex and repeat retrobulbar injection of amphotericin B (1 ml of 3.5 mg/ml) while under general anesthesia. The patient’s clinical course continued to wax and wane with VA deteriorating to 20/70 at its nadir.

Retrobulbar amphotericin B (1 ml of 3.5 mg/ml) injection was repeated on days 14, 17, and 20. On the morning of day 21, the patient developed rapid-onset proptosis of the left eye (Fig. 2A).

Bedside examination of the left eye documented VA 20/200, complete external ophthalmoplegia and intraocular pressure as measured by Tonopen (Medtronic, Minneapolis, MN) consistently at or above 47 mmHg. Acute orbital compartment syndrome was diagnosed and canthotomy with cantholysis of the upper and lower eyelids was performed. Intraocular pressure immediately fell to 31 mmHg. Urgent MRI revealed diffuse edema of retrobulbar fat inducing proptosis and optic nerve stretch, and the imaging did not support extension of the infection (Fig. 2B). Twenty-four hours following canthotomy/cantholysis VA returned to 20/25 in the left eye.

Given significant improvement in proptosis and stability of vision, the patient was discharged on hospital day 23 with intravenous systemic antifungals administered by home nursing. Two weeks after discharge, aside from limitation in depression OS, the patient’s ophthalmologic exam was within normal limits in both eyes. Two years following discharge, although VA and ophthalmic exam were unchanged (Fig. 3), the patient’s cadaveric transplant eventually failed as a result of discontinuation of immunosuppression and he is currently on dialysis awaiting repeat renal transplantation.

3. Discussion

No evidence-based consensus exists for the management of invasive sino-orbital fungal infections. Although nearly all patients receive intravenous antifungals plus endoscopic sinus debridement, the treatment of orbital disease remains controversial and can range from globe-sparing to radical exenteration [1-3]. To date, the most frequently reported globe-sparing therapy has been local irrigation of amphotericin B via a catheter or drain, with or without conservative orbital debridement [7,8].

To our knowledge, only four previously published cases of sino-orbital aspergillosis have employed retrobulbar injections of amphotericin B [3-6]. In these reports, the quantity of amphotericin B administered ranged from 1 to 5.25 mg every 2-7 days. In all four cases, retrobulbar injections were without complication and VA was maintained or improved. However, in two cases patients eventually succumbed to systemic infection [4,5].
Amphotericin B, a polyene antibiotic, binds to cell-membrane sterols, causing leakage of intracellular electrolytes and derangement of metabolic activity [9]. Given that both yeast and human cell-membranes contain sterols, the medication is toxic to both pathogen and host. Although systemic side effects such as fever, bone marrow suppression and renal toxicity are well documented, amphotericin B is also locally cytotoxic [9,10]. In vitro mouse osteoblasts and fibroblasts studies have shown that exposure to amphotericin B concentrations beyond 100 μg/ml for greater than 1 h causes widespread cell death [10]. Intra-articular amphotericin B injection can cause synovitis and, in rare instances, subcutaneous amphotericin B injection has induced acute soft-tissue edema [11–13].

It is not clear why our patient developed acute orbital compartment syndrome subsequent to his fifth retrobulbar injection. Each injected vial was prepared in the exact same fashion and was buffered, as required by the medication package insert, with sterile water and 5% dextrose [14]. Intravenous amphotericin B has an initial plasma half-life of 24 h, followed by an elimination half-life of 15 days [14]. Our patient had normal creatinine clearance at the time of the orbital compartment syndrome. Additionally, review of his other medications did not suggest any cross reactivity to amphotericin B or that would affect amphotericin B metabolism.

The rate of amphotericin B elimination from the normal human orbit is unknown. Because aspergillosis causes ischemic vasculitis, it is likely that arterial perfusion and venous return within our patient’s orbit were grossly diminished. We hypothesize that with each successive injection of amphotericin B, intraorbital concentration increased until a massively cytotoxic quantity was reached, possibly precipitating the compartment syndrome.

4. Conclusion

Retrobulbar amphotericin B injection is an infrequently reported globe-sparing technique that can aid in the management of invasive sino-orbital aspergillosis. To our knowledge, this is the first documented case of acute orbital compartment syndrome subsequent to retrobulbar injection of amphotericin B. Although our patient had an excellent long-term outcome, physicians attempting retrobulbar injection of amphotericin B should be aware of this potentially urgent complication.

Disclosure

No conflicting relationship exists for any author.

Acknowledgments

Supported by grants from Research to Prevent Blindness.

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