Case Report

Treatment of Bilateral Endogenous *Aspergillus* Endophthalmitis with Multiple Intravitreal Voriconazole Injections with Good Visual Outcome

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Abstract
Endogenous endophthalmitis caused by *Aspergillus* species tends to be very aggressive, often leading to devastating visual outcomes. Historically, intravitreal amphotericin injections have played a central role in management, but with variable visual outcomes and a risk of toxicity. Limited reports suggest that use of intravitreal voriconazole is a safe and efficacious alternative, though these cases were treated with only few intravitreal injections. Here, we report a case of bilateral endogenous *Aspergillus* endophthalmitis treated with 8 intravitreal voriconazole injections in the right eye and 11 in the left eye with good best-corrected final visual outcome (20/50 right eye and 20/40 left eye).

Introduction

*Aspergillus* species have been isolated in approximately 15% of cases of endogenous fungal endophthalmitis, usually in the setting of immunocompromise or intravenous drug use [1, 2]. Treatment generally involves some combination of intravenous and intravitreal antifungals, along with possible vitrectomy [3]. Visual outcomes are generally poor, with most patients having final visual acuity of 20/200 or worse [4]. Only 2 prior published reports have
investigated use of the newer antifungal agent voriconazole for endogenous *Aspergillus* endophthalmitis, with final visual acuity in the 20/20 to 20/50 range [5, 6]. However, in these reports, only 1–5 intravitreal injections were administered; the outcomes in cases requiring more injections have not been reported. Herein, we present a case of bilateral endogenous *Aspergillus* endophthalmitis treated with 8 intravitreal voriconazole injections in the right eye and 11 injections in the left eye with relatively good final visual outcome and no signs of ocular toxicity.

**Case Report/Case Presentation**

A 61-year-old male with history of renal transplant requiring chronic immunosuppression presented with left eye pain and decreased vision. Vision was 20/20 in the right eye and 20/150 in the left eye. Slit-lamp exam showed anterior chamber cells in the right eye and a hypopyon in the left eye. Fundus examination showed vitritis and fluffy yellow-white peripheral preretinal lesions in both eyes (Fig. 1).

Systemic workup was notable for positive serum beta-d-glucan and vitreous cultures grew *Aspergillus fumigatus*. Transesophageal echocardiogram revealed mitral valve vegetation. Systemic antimicrobials were narrowed to intravenous mexitafungin and oral voriconazole once cultures grew *Aspergillus*.

The patient received 2 amphotericin injections (10 μg/0.1 mL) in each eye before being switched to intravitreal voriconazole (100 μg/0.1 mL) on hospital day 9 to minimize risk of
ocular toxicity (Table 1). A day later, he underwent pars plana vitrectomy in the left eye given worsening vitritis. His hospital course was subsequently complicated by intracranial hemorrhage, causing cardiac surgery for infective endocarditis to be postponed. Without source control, intravitreal voriconazole injections were performed every 48–72 h in each eye until all lesions were inactive and stable.

The patient was discharged after 1.5 months. Ocular exam remained stable until 8 weeks post-discharge, at which point the left eye had worsening pain and recurrent inflammation. He received repeat injections of intravitreal voriconazole and subsequently underwent pars plana vitrectomy and pars plana lensectomy (given dense white cataract). Shortly thereafter, and 4 months after initial presentation, he underwent successful cardiac surgery for source control.

Ten months after presentation, vision was 20/50 in the right eye after cataract surgery and 20/40 in the left eye with +11.0 D lens (given aphakia); inactive preretinal lesions were noted in both eyes (Fig. 1). OCT showed improvement from earlier in the disease course and an intact foveal contour in both eyes (Fig. 2). In total, he received 8 intravitreal voriconazole injections in the right eye and 11 injections in the left eye (Table 1).

### Table 1. Summary of course of each eye

| Timepoint | Intervention                                                                 | Visual acuity right eye | Visual acuity left eye |
|-----------|-----------------------------------------------------------------------------|--------------------------|------------------------|
| Day 0     | Vancomycin/ceftazidime/amphotericin (left eye)                              | 20/20                    | 20/150                 |
| Day 3     | Vancomycin/ceftazidime/amphotericin (right eye)                             | 20/30                    | –                      |
| Day 7     | Amphotericin (both eyes)                                                    | 20/400                   | 20/400                 |
| Day 9     | Voriconazole (both eyes)                                                    | 20/60                    | 20/125                 |
| Day 10    | Pars plana vitrectomy + voriconazole (left eye)                             | –                        | CF at 2'               |
| Day 12    | Voriconazole (right eye)                                                    | 20/80                    | –                      |
| Day 13    | Voriconazole (left eye)                                                     | –                        | 20/125                 |
| Day 14    | Voriconazole (right eye)                                                    | 20/125                   | –                      |
| Day 15    | Voriconazole (left eye)                                                     | –                        | 20/125                 |
| Day 16    | Voriconazole (right eye)                                                    | 20/60                    | –                      |
| Day 17    | Voriconazole (left eye)                                                     | –                        | 20/70                  |
| Day 18    | Voriconazole (right eye)                                                    | 20/70                    | –                      |
| Day 22    | Voriconazole (both eyes)                                                    | Unable*                  | Unable*                |
| Day 24    | Voriconazole (both eyes)                                                    | Unable*                  | Unable*                |
| Day 26    | Voriconazole (both eyes)                                                    | Unable*                  | Unable*                |
| Month 3.5 | Voriconazole (left eye)                                                     | –                        | CF at 3'               |
| Month 3.5 | Voriconazole (left eye)                                                     | –                        | CF at 3'               |
| Month 3.5 | Pars plana vitrectomy + pars plana lensectomy + voriconazole (left eye)     | –                        | CF at 3'               |
| Month 4   | Cardiac surgery for source control                                          | –                        | –                      |
| Month 5.5 | –                                                                           | 20/80                    | 20/100 (with +12.0 D lens) |
| Month 10  | –                                                                           | 20/50                    | 20/40 (with +11.0 D lens) |

*VA, unable to be obtained at these visits due to aphasia in setting of intracranial hemorrhage.*
Discussion/Conclusion

Historically, visual outcomes in cases of endogenous *Aspergillus* endophthalmitis were poor. In a case series of 12 patients with culture-proven *Aspergillus* endophthalmitis treated with a combination of intravitreal amphotericin (92%), vitrectomy (83%), and systemic antifungals (75%), only 3/12 patients (25%) had visual acuity better than 20/200 [4]. Three of the 12 eyes (25%) had visual acuity of 20/400, 4/12 eyes (33%) had visual acuity worse than 5/200 and 2/12 eyes (17%) were enucleated.

In addition, there is a risk of retinal necrosis with the use of intravitreal amphotericin, which has historically played a central role in management. Studies in rabbits demonstrate risk of retinal necrosis with doses as small as 1 μg/0.1 mL [7]. While no studies in humans have reported toxicity at standard treatment doses (5–10 μg/0.1 mL), toxicity has been reported in cases where larger doses were inadvertently administered [8].

Voriconazole is a newer antifungal agent that has been demonstrated to have good efficacy and a low risk profile in *Aspergillus* infections [9]. A randomized, unblinded trial demonstrated higher rates of successful treatment response and improved survival in patients receiving intravenous voriconazole compared to intravenous amphotericin for systemic invasive aspergillosis infection [10]. There were also fewer drug-related adverse events in the voriconazole group. Additionally, intravitreal administration of voriconazole has not been found to cause any ocular toxicity in studies in rats and in cultured human retinal pigment epithelium cells [11, 12]. A recent case series in human patients who received up to 9 injections for *Candida* endophthalmitis also did not report any photoreceptor toxicity [13].

Kramer et al. [5] first reported the successful use of intravitreal voriconazole in a case of endogenous *Aspergillus* endophthalmitis in 2006. The patient initially presented with visual acuity of 20/150; she received intravitreal vancomycin, ceftazidime, and amphotericin injections, along with intravenous voriconazole. Two days later she developed worsening vision to light perception, at which point she underwent pars plana vitrectomy and intravitreal voriconazole (100 μg/0.1 mL) injection. Visual acuity subsequently improved to 20/50 in the right eye with no re-accumulation of vitreous debris.

Fig. 2. Macula OCT of both eyes at 6-week, 8-month, and 10-month follow-up. Macula OCT at 6 weeks post-presentation showed significant vitreous debris in the left eye. By month 8, the debris largely improved through an inflammatory deposit remained on the retinal surface in the left eye. At 10-month follow-up, both eyes had relatively clear media with an intact foveal contour and relatively preserved foveal ellipsoid zone; the inflammatory deposit in the left eye was no longer present.
Ferreira et al. [6] also reported successful visual and anatomic outcomes with the use of intravitreal voriconazole (50 μg/0.1 mL) in a case of endogenous Aspergillus endophthalmitis. The patient initially had count fingers vision, received 2 intravitreal voriconazole, followed by pars plana vitrectomy and intravitreal voriconazole, followed by an additional 2 intravitreal voriconazole injections post-operatively. Final visual acuity was 20/20 in the left eye.

Our patient received several more intravitreal voriconazole (100 μg/0.1 mL) injections in both eyes than all prior published reports. Source control with cardiac surgery to remove the vegetation on the mitral valve was not performed until 4 months after presentation because the patient developed intracranial hemorrhage and was systemically unstable for cardiac surgery for an extended period of time. In total, he received 2 amphotericin injections followed by 8 voriconazole injections in the right eye, with final visual acuity of 20/50 after cataract surgery. The left eye underwent 2 amphotericin injections, 11 voriconazole injections, pars plana vitrectomy twice, and pars plana lensectomy with final visual acuity of 20/40 with a +11.0 D lens. He remained on oral voriconazole until source control was achieved.

In summary, this case highlights that multiple intravitreal voriconazole injections can be safely administered without any signs of ocular toxicity and is an efficacious method to treat aggressive Aspergillus endophthalmitis, especially when source control cannot be achieved immediately. Prospective studies investigating visual and anatomic outcomes with intravitreal voriconazole compared to intravitreal amphotericin are warranted to help identify the optimal treatment regimen.

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We would like to thank the patient for giving permission to share this case with the broader ophthalmology community.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. It is the policy of Johns Hopkins Medicine (JHM) that a single case report or case series (3 or fewer cases) does not constitute human subjects research requiring review and approval by the JHM IRB.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

I.F.A., S.S.O., and J.F.A. wrote the case report. All authors contributed to the care of the patient and critical review of the manuscript.
Data Availability Statement

This case report did not result in any data generation or analysis. Given need for patient confidentiality, further information about the case cannot be openly available. Please direct any further inquiries to the corresponding author.

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