An Outbreak of Fungal Endophthalmitis After Intravitreal Injection of Compounded Combined Bevacizumab and Triamcinolone

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IMPORTANCE Our experience may be useful to other practitioners using compounded intravitreal agents, those suspecting infectious outbreaks, and those managing fungal endophthalmitis.

OBJECTIVE To describe a series of patients with fungal endophthalmitis following intravitreal injection of combined bevacizumab and triamcinolone acetonide prepared by the same compounding pharmacy.

DESIGN AND SETTING Noncomparative case series.

PARTICIPANTS Eight eyes of 8 patients who received an intravitreal injection of compounded combined bevacizumab-triamcinolone in a period of 3 weeks had subtle, nonspecific findings that were later diagnosed as fungal endophthalmitis.

MAIN OUTCOME MEASURES Visual acuity, response to antimicrobial therapy, and number of vitreoretinal surgical operations after diagnosis of fungal endophthalmitis.

RESULTS Eight patients developed endophthalmitis 41 to 97 days after receiving the intravitreal injection, which was prepared by the same compounding pharmacy. The injections occurred at the same location in New York. Treatment was based on clinical examination findings and knowledge of the etiology of the endophthalmitis. Eventually, all patients were treated with oral voriconazole. Five of 8 patients were initially treated with intravitreal antimicrobial agents. After 3 months of follow-up, visual acuities ranged from 20/50 to hand motions. Local, state, and federal health department officials were involved in investigating the source of the outbreak.

CONCLUSIONS AND RELEVANCE In the current study, we report a fungal endophthalmitis outbreak after intravitreal injection of contaminated, compounded combined bevacizumab-triamcinolone. In this series, Bipolaris hawaiiensis was the identified causative agent. The challenge of medical diagnosis, identification of the source of the outbreak, and management experience are highlighted in our series. Our experience may be useful to other practitioners using compounded intravitreal agents, those suspecting infectious outbreaks, and those managing fungal endophthalmitis.
Diabetic macular edema is an important cause of visual loss. There has been increasing use of vascular endothelial growth factor inhibitors and corticosteroids (triamcinolone acetonide) injected intravitreally in an attempt to control macular edema and proliferative retinopathy, as well as improve vision. Among the most feared complications of intravitreal injection is the development of endophthalmitis. Numerous large prospective studies have found the rates of endophthalmitis associated with these injections to be between 0.02% and 0.05%. More recently, compounded preparations of bevacizumab in combination with triamcinolone acetonide have been made available for intravitreal injection and are commonly used off-label in the treatment of diabetic macular edema and ischemic proliferation. This combination has been reported to be well tolerated with a similarly low overall complication rate.

We report here the first outbreak of infectious fungal endophthalmitis after intravitreal injection of compounded combined bevacizumab and triamcinolone. All patients received injections compounded by the same pharmacy. In light of the recent outbreak of fungal meningitis from contaminated methylprednisolone acetate compounded at the New England Compounding Center, we believe it is imperative to make physicians and the public aware of this potential problem. This is the largest reported outbreak of fungal endophthalmitis after intravitreal injection of a contaminated batch of medication.

Methods

The medical records of all 8 patients who received injections from the contaminated lot were retrospectively reviewed in accordance with guidelines set forth by the Declaration of Helsinki. This study was exempt from institutional review board approval. The data collected include the age and sex of each patient, the affected eye, indication for intravitreal bevacizumab-triamcinolone, preinjection visual acuity, lens status, and date of injection. Presentation and diagnostic data were recorded, including clinical examination at follow-up visits, date of presentation with endophthalmitis, visual acuity at that visit, and presenting signs and symptoms. Cultures and cytopathologic findings were analyzed when available. The patients’ clinical courses were recorded, including the number of intravitreal antibiotic injections, use of systemic antibiotic therapy, the number of pars plana vitrectomies, and the last recorded visual acuity outcome at the 3-month follow-up.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age, y</th>
<th>Condition Treated</th>
<th>Date of Injection</th>
<th>Preinjection VA</th>
<th>Time to Presentation, d</th>
<th>Presenting VA</th>
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<tbody>
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<td>1</td>
<td>F/77</td>
<td>CME</td>
<td>January 2012</td>
<td>20/30</td>
<td>47</td>
<td>CF</td>
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<td>CME</td>
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<td>CME</td>
<td>January 2012</td>
<td>20/50</td>
<td>60</td>
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<td>20/60</td>
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<td>CME + BRVO</td>
<td>January 2012</td>
<td>20/40</td>
<td>62</td>
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<td>February 2012</td>
<td>20/200</td>
<td>93</td>
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<td>7</td>
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<td>CME</td>
<td>February 2012</td>
<td>20/50</td>
<td>72</td>
<td>CF</td>
</tr>
<tr>
<td>8</td>
<td>F/57</td>
<td>CME</td>
<td>January 2012</td>
<td>20/70</td>
<td>97</td>
<td>CF</td>
</tr>
</tbody>
</table>

Abbreviations: BRVO, branch retinal vein occlusion; CF, counting fingers; CME, cystoid macular edema; LP, light perception; VA, visual acuity.
The affected patients were injected over a span of 3 weeks at the same office by 1 vitreoretinal surgeon (B.Z.C.). All patients were initially injected and subsequently managed by the same vitreoretinal surgeon. The treating physician reported a similar injection technique for all patients, including the use of povidone-iodine and sterile eyelid speculums. All patients were given a fourth-generation fluoroquinolone topical antibiotic drop (besifloxacin or moxifloxacin hydrochloride) for postinjection endophthalmitis prophylaxis. All patients also received several applications of these antibiotics before injection for prophylaxis.

The range of presentation was 41 to 97 days after injection. Presenting visual acuities ranged from 20/50 to light perception. Clinical examination findings included unremarkable conjunctival examinations and, at most, trace flare and rare cells in the anterior chamber for all 8 patients.
All 8 patients had symptoms of floaters. In several patients, small, fluffy white vitreous cells were present on the visible compound injected within the vitreous. Each patient had an interval office visit before the diagnosis of endophthalmitis with stable or improved clinical examination.

Initial management at presentation varied based on clinical findings and are summarized in Table 2. Four of the 8 patients underwent pars plana vitrectomy with bacterial and fungal cultures taken, and they were treated with combinations of broad-spectrum intravitreal agents, including amphotericin B, voriconazole, vancomycin, and ceftazidime. Therapy was narrowed for patients presenting at later dates as the etiology of the endophthalmitis was clarified. All patients received oral voriconazole, which has been shown to have excellent intravascular bioavailability.

Further therapy was dictated by clinical course. Four patients received repeat intravitreal amphotericin B and voriconazole. Two patients underwent repeat vitrectomy for further washout. Three patients were treated with oral voriconazole alone. These patients were treated when the etiology of this phenomenon became clearer. One patient who initially received intravitreal amphotericin B and voriconazole then also underwent vitrectomy. One patient also eventually received intravenous voriconazole therapy. This same patient developed retinal neovascularization and vitreous hemorrhage.

Five of the 8 patients had vitreous biopsy samples sent for pathologic analysis at the Mount Sinai Ophthalmic Pathology laboratory. Three patients had positive histologic analysis from the vitreous biopsy specimens. The vitreous fluid was inoculated on Sabouraud dextrose agar. The resulting fungal cultures from 3 patients were transferred to potato dextrose agar to induce conidia formation. The organisms were initially identified as *Exserohilum* by microscopic analysis with lactophenol cotton blue stain at Mount Sinai. Four of 5 patients had confirmed fungus on either culture or histopathologic analysis. The isolates were sent to the Mycotic Diseases Branch of the Centers for Disease Control and Prevention for further identification. The isolates from 3 patients were identified as *Bipolaris hawaiiensis* by sequencing of the ITS2 and 28S regions of the recombinant DNA. No organism was grown from the vitreous specimens of 2 patients. *Bipolaris* is a dematiaceous, filamentous fungus that is ubiquitous in the environment.

Local and state departments of health, as well as the Centers for Disease Control and Prevention and the Food and Drug Administration, were contacted and have been investigating the source of contamination. Upon further investigation at the pharmacy, it was revealed that the contamination occurred before the storage of the drug in a single bottle with a rubber stopper. This contaminated bottle was then reused and the contents were transferred to several syringes of medication.

Figure 6. Vitreous Specimen

Vitreous specimen with fungal colonies of patient 3.

Table 2. Summary of Initial Treatment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Preinjection VA</th>
<th>VA at Presentation</th>
<th>Initial Treatment</th>
<th>Follow-up VA 3 Months After Presentation</th>
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<tbody>
<tr>
<td>1</td>
<td>20/30</td>
<td>CF</td>
<td>PPV with amphotericin B, voriconazole, vancomycin, and ceftazidime&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20/70</td>
</tr>
<tr>
<td>2</td>
<td>20/25</td>
<td>20/60</td>
<td>Intravitreal amphotericin B and voriconazole&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20/80</td>
</tr>
<tr>
<td>3</td>
<td>20/50</td>
<td>20/50</td>
<td>PPV with amphotericin B and voriconazole</td>
<td>20/50</td>
</tr>
<tr>
<td>4</td>
<td>20/60</td>
<td>CF</td>
<td>PPV with amphotericin B, voriconazole, vancomycin, and ceftazidime</td>
<td>20/200</td>
</tr>
<tr>
<td>5</td>
<td>20/40</td>
<td>CF</td>
<td>PPV with amphotericin B, voriconazole, vancomycin, and ceftazidime</td>
<td>HM&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>20/200</td>
<td>LP</td>
<td>Oral voriconazole</td>
<td>20/400</td>
</tr>
<tr>
<td>7</td>
<td>20/50</td>
<td>CF</td>
<td>Oral voriconazole</td>
<td>20/200</td>
</tr>
<tr>
<td>8</td>
<td>20/70</td>
<td>CF</td>
<td>Oral voriconazole</td>
<td>20/200</td>
</tr>
</tbody>
</table>

Abbreviations: CF, counting fingers; HM, hand motions; LP, light perception; PPV, pars plana vitrectomy; VA, visual acuity.

<sup>a</sup> This patient initially visited an outside ophthalmologist with signs of anterior uveitis. He was initially treated with prednisolone acetate every hour. However, 1 week later, he developed signs more consistent with endophthalmitis and then underwent intravitreal amphotericin B-voriconazole injection.

<sup>b</sup> This patient presented 3 days after injection with painful loss of vision (from 20/30 to counting fingers). This patient was treated for possible endophthalmitis with intravitreal culture and injection of vancomycin. One week later, she underwent pars plana vitrectomy, with injection of vancomycin. She then recovered her vision to 20/40, but again presented 47 days after injection with a vision of counting fingers and evidence of endophthalmitis.

<sup>c</sup> This patient has since developed vitreous hemorrhage from retinal neovascularization and rubeosis iridis.
Discussion

Infectious endophthalmitis after intravitreal injection is an uncommon occurrence.1,2 Fungal endophthalmitis following intravitreal injections is less common than bacterial endophthalmitis,3 and appropriate diagnosis is often delayed. In this case series, one of the more challenging factors in establishing the diagnosis was the relatively long period between intravitreal injection and presentation of endophthalmitis. All patients were seen between the initial injection and presentation with endophthalmitis for follow-up care, and all had a stable or improving clinical examination. Furthermore, our patients presented with relatively unremarkable anterior ocular examinations and vague, nonspecific vitreous debris. The mysterious vitreous debris was all the more challenging to diagnose when these cases had not yet been linked together.

The physician’s suspicion for a contaminated lot was raised after a handful of patients came to us with endophthalmitis. A medical record review at that time indicated that those patients received an intravitreal injection from 1 lot of medication. It should be emphasized that the standard practice at this treatment center was to place the label of the injected medication in the patient’s medical record. This proved to be of paramount importance in linking the cases together and determining the etiology of the outbreak. Patients who received an injection from that lot and who subsequently developed endophthalmitis were treated only for a fungal infection.

The choice of initial treatment was largely based on clinical suspicion. The first patients who developed endophthalmitis were treated aggressively with a low threshold for vitrectomy, both for diagnostic and therapeutic purposes. Five patients underwent vitreous biopsy for this reason, with a positive culture in 4 of 5 specimens.

Given the relative infrequency of fungal endophthalmitis, most previous studies regarding diagnosis and therapy have been retrospective medical record reviews. A recent study from the Bascom Palmer Eye Institute of 65 eyes with endogenous fungal endophthalmitis suggests that the most common presenting symptom in these patients was decreased vision.2 Notably, only 34% of patients within their series presented with pain. Candida albicans was the most common yeast isolated, and Aspergillus was the most common mold identified. Visual recovery is generally poor, although infection with yeast offers a slightly improved prognosis compared with infection with molds.

Initial treatment options have included pars plana vitrectomy with intravitreal injection of antifungals, intravitreal culture and injection, and systemic therapy. Given the relative rarity of fungal endophthalmitis, there are no definitive treatment approaches as yet. In the case series from Bascom Palmer, 91% of eyes underwent vitrectomy during the treatment course. In a case series of 7 patients with post–cataract extraction fungal endophthalmitis, Yang4 advocated initial vitrectomy, along with the removal of the lens cortical remnant and lens capsule. Therapy thereafter could include any aforementioned combination, often depending on the clinical course.

More recently, there have been improvements in the intracocular bioavailability of oral antifungal medications. In our series, 3 patients were treated solely with oral voriconazole and close monitoring. Visual acuities in these patients were comparable to those treated with a more aggressive surgical approach, which suggests oral therapy alone does not lead to a worse outcome.

This is the first reported outbreak of fungal endophthalmitis following an intravitreal injection. Nearly 4 months after our first patient came to us, the Centers for Disease Control and Prevention notified the medical community of a multistate outbreak of postprocedural fungal endophthalmitis associated with the same compounding pharmacy.5 The initial investigation was based out of the Los Angeles County Department of Public Health and identified a group of patients who had undergone vitrectomy with epiretinal membrane peeling with the use of a dye, Brilliant Blue G. The dye was contaminated, leading to multiple cases of fungal endophthalmitis. This outbreak brings into question practices that may be quite common at compounding pharmacies. A scenario in which individual doses are aliquoted from a larger solution with a removable and replaceable stopper may suggest the acceptability of repeat use. However, this is a potential source of contamination that could in turn affect a large number of patients. With recent stories similar to ours, such as the fungal meningitis outbreak following contaminated methylprednisolone acetate prepared at one compounding pharmacy,4 the oversight of drug dispensing should be readressed.

This outbreak highlights the importance of maintaining a high index of suspicion of fungal endophthalmitis, even months after intravitreal injection. It also shows the utility of seeking the assistance of the Centers for Disease Control and Prevention and the sources of drug dispensing when suspicion of a rare, possibly infectious disease state is suspected. The aforementioned measures, as well as close follow-up and offering of multiple treatment options, were of key importance in helping preserve vision in our patients. There is a need for prospective clinical studies in an effort to determine the optimal treatment paradigm to manage this difficult condition.

Critical revision of the manuscript for important intellectual content: Sheyman, Friedman, and Ackert.
Statistical analysis: Sheyman, Cohen, and Ackert.
Administrative, technical, and material support: Sheyman and Ackert.
Study supervision: Friedman and Ackert.

Conflict of Interest Disclosures: None reported.
Fungal Endophthalmitis

Additional Contributions: Shawn R. Lockhart, PhD, Mycotic Diseases Branch, Centers for Disease Control and Prevention, identified and studied the fungal and genetic sequencing in our specimens.

REFERENCES

OPHTHALMIC IMAGES

Extensive Retinal Involvement of Metastatic Neuroblastoma

Kim Kramer, MD; David H. Abramson, MD

A. Retinal masses of metastatic neuroblastoma found 7 months after multiagent chemotherapy following initial diagnosis at 6 weeks of age for favorable histology metastatic neuroblastoma. B. After treatment including chemotherapy, craniospinal radiation, immunotherapy, and intra-Ommaya radiotherapy, the patient has no evidence of systemic or retinal neuroblastoma.