This article describes the histopathology in 5 eyes, which were from a clinical series of 14 cases of mold-induced endophthalmitis following intravitreal injections of triamcinolone. The organism responsible, Bipolaris hawaiensis, is a rare cause of human ocular infection and its morphology in ocular tissues has not been well described.

Methods

We conducted a histopathologic review of 5 eyes from a series of 17 treated with intravitreal triamcinolone for retinal vascular disease and diabetes mellitus over 1 year from 1 lot prepared by a compounding pharmacy (Table 1). This article received University of California, Irvine, institutional review board approval (HS 2012-8716); patient consent was waived.

Results

Three of the eyes (cases 3, 4, and 11 designated by chronology in the series of 17) were clinically and pathologically phthisical, evidenced by gross shrinkage, scleral infolding, and internal disorganization.

Retinal and choroidal architecture were poorly preserved in all eyes including eye 9, which was grossly normal. However, eye 9 demonstrated equatorial granulomas containing numerous fungal elements obvious in periodic acid–Schiff (PAS) and hematoxylin and eosin–stained sections (Figure). Optic nerve and scleral extension were not found in any of our specimens. The choroid in all eyes was markedly disorganized and expanded by inflammatory debris but did not demonstrate organisms. Remnants of retinal pigment epithelium and choriocapillaris persisted in several eyes. In all cases, hyphae were found by both PAS and Gomori methenamine silver staining in inflammatory foci or vitreous remnants (Figure). The results from cultures taken from cases 3, 4, and 11 in the pathology laboratory were negative.

Discussion

Bipolaris hawaiensis is a demitaiceous mold and member of a large genus of fungi that includes at least 30 species. It is a
well-known saprophyte and plant pathogen. Human infections are rare and generally limited to tropical and subtropical regions. The most common human infections have occurred in nasal tissues, skin wounds and burns, or lung. Allergic sinusitis and onychomycosis are relatively common. Endophthalmitis from the same compounding pharmacy was recently reported but without ocular histology. Very rarely, central nervous system infections have been described. Immunocompromised individuals are at the highest risk for infection by Bipolaris species.

To our knowledge, this is the first reported ocular histology on a series of intraocular infections due to Bipolaris hawaiiensis. The clinical findings of another 9 cases of Bipolaris hawaiiensis endophthalmitis from the same pharmacy (Franck’s Compounding Pharmacy, Ocala, Florida) and same lot number were recently reported by Sheyman et al. The same pharmacy a few months earlier had been involved in Brilliant Blue dye fungal contamination. The Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report described 33 cases of fungal endophthalmitis from 7 different states from March to April 2012. Subsequently, triamcinolone was also suspected to have been contaminated in 13 cases. Isolates from 7 confirmed Brilliant Blue dye cases by genetic testing or culture were due to Fusarium incarnatum-equiseti.

Microscopy demonstrated well-preserved hyphal forms and spore forms except in the eviscerated case 2, in which only fragments of hyphae were found with PAS and Grocott methenamine silver staining. The results from cultures obtained via pars plana vitrectomy were positive for Bipolaris in our cases 2 and 3 and suspect in case 9. DNA sequencing of vitrectomy samples from early clinical cases by the Centers for Disease Control and Prevention documented the species to be identical to those from New York. The most rapid and effective proof that fungi were present was PAS staining of cytospin specimens obtained via vitrectomy (Table 2). The morphology of Bipolaris hawaiiensis in our cases was remarkably variable including

<table>
<thead>
<tr>
<th>Case No./Age, y</th>
<th>Specimen Type</th>
<th>Gross State</th>
<th>Surgery Date</th>
<th>Side</th>
<th>Clinical Dx</th>
<th>Preoperative Vision</th>
<th>IOP, mm Hg</th>
<th>First IVTA Injection</th>
<th>Date of Endophthalmitis Dx</th>
<th>VA at Endophthalmitis Dx</th>
<th>Time After Injections, d</th>
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<td>2/55&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td>Evisceration</td>
<td>8/1/2012</td>
<td>OD</td>
<td>CME</td>
<td>20/400</td>
<td>17</td>
<td>1/11/2012</td>
<td>3/12/2012</td>
<td>HM</td>
<td>60</td>
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<tr>
<td>3/64&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Enucleation</td>
<td>Phthisis</td>
<td>9/12/2012</td>
<td>OS</td>
<td>PDR, DME</td>
<td>CF 2’</td>
<td>13</td>
<td>2/1/2012</td>
<td>4/5/2012</td>
<td>20/50</td>
<td>64</td>
</tr>
<tr>
<td>4/72&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Phthisis</td>
<td>10/12/2012</td>
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<td>BRVO, CME</td>
<td>20/50</td>
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<td>Normal</td>
<td>7/2012</td>
<td>OS</td>
<td>CRVO, CME</td>
<td>20/50</td>
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</table>

Abbreviations: BRVO, branch retinal vein occlusion; CF, counting fingers; CME, cystoid macular edema; CRVO, central retinal vein occlusion; DME, diabetic macular edema; Dx, diagnosis; HM, hand motion; IOP, intraocular pressure; IVTA, intravitreal triamcinolone; OD, right eye; OS, left eye; PDR, proliferative diabetic retinopathy; VA, visual acuity.

<sup>a</sup> Male.
<sup>b</sup> Lens status = aphakic.
<sup>c</sup> Lens status = posterior chamber intraocular lens.
<sup>d</sup> Female.
<sup>e</sup> Lens status = phakic.

Figure. Histopathology

A. Hematoxylin and eosin (H&E) stain of case 9 demonstrating massive obliteration of the retina, choroidal expansion, fibrosis, subretinal hemorrhage, and an inflammatory focus temporally encompassing the retina and choroid (original magnification × 1). B. Myriad hyphae obvious with H&E or periodic acid–Schiff histology were present within the abscess in case 9 (H&E, original magnification × 40). C. Spore chains (chlamydoconidia) from case 3 (Gomori methenamine silver, original magnification × 40). D. Variety of hyphal forms from case 3 (Gomori methenamine silver, original magnification × 788).
First, the clinical onset of fungal endophthalmitis can be subtle and painless. Second, in our cases, the onset of symptoms was delayed for between 5 days (case 2) to 64 to 174 days (Table 1), substantially longer than expected for bacterial endophthalmitis. Third, when fungal endophthalmitis is suspected, vitrectomy and PAS staining of cytospin material has the highest likelihood of demonstrating organisms. Fourth, and most importantly, all of our 5 cases reported here received multiple intravitreal doses of voriconazole and 4 of 5 took voriconazole by mouth and still contained apparently viable organisms in ocular tissues. Clearly, appropriate antifungals cannot always kill these organisms. Because the worldwide ophthalmic community is doing many thousands of intravitreal injections of anti-vascular endothelial growth factor and steroids per year, especially in diabetic patients, great concern is appropriate for the sterility of compounded drugs.

Conclusions

The Bipolaris hawaiieses endophthalmitis cases described in this article convey at least 4 important clinical messages.

### ARTICLE INFORMATION

**Accepted for Publication:** January 21, 2014.
**Published Online:** March 13, 2014. doi:10.1001/jamaophthalmol.2014.257.
**Author Contributions:** Drs Minckler and Small had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.  
Study concept and design: All authors.  
Acquisition of data: Minckler, Small.  
Analysis and interpretation of data: All authors.  
Drafting of the manuscript: All authors.  
Critical revision of the manuscript for important intellectual content: Minckler, Walsh.  
Administrative, technical, and material support: All authors.  
Study supervision: Minckler.  
Conflict of Interest Disclosures: None reported.

### REFERENCES