Retinal Neovascularization and Endogenous Fungal Endophthalmitis in Intravenous Drug Users

Intravenous (IV) heroin abuse in persons aged ≥12 has nearly doubled between the 2002 and 2012. Intravenous drug users (IVDU) are a high-risk group for developing endogenous fungal endophthalmitis (EFE), with Candida albicans being the most commonly identified causative organism. Endogenous fungal endophthalmitis is a potentially blinding disease in which the causative organism reaches the eye through hematogenous dissemination. The frequency of chorioretinitis and endophthalmitis in patients with documented fungemia ranges from 2% to 26% and 0% to 6%, respectively. Factors contributing to poor visual outcomes include macular involvement, subretinal and choroidal neovascularization (NV), retinal detachment, and insufficient or delayed treatment.

However, to our knowledge, this is the first case series characterizing retinal NV as a potentially blinding complication of EFE in IVDU.

This retrospective, observational, case series of 5 patients presenting over 10 years with retinal NV in the setting of IVDU-related EFE reviews clinical, laboratory, photographic, and surgical records, along with a systematic search of the literature. Patient clinical characteristics are presented in Table 1 (available at www.aaojournal.org). All patients reported decreased vision and floaters, and 3 of 5 patients reported eye pain and redness. The time between symptom onset and initial patient presentation ranged from 2 to 12 weeks. Two patients had a history of diabetes mellitus without evidence of diabetic retinopathy in the contralateral eye. The remaining 3 patients had no significant medical history. Notably, all patients denied IV drug use when asked at the initial visit. On subsequent visits, all patients admitted to IV heroin use, with 2 reporting polysubstance abuse.

The best-corrected visual acuity at presentation ranged from 20/40 to 20/300. Nongranulomatous anterior segment inflammation and mild to moderate vitritis were noted in all patients at presentation. All patients displayed whitish retinal lesions with indistinct borders in the macular region (Fig 1A, E, J, L [upper], O, and Q [upper]; available at www.aaojournal.org), and 1 patient had an additional lesion outside of the macula. Vitreous aspirates were removed in each case, and fungal and bacteria cultures as well as polymerase chain reaction were performed. Candida species were identified in 3 of 5 patients (60%); no organisms were identified in the remaining 2 patients. All patients received intravitreal amphotericin B or voriconazole injections within 48 hours of presentation or intraoperatively (cases 4 and 5). Treatment was delayed in all cases either owing to delay in seeking care (≤12 weeks), misdiagnoses as noninfectious uveitis (≤2 weeks), or initial refusal of intravitreal injections or surgical intervention (<3 weeks). Four patients, including one with known fungemia (case 1), were treated with systemic fluconazole, and 1 patient (case 2) did not complete follow up.

Retinal NV was noted in 2 patients upon presentation (Fig 1J, O; available at www.aaojournal.org) and developed within 10 to 60 days after presentation in the remaining 3 patients, despite improvement of ocular inflammation after intravitreal and systemic antifungal therapy (Fig 1A-D, E, F; available at www.aaojournal.org). All patients demonstrated NV of the optic disc and exhibited fibrovascular extensions from the disc to fungal lesions in the macula. Four of the 5 patients had macula-involving tractional retinal detachments and underwent pars plana vitrectomy with membrane peeling (Table 1; available at www.aaojournal.org). The macular traction was successfully relieved in all cases (Fig 1G, K-L [lower], P, Q [lower]; available at www.aaojournal.org), and the preretinal/retinal fungal masses were excised. Histopathology revealed the presence of small, thin-walled blood vessels with plump endothelium consistent with NV (Fig 1H, N; available at www.aaojournal.org), focally dense mixed inflammatory infiltrates and focal necrosis (Fig 1I; available at www.aaojournal.org). Budding yeast and pseudohyphae consistent with Candida species were observed in the preretinal/retinal mass from a patient who had refused intravitreal voriconazole preoperatively but agreed to an intraoperative injection (Fig 1M; available at www.aaojournal.org). Postoperative visual acuity was ≥20/25 in 3 of 4 patients who underwent operative intervention. The remaining surgical patient developed a submacular hemorrhage with macular traction 46 days after presentation and subsequently received an intravitreal bevacinazumab injection 2 days before the scheduled surgery. His visual acuity improved from 20/150 to 20/60 postoperatively (Table 1).

Intravenous drug use-related endophthalmitis accounts for ≤70% of all cases of EFE seen at tertiary referral centers, and an awareness of the potentially blinding complications of EFE and their clinical management is important. Often, EFE is a clinical diagnosis, which poses a challenge, because patients with IVDU may not be forthcoming with their drug use history at presentation. Indeed, 1 patient denied IVDU until the operative day when she asked that we x-ray her arm for needle fragments (Fig 1R; available at www.aaojournal.org). Furthermore, the causative agent is identified in only 46% to 68.4% of patients. Finally, as illustrated in our case series, treatment may be delayed owing to postponement in seeking care, initial misdiagnoses, refusal, or inability to follow through with treatment in a timely manner. Therefore, careful examination and high clinical suspicion are imperative to mitigate any delay in treatment.

Retinal NV is a well-known complication in diabetes, ischemia, vasculitis, and chronic inflammation. However, our literature review revealed only 4 cases that showed retinal NV in the setting of EFE (Table 2; available at www.aaojournal.org). Interestingly, all of the neovascular and fibrovascular membranes in our cases occurred at the optic nerve head and extended to the retinal fungal lesions. One explanation is that fungal elements lead to intense local inflammatory cell recruitment at the lesion. These inflammatory cells, especially macrophages, are capable of releasing angiogenic factors under hypoxic conditions. Although retinal NV can develop separately as a result of ischemic events from IVDU in the absence of EFE, it seems to be a less likely mechanism in our cases, given that all retinal NV involved the fungal retinal lesions. The location of the fungal lesion may also be of importance in predicting the occurrence of NV. In our case
series, all patients developed abnormal retinal vessels at lesions localized to the macula.

In conclusion, retinal NV in IVDU-related EFE can occur rapidly and involve the macula. These patients would benefit from close clinical monitoring for this complication because antifungal treatment and vitrectomy may be effective in improving visual outcomes.

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References


Figure 1. Cases of retinal neovascularization (NV) in intravenous drug use-related endogenous fungal endophthalmitis. (A) Fundus images of a 33-year-old man (case 1) on presentation, (B) at 60 days documenting the onset of retinal NV, and (C) at 11 weeks with fluorescein angiography demonstrating retinal NV with leakage (D). Fundus images of a 27-year-old man (case 3) on presentation (E), at 4 weeks showing prominent retinal NV, submacular hemorrhage, and focal retinal traction as indicated by distortion of retinal vessels (F, arrowhead), and after pars plana vitrectomy (PPV) and membrane peel (MP; G). Histopathology of the preretinal mass demonstrates mixed inflammation and small vessels with plump endothelium characteristic of NV (H; stain: CD31 antibody; arrows; original magnification, ×400) and focal necrosis (I; stain: hematoxylin and eosin, arrowhead; original magnification, ×400). Fundus photos of a 33-year-old woman (case 4) showing a large preretinal mass with associated retinal NV and traction on presentation (J), and status post–PPV/MP (K). (L) Spectral-domain optical coherence tomography images of the retina prior and after PPV/MP demonstrating the resolution of macular edema and subretinal fluid postoperatively. Grocott-Gomori methenamine silver stain of the preretinal mass reveals budding yeast and pseudohyphae (M). Neovascularization is identified in other regions of the biopsy and confirmed with CD31 immunostaining (N; arrows; original magnification, ×400). Fundus images of an 18-year-old girl (case 5) demonstrating a fibrovascular band extending from the optic nerve to the fovea on presentation (O) and after PPV/MP (P). Spectral domain optical coherence tomography images illustrate macular traction beneath the preretinal mass and fibrovascular traction band with resolution of the macular traction after PPV/MP (Q). Radiograph of the patient’s left arm reveals a retained needle fragment (R, arrowhead). Post-op = postoperative; pre-op = preoperative.
Table 1. Clinical Characteristics of Intravenous Drug Users Who Developed Retinal Neovascularization in the Setting of Endogenous Fungal Endophthalmitis

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Organism</th>
<th>Onset of NV From Presentation (d)</th>
<th>Duration Of Macular traction to PPV (d)</th>
<th>Treatment</th>
<th>Initial BCVA</th>
<th>Final BCVA</th>
<th>Follow-Up (mo)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>Male</td>
<td>C albicans</td>
<td>OS: 60</td>
<td>12</td>
<td>Ivit amphotericin B, PPV, MP</td>
<td>20/50</td>
<td>20/20</td>
<td>25</td>
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<tr>
<td>2</td>
<td>55</td>
<td>Male</td>
<td>*</td>
<td>OS: 10</td>
<td>NA</td>
<td>Ivit voriconazole</td>
<td>20/40</td>
<td>20/20</td>
<td>0.57</td>
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<tr>
<td>3</td>
<td>27</td>
<td>Male</td>
<td>*</td>
<td>OD: 30</td>
<td>10</td>
<td>Ivit voriconazole, Ivit bevacizumab, PPV, MP</td>
<td>20/150</td>
<td>20/150</td>
<td>2.85</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>Female</td>
<td>C albicans</td>
<td>OS: on presentation</td>
<td>29</td>
<td>Ivit voriconazole, PPV, MP</td>
<td>20/200</td>
<td>20/20</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>Female</td>
<td>Candida spp.</td>
<td>OD: on presentation</td>
<td>20</td>
<td>Ivit voriconazole, PPV, MP</td>
<td>20/300</td>
<td>20/25</td>
<td>10</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; Ivit = intravitreal; MP = membrane peel; NA = not applicable; NV = neovascularization; OD = right eye; OS = left eye; PPV = pars plana vitrectomy.

*Organism unknown.

Table 2. Review of Previously Published Cases of Retinal Neovascularization in Patients with Endogenous Fungal Endophthalmitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Risk Factor</th>
<th>Organism</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naoi and Sawada, Jpn J Ophthalmol 1996; 40:434-8.</td>
<td>64</td>
<td>Female</td>
<td>Hyperalimentation</td>
<td>no data</td>
<td>OS: Fibrovascular membrane from optic disc to macula</td>
</tr>
<tr>
<td>Betis et al, J Fr Ophtalmol 2003; 26:650-3.*</td>
<td>30</td>
<td>Female</td>
<td>Intravenous drug use (heroin)</td>
<td>Candida albicans</td>
<td>OS: Neovascularization of the disc and tractional retinal detachment</td>
</tr>
</tbody>
</table>

OD = right eye; OS = left eye.

*Article in French.

†Organism unknown.