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Retinal Neovascularization and Endogenous Fungal Endophthalmitis in Intravenous Drug Users

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Intravenous heroin abuse in persons aged 12 or older has nearly doubled between the years of 2002 and 2012.¹ 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.² EFE 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 2–26% and 0–6%, respectively.³ Factors contributing to poor visual outcomes include macular involvement, subretinal and choroidal neovascularization, retinal detachment, and insufficient or delayed treatment.^{4,5} However, to our knowledge, this is the first case series characterizing retinal neovascularization as a potentially blinding complication of EFE in IVDU.

This is a retrospective observational case series of five patients presenting over 10 years with retinal neovascularization in the setting of IVDU-related EFE. A review of clinical, laboratory, photographic, and surgical records was conducted, along with a systematic search of the literature. Patient clinical characteristics are presented in Table 1 (available at www.aaajournal.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 three 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 two reporting polysubstance abuse.

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The best corrected visual acuity at presentation ranged from 20/40-20/300. Non-granulomatous 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 [Figure 1A, 1E, 1J, 1L (upper), 1O, 1Q (upper)], and one patient had an additional lesion outside of the macula. Vitreous aspirates were removed in each case, and fungal and bacteria cultures as well as PCR were performed. *Candida* species were identified in 3 of 5 patients (60%), while 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 due to delay in seeking care (up to 12 weeks), misdiagnoses as non-infectious uveitis (up to 2 weeks) or initial refusal of intravitreal injections or surgical intervention (up to 3 weeks). Four patients, including one with known fungemia (Case 1), were treated with systemic fluconazole, while one patient (Case 2) did not follow up.

Retinal neovascularization (NV) was noted in two patients upon presentation (Figure 1J, 1O) and developed within 10–60 days after presentation in the remaining three patients, despite improvement of ocular inflammation after intravitreal and systemic antifungal therapy (Figure 1A–D; 1E–F). All patients demonstrated neovascularization of the optic disc and exhibited fibrovascular extensions from the disc to fungal lesions in the macula. Four of the five 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 [Figure 1G, K–L (lower), P–Q (lower)], and the pre-retinal/retinal fungal masses were excised. Histopathology revealed the presence of small, thin-walled blood vessels with plump endothelium consistent with neovascularization (Figure 1H, N), focally dense mixed inflammatory infiltrates and focal necrosis (Figure 1I). Budding yeast and pseudohyphae consistent with *Candida* species were observed in the pre-retinal/retinal mass from a patient who had refused intravitreal voriconazole preoperatively but agreed to an intraoperative injection (Figure 1M). Post-operative visual acuity was 20/25 or better in three of four patients who underwent surgical intervention. The remaining surgical patient developed a submacular hemorrhage with macular traction 46 days after presentation and subsequently received an intravitreal bevacizumab injection two days prior to the scheduled surgery. His visual acuity improved from 20/150 to 20/60 postoperatively (Table 1; available at www.aaojournal.org).

Intravenous drug use-related endophthalmitis accounts for up to 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.² EFE is often a clinical diagnosis, which poses a challenge, as patients with IVDU may not be forthright with their drug use history at presentation. Indeed, one patient denied IVDU until the operative day when she asked that we X-ray her arm for needle fragments (Figure 1R). Furthermore, the causative agent is identified in only 46% to 68.4% of patients.² Finally, as illustrated in our case series, treatment may be delayed due 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 neovascularization is a well-known complication in diabetes, ischemia, vasculitis, and chronic inflammation. However, our literature review revealed only four cases that showed retinal neovascularization 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. While retinal NV can develop separately as a result of ischemic events from IVDU in the absence of EFE, it appears 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 neovascularization. In our case series, all patients developed abnormal retinal vessels at lesions localized to the macula.

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

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Figure 1.

Cases of Retinal Neovascularization in Intravenous Drug Use-Related Endogenous Fungal Endophthalmitis. Fundus images of a 33 year-old man, Case 1, on presentation (A), at 60 days documenting the onset of retinal neovascularization (NV) (B), and at 11 weeks (C) 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 neovascularization (H; CD31 antibody stain, arrows; original magnification, 400X) and focal necrosis (I; hematoxylin-eosin, arrowhead; original magnification, 400X). Fundus photos of a 33 year-old woman, Case 4, showing a large pre-retinal mass with associated retinal NV and traction on presentation (J), and status post PPV/MP (K). (L) Spectral domain optical coherence tomography (SD-OCT) images of the retina prior and after PPV/MP demonstrating the resolution of macular edema and subretinal fluid post-operatively. Grocott-Gomori methenamine-silver (GMS) stain of the pre-retinal 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, 400X). 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). SD-OCT images illustrate macular traction beneath

the preretinal mass and fibrovascular traction band with resolution of the macular traction after PPV/MP (Q). X-ray of the patient's left arm reveals a retained needle fragment (R, arrowhead).

Clinical Characteristics Of Intravenous Drug Users Who Developed Retinal Neovascularization In The Setting of Endogenous Fungal Endophthalmitis

Table 1

Case	Age (years)	Gender	Organism	Onset of NV from presentation (days)	Duration of macular traction to PPV (days)	Treatment	Initial BCVA	Final BCVA	Follow-up (months)
1	33	Male	<i>Candida albicans</i>	OS: 60	12	I _{vit} /Amphotericin B, PPV, MP	20/50	20/20	25
2	55	Male	?	OS: 10	NA	I _{vit} /Voriconazole	20/40	20/20	0.57
3	27	Male	?	OD: 30	10	I _{vit} /Voriconazole, I _{vit} /Bevacizumab, PPV, MP	20/150	20/60	2.85
4	31	Female	<i>Candida albicans</i>	OS: on presentation	29	I _{vit} /Voriconazole, PPV, MP	20/200	20/20	42
5	18	Female	<i>Candida spp.</i>	OD: on presentation	20	I _{vit} /Voriconazole, PPV, MP	20/300	20/25	10

OD, right eye; OS, left eye; BCVA, best corrected visual acuity; NV, neovascularization; I_{vit}, Intravitreal; PPV, pars plana vitrectomy; MP, membrane peel; NA, not applicable.

Table 2

Review of Previously Published Cases of Retinal Neovascularization in Patients With Endogenous Fungal Endophthalmitis

Reference	Age (years)	Gender	Risk Factor	Organism	Clinical features
Naoi N & Sawada A, <i>Jpn J Ophthalmol</i> 1996;40:434–438	64	Female	Hyperalimentation	?	OS: Fibrovascular membrane from optic disc to macula
Naoi N & Sawada A, <i>Jpn J Ophthalmol</i> 1996;40:434–438	56	Male	Hyperalimentation	?	OD: Fibrovascular membrane distal to obstructed vein with retinal detachment
Betis F et al., <i>J Fr Ophthalmol</i> 2003;26:650–653 *	30	Female	Intravenous drug use (heroin)	?	OS: Neovascularization of the disc and tractional retinal detachment
Arroyo JG et al., <i>Jpn J Ophthalmol</i> 2004;48:30–33	43	Male	Deep vein thrombosis	<i>Candida albicans</i>	OS: Fungal abscess with neovascularization extending to the vitreous

OD, right eye; OS, left eye.

* Article in French