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Aflibercept high-dose (8mg) related intraocular inflammation (IOI) – a case series

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Abstract

Background Monitoring for potential inflammatory events following intravitreal anti-vascular endothelial factor (VEGF) injection is crucial with the use of new agents such as aflibercept 8 mg. Despite a safety profile comparable to aflibercept 2 mg in pivotal and phase 3 studies, reporting such cases in clinical practice helps evaluate potential risk of these agents.

Case presentation In this case series, a cluster of 8 patients manifesting acute intraocular inflammation (IOI) after intravitreal aflibercept 8 mg injection at three different centers are described. All patients developed inflammation of the vitreous and anterior chamber within 2–17 days following the injection. All subjects had previously received intravitreal anti-vascular endothelial growth factor (VEGF) therapy (ranibizumab, aflibercept 2 mg or faricimab) without injection-related complications. No signs of vasculitis, papillitis or retinitis were noted. In view of the clinical presentation, vitreous cultures were not performed. Inflammation resolved with topical steroids and non-steroidal anti-inflammatory drugs over a course of 11–24 days with excellent visual recovery.

Conclusions We report a cluster of injection-related ocular inflammation following intravitreal aflibercept 8 mg with at present unknown cause. It underlines the need for clinical awareness to detect such cases despite the low-risk safety profile in pivotal studies.

Keywords Adverse event, Aflibercept 8 mg, Intraocular inflammation, High dose, Anti-VEGF

Background

The use of intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors is currently the gold standard for treating various neovascular retinal diseases [1, 2]. The recent approval of novel anti-VEGF agents has expanded treatment options, including bevacizumab, ranibizumab, aflibercept, brolucizumab, and faricimab. To reduce treatment burden, a high-dose formulation of intravitreal aflibercept (8 mg) was developed to extend dosing intervals for neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) [3–5]. Pivotal trials report longer dosing intervals with aflibercept 8 mg compared to the2 mg formulation. With increasing frequency of the application of anti-VEGF agents, the recognition of potential adverse effects is crucial. In pivotal trials for high dose aflibercept, the incidence of ocular adverse events was similar across groups [3]. High-dose aflibercept is currently primarily used in the United States, with insurance contract negotiations still pending in Europe.

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Sterile IOI differs from true endophthalmitis as it resolves without antibiotic treatment [6]. IOI rates after intravitreal anti-VEGF therapy range from 0.03 to 4.6%, with varying incidences and clinical presentations depending on the agent used [7, 8]. Symptoms typically include blurred vision and floaters occurring 24 h to 7 days post-injection, with or without pain [9, 10]. After the approval of the aflibercept 2 mg formulation, reports of injection-associated ocular inflammation suggested possible batch-specific issues [11]. IOI associated with aflibercept involves pain more often than with other agents, complicating differentiation from infectious endophthalmitis [12, 13]. Unlike the predominantly vitreous and anterior chamber inflammation seen with aflibercept, brolucizumab has been linked to severe visual acuity (VA) impairment due to retinal vasculitis and/or retinal artery occlusion [14–17]. Hypotheses regarding sterile injection-related inflammation etiology include bacterial endotoxin contamination, agent degradation with increased immunogenicity, and treatment-induced or enhanced antidrug antibodies [6].

Since the approval of high-dose aflibercept in Switzerland, we report a cluster of eight acute IOI cases across three different clinics. This case series aims to alert ophthalmologists to a potentially higher incidence of IOI following high-dose aflibercept than previously indicated by clinical trials.

Case presentations

The eight cases of sterile IOI were identified at three different tertiary clinics. All intravitreal procedures were conducted in a room specifically dedicated to intravitreal injections, adhering to strict aseptic conditions. The preparation process involved multiple applications of proparacaine 0.5% and povidone-iodine 5% (Betadine) directly to the injection site. The intravitreal injections were administered using either 30-gauge or 33-gauge needles. No pre- or post-injection topical antibiotics were prescribed. Batch number was the same in all cases (KT0LKCK). In total, 214 vials of aflibercept 8 mg of this batch number have been distributed across all three clinics until August 2024 (63 at clinic A, 41 at clinic B and 110 at clinic C). All described cases were reported to Swissmedic. Clinical characteristics of all cases are resumed in Table 1.

Case 1

An 84-year-old male with a history of nAMD type 1 in his right pseudophakic eye, managed with intravitreal anti-VEGF injections since September 2015, was switched to aflibercept 8 mg. The patient had no ocular comorbidities and was systemically treated for dyslipidemia. His previous ocular treatments included 11 ranibizumab injections, 74 aflibercept 2 mg injections, and 16

Table 1 Patient characteristics and outcomes. Counting fingers (CF), visual acuity (VA), anterior chamber (AC), diagnosis (dx), intravitreal aflibercept injection (IAI), intravitreal injection (IVI), nonsteroidal antiinflammatory drugs (NSAID), neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), central retinal vein occlusion (CRVO)

Case	Institution	Sexe	Age (years)	Dx	Prior IAI	Number of prior IVI	Days to presentation	Injection VA	VA at presentation	Type of inflammation	treatment	Days to resolution	VA at resolution
1	A	male	84	nAMD	yes	18	2	20/20	20/50	Vitreous and spillover AC	Topical steroids	11	20/25
2	A	female	69	nAMD	yes	127	3	20/63	20/80	Vitreous and AC inflammation	Topical steroids and antibiotics	24	20/80
3	A	female	85	nAMD	yes	19	4	20/25	20/40	Vitreous and spillover AC	Topical steroids	12	20/32
4	B	male	89	nAMD	no	7	4	20/20	20/25	Vitreous	Topical steroid and antibiotics	30	20/25
5	B	female	87	nAMD	no	8	17	20/50	20/80	Vitreous and AC inflammation	Topical steroids	18	20/50
6	B	male	63	DME	no	8	3	20/32	20/125	Vitreous and AC inflammation	Topical and systemic steroids	9	20/50
7	C	female	70	DME	yes	14	4	20/20	20/50	Vitreous inflammation	Topical steroids	10	20/20
8	C	male	76	CRVO	yes	13	10	20/100	CF	Vitreous and AC inflammation	Topical steroids and NSAID	14	20/200

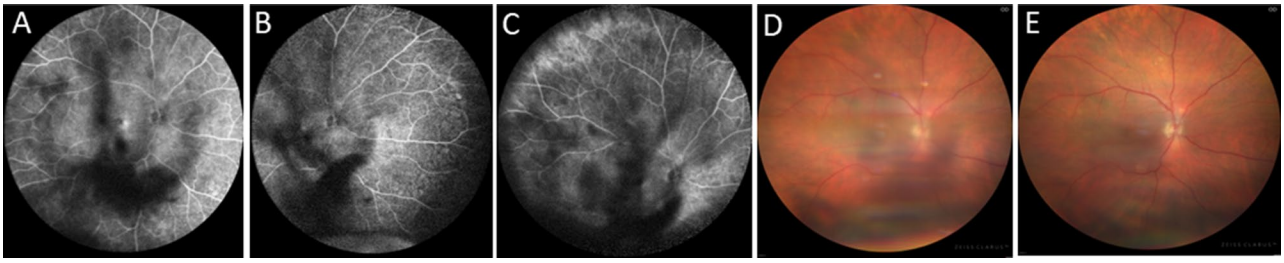

Fig. 1 Fluoresceine angiography and color fundus imaging at presentation showing vitritis in the absence of vasculitis (**A**-**D**). After 5 days, fundus imaging (**E**) showing improved vitritis after topical steroid therapy

faricimab injections at intervals of 4–6 weeks. Two earlier injections of aflibercept 8 mg at similar intervals were uneventful. However, two days after the third aflibercept 8 mg injection, the patient experienced a vision loss from 20/20 to 20/50, along with vitreous floaters, but reported no pain. Upon examination, vitreous cells (grade 2) with spillover into the anterior chamber (grade 1) was observed, without hypopyon or conjunctival injection. Fluorescence angiography did not reveal signs of vasculitis, papillitis, or retinitis (Fig. 1). Optical coherence tomography (OCT) imaging showed an improvement in macular edema. The patient was initially treated with hourly topical prednisolone drops with consecutive tapering, leading to a resolution of the vitritis and a near return to baseline VA (20/25) within 11 days.

Case 2

A 69-year-old female with nAMD in her left pseudophakic eye, managed with a total of 127 intravitreal anti-VEGF injections (including ranibizumab, aflibercept 2 mg, and faricimab), was switched to aflibercept 8 mg. Her ocular comorbidities included primary open-angle glaucoma, treated with a trabeculotomy, and an idiopathic anterior uveitis in the same eye six years prior. The first anterior uveitis occurred seven weeks after an aflibercept 2 mg injection and was attributed to the begin of prostaglandin analogues drops. Afterwards, the treatment with aflibercept 2 mg was continued uneventfully until the switch to aflibercept 8 mg. Three days after the second aflibercept 8 mg injection, she presented with pain presumably related to ocular hypotony of 3mmHg, photophobia, and visual impairment, with her baseline VA dropping from 20/63 to 20/80. Clinical examination revealed conjunctival hyperemia, Descemet membrane folds, and anterior chamber (grade 3) and vitreous cells (grade 2), but no fibrin or hypopyon. There were no retinal or choroidal infiltrates or signs of vasculitis. The patient was treated with topical broad-spectrum antibiotics and steroid drops every hour, resulting in complete resolution of inflammation over the next 24 days, with a VA of 20/80. In this case, ocular hypotony may have contributed to the development of IOI. Optical coherence tomography (OCT) showed a recurrence of subretinal fluid six weeks after the aflibercept 8 mg injection. Subsequent treatment for the subretinal fluid continued with aflibercept 2 mg, administered six weeks after the last aflibercept 8 mg injection, with no side effects and resolution of the subretinal fluid.

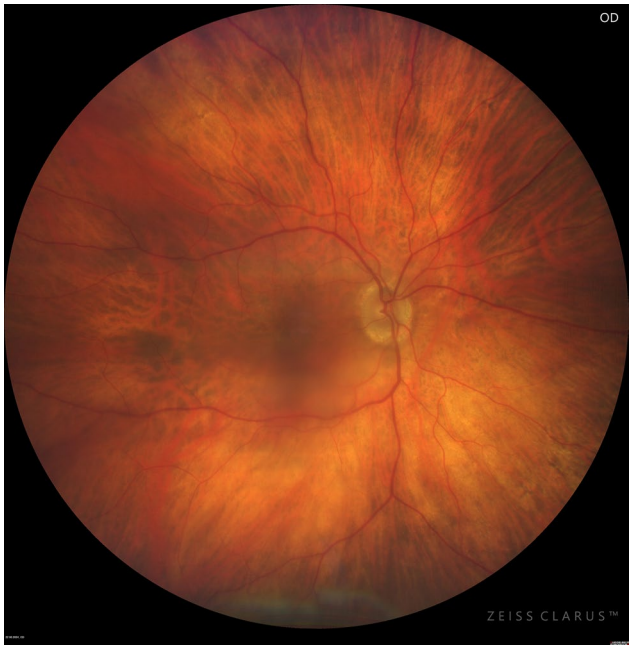

Fig. 2 Color fundus imaging of a central vitreous opacity in the absence of vasculitis or retinitis

Case 3

A 85-year-old female was treated with 5 intravitreal aflibercept 2 mg and 13 brolucizumab injections in the right eye for nAMD. Ocular history was significant for nAMD in the fellow eye and corticonuclear cataract. After the first injection with aflibercept 8 mg, the patient noticed mild transient visual decrease and floaters, but she did not present for clinical examination. Four days following the second injection, the patient noted a visual decrease and floaters. The last recorded VA of 20/25 decreased to 20/40. On exam vitreous cells and spill-over anterior chamber cells (grade 1) were noted in the absence of retinal or vascular involvement (Fig. 2).

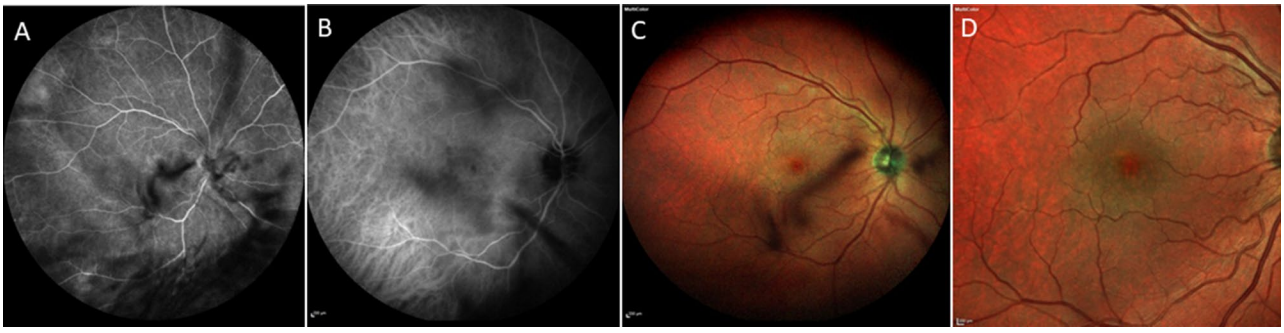

Fig. 3 Fluoresceine, indocyanine green and color fundus imaging at presentation reveal vitritis without retinal-choroidal inflammation or vitritis (**A**-**C**). After steroid treatment the vitritis resolved (**D**)

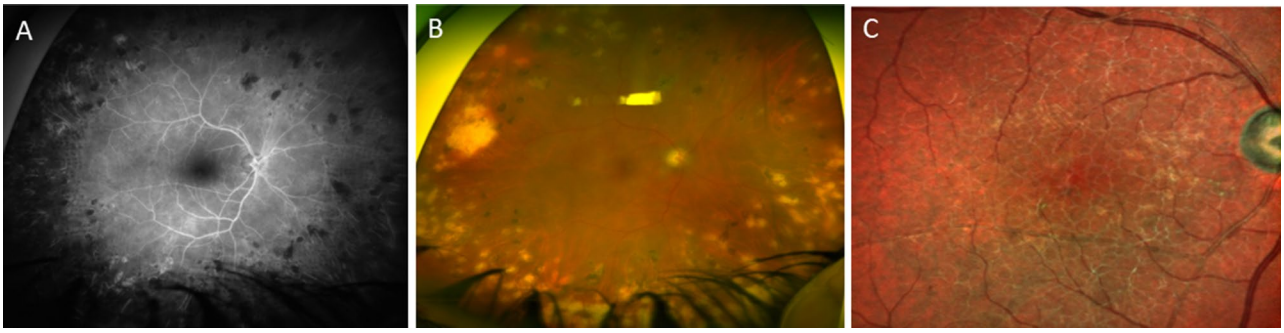

Fig. 4 Fluoresceine angiography and fundus imaging (**A**, **B**) show mild vitritis without vasculitis or papillitis. Inflammation resolved after topical steroids (**C**)

Treatment with hourly topical steroids which were consecutively tapered led to a resolution of the inflammation within 12 days. VA improved to 20/32.

Case 4

An 89-year-old male, undergoing treatment with seven intravitreal faricimab injections for nAMD in his right eye, was switched to high-dose aflibercept. The patient had no ocular comorbidities but was receiving systemic treatment for arterial hypertension.

Four days after his first high-dose aflibercept injection, he presented with floaters and visual impairment, with his VA decreasing from 20/20 to 20/25. Clinical examination revealed vitritis without anterior chamber involvement. On fluoresceine angiography no signs of retino-choroidal inflammation or vasculitis were observed (Fig. 3). Due to the inability to exclude an infectious etiology, the patient was started on systemic antibiotics as well as topical antibiotics and steroids. Subsequently, treatment was reduced to solely topical steroids. Complete resolution of vitreous inflammation took 30 days and VA remained 20/25.

Case 5

An 87-year-old female with a history of nAMD type 3 in her right eye, previously treated with eight ranibizumab injections, was administered high-dose aflibercept. Her systemic comorbidity included hypercholesterolemia. Seventeen days after her first high-dose aflibercept injection, she presented with floaters and visual impairment. Her VA decreased from 20/50 to 20/80. Clinical examination revealed inflammation in both the vitreous and anterior chamber. Treatment with hourly topical steroids resulted in regression of the inflammation within 18 days, and her VA returned to 20/50.

Case 6

A 63-year-old male with proliferative diabetic retinopathy complicated by macular edema had previously received 6 intravitreal ranibizumab injections at 4-weekly intervals between December 2023 and May 2024, with no reported side effects. After these 6 ranibizumab injections, his best-corrected VA was 20/32, but macular edema persisted. As a result, a switch to aflibercept 8 mg was proposed and the patient subsequently received 3 monthly aflibercept 8 mg injections. However, 3 days after the third injection, the patient experienced pain and a decrease in vision to 20/125.

A slit lamp examination revealed significant inflammation with 3+anterior chamber cells, a Tyndall effect, and 2+anterior vitreous inflammation, along with mild vitritis. Fluorescein and indocyanine green angiography showed no signs of retinal-choroidal inflammation or vasculitis (Fig. 4). The patient was treated with

prednisolone eye drops 8 times a day and oral prednisone at 1 mg/kg. At a two-day follow-up, his vision improved to 20/50, and the inflammation decreased, leading to a reduction in the systemic treatment to 40 mg/kg while maintaining the same topical dosage.

Optical coherence tomography imaging continued to show persistent diabetic macular edema. After 9 days of both topical and systemic steroid treatment, the inflammation in the anterior chamber and vitreous resolved, but there was no further improvement in VA.

Case 7

A 70-year-old female received 12 intravitreal aflibercept 2 mg in the left eye for severe proliferative diabetic retinopathy with macular edema (DME) during July 2021 and January 2024 without complications. She was treated for diabetes type 1 since 1955. The first two high-dose aflibercept injections were given in 8-weekly intervals without side effects with a VA of 20/20. Four days following the third injection, the patient presented with foggy vision of 20/50 in the absence of pain. Clinically, the anterior segment was quiet but severe vitreous cells without retinal infiltration or vitreous condensation were noted. The neovascularizations remained stable. Treatment with topical steroids six times daily with consecutive tapering led to a resolution of the vitreous inflammation over the following 10 days. The baseline VA of 20/20 was reached after one week of treatment. Consecutive treatment of macular edema has not been resumed yet.

Case 8

A 76-year-old male with central retinal vein occlusion and massive cystoid macular edema had been previously treated with 13 intravitreal aflibercept 2 mg injections at 4–6-week intervals between December 2022 and January 2024, with no side effects. His VA ranged between 20/200 and 20/80. The patient had systemic comorbidities of diabetes and arterial hypertension and ocular comorbidities of prior vitrectomy for retinal detachment and primary open-angle glaucoma. The switch to aflibercept 8 mg constituted a consensual off-label use since aflibercept 8 mg is currently only approved for the treatment of nAMD and DME. Nine days after his first high-dose aflibercept 8 mg injection, administered with an Omnifix F-Luer Lock Solo syringe and a 33-gauge needle (Mesoram), he presented with anterior chamber cells, Tyndall effect, and vitritis. There were no retinal infiltrates or vitreous opacities observed. Optical coherence tomography (OCT) imaging showed a significant reduction in cystoid macular edema (Fig. 5). However, his VA dropped to below 20/200. Treatment with hourly prednisolone drops and topical nonsteroidal anti-inflammatory drugs (NSAIDs) twice daily led to an improvement in anterior chamber and vitreous inflammation within 4 days. After 10 days, only the anterior chamber reaction persisted. The treatment was stopped after 2 weeks, and his VA returned to 20/200. Ten weeks after the initial injection, the cystoid macular edema recurred. The patient opted to delay further treatment and resumed aflibercept 2 mg one month later without any side effects.

Discussion and conclusions

In this case series, we report a cluster of intraocular inflammation (IOI) occurring after intravitreal aflibercept 8 mg injections. Until now, only one case report described retinal vasculitis after aflibercept 8 mg in the absence of pronounced vitreous inflammation [16]. Ocular inflammation after intravitreal injection is categorized into acute onset sterile inflammation and delayed onset vasculitis, the latter being associated with brolucizumab [6].

A retrospective review reported rates of sterile endophthalmitis following aflibercept 2 mg to be 0.16%, compared to 0.10% for bevacizumab and 0.02% for ranibizumab [7]. Pivotal studies for aflibercept 8 mg indicated a safety profile comparable to aflibercept 2 mg [3–5]. Akiyama et al. recently described retinal vasculitis (localized retinal narrowing) following intravitreal aflibercept 8 mg in three out of 35 treated eyes (8,6%) [16]. However, none of these patients reported symptoms or a visual decline and only in one case mild vitreous cells were detected. Inflammation resolved with a posterior sub-tenon injection of triamcinolone acetonide with or without betamethasone eye drops. The authors discussed an endothelial cell damage due to a potent VEGF inhibition with subsequent monocyte migration and retinal narrowing. Until now, marked vitreous inflammation has only been described within the first three months following the approval of aflibercept 2 mg with a cluster of 15 cases of sterile IOI, which subsequently ceased [11, 12]. Although no definitive cause was identified, a possible batch-specific composition or contamination was suggested.

Previously, IOI following aflibercept 2 mg injection has been associated with higher rates of pain compared to other anti-VEGF agents, possibly leading to a bias towards an initial diagnosis of infectious endophthalmitis [10]. In our series, only one patient reported significant pain presumably due to ocular hypotony, and all cases resolved with topical steroids. Given the clinical presentation of our cases, vitreous specimens were not obtained.

The second mechanism of sterile inflammation with intravitreal anti-VEGF agents is delayed onset retinal vasculitis, which has currently only been associated with brolucizumab and a milder with aflibercept 8 mg. The incidence of IOI after intravitreal brolucizumab injection was reported at 4.6%, with a median interval of 25

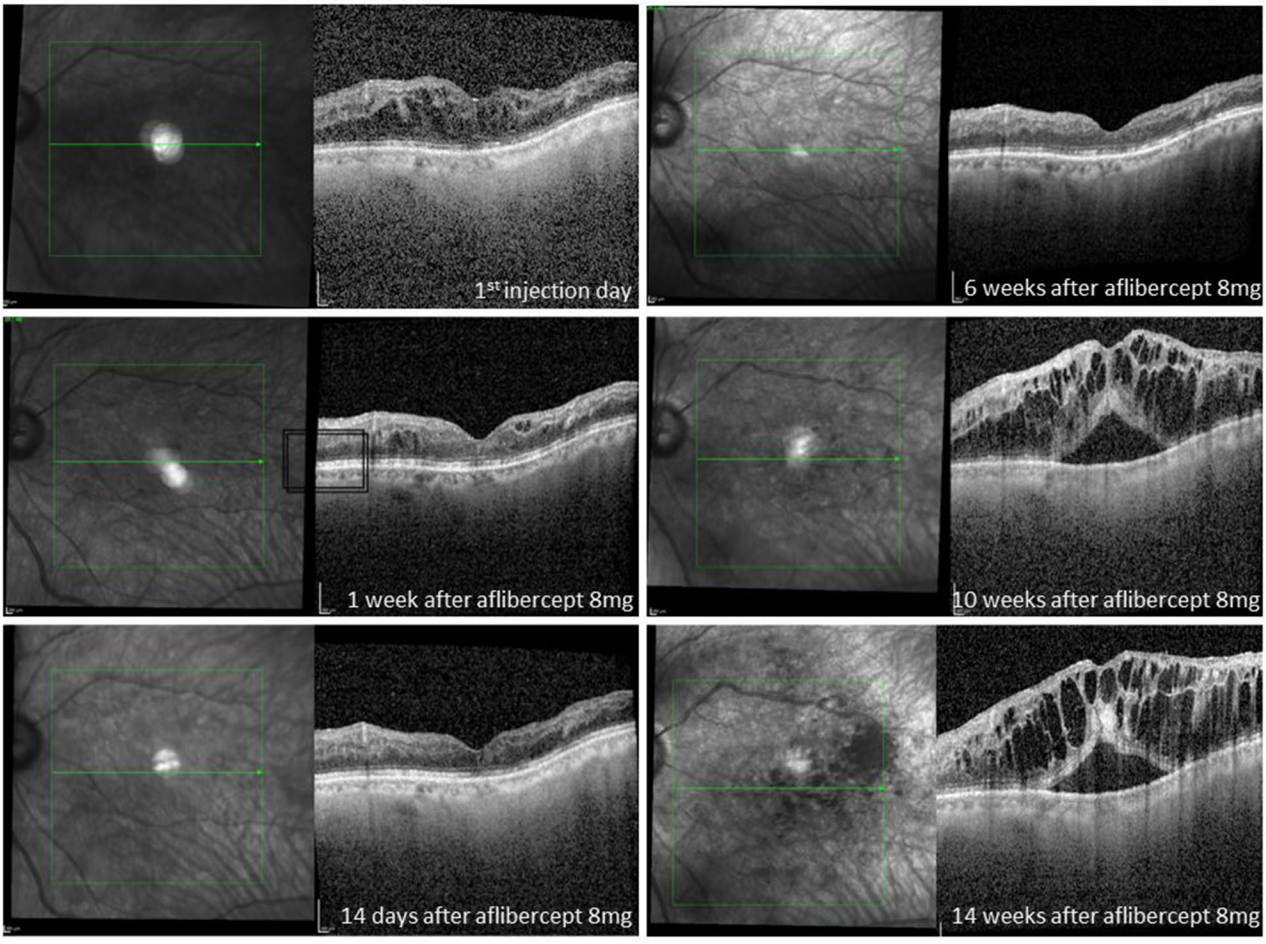

Fig. 5 OCT imaging shows initial regression of macular edema with a recurrence 10 weeks after aflibercept 8 mg

days following the injection [17]. Clinical findings typically include vitreous cells, segmental sheathing, and discontinuity of retinal arteries, vascular nonperfusion, and irregular venous caliber [14–17]. In a post-hoc analysis, three-quarters of subjects experienced their IOI-related event within six months of brolucizumab initiation [17].

Consistent with prior reports of IOI after intravitreal injection, visual recovery in our case series was good [9, 13]. All patients improved with topical steroids and/or topical antibiotics and nonsteroidal anti-inflammatory drops over a course of 11–24 days. In all cases, IOI was primarily noted in the vitreous cavity with spillover into the anterior chamber. Unlike the retinal occlusive vasculitis described with intravitreal brolucizumab [18], our cases showed no signs of papillitis, retinal infiltrates, or vasculitis, as documented in the fluorescence angiography images. When fluorescein angiography was not obtained, ophthalmoscopy did not show areas of inflammation along arterioles and venules.

A history of prior intravitreal anti-VEGF injections has not been shown to increase the risk of IOI with subsequent injections [19]. Likewise, previous studies have found recurrent IOI to be uncommon [9]. In our series, all subjects had previously received intravitreal anti-VEGF injections, with more than half having been treated with aflibercept 2 mg and two having additionally received prior uneventful aflibercept 8 mg injections.

Patient susceptibility factors contributing to IOI after intravitreal anti-VEGF injections may include variability in anti-drug antibodies (ADA) [6, 12]. Baseline aflibercept ADA were reported at 1–3% in the VIEW trials [2]. In our series, all but one patient had previously been treated with aflibercept 2 mg. Other contributing factors include breakdown of the blood-retina barrier, as observed in nAMD, or a history of uveitis, as seen in one case. Furthermore, protein aggregation, particularly induced by released silicone oil from syringes, is discussed as creating immunogenic protein complexes [6, 20]. Improper production, dosage, or storage can also contribute to protein deterioration. The primarily vitreous inflammation sparing the retina seen in our subjects may point towards an impurity or formulation composed of a large protein molecule not entering the retina.

To conclude, we report a cluster of seven acute severe IOI events following the approval of intravitreal aflibercept 8 mg injection at three different institutions. Inflammation was limited to the vitreous and anterior chamber and resolved with good visual outcomes after initiation of topical steroid therapy.

These cases highlight the importance of continued monitoring of the real-world safety profile of aflibercept 8 mg following pivotal studies.

Abbreviations

VEGF	Vascular endothelial growth factor
nAMD	Neovascular age-related macular degeneration
DME	Diabetic macular edema
IOI	Intraocular inflammation
AC	Anterior chamber
VA	Visual acuity
IVI	Intravitreal injection

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Author contributions
Writing of initial manuscript, L.H.; Data acquisition, L.H., M.K, E.O.; Conceptualization, S.M. ,C.E., K.H., Review of manuscript S.M., M.K, E.O, C.E., K.H.; Supervision, K.H. All authors reviewed the manuscript.

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Data availability
The datasets used and/or analyzed in this report are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki.

Consent for publication
Written informed consent has been obtained from the patients to publish this paper.

Competing interests
K.H. received fees for consultancies and advisory board participations from Novartis, Bayer, Roche, and Allergan/Abbvie. S.M. received fees for advisory boards of Bayer, Novartis and Roche and grant support from Bayer, Apellis.

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