Ophthalmology Practice

Batch-related sterile endophthalmitis following intravitreal injection of bevacizumab

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Background: To report a series of patients with sterile endophthalmitis after intravitreal bevacizumab (IVB) injection from 2 different batches of bevacizumab. **Materials and Methods:** Records of 11 eyes with severe inflammation after IVB injections from two different batches (7 eyes from one and 4 from the other) on two separate days were evaluated. Fifteen eyes of 15 patients in one day were treated with one batch and 18 eyes of 17 patients were treated another day using another batch injected for different retinal diseases. Each batch was opened on the day of injection. We used commercially available bevacizumab (100 mg/4 ml) kept at 4°C. Severe cases with hypopyon were admitted to the ward and underwent anterior chamber and vitreous tap for direct smear and culture. **Results:** Pain, redness and decreased vision began after 11-17 days. All had anterior chamber and vitreous reactions and 5 had hypopyon. Antibiotics and corticosteroids were initiated immediately, but the antibiotics were discontinued after negative culture results. Visual acuity returned to pre-injection levels in 10 eyes after 1 month and only in one eye pars plana vitrectomy was performed. Mean VA at the time of presentation with inflammation (1.76 ± 0.78 logMAR) decreased significantly (P = 0.008) compared to the initial mean corrected VA (1.18 ± 0.55 logMAR); however, final mean corrected VA (1.02 ± 0.48 logMAR) improved in comparison with the baseline but not to a significant level (P = 0.159). **Conclusions:** We report a cluster of sterile endophthalmitis following intravitreal injection of bevacizumab from the same batch of bevacizumab that has a favorable prognosis.

Key words: Bevacizumab, inflammation, sterile endophthalmitis

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Bevacizumab (Avastin, Genetech, San Francisco, CA) is a full length humanized monoclonal antibody against VEGF-A and has been approved as a systemic adjuvant treatment for metastatic colon cancer.[1] Used as an intraocular injection, this drug is a common off-label treatment for various VEGF-mediated ocular diseases. Due to the broad spectrum of therapeutic indications and the need for repeated administrations, numerous injections are performed worldwide nowadays. Therefore, the safety and tolerability of such an intervention is important.[2-16]

Following any intravitreal injection, there is always a risk of infectious or non-infectious endophthalmitis. The rate of infectious and non-infectious endophthalmitis with intravitreal injections of bevacizumab is reported to be 0.1% and 1.5% per injection, respectively.[17,18] Differentiating between these two complications is important as the delay in treatment or unnecessary treatment could have unfavorable consequences.

In late 2008, Genetech issued a letter informing ophthalmologists of 36 cases of intraocular adverse reactions after off-label use of intravitreal bevacizumab (IVB). Most of their cases occurred in patients who received IVB from a single batch. However, the precise ocular symptoms, reactions to treatment and visual prognosis were not stated. Recently, Yamashiro *et al*. Reported that 14 eyes developed sterile endophthalmitis after IVB injections from a single batch.[19] To the best of our knowledge, this is the only published report of single batch-related sterile endophthalmitis occurring after IVB injection which is available in the literature.

In the present series, we describe 11 cases of sterile endophthalmitis after IVB treatment that originated from 2 separate batches.

Materials and Methods

This study was approved by the review board/ethics committee of the ophthalmic research center of the university.

A total of 33 eyes received IVB (1.25 mg/0.05 ml) injections for the treatment of different retinal diseases on 2 separate days one week apart, 15 eyes of 15 patients on one day using one batch and 18 eyes of 17 patients on another day using another batch. Each batch was opened on the same day of the injections. All patients were Caucasian. We used commercially available bevacizumab (100 mg/4 mL) kept at 4°C. Bevacizumab was aliquoted into smaller doses (1.25 mg/0.05 mL under sterile conditions in the operation room during injections.

All injections were performed in an operation room under complete sterile conditions. After topical anesthesia, the eye and lids were disinfected. Bevacizumab was injected into the vitreous cavity at a distance of 3.5 to 4 mm posterior to the corneal limbus in the supratemporal quadrant with a 30-gauge needle. To avoid reflux, the injection site was compressed for 30 seconds with a cotton swab. Chloramphenicol drops were prescribed 4 times daily for one week after the injection.

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Patients are instructed to return immediately to the clinic in any occurrence of pain, redness of the eye or decreased visual acuity. Otherwise, they would be scheduled to have a complete routine ophthalmic examination 1 day, 1 week, and 1 month after injection.

A total of 11 out of 33 eyes that received IVB from the two batches during the two mentioned days developed severe intraocular inflammation. The clinical characteristics of these cases are reported in this study focusing on the presence of pain, decreased visual acuity, conjunctival injection, corneal endothelial precipitates, anterior chamber and vitreous reactions, hypopyon, intraocular pressure, and any fundus findings.

The data are presented as mean ± standard deviation and frequencies are reported as percents. To compare the visual outcomes at pretreatment, presentation, and final examination we used Wilcoxon signed rank test.

Results

Four eyes (4 patients) out of 15 eyes (27%) that received IVB from the first batch of bevacizumab on one day and 7 eyes (6 patients) out of 18 eyes (39%) that received IVB from the second batch on another day, developed ocular inflammation. The remaining 22 eyes did not show inflammation on the follow-up examinations. All data regarding the 11 eyes with ocular inflammation are presented. The age, gender, laterality, lens status, background ocular disease, history of prior IVB injection, and primary corrected visual acuity (VA) of the cases are shown in Table 1.

The mean time of the first presentation with ocular inflammation following IVB injections was 13.45 ± 1.63 days (ranged 11-17). The presenting symptoms were eye pain, redness and decreased vision. The detailed data of patients' symptoms and ocular findings on the day of presentation for each case are presented separately in Table 2. None of the eyes had lid swelling, chemosis, and severe ocular pain.

Hypopyon formation occurred in 5 eyes (2 with a history of prior injection) of 4 patients, who were admitted to the hospital [Fig. 1]. All admitted cases underwent anterior chamber and vitreous tap for direct smear and culture. Intravenous antibiotics (ceftazidime and vancomycin) and oral prednisolone, as well as topical eye drops including ciprofloxacin, betamethasone and a cycloplegic, were administered on the day of admission after taking anterior chamber and vitreous samples. Smear and culture results were negative in all cases. Systemic and topical antibiotics were discontinued after 3 to 5 days, depending on the patients' conditions.

For the other cases (6 patients) who were followed as outpatients, oral ciprofloxacin, oral prednisolone, and the same topical eye drops were prescribed.Systemic and topical antibiotics were continued for only 2-3 days.

In all eyes, the inflammatory reaction subsided in the anterior chamber within 1 week and in the vitreouss opacity within 1 month. The medications were tapered off within 14 to 31 days depending on the treatment response. One patient, who discontinued his drugs by himself after 22 days, developed reactivation of the inflammation with hypopyon formation on day 16 of discontinuation. He was treated with the drugs mentioned for the admitted cases. After tapering steroids, the inflammation was aggravated in this patient. Consequently, pars plana vitrectomy was performed.

Corrected VA improved in all eyes compared to their pretreatment levels, except in one. Mean VA at the time of presentation with inflammation (1.76 ± 0.78 logMAR) decreased significantly ($P = 0.008$) in comparison to the mean initial corrected VA (1.18 ± 0.55 logMAR); however, final mean corrected VA (1.02 ± 0.48 logMAR) improved in comparison with the baseline but not to a significant level ($P = 0.159$).

Discussion

This study presented 11 consecutive cases of endophthalmitis after intravitreal injection of bevacizumab that had been drawn from 2 batches on 2 separate days. Although the occurrence of a consecutive series of endophthalmitis after using a single batch would be in favor of an infectious diagnosis, we

Table 1: Patients' characteristics

Case No.	Age (year)	Gender	Eye	Background Disease	Prior IVB injection	Onset of symptoms after injection (days)	Initial VA	VA at the time of endophthalmitis	Final VA
1	40	male	L	BRVO	0	13	5/10	4/10	6/10
2	51	male	L	CSME	0	14	8/100	6/100	9/100
3	39	male	L	CSR	0	15	2/10	6/100	1/10
4	77	female	R	CNV	0	11	1/100	HM	8/100
5	*	*	L	CNV	0	13	2/100	1/100	8/100
6	61	male	R	PDR	0	13	1/100	HM	1/100
7	80	female	L	CNV	2	12	5/100	2/100	5/100
8	50	female	R	CNV	4	14	6/100	HM	6/100
9	64	female	L	BRVO	0	14	8/100	6/100	8/100
10	68	female	L	NAION	0	12	1/10	8/100	1/10
11	59	male	R	CNV	1	17	2/10	HM	5/100

IVB: Intravitreal bevacizumab, VA: Visual acuity, R: Right, L: Left, BRVO: Branch retinal vein occlusion, CSME: Clinically significant macular edema, CSR: Central serous retinopathy, CNV: Choroidal neovascularization, PDR: Proliferative diabetic retinopathy, NAION: Nonarteritic ischemic optic neuropathy, HM: Hand motion, *Sound eye of case no 4

Table 2: Clinical findings of eyes with sterile endophthalmitis after intravitreal injection of bevacizumab

Case No.	Pain	Decreased vision	Conjunctival hyperemia	Corneal endothelial precipitates	AC cells	hypopyon	PS	Vitreous opacity	Culture
1	+	-	+	-	1+	-	-	1+	N/A
2	+	-	+	-	2+	-	-	1+	N/A
3	+	-	+	+	3+	-	-	2+	N/A
4	+	+	+	+	3+	+	+	3+	Negative
5*	+	+	+	+	3+	+	+	3+	Negative
6	+	-	+	-	3+	+	-	3+	Negative
7	+	+	+	+	3+	-	-	3+	N/A
8	+	+	+	-	3+	+	+	3+	Negative
9	+	+	+	+	2+	-	+	1+	N/A
10	+	-	-	-	2+	-	-	1+	N/A
11	+	+	+	-	3+	+	-	3+	Negative

PS: Posterior synechia, AC: Anterior chamber, *Sound eye of case no 4

Anterior chamber cells were graded as follows: +, 5 to 20 cells; ++, 20 to 50 cells; and +++,>50 cells per 1 × 1-mm slit-beam field, Vitreous opacity grades: 1 +, retinal vessels are hazily visible; 2+, optic nerve head is visible but border of the optic nerve head is quite blurry; and 3+, optic nerve head is obscure,

The authors have no interest in the materials presented in the study

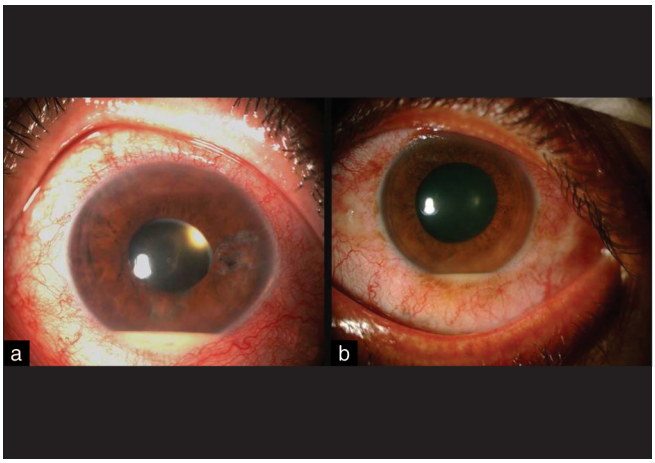

Figure 1: A Slit- lamp photographs of case 5 (a) and case 8 (b)

considered sterile endophthalmitis as the diagnosis, since 10 patients were effectively treated with medications despite receiving short antibiotic courses and only in one eye was pars plana vitrectomy performed. In addition, none of the eyes presented with symptoms and signs in favor of infectious endophthalmitis such as lid swelling, chemosis, and severe ocular pain and all cases had good visual outcomes. Moreover, the smears and cultures which were performed in the severe cases were negative for any microorganism.

Endophthalmitis after IVB injection from a single batch had also been reported in 14 cases by Yamashiro *et al.* The batch was aliquoted into smaller doses for 20 cases. Presentation times for their cases were 1-3 days after the injections which were shorter than those of our patients (11-17 days). They performed pars plana vitrectomy for 5 eyes that had a 3 + vitreous opacity. None of these eyes had a positive culture. In most of their cases (12 of 14) VA returned to pre-endophthalmitis levels 1 month after the injections. They concluded that their cases developed a sterile endophthalmitis after IVB injection from a single batch and had a favorable prognosis. Of their cases, 3 developed hypopyon that underwent pars plana vitrectomy with installation of intravitreal antibiotics (vancomycin and ceftizidime) on the third day, and cultures were all negative for gram-positive bacteria, gram-negative bacteria, and fungi.[19] Our cases, similarly, had good visual outcomes. However, all of them, except one,treated successfully by nonsurgical approaches, even in cases having the same severity of inflammation with hypopyon (4 of 5 eyes).

In one of our patients, reactivation of inflammation with hypopyon formation developed on day 16 after discontinuation of the drugs. He treated medically. After tapering steroids, the inflammation was aggravated again. Then, the patient underwent vitrectomy,smears and cultures were negative for any microorganism. The possibility of low-grade infective endophthalmitis could not ruled out.

Georgopoululos *et al.* Reported an early onset (up to 2 days) intraocular inflammation with painless loss in VA and mostly without conjunctival or ciliary injection in 8 patients following IVB injections from multiple batches. None of their cases experienced hypopyon formation. Therefore, the severities of inflammation in their cases were less than those of the present report and that of Yamashiro *et al.* These patients responded to systemic or topical corticosteroid treatment with a slow recovery but without permanent damage.[20]

Sophie *et al.* Reported 2 patients with iritis and 2 other patients with vitritis 2-7 days following IVB injections. Their cases improved with topical cycloplegic and corticosteroid therapy.[21] Wickremasingle *et al.* have also reported 19 cases of acute severe intraocular inflammation after IVB treatment at 6 different clinical practices. They suggested the possibility that trace endotoxin contamination of the bevacizumab, a contamination of a level not sufficient to cause any signs when administered systemically, might have resulted in the intraocular inflammation. In addition, bevacizumab is a full-length humanized IgG antibody; therefore, repeated injection might increase the risk of sterile endophthalmitis.[22] In our study, 3 eyes had prior IVB injections, of which, 2 developed hypopyon.

Postoperative inflammation is a rare, but serious, complication because progression to endophthalmitis might result in irreversible vision loss. Differentiating cases of sterile from infectious endophthalmitis may be challenging. We believed that endotoxin contamination or chemical changes in these two batches of bevacizumab might be responsible for causing an immunologic reaction in our cases. However, late onset presentation of our cases, as apposed to other studies,[22,23] was not in favor of such diagnosis and reminded the diagnosis of late infectious endophthalmitis. Not analyzing bevacizumab vials for bacterial endotoxin, however, was a shortcoming in our series.

As shown in our study, the presentation of sterile endophthalmitis in some cases was so severe that its differentiation from the infectious type was clinically impossible, especially in cases with hypopyon formation. Therefore, one would start antibiotics and wait for the culture results and the patient's response to treatment, to make the final diagnosis. We considered sterile endophthalmitis as the diagnosis in our cases. Nonetheless, we did not have sufficient data for making such a diagnosis, since smear and culture were not performed for all cases and none of the cases underwent polymerase chain reaction test. In addition, all patients received a course of antibiotic treatment, although for a short period in most cases, which made the diagnosis suspicious.

In summary, sterile endophthalmitis may occur in a series of patients after IVB injection from a single batch. Some of these inflammations are very severe, inspiring the diagnosis of infectious endophthalmitis; nevertheless, the prognosis is generally favorable and the patients usually respond to non-surgical management. To be on the safe side, however, one should always consider an infectious cause at initial presentation until further clues prove otherwise. Given that the number of IVB injections is growing rapidly, more studies covering postinjection endophthalmitis are warranted, focusing on useful hints for a better diagnosis.

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