Vitrectomy does not Cure Bevacizumab Induced Uveitis

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ABSTRACT
Non-infectious inflammation associated with intravitreal antivascular endothelial growth factor injections has been reported recently. Failure to recognize this sterile inflammation can result in unnecessary treatment for endophthalmitis.

We describe a case of acute noninfective intraocular inflammation following the third intravitreal injection of bevacizumab for nonischemic central retinal vein occlusion-associated cystoid macular edema in a 74-year-old man who responded temporarily to repeated intravitreal antibiotics and vitrectomy. Prolonged use of systemic steroid (oral prednisolone monotherapy) resulted in resolution of the uveitis. No organisms could be demonstrated even on repeated aqueous and vitreous taps.

Bevacizumab-induced uveitis is a rare event and its pathogenesis remains unclear. With the increasing use of bevacizumab, it is important to be aware of its potential to be associated with intraocular inflammation and to differentiate it from infective endophthalmitis.

Keywords: Intravitreal bevacizumab, Uveitis, Vitrectomy, Bevacizumab-associated uveitis.

INTRODUCTION
Vascular endothelial growth factor (VEGF) is a mediator of many pathologic conditions, including events following central retinal vein occlusion. Bevacizumab (Avastin; Genentech, Inc.) is a humanized monoclonal antibody which nonselectively targets all isoforms of VEGF and has been found to be efficacious for treating cystoid macular edema (CME) secondary to central retinal vein occlusion (CRVO).1 Intravitreal bevacizumab has been shown to slow the rate of vision loss with regression of macular edema.

CASE HISTORY
A 74-year-old gentleman underwent two uneventful intravitreal bevacizumab injections at two-month intervals for CME associated with nonischemic CRVO in his left eye. After each injection, his vision improved by four lines (6/24 to 6/9) along with regression of CME. The third intravitreal bevacizumab injection was administered 2 months later for recurrent CME.

The day after the third injection was administered, an intense anterior segment reaction with 3+ cells, streak of hypopyon and vitreous cells was noted. There was absence of conjunctival hyperemia, circumciliary injection and pain. Vitreous cells were presented and details of the first order retinal vessels were seen. His vision continued to deteriorate. The vitritis worsened obscuring fundus details, despite intense topical steroids, antibiotics and intravitreal vancomycin, cefazidime and dexamethasone. He was presumed to have infective endophthalmitis caused by a very virulent bacteria, considering the hyperacute first postinjection day presentation. He underwent vitrectomy with injection of intravitreal antibiotics and dexamethasone, three days after intravitreal bevacizumab injection (after a waiting period of 48 hours of intravitreal antibiotics).

Vitrectomy with intravitreal injection of antibiotic and steroid resulted in transient improvement of vision and resolution of vitritis which lasted for two days. Repeat injection of antibiotic-steroid combination also had only a transient effect. The anterior chamber and multiple vitreous aspirates were cultured and smear negative for microorganisms. The patient did not develop keratic precipitates but showed intense cellular reaction in the anterior chamber and vitreous. He was then presumed to have bevacizumab related uveitis and was treated with oral prednisolone and topical steroid antibiotic resulting in resolution of vitritis and improvement in vision to 6/24. Subtenon or intravitreal triamcinolone was not opted as the patient also suffered from primary open angle glaucoma (POAG).

DISCUSSION
It is imperative to differentiate infective endophthalmitis from bevacizumab uveitis as the treatment and prognosis are vastly different. The clinical features of bevacizumab uveitis: gathered from previous studies and our patient—are as follows:2-7
- Presentation on the first or second day after injection
- Absence of pain
• Loss of vision—the primary symptom
• No conjunctival hyperemia
• No circumciliary injection
• Negative anterior chamber/vitreous tap
• Granulomatous anterior chamber and vitreous inflammation.

Unlike in the reported series, our patient showed non-granulomatous inflammation that did not respond to intense topical steroid or intravitreal dexamethasone, necessitating vitrectomy. He also showed a hypopyon that could be aspirated on anterior chamber tap. Our patient also underwent vitrectomy and the transient improvement was possibly due to the intravitreal dexamethasone administered along with the intravitreal antibiotics at the conclusion of surgery. The transient nature of the improvement probably signifies that the anti-VEGF was already bound to the VEGF rich vascular tissue in the eye, inciting repeated immunologic response despite removal of the vitreous. This explains why some patients in a prior report needed steroid therapy for up to two months. Studies having shown the presence of bevacizumab in the vitreous for up to three months and as in our patient, prolonged systemic steroid may be necessary. Alternatively, systemic steroids can be substituted with long acting intravitreal or periocular steroids. This was, however, avoided in our patient due to pre-existing POAG.

With the ever increasing usage of intravitreal bevacizumab for treating vitreoretinal diseases, it is imperative to differentiate bevacizumab associated uveitis from the dreaded infective endophthalmitis as the treatment and prognosis vary vastly. One can differentiate the two conditions by the clinical features mentioned above. The transient response to intravitreal dexamethasone indicates that longer acting steroid, such as intravitreal/subtenon triamcinolone or systemic steroid may be more appropriate in treating bevacizumab associated uveitis. Further, bevacizumab injections may have to be avoided in patients developing bevacizumab associated uveitis. Whether the immunologic response recurs in these patients with eye specific anti-VEGF agents remains to be seen.

REFERENCES