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Anterior Uveitis Secondary to Intravitreal Bevacizumab Injection: A Case Report

İntravitreal Bevacizumab Enjeksiyonuna Sekonder Anterior Üveit: Olgu Sunumu

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ÖZ

Amaç: İntravitreal bevacizumab enjeksiyonuna sekonder gelişen anterior üveit olgusunun klinik özellikleri ve takibini sunmak.

Olgu Sunumu: 73 yaşında neovasküler tip yaşa bağlı makula dejenerasyonu (YBMD) nedeniyle kliniğimiz retina biriminde takipli kadın hasta, sol göz intravitreal bevacizumab enjeksiyonundan 13 gün sonra başlayan sol gözde ağrı ve görmede azalma yakınmaları ile tarafımıza başvurdu. Yapılan oftalmolojik muayenesinde görme keskinlikleri sağda 1.5 logMAR, solda 2.3 logMAR seviyesindeydi. Göz içi basınçları sağda 20 mmHg, solda 40 mmHg olarak ölçüldü. Biyomikroskobik muayenesinde sağda ön segment doğal, solda kornea alt parasantralinde granülomatöz keratik presipitatlar, ön kamarada +3 flare mevcuttu. Ayrıca psödoeksfoliasyon mevcuttu, pupil sınırları düzgündü, posterior sineşi izlenmedi. Dilate göz dibi bakısında, sağda YBMD ile uyumlu skar, solda ise retina flu izlenmekteydi. Oküler ultrasonografide solda retina yatışık izlendi, vitreusda reaksiyon görülmedi. Hasta intravitreal bevacizumab enjeksiyonuna sekonder üveit olarak değerlendirildi ve servisimize takip ve tedavi amacıyla yatırıldı. Topikal kortikosteroid tedavisi ve anti-glokomatöz tedavi ile bulgularında gerileme görüldü ve 3 ay süre ile takip edildi.

Sonuç: İntravitreal bevacizumab enjeksiyonuna bağlı anterior üveit nadir görülen bir komplikasyondur. Ayırıcı tanıda endoftalmi mutlaka düşünülmeli ve steril intraoküler enflamasyonda, uygun vakalarda, topikal kortikosteroid tedavisi ile başarılı sonuçlar alınabilmektedir.

Anahtar Sözcükler: Anti-vasküler endotelyal büyüme faktörü (anti-VEGF); anterior üveit; bevacizumab; intraoküler enflamasyon

ABSTRACT

Objective: To present the clinical features and follow-up of a case of anterior uveitis secondary to intravitreal bevacizumab injection.

Case Presentation: A 73 year old female patient, under follow up in our retina unit for neovascular age-related macular degeneration (AMD), presented with complaints of pain and decreased vision in the left eye that started 13 days after an intravitreal bevacizumab injection. On ophthalmologic examination, best corrected visual acuity was 1.5 logMAR in the right eye and 2.3 logMAR in the left eye. Intraocular pressure was measured as 20 mmHg in the right eye and 40 mmHg in the left eye. Biomicroscopic examination revealed a normal anterior segment in the right eye, while in the left eye, granulomatous keratic precipitates were observed in the inferoparacentral cornea, along with +3 flare in the anterior chamber. Pseudoexfoliation was present; the pupillary margins were regular, and posterior synechiae were not detected. Dilated fundus examination revealed a scar consistent with AMD in the right eye, while the retina appeared hazy in the left eye. Ocular ultrasonography demonstrated an attached retina in the left eye without vitreous opacities. The patient was evaluated as anterior uveitis secondary to intravitreal bevacizumab injection and was hospitalized for follow-up and treatment. Topical corticosteroid and anti-glaucomatous therapy were initiated, leading to regression of findings, and the patient was followed up for 3 months.

Conclusion: Anterior uveitis secondary to intravitreal bevacizumab injection is a rare complication. Endophthalmitis should always be considered in the differential diagnosis, and in appropriate cases, successful outcomes can be achieved with topical corticosteroid therapy at sterile intraocular inflammation.

Key Words: Anti-vascular endothelial growth factor (anti-VEGF); anterior uveitis; bevacizumab; intraocular inflammation

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INTRODUCTION

Anti-VEGF (vascular endothelial growth factor) agents are increasingly used for the treatment of a wide variety of retinal diseases, including age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vascular occlusions, and retinopathy of prematurity (1,2).

Bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA, USA) is a full-length (Fab and Fc) humanized murine IgG1 monoclonal antibody against VEGF-1. It first received U.S. Food and Drug Administration (FDA) approval for the treatment of colorectal cancer and later other malignancies in 2004, but has been used off-label to treat neovascular AMD and other retinal diseases. This is the most widely used anti-VEGF agent, according to the 2018 ASRS survey, which found bevacizumab to be the agent of the first choice in neovascular AMD for 70.2% of US retinal specialists (2,3).

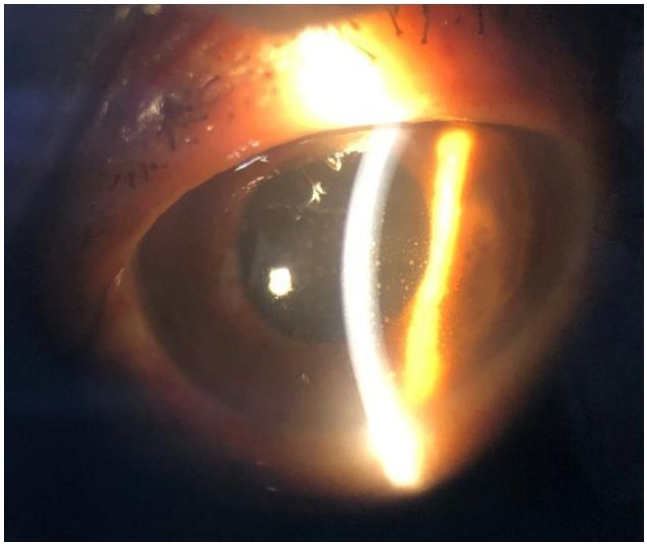
Although intravitreal agents are well tolerated and safe, the number of reports on rare inflammatory reactions after their use has increased in recent years. These reactions, called sterile endophthalmitis or non-infectious endophthalmitis, cause a marked decrease in visual acuity and can be difficult to differentiate from infectious endophthalmitis. Developing rapidly and typically within 1-4 days after intravitreal injection, patients often complain of decreased visual acuity and floaters (4).

In this case report, we aimed to present the clinical features and follow-up of a case with anterior uveitis secondary to intravitreal bevacizumab injection.

CASE REPORT

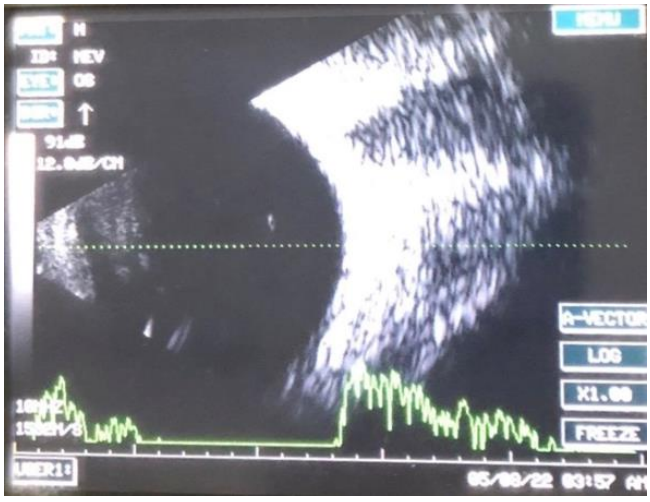
A 73-year-old woman came to our clinic with complaints of reduced vision and mild eye pain in her left eye, which had lasted for two days. These symptoms started 13 days after she received an injection of intravitreal bevacizumab. The patient had high blood pressure but no other systemic diseases. There was no history of glaucoma or uveitis. Her medical records showed that she had received three injections of intravitreal bevacizumab in her right eye two years ago, and two injections in her left eye related to AMD, with the last one given four months before this episode. She had not received any other anti-VEGF injections besides bevacizumab. No inflammatory reactions had been noted after her previous injections. Her records indicated that her visual acuity before the latest injection was 1.5 logMAR in the right eye and 1.4 logMAR in the left eye. During the eye exam, her best-corrected visual acuity was 1.5 logMAR in the right eye and 2.3 logMAR in the left eye. The intraocular pressure measured 20 mmHg in the right eye and rose to 40 mmHg in the left eye. A slit-lamp examination showed a normal anterior segment in the right eye. In the left eye, there were granulomatous keratic precipitates in the inferior paracentral cornea and +3 flare in the anterior chamber. Pseudoexfoliation was also observed. The pupils were equal, round, and responsive to light, with no afferent pupillary defect (Figure 1).

Figure 1: Granulomatous keratic precipitates in the lower paracentral cornea in the slit-lamp examination



A dilated fundus exam showed a clear vitreous and a macular scar consistent with AMD in the right eye. However, the retinal image in the left eye was blurred. Ocular ultrasonography revealed no vitreous opacities in the left eye (Figure 2).

Figure 2: On ocular USG, no reaction was observed in the vitreous on the left eye



In the differential diagnosis of granulomatous anterior uveitis, we considered systemic inflammatory and infectious causes, including sarcoidosis, tuberculosis, syphilis, and autoimmune rheumatologic diseases. The patient had no previous history of uveitis or systemic inflammatory disease. We consulted internal medicine, but no clinical or laboratory findings indicated systemic granulomatous or autoimmune disease. Based on the clinical presentation, the timing with the intravitreal bevacizumab injection, lack of vitreous involvement, and the positive response to corticosteroid therapy, we diagnosed sterile anterior uveitis. The patient was assessed as having uveitis due to the intravitreal bevacizumab injection and was admitted to our service for follow-up and treatment.

As medical treatment, the patient was started on topical moxifloxacin 0.5% eye drops six times daily, prednisolone acetate 1% eye drops 24 times daily, and cyclopentolate 1% eye drops three times daily. In addition, oral acetazolamide 250 mg was administered twice daily, along with a fixed combination of brimonidine tartrate (2 mg/mL) and timolol maleate (5 mg/mL) eye drops twice daily to control the elevated intraocular pressure. A subconjunctival injection of dexamethasone (4 mg/mL) was also administered.

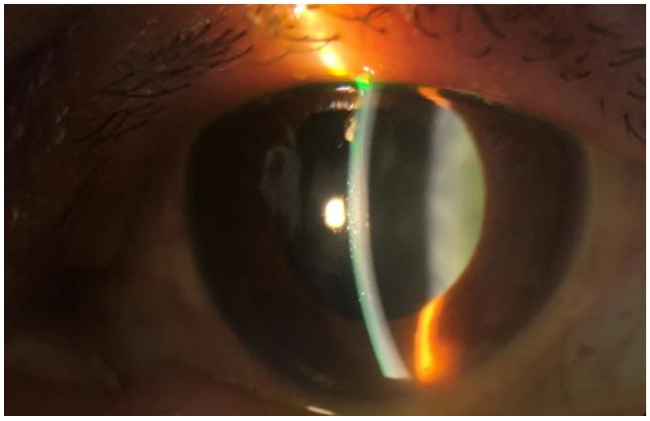
On the first day of follow-up, best-corrected visual acuity was 1.5 logMAR in the right eye and improved to 1.3 logMAR in the left eye. Intraocular pressure measured 22 mmHg in the right eye and 30 mmHg in the left eye, and topical brinzolamide 1% eye drops were added twice daily. Slit-lamp examination showed a marked regression of anterior segment inflammation, with +1 flare and residual keratic precipitates in the left eye, while the anterior segment was normal in the right eye. Dilated fundus examination revealed findings consistent with AMD in both eyes.

At discharge on the third day of treatment, best-corrected visual acuity remained stable at 1.5 logMAR in the right eye and 1.3 logMAR in the left eye. Intraocular pressure was 22 mmHg in the right eye and 28 mmHg in the left eye. The patient was discharged with prednisolone acetate 1% eye drops 24 times daily, a fixed combination of brimonidine tartrate and timolol maleate eye drops twice daily, brinzolamide 1% eye drops twice daily, cyclopentolate 1% eye drops three times daily, oral acetazolamide 250 mg twice daily, and oral potassium citrate and potassium bicarbonate once daily.

At the 1-month follow-up visit, best-corrected visual acuity was 1.5 logMAR in the right eye and improved to 0.8 logMAR in the left eye. Intraocular pressure measured 21 mmHg in the right eye and 25 mmHg in the left eye. The patient was continued on loteprednol etabonate 0.05% eye drops four times daily, a fixed combination of brimonidine tartrate (2 mg/mL) and timolol maleate (5 mg/mL) eye drops twice daily, and brinzolamide 1% eye drops twice daily.

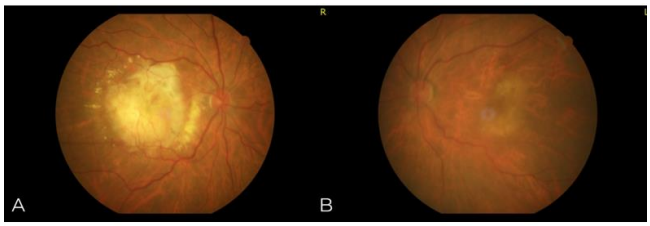
Slit-lamp examination was unremarkable in the right eye, while mild anterior chamber inflammation (+1 flare) with residual keratic precipitates was observed in the left eye (Figure 3).

Figure 3: At the 1st month follow uo +1 flare was seen on the left and keratic precipitates were observed in the slit-lamp examination



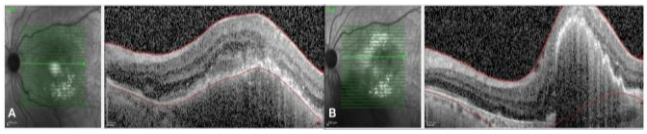
Dilated fundus examination revealed findings consistent with AMD in both eyes (Figures 4A and 4B).

Figure 4: (A) Dilated fundus examination revealed findings related to neovascular age-related macular degeneration in the right and (B) left eye



Optical coherence tomography (OCT) images obtained before the intravitreal injection and at the 1-month follow-up demonstrated findings compatible with AMD, without new inflammatory changes (Figures 5A and 5B).

Figure 5: (A) Optical coherence tomography findings before and (B) after intravitreal injection at the 1st month follow up. Optical coherence tomography findings before intravitreal injection and at the 1st month follow up were compatible with neovascular age-related macular degeneration and edema was regressed after intravitreal injection



At the 3-month follow-up, anterior uveitis findings had completely resolved. Intraocular pressure was 20 mmHg in the right eye and 22 mmHg in the left eye, and retinal findings remained stable.

DISCUSSION

In the present case, a 73-year-old woman developed acute anterior uveitis characterized by granulomatous keratic precipitates, increased anterior chamber flare, mild ocular pain, elevated intraocular pressure, and reduced visual acuity 13 days after intravitreal bevacizumab injection. Notably, there was no evidence of vitreous involvement on clinical examination or ocular ultrasonography, and hypopyon or fibrin formation was absent. Despite the presence of ocular pain, the inflammation was confined to the anterior segment and showed a rapid and favorable response to topical and periocular corticosteroid therapy. These clinical features, together with the subacute onset and lack of progressive deterioration, supported the diagnosis of sterile intraocular inflammation presenting as anterior uveitis rather than infectious endophthalmitis.

While eye pain often indicates infectious endophthalmitis, the intensity of the pain and other accompanying signs are more revealing than simply having pain. In this case, the reported pain was mild, and there was no eyelid swelling, purulent discharge, significant conjunctival chemosis, hypopyon, or fibrin formation. Anterior segment inflammation was confined to the anterior chamber, and ocular ultrasonography did not reveal vitreous opacities suggestive of vitritis. Additionally, the onset was not hyperacute, and the clinical presentation did not show the rapid decline typically associated with infectious endophthalmitis. Based on these observations, we decided to diagnose sterile intraocular inflammation presenting as anterior uveitis.

Sterile intraocular inflammation was defined as acute onset, non-infectious, and resolved intraocular inflammation without antibiotic therapy, and its reported incidence ranges from 0.02% to 0.37%, depending on the study. Sterile intraocular inflammation is also called pseudoendophthalmitis (2,5,6).

It is difficult to distinguish between infectious endophthalmitis and non-infectious inflammation. Inflammation severity and duration are the main distinguishing factors but may overlap. The presentation within 24-48 hours, a significant decrease in visual acuity, eyelid edema, purulent discharge, severe conjunctival inflammation, +3 or more cells and flare, fibrin, and hypopyon in the anterior chamber is more suggestive of infectious endophthalmitis. In non-infectious inflammation, although the duration is very variable, it usually presents after days, and pain is usually absent or may be mild. Visual acuity may range from mild to severe, with mild cell and flare, and fibrin and hypopyon usually absent. If the inflammation is relatively mild, it is well-advised to start topical corticosteroids (with or without cycloplegia) and monitor closely. Infectious endophthalmitis is more likely in patients with more severe inflammation, and aqueous or vitreous sampling (vitreous tap or pars plana vitrectomy) and broad-spectrum intravitreal antibiotics should be considered (7).

Acute onset sterile inflammation occurs clinically in a wide spectrum ranging from anterior chamber inflammation to significant inflammation mimicking endophthalmitis. In addition to decreased vision in our case, mild pain in the eye, presence of anterior uveitis findings without hypopyon, and clear vitreous on ultrasound suggested that the clinical picture was sterile intraocular inflammation presenting as anterior uveitis. Sterile inflammations often begin within the first 5 days after intravitreal injection. It may not draw attention in patients who are asymptomatic in whom pain is not evident and whose control examination is performed at late intervals. In our case, the patient stated that mild pain and decreased vision started on the 11th day after the intravitreal injection, and she presented to us on the 13th day. Considering the level of anterior uveitis findings, we think that the inflammation starts within the 1st week after the injection.

Among the possible causes of acute-onset sterile endophthalmitis, patient-related, and drug-related causes are suggested. These include the patient's susceptibility to immunological reaction, the patient's history of uveitis and autoimmune disease, the increased permeability of the blood-retinal barrier secondary to exudative type AMD, the presence of

anti-drug (ADA) antibodies in the patient, the presence of endotoxin related to the production of anti-VEGF agents by recombinant deoxyribonucleic acid (DNA) technology. There are reasons such as changes in protein aggregation and conformation, the increase in protein denaturation of the silicon on the inner surface of the syringes, and the immunological reaction of injected silicon-protein complexes in the vitreous (8). Despite all these explanations, it is still not possible to fully explain the cause of sterile inflammation.

It is known that sterile uveitis/endophthalmitis develops after intravitreal use of all anti-VEGF in clinical use. In a recent publication, the rate of sterile uveitis/endophthalmitis was reported as 0.05–1.1% after intravitreal bevacizumab, 0.005–1.9% after ranibizumab, and 0.05–2.1% after aflibercept (8). Fung et al. bevacizumab-associated ocular inflammation was documented in 0.14% of patients, according to an international intravitreal bevacizumab safety survey study (9). Most cases were graded as mild to moderate and occurred 2 to 7 days after injection. None of the cases had hypopyon or progressed to endophthalmitis. Wickremasinghe et al. found that 19 of 1278 intravitreal bevacizumab injections over 12 months were associated with acute inflammation (1.49%) (10). Looking at the epidemiological data, the Age-Related Macular Degeneration Treatment Trials (CATT) Comparison between ranibizumab and bevacizumab, according to the 2nd year results, respectively, for pseudoendophthalmitis (0.3% vs. 0.0%; P=1.00) or endophthalmitis (0.7% vs. 1.2%; P = 0.38) rates were not different (11).

In the literature, case reports of anterior uveitis after bevacizumab injection show similar features to our case. Antonopoulos et al. reported a case of a 75-year-old female patient who presented with complaints of watering in the right eye, light sensitivity and decreased visual acuity on the 5th day after the second dose of intravitreal bevacizumab injection for the treatment of neovascular AMD. There was a history of hypothyroidism as an additional disease. Snellen's visual acuity decreased from 20/50 to counting fingers. In the slit lamp examination, 1+flare and 1+corneal edema were accompanied, and hypopyon and vitreous were not observed. The case was also diagnosed with decompensated corneal dystrophy and prednisolone acetate % 1 and hypertonic eye drops %5 were started, and the patient's symptoms returned to baseline within a week. After 4 months, Snellen's visual acuity was found to be 20/30. OCT showed serous pigment epithelial detachment without subretinal fluid or hemorrhage, and follow-up was recommended. After 2 months, visual acuity decreased to 20/70, and an increase in pigment epithelial detachment was detected in OCT. The patient was started on intravitreal ranibizumab (0.5 mg/0.05 mL) for 3 months, and a significant decrease was observed in pigment epithelial detachment in OCT, and visual acuity has reached the 20/40 level. The bevacizumab injection was started again due to patient preference, and 12 days after the bevacizumab injection, the patient had an anterior uveitis attack again (12).

Damasceno et al. reported a case of a 78-year-old female patient who presented with anterior uveitis in the left eye on the 3rd day after intravitreal ranibizumab. The patient had a history of 5 intravitreal ranibizumab injections due to neovascular type AMD within 1 year. The inflammation subsided after 1 month with cycloplegic and topical corticosteroids. After 3 months, the bevacizumab injection was started in the right eye, and anterior uveitis was similarly observed after the 2nd injection. With the same treatment, cycloplegic and topical corticosteroids, the inflammation subsided after 1 month (13).

In our case, a 73-year-old female patient presented with similar complaints in the left eye. In our case, topical and periocular steroids achieved an anti-inflammatory response with a significant visual improvement in the first three days. The patient's visual acuity level reached the pre-intravitreal injection level in the first week after the treatment.

A limitation of this case report is the lack of polymerase chain reaction PCR testing from the anterior chamber, which prevented us from definitively ruling out viral anterior uveitis.

In conclusion, sterile inflammation may develop after intravitreal bevacizumab, and it is very important to differentiate it from infectious endophthalmitis. In our case, sterile inflammation formed the anterior uveitis clinic and was successfully treated with topical/periocular steroid therapy. Although the factors related to the patient under the development of sterile inflammation, the factors that may occur during the delivery of the drug, and the factors related to the drug are known, it is still not possible to know the cause on a case-by-case basis.

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