Case Report

Delayed-Onset Endophthalmitis after Intravitreal Aflibercept Injection

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Abstract

Purpose: To describe delayed-onset infectious endophthalmitis 4 months after intravitreal aflibercept injection.

Methods: An 80-year-old female was referred with signs and symptoms of clinical endophthalmitis 4 months after intravitreal injection of aflibercept for choroidal neovascularization. Noninfectious causes of panuveitis were excluded and she was diagnosed with delayed-onset postinjection infectious endophthalmitis. Vitreous and aqueous specimens were prepared and antibiotics (vancomycin and ceftazidime) were injected intravitreally.

Results: Vitreous culture was positive for *Staphylococcus epidermidis*. During the 1st month after the antibiotic injections, symptoms and signs of the patient improved and became stable during the 6-month follow-ups.

Conclusions: Delayed-onset infectious endophthalmitis can be presented following intravitreal injections. Late presentation of uveitis in postinjected eyes needs complete investigations to rule out infectious endophthalmitis as an ophthalmic emergency.

Keywords: Aflibercept, Anti-vascular endothelial growth factor, Chronic, Delayed onset, Infectious endophthalmitis, Intravitreal injection

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Introduction

Intravitreal anti-vascular endothelial growth factor (VEGF) agents, including ranibizumab, bevacizumab, and aflibercept, have changed the care for many vitreoretinal disorders such as choroidal neovascularization (CNV), proliferative diabetic retinopathy, diabetic macular edema, retinopathy of prematurity, neovascular glaucoma, and macular edema following retinal vein occlusions.[1]

This route of drug administration may have noteworthy adverse events, especially infectious endophthalmitis.[2] Several studies have reported different incidence rates of postinjection infectious endophthalmitis, ranging from 0.007% to 1.6% per injection.[3]

In general, postintravitreal injection infectious endophthalmitis is acute and usually presents 1–14 days after the injection. The main responsible microorganisms of this condition are coagulase-negative *Staphylococcus* species (e.g. *Staphylococcus epidermidis*), *Streptococcus* species, and *Corynebacterium*, respectively.[4] Chronic and delayed-onset infectious endophthalmitis have been reported mainly after cataract extraction and glaucoma surgeries. The majority of these conditions are caused by low virulence microorganisms, especially *Propionibacterium acnes*.[5] However, delayed-onset infectious endophthalmitis after intravitreal injections is rare, and very few studies reported this presentation.[6-8]

Here, we report a delayed-onset postintravitreal aflibercept injection infectious endophthalmitis secondary to *S. epidermidis* as a rare presentation.

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Case Report

This case report was approved by the Ethics Committee of the Iran University of Medical Sciences with ethical code IR.IUMS.REC.1400.830. Written informed consent was obtained from the patient. The patient was an 80-year-old female who underwent intravitreal injections of anti-VEGF agents in her right eye due to age-related macular degeneration (AMD) - associated CNV, without any evidence of uveitis [Figure 1a and b]. She had a history of cataract surgery in both eyes about 10 years ago. The right eye had been treated with 5 intravitreal bevacizumab injections (2.50 mg/0.1 cc), previously. Due to poor anatomical response, the drug was changed to aflibercept. Treatment with intravitreal aflibercept (2 mg/0.05 cc, EYLEA®, Bayer Pharma, Berlin, Germany) was performed four times for the patient with 2-month intervals between the injections. The last injection was done 4 months before presentation, with Snellen best-corrected visual acuity (BCVA) of 20/63. In the early follow-up visit (in month 1 after the injection, 3 months prior to presentation), she did not have any signs of uveitis and vitreous media was completely clear, with BCVA of 20/50 [Figure 1c]. Then, mild wax and wane anterior uveitis with vitreous haziness was detected in the affected eye 1 month before presentation, with BCVA of 20/80 [Figure 1d] and was treated with topical steroids. At presentation, she complained of moderate ocular and periorbital pain with a gradually decreased visual acuity from 3 days ago. On examination, visual acuity of the right eye was decreased to perception of hand motions. In slit-lamp examination, diffuse conjunctival injection, moderate and diffuse corneal stromal edema, Grade 3 anterior chamber cell, and flare, with 4 mm nonshifting hypopyon formation in the anterior chamber were observed. Intraocular pressure of the affected eye was 8 mmHg with Goldmann tonometer. Dilated fundus examination showed severe vitreous haziness (Grade 4 vitritis) in the right eye, and the details of the retina were not visible. The examinations of the left were unremarkable and revealed macular drusen, which was compatible with dry AMD.

The diagnosis of delayed onset postinjection infectious endophthalmitis was made. Endogenous endophthalmitis was not probable in this patient, because she did not have any associated comorbidities. In addition, her blood and urine cultures were negative. In further investigations, the common causes of panuveitis, including tuberculosis, sarcoidosis, and syphilis were investigated, and the results were unremarkable. The human leukocyte antigen B-5 was positive; however, the patient did not have oral, genital, and skin ulcers. Furthermore, in the baseline fluorescein angiography (FA) image [Figure 1a], she did not have any evidence of retinal vasculitis which is an important hallmark for the diagnosis of ocular manifestations of Behcet's disease.

The patient underwent treatment with empiric intravitreal antibiotics. At first, aqueous and vitreous specimens were prepared and sent for bacterial and fungal staining and culture. Then, vancomycin (1 mg/0.1 cc), ceftazidime (2.25 mg/0.1 cc), and dexamethasone (0.4 mg/0.1 cc) were injected intravitreally. Topical fortified eye drops of vancomycin and ceftazidime (four times/day) and topical dexamethasone (6 times/day) were administrated.

Two days after intravitreal antibiotics injections, the visual acuity improved to counting fingers at 2 m. In addition, hypopyon and anterior chamber reaction were resolved and vitritis was decreased to Grade 2. The culture of vitreous specimen was positive for *S. epidermidis*. Topical eye drops were discontinued after 2 weeks. Four weeks after intravitreal antibiotics injections, her visual acuity was fingers counting at 4 m and vitritis was decreased [Figure 1e]. At this time, the FA image did not show any evidence of retinal vasculitis or occlusion [Figure 1f]. The examinations were stabled during the next 6 months follow-up visits and vitritis was diminished,

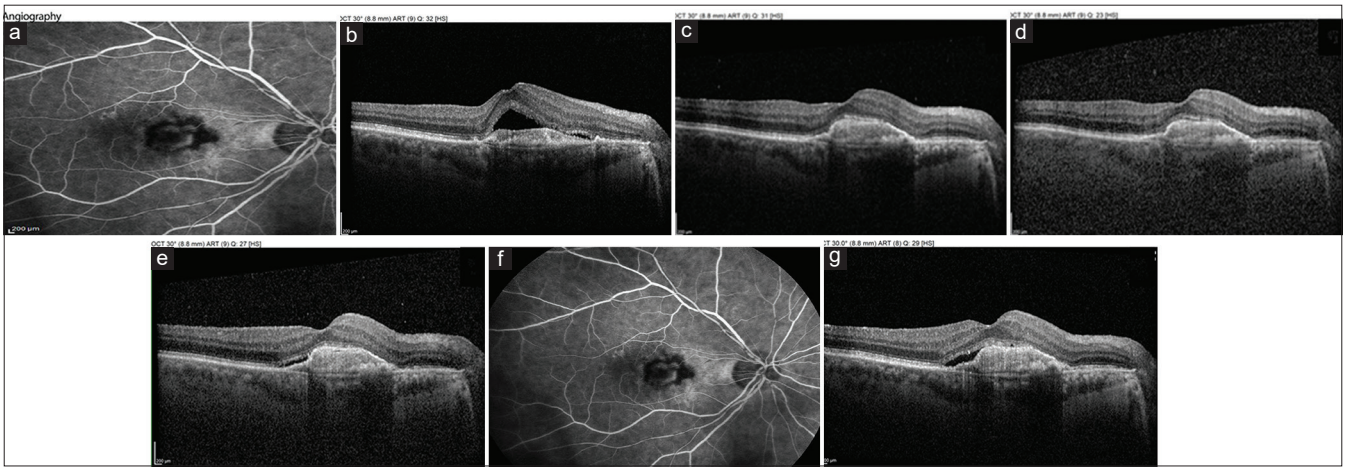

Figure 1: (a and b) Fluorescein angiography (FA) and optical coherence tomography (OCT) images showing choroidal neovascularization and absence of uveitis, at baseline. (c) OCT image 3 months before endophthalmitis. Vitreous media is completely clear. (d) OCT image 1 month before endophthalmitis. Haziness of vitreous media was visible. (e) OCT image 1 month after presentation of endophthalmitis, showed vitreous haziness. (f) FA image 1 month after presentation of endophthalmitis, revealed absence of retinal vasculitis findings. (g) OCT image 6 months after endophthalmitis. Haziness of vitreous media was diminished

with a BCVA of 20/80 [Figure 1g]. The patient had two additional uneventful intravitreal aflibercept injections, 3 and 5 months after endophthalmitis.

Discussion

Postoperative infectious endophthalmitis is a rare sight-threatening complication of any intraocular surgery. The reported incidence of postoperative endophthalmitis is varied among different intraocular procedures and it is estimated between 0.01% and 0.367%.[5] Coagulase-negative *Staphylococcus* species, *Streptococcus* species, and *Corynebacterium* are the most reported microorganisms responsible for acute infectious endophthalmitis postoperatively.[4] The causative microorganisms of chronic postoperative infectious endophthalmitis are different from the acute type. They are usually low-virulent organisms such as *Propionibacterium* species, coagulase-negative *Staphylococcus* species, and fungi.[5] In patients with chronic infectious endophthalmitis, vitritis is usually mild but can be severe and dense in eyes infected with *S. epidermidis*, similar to our patient.[9]

Commonly, the early presentation of chronic infectious endophthalmitis is recurrent and mild anterior uveitis after months or even years (typically 2–3 months) postoperatively. Then, uveitis involves the vitreous and causes panuveitis.[10] The uveitis may be granulomatous with keratic precipitates on the corneal endothelium or intraocular lens. Forming hypopyon is not common in this type of infectious endophthalmitis.[5] A white intracapsular nidus may represent the accumulation of microorganisms (especially *Propionibacterium* species) and is suggestive of the infection.[11] Pain is not a hallmark of chronic infectious endophthalmitis, in contrast to the acute type.[10] In these patients, steroid administration may control intraocular inflammation temporarily, but the condition recurs after discontinuation of the drug.[9,11] Our patient did not have a capsular plaque to suggest chronic postcataract surgery endophthalmitis.

Exogenous endophthalmitis is relatively less occurred in patients with intravitreal injections, in comparison to other ocular procedures including phacoemulsification and glaucoma surgeries (bleb-associated). Almost all cases of postintravitreal injection endophthalmitis have acute onset presentation within a few days after the injection. The most common pathogens in these cases are coagulase-negative *Staphylococcus* species including *S. epidermidis*, similar to our patient's extracted pathogen.[12-14] Delayed-onset postintravitreal injection infectious endophthalmitis is very rare. Mercer *et al*.[6] reported delayed onset endophthalmitis secondary to *Streptococcus viridans*, 7 weeks after intravitreal injection of aflibercept in a patient with CNV. The patient had mild pain sensation in the eye with a progressive decline in visual acuity. In examinations, severe anterior chamber reaction with vitreous haziness was revealed. The patient had good response to vitrectomy and intravitreal antibiotics injections. Mammo *et al*.[7] reported a postintravitreal injection infectious endophthalmitis secondary to *Turicella otitidis* in an AMD-associated CNV patient, 4 weeks after the injection of aflibercept. The patient had a painless gradually worsening vision, with moderate anterior chamber reaction, keratic precipitates, and vitritis. The patient had a dramatic response to intravitreal antibiotics. Boeke and Gottlieb[8] presented a case of late-onset endophthalmitis secondary to *Stenotrophomonas maltophilia*, 23 days after intravitreal injection of aflibercept for the treatment of diabetic macular edema. The patient had mild ocular pain and moderate anterior chamber reaction that progressed to hypopyon formation and dense vitritis in the next few days. The patient was treated with intravitreal antibiotics with satisfactory results. In our report, we described a patient with postinjection infectious endophthalmitis, 4 months after the injection which was considered as delayed-onset infectious endophthalmitis. The patient had mild anterior uveitis initially which was progressed to panuveitis (compatible with the scenario of chronic infectious endophthalmitis). At presentation, she had moderate ocular pain, frank hypopyon (as a less common presentation in eyes with chronic infectious endophthalmitis), sever vision impairment, and dense vitritis with response to intravitreal antibiotics.

Explaining the cause of the infection in our case was difficult. Concerning our procedure for injection, it was performed in the sterile and standard method for intravitreal injections.[15] Pertaining to the delayed presentation, *S. epidermidis* endophthalmitis after cataract surgery had been reported rarely in the delayed onset type of the disease.[16,17] We hypothesized the probable reason for the delayed presentation of the initial signs (until month 3 after the injection) in our case, maybe the smaller inoculum associated with the injection compared with intraocular surgeries including phacoemulsification. Recently, a case report described inadvertent filtering bleb creation after intravitreal injections.[18] Potentially, these iatrogenic filtering blebs may lead to intraocular entrance of pathogens and endophthalmitis. Rationally, these blebs are more likely created after multiple injections, and their potential subsequent endophthalmitis may be presented with similar signs of bleb-associated endophthalmitis, as well described in patients with history of glaucoma surgeries (delayed onset presentation).[19] About our patient, no bleb formation was detected in any follow-up visits to justify the source of the infection.

Noninfectious panuveitis is a rare complication in eyes with anti-VEGF injections and may mimic infectious endophthalmitis. It can occur several days to a week after the injection and the prevalence varies from 0.02% to 0.37% of injections. Patients complain from mild blurred vision, new-onset floaters, and mild-to-moderate ocular pain. In examinations, mild anterior chamber reaction and mild vitritis are the most common findings. This complication can be controlled by the administration of topical and/or systemic steroids.[20] In our patient, delayed-onset of the inflammation, the severity of the disease, and positive vitreous specimen culture were against this diagnosis.

In conclusion, delayed-onset infectious endophthalmitis following intravitreal injections is very rare and late presentation of symptoms and signs of uveitis in postinjected eyes needs close follow-up and complete investigations to rule out intraocular infectious processes as a sight-threatening condition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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