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Case Report Open Access

Massive Hemorrhagic Complications after Intravitreal Injection of Aflibercept in Patients with Presumed Polypoidal Choroidal Vasculopathy

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Abstract

Introduction: Subretinal hemorrhage (SRH) is a complication associated with intravitreal injections of anti-vascular endothelial growth factor for wet age-related macular degeneration (AMD). We recently experienced three cases of massive hemorrhage after intravitreal aflibercept injection (IAI) for wet AMD that was suspected to be polypoidal choroidal vasculopathy (PCV).

Case reports: A 75-year-old woman presented with decreased vision in her left eye. She had subfoveal choroidal neovascularization (CNV) that was suspected to be PCV. Two weeks after the second IAI, massive SRH developed. Although additional treatment was provided, her vision was reduced to counting fingers.

A 67-year-old man presented with a history of wet AMD in his left eye. Subfoveal CNV, which was suspected to be PCV, was present in his right eye. Although three monthly injections of ranibizumab were given, the pigmented epithelium detachment (PED) was still present and IAI was started. One month after the first IAI, massive SRH was noted; two weeks later, vitreous hemorrhage developed. Although vitrectomy and additional bevacizumab injection were performed, his vision was reduced to counting fingers.

An 81-year-old woman presented with a history of wet AMD in her left eye, which had been treated with several bevacizumab injections. She had bilateral subfoveal CNV and started IAI in her right eye; she initially refused treatment for her left eye. After two monthly IAIs in the right eye, SRH developed and progressed in the left; IAI treatment was thus expanded to both eyes. One month after IAI of her left eye, a thick vitreous hemorrhage developed. However, the patient refused further treatment.

Conclusion: The present study is the first case series of hemorrhagic complications after IAI for wet AMD that was suspected to be PCV. IAI is believed to be a potent treatment for wet AMD, especially with the PED; however, the risk of hemorrhagic complications should still be carefully considered.

Keywords: Aflibercept; Polypoidal choroidal vasculopathy; Subretinal hemorrhage; Vitreous hemorrhage; Wet age-related macular degeneration

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in people over 50 years old. About 10% of patients with AMD have the neovascular form (wet AMD) [1]. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection has become the standard therapy for wet AMD.

Aflibercept (Eylea; Regeneron, Tarrytown, NY, USA and Bayer HealthCare, Berlin, Germany) is a recently developed anti-VEGF agent that binds to members of the VEGF family, including VEGF-A and VEGF-B, as well as to placental growth factor. [2] The efficacy of aflibercept for the treatment of wet AMD has been demonstrated [3], and the binding affinity of intravitreal aflibercept to VEGF is known to be greater than that of bevacizumab or ranibizumab [2]. Intravitreal aflibercept is reportedly effective in previously treatment-resistant wet AMD [4], and it may be effective in reducing pigment epithelium detachment (PED) [5].

Although the risk of complication after intravitreal anti-VEGF injection seems to be very low [6], several reports have described hemorrhagic complications following anti-VEGF injection for wet AMD. We recently experienced three cases of massive subretinal or vitreous hemorrhage after intravitreal aflibercept injection (IAI) for wet AMD that was suspected to be polypoidal choroidal vasculopathy (PCV).

Cases Report

Case 1

A 75-year-old woman presented with decreased vision in her left eye (best-corrected visual acuity [BCVA] of 8/20). Fundus examination showed a yellowish subretinal membrane in her left eye (Figure 1A). Fluorescein angiography (FA) showed a well-demarcated hyperfluorescent spot in the superior nasal to foveal region in the early phase and diffuse hyperfluorescence of the macula in the late phase (Figure 1B and 1C). Optical coherence tomography (OCT) showed PED with subretinal fluid and a peak of PED arising from a flatter region at the site corresponding to the early hyperfluorescent area on

FA, raising suspicion for a PCV-associated polyp (Figure 1D). We diagnosed the patient with neovascular AMD with suspicion for PCV and started treatment with IAI (2.0 mg per 0.05 ml).

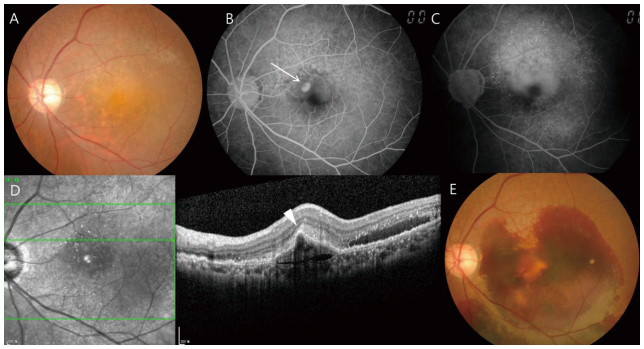

Figure 1: Ophthalmic examination in case 1. **A:** Fundus photography at the first visit. **B:** Early-phase fluorescein angiography. **C:** Late-phase fluorescein angiography. **D:** Optical coherence tomography shows a suspicious polyp (arrow head) at the site corresponding to the early hyperfluorescent spot on fluorescein angiography (arrow). **E:** Fundus photography two weeks after the second aflibercept injection.

One month after the first IAI, the subretinal fluid disappeared, but the PED remained. Two weeks after the second IAI, the patient visited our clinic complaining of decreased vision, and massive subretinal hemorrhage (SRH) was noted (Figure 1E). Although additional bevacizumab injections were given and pneumatic displacement was performed, her vision was reduced to counting fingers.

Case 2

A 67-year-old man presented with a history of wet AMD in his left eye. However, a wet AMD lesion was also present in his right eye, which exhibited decreased vision (BCVA of 4/20). FA examination of his right eye revealed a diffuse hyperfluorescent area on the macula with blocked fluorescence as well as multiple brighter spots (Figures 2A, 2B). OCT showed PED notches with localized hyper-reflectivity underneath the dome, indicating a PCV-associated polyp; these notches also corresponded to the more brightly fluorescent spots (Figure 2C). Although three monthly injections of ranibizumab were performed in the right eye, the PED was still present, and some SRH developed without vision improvement (Figure 2D). Therefore, IAI (2.0 mg per 0.05 ml) was started. One month after the first IAI, the patient complained of decreased vision in his right eye, and massive SRH was noted (Figure 2E). Two weeks later, vitreous hemorrhage developed (Figure 2F). Despite vitrectomy and additional bevacizumab injections, the patient's BCVA was reduced to counting fingers.

Case 3

An 81-year-old woman presented with known wet AMD of her left eye. Her BCVA was 0.16 in the right eye and hand movement in the left eye. She had been treated with several intravitreal bevacizumab injections in her left eye. FA and OCT showed occult choroidal neovascularization (CNV) in her right eye. Her left eye exhibited a focal round hyperfluorescent lesion on the fovea with diffuse leakage at the macula in the late phase (Figures 3A-3C).

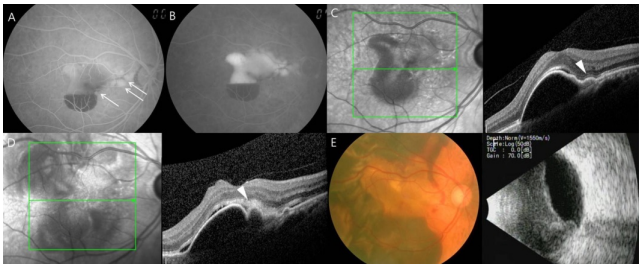

Figure 2: Ophthalmic examination in case 2. **A:** Early-phase fluorescein angiography shows a hyperfluorescent area on the macula with blocked fluorescence and multiple brighter spots (arrows). **B:** Late-phase fluorescein angiography. **C:** Optical coherence tomography shows pigmented epithelium detachment with hyper-reflectivity localized underneath the dome, raising suspicion for a polypoidal choroidal vasculopathy-associated polyp at the site corresponding to the early brighter spot on fluorescein angiography (arrow head). **D:** Optical coherence tomography after three monthly injections of ranibizumab with a suspicious polypoidal choroidal vasculopathy-associated polyp (arrow head). E. Fundus photography one month after the first aflibercept injection. F. B-scan ultrasonography six weeks after the first aflibercept injection.

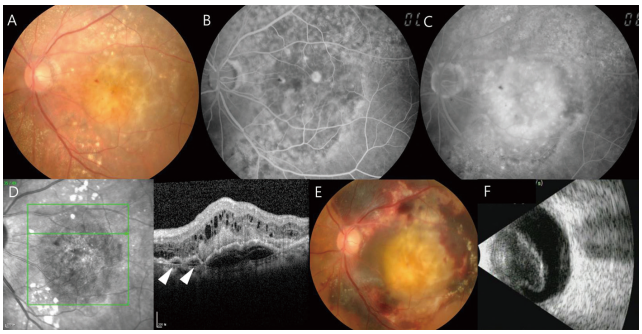

Figure 3: Ophthalmic examination in case 3. **A.** Fundus photography at the initial visit. **B.** Early-phase fluorescein angiography. **C.** Late-phase fluorescein angiography. **D**. Optical coherence tomography shows bumpy areas of pigment epithelial detachment and an area of peaked pigment epithelial detachment from a flatter region of pigment epithelial detachment, raising suspicion for a polypoidal choroidal vasculopathy-associated polyp (arrow head). **E**. Fundus photography three months after the initial visit. **F**. B-scan ultrasonography one month after aflibercept injection.

OCT examination of her left eye showed regions of bumpy PED and a PED peak arising from a flatter area, raising suspicion for a PCV-associated polyp (Figure 3D). Although we recommended treatment for both eyes, she refused treatment for her left eye because of its poor vision. Her right eye was treated with two monthly IAIs, but SRH developed and progressed in her left eye (Figure 3E). Thus, her left eye was also treated with aflibercept (2.0 mg per 0.05 ml). One

month after aflibercept injection in her left eye, a thick vitreous hemorrhage developed (Figure 3F). However, the patient refused further treatment.

Discussion

This is the first documented report of acute subretinal or vitreous hemorrhage after aflibercept injection for wet AMD that was suspected to be PCV. SRH is a complication that may occur after intravitreal anti-VEGF injection for wet AMD. One report estimated the incidence of SRH as 8.3/1000 patient-years after intravitreal ranibizumab injection [7]. However, Goverdhan et al. [8] reported that fresh submacular hemorrhage was seen in 4 of 53 patients (8%) after bevacizumab injection. Krishnan et al. [9] reported that fresh submacular hemorrhage was seen in 4 of 14 patients (29%) after bevacizumab injection for large (≥ 15 mm^3) occult CNV, while 0 of 22 patients showed submacular hemorrhage after ranibizumab injection. In another study of PCV, five cases of fresh SRH occurred among 54 patients (8.9%) after intravitreal ranibizumab injection [10].

We reviewed the incidence of SRH or vitreous hemorrhage after aflibercept or ranibizumab injection. From April 2014 to March 2015, we experienced 3 cases (16.7%) of massive subretinal or vitreous hemorrhage after IAI among 18 patients (47 injections). During the same time period, we treated 72 patients with neovascular AMD (209 injections) with ranibizumab and encountered only one case of massive SRH approximately three months after the injection. Calculation of the actual incidence of SRH in this study was impossible because of the small number of cases and large confidence interval. However, the incidence of subretinal or vitreous hemorrhage after IAI was not higher than that in previous reports.

SRH after anti-VEGF injection for wet AMD or PCV may occur as a consequence of the natural history of the disease. In particular, patients with PCV sometimes develop spontaneous massive SRH. Sudden vision deterioration secondary to SRH was observed in approximately 33% (14 of 42 eyes) in a report of the natural course of PCV over a one-year follow-up [11]. However, the higher rate of massive hemorrhage after aflibercept injection (3 of 18 eyes) than after ranibizumab within one month of treatment cannot be explained only by the natural history.

Although the mechanism of massive hemorrhage after aflibercept injection remains unclear, the robust effect of aflibercept on abnormal choroidal vessels could contribute to the hemorrhage. One study reported that a significantly higher rate of submacular hemorrhage occurred following intravitreal bevacizumab for ≥ 15 mm^3 occult CNV than following intravitreal ranibizumab because bevacizumab has a longer half-life and more strongly influences contraction of the CNV membrane, resulting in rupture of blood vessels [9]. Aflibercept has a half-life of 4.7 days in rabbits, and its binding affinity to VEGF is thought to be greater than that of bevacizumab or ranibizumab [12]. Strong blood vessel contraction and subsequent hemorrhage can occur after IAI.

All three of the herein-described cases of massive hemorrhage after IAI have common features. First, they had large areas of CNV on FA (Figures 1B, 1C, 2A, 2B; and 3B, 3C). Second, they had ≥ 3 mm diameter areas of PED with hyporeflectivity on OCT before IAI (Figures 1D, 2C, 2D and 3D). Third, they had signs consistent with polyps on OCT and were suspected to involve PCV (Figures 1D; 2C, 2D and 3D; white arrowheads), although PCV diagnosis was not confirmed by indocyanine green angiography (ICG). The lack of ICG images to confirm the diagnosis of PCV is a limitation of this case report. There is one case report of acute SRH after IAI for PCV with large PED [13]. Other reports of SRH after anti-VEGF injection have suggested that large (≥ 15 mm^3) CNV or PCV is associated with a higher rate of SRH, especially after bevacizumab injection [8, 10]. Therefore, the use of aflibercept, which has strong binding affinity and a long half-life, should be carefully considered when the CNV lesion has high-risk features for hemorrhage such as suspicion for PCV, a large CNV area, and large PED on OCT.

Conclusion

This case series is the first description of hemorrhagic complications after IAI for presumed PCV. Although IAI is believed to be a potent treatment method for wet AMD, especially with PED, the risk of hemorrhagic complications should be carefully considered.

Acknowledgments

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