American Journal of Ophthalmology Case Reports 16 (2019) 100549

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.elsevier.com/locate/ajoc

Case report

Branch retinal artery occlusion in the untreated contralateral eye following aflibercept injections during heparin treatment: Possible contribution of a heparin-induced thrombocytopenia-like condition

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ARTICLE INFO

Keywords:
Vascular endothelial growth factor
Hemodialysis
Diabetic retinopathy
Bevacizumab

ABSTRACT

Purpose: In this study, we report a case of branch retinal artery occlusion (BRAO) in the contralateral eye the day after aflibercept treatment during systemic heparin administration.

Observations: A 63-year-old woman with diabetic macular edema underwent repeated intravitreal injection of anti-VEGF drugs (0.5mg ranibizumab or 2mg aflibercept) for her left eye. The day after intravitreal injection of aflibercept, she presented with sudden painless blurred vision that was limited to the inferior visual field defect in the contralateral eye (right eye) during hemodialysis with the anti-coagulant heparin. Optical coherence tomography angiography (OCTA) showed decreased artery perfusion and the patient was diagnosed with contralateral BRAO.

Conclusions: Previous *in vitro* and *in vivo* studies have reported that the Fc portion of anti-VEGF drugs activates platelets with heparin. Therefore, careful anti-VEGF drug selection may be necessary in cases with concomitant heparin treatment.

1. Introduction

Intraocular administration of vascular endothelial growth factor (VEGF) inhibitor drugs such as bevacizumab (Avastin; Genentech, Inc.), ranibizumab (Lucentis; Genentech, Inc.) and aflibercept (Eylea; Regeneron Pharmaceuticals, Inc., NY, USA) have drastically increased in recent years.[1] Thrombo-occlusive vascular events have been raised as potential adverse effects resulting from the systemic suppression of VEGF by intraocular anti-VEGF treatment.[2,3] Preliminary case series also suggest a possible temporal link between these injections and subsequent ocular and systemic vascular events.[4–7] However, the relationship between the type of VEGF inhibitor and its thrombotic side effects remains controversial.[8–10]

Some diabetes patients with diabetic retinopathy have kidney failure that require hemodialysis (HD).[11] For the extracorporeal circuit, heparin is usually used to prevent the activation of plasmatic coagulation cascade during the HD procedure.[12] Although heparin inhibits thrombin via activation of anti-thrombin, the concept of heparin-induced thrombocytopenia (HIT) where IgG antibodies form immunocomplexes (IC) with heparin and platelet factor 4 (PF4) antigens on the platelet surface and activate FcγRIIa has been proposed.[13] HIT is also known to be strongly associated with thrombosis.[13] A recent study reported that bevacizumab could activate platelets and induce thrombosis in the presence of heparin.[14] Furthermore, another study by Nomura et al. showed that aflibercept but not ranibizumab activates platelets via FcγRIIa.[15] However, there has been no case report documenting a thrombo-occlusive vascular event that developed after simultaneous administration of anti-VEGF therapy and heparin.

In this article, we report a case of branch retinal artery occlusion (BRAO) in the untreated contralateral eye following injections of aflibercept for diabetic macular edema (DME) during HD with heparin treatment.

2. Case report

A 63-year-old woman was diagnosed with DME two years ago and underwent repeated intravitreal injection of anti-VEGF drugs (0.5mg ranibizumab or 2mg aflibercept) for her left eye. Spectral-domain optical coherence tomography (SD-OCT) (Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA) and fluorescein angiography (FA) revealed

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https://doi.org/10.1016/j.ajoc.2019.100549
Received 14 March 2018; Received in revised form 26 April 2019; Accepted 26 August 2019
Available online 28 August 2019

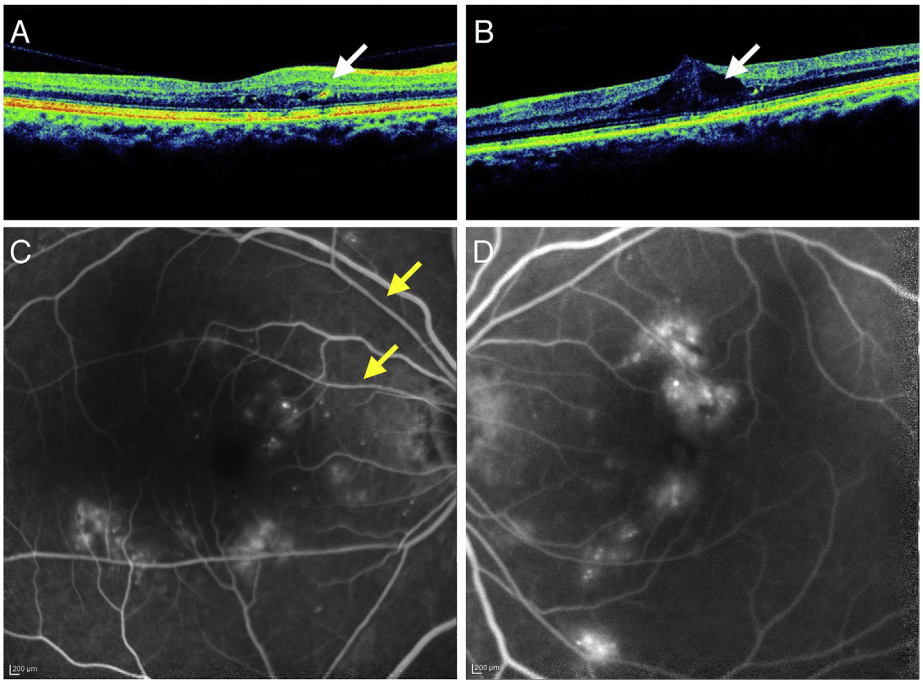

Fig. 1. Clinical findings of diabetic macular edema before anti-VEGF therapy (2mg aflibercept). Spectral-domain optical coherence tomography (SD-OCT) showed a hyperreflective area (arrow) in the right eye (A) and cystic macular edema (arrow) in the left eye (B). (C, D) Fluorescein angiography shows hyperfluorescence and leakage from microaneurysms during the late phase. Yellow arrows in C indicates perfusion of branch retinal arteries.

significant macular edema and leakage in the left eye and weak leakage in the right eye (Fig. 1A, B, C and D). The patient's medical history was positive for myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA), diabetes mellitus (DM) and chronic renal failure due to DM. However, she had a normal titer of MPO-ANCA with systemic administration of steroids. She had also been undergoing hemodialysis (HD) for two years.

The day after intravitreal injection of aflibercept, she presented with sudden painless blurred vision that was limited to the inferior visual field defect in the fellow eye (right eye) during HD. She had thus far been administered twice with an intravitreal injection of ranibizumab and six times with an intravitreal injection of aflibercept. This injection of aflibercept was the first time in nine months. The HD was a routine procedure with no overt complications. After HD, the patient underwent comprehensive ophthalmic assessment including Snellen visual acuity, slit-lamp biomicroscopy, indirect ophthalmoscopy, SD-OCT and OCTA. Her best-corrected visual acuity (BCVA) was 20/20 in the right eye and 10/20 in the left eye. Intraocular pressure was 15 mmHg in the right eye and 16 mmHg in the left eye. Anterior segment examination was unremarkable in both eyes. Fundus examination of the right eye revealed the presence of plaques within the superior branch retinal artery and a sectorial grayish retina along the superior foveal area (Fig. 2A). Optical coherence tomography angiography (OCTA) (Optovue, Fremont, CA) images showed decreased arterial vascular perfusion and superior capillary nonperfusion in the right eye (Fig. 2B). Visual field examination by Goldman perimeter showed paracentral inferior scotoma corresponding with a decrease in vascular perfusion area (Fig. 2C).

Biochemical findings of WBC 8270/μl, RBC 445 × 10^4/μl, platelet 195 × 10^3/μl, hemoglobin 13.8 g/dL, hematocrit 45.6%, creatinine 4.94 mg/dL, erythrocyte sedimentation rate (ESR) of 99 mm/1 h and C-reactive protein (CRP) of 0.23 mg/dL were suggestive of negative inflammatory reactions before BRAO. DM was under good glycemic control (glycoalbumin 11.9%). Rheumatoid factor, anti-nuclear antibodies, anti-phospholipid antibodies, proteinase-3-ANCA and MPO-ANCA (1.0 U/mL) were all undetectable. Echocardiogram and sonographic examination of the carotid artery showed no masses or thrombi. In view of the medical history, physical and biochemical findings, the patient was diagnosed with contralateral branch retinal artery occlusion (BRAO) associated with intravitreal injection of anti-VEGF therapy.

3. Discussion

The theoretical increased risk of vascular events following intravitreal injection of VEGF inhibitors (ranibizumab, bevacizumab, and aflibercept) remains controversial and is a widely discussed topic.[2,8,16] There are several hypotheses regarding the mechanism underlying the increased risk of arterial thrombosis with VEGF inhibitor treatment. The vascular events following anti-VEGF therapy could be caused by vasoconstriction and a post-injection increase in intraocular pressure.[17] However, the mechanism underlying thrombo-occlusive vascular events remains poorly understood.

The patient in our case study was undergoing HD with heparin to prevent thrombosis in the blood circulation. However, she presented with a thrombo-occlusive vascular event, BRAO, during HD. A recent report by Nomura showed that bevacizumab and aflibercept, but not ranibizumab, could activate platelets through FcγRIIa *in vitro*.[15] In addition, *in vivo* studies showed that bevacizumab-VEGF-heparin complexes can bind to and subsequently activate platelets through FcγRIIa in a manner similar to HIT.[14] However, although the platelet count on day 3 after onset of BRAO (156 × 10^3/μl) was 20% lower than the previous platelet count in HD (195 × 10^3/μl), these were within normal range and did not support a diagnosis of HIT.

The patient with MPO-ANCA developed a sudden decrease in visual acuity of the contralateral eye and was diagnosed with BRAO. A few case studies have reported RAO in ANCA-associated vasculitis with a high CRP.[18,19] Therefore, we cannot exclude the impact of P-ANCA-related vasculitis on BRAO although the laboratory data did not indicate active inflammatory reactions.

In this case, we observed BRAO in the untreated contralateral eye following intravitreal injections of anti-VEGF. Thrombo-occlusive vascular events in the contralateral eye have been reported to be rare adverse side effects of anti-VEGF therapy including contralateral CRAO.[7,20] In addition, it is known that end stage renal disease (ESRD) and HD independently increase the risk of RAO and RVO even in the absence of DM,[21,22] particularly in ESRD patients with hypertension.[23] Therefore, clinicians should be mindful of the risk of RAO and RVO

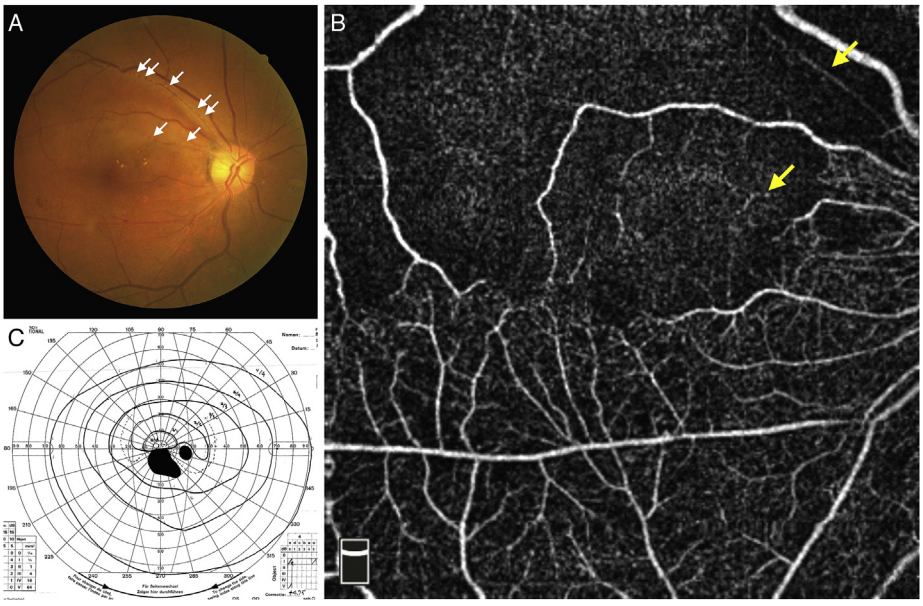

Fig. 2. Clinical findings of branch retinal artery occlusion after anti-VEGF therapy in the right eye. (A) Color fundus photograph shows the presence of plaques within the superior branch retinal artery (arrows) and a sectorial grayish retina along the superior foveal area in the right eye. (B) An 8 mm × 8 mm OCT angiography image of the superficial capillary plexus shows decreased arterial vascular perfusion and capillary nonperfusion in the superior area. Yellow arrows indicate the loss of perfusion of branch retinal arteries. (C) Goldman perimeter 2 weeks after the development of BRAO in the right eye shows paracentral inferior scotoma corresponding with a decrease in vascular perfusion area.

during HD, especially in the setting of anti-VEGF therapy.

In this case study, we report the development of BRAO in the untreated contralateral eye in a case of DME treated with injections of anti-VEGF during HD with heparin treatment.

4. Patient consent

Written informed consent for the research and publication of this study and all accompanying images was obtained from the patient.

Acknowledgement

Funding

This study was supported by grants from JSPS KAKENHI, Grant-in-Aid for Scientific Research (C) No. 17K11456 (SN).

Conflicts of interest

All authors have no financial disclosures.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Financial support

None.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2019.100549.

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