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Case report

Rapid formation of macular pucker following intravitreal ranibizumab injection for branch retinal vein occlusion

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ABSTRACT

Purpose: To report a case of branch retinal vein occlusion (BRVO) in which rapid formation of macular pucker was observed after an intravitreal ranibizumab (IVR) injection.

Observations: A 66-year-old patient was referred to our department for the treatment of macular edema (ME) secondary to BRVO in the left eye. On the initial visit, widespread retinal hemorrhage was observed around the superior temporal vascular arcade, and the decimal best-corrected visual acuity (BCVA) was 0.7 (Snellen equivalent 20/29) in the left eye. Optical coherence tomography demonstrated a thin epiretinal membrane (ERM) accompanied by diffuse retinal thickening. A 0.5 mg IVR injection was administered for the treatment of ME and prompt resolution of retinal hemorrhage. Fourteen days after IVR administration, the ERM had progressed remarkably into a macular pucker and had spread from the superior macula to the equator, accompanied by partial tractional retinal detachment. We performed pars plana vitrectomy combined with encircling scleral buckling. Three months after the surgery, the decimal BCVA was 0.4 (Snellen equivalent 20/50), the retina was attached, and no recurrence of ME or proliferation was observed.

Conclusions and Importance: IVR for BRVO may cause rapid formation of macular pucker in the eye, especially in the presence of pre-existing ERM. Careful observation of patients with BRVO is essential after administration of anti-VEGF agents, especially in eyes with pre-existing ERM.

1. Introduction

Retinal vein occlusion (RVO) is a retinal vascular disease that can be classified into central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). In both diseases, elevated levels of intraocular vascular endothelial growth factor (VEGF) are known to contribute to macular edema (ME), which is the main cause for reduced vision.[1] In a clinical trial of ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) for treating ME following CRVO, the aforementioned anti-VEGF agent not only reduced ME and improved visual acuity, but also led to early resolution of retinal hemorrhages.[1] However, a variety of side effects of intravitreal anti-VEGF agents have been reported.[2] Herein, we report a case of BRVO treated with an intravitreal ranibizumab (IVR) injection, followed by a rapid formation of macular pucker and tractional retinal detachment (TRD).

2. Case report

A 66-year-old man was referred to the University of the Ryukyus Hospital for treatment of ME secondary to BRVO in the left eye. He had systemic hypertension, for which he was being treated with oral hypertensive medication. The decimal best-corrected visual acuity (BCVA) was 0.9 (Snellen equivalent 20/22) in the right eye and 0.7 (Snellen equivalent 20/29) in the left eye. Slit-lamp examination revealed bilateral mild cataract; otherwise, his anterior segment was normal. Widespread retinal hemorrhage was seen around the superior temporal vascular arcade (Fig. 1). On optical coherence tomography (OCT), a thin epiretinal membrane (ERM) was observed extending superiorly from the fovea and accompanied with diffuse retinal thickening. Based on these findings, we diagnosed the patient as BRVO with ERM.

Accordingly, 0.5mg IVR injection was administered for the treatment of ME and prompt resolution of retinal hemorrhage. Fourteen days after IVR administration, the patient returned to our hospital with symptoms of sudden vision deterioration in the left eye. By then, the retinal

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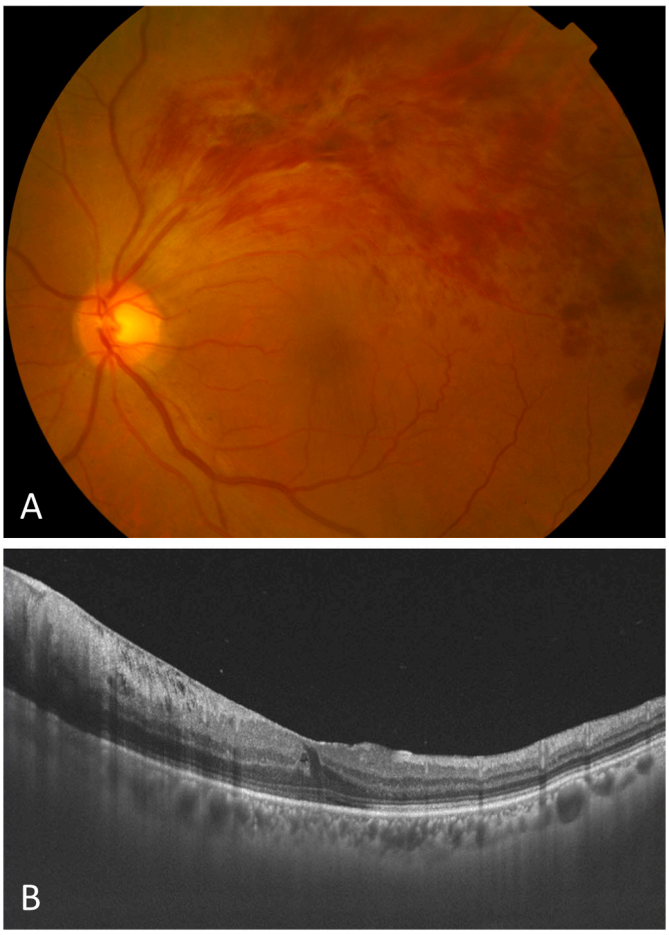

Fig. 1. Photographs of the left eye on the initial visit. The color fundus photograph (A) demonstrates widespread retinal hemorrhage around the superior temporal vascular arcade. The vertical optical coherence tomography through the foveal center (B) reveals thin epiretinal membrane extending superiorly from the fovea accompanied by diffuse retinal thickening. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

hemorrhage had decreased; however, the ERM had progressed remarkably into a macular pucker, causing severe retinal folds (Fig. 2). The decimal BCVA had also decreased to 0.2 (Snellen equivalent 20/100). The macular pucker had spread from the superior macula towards the equator, accompanied by partial TRD. OCT showed a thick proliferative membrane on the retina, causing prominent retinal folds and traction.

Seventeen days after IVR administration, we performed 25-gauge microincision pars plana vitrectomy combined with phacoemulsification cataract surgery and intraocular lens implantation. There was extensive proliferative change from the posterior to the equator and beyond, thus, the membrane was carefully removed to an appropriate extent. The peripheral retina had tractional detachment, and an encircling scleral buckle was added to release the wide range of traction. Scatter laser photocoagulation was also performed in the area of the retinal hemorrhage, followed by gas tamponade. Twenty days after the surgery, the decimal BCVA in the left eye improved to 0.3 (Snellen equivalent 20/67), and the retina was attached. On OCT, neither recurrence of ME nor proliferative changes were observed; however, thickening of the central fovea and loss of the ellipsoid zone was evident (Fig. 3). Three months after the surgery, the decimal BCVA was 0.4 (Snellen equivalent 20/50), and the other ocular findings remained unchanged.

3. Discussion

We present a case of BRVO in which rapid formation of macular pucker was observed following a single IVR administration. In a previous report by Wise,[3] "fibrosis and retinal folds" often appeared within 6–12 months after the onset of RVO. However, in this case, formation of macular pucker and TRD occurred within 14 days of IVR administration, suggesting that IVR may trigger and accelerate proliferative changes in the eye. An intravitreal injection itself is known to induce posterior vitreous detachment (PVD)[4] as well as glial cells[5] and cortical vitreous remnants[6] that may have proliferated in the vitreoretinal interface to form the macular pucker. However, since we had already detected PVD in our case at the initial visit, it is unlikely that the injection itself triggered proliferative reactions.

The mechanism of proliferation and contraction of ERM presumably involves a variety of cytokines. Marticorena et al.[7] reported new ERM development in patients with RVO after administration of intravitreal bevacizumab (IVB). The authors hypothesized that anti-VEGF agents reduced nitric oxide production in vascular endothelial cells, leading to arteriolar constriction and retinal hypoxia. Hypoxia increases the production of pigment epithelium-derived factor (PEDF), which inhibits the effects of VEGF on angiogenesis and leads to fibrotic changes. Furthermore, in a study of proliferative diabetic retinopathy (PDR),

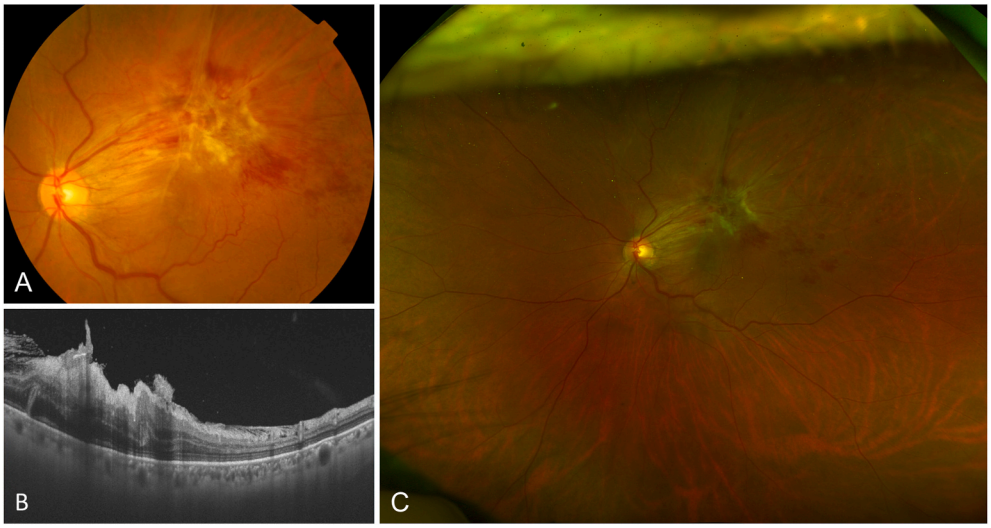

Fig. 2. Photographs of the left eye 14 days after intravitreal injection of ranibizumab. The color fundus photograph (A) shows a macular pucker and severe retinal folds. The vertical optical coherence tomography through the foveal center (B) demonstrates thick proliferative membrane on the retina accompanied by retinal folds predominantly in the superior macula. The widefield color fundus photograph (C) shows proliferative membrane over the equator and peripheral tractional retinal detachment. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

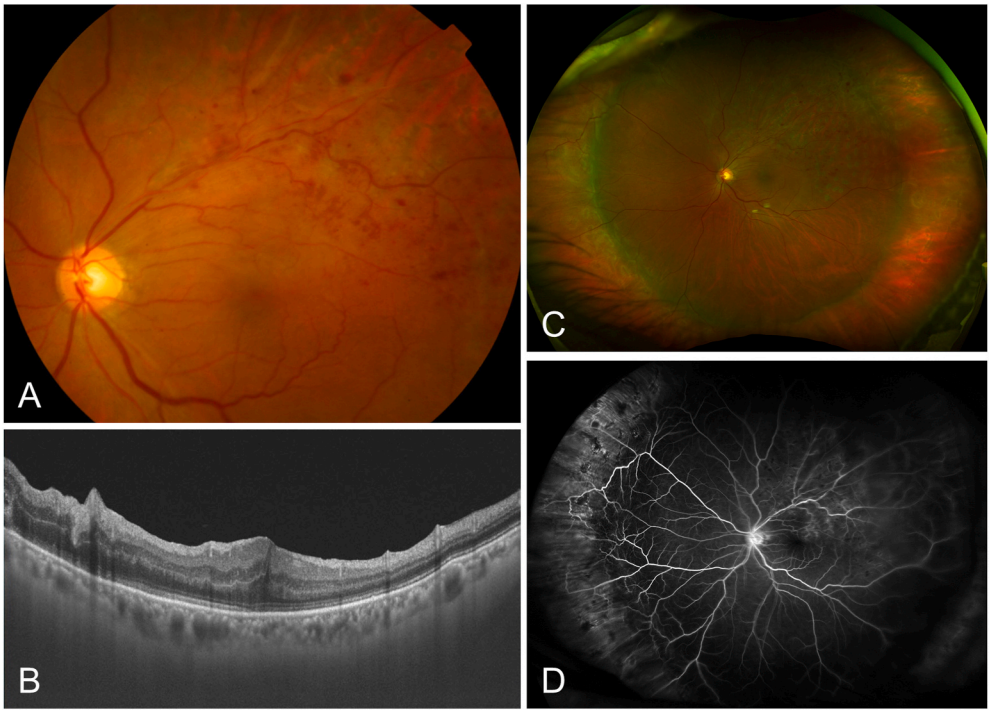

Fig. 3. Photographs of the left eye 20 days after the surgery. The color fundus photograph (A) demonstrates residual retinal hemorrhages around the superior temporal vascular arcade and scatter laser scars, but no evident proliferation. The vertical optical coherence tomography shows residual retinal folds without epiretinal membrane proliferation. The widefield color fundus photograph (C) shows retinal protrusion caused by encircling scleral buckling. The widefield fluorescein angiogram (D) revealed no evident nonperfused areas and neovascular membranes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

transforming growth factor (TGF)-β and connective tissue growth factor (CTGF) increased after IVB administration, promoting fibrotic changes in the ERM and its contraction.[8] Collectively, intravitreal anti-VEGF agents may cause elevation of PEDF, TGF-β, and CTGF, resulting in the progression and contraction of ERM.

Proliferative changes have been reported in several retinal and choroidal vascular diseases, such as PDR,[9] retinopathy of prematurity,[10] BRVO,[7] Coats' disease,[11] and neovascular age-related macular degeneration (AMD)[12] after administration of anti-VEGF agents. Arevalo et al.[9] reported that 11 patients with severe PDR developed TRD, induced by shrinkage of fibrovascular membrane after IVB administration as an adjuvant to vitrectomy. In that report, the mean period between IVB administration and TRD was 13 days (range, 3–31 days). Furthermore, a recent report demonstrated worsening of pre-existing ERM during three monthly injections of intravitreal aflibercept in an eye with neovascular AMD.[12] In terms of BRVO, four of 25 eyes developed a new ERM within 6–7 weeks of IVB administration.[7] However, the severity of ERM in that study appeared much milder when compared to the macular pucker in our case, as it did not cause further deterioration of visual acuity or metamorphopsia. In our case, the pre-existing ERM rapidly worsened and proliferated within 14 days of a single IVR administration. To our knowledge, our case is the first to report macular pucker induced by IVR. This suggests that any type of currently administered anti-VEGF agent for retinal and choroidal diseases may lead to proliferative changes in the eye. Furthermore, in a previous report, spectral-domain OCT revealed the prevalence of ERM in 34 % of normal eyes.[13] Therefore, careful observation of patients with BRVO is essential after administration of anti-VEGF agents, especially in eyes with pre-existing ERM.

4. Conclusions

We experienced a case of BRVO in which the pre-existing ERM progressed rapidly into macular pucker after IVR administration, leading to TRD. Remarkable proliferative changes may occur in the eye after administration of anti-VEGF agents, especially in cases with accompanying ERM.

Patient consent

The patient provided verbal consent for the publication of their case.

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Authorship

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

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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