

Short-term outcomes following treatment of recalcitrant cystoid macular edema secondary to radiation maculopathy using intravitreal brolocizumab

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ABSTRACT

Purpose: To assess the efficacy of intravitreal brolocizumab (Beovu®, Novartis Pharmaceuticals) in a case of recalcitrant cystoid macular edema associated with radiation maculopathy secondary to retinoblastoma which was suboptimally responsive to other intravitreal anti-vascular endothelial growth factor (VEGF) therapies.

Observations: A 42-year old patient with a history of radiation maculopathy complicated by cystoid macular edema after chemoreduction treatment and radiation therapy for retinoblastoma was treated with intravitreal brolocizumab. Best-corrected visual acuity and central macular thickness assessed by optical coherence tomography were used to assess the clinical outcomes. The treated eye was also assessed for evidence of intraocular inflammation following injection. Cystoid macular edema showed marked reduction and near resolution two weeks after injection and improvement in best-corrected visual acuity which was maintained for 2 months of follow-up. No ocular inflammatory reactions or other adverse events were reported.

Conclusions and Importance: This case of radiation maculopathy refractory to other intravitreal anti-VEGF treatments showed good treatment response to brolocizumab therapy.

1. Introduction

Radiation maculopathy (RM) is one of the causes of severe vision loss after radiation therapy to treat tumors or inflammation of the choroid, retina, orbit and paranasal sinuses.¹ The risk for development of radiation maculopathy is related to the total dose, radiation dose rate, comorbidity and the usage of radiation sensitizers. Radiation maculopathy has been reported to be a progressive disease characterized by cystoid macular edema (CME) and retina ischemia.² Panretinal laser photocoagulation has been recommended for treatment of the retinal ischemia in eyes with radiation-related neovascular glaucoma, while focal photocoagulation laser has been suggested by some for the treatment of radiation-induced retinal neovascularization.³ Intravitreal injections of anti-vascular endothelial growth factor (VEGF),⁴ dexamethasone implant⁵ and triamcinolone (IVTA)⁶ have also been described with variable results. Herein, we report a case of RM with recalcitrant macular edema treated with a newly available intravitreal anti-VEGF (Beovu®, Brolucizumab dbll, Novartis Pharmaceutical Corporation, Basel, Switzerland).

2. Case report

A 42-year old female has been managed for several years at the Doheny UCLA Eye Centers for radiation maculopathy. The patient has a history of multiple tumors diagnosed at the age of 8 months, including bilateral retinoblastoma for which she underwent enucleation of the left eye and chemoreduction therapy with Cytoxan and Vincristine and charged-particle radiation therapy for the right eye. The total dose of external radiation therapy was 50 Gy. At 16 years of age, the patient was first diagnosed with radiation maculopathy in the right eye. She was first referred to our retina center at 37 years of age for further retinal management after undergoing cystectomy and additional chemotherapy to treat urinary bladder tumor.

At her baseline visit at our eye center, the best-corrected visual acuity (BCVA) was 20/40 in the right eye. Dilated fundus examination of the right eye revealed the region of the largest treated retinoblastoma lesion along the superotemporal arcade extending centrally, as well as multiple other areas of chorio-retinal atrophy within and outside the retinal vascular arcades (Fig. 1A). A spectral domain optical coherence

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tomography B-scan centered on the fovea showed CME with a central macular thickness (CMT) of 426 μm . A structural B-scan image centered on the original retinoblastoma lesion location superior to the fovea, demonstrated a staphyloma with retinal pigment epithelial (Fig. 1 B) and central cystoid macular edema (Fig. 1 C). Fluorescein angiography (Fig. 1 D and E,F) shows evidence of telangiectatic capillaries and lipid exudates (white arrow, Fig. 1 F) in the temporal macula. Late phases of the angiogram (Fig. 1 E) demonstrate dye leakage from these microvascular abnormalities. En face Spectral-Domain Optical Coherence Tomography Angiography (SD-OCTA) of the retinal capillary plexus shows some areas of capillary nonperfusion (white arrowheads, Fig. 1 G). The patient received multiple injections of aflibercept 2 mg (Eylea®, Aflibercept, Regeneron Pharmaceuticals, Inc. Tarrytown, NY) every 4 weeks without significant improvement. To determine if the edema was at all responsive to anti-VEGF treatment, the patient was re-evaluated 2-weeks after aflibercept injection and a mild reduction in edema was evident. By one month follow from the injection, the CME returned to pre-treatment levels (Fig. 2 A, B, C). The patient was then switched to ranibizumab 0.5 mg (Lucentis®, Genentech/Roche, San Francisco, CA) but no significant improvement in the CME and CMT was observed (Fig. 2 D, E, F). As the patient was relatively young and phakic, she declined steroid therapy. Given the persistent CME and progressive worsening of vision to a BCVA level of 20/60 despite monthly aflibercept and ranibizumab, a trial of intravitreal brodalumab 6 mg was proposed. Prior to injection, an extensive informed consent process was undertaken to clearly indicate that the treatment was off-label, and the

risks and benefits of the treatment for radiation retinopathy-associated macular edema were not known. Treatment was performed before recent reports of rare cases of severe intraocular inflammation and vascular occlusions associated with brodalumab. Two-weeks after brodalumab injection, structural OCT demonstrated a marked anatomic improvement, with minimal residual CME and CMT of 240 μm with improved vision to 20/25 OD. At 8-weeks follow-up, the CME had only increased mildly and was still well below pre-treatment levels (Fig. 2 G, H, I). BCVA remained stable at 20/25. The patient also reported that the quality of vision was much improved subjectively. Before and 2 and 8-weeks after brodalumab injection, intraocular pressure OD was stable at 14 mmHg. No evidence of inflammation or vascular occlusion was noted at 2 or 8 weeks and patient did not observe any subjective adverse symptoms.

3. Discussion

Radiation maculopathy is a progressive retinal microangiopathy secondary to high-dose radiation therapy. It is hypothesized that radiation treatment causes direct damage to the endothelial cells generating the production of free radicals. This damage is thought to cause occlusion of retinal capillaries and the formation of microaneurysms. The ischemia is caused by the hypoperfusion of certain areas of the retina, especially in the periphery, ultimately leading to the onset of macular edema and macular neovascularization.⁷ Radiation therapy can be utilized as a primary or secondary treatment in the management of

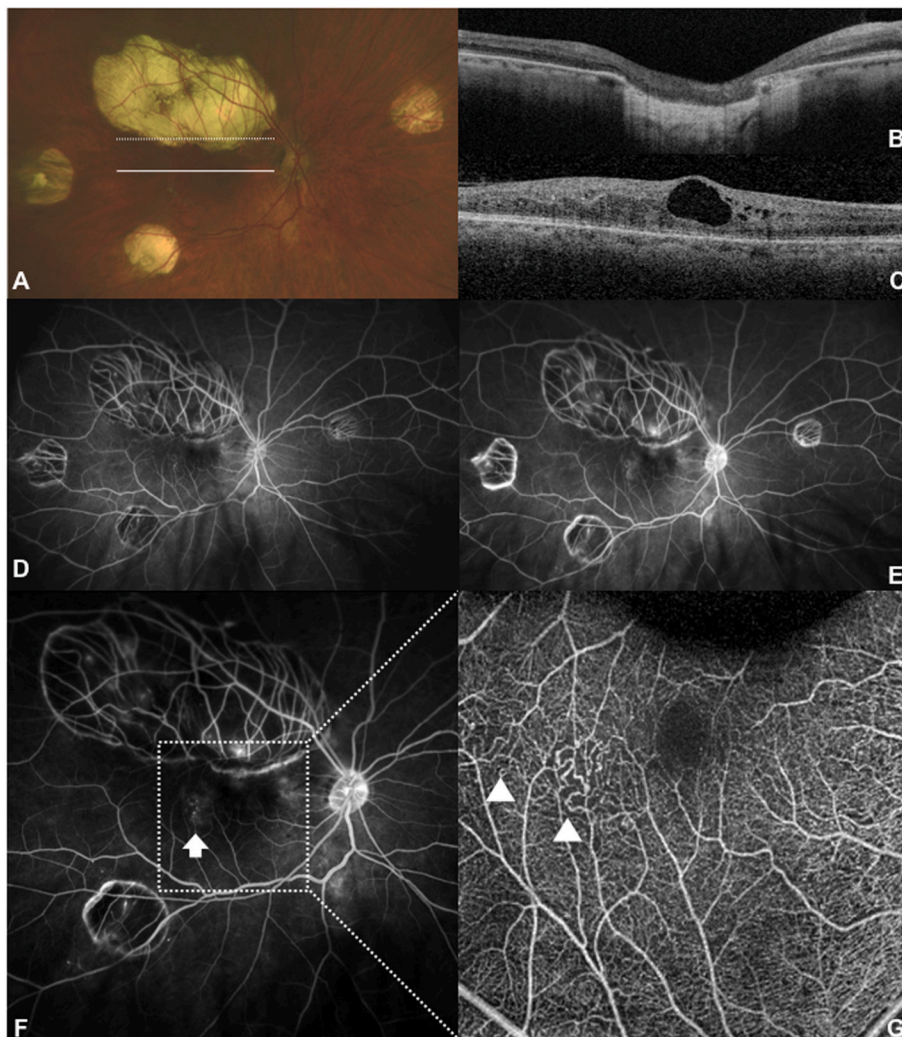


Fig. 1. (A) Widefield Pseudocolor image of the right eye of a patient with radiation maculopathy secondary to retinoblastoma, showing the main treated tumor location superior to the fovea and multiple additional areas of chorio-retinal atrophy elsewhere. Optical coherence tomography (OCT) demonstrates a marked staphyloma and retinal pigment epithelial (RPE) atrophy superior to the fovea (B) and central cystoid macular edema (C). (D,E) Widefield fluorescein angiography (FA) show macular edema with temporal lipid exudation. Late phases of the angiogram (E) show an increased vascular leakage temporally, nasally and superiorly to the macula. Mild leakage of the optic nerve is also present on the late phases of the fluorescein angiogram (E). Areas of chorio-retinal atrophy are also noted on FA. The tumoral lesion is located superiorly to the macula over the supero-temporal vascular arcade. (F) A higher magnification angiogram shows the macular edema associated with lipid exudation temporally to the macula (white arrow), corresponding to an area of capillary non-perfusion and hypoperfusion showed by the vascular capillary plexus slab (white arrowheads) on OCTA (G).

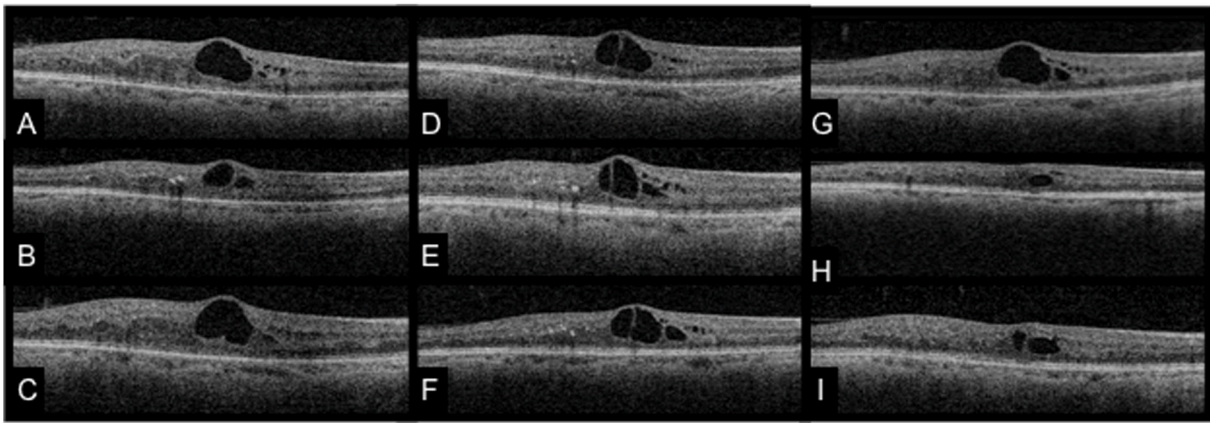


Fig. 2. Structural optical coherence tomography (OCT) B-scans demonstrating the status and extent of cystoid macular edema at various points during the course of treatment: (A) before aflibercept 2mg injection, (B) 2 weeks after aflibercept injection, (C) 8 weeks after aflibercept injection, (D) before ranibizumab 0.5mg injection, (E) 4 weeks after ranibizumab injection, (F) 8 weeks after ranibizumab injection, (G) before brolocizumab 6mg injection, (H) 2 weeks after brolocizumab injection, (I) 8 weeks after brolocizumab injection.

retinoblastoma after chemoreduction of the tumor, and a major concern is that the combination of both therapies can manifest in worse severe radiation damage.⁸

Several studies have shown that the risk for developing radiation maculopathy is related to the total dose of radiation as well as to the daily fraction size.² A retrospective series reported a cohort of 84 eyes with retinoblastoma treated with brachytherapy and estimated that 19% of the eyes developed radiation maculopathy at 5 years.⁸ Other reports described the treatment of radiation maculopathy secondary to retinoblastoma with focal laser photocoagulation and anti-VEGF injections.^{1,9}

Nevertheless, at present there is no proven optimal therapy for the treatment of radiation maculopathy. Given that human solid tumors, such as retinoblastoma and uveal melanomas, are angiogenesis-dependent, anti-VEGF treatments are believed to play an important role in the management of the growth of these tumors and in the treatment of the associated complications.¹⁰ Recently Patel et al.¹¹ have described a case of off-label use of brolocizumab in conjunction with diode laser photocoagulation for the treatment of Coat's disease, and demonstrated a favorable response. In our case, despite chronic and continuous treatment with ranibizumab or aflibercept therapy, the patient had persistent macular edema. A single brolocizumab injection was associated with marked reduction in edema by 2 weeks with a persistent treatment benefit through 8 weeks. Although no conclusion can obviously be drawn based on this single case, our experience would suggest that the use of brolocizumab for cases of refractory edema associated with radiation retinopathy warrants further evaluation. The potential benefits, however, will need to be weighed against the potential serious risks of recently reported rare cases of severe intraocular inflammation.

4. Conclusions

As presented in this case report, brolocizumab may be effective in eyes affected by radiation maculopathy complicated by chronic and refractory macular edema, when the response to other anti-VEGF intravitreal agents is suboptimal or steroids are relatively contraindicated.

Patient consent

Written consent to publish this case report was not obtained from the patient. Therefore, this report does not include any personal information that could identify the patient. The study and data accumulation were carried out with approval from the appropriate Institutional Review Board (IRB).

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Authorship

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

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Declaration of competing interest

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