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Intravitreal brolucizumab as treatment of early onset radiation retinopathy secondary to plaque brachytherapy for choroidal melanoma

Natacha C. Villegas [a], Kapil Mishra [b], Nathan Steinle [c], Wu Liu [d], Beth Beadle [d], Prithvi Mruthyunjaya [a,d,*]

[a] Department of Ophthalmology, Stanford University School of Medicine, 2452, Watson Ct, Palo Alto, CA, United States
[b] Retina Service, Department of Ophthalmology, Stanford University School of Medicine, 2452, Watson Ct, Palo Alto, CA, United States
[c] California Retina Consultants, 525 E Micheltorena St A, Santa Barbara, CA, United States
[d] Department of Radiation Oncology, Stanford University School of Medicine, 291 Campus Drive, Stanford, CA, United States

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ABSTRACT

Purpose: To describe the efficacy and safety of brolucizumab (Beovu®, Novartis Pharmaceuticals) in a case of cystoid macular edema associated with radiation retinopathy as a result of iodine-125 plaque brachytherapy (PBT) for choroidal melanoma, resistant to treatment with other anti-vascular endothelial growth factor (VEGF) agents.

Observations: A 67-year-old woman with choroidal melanoma in the right eye and best-corrected visual acuity (BCVA) of 20/20, underwent uncomplicated PBT. On post-operative month 7, the patient developed early onset radiation retinopathy. She failed to improve significantly with sub-tenon triamcinolone and 3 injections of intravitreal bevacizumab; BCVA was 20/200. Intravitreal brolucizumab was administered, and one month after, macular edema had resolved completely on optical coherence tomography, and BCVA improved to 20/50. At last follow up, 1 month after the third brolucizumab injection, BCVA was 20/60 and there was sustained resolution of intraretinal fluid. There were no signs of intraocular inflammation, progressive RR or optic neuropathy on exam or fluorescein angiography.

Conclusions: This case suggests a positive effect of brolucizumab in the management of radiation retinopathy following PBT refractory to other anti-VEGF agents. However, one must consider the risk of severe vision loss associated with retinal vasculitis from use of brolucizumab.

1. Introduction

Radiation retinopathy (RR) can cause severe vision loss due to cystoid macular edema (CME) following radiation treatment for choroidal melanoma (CM), with an incidence as high as 64% in some studies.[1] This is due to radiation-induced vascular endothelial damage, resulting in capillary occlusion and retinal ischemia manifestations such as neovascularization and macular edema.[2] RR may present on average 2 years after ocular radiation, with clinical signs such as cotton-wool spots, hard exudates, microaneurysms, macular edema, neovascularization, and vitreous hemorrhage.[3]

Historically, treatments for RR have included focal laser,[4] panretinal photocoagulation,[4] intravitreal triamcinolone,[5] photodynamic therapy,[6] and most recently, off-label use of intravitreal anti-vascular endothelial growth factor (anti-VEGF).[7] Studies on anti-VEGF agents including bevacizumab (Avastin®, Genentech/Roche, San Francisco, CA), ranibizumab (Lucentis®, Genentech/Roche, San Francisco, CA), and aflibercept (Eylea®, Aflibercept, Regeneron Pharmaceuticals, Inc. Tarrytown, NY), have shown their safety and efficacy in treating RR.[7–9] Recently, a new anti-VEGF agent for intravitreal use, brolucizumab (Beovu®, Brolucizumab, Novartis Pharmaceutical Corporation Basel, Switzerland), was approved by the U.S. Food and Drug Administration (FDA) for neovascular age-related macular degeneration (nAMD). This drug inhibits all isoforms of VEGF-A and has the smallest size amongst available agents, allowing it to deliver a high molar concentration and making it potentially longer-lasting than other anti-VEGF agents.[10] Pivotal trials in nAMD showed the macular drying efficacy of brolucizumab to be superior to aflibercept within a 48-week follow-up period.[10] Nevertheless, subsequent studies found a rare but severe association with occlusive retinal vasculitis and intraocular inflammation.[11]

* Corresponding author. Department of Ophthalmology, Stanford University School of Medicine, 2452, Watson Ct, Palo Alto, CA, United States.
E-mail address: prithvi9@stanford.edu (P. Mruthyunjaya).

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Strategies for safe use of this new drug have been developed[12] and its use in this patient followed these recommendations.

Herein we describe the use of intravitreal brolucizumab for the treatment of cystoid macular edema secondary to iodine-125 plaque brachytherapy (PBT) for CM, in a patient refractory to other anti-VEGF agents.

2. Case report

A 67-year-old woman presents with concerns of a new choroidal lesion in her right eye. She has a history of previous pars plana vitrectomy with membrane peel for epiretinal membrane on the right eye, and subsequent cataract extraction complicated by CME treated with sub-tenon triamcinolone. She was referred to the Stanford Ocular Oncology service where her best-corrected visual acuity (BCVA) in the right eye was 20/20 and intraocular pressure was 14 mmHg. A dilated fundus exam revealed an amelanotic choroidal tumor located 3 mm temporal to the fovea (Fig. 1A). Ultrasonography demonstrated low internal reflectivity with associated retinal detachment that was 9 × 8.7 mm in base and 4.2 mm in thickness (Fig. 1B). Optical coherence tomography (OCT) of the tumor was consistent with a melanocytic choroidal lesion demonstrating a smooth, dome-shaped mass with subretinal fluid and compaction of the choriocapillaris (Fig. 1C) while OCT of the macula demonstrated a mildly blunted foveal contour from the prior epiretinal membrane and membrane peel, with intact ellipsoid zone, no subretinal fluid, mild thickening nasally, and central macular thickness (CMT) of 424 μm (Fig. 1D). A diagnosis of medium sized CM (American Joint Committee on Cancer staging 8th edition T2a N0 M0) was confirmed.

After appropriate evaluation demonstrating no evidence of metastatic disease, the patient underwent uncomplicated iodine-125 PBT treatment along with a 27-gauge transvitreal vitrectomy-guided choroidal tumor biopsy, endolaser, air-fluid exchange, and posterior sub-tenon triamcinolone administration. The total radiation dose delivered was 85 Gy to a depth of 4.2 mm (Fig. 2). The dose to the nerve was 7.66 Gy, and the dose to the fovea was 42.6 Gy. Genetic expression profile (GEP) revealed a class 2, PRAME positive CM.

Three months after plaque removal, the tumor had regressed, the exudative retinal detachment had improved, and vision was 20/40. Intravitreal bevacizumab was administered for prevention of RR, as planned.[7] On post-operative month 7, OCT demonstrated CME and vision had decreased to 20/50, consistent with early onset RR. The patient was treated with an injection of sub-tenon triamcinolone and 3 monthly injections of intravitreal bevacizumab. Despite these interventions, the patient still had worsening CME with CMT of 615 μm (Fig. 3A) and visual acuity had decreased to 20/200. After a detailed discussion of risks, benefits, and alternative agents, the patient opted to try brolucizumab given the potential to decrease injection frequency. An off-label intravitreal injection of 6 mg in 0.05 cc of brolucizumab was administered. One month after the first injection of brolucizumab, macular edema resolved completely, with CMT reduction to 298 μm (Fig. 3B) and BCVA improved to 20/50. At last follow up, 16 months after PBD treatment and 3 total brolucizumab injections, visual acuity was 20/60 with no macular edema on OCT, no signs of intraocular

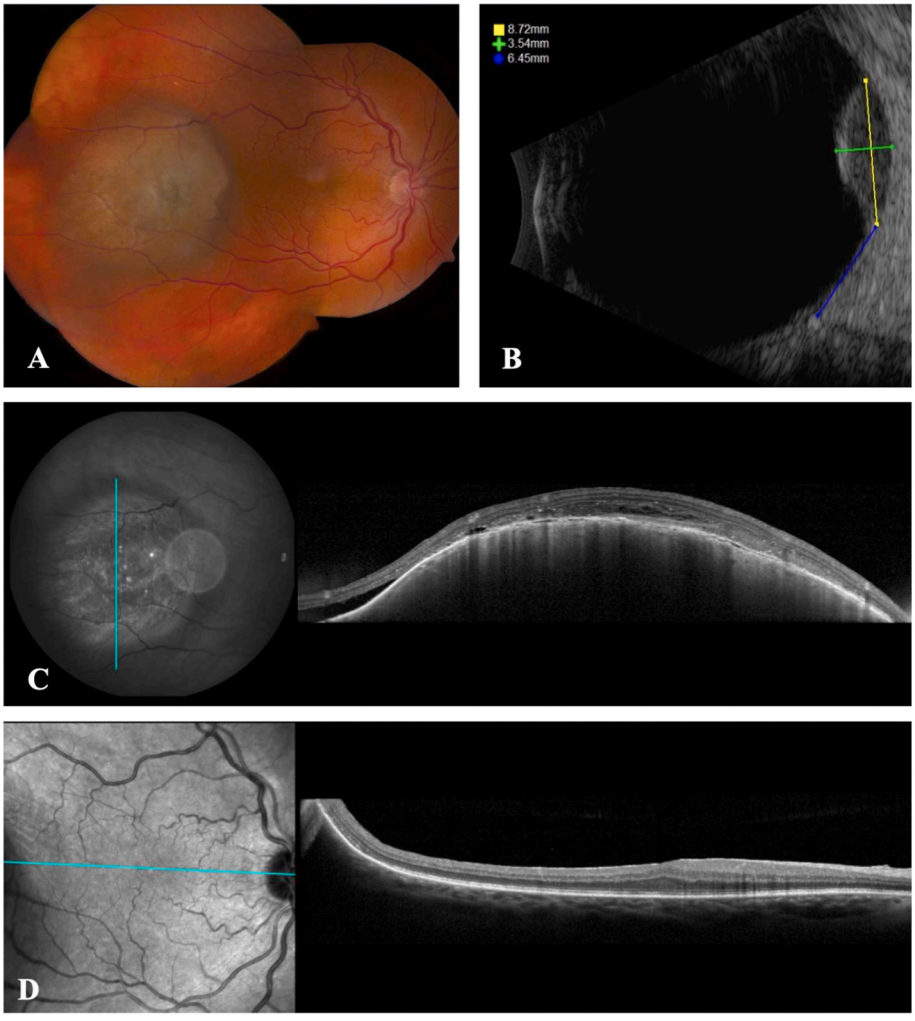

Fig. 1. Color fundus photo demonstrating a round, amelanotic choroidal mass temporal to the fovea (A). B-scan ultrasound of the choroidal mass, measuring 9 × 8.72 mm in basal diameter, located 6.4 mm from the optic nerve head (B). Spectral-domain OCT over lesion demonstrates a smooth, dome-shaped choroidal mass with choriocapillaris compaction, disrupted outer retinal layers, and overlying subretinal fluid (C). OCT of the macula shows slightly blunted foveal contour from a prior membrane peel with no subretinal fluid, and mild nasal thickening (D). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

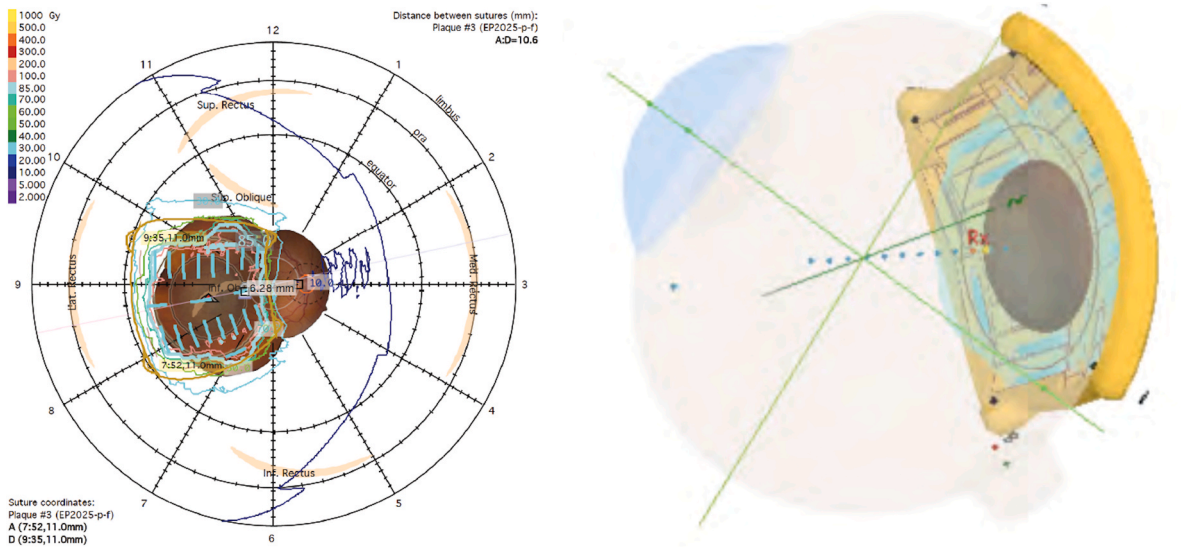

Fig. 2. Plaque Simluator (EyePhysics, LLC, Los Alamitos, California) showing coordinates for plaque placement, determined by an aggregate of fundus photos, B-scan ultrasound, and neuroimaging. This ensures the plaque completely covers the tumor and minimizes unnecessary radiation to other structures. The plaque contained 21 seeds.

inflammation, progressive RR or optic neuropathy on exam or on repetitive fluorescein angiography (Fig. 3C and D, 4). Given the improved visual acuity and absence of intraocular inflammation, the plan is to follow a treat-and-extend protocol.

3. Discussion

Radiation maculopathy is a common complication of radiotherapy for ocular cancers and other head and neck malignancies.[13] Prophylactic regimens have been employed to prevent vision loss, with studies showing decreased incidence of CME and lower rates of vision loss with the use of sub-tenon triamcinolone or bevacizumab every 4 months.[14,15] Regarding treatment, studies have demonstrated an improvement or stabilization of visual acuity and decreased CME with bevacizumab, aflibercept and ranibizumab.[7–9] However, most patients in these studies required prolonged treatment every 6–8 weeks.[7]

Additionally, a significant number of patients remain resistant to treatment with these anti-VEGF agents.[16,17] In a study by Finger et al., some patients remained unresponsive to treatment even after dose escalation to 2.0 mg ranibizumab,[18] highlighting the severe ischemia that characterizes RR. Furthermore, Murray et al. showed an inability to decrease frequency in aflibercept injections for RR further than 6 weeks between injections in a period of 1 year, demonstrating the chronic and persistent course of the disease.[8]

In the pivotal trials leading to brolucizumab's FDA approval for nAMD, 38.6–45.4% of patients had adequate nAMD control on treatment every 12 weeks,[10] and real-world outcome studies have shown the ability of brolucizumab to improve vision in patients resistant to other anti-VEGF agents.[19] Therefore, the potential of brolucizumab to decrease treatment burden and to improve vision in other conditions such as RR is promising.

In regard to safety, some may suggest a theoretically higher risk of occlusive vasculitis from brolucizumab treatment in RR patients given the ischemic nature of the disease. A study of 43 patients who underwent brolucizumab treatment for RR, with a minimum of 60-days follow-up after injection, showed no vitritis or vasculitis.[20] More studies are needed to determine if brolucizumab use in patients with RR confers a higher risk of occlusive vasculitis than its on-label use for nAMD. This highlights the need to continuously update of the risk-benefit discussion in the informed consent as more information on safety arises.

A recent case report described the use of brolucizumab in a patient with history of charged-particle radiation therapy with a total dose of 50 Gy for retinoblastoma, who developed RR and had been treated with anti-VEGF agents for many years with poor response.[21] The patient opted to try brolucizumab, and 2 weeks after the first treatment there was an improvement in BCVA from 20/60 to 20/25, which was maintained during the 2-month follow up period reported. In our case, the patient was refractory to sub-tenon triamcinolone and 3 intravitreal injections of bevacizumab. However, after only one injection of intravitreal brolucizumab, macular edema resolved completely, and BCVA improved from 20/200 to 20/50 with sustained short term macular drying and visual acuity of 20/60 at 6 months.

4. Conclusion

We present a case of early onset cystoid macular edema secondary to RR from iodine-125 PBT for CM, which had been refractory to sub-tenon triamcinolone and bevacizumab, and responded with complete resolution of fluid 4 weeks after a single administration of off-label intravitreal brolucizumab. We recognize the limited follow up and the long-term vision implications of microvascular changes due to the macular location of this tumor may be independent of the anti-VEGF therapy. Our case suggests a positive effect of this new agent in the management of this challenging condition. However, one must consider the risk of severe vision loss associated with retinal vasculitis from use of brolucizumab, and a thorough discussion with the patient regarding these risks is warranted.

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).

Funding/support

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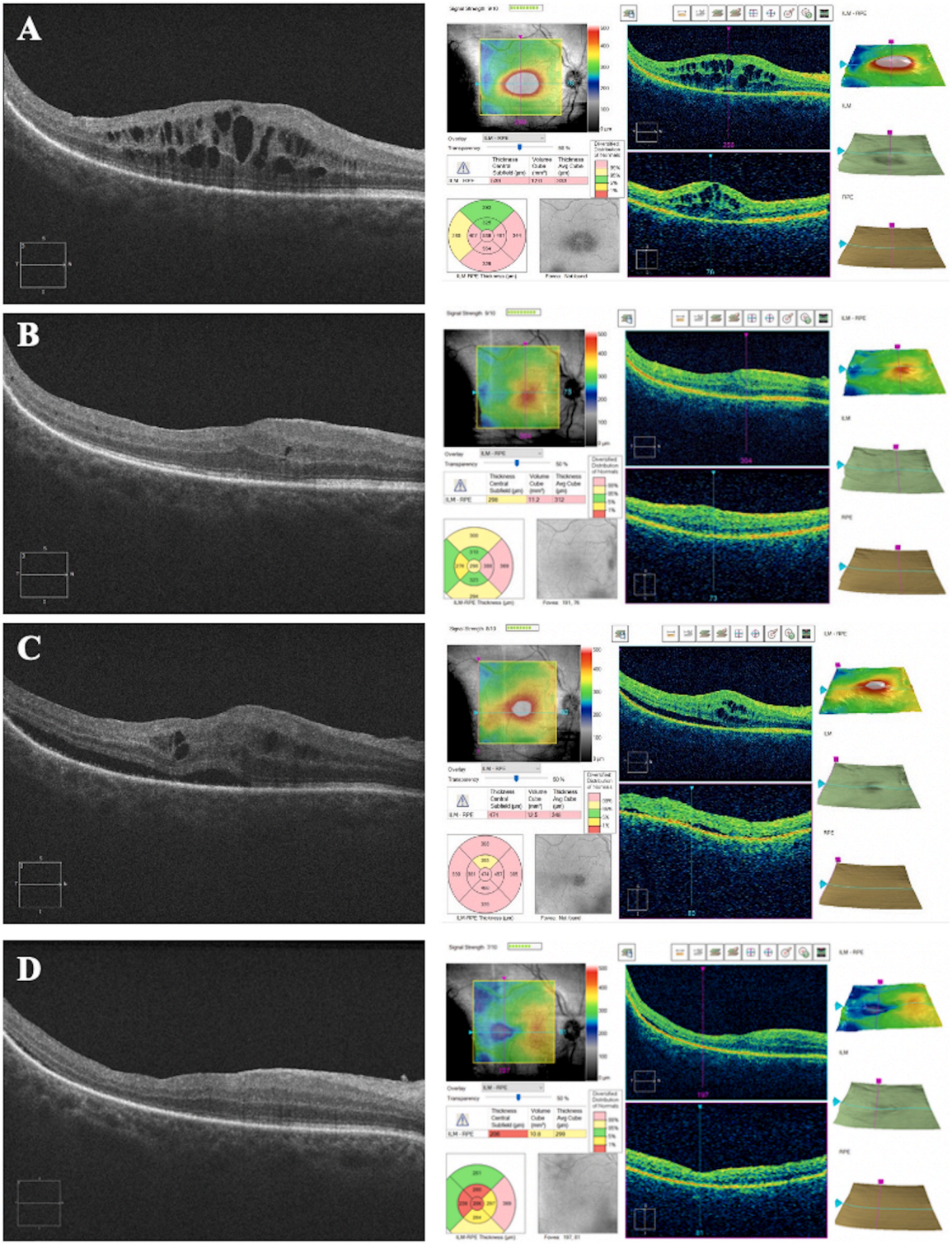

Fig. 3. OCT of the macula on post-operative month 9, after 3 intravitreal injections of bevacizumab and a sub-tenon injection of triamcinolone, demonstrating persistent foveal-involving intraretinal fluid (A). OCT of the macula one month after the first administration of intravitreal brolucizumab, demonstrating complete resolution of intraretinal fluid, with some residual, pre-existing nasal thickening (B). OCT of the macula one month after the second administration of intravitreal brolucizumab, demonstrating mild recurrence of intra- and sub-retinal fluid (C). OCT imaging one month following the third and most recent brolucizumab injection showing near complete resolution of all intraretinal and subretinal fluid (D).

Authorship

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

Declaration of competing interest

Nathan Steinle: Novartis (C). Prithvi Mruthyunjaya: Aura Biosciences (C), Castle Biosciences (C). The following authors have no financial

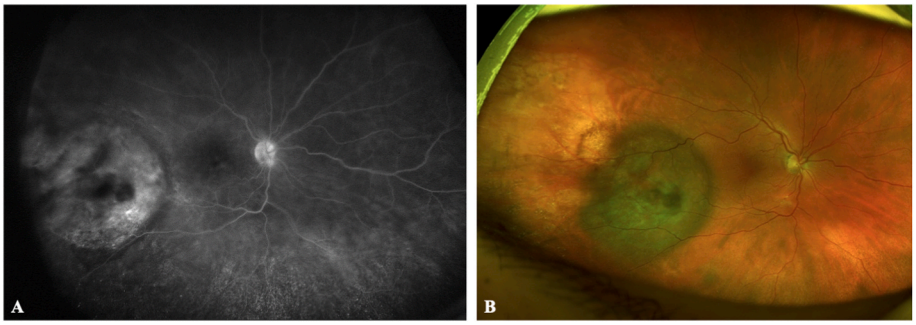

Fig. 4. Fluorescein angiogram of the right eye at 5:32 minutes, performed two weeks after the second administration of brolucizumab, demonstrating late staining and blocking of the lesion, notably without evidence of vasculitis. There is mild parafoveal leakage and late staining of the optic nerve, but no signs of neovascularization or significant non-perfusion (A). Ultra-widefield color fundus photograph demonstrating a treated CM following plaque therapy, no retinal hemorrhages, and no neovascularization (B). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

disclosures, NCV, KM, WL, BB.

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