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Longitudinal optical coherence tomography angiography (OCT-A) in a patient with radiation retinopathy following plaque brachytherapy for uveal melanoma

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ABSTRACT

Purpose: Patients with choroidal melanoma treated with brachytherapy lose vision over time due to radiation retinopathy and optic neuropathy. Newer imaging modalities such as optical coherence tomography angiography (OCT-A) may provide further insight into the ultrastructural vascular changes that occur over time. We studied the progressive OCT-A derived reduction in capillary density that occurred in the macula and juxtapapillary region of a patient treated with plaque brachytherapy for posterior uveal melanoma.

Methods: A patient with medium-sized choroidal melanoma in the inferonasal mid-periphery of the right eye was followed with OCT-A imaging in addition to standard imaging (color fundus photography, standardized echography, OCT) over a four-year time period following brachytherapy. Images were analyzed to measure vascular density in nine discrete areas of the macula at each time point as a function of region-specific radiation dose.

Results: OCT-A over time showed focal capillary loss and enlargement of the foveal avascular zone in addition to vascular re-modeling. These changes progressed over time despite improvement in the clinical markers of radiation retinopathy (cotton wool spots, retinal hemorrhages). Radiation dose significantly correlated with rate of reduction in vascular density assessed within 9 square sectors of the macula, and was greatest in sectors closest to the plaque, which had received the highest radiation dose. There was no change in the choriocapillaris flow area over time. The patient developed cystoid macular edema, but maintained 20/30 vision.

Conclusions and Importance: Longitudinal OCT-A demonstrates the microvascular changes that occur in response to radiation over time. Identification of these features may help define therapeutic windows to prevent vision loss associated with radiation retinopathy and optic neuropathy. Ongoing studies will describe a larger cohort of patients followed with this modality over time.

1. Introduction

Plaque brachytherapy provides an alternative to enucleation for patients with uveal melanoma, allowing for preservation of the eye. However, most patients treated with brachytherapy will lose vision over time. The Collaborative Ocular Melanoma Study (COMS) showed that 43% of patients had vision of 20/200 or worse by three years after treatment, and data from a large retrospective study prior to the anti-vascular endothelial growth factor (VEGF) era showed a vision of 20/200 or worse in 34% of patients at 5 years and 68% of patients at 10 years after treatment with brachytherapy.[1,2] The use of anti-VEGF agents has been shown to delay the progression of visual acuity loss in radiation retinopathy, but the optimal timing of therapy, patients most likely to benefit, and most effective agents have not been studied in a

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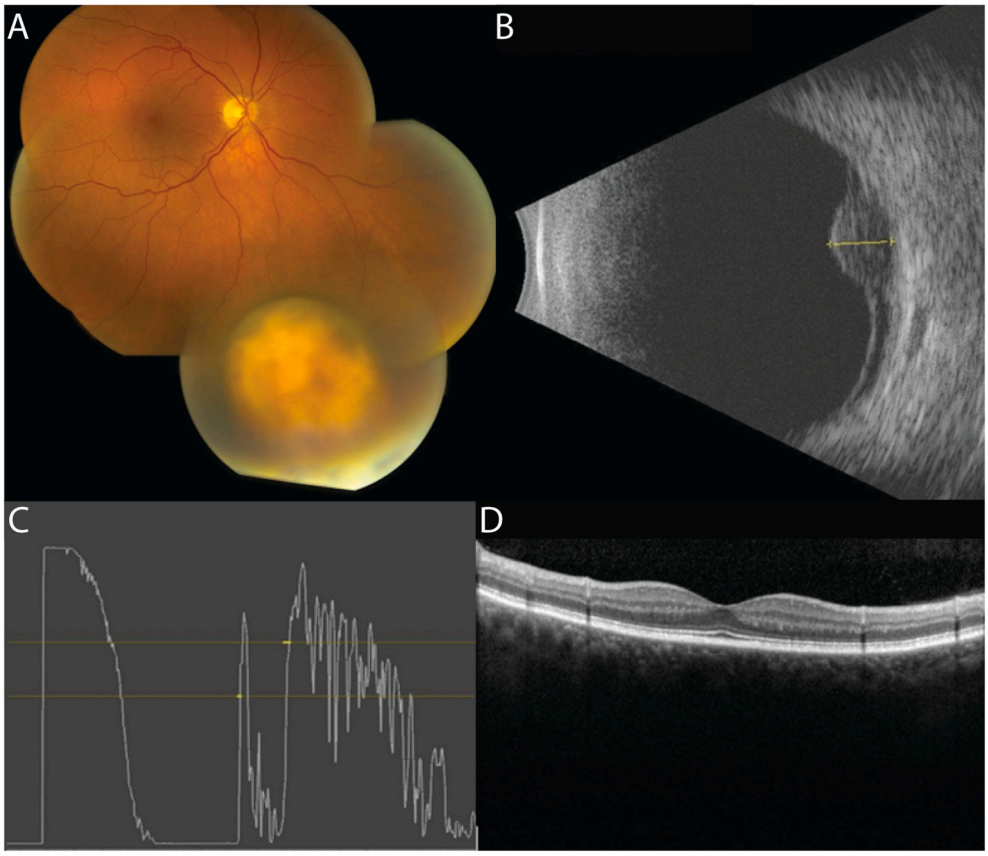

Fig. 1. Images at presentation. Color fundus photograph showed a dome-shaped, elevated, mostly amelanotic choroidal mass with surrounding subretinal fluid in the inferior periphery of the right eye (A). Standardized B-scan ultrasound (T6AE) showed a dome-shaped mass measuring 4.2 mm in thickness (B). Standardized A-scan ultrasound showed low internal reflectivity (C). Optical coherence tomography of the macula showed no cystoid macular edema (D). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

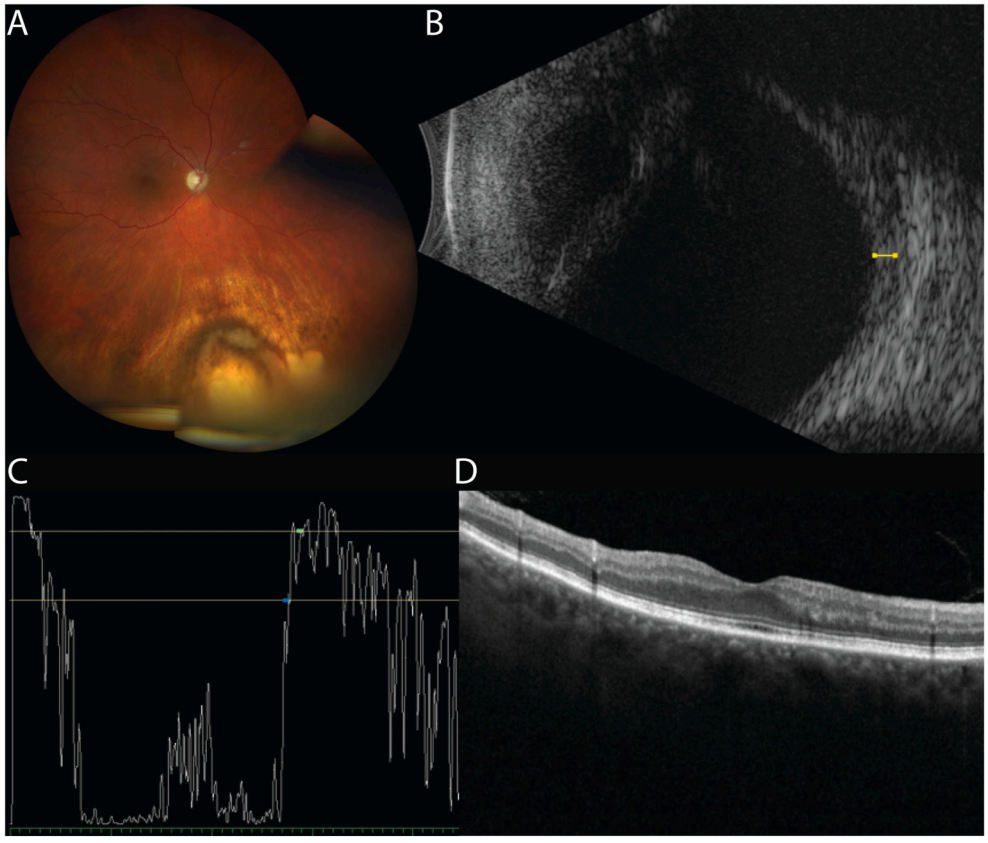

Fig. 2. Images four years following brachytherapy. Color fundus photograph shows an involuted choroidal lesion with surrounding retinal pigment epithelial atrophy in the inferior periphery. There were cotton wool spots nasal to the optic disc (A). Standardized B-scan ultrasound (T6AE) showed reduced thickness of the choroidal lesion compared to presentation (1.1 mm) (B). Standardized A-scan ultrasound showed high internal reflectivity and decreased thickness of the lesion (C). Optical coherence tomography of the macula showed irregular retinal laminations and mild atrophy but no cystoid macular edema. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

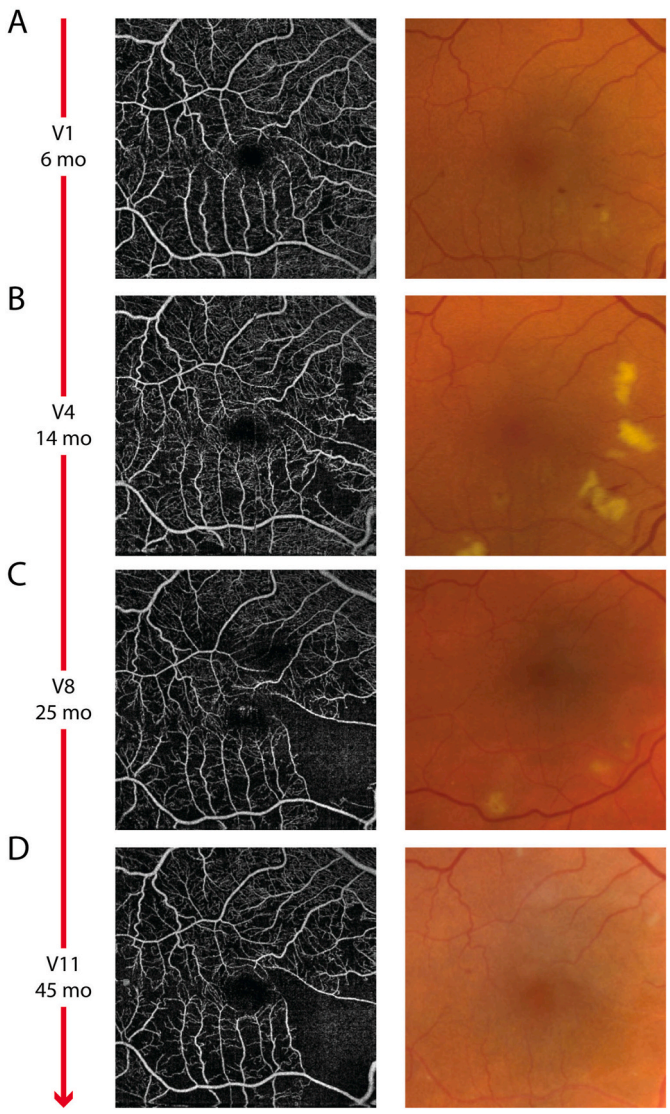

Fig. 3. Optical coherence tomography angiography (OCT-A) en-face images of the macula compared to color fundus photographs. 6 × 6 mm2 OCT-A scan centered on the foveal avascular zone (FAZ) at 6 months (A), 14 months (B), 25 months (C), and 45 months (D) compared to color fundus photographs at 47 the same time points show progressive capillary dropout despite resolution of cotton wool spots. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

large randomized trial.[3,4]

Further, vision loss from radiation-related sequelae is complex and often involves components of optic neuropathy, retinopathy, and choroidopathy, which can also be confounded by underlying vascular changes from the tumor itself.[5–8] The retinal capillary endothelial cell appears to be a site of primary vascular damage, but the interplay of radiation retinopathy, optic neuropathy, choroidopathy and their ensuing effects on visual outcomes are complex.[9] Patient variables such as the presence of underlying diabetes or other vascular disease may also predispose to radiation damage following brachytherapy.[9]

Newer imaging modalities such as optical coherence tomography (OCT), and optical coherence tomography angiography (OCT-A) have provided insight into the ultrastructural changes that occur in patients with radiation retinopathy.[10–12] Here we describe a patient treated with plaque brachytherapy for choroidal melanoma who was followed longitudinally with OCT-A over a period of four years. We describe the evolution of the ultrastructural vascular changes that occurred in the "real-world" setting of treatment with intravitreal anti-VEGF agents and measurement of vascular density across 9 square sectors of the macula as a function of radiation dose to each sector.

2. Methods

A 60-year-old man with newly diagnosed medium-sized choroidal melanoma in the right eye agreed to participate in a study of longitudinal imaging including optical coherence tomography angiography following ^{125}I-plaque brachytherapy. Approval for this study was obtained from the institutional review board at the University of Iowa Hospitals and Clinics and this study adhered to the tenets of the Declaration of Helsinki. The patient's past medical history was significant for type 2 diabetes, with mild non-proliferative diabetic retinopathy at presentation and visual acuity of 20/20 in each eye. The melanoma was diagnosed by clinical examination and standardized ultrasound by an experienced ocular oncologist. The lesion measured 13.0 x 10.0 × 4.2 mm and was located in the inferonasal mid-periphery (Fig. 1). Standardized echography showed a dome-shaped, low-reflective, vascular lesion consistent with a choroidal melanoma (Fig. 1). After a negative metastatic evaluation, the patient elected to undergo episcleral plaque brachytherapy to the right eye. An 18 mm, COMS-style ^{125}I-plaque was applied for 5 days with a total dose of 85 Gy to the tumor apex (0.71 Gy/h). Intravitreal bevacizumab was given at the time of plaque removal. He was then followed with serial standard imaging (color fundus photography, standardized echography, OCT) in addition to OCT-A of the macula and juxtapapillary region. A single 6 × 6 mm^2 OCT-A scan centered on the foveal avascular zone (FAZ), and a 4.5 × 4.5 mm^2 scan centered on the optic nerve head were acquired in both eyes (Optovue XR Avanti System, Optovue, Inc.) at 1–6 month intervals following treatment (images at 6, 9, 11, 14, 16, 17, 24, 25, 32, 29, and 45 months).

While ^{125}I-plaque brachytherapy is a focal treatment, it features a steep dose drop-off over the adjacent normal retinal tissue. The radiation dose distributed across the entire macular area imaged by OCT-A may vary dramatically and subsequently affect the retinal tissue to varying degrees. To identify relationships between focal pathology and radiation dose, we constructed a custom three-dimensional dose model using the patient's OCT-A scans, fundus photograph, tumor dimensions, and radiation prescription in the ocular brachytherapy planning software Plaque Simulator (v.6.6, EyePhysics, LLC; Fig. 6A). A 3 x 3 grid was superimposed on the macular OCT-A scan to produce 9 vascular grids (Fig. 5B). Nine points were placed in each grid, for a total of 81 points across the macula, to calculate mean radiation dose to each of the grids. Choriocapillaris scans were likewise obtained using Optovue's automated segmentation with flow area calculated over the entire image area at each visit (Fig. 4A–E).

To identify relationships between magnitude of radiation dose and changes in capillary density, macular OCT-A scans were processed in ImageJ (v. 1.52p, NIH) following our previously established protocol.[13] Processed scans were then divided into nine 2 × 2 mm^2 grids using the Divide Slice function in Adobe Photoshop (release 19.1.0). Once divided, slices were opened in ImageJ and processed to calculate vessel skeleton density in each grid.[13] The mean dose to each grid was then compared to changes in vessel density in that same area (Fig. 6C–E).

3. Results

At his six month follow up post-brachytherapy, the tumor was involuting appropriately and his visual acuity remained 20/20. However, he had developed cystoid macular edema in the right eye and was treated with intravitreal bevacizumab at that time. He underwent cataract extraction in the right eye 28 months following brachytherapy. He has been maintained on a 6–12 week bevacizumab injection interval since that time and has maintained 20/30 visual acuity. His tumor remained involuted at his most recent follow-up visit, four years post-brachytherapy (Fig. 2).

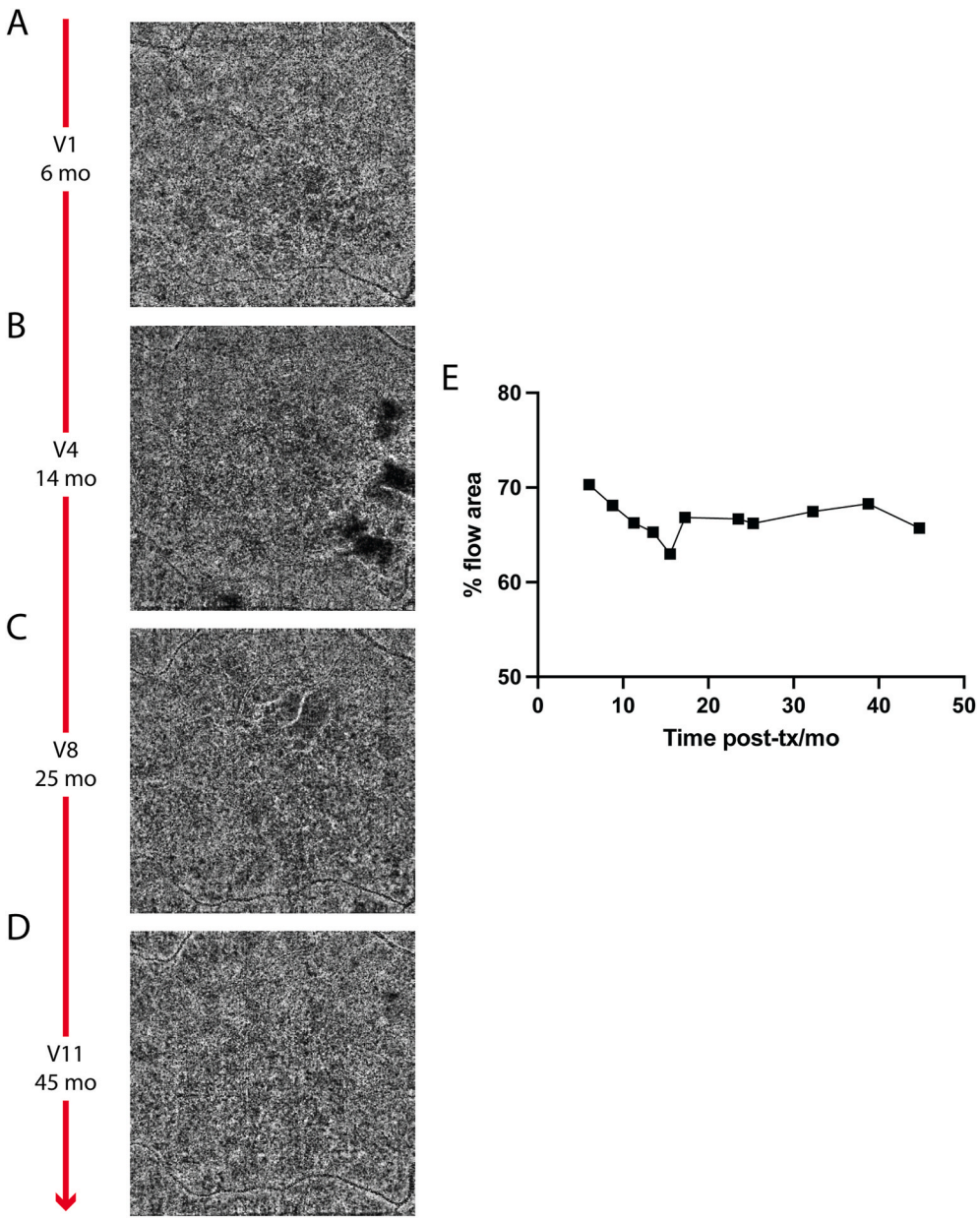

Fig. 4. Choriocapillaris analysis. Optical coherence tomography angiography (OCT-A) en-face images of the choriocapillaris at 6 months (A), 14 months (B), 25 months (C), and 45 months (D). There was no change in the flow area in the choriocapillaris over time (D).

Longitudinal OCT-A over time demonstrated progressive capillary loss in the inferonasal macula, with gradual enlargement of the foveal avascular zone and re-modeling of the deep retinal vessels temporal and inferior to the optic disc, there was no change in the choriocapillaris over time (Figs. 3–5). The retinal vascular changes progressed over time despite improvement in the clinical findings consistent with radiation retinopathy (cotton wool spots, microaneurysms) (Figs. 3 and 5).

Changes in vessel density relative to the first, 6-month time point showed the strongest decreases at higher doses (Fig. 6C), especially by 17 months post-brachytherapy, where vessel density had decreased by 25% and 26% in the inferonasal grids exposed to 30 and 39 Gy, respectively (Fig. 6A–C). For each grid, the relationship between vessel density and time from brachytherapy was calculated by simple linear regression (Fig. 6D), and compared to the radiation dose to that grid (Fig. 6E). This analysis showed a statistically significant decrease in slope with increasing radiation dose ($R^2 = 0.6443$, $p = 0.0092$), indicating more rapid loss of vessel density at higher doses (Fig. 6E). There was no change in the choriocapillaris flow area over time (Fig. 4E).

4. Discussion/conclusion

The effects of radiation on the retina and optic nerve have been known since the 1930's, however, newer imaging modalities have allowed us to better define the ultrastructural changes that occur early in the course of radiation-associated damage.[2,6,10,11,14] One of the challenges in both studying and managing radiation-associated sequelae is the delayed onset of vision loss and variable progression of changes over time. Given the more recent development of OCT-A technology, fewer studies have reported long-term findings post-brachytherapy or the effects of anti-VEGF treatment long-term.

One of the largest longitudinal series of patients followed with OCT-A post-brachytherapy followed patients for two years post-treatment and showed a decrease in vascular density that preceded clinically visible radiation retinopathy. Further, they additionally showed increased vascular loss in patients who received a greater than 45 Gy dose to the fovea.[15] These findings are similar to ours, which show progressive capillary loss and enlargement of the foveal avascular zone

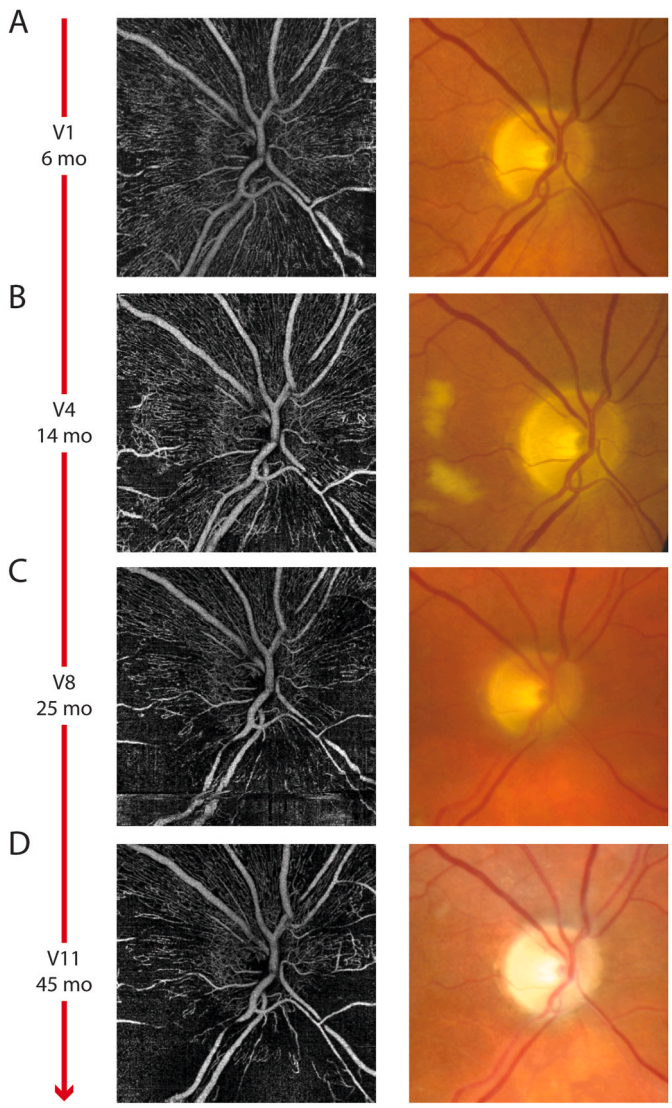

Fig. 5. Optical coherence tomography angiography (OCT-A) en-face images of the juxtapapillary area compared to color fundus photographs. 4.5 × 4.5 mm2 scans centered on the optic nerve head at 6 months (A), 14 months (B), 25 months (C), and 45 months (D) compared to color fundus photographs at 78 the same time points show progressive capillary dropout despite improvement in cotton wool spots. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

over a four-year time period. We likewise found increased capillary loss in areas of the macula receiving higher doses of radiation. Our patient demonstrated a dramatic reduction in vascular density around 17 months post-treatment. This is consistent with prior work that has shown radiation retinopathy to have a delayed clinical onset, with a latent time closer to 6 months in animal models and 19 months in one clinical study.[9,16] The precise mechanism behind this latency is unknown. It is likely related to a reserve of healthy vascular endothelial cells initially being able to maintain function, but later reaching a point at which the remaining cells are no longer sufficient, the vasculature become incompetent, and the coagulation cascade ensues.[9] One of the remarkable findings illustrated by our case was the preservation of good central visual acuity despite these ischemic changes. Our patient was expected to experience relatively early vision loss given his underlying diabetes, however, he has maintained 20/30 vision four years post-treatment.

We also demonstrated that acute and subacute signs of radiation retinopathy, namely cotton wool spots, and retinal hemorrhages can disappear as reductions in capillary density and retinopathy progress. We show that cotton wool spots disappear over time, associated with axon loss and progressive capillary dropout. This highlights the importance of following patients longitudinally, as markers on fundus exam may fluctuate over time, while reductions in vascular density continue to progress. We also applied a unique strategy of correlating vascular density changes over discrete macula sectors where dose of radiation varied in order to better elucidate their dependence on radiation dose and time. This allowed us to measure more precisely the non-linear changes that occur over time and as a function of radiation dose. A greater understanding of these aspects will benefit from a prospective longitudinal study.

Interestingly, we found no change in the choriocapillaris in the area imaged over time. Much prior work has focused on the retinal vasculature, while more recent work has shown the important role that changes in the choroidal vasculature play in radiation-related sequale.[17] Work by Platt et al. showed that on histopathologic analysis of patients who underwent enucleation following brachytherapy for choroidal melanoma, some cases had only intratumoral choroidal vasculopathy, some only extratumoral choroidal vasculopathy, and some both.[17] Our work focused on the macular region as this area is most important area for visual function, and it is interesting that there was no change to the chroiocapillaris as these vessels receive a radiation dose similar to the retinal vasculature. Future work should address the degree of damage to the choroidal vasculature in a series of patients imaged both over the tumor and in the macula. We plan to study this in the future using wide-field OCT-A.

Early and repeated treatment of our patient's cystoid macula edema with bevacizumab likely helped to preserve visual acuity, and the effects on retinal edema and reductions in microvascular density observed on OCT-A are an important area for future study. Daruich et al. have previously shown that foveal avascular zone enlargement on OCT-A was reduced with every two month anti-VEGF injection in patients treated with proton beam radiation for choroidal melanoma.[18] While we describe a single patient, we suspect that our findings are similar to theirs where the degree of capillary loss would have likely been greater without anti-VEGF treatment. Given that anti-VEGF therapy has now been shown to delay the progression of radiation retinopathy and its clinical signs such as retinal edema, and is more commonly being used following brachytherapy, we believe that our patient illustrates a "real-world" scenario in which a patient has been treated with anti-VEGF agents over time.[3]

In summary, we show longitudinal reduction in capillary density by OCT-A imaging over a four-year time period in a patient treated with plaque brachytherapy for choroidal melanoma. Dosimetry analysis showed decreasing vascular density and the highest rate of decrease in areas of the macula exposed to higher radiation doses, with the greatest reductions in vascular density occurring in areas closest to the plaque. Further work will report on a larger cohort of patients followed with OCT-A over time in order to better define the microvascular changes that occur after radiation treatment and to better define the therapeutic window for interventions developed to reduce retinopathy and subsequent vision loss.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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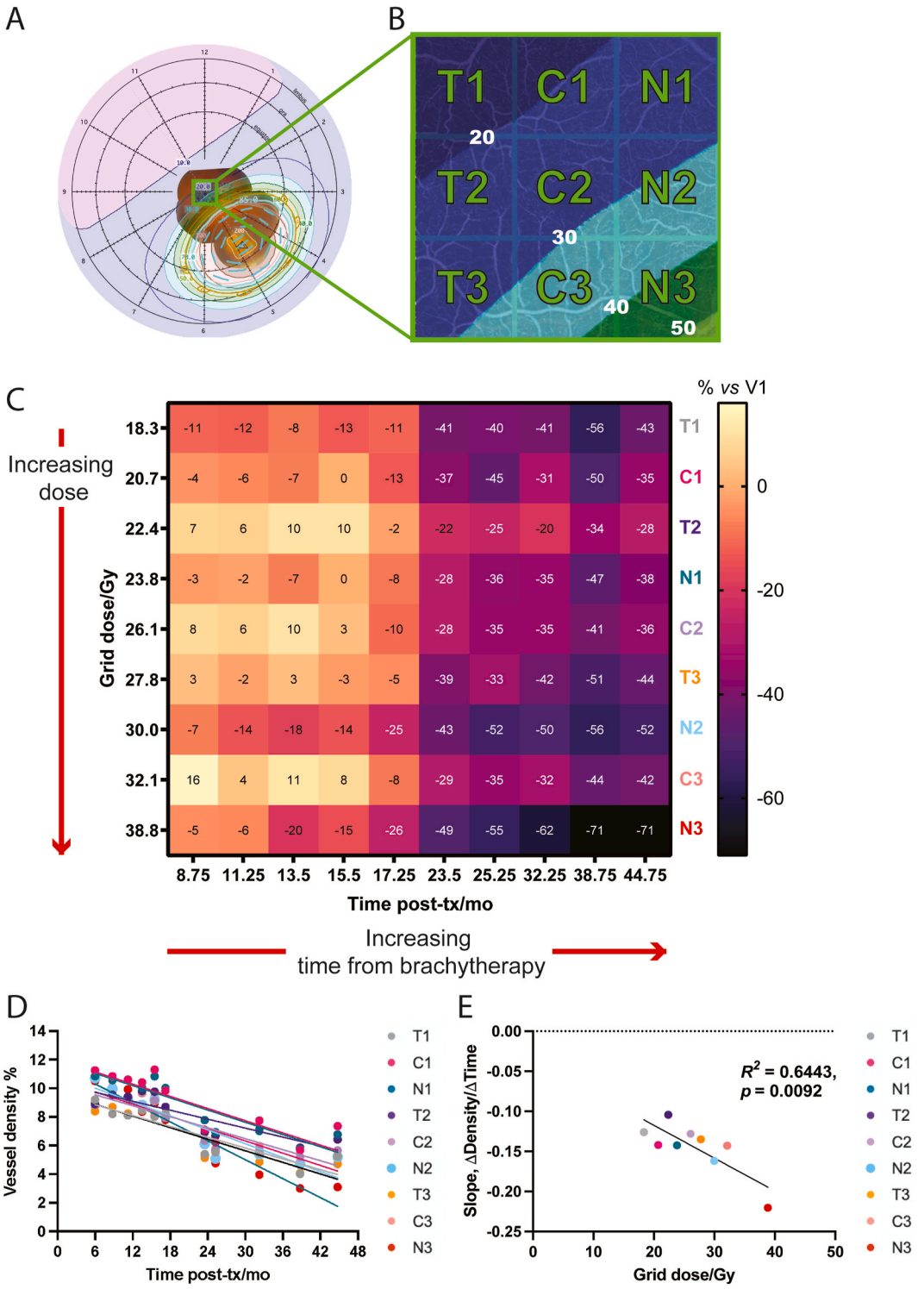

Fig. 6. Vascular dropout with increasing dose and time from brachytherapy. A custom three-dimensional dosimetry model (A) constructed using the patient's fundus photograph and OCT-A scans was used to calculate radiation dose to 9 grids over the 6 × 6 mm^2 macula OCT-A scan (B). (C) Percent change in vessel density compared to first visit (V1, 6 months post-brachytherapy) for each macular grid shown in (B). Each cell is color-coded by percent change in vessel density, and labeled with its value. A negative value indicates a loss of vasculature compared to V1. (D) Percent vessel density calculated in each grid plotted against time post-brachytherapy. For each grid, a linear regression trendline was fit to the data to yield rate of change in density versus time from brachytherapy. The slope of each grid's trendline was plotted against the dose received in that grid (E). A more negative slope indicates a greater decrease in vessel density with time from brachytherapy. R^2 and its p-value calculated by linear regression. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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Authorship

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

Declaration of competing interest

The following authors have no financial disclosures: EMB, MRT, AHV, HCB, RHK, IMG.

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References

1. Shields CL, Shields JA, Cater J, et al. Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1106 consecutive patients. *Archives of ophthalmology (Chicago, Ill : 1960*. 2000;118(9):1219–1228.
2. Melia BM, Abramson DH, Albert DM, et al. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16. *Ophthalmology*. 2001;108(2):348–366.
3. Shields CL, Dalvin LA, Chang M, et al. Visual outcome at 4 Years following plaque radiotherapy and prophylactic intravitreal bevacizumab (every 4 Months for 2 Years) for uveal melanoma: comparison with nonrandomized historical control individuals. *JAMA ophthalmology*. 2020;138(2):136–146.
4. Murray TG, Latiff A, Villegas VM, Gold AS. Aflibercept for radiation maculopathy study: a prospective, randomized clinical study. *Ophthalmology Retina*. 2019;3(7):561–566.
5. Takahashi K, Kishi S, Muraoka K, Tanaka T, Shimizu K. Radiation choroidopathy with remodeling of the choroidal venous system. *Am J Ophthalmol*. 1998;125(3):367–373.
6. Li Y, Say EA, Ferenczy S, Agni M, Shields CL. Altered parafoveal microvasculature IN treatment-naive choroidal melanoma eyes detected BY optical coherence tomography angiography. *Retina*. 2017;37(1):32–40.
7. Gündüz K, Shields CL, Shields JA, Cater J, Freire JE, Brady LW. Radiation retinopathy following plaque radiotherapy for posterior uveal melanoma. *Archives of ophthalmology (Chicago, Ill : 1960*. 1999;117(5):609–614.
8. Groenewald C, Konstantinidis L, Damato B. Effects of radiotherapy on uveal melanomas and adjacent tissues. *Eye*. 2013;27(2):163–171.
9. Archer DB, Amoaku WM, Gardiner TA. Radiation retinopathy–clinical, histopathological, ultrastructural and experimental correlations. *Eye*. 1991;5(Pt 2):239–251.
10. Preziosa C, Corvi F, Staurenghi G, Pellegrini M. *Extended FIeld Imaging Optical Coherence Tomography Angiography for the Study of Retinal and Choroidal Changes after Radiation Therapy for Choroidal Melanoma: Comparison with Wide-Field Angiography*. Philadelphia, Pa): Retina; 2020.
11. Matet A, Daruich A, Zografos L. Radiation maculopathy after proton beam therapy for uveal melanoma: optical coherence tomography angiography alterations influencing visual acuity. *Investig Ophthalmol Vis Sci*. 2017;58(10):3851–3861.
12. Adeniran JF, Sophie R, Adhi M, Ramasubramanian A. Early detection of radiation retinopathy in pediatric patients undergoing external beam radiation using optical coherence tomography angiography. *Ophthalmic Surg.Laser Imag retina*. 2019;50(3):145–152.
13. Tamplin MR, Deng W, Garvin MK, et al. Temporal relationship between visual field, retinal and microvascular pathology following 125I-plaque brachytherapy for uveal melanoma. *Investig Ophthalmol Vis Sci*. 2021;62(1):3.
14. Durkin SR, Roos D, Higgs B, Casson RJ, Selva D. Ophthalmic and adnexal complications of radiotherapy. *Acta Ophthalmol Scand*. 2007;85(3):240–250.
15. Green KM, Toy BC, Ashimatey BS, et al. Quantifying subclinical and longitudinal microvascular changes following episcleral plaque brachytherapy using spectral domain-optical coherence tomography angiography. *J Vitreoretin Dis*. 2020;4(6):499–508.
16. Midena E, Segato T, Valenti M, Degli Angeli C, Bertoja E, Piermarocchi S. The effect of external eye irradiation on choroidal circulation. *Ophthalmology*. 1996;103(10):1651–1660.
17. Platt S, Salomao DR, Pulido J. Histologic findings of choroidal vasculopathy in eyes enucleated following radiation therapy for uveal melanoma: radiation choroidopathy. *Klinische Monatsblatter fur Augenheilkunde*. 2021;238(5):584–590.
18. Daruich A, Matet A, Schalenbourg A, Zografos L. Intravitreal anti-vascular endothelial growth factor treatment at 2-MONTH intervals reduces foveal avascular zone enlargement and VISION loss IN radiation maculopathy: a pilot study. *Retina*. 2019;39(8):1519–1526.