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Intraocular Dissemination of Uveal Melanoma Cells Following Radiotherapy: Evolving Management Over the Past Decade

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Abstract

BACKGROUND AND OBJECTIVE: To describe the presentation and the authors' evolving management strategy for intraocular dissemination of uveal melanoma cells following radiotherapy during the past decade.

PATIENTS AND METHODS: Patients with uveal melanoma who developed intraocular dissemination of pigmented cells following radiotherapy. Histopathology was available in two cases.

RESULTS: Four patients underwent treatment for progressive intraocular dissemination of uveal melanoma cells at 9 to 41 months following I-125 plaque radiotherapy (three patients) or proton beam radiotherapy (one patient). Treatments included primary enucleation (one patient), vitrectomy followed later by enucleation (one patient), and vitrectomy followed by intravitreal chemotherapy (two patients). Enucleated eyes demonstrated diffuse invasion of intraocular tissues by viable melanoma cells. No patient has developed systemic metastasis to date.

CONCLUSIONS: Intraocular dissemination of pigmented cells following radiotherapy for uveal melanoma should raise suspicion for viable invasive melanoma cells. Prompt vitrectomy with intravitreal chemotherapy can be effective in avoiding enucleation in selected cases.

INTRODUCTION

Plaque brachytherapy and proton beam radio-therapy are the most common treatments for uveal melanoma (UM), resulting in excellent local control rates in experienced ocular oncology centers.^{1–3} Local tumor recurrence following radiotherapy usually presents as a tumor enlargement at the margin or apex of the treated tumor.⁴ Rarely, however, post-radiation tumor recurrence can manifest as seeding and proliferation of viable melanoma cells in the vitreous.^{5–8} Owing to the rarity of this condition, management guidelines are not

well-established. Here, we present four cases that illustrate our evolving management of this condition during the past decade.

PATIENTS AND METHODS

This was a retrospective case series conducted with institutional review board approval in adherence to the tenets of the Helsinki Declaration. All available clinical records and images were reviewed. Subjects included four patients with UM who underwent plaque or proton beam radiotherapy and subsequently developed pigmented cells in the vitreous that increased over time. Localized vitreous pigment overlying the primary tumor was noted prior to plaque radiotherapy in two cases, both of which received dosimetric adjustment to deliver 85 Gy to a point 2 mm above the tumor apex. In patients undergoing pars plana vitrectomy, a modified technique was used to reduce the risk of extraocular tumor extension, which included localized conjunctival peritomies at sclerotomy sites, 23- or 25-gauge instrumentation with valved trocar cannulas, closure of sclerotomies with 8-0 vicryl and application of triple freeze-thaw cryotherapy to closed sclerotomies. Extensive vitreous removal, including detachment of the posterior hyaloid, and peeling of the internal limiting membrane was performed to remove as many pigment cells as possible. Vitreous samples were sent for cytopathologic evaluation. Intravitreal injections were performed in two patients using methotrexate (400 µg in 0.1 mL) or melphalan (32 µg in 0.075 mL).

RESULTS

Patient characteristics are summarized in Table 1.

Case 1

A 63-year-old man presented with a superotemporal choroidal melanoma of the right eye (OD) with a “collar button” at the tumor apex, due to rupture of the tumor through the overlying Bruch’s membrane (Figure 1A). At baseline, there was tumor invasion of the overlying retina, with a small clump of pigmented cells were present in the vitreous immediately overlying the tumor. He underwent transvitreal fine needle aspiration biopsy (FNAB) and I-125 plaque brachy-therapy. Subsequently, the primary tumor regressed markedly, but the pigmented cells in the vitreous became more numerous (Figure 1B). At 17 months after brachytherapy, the proliferating pigmented cells had settled onto the retina. A pars plana vitrectomy was performed to debulk the pigmented cells and to determine whether they were melanoma cells or melanophages. During vitrectomy, attempts to remove the pigmented cells from the retinal surface were unsuccessful despite peeling of the internal limiting membrane because the cells had invaded into deeper layers of the retina. Cytopathologic examination showed that most of the pigmented cells were epithelioid melanoma cells (Figure 1C), confirmed with Melan-A-red immunostain (not shown), along with some melanophages. Molecular prognostic testing of the biopsy specimen revealed a low metastatic risk class 1A gene expression profile. Despite surgical debulking, the melanoma cells continued to proliferate with diffuse invasion of the retina and optic nerve head (Figure 1D). Consequently, the eye was enucleated. Histopathologic examination confirmed that the original choroidal melanoma was regressed and inactive (with apical necrosis, areas of fibrosis, and no mitotic figures seen), and it revealed extensive melanoma

cell invasion of the retina (Figure 1E), optic disc (superficial pre-laminar), anterior chamber angle, and iris (Figure 1F) with mixed spindle and epithelioid tumor cell morphology. The patient remained free of metastasis through 25 months of follow-up.

Case 2

A 66-year-old woman presented with a mushroom-shaped choroidal melanoma along the inferotemporal retinal vascular arcade OD with invasion of the overlying retina and subtle localized pigment clumps on the surrounding retina and overlying vitreous (Figures 2A and 2B). Treatment was undertaken by an outside physician using I-125 plaque brachytherapy. She did not undergo FNAB. The patient was referred to our ocular oncology service 27 months later, due to increasing proliferation of pigmented cells in the vitreous and on the retina (Figures 2C and 2D). Enucleation was performed, and histopathology showed massive proliferation of spindle and epithelioid melanoma cells in the vitreous and on the retina, optic disc, vitreous, lens surface, iris, and trabecular meshwork, with focal areas of retinal invasion (Figure 2E). Melanoma cells from the enucleated eye were viable and proliferative when placed in culture (Figure 2F). Molecular classification revealed a class 1A gene expression profile, and the patient remained free of metastasis through 48 months follow-up.

Case 3

A 64-year-old man previously had been treated with proton beam radiotherapy for a choroidal melanoma of the left eye (OS) at an outside institution. No biopsy was performed. He was referred to our ocular oncology service 41 months later due a progressive increase in pigmented vitreous cells. No molecular prognostic testing was performed. On presentation, fundus examination showed a superotemporal choroidal melanoma with an apical collar button and tumor invasion of the overlying retina (Figure 3A). The tumor had a regressed inactive appearance with surrounding chorioretinal atrophy, but there was marked dissemination of pigmented cells in the vitreous and settling inferiorly on the retinal surface (Figure 3B). Ultrasonography showed that the vitreous cells were concentrated along the face of the detached posterior hyaloid (Figure 3C). Pars plana vitrectomy was performed to debulk the pigment cell proliferation. Cytopathology confirmed that the pigment cells were mostly spindle melanoma cells. Surgery was followed by five monthly intravitreal injections of methotrexate (400 µg in 0.1 mL). The eye has remained stable without recurrence of pigment cell proliferation (Figure 3D), and the patient has remained free of metastasis through 98 months of follow-up.

Case 4

A 65-year-old woman presented with a ciliochoroidal melanoma located in the temporal periphery OS. The tumor was readily visualized through the dilated pupil using slit-lamp examination, which revealed diffuse tumor invasion of the overlying ciliary body epithelium and a subtle wisp of pigmented cells emanating from the apex of the tumor (Figure 4A). The tumor was treated with I-125 plaque brachytherapy, and trans-scleral FNAB sample for molecular classification revealed a class 2 gene expression profile. The vitreous pigment cell proliferation continued to increase (Figure 4B), which prompted a pars plana vitrectomy 9 months later for debulking. Cytopathology of the vitreous showed predominantly epithelioid melanoma cells. Surgery was followed by five monthly injections of methotrexate (400 µg in

0.1 mL) and one injection of melphalan (30 µg in 0.075 mL). After 61 months' follow-up, there has been no recurrence of intraocular pigment cell dissemination (Figure 4C), and the patient remains free of metastasis.

DISCUSSION

Although uncommon, intraocular dissemination of uveal melanoma cells is well-attested in the literature both prior to treatment^{6,7,9,10} and following radiotherapy.^{8,11} A common feature in many reported cases is tumor rupture through Bruch's membrane with invasion of the overlying retina,⁸ which was seen in all of our cases. As such, transretinal tumor invasion into the vitreous is the presumed route of tumor progression in these cases. It has been speculated that this finding might reflect a more aggressive tumor type,⁷ but we did not find this to be the case. Two of the four cases were class 1A, the least aggressive form,¹² and none of the patients has developed metastasis to date. This is consistent with a recent report showing no increase in metastasis associated with intraocular dissemination.¹⁰ Our series also demonstrates that intraocular melanoma cell dissemination is not unique to patients who have undergone transvitreal needle biopsy or plaque radiotherapy, as two patients did not undergo biopsy and one was treated with proton beam radiotherapy.

The differential diagnosis of intraocular dissemination of pigmented cells includes viable melanoma cells, pigment-laden macrophages (melanophages), vitreous hemorrhage, and proliferative vitreoretinopathy. The main diagnostic dilemma is usually between melanoma cells and melanophages. In our experience, melanoma cells demonstrate progressive proliferation and tend to invade the retina, optic disc, iris, and other ocular structures, whereas these features are less common with melanophages. Our findings are in agreement with Metz and colleagues that intraocular pigment cell proliferation cannot be assumed to represent benign melanophages, particularly when features of proliferation or invasion are observed.¹⁰ Unlike that report, however, we found that enucleation was not necessary if intraocular melanoma dissemination was managed early and aggressively with vitrectomy and intravitreal chemotherapy.

For intravitreal chemotherapy, we initially used methotrexate because it is less toxic (but also less potent) than other intravitreal agents such as melphalan.¹³ We found that five monthly injections of methotrexate (400 µg in 0.1 mL) following vitrectomy was quite effective. In one patient, we also used melphalan (32 µg in 0.075 mL) without observing intraocular toxicity. However, due to the well-documented and potentially visually significant chorioretinal toxicity that has been reported with intravitreal melphalan,¹⁴ we currently recommend starting with methotrexate and escalating to melphalan only if the process is not well controlled. A recent case report described a similar patient who did not undergo vitrectomy and required 12 monthly injections of melphalan.¹¹ We believe that an initial vitrectomy and thorough debulking of intraocular cells can substantially reduce the number of injections, minimize the need for melphalan, and potentially improve visual function by removing vitreous opacities. We have developed a modified vitrectomy technique for eyes harboring a uveal melanoma that is safe and effective with minimal risk of intra- or extra-ocular tumor dissemination, as described in the Methods section of this

paper. This case series may inform the future management of intraocular dissemination of uveal melanoma cells and safely avoid enucleation in selected patients.

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Dr. Harbour is the inventor of intellectual property used in the study and receives royalties from its commercialization; he is also a paid consultant for Castle Biosciences, licensee of this intellectual property. Dr. Walter served on an advisory board for Castle Biosciences. The remaining authors report no relevant financial disclosures.

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Figure 1.

(A) Pretreatment fundus photograph of the right eye showing a superotemporal dome-shaped choroidal melanoma with overlying collar button configuration. (B) Fundus photograph 8 months after plaque radiotherapy showing pigmented cells in the vitreous tracking inferiorly. (C) Photomicrograph of vitreous cytopathology sample taken 17 months after radiotherapy and stained with DiffQuick showing mixed spindle and epithelioid melanoma cells (original magnification x600). (D) Fundus photograph taken 25 months after radiotherapy and 8 months following vitrectomy showing extensive intraocular dissemination of pigmented cells on the retinal surface and optic disc. (E) Histopathology of enucleated eye stained with Diff-quick showing invasion of iris stroma (original magnification x100) and (F) neuro-sensory retina (original magnification x400).

Figure 2.

(A) Fundus photograph at baseline visit to Bascom Palmer, 4 months after plaque radiotherapy by an outside provider showing a mushroom-shaped choroidal melanoma along the inferotemporal arcade of the right eye. The dusky gray-brown color was consistent with regression following prior radiation. Additionally, there were pigmented cells forming a cloud in the overlying vitreous and settling onto the retinal surface. (B) B-scan ultrasonography at baseline showing the choroidal tumor with a tuft of hyperechoic vitreous opacities, corresponding to the pigmented vitreous cells, emanating from near its apex. (C) Fundus photograph and (D) slit-lamp photograph 27 months after radiotherapy showing massive proliferation of pigmented cells in the vitreous and on the retinal surface. (E) Enucleated eye gross specimen showing melanoma cells suspended in the vitreous and diffusely invading the retina and adherent to the posterior lens capsule. The iris and trabecular meshwork were also involved. (F) Post-enucleation cell culture photomicrograph

of melanoma cells obtained from the vitreous showing viable type-B spindle and epithelioid shaped melanoma cells (original magnification x20).

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Figure 3.

(A) Fundus photograph at baseline visit to Bascom Palmer 41 months after proton beam radiotherapy at an outside facility showing a treated choroidal melanoma with apical collar button configuration along the superotemporal arcade of the left eye and (B) marked pigment cell accumulation in the inferior vitreous and retina. (C) B-scan ultrasonography at baseline showing hyperechoic opacities along the posterior hyaloid surface which is adherent to the tumor apex. (D) Fundus photograph at 46 months after vitrectomy and five intravitreal methotrexate injections showing resolution of intraocular pigmented cells. The melanoma remained stably regressed.

Figure 4.

(A) Pretreatment slit-lamp photograph showing ciliochoroidal melanoma located in the temporal periphery of the left eye, with a subtle tuft of pigmented cells emanating from the tumor apex (arrow). (B) Fundus photo 9 months after plaque radiotherapy showing pigmented cells proliferating along vitreous strands. (C) Fundus photograph taken 40 months after vitrectomy plus five monthly intravitreal injections of methotrexate and one intravitreal injection of melphalan showing resolution of intraocular pigmented cells.

TABLE 1

Clinical Features of Four Patients With Intraocular Dissemination of Uveal Melanoma Cells Following Radiotherapy for Posterior Uveal Melanoma

Characteristic	Case 1	Case 2	Case 3	Case 4
Baseline Features				
Age (years)	63	66	64	65
Sex	Male	Female	Male	Female
Basal dimensions (mm)	10 × 9	10 × 8.5	16 × 12	15 × 14.5
Thickness (mm)	5.2	5.4	5.1	10
Collar button	Yes	Yes	Yes	Yes
Tumor location	Choroidal	Choroidal	Choroidal	Ciliochoroidal
Vitreous pigment prior to radiotherapy	Trace	Not mentioned	Not mentioned	Trace
Vitreous hemorrhage	No	No	No	No
Initial treatment	I-125 Plaque Brachytherapy (85 Gy)	I-125 Plaque Brachytherapy (85 Gy)	Proton Beam Radiotherapy (70 Gy)	I-125 Plaque Brachytherapy (85 Gy)
Biopsy	Transvitreal	No	No	Transscleral
Melanoma cell type	Mixed spindle and epithelioid	Mixed spindle and epithelioid	Predominantly spindle	Predominantly epithelioid
Gene expression profile	Class 1A	Class 1A ^a	Not available	Class 2
Follow-up features				
Follow-up since primary treatment (months)	25	48	98	61
Last ocular status	Enucleation	Enucleation	Stable	Stable
Last systemic status	Alive with no metastasis	Alive with no metastasis	Alive with no metastasis	Alive with no metastasis

^aDetermined after enucleation