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Delayed recurrence of an iridociliary malignant melanoma 180° from the primary tumor

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ABSTRACT

Purpose: We report the case of a 66-year-old female who returned with a rare recurrence of iridociliary melanoma 180° from the original lesion.

Observations: Upon initial presentation eleven years prior, a pigmented iris lesion suspicious for primary uveal melanoma was noted in the right eye at 9 o'clock. After one year of observation, inferior growth of the iris lesion prompted treatment via primary iridectomy with excisional biopsy and pupilloplasty. Postoperative biopsy confirmed spindle B type melanoma with epithelial foci, and adjuvant brachytherapy was performed to treat the reported positive anterior ciliary body involvement. Ten years after initial plaque brachytherapy treatment, the patient returned with a pigmented iris lesion in the right eye at 3:30–5 o'clock, which was treated with enucleation. On pathology, the new melanoma was predominantly epithelioid, consistent with a transformed recurrent iridociliary melanoma. The patient remains metastasis free 13 years after initial diagnosis.

Conclusions and importance: This case describes a rare, late recurrence of an iridociliary melanoma 180° away eleven years after initial presentation, emphasizing the importance of lifelong follow-up for patients with iridociliary melanoma. This rare form of recurrence has not been previously reported in the literature. We hypothesize the original lesion contained radiotherapy resistant epithelioid cells which grew superficially on the posterior iris and anterior ciliary body, ultimately breaking back through the anterior iris 180° away.

1. Introduction

Uveal melanoma (UM) is the most common primary, intraocular malignancy of the eye in adults with an incidence of approximately 5 per million in the United States.[1,2] UM arises from the melanocytes of the uveal tract including the choroid, ciliary body, and iris. Tumors are unilateral and equally distributed between right and left eyes, and typically present in the 5th decade of life.[3,4] Iris melanoma is rare, making up just 4% of uveal melanoma. Iris melanoma equally affect males and females and occur primarily in Caucasians.[4] Most iris melanoma arise from an existing nevus, with transformation from nevus to melanoma occurring in only 2% of existing iris nevi.[3] Risk factors for transformation include increasing age; light hair, skin, or eye color; uveal nevi; and oculodermal melanocytosis.[5,6] Iris melanoma is diagnosed clinically with the aid of gonioscopy and anterior segment ultrasonography. Biopsy of the lesion may be required and can be used to direct further treatment.

Ciliary body melanoma comprise 10% of uveal melanoma and patients are frequently asymptomatic.[7,8] Due to their posterior location, ciliary body melanoma are difficult to see on routine dilated funduscopic examination, causing delays in diagnosis. Signs of a ciliary body melanoma include: episcleral sentinal vessels, peripheral iris lesions, sectoral cataracts, episcleral pigmentation, iris bulge, and lens displacement.[7] Anterior and posterior segment ultrasonography can assist in diagnosis in addition to a thorough dilated funduscopic examination. The goal of treatment of iris and ciliary body melanoma is the eradication of the

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tumor with surgery and/or radiotherapy in order to decrease the risk of metastasis, while preserving the best visual outcome for the patient. Treatment modalities include observation, tumor resection, proton beam therapy, plaque brachytherapy, and enucleation. The course of treatment depends on the patient's history, initial tumor size, thickness, seeding, and angle or iris root involvement. Risk of recurrence for iris and ciliary body melanoma at 10 years is 3% and 11% respectively and is typically managed by enucleation.[9]

We present a rare case of an iridociliary melanoma initially treated with local resection and adjuvant plaque brachytherapy with subsequent recurrence 180° away from the initial tumor ten years after primary treatment.

2. Case report

A 66-year-old Caucasian female with a history of hypertension and hyperthyroidism was referred for evaluation of a pigmented iris lesion in the right eye, first noticed by her spouse. The lesion had not been noticed on prior eye examinations, and the patient had no visual symptoms or ocular complaints.

The patient had no significant past surgical history, was a nonsmoker and occasionally consumed alcohol. Of note, both of the patient's parents succumbed to cancers of unknown etiology. At presentation, the visual acuity in the right eye was 20/25 and the intraocular pressure was within normal limits. Slit lamp examination revealed a dome-shaped, pigmented iris lesion at 9 o'clock extending for approximately 1 clock hour (Fig. 1A). On gonioscopy, the lesion blocked direct visualization of the angle without evidence of posterior iris displacement at 9 o'clock. There was no anterior chamber seeding. Ultrasound biomicroscopy (UBM) (clearscan 50 MHz probe) did not show any evidence of a posterior extending mass. Examination was also notable for a mild age-related nuclear cataract. The patient elected for observation with close follow up. There was no change in the lesion at the 6 month follow up on slit lamp exam and UBM. One year later, the tumor had grown 1.5 mm inferiorly at the lesion margin from 7 to 8 o'clock without invasion into the angle (Fig. 1B).

The patient underwent a primary iridectomy with excisional biopsy of the iris and anterior ciliary body and repair of the pupillary margin, which showed malignant melanoma of predominantly spindle B type with focal areas of epithelioid cells (Fig. 1C and D). The posterior margin of the lesion extending into the ciliary body was positive and the patient underwent adjuvant brachytherapy with an iodine-125 radioactive plaque (85 Gy treated to 5 mm apical dose) in a half moon configuration between 6 and 12 o'clock for one week. Postoperatively, the patient experienced one episode of iridocyclitis, which was treated with prednisolone acetate. Despite a large residual pupillary defect, she did not complain of photophobia nor glare. The patient was followed every 6 months for clinical surveillence of iridociliary melanoma recurrence through the five years post-operative period and annually thereafter. Follow up visits were coordinated with her oncologist for monitoring including systemic imaging (consisting of a combination of CT chest, abdomen, pelvis; and/or abdominal ultrasound; and/or chest X-rays) for metastatic surveillence. Several years later, she underwent phacoemulsification and posterior chamber intraocular lens (IOL) implantation in the right eye which was complicated by cystoid macular edema during the post-operative period and treated with prednisolone acetate and bromfenac. Resultant visual acuity after treatment and IOL implantation was 20/20.

Ten years after the initial plaque brachytherapy, the patient noticed a new pigmented iris lesion in her right eye. She had no pain or discomfort. Vision in the right eye was 20/50, and IOP was 15 mmHg with no evidence of secondary glaucoma. A new pigmented lesion was seen from 3:30–5 o'clock (Fig. 2A). UBM showed a focal ciliary body lesion measuring 2.3 × 4.2 × 3.6mm with extension through the iris and without evidence of extraocular extension (Fig. 2B and C). The remainder of the ciliary body appeared normal. The findings were suspicious for disease recurrence within the ciliary body inferonasally with anterior segment invasion from 3:30–5 o'clock. Given the presumed ring extension, the recurrence was not amenable to local treatment. Systemic evaluation did not show evidence of metastasis and the patient underwent enucleation. Pathology showed a mixed spindle B and epithelioid cell population that was predominantly epithelioid cells involving the iris and anterior ciliary body 180° apart (Fig. 3A–F). Surgical margins were free of tumor on pathology evaluation. Tumor staging via AJCC 7th edition was pT2,pN0X0.[10] The patient remains free of metastasis 13 years after her initial presentation.

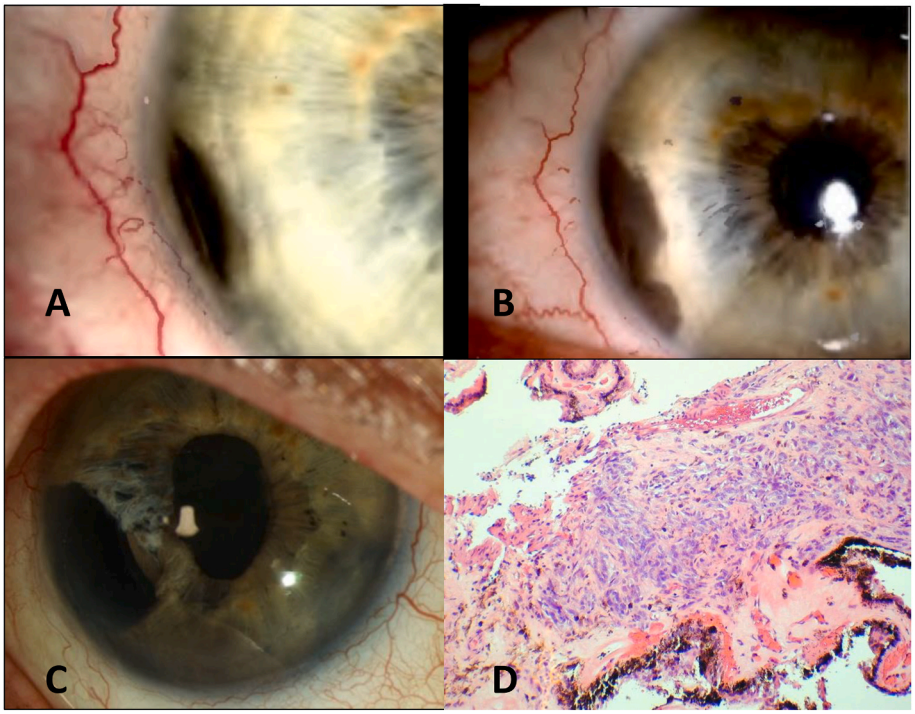

Fig. 1. A. Magnified slit lamp photo showing initial presentation of the iris lesion of the right eye from 8 to 9 o'clock.
Fig. 1 B. Slit lamp photo 1 year after initial presentation showing notable tumor extension inferiorly from 7 to 8 o'clock.
Fig. 1 C. Slit lamp photo showing the iris after tumor resection and adjuvant brachytherapy.
Fig. 1 D. H&E stained section of resected iridociliary body melanoma with spindle B and epithelioid cells.

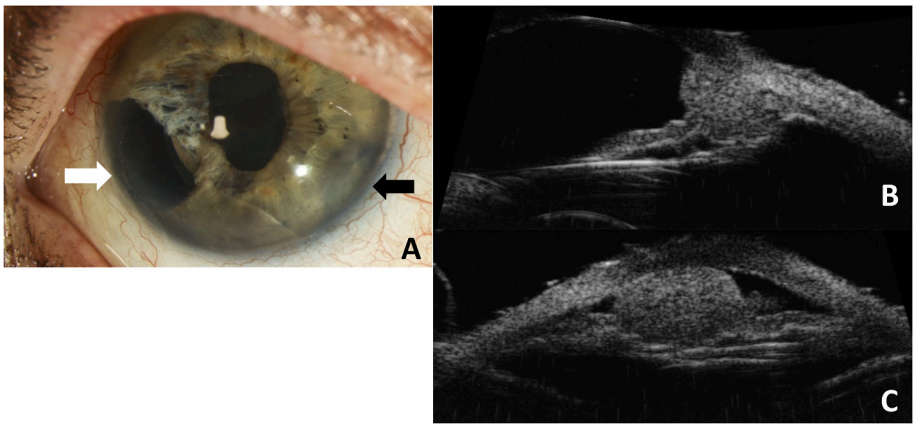

Fig. 2. A. External slit lamp photo of tumor recurrence from 3:30–5 o'clock (black arrow) and iris resection from 7 to 9 o'clock (white arrow).
Fig. 2 B and C. Ultrasound biomicroscopy radial (B) and transverse (C) scans at the 4 o'clock meridian showing an iridociliary solid homogenous lesion (radial 4.2 mm, height: 2.3 mm, transverse 3.6 mm) with medium-reflectivity and local angle closure.

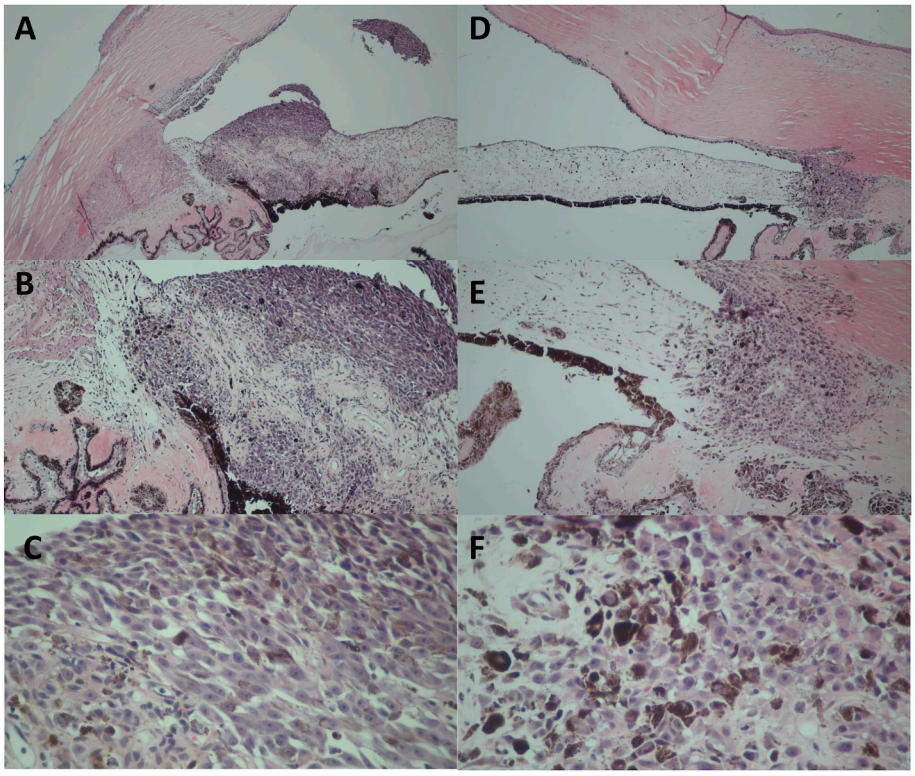

Fig. 3. H&E stained sections of the right eye enucleation specimen following iris melanoma recurrence. Figures A–C show the recurrent iris lesion at 3 o'clock at 4× (A), 20× (B), and 40× (C) magnification. The lesion is composed of mixed spindle B and epithelioid cells (C). Figures D–F show the treated 9 o'clock lesion at 4× (D), 20× (E), and 40× (F) magnification. The lesion is composed of predominantly epithelioid cells with spindle B cells (F). Tumor invades the angle and extends into the anterior ciliary body (B, E).

3. Discussion

Iris melanoma is the least common variant of UM and carries a significantly better prognosis than ciliary body or choroidal melanoma.[11] This case discusses a rare recurrence of an iridociliary melanoma 180° from the original tumor, which has not previously been reported in the literature. We propose two mechanisms for recurrence: 1) a marginal recurrence from the anterior ciliary body of the original lesion which grew in a circumferential manner; or 2) the primary lesion was an incomplete iris ring melanoma, and the brachytherapy field did not adequately cover the margins.

Histologically, uveal melanoma can be composed of spindle cells, epithelioid cells, or a mixture of both. Tumor type is described based on the predominant cell type. Iris melanoma tend to be composed of spindle cells, which have a better long-term prognosis, while ciliary body melanoma have higher rates of epithelioid cells and a worse prognosis.[12,13] In our patient, the initially treated melanoma at 9 o'clock was predominantly spindle B with few epithelioid cells (Fig. 1D). The more aggressive epithelioid cells likely survived initial brachytherapy and grew on the posterior iris and anterior ciliary body in a partial ring shape from initial tumor. Ultimately, the ciliary body mass from 3:30–5 o'clock extended back through the anterior iris stroma and became visible to the patient. This new mass was predominantly epithelioid cells (Fig. 3A–C). The pathologic similarity of the recurrent tumor cells at the initial and recurrent sites are highly suggestive of a ring extension.

Ring melanoma is a rare form of ciliary body melanoma comprising 0.3% of all uveal melanoma and were initially described by Ewtzky in 1898.[14] These melanomas grow in a diffuse, circumferential pattern along the posterior iris and anterior ciliary body extending at least 6 clock hours. Due to this pattern, diagnosis is frequently delayed, often

presenting as unilateral inflammatory or pigmentary glaucoma, or uveitis.[15–17] Our patient's initial tumor was only two clock hours with a recurrent separate two clock hour tumor discontinuous from the initial lesion. While it is possible that the tumor may have spread in a circumferential pattern mimicking a ring melanoma, it does not meet criteria to be classified as such with only 4 clock hours total iris and ciliary body involvement. The delay in diagnosis of ring melanomas is associated with a higher metastatic rate of 52% at 5 years compared to 5% of iris melanomas at 5 years.[14]

Given the pathologic transformation of the recurrence from spindle B to epithelioid cells, the delay in time of ten years following initial treatment, and the incomplete nature of the two areas of tumor growth equaling four clock hours, we believe our findings are most consistent with a marginal recurrence arising from the previously radiated anterior ciliary body. A review of the literature found 9 reports of late recurrences of primary iris melanoma ranging from 16 to 45 years after initial presentation.[18–24] These late recurrences emphasize the importance of lifelong surveillance. As this case demonstrates, the majority of iris melanoma arise from preexisting nevi, however few nevi ultimately transform (2%).[11] Most patients present without ocular symptoms. Patients are frequently referred after either they or their providers note a new iris lesion on routine eye examination. The inferior quadrant is the most common location of iris nevi and melanoma.[25] In 2012, Shields et al. proposed the ABCDEF guide on iris nevi risk factors for transformation to melanoma as follows: A = young age, B = blood, C = inferior clock hour, D = diffuse, E = ectropion uvea, and F = feathery margin3.

Historically, iris and ciliary body melanoma were primarily managed by enucleation or resection alone. Presently, treatment emphasizes globe and vision salvage including plaque brachytherapy, proton beam, and local iris and ciliary body resection (iridotomy and anterior iridotrabeculo-cyclectomy). One Danish study of 53 patients with iris and iridociliary melanomas treated with resection alone found no metastasis or melanoma related deaths following resection (median follow up time 7.15 years).[26] Although 5 patients had positive margins, only one recurrence was noted. Patients maintained good visual outcomes, with cataract and photophobia being the most common long-term effects.[26] Multiple studies on plaque brachytherapy (iodine-125, palladium-103, cobalt-60, iridium-192, and ruthenium-106) in iris and ciliary body melanoma have shown good tumor control (92–100%) and globe salvage (85–100%) with low rates of metastasis (4–32%).[7,27–29]

In younger patients, treatment with resection alone is more often chosen over radiation therapy due to the high rate of complications with radiation. Reasons for plaque brachytherapy include a large tumor base, presence of glaucoma, and residual tumor after resection.[30] Radiation therapy complications include cataract, corneal toxicity, radiation retinopathy, and neovascular glaucoma.[30,31] Proton beam therapy in iris melanoma achieves good tumor control with comparable complication rates to plaque brachytherapy.[32] Recurrence of iris melanoma is rare, with an estimated rate of recurrence of 3–8% versus 11% of ciliary body and choroidal melanoma.[9,25,32] Recurrences are typically marginal and are associated with an increased risk of systemic metastasis.[9,33] Metastasis of iris melanoma occurs in 5% and 9% of patients at 5 and 10 years,[25] with a mortality of 4% and 7% at 5 and 10 years.[34] Risk factors for metastasis include elevated intraocular pressure and extraocular extension at diagnosis, increased tumor thickness, iris root extension, local recurrence, and mutation of the *BAP1* gene.[9,25,34,35] Ciliary body and choroidal melanoma metastasis occur in 13–18% at 5 years and 29–38% at 10 years depending on the presence of tumor recurrence.[9] Mortality varies based on tumor size at diagnosis from 5 to 40% and 5–50% at 5 and 10 years respectively.[34]

4. Conclusion

This case describes a rare, late recurrence of an iridociliary melanoma 180° away from the initial tumor ten years after initial treatment. The risk of late recurrence emphasizes the importance of lifelong follow-up for patients with iridociliary melanoma. Annual follow up visits should utilize a multimodal approach including gonioscopy, slit lamp photography, and anterior segment ultrasonography.

Patient consent

All subjects have given their written informed consent to publish their case, including publication of images.

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Submission declaration

This case has not been previously published.

Authorship

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

Declaration of competing interest

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