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Case report

Iris melanoma presenting as childhood glaucoma

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1. Introduction

Glaucoma in pediatric patients is relatively rare, occurring with an estimated incidence of 2.29 in 100,000 patients under 20 years of age. Primary congenital glaucoma may be the most common form of pediatric glaucoma with an incidence of approximately 1 in 10,000–18,000 live births, though this varies greatly among populations. Secondary glaucoma is rare in pediatric patients, and the differential diagnosis in such cases is broad, including uveitis, trauma and its sequelae, infection, iridocorneal endothelial syndrome, neovascularization, drug-induced or corticosteroid-associated glaucoma, lens-associated glaucoma, complications of intraocular surgery, elevated episcleral venous pressure, and malignancy. In children, malignancy can be particularly unexpected and, as a result, overlooked.

2. Case report

An otherwise healthy 7 year-old Caucasian female presented with a complaint of headaches and blurry vision. An irregular left (OS) pupil was noted and the patient refracted to a +0.75D spherical equivalent (SE) OS with an otherwise unremarkable examination. Her intraocular pressure (IOP) was not checked at this time. Two years later, she was seen for biannual examination, at which time she was found to have a persistently irregular pupil with a new, pigmented iris lesion temporally OS. Her best corrected visual acuity (BCVA) was 20/20 bilaterally (OU) with negligible refractive error, an IOP of 12 OU, and full confrontation visual fields. The patient was seen again two years later for routine eye examination. She had complaints of occasional bilateral headache and worsening vision OS. Review of systems was otherwise negative. She was referred for further evaluation.

On examination, the patient’s uncorrected vision was 20/20 in the right eye (OD) and 20/200 OS with pin-hole vision of 20/70. The patient had a relative afferent pupillary defect OS. Intraocular pressure was 15 mmHg OD and 50 mmHg OS by Goldmann applanation. Her examination was normal OD (Fig. 1A). Examination of the left eye revealed normal adnexa and lids, white and quiet conjunctiva, clear cornea without endothelial abnormality or posterior embryotoxon, and quiet anterior chamber. The patient had an irregular pupillary margin with uveal ectropion, corectopia, and multiple patches of a thin, tapaoca-like tissue overlying the iris with prominent underlying blood vessels OS (Fig. 1B-D). Gonioscopy demonstrated a fine membrane with light pigmentation and scattered tan nodules overlying the trabecular meshwork in all quadrants. Fundus examination was unremarkable OD (Fig. 2A) but revealed marked cupping of the optic nerve OS with a normal peripheral examination (Fig. 2B). After receiving 250 mg of acetazolamide and topical brimonidine 0.1% and timolol 0.2% OS, the patient’s pressure was 12 OD and 24 OS.

The patient was treated with latanoprost 0.005% before bed (QHS)
OS, timolol-dorzolamide twice daily (BID) OS, brimonidine 0.15% three times daily (TID) OS, and acetazolamide 250mg four times daily (QID), which maintained her IOP in the mid-to-high twenties. Her BCVA OS was found to be 20/40 with −1.50 SE. Humphrey visual field 24-2 demonstrated a full field OD and a small, central island of vision OS. Anterior segment optical coherence tomography (OCT) and ultrasound biomicroscopy revealed areas of thickening of the iris (Fig. 3A and B). Anterior segment fluorescein angiogram exhibited hyperfluorescence corresponding to the iris lesion (Fig. 4A–D). Endothelial cell count was 4255 cells/mm² OD and 5025 cells/mm² OS, inconsistent with an iridocorneal endothelial (ICE) syndrome, in which specular microscopy shows an asymmetric loss of endothelial cells in the affected eye.

The patient was taken to the operating room and trans-corneal fine needle aspiration biopsy of the lesion overlying the iris was performed in a similar manner as described by Shields et al. Under the surgical microscope, a 26 gauge needle was passed through a translimbal approach approximately 3 clock hours superior to the temporal portion of the iris lesion. The needle was directed into the lesion in a bevel up configuration. Straight polyethylene connector tubing was used to attach the needle to a 10 cc syringe. Aspiration was applied to the syringe to obtain the biopsy. Identical biopsies were repeated for a total of three passes through the lesion. The specimen showed a paucicellular aspirate with rare atypical cells with nuclear enlargement, prominent nucleoli, and wispy cytoplasm consistent with melanoma (Fig. 5). The pathology specimen was confirmed by the Emory Eye Center. Cytospin H&E specimen contained 95% tumor in the sample. Genetic testing using a 50-Gene Solid Tumor Cancer Panel by Next Generation Sequencing revealed that the patient had GNAQ exon 5 missense variant p Q209L (NM_002072.4:c.626A > T; NP_002063.2:p.Gln209Leu) in 60% of the alleles tested, suggestive of iris melanoma. No additional mutations were identified. Gene expression profiling utilizing reverse transcriptase polymerase chain reaction by Castle Bioscience© revealed a Class 1A molecular signature. Subsequent metastatic work-up found no metastasis or lymph node involvement, identifying the patient as having cT1cN0M0 stage IIA left iris melanoma. The patient was treated with custom designed Iodine-125 plaque brachytherapy covering the entire anterior chamber with three fixation points. The radioactive plaque delivered a dose of 85 Gray to a 4 mm depth across the entire anterior chamber over a 4 day period.

Four months after irradiation, the patient’s visual acuity was 20/200.

Fig. 1. (A) External examination revealed a normal right eye but (B) demonstrated marked abnormalities of the left iris, including uveal ectropion, corectopia, and multiple patches of tapioca-like tissue overlying the iris. Magnified views of the left iris further illustrate the (C) uveal ectropion and (D) overlying iris membrane. The membrane limits the view of the prominent underlying blood vessels.

Fig. 2. Bilateral fundus examination revealed (A) normal findings in the right eye and (B) marked cupping of the left optic nerve with nasalization of vessels and excavation of the optic disc rim.

Fig. 3. Ultrasound biomicroscopy demonstrates (A) mild thickening of the iris nasally and (B) marked thickening of the iris temporally with iridolenticular and iridotrabecular contact with occlusion of the angle.
with her old glasses and her IOP was 26 mmHG OS by Goldmann applanation on topical latanoprost 0.005% QHS, timolol-dorzolamide BID, brimonidine 0.15% TID OS, and oral acetazolamide 250mg QID. Her conjunctiva was well healed after placement of the plaque. The iris mass appeared regressed. Gonioscopy revealed pigmented trabecular meshwork without any masses. Specular microscopy revealed minimal endothelial cell loss. Follow-up PET-CT revealed no metastasis, and continued surveillance with PET-CT was planned.

3. Discussion

Melanoma involving the eye and adnexa is rare, comprising only 5% of all melanomas in the United States.7 Uveal melanoma occurs even less frequently in children, with only 1% of cases occurring in patients below the age of 21 in a review of 8033 cases of uveal melanoma.7 A large meta-analysis identified the age-specific incidence of uveal melanoma in children between 10 and 14 years as 0.2 males and 0.0 females per million, which increases to 0.4 males and 0.6 females for every million in 20–24 year-olds.8 A review of 122 cases of uveal melanoma in children and adolescents evaluated by the Ocular Oncology Service at Wills Eye Hospital over 38 years demonstrated that approximately 25% of these rare cases primarily involve the iris.8

Differentiation of benign and malignant iris lesions can be difficult. Characteristics that help differentiate melanoma from nevus include larger tumor size with a mean basal dimension of 6mm and 2.3mm thickness, seeding to other locations on the iris or adjacent trabecular meshwork, secondary glaucoma, secondary cataract, documented enlargement, and prominent vascularity. Pediatric iris melanoma differs from that of adults due to the generally smaller tumor size, less frequent seeding, and rarer cases of secondary glaucoma.9,10

There are multiple mechanisms through which uveal melanoma may cause secondary glaucoma, including invasion of the angle, rotation of the ciliary body, melanomalytic glaucoma, and pigment dispersion. The prevalence of glaucoma due to intraocular melanoma varies greatly, with reports ranging from 3 to 57%.11,12 Management of glaucoma in these cases entails medical stabilization of pressure until the tumor can be treated appropriately. Laser trabeculoplasty may be considered in uninvolved regions of the trabecular meshwork, but has the theoretical risk of seeding the tumor to previously unaffected areas. Transscleral cyclophotocoagulation may be effective but is contraindicated in regions of the ciliary body or iris that contain tumor due to possible liberation of malignant cells. Filtering surgery has been demonstrated to provide a conduit for extrascleral extension of uveal melanomas13–15 and may increases the risk of metastasis and death.16 Pediatric patients that underwent surgical intervention prior to diagnosis of melanoma demonstrated higher rates of metastasis and mortality, including death due to metastatic disease in two out of three patients that underwent filtering surgery in one series.17 Successful treatment of these tumors prior to filtering surgery may reduce the likelihood of extrascleral spread and systemic metastases in the short term.18,19 Though little data is available on long-term risk, present data suggests that the risk of extrascleral spread, systemic metastasis, and death does increase with time (Table 1), even with treatment of the tumor.15,18 In a pediatric patient with a life expectancy of several decades, the life-time risk of metastasis and premature death, even after treatment of the melanoma, must be weighed with appropriate gravity.

The management of iris melanoma includes either plaque radiotherapy, local excision, or enucleation. In this case the patient elected to undergo plaque radiotherapy. In a recent review of 144 iris melanomas treated with plaque radiotherapy, Shields et al. reported a local control rate of 85% at 7 years following radiotherapy with 80 grey delivered to the tumor.20

In the absence of intraocular surgery, metastasis for uveal melanoma was found to be 8.8% at 10 years and 20.2% at 20 years for
children less than 21 years of age, increasing to 25% at 10 years and 36% at 20 years for patients of all ages. Barr et al. identified an 8% mortality risk for pediatric iris melanoma at 5 and 10 years that increased to 13% by 15 years. Mortality in pediatric choroidal and ciliary body melanoma is even higher at 21% at 5 and 10 years and 25% at 15 years. The risk for mortality was found to be highest in patients with glaucoma, angle involvement, and secondary glaucoma. The patient will need long-term surveillance for recurrence or metastasis.

4. Conclusions

In this case, a patient with an abnormal pupil at age 7 was identified but failed to receive further evaluation of her irregular pupil. At age 9, she returned to the same clinic with a new iris nevus and a persistently irregular pupil OS. This new nevus was not closely monitored and, two years later, the patient was found to have an iris melanoma with extensive involvement of the angle and secondary glaucoma. The patient underwent treatment with plaque brachytherapy and demonstrated no short-term metastasis, but delay in diagnosis led to extensive local progression of the tumor and advanced glaucomatous optic neuropathy and field loss. With residual elevated pressure after treatment and a complex decision tree in which medical management poses the risks of side effects and surgical management presents the long-term risks of metastasis, further treatment must involve an extensive discussion of risks, benefits, alternatives, and prognosis of all treatment options. Regardless of further interventions, the patient will need long-term surveillance for recurrence or metastasis.

Though uveal melanoma is low on the differential diagnosis of secondary glaucoma, it is important to maintain a high index of suspicion for this condition. Patients who develop glaucoma are more likely to have high risk melanomas because elevated intraocular pressure is associated with more advanced tumors, angle involvement, and increased risk of metastasis. Prompt identification of malignancy in these cases allows for referral for systemic evaluation and appropriate treatment of the tumor. This, in turn, can prevent progression of secondary glaucoma and allow for safer treatment of intraocular pressure. Missed or late diagnosis can result in delayed treatment, which may lead to irreversible vision loss and further increase the risk of metastasis and mortality.

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### Table 1

Summary of reports describing filtering surgery in patients with uveal melanomas, with and without treatment of melanomas, specifying incidence of local recurrence, systemic metastasis, and death due to metastasis.

<table>
<thead>
<tr>
<th>Article</th>
<th>Eyes</th>
<th>Tumor (melanoma)</th>
<th>Treatment</th>
<th>Filtering surgery</th>
<th>Local recurrence/extension</th>
<th>Systemic metastasis</th>
<th>Death due to metastasis</th>
<th>Follow-up post-filtering surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichardt et al.</td>
<td>15</td>
<td>Uveal (Various)</td>
<td>PBT</td>
<td>Trab</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5 yr (n = 4/15)</td>
</tr>
<tr>
<td>Gray et al.</td>
<td>1</td>
<td>CB</td>
<td>1-125 × 2</td>
<td>Trab, GDD</td>
<td>0</td>
<td>0</td>
<td>No long-term data</td>
<td>14 mo</td>
</tr>
<tr>
<td>Grossniklaus et al.</td>
<td>1</td>
<td>CB</td>
<td>None</td>
<td>Trab, Trab (various)</td>
<td>Trab, Trab, MMC</td>
<td>Trab</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Liang et al.</td>
<td>1</td>
<td>Iris</td>
<td>EBT PO</td>
<td>Trab, MMC</td>
<td>Enucleated</td>
<td>NS</td>
<td>NS</td>
<td>9 mo</td>
</tr>
<tr>
<td>Pasternak et al.</td>
<td>1</td>
<td>Iris/CB</td>
<td>None</td>
<td>Phaco/Trab</td>
<td>0</td>
<td>0</td>
<td>1 yr</td>
<td>2 yr after enucleation</td>
</tr>
</tbody>
</table>

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### Patient Consent

Verbal consent was obtained for the publication of this paper from the patient's legal guardian. All patient identifiers were excluded.

### Conflicts of interest

No conflicting relationship exists for any author. The authors do not have any commercial or proprietary interest in the product or company discussed (BCG, NAW, MJN, LAB, SLC, MA, HG, GNM) George Magrath, M.D. has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### Authorship

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

### Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ajoc.2018.05.009.

### References