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Heterochromia following intravitreal chemotherapy in two cases

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Intravitreal chemotherapy is recognized as an effective treatment for retinoblastoma with vitreous (and occasionally subretinal) seeding refractory to intravenous or intra-arterial chemotherapy. However, this treatment carries with it the risk of toxicity to both the posterior and anterior segments of the eye, including retinal pigment epithelial mottling, ischemic/hemorrhagic retinopathy, posterior synechia, cataract, scleral necrosis, and focal iris depigmentation. We report 2 cases of iris heterochromia secondary to profound iris stromal depigmentation following intravitreal melphalan and topotecan injections.

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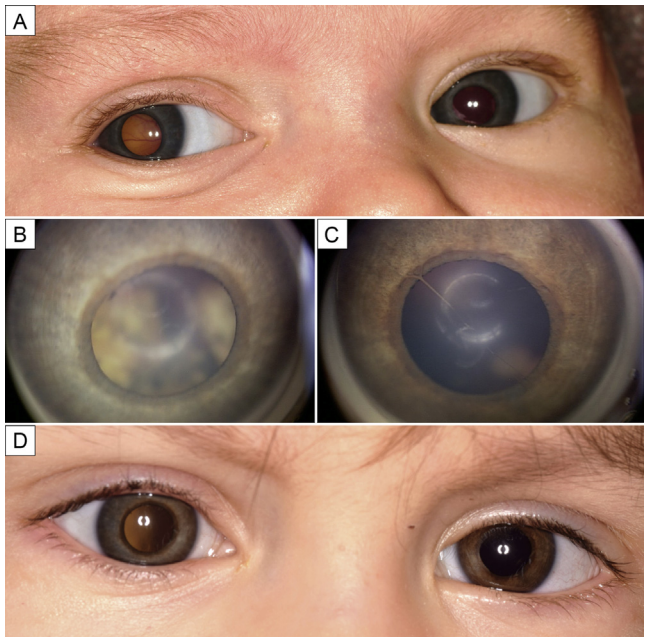

FIG 1. A 2-month-old white girl referred for evaluation of bilateral retinoblastoma. Prior to treatment (A), symmetric irides were noted; over time pigmentation increased. One month following intravitreal melphalan and topotecan in the right eye, diffuse iris stromal depigmentation led to heterochromia with lighter iris in the right eye (B), compared to the darker iris in the left eye (C). Following the third session of intravitreal injections (D), notable heterochromia was observed.

Case 1

A 2-month-old white girl with symmetric blue irides was referred to Wills Eye Hospital for evaluation of bilateral retinoblastoma (Figure 1A). On examination, the right eye showed a large, partially calcified retinoblastoma with total retinal detachment (group E); the left eye, 4 small retinoblastomas in the macula (group B). Despite intravenous chemotherapy (vincristine, etoposide, carboplatin) with consolidation and additional intra-arterial chemotherapy (melphalan, topotecan), the right eye demonstrated localized recurrent subretinal seeding. The seeding was managed with 6 sessions of trans pars plana precision intravitreal injections[1] of melphalan (20–30 mcg/0.1–0.15 cc) and topotecan (20–30 mcg/0.1–0.15 cc), using a 31-gauge needle directly on the recurrent seed with ultimate tumor control. At this time, the patient demonstrated symmetric hazel irides. One month after the first injection, slight heterochromia was observed (Figures 1B, 1C), leaving the affected right iris blue and unaffected left iris hazel. One month after the third injection, the heterochromia persisted (Figure 1D).

Case 2

A 10-month-old white boy with symmetric patchy light brown irides was referred for evaluation of bilateral

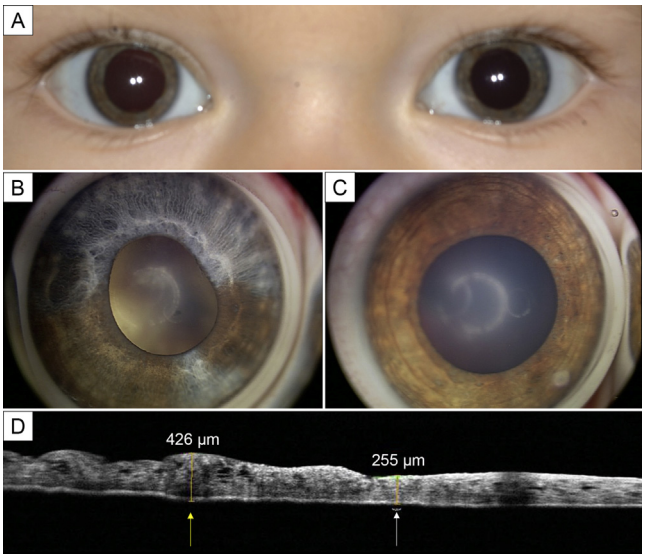

FIG 2. A 10-month-old white boy referred for evaluation of bilateral retinoblastoma. Prior to treatment (A), symmetric light brown irides were noted bilaterally; over time they assumed a symmetric brown color. Two years following intravitreal melphalan and topotecan in the right eye, diffuse iris stromal depigmentation led to heterochromia with patchy blue/brown iris in the right eye (B) and brown iris left eye (C). Anterior segment optical coherence tomography of the right eye taken horizontally across the inferior iris from 5:00 to 7:00 (D) revealed segments of iris thinning with reduction in vascularity and crypts (white arrow) corresponding to the atrophic blue sector and normal iris with vascularity corresponding to the brown sector (yellow arrow).

retinoblastoma (Figure 2A). On examination, the right eye showed 5 tumors, shallow retinal detachment, and vitreous and subretinal seeds (group D); the left eye, 2 tumors and overlying vitreous seeding (group C). Despite intravenous chemotherapy (vincristine, etoposide, carboplatin) with consolidation and additional intra-arterial chemotherapy (melphalan, topotecan), the right eye showed recurrent vitreous seeding. At this point, both eyes demonstrated brown irides. To control the vitreous seeding in the right eye, the patient received 5 sessions of trans pars plana intravitreal injections of both melphalan (20 mcg/0.1 cc) and topotecan (20 mcg/0.1 cc), using a 31-gauge needle over 26 days. Tumor control was achieved. However, following the final session, heterochromia was noted, with the affected right iris patchy blue/brown (Figure 2B) and the unaffected left iris brown (Figure 2C). Optical coherence tomography of the right iris demonstrated segments of iris thinning with reduction in vascularity and crypts corresponding to the atrophic blue sector and normal iris with vascularity corresponding to the brown sector (Figure 2D). However, the iris pigment epithelium would also have to have been involved to explain the heterochromia.

Discussion

Eyes that would have previously been enucleated for vitreous retinoblastoma seeding are now being salvaged using intravitreal chemotherapy.[2-4] However, this treatment poses risks for toxicity to both the anterior and posterior segment of the eye.[5,6] In an analysis of 192 injections of chemotherapy in 40 eyes with retinoblastoma, toxicities included retinal pigment epithelial mottling (13 [32%]), focal cataract (10 [25%]), transient vitreous hemorrhage (5 [13%]) hypotony (3 [8%]), optic disk edema (1 [3%]), and hemorrhagic retinal necrosis (1 [3%]).[3] There were no cases of iris heterochromia. In a study including 251 eyes managed with intravitreal chemotherapy, iris atrophy occurred in 3 (1.2%).[5] Others found iris depigmentation and thinning in 1 of 76 patients.[6] Munier and colleagues[7] reported a case of hypochromic heterochromia with no pigment epithelial loss and no stromal thinning following multiple intracameral injections of melphalan for aqueous seeding of retinoblastoma.

Factors related to iris depigmentation following intravitreal chemotherapy remain unclear. Injections close to the iris or trapping of chemotherapy in a liquified vitreous pocket behind the ciliary body might lead to a higher exposure to the ciliary body, as has been speculated for other toxicities, particularly retinal pigment epithelium mottling. It is possible that ciliary body toxicity progresses toward the iris. This proposed mechanism is supported by the fact that there are no islands of decreased iris pigmentation in the pupillary portion of the iris. Another possible mechanism is that the eyes are unicameral, and the melphalan is being transferred to the anterior chamber in part by a pressure gradient created by performing an anterior chamber tap prior to intravitreal injection.

Both patients in this series maintained their globe without inflammatory signs. Further investigation to better quantify anterior segment toxicity to the anterior segment following intravitreal chemotherapy is warranted.

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Diagnosis and treatment of bilateral Coats disease in a 5-year-old girl

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A 5-year-old girl presented with decreased vision and outward deviation of her right eye. Fundus examination revealed multiple hard exudates in the macula in the right eye and nasal to the disk in the left eye. The patient was lost to follow-up in the near term but presented 9 months later with reduced vision and an increase in exudates in both eyes. RetCam fluorescein angiography confirmed the diagnosis of bilateral Coats disease.

Coats disease is an isolated nonhereditary retinal vascular anomaly characterized by vascular telangiectasias and abnormally dilated aneurysmal vessels that cause subretinal and intraretinal exudation and exudative retinal detachment.[1] Coats disease is primarily a disease of young male patients with a predominant unilateral presentation.[1-4] In two large case series from the United States and India, bilaterality was reported in 5% and 10% patients, respectively. Female sex with Coats disease was reported in 24% and 17.2% patients, respectively.[1,3] A combination of these 2 scenarios is relatively rare. We report a case of bilateral presentation of Coats disease in a girldiagnosed and managed with the aid of RetCam-based fluorescein angiography (FA; Natus Medical Incorporated, Pleasanton, CA).

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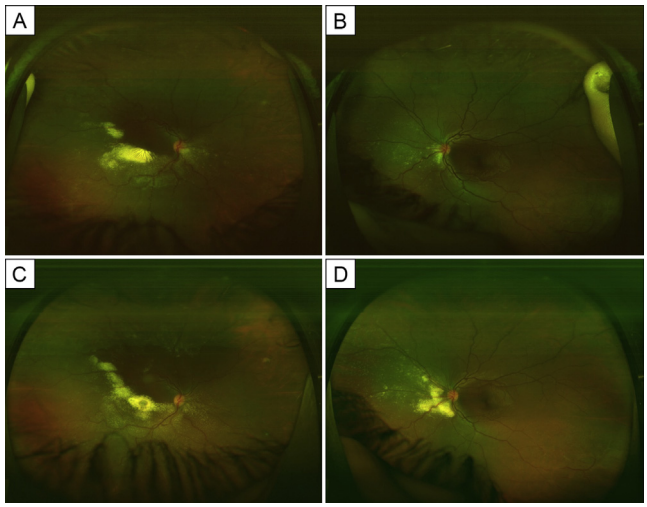

FIG 1. Pseudo-color fundus images of a 5-year-old girl with bilateral Coats disease (Optos 200Tx, Dunfermline, Scotland, UK). A, Right eye fundus at presentation showing deposition of hard exudates at the posterior pole. B, Left eye fundus at presentation showing speckled deposition of hard exudates nasal to the disk. C, Right eye after 9 months showing increase in the hard exudates at the posterior pole with fibrotic focus at the fovea. D, Left eye after 9 months showing increase in the hard exudates nasal to the disk but with sparing of the foveal center.

Case Report

A 5-year-old girl was brought by her parents for evaluation of decreased vision in her right eye of 4 months' duration. There was no associated pain, redness, or photophobia. Past history was significant for outward deviation of her right eye since 2 years of age, but no treatment was sought. The child was born at term with an unremarkable perinatal history. On general physical examination, the child was healthy and had attained appropriate developmental milestones.

At presentation, best-corrected visual acuity was 6/36 in the right eye and 6/6 in the left eye. An exotropia of 60^{Δ} was noted in the right eye. Pupillary reactions and anterior segment examination were unremarkable. Posterior segment examination of the right eye showed multiple yellowish hard exudates in the posterior pole, confined to the inferotemporal area of the macula (Figure 1A). The left eye revealed scanty hard exudates nasal to the optic disk (Figure 1B). Widefield FA was planned on the Optos imaging system (Optos 200Tx, Dunfermline, Scotland, UK). The child was uncooperative for imaging, and the parents were counseled on the need for examination under anesthesia; however, they did not consent.

The child was lost to follow-up for 9 months, at which time she presented again with complaints of further deterioration of vision in the right eye. Best-corrected visual acuity was 3/60 in the right eye and 6/9 in the left eye. Fundus examination of the right eye revealed increase in the exudation at the macula and a subfoveal fibrotic scar (Figure 1C). The left eye also showed increase in the exudation nasal to the optic disk (Figure 1D). The