Secondary glaucoma in retinoblastoma

ABSTRACT

Objective
To investigate the causes of secondary glaucoma in retinoblastoma (RB) and underscore the significance of glaucoma as a presenting sign of RB.

Methods
A 7-month-old boy, initially diagnosed with congenital glaucoma in the left eye (OS), revealed an intraocular RB on further work-up. The eye was eventually enucleated and histopathology showed iris neovascularization (NVI) and a large solitary posterior-pole RB tumor with total retinal detachment. Using this as an illustrative case, a literature search on the relationship of glaucoma and RB was done to determine the incidence and the most common mechanisms of RB-induced glaucoma.

Results
The most common mechanisms of secondary glaucoma in RB were: iris neovascularization (30–72%), pupillary block (27%), and tumor seeding of the anterior chamber (2%).

Conclusion
We presented a case of RB-induced glaucoma that mimicked congenital glaucoma. Awareness that RB may present initially as glaucoma is essential for appropriate evaluation and management.

Keywords: Retinoblastoma, Secondary glaucoma, Neovascularization, Pupillary block
THE ASSOCIATION between retinoblastoma (RB) and secondary glaucoma was first noted in 1965 and reported in literature to occur in 1% to 23% of cases. Glaucoma and iris neovascularization (NVI) are two of the anterior-segment conditions described in RB. Certain histological features in the anterior segment of enucleated eyes with RB also suggest the presence of otherwise undetected glaucoma.

Yoshizumi and colleagues found that 34 (22.8%) of 149 eyes with RB examined histopathologically had clinically proven increased intraocular pressure (IOP) (Group 1) and 38 (25.5%) of 149 eyes with RB had histopathological findings consistent with glaucoma (termed glaucoma mechanisms) but without clinically recorded IOPs (Group 2). Table 1 shows that the distribution of glaucoma mechanisms in both groups was similar and the authors concluded that the clinical and histopathological concordance validates the actual existence of secondary glaucoma in RB. These authors also concluded that the actual incidence of glaucoma in eyes with RB is much higher than reported in previous studies.

In another study by Shields and colleagues of 248 patients with unilateral or bilateral RB managed during a 12-year period, 303 eyes had RB, out of which 51 (17%) developed secondary IOP elevation occurring primarily in advanced tumors that replaced most of the vitreous cavity. Walton and Grant reported that 39 (44%) of 88 eyes enucleated for RB had NVI but did not mention the frequency of glaucoma in their series. In the same study, they looked at eyes enucleated from children 5 years old or younger from 1952 to 1968 and found that NVI was most commonly associated with RB. Of the 56 eyes with NVI seen on pathologic specimens, 38 (68%) had untreated retinoblastoma.

Other older studies had also demonstrated the association of RB and secondary glaucoma. Howard and Ellsworth reported glaucoma as an initial clinical finding in only 2% of cases of RB but did not describe the frequency of glaucoma as an associated finding among the 235 RB eyes studied. Stafford and colleagues reported that 14 (2.3%) of 618 cases of RB were initially misdiagnosed as primary glaucoma.

METHODOLOGY
A 7-month-old boy was referred to the glaucoma service of the Massachusetts Eye and Ear Infirmary (MEEI) with the classic triad of congenital glaucoma (pain, tearing, and photophobia). He was born via caesarian section with no birth abnormalities. At 3 to 4 months, the parents noted that they could “see into the left eye” at a certain angle. The right eye (OD) was normal. The left eye (OS) was buphthalmic but not proptotic, with corneal edema, conjunctival injection, tearing, swelling, and erythema of both the upper and lower lids. Intraocular pressure (IOP) was 30 OD and 8 OD. Extraocular motility was full in both eyes. Retinal examination in OS revealed a tumor mass occupying the entire posterior pole with total retinal detachment. Computed tomography (CT) showed a 1.5 cm round, homogenous density in the mid-orbit, lateral to the superior orbital fissure. The diagnosis was retinoblastoma (RB) with secondary glaucoma OS and the eye was eventually enucleated. Histopathology showed iris neovascularization (NVI), RB cells filling the vitreous space, and a posterior-pole RB tumor with total retinal detachment.

A literature search on the relationship of glaucoma and RB was subsequently done to determine the incidence and the most common mechanisms of RB-induced glaucoma.

RESULTS
The clinical presentation of glaucoma in RB includes neovascular glaucoma with or without angle closure, pupillary-block glaucoma, or uveitic glaucoma. Symptoms, which may include pain, tearing, and photophobia are all unusual for RB. Enlargement of the globe (buphthalmos), increased IOP, corneal edema, hyphema, or eye redness may be present.

Shields and colleagues noted that the most common mechanisms of IOP elevation was NVI 74% (36/51), followed by angle closure (pupillary block) secondary to anterior displacement of the lens–iris diaphragm at 27% (14/51), and tumor seeding of the trabecular meshwork at 2% (1/51). Yoshizumi and colleagues found similar results. Each of these glaucoma-inducing mechanisms in RB is described in detail.

Iris neovascularization (NVI)
In 1967, Richard Schulze was the first to call attention to an association between NVI and RB. Histological studies identified NVI in 30 to 72% of eyes with RB (Table 2). Two studies also reported the role of NVI in causing glaucoma in eyes harboring RB.

Clinically, iris or angle neovascularization is a spectrum that can range from the preglaucoma stage with normal IOP that progresses to an open-angle glaucoma stage with increased IOP, hyphema, vitreous hemorrhage, or fibrovascular membranes. These fibrovascular membranes may contract, causing ectropion uvea, and form peripheral anterior synechiae (PAS), leading to angle-closure glaucoma with a very high IOP. In RB, synechial angle closure and NVI were closely correlated; a closed angle was observed in 61% of enucleated RB eyes with NVI compared with 5% without NVI.

NVI is judged to be present histologically when an
abnormal fibrovascular layer composed of thin-walled vessels and variable amounts of fibrous tissue are found on the anterior surface of the iris. This fibrovascular layer is usually conspicuous and often associated with ectropion uveae and synechial angle closure resulting in elevation of IOP via impairment of aqueous outflow. New blood vessels frequently become incorporated into the synechial growth. Most eyes with RB and NVI contain large tumors located at the posterior pole with involvement of the central retinal vessels or large branch retinal vessels. Occlusion of these large vessels results in ischemic retinopathy, which may secondarily cause NVI. However, there have been two variant cases reported of anteriorly located RBs with minimal posterior pole involvement associated with NVI as well. These cases are exceptions to the general observation that RB with large posterior-pole vascular compromise are usually associated with NVI. These cases also support the theory of the role of tumor angiogenic factor in the etiology of NVI. The two cases are described in detail below:

- The first variant case described a diffuse anterior RB involving primarily the anterior ocular structures with only one microscopic focus in the peripheral retina. This patient presented with glaucoma with increased IOP and anterior and posterior uveitis, but had a normal retina in the affected eye. Histopathology showed NVI and PAS with trabecular-meshwork occlusion. The retina and the optic nerve displayed glaucomatous atrophy. The RB tumor circled the lens zonules and ciliary body for a full 360 degrees, extended around the iris, invaded the ciliary body, and seeded the vitreous base and anterior chamber.

- The second variant case of RB and NVI was reported in one eye where the RB tumor was limited exclusively to the retina anterior to the equator. The tumor mass involved less than a 90-degree quadrant of the retina and the tumor cells were found in the anterior chamber seeding the corneal endothelium and the iris.

The most important factors leading to NVI are ischemia, necrosis, inflammation, and possibly tumor-angiogenesis factor. Minoda observed that in RB, NVI was not always accompanied by malignant iris infiltration. He suggested that NVI might be promoted by a factor caused by tumor proliferation in the retina–vitreous cavity. Studies have shown that circulating angiogenic factors produced by the RB tumor itself may play a role in the development of NVI. Although many intraocular tumors produce diffusible tumor-angiogenic factors that stimulate both iris and retinal neovascularization distant from the tumor, the tumor-angiogenic factor released from RB does not cause retinal neovascularization, although it can initiate and sustain NVI, and it was suggested that a hypoxic retinal diffusible vasculogenic factor (HRDVF) accounts for NVI in RB. Upregulation of an angiogenic factor, the vascular-endothelial-growth factor (VEGF), has been demonstrated within RB and has been shown to be induced in hypoxic and necrotic regions of RB tumors stimulating vascular stromal formation. Factors other than hypoxia may also regulate VEGF expression in RB cells. Aside from the RB tumor cells producing VEGF, hypoxic normal retinal cells may also produce VEGF. In situ hybridization analysis using mRNA-labeled VEGF revealed VEGF in the outer nuclear layer of detached retinas in eyes with RB.

Many histological features in eyes with RB are correlated with NVI. A study by Spaulding showed greater NVI in eyes with endophytic and large RB tumors. Other studies showed that NVI is associated with orbital, choroidal, scleral, anterior-chamber, and optic-nerve invasion and calcifications. In addition, greater amounts of tumor necrosis and the presence of basophilic staining, which results from sedimentation of DNA from necrotic cells,
were associated with NVI.\(^9\) In a study by Walton and colleagues of 88 patients who had anterior segment RB, 33 (38\%) had NVI and 14 (16\%) had none.\(^{11}\) Spaulding\(^9\) showed in histopathologic RB specimens with vitreous seeding, that 90\% had NVI and 54\% had none. The presence of Flexner–Wintersteiner rosettes, which reflects a higher state of differentiation of RB and, indirectly, a less-advanced stage, is associated with less NVI.\(^7,11,17\) Other histological factors such as the focality of tumor, number of mitotic figures, and seeding of the tumor cells to the vitreous and subretinal space, were not associated significantly with NVI.

Patient’s age and duration of the tumor also appear to be related to the development of NVI in eyes with RB. Walton and Grant found the mean age at the time of enucleation to be 26 months for patients with RB and NVI, compared with 14 months for patients without NVI.\(^{11}\) Similarly, two studies\(^9,17\) have shown that NVI is associated with advanced stages of RB.

Interestingly, conditions such as retinopathy of prematurity (ROP) and Coats’ disease that may clinically be confused for RB are also associated with NVI. Two studies\(^9,20\) demonstrated that an equal or even higher incidence of NVI exists in other conditions that may clinically resemble RB (Table 3).

**Pupillary block**

Anterior displacement of the lens with resultant pupillary block and angle closure is the second (27\%) most common mechanism of glaucoma in eyes with RB.\(^7,10,11\) In one study, the most common cause of pupillary block was seen in cases with total retinal detachment with massive subretinal exudation and the retina being close to or in contact with the posterior-lens capsule, causing anterior displacement of the lens. In most cases, the tumor was present within and under the retina.\(^7\) The tumor and subretinal fluid displace the lens anteriorly, resulting in pupillary block and angle closure.

**Tumor seeding of the anterior chamber**

A less frequent (2\%) mechanism of glaucoma in eyes with RB is via direct involvement of the anterior chamber structures by necrotic tumor cells and/or inflammatory cells. RB tumor cells can break free from the main tumor mass in the retina and migrate into the anterior chamber. The tumor cells then can deposit in the inferior anterior chamber angle and resemble a hypopyon. Glaucoma occurs as a result of the obstruction of the outflow of aqueous humor through the trabecular meshwork by the tumor cells.\(^{27}\)

In the study by Walton and colleagues, 38\% (33/88) of RB specimens had anterior-segment involvement with NVI while 16\% (14/88) had anterior-segment involvement without NVI but had deposits of tumor cells on the anterior surface of the iris, corneal endothelium, and trabecular meshwork.\(^{11}\)

**DISCUSSION**

The management of glaucoma in RB is preceded by the need for instituting the appropriate management for RB. Generally, glaucoma in RB is managed medically with aqueous suppressants, but once neovascular glaucoma develops, medical management usually fails and enucleation is often required.\(^{11}\) Glaucoma filtration or shunt operations are absolutely contraindicated because of the risk of extraocular spread of viable tumor cells.

The presence of a large RB with secondary glaucoma and vitreous hemorrhage is predictive of optic-nerve involvement;\(^27\) thus, glaucoma in RB is arguably an indication for performing an enucleation.

Development of neovascular glaucoma as a consequence of obstruction or closure of the angle by fibrovascular tissue is of little practical significance in eyes that are to be enucleated for RB, but it is a considerable complication if it occurs in the better eye.\(^{11}\)

Later studies seem to indicate that the actual incidence of glaucoma in eyes with RB is much higher than reported in previous studies. These studies show that increased IOP is seen in 17\% (51/303)\(^{10}\) to 22.8\% (34/149)\(^7\) of patients with RB. In addition, histopathologic glaucoma mechanisms are also found frequently in RB eyes with clinically increased IOPs (Table 1).\(^7\) Moreover, in RB eyes with NVI as the sole glaucoma mechanism, a tumor involving the posterior pole was consistently present and served as a predictor for the presence of NVI on the pathological sections.

A study by Shields\(^28\) pointed out certain unique aspects of children with RB that manifest at an older age, namely pain, inflammation, conjunctival chemosis, and glaucoma, and showed that these characteristics alert the clinician to the potential atypical presentation of the tumor in children. Another study\(^12\) suggested that these atypical manifestations of RB carry a higher risk of death due primarily to a delay in diagnosis. Vitreous hemorrhage from NVI may also make the diagnosis and management of retinoblastoma more difficult.\(^29\)

NVI in association with RB has received little clinical attention and the studies above have shown that NVI indicates a more advanced disease and is correlated with other histological tumor features that herald a worse prognosis for the RB tumor. The posterior pole seems to attract so much attention compared with the anterior segment that the presence of NVI often seems to be neglected or overlooked. The presence of anterior-segment involvement (i.e., raised IOP, NVI, and angle-closure configuration) in RB carries a graver prognosis.\(^30\)
However, if slit-lamp biomicroscopy of the anterior segment, particularly gonioscopy, were done systematically and comprehensively, NVI as well as occasional clumps of RB tumor cells in the anterior chamber may be recognized more frequently. Dilated bilateral fundus examination with a 360-degree scleral depression is the most important part of the ophthalmologic examination, often done under general anesthesia.\(^6\) Careful retinal and ciliary body examination with the procedures described above should be performed to exclude medulloepithelioma in the ciliary body region.\(^7\) Further ancillary exams such as ultrasound and CT may be needed to be certain about the diagnosis of RB since the view of the anterior and/or posterior segment may be obscured by corneal edema and/or hemorrhage.

Commenting on Minoda’s study that used light and electron microscopy to study NVI in enucleated RB eyes, Henkind\(^16\) said that since NVI may be less than 10 µm in diameter and would be virtually invisible with slit-lamp biomicroscopy, especially in dark-eyed children, it might prove instructive though somewhat difficult to perform anterior-segment fluorescein angiograms in patients with RB or entities similar to RB to ascertain whether neovascularization can be better demonstrated clinically. However, NVI itself would not seem to be a significant differentiating feature between RB and these other entities similar to RB, which also may present with NVI (Table 2).\(^16\)\(^,\)\(^20\) There also appears to be no histological difference between NVI as it occurs in RB or another disease category;\(^9\) therefore, NVI is not pathognomonic for RB.

In conclusion, although glaucoma may be a secondary clinical issue in the shadow of a grave pediatric eye tumor, awareness of its coexistence with RB through a more thorough ocular examination, particularly of the anterior segment, can guide the clinician in assessing the overall evaluation of the affected eye.

References