Stargardt Disease in a Patient With Retinoblastoma

Retinoblastoma is the most common primary ocular malignancy of young children, with an incidence of 1:17,000 to 1:34,000 new births. Retinoblastoma is bilateral in about 30% of cases. Although new modalities offer an enhanced chance of eye salvage, in bilateral disease, management often leads to enucleation of the more-involved eye, with more conservative treatment of the better eye. Subsequently, the child is watched carefully for recurrence and for any evidence of central nervous system involvement or other malignancies. The retinoblastoma gene (Rb) is located in the 14 band of the q, or long arm, of chromosome 13. The Rb gene causes cancer when its protein product is absent or dysfunctional.

We describe a child with bilateral retinoblastoma after enucleation of the more-involved eye at 13 months of age, who was diagnosed as having Stargardt disease in the preserved eye at age 10 years. The significant points we wish to highlight are the difficulty in diagnosing Stargardt disease because of subtle retinal findings, and the opportunity this case affords for investigating early preclinical stages of Stargardt disease. To our knowledge, there is only 1 previously reported case of these 2 disorders in the same patient.

Report of a Case. A 10-year-old white boy was assessed at Wilmer Eye Institute (Baltimore, Md) in April 2002 because of decreased vision in the right eye. He had been diagnosed as having retinoblastoma in both eyes in October 1992, when he was 7 months old, after having symptoms of leukocoria and esotropia of the left eye. His medical history included a normal pregnancy and delivery, and normal development thereafter. His family history was significant only for adult-onset diabetes mellitus in the maternal grandfather as well as associated cardiac arrhythmias. His social history was notable for normal school progression in the years that followed the diagnosis.

At the time of diagnosis of the right eye, examination under anesthesia demonstrated a normal disc and macula, although the vessels were somewhat dilated and tortuous. There were 2 tumors, 1 supertemporal and 1 inferior to the posterior pole. In the left eye, about three quarters of the retina was involved with tumor, and the one quadrant that was not had multiple vitreous seeds (Figure 1). There were some areas of hemorrhage on the surface of the tumor. Ultrasound examination showed questionable involvement of the optic nerve in the left eye. Both eyes were treated with external beam radiation (total dose of 4680 rad [46.8 Gy]), although it was unlikely that the left eye could be salvaged. The left eye was enucleated in April 1993, owing to the development of chronic retinal detachment, although the tumors in both eyes shrunk and had the appearance of cottage cheese. There was no recurrence in the right eye or elsewhere thereafter.

Visual acuity of the right eye stabilized at a level of 20/30 through November 2000, despite the presence of mild posterior subcapsular cataractous changes. The patient was followed semiannually by an ocular oncologist, and his visual acuity was 20/30 since at least 1998. In September 2001, he was noted to have decreased visual acuity during an evaluation for glasses. He saw a pediatric ophthalmologist, who referred him to an ocular genetics specialist. Findings on magnetic resonance imaging to rule out central nervous system metastasis were normal. Although macular thickening was not appreciated clinically, optical coherence tomography was performed, and the findings were normal as well. The patient was subsequently referred to a neuro-ophthalmologist, who found the patient’s visual acuity to be 20/100 and did not find evidence of optic neuropathy. He was then referred to the visual function service at Wilmer for electrophysiologic testing and further evaluation of his decreased visual acuity.

On initial examination in April 2002, the best-corrected visual acuity with a compound astigmatic refraction measured 20/100 OD. The visual field was full to confrontation. There was a mild posterior subcapsular opacity of the lens. Dilated fundus examination was somewhat difficult. The disc appeared normal. Evidence of a regressed retinoblastoma in the preserved eye was present, with small white opacities in the periiphery.
terior vitreous overlying the macula, which were old. The macula was difficult to assess because of eye movement during ophthalmoscopy.

A visual evoked response was obtained and did not show evidence of an optic neuropathy. An electroretinogram showed minimally reduced rod responses and normal cone responses. A multifocal electroretinogram showed a loss of the central peak and reduced responses in a circular region of about 15° in diameter, centered on the fovea (Figure 2).

The patient returned in May 2002 for further evaluation. Scanning laser ophthalmoscope imaging and perimetry were performed to assess the basis of the decreased vision. Infrared imaging showed a central macular lesion between 1 and 2 disc areas in size. This region had a dense scotoma on scanning laser ophthalmoscope perimetry (Figure 3). Fixation was placed significantly superior to the edge of the dense scotoma and lesion. Yellow flecks were also noted in the infrared image. Argon imaging showed tiny white spots near the arcades. Autofluorescence imaging showed the center lesion to have a loss of autofluorescence. Fundus photographs showed a beaten-bronze appearance of the central macula and yellow flecks (Figure 4). Fluorescein angiography showed a dark choroid pattern and flecks in the posterior pole as well as early and late central hyperfluorescence in a bull's-eye pattern (Figure 5). The diagnosis appeared to be classical Stargardt disease.

Electron microscopic examination of ocular tissue of the left eye stored in formalin for 9 years before the development of symptoms from Stargardt disease in the fellow eye showed an abundance of lipofuscin granules in the cytoplasm of retinal pigment epithelial cells (Figure 6).

The patient’s DNA was screened for sequence variants in the recessive Stargardt disease gene, ABCA4, on the recently introduced ABCR400 microarray.3 The array (gene chip) contains all known (>400) ABCA4 variants and allows screening for all mutations in one step at greater than 98% efficiency. Currently, the chip reveals about 60% of disease-associated mutations in an average

Figure 2. A multifocal electroretinogram of the right eye shows reduced responses in a circular region of about 15° in diameter, centered on the fovea.

Figure 3. Color fundus photograph of the right eye shows beaten-bronze appearance of the central macula (arrowhead) and yellow flecks in the posterior pole (arrows).
cohort of Stargardt patients, detecting both mutations in about 35%, one mutation in about 40%, and no mutations in about 25% of patients diagnosed as having Stargardt disease. This efficiency can be explained by the 2 main reasons: (1) inclusion of phenocopies associated with mutations of other genes, which cannot be avoided completely due to the selection methods and, (2) many disease-associated ABCA4 alleles remain currently unknown.

In this patient, the chip detected 5 sequence variants: H423R, P1401P, IVS33+48 C>T, N1868I, and L1894L, all of which are considered nonpathogenic polymorphisms. Since the patient’s diagnosis is consistent with autosomal recessive Stargardt disease, the negative finding has to be explained by the current limitations of the diagnostic method.

Comment. We found that this 10-year-old child with retinoblastoma in both eyes, who underwent enucleation of the left eye for this condition, had evidence for classic Stargardt disease in the remaining right eye. He had a central scotoma with a central atrophic retinal lesion, a dark choroid on fluorescein angiography, and yellow-white flecks. He had a fixation pattern that is characteristic of Stargardt disease and evidence of lipofuscin granules in the cytoplasm of the retinal pigment epithelial cells by electron microscopy. Lipofuscin granules are usually found in older individuals and not in the retinal pigment epithelium of an eye enucleated at such a young age. Similar findings were reported in previous electron microscopic examinations of an enucleated eye of a young patient with Stargardt disease.

Despite evaluations by 5 ophthalmologists, the macula was not visualized adequately to make the diagnosis. This is not uncommon in Stargardt disease, in which children are sometimes referred for psychiatric evaluation for their decreased vision because no macular lesion is seen. Fundus photography, and in this case, scanning laser ophthalmoscope imaging, may be of great value in assessing the macula, with fluorescein angiography providing additional data.

We have consulted several ophthalmologists with vast experience in the field of ophthalmic oncology, and they have not seen a patient with both retinoblastoma and Stargardt disease (Theodore Dryja, MD, e-mail communication, and Carol Shields, MD, written communication 2002). However, a literature search revealed a similar case published by Steinmetz et al. Presumably, these 2 conditions occurred coincidentally in the same patient, in this case and in ours. The paucity of other cases suggests that the 2 conditions are not related genetically.

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**Glaucoma Care in a Patient With Previous Anterior Ciliary Sclerotomy and Scleral Expansion Procedure**

Presbyopia is a gradual decrease of accommodation that becomes clinically significant during the fifth decade of life. Its pathophysiological changes remain uncertain and controversial. In recent years, Schachar and associates\(^1\) suggested that presbyopia occurs because of growth in the equatorial diameter of the lens, and the ciliary muscle contraction can no longer tense the zonule and expand the lens coronally. Based on this theory, scleral expansion by making radial relaxing incisions in the sclera or implanting plastic bands intrasclerally to expand the scleral ring were postulated to restore the accommodation. Although the clinical efficacy of these surgical techniques remains to be proven, they are being offered widely as a means to correct the inevitable ocular affliction of presbyopia. We report an unusual case of glaucoma care in a patient with previous anterior ciliary sclerotomy and scleral expansion procedure.

**Report of a Case.** A 59-year-old white man had ocular discomfort and evidence of bleb leakage in the left eye. Two years before consultation, he underwent anterior ciliary sclerotomy for presbyopia in both eyes. Six months later, his left eye required glaucoma medication for increased intraocular pressure (IOP). He subsequently underwent a scleral expansion procedure (SEP) for his left eye in an attempt to restore the accommodation and reduce the IOP. Nonetheless, his IOP remained uncontrolled, and he required a trabeculectomy without antimetabolite.

Examination of his left eye revealed best-corrected visual acuity of 20/100 and IOP of 10 mm Hg. A small superior conjunctival bleb was noted to be thin, leaking, and extending 3 mm anteriorly onto the superior cornea. The surrounding conjunctiva was hyperemic, scarred, and retracted. Deep conjunctival scars were associated with the insertion sites of 4 silicone expansion bands. Two bands were exposed, and 1 was extruded (Figure 1).

Bleb revision was performed by excision of the anterior extension onto the cornea and the leaky avascular portion of the bleb, with mobilization of the surrounding conjunctiva to cover the trabeculectomy site. The conjunctiva was secured to the limbus with interrupted 9-0 polyglactin sutures at 2 wings. The conjunctiva overlying the expansion bands was dissected, and the bands were removed. Four weeks after surgery, visual acuity improved to 20/30, with the IOP controlled at 12 mm Hg (Figure 2).

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**Figure 6.** Electron microscopy examination discloses an unremarkable Bruch membrane covered by retinal pigment epithelium measuring 8.3 mm in height. The pigment epithelium has normal-appearing melanin pigment granules and numerous lipofuscin granules (arrows) (original magnification ×8000). BM indicates Bruch membrane; CC, choriocapillaries.