Retinal Vasoproliferative Tumors in 6 Patients With Neurofibromatosis Type 1

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In 1983, Shields and associates reported 12 cases of a retinal vascular mass with distinct clinical features that had not been clearly defined previously.1 Numerous subsequent publications2-25 further characterized the clinical and histopathologic features of this tumor, which is now most often called retinal vasoproliferative tumor (RVPT). Initially, RVPT was reported to have no major ocular or systemic associations.1 However, in a report26 in 1995 of 129 RVPTs in 103 patients, 74 (72%) were idiopathic and 29 (28%) were found in patients who had other conditions, including intermediate uveitis, retinitis pigmentosa, and several others. Hence, the authors classified RVPTs into primary (idiopathic) and secondary types.2 Since that publication, the list of secondary RVPTs has continued to expand.2-9-23 The pathogenesis and histopathologic characteristics of RVPT have been the subject of controversy.4-8,24,25

Neurofibromatosis type 1 (NF1) is a well-known oculoneurocutaneous syndrome with extensive clinical manifestations, including a variety of uveal and retinal findings, such as iris Lisch nodules and multiple choroidal nevi.29-42 An intriguing association that has been recently recognized is the finding of RVPTs in patients with NF1.9,10,22 This report describes the clinical findings of RVPTs in 6 patients with NF1 and underscores the risk of severe vision loss in such patients.
Methods

Institutional review board approval was obtained from the Wills Eye Institute for this study. No informed consent was required because this is a retrospective study. The clinical findings were studied in 6 eyes of 6 patients with RVPTs who also had NF1. Data collected included age at time of referral for the RVPT, sex, race, medical and ocular history, best-corrected visual acuity, and intraocular pressure (IOP) of each eye. The age at diagnosis of NF1 was recorded.

Slitlamp examination was performed, looking specifically for Lisch nodules, iris neovascularization (NVI), cataract, and anterior chamber cells and flare. Detailed fundus examination with fundus photography, fluorescein angiography, and ultrasonography was performed when possible, and clinical findings were recorded by detailed anterior segment and fundus drawings. Clinical information related to the RVPT included size (basal diameter and thickness), location, laterality, number of lesions, tumor color, presence of feeder and draining vessels, and distance of the tumor to the optic disc and foveola. Additional vitreoretinal findings that were recorded included presence of exudation, serous retinal detachment, vitreous cells, vitreous hemorrhage, epiretinal membrane, intraretinal edema, and retinal neovascularization.

Results

The demographics and ocular features are listed in Table 1. At the time of referral for the RVPT, patient age ranged from 9 to 36 years (mean age, 18 years; median age, 12 years). One patient (patient 6) had ocular pain, and 5 presented with painless visual loss, with visual acuity ranging from 6/7.5 to light perception. All RVPTs were unilateral, but 1 child (patient 5) had undergoneenucleation of the fellow eye for painful neovascular glaucoma (NVG) of undetermined origin, and histopathologic analysis of the eye could not be performed.

The clinical details and complications of the RVPTs are listed in Table 2. The lesions were located mainly in the equatorial region, had slightly dilated retinal feeder vessels and draining veins, and were associated with intraretinal or subretinal lipoproteinaceous exudation in all cases. Results of imaging studies are given in Table 3. The RVPTs uniformly had high internal reflectivity with A-scan and acoustic solidity with B-scan ultrasonography. Fluorescein angiography in 4 patients revealed hyperfluorescence of the RVPT by the venous phase, with late staining of the mass with slight leakage into the vitreous cells. Optical coherence tomography performed in 3 patients confirmed remote cystoid macular edema.

**Patient 1**

A 28-year-old woman was referred in 2005 for painless visual loss and a mass in her right eye. She had been previously diagnosed as having segmental neurofibromatosis. Ocular examination results were normal, but magnetic resonance imaging detected enlargement of the left optic nerve compatible with an asymptomatic optic nerve glioma. Cutaneous neurofibromas and café au lait spots were evident on the right aspect of her abdomen and right thigh.

The left eye was normal, with a visual acuity of 6/6, and the right eye had a vision of hand movements. There was a yellow retinal mass located at the equator inferiorly, measuring 13 × 12 mm in diameter with slightly dilated retinal blood vessels (Figure 1A). There was a shallow retinal detachment inferiorly with exudation that extended to the optic disc and macular region. Fluorescein angiography revealed early and late hyperfluorescence of the mass (Figure 1B), and B-scan ultrasonography revealed an acoustically solid mass 5 mm thick (Figure 1C). The tumor was treated with a radioactive plaque with 40 Gy to the tumor apex. The tumor had subsequent regression, and the exudation and retinal detachment resolved. In November 2012, the tumor remained controlled, vision was light perception, and the patient had a dense white cataract. Visual acuity in the right eye was 6/6, and the right optic nerve glioma was stable.

**Patient 2**

In September 2008, an 11-year-old girl was referred because of floaters and a fundus mass in her left eye. A diagnosis of NF1 was made several years earlier based on café au lait spots, axillary freckling, and magnetic resonance imaging evidence of...
brain lesions compatible with NF1. The visual acuity was 6/6 OD and 6/7.5 OS. The iris had subtle bilateral Lisch nodules. Funduscopy revealed a normal posterior pole, but there was a yellow-red vascular mass at the equator temporally that measured 12 × 12 mm in diameter. Intraretinal and subretinal exudation extended around the equator to the inferonasal quadrant but spared the posterior fundus (Figure 1D). The mass was hyperfluorescent with fluorescein angiography (Figure 1E), and ultrasonography revealed it to be acoustically solid and 3 mm thick (Figure 1F). The tumor was treated with cryotherapy and intravitreal injection of bevacizumab. One year later, visual acuity was 6/6, the exudation had largely resolved, and there was no subretinal fluid. In December 2012, the visual acuity was 6/6 in each eye, and the tumor was regressed.

**Patient 3**

In April 2010, a 14-year-old boy with a history of NF1 was referred for a fundus mass in his left eye. He had multiple café au lait spots. Visual acuity was 6/6 OD and 6/15 OS. Funduscopy of the left eye revealed an inferotemporal...
yellow-orange mass that measured 9 × 9 mm in diameter, with prominent blood vessels, retinal hemorrhage, and surrounding exudative retinal detachment (Figure 1G). The tumor was hyperfluorescent in early and late fluorescein angiograms (Figure 1H) and measured 4 mm in thickness with ultrasonography (Figure 1I). It was treated with double freeze-thaw cryotherapy and intravitreal bevacizumab. When vision decreased abruptly 4 months later, examination revealed total tractional retinal detachment, and the patient underwent pars plana vitrectomy 4 times elsewhere. However, the tractional retinal detachment persisted, visual acuity decreased, and retina specialists involved thought that there was no hope for restoration of vision. Recent follow-up from elsewhere revealed that the eye was blind but comfortable.

**Patient 4**

A 3-month-old white girl was diagnosed as having NF1 with café au lait spots and magnetic resonance imaging evidence of hamartomas in the caudate nucleus compatible with NF1. Ocular abnormalities were noted at that time. In July 1995, when the patient was 11 years old, she was referred to us because of sudden onset of pain, elevated IOP, and a peripheral fundus mass in her left eye. The right eye was normal. The visual acuity was 6/6 OD and 6/30 OS. The IOP was 35 mm Hg despite treatment, and anterior segment examination revealed NVI, ectropion iridis, and scattered Lisch nodules. Fundus examination of the left eye was limited because of vitreous hemorrhage, but funduscoppy disclosed an equatorial amelanotic mass that measured 10 × 9 mm in diameter (Figure 2A) and 2 mm in thickness as measured with ultrasonography. Moderately di-
lated and tortuous retinal blood vessels fed and drained the mass, and there was peripheral exudation and shallow subretinal fluid for 360°.

The RVPT was treated with cryotherapy, resulting in gradual decrease in the exudation and vitreous hemorrhage and a flat scar (Figure 2B). The NVG was managed elsewhere with topical corticosteroids, atropine, and acetazolamide, and the NVI resolved. The IOP remained difficult to control. Eventually, an Ahmed valve was inserted (Figure 2C), and the IOP returned to normal. In January 1997, the visual acuity was 6/12, and the RVPT was still controlled. In November 2012, the visual acuity was 6/9 in the affected eye, the tumor was regressed, and IOPs were normal.

Patient 5
A newborn girl was diagnosed as having NF1 with giant subcutaneous neurofibroma of the neck and face and a chiasmal glioma. She had undergone enucleation of the right eye at 5 years of age for painful NVG. Histopathologic analysis of the eye could not be performed, but a pathology report from elsewhere described disorganized intraocular contents, and no specific cause of the NVG was recognized. She was referred to us at 9 years of age. Our examination revealed an enucleation prosthesis right eye (Figure 2D) and a tracheostomy tube (Figure 2E). Visual acuity was 6/7.5 OS, and the IOP was normal. Fundus examination was limited because of diffuse vitreous hemorrhage. There was a hazy view of an equatorial superotemporal fundus mass (Figure 2F), dilated feeding artery and draining vein with adjacent subretinal blood, and yellow subretinal exudation. The RVPT was treated with cryotherapy. After 11 years, the visual acuity is still 6/7.5 OS, and the tumor was flat with no hemorrhage, and the macular area is normal.

Patient 6
A 36-year-old man was diagnosed elsewhere as having retinal detachment and a fundus mass, but he declined treatment. Examination of his right eye disclosed bare light perception, an IOP of 56 mm Hg, conjunctival hyperemia (Figure 2G), corneal edema, florid NVI with ectropion iridis, and a hazy view of a vascular mass inferonasally. The left eye had prominent Lisch nodules (Figure 2H), a small optic disc, and thin irregular retinal blood vessels. Our examination disclosed more than 200 cutaneous neurofibromas on the chest, back, arm, and face; café au lait spots on the abdomen; and axillary freckling, all consistent with NF1 (Figure 2I). Enucleation of the blind, extremely painful right eye was performed. The enucleated eye had total retinal detachment and an ill-defined peripheral retinal mass with blood vessels and glial tissue and was reported as “compatible with a vasoproliferative tumor.” In November 2012, the patient had a visual acuity of 6/6 OS in his remaining normal eye.

Discussion
The 6 patients described in this report had findings typical of NF1. In addition, each had a fundus lesion typical of RVPT. Although the relationship between these seemingly different entities may appear unusual, a review of our cases and the literature on NF1 and secondary RVPTs might clarify this relationship.

The list of conditions associated with secondary RVPTs continues to expand and includes intermediate uveitis (pars planitis), Coats disease, retinopathy of prematurity, familial exudative retinopathy, some cases of retinitis pigmentosa, long-
standing retinal detachment, and a long list of other conditions, most of which are characterized by areas of retinal ischemia, retinal neovascularization, and exudative retinopathy.\textsuperscript{5,10} Not so widely recognized is the fact that patients with NF1 can also have a number of retinal microvascular abnormalities that can cause retinal neovascularization and even NVG.\textsuperscript{27,31–35} It is most likely that in our patients with NF1, such vascular abnormalities were present and induced the sequence of vascular events that culminated in RVPTs. All 6 patients in this report had clinical evidence of NF1, and all 6 had fundus lesions consistent with RVPTs. It is clear that some patients with NF1 will develop RVPTs and that NF1 should be listed as one of the causes of secondary RVPTs.

Even though RVPT has been the subject of several clinical and histopathologic reports in recent years, some controversy still exists regarding the pathogenesis and histopathologic characteristics of this entity.\textsuperscript{2,4,6,8,11} It has long been our contention, and the belief of others, that RVPT is not a true neoplasm but rather begins as an area of retinal ischemia or retinal insult with a reactive proliferation of blood vessels.\textsuperscript{2,6,8–10} The blood vessels continue to proliferate, producing a vascular mass with retinal feeder vessels and exudation, classic findings of an RVPT. With time or after treatment, reactive gliosis supervenes, and in such eyes that have been enucleated, the histopathologic findings suggest a glial tumor.\textsuperscript{2,6,8,11,24,25} This scarred, end-stage appearance is not representative of RVPT in its early stages. When first seen clinically, RVPT is almost always red or pink with exudation and does not have the white color that typifies a glial lesion.\textsuperscript{24–25} Over time and with multiple therapies, this tumor assumes a more grayish-white fibrotic-gliotic appearance. Hence, we continue to believe that the term RVPT is appropriate because it is a retinal mass composed of a reactive proliferation of blood vessels.

Concerning treatment of RVPTs, the outcomes in our 6 patients with NF1 and in our larger series\textsuperscript{46} were variable and somewhat unpredictable. One patient in this series had cryotherapy with an excellent visual outcome (patient 2), and another (patient 3) who had cryotherapy developed proliferative vitreoretinopathy and a blind eye. However, 1 patient (patient 1) who had plaque radiotherapy had a poor visual outcome, but retinal detachment and extensive exudation were present before treatment, and a good visual outcome was not expected. However, plaque radiotherapy has been found to be effective in treatment based on a report of 30 patients with RVPTs not associated with NF1.\textsuperscript{23} In our experience with RVPTs, cryotherapy is an effective treatment in most cases.\textsuperscript{5,2–9,10}

Our series of 6 cases of RVPTs in patients with NF1 did not allow us to draw specific guidelines regarding treatment of RVPTs. Many of the described patients have had several treatments, making interpretation of the data difficult. However, our anecdotal experience allows us to provide guidelines regarding management of RVPTs in general and those associated with NF1. Periodic observation without prompt treatment appears to be acceptable for small asymptomatic lesions that have no exudation, subretinal fluid, or vitreous hemorrhage. Such lesions are occasionally discovered on routine examination and may remain stable for years, but follow-up is warranted. However, most patients already have visual symptoms when the lesion is first recognized, and they require more treatment.

For RVPTs that threaten vision and are less than 10 mm in diameter and 5 mm in thickness, double freeze-thaw cryotherapy appears to be preferable.\textsuperscript{33–30} There is also information to suggest that photodynamic therapy may provide favorable results.\textsuperscript{43–45} It is theoretically possible that intravitreal antivascular endothelial growth factors could assist in alleviating the symptoms, but results have not been highly favorable thus far. Larger tumors or those that do not respond to cryotherapy are sensitive to plaque brachytherapy.\textsuperscript{25,46} Pars plana vitrectomy and endoresection of the lesion have also been used.\textsuperscript{5,47} These same principles apply to RVPTs that occur in patients with NF1, described in this report. However, all of the RVPTs associated with NF1 in this series were aggressive and required more definitive treatment, usually with cryotherapy or plaque radiotherapy.

In conclusion, we report the clinical features, course, management, and outcomes of 6 patients with NF1 who developed RVPTs. Even though the fundus lesions are often minor and asymptomatic, RVPTs seen in patients with NF1 can cause serious complications and lead to severe visual loss and blindness. We recommend that patients with NF1 undergo periodic ophthalmic examination for detection and treatment of this tumor.
Research Original Investigation

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