Retinal Glioneuronal Hamartoma in Neurofibromatosis Type 1

Retinal tumors occasionally arise in patients with neurofibromatosis type 1 (NF1). There have been reports of astrocytic hamartomas, capillary hemangiomas, and combined hamartomas of the retina and retinal pigment epithelium (CHRRPE)—typically without pathologic confirmation of the diagnosis.\(^1\,^2\) We report a case of a child with NF1 with an unusual retinal tumor, a glioneuronal hamartoma.

Report of a Case. Our patient was born at term with buphthalmos and proptosis of her right eye, accompanied by corneal clouding and increased tearing. She was subsequently noted to have right sphenoid wing dysplasia, multiple cutaneous plexiform neuromas of the right eyelids and face (fifth nerve distribution), right hemispheric dysplastic polymicrogyria, and a seizure disorder. She was diagnosed as having NF1. The left eye was within normal limits. The patient received a Baerveldt glaucoma drainage implant at age 5.5 months. At age 8 months, a dilated fundus examination revealed temporal retinal whitening and posterior retinal hemorrhages, which were initially attributed to a retinal vein occlusion. Four months later, the patient was diagnosed clinically as having a CHRRPE (Figure 1). Enlargement of the retinal tumor was noted over the following 8 months, accompanied by the development of a vitreous hemorrhage, tractional retinal detachment, and proliferative vitreoretinopathy. At age 20 months, the right eye was enucleated owing to it being blind and painful with a fixed pupil and corneal haze. Postoperatively, she was more comfortable, no longer photophobic, and without tearing.

Gross pathologic examination revealed a buphthalmic eye with a Baerveldt glaucoma drainage implant on the superonasal sclera. On oblique sectioning, the cornea was clear but thinned. The anterior chamber was filled with a tan, milky fluid. The pupil was widely dilated and the iridocorneal angle was closed by peripheral anterior synechiae. The lens and uveal tract were unremarkable. There was a funnel-shaped retinal detachment.

Microscopic examination revealed an absent Bowman layer, which was replaced by an area of thin cellular fibrosis. A membrane composed of corneal endothelial cells was present over the surface of the severely contracted iris and ciliary body. The lens showed cataract formation with anterior calcific degeneration and posterior migration of the lens epithelium.

The uvea was thickened by a diffuse neurofibroma typical for eyes involved with NF1. The predominant spindle cells within the neurofibroma reacted positively with S-100 protein and microtubule-associated protein 2 but were negative for glial fibrillary acidic protein, CD56 (neural cell adhesion molecule—a marker of neurons, astrocytes, and nonmyelinating Schwann cells), neurofilament, and Ki-67. Scattered clusters of larger neuronal cells with comparatively more abundant cytoplasm and large round nuclei with prominent nucleoli were also present and were positive for synaptophysin, microtubule-associated protein 2, and neurofilament (Figure 2).

The detached retina was displaced anteriorly and centrally by a fibrovascular proliferation in the vitreous. A retinal tumor replaced a broad area of the inner retina.
in a diffuse but irregular manner, focally extending into the vitreous. The outer retinal layers were comparatively preserved. Scattered larger neuronal cells resembling those seen in the choroid were also present.

The abnormal spindle cells within the retina were immunoreactive for S-100 protein, glial fibrillary acidic protein, and CD56. The larger neuronal cells were positive for both synaptophysin and microtubule-associated protein 2, providing evidence of neuronal differentiation. These cells were fewer in number than in the choroid. Where the retinal architecture was relatively preserved, neuronal cells were seen subjacent to the inner nuclear layer. Scattered intact axons were identified in the nerve fiber layer on a neofilament immunohistochemical stain. No mitotic figures were identified, and a Ki-67 stain showed no proliferative activity.

The retinal pigment epithelium was unremarkable except for the presence of drusen. No retinal pigment epithelial cells were seen in the retina. There was no CHRRPE.

Comment. Clinical diagnosis of retinal tumors may be inaccurate, as pathologic evaluation may result in a different diagnosis. Initially, the dilated fundus examination revealed posterior hemorrhages and temporal retinal whitening similar in clinical appearance to a retinal vein occlusion. Four months later, the patient was diagnosed clinically as having a CHRRPE. As the tumor enlarged and penetrated the internal limiting membrane, it expanded into the vitreous, resulting in retinal detachment. Histopathologic analysis of the lesion showed a proliferation of spindle cells with scattered admixed neurons. The histogenetic origin of the spindle cells cannot be identified with certainty, but the morphology along with the coexpression of CD56 and S-100 protein in the retina suggest nonmyelinating Schwann cells.

The nomenclature in this case is difficult. We favor the term glioneuronal hamartoma given that the tumor was composed of both glial and neuronal cells. The lack of proliferative activity argues for a hamartomatous etiology over a neoplasm such as ganglioneuroma. Aggressive retinal astrocytomas have been described in patients with tuberous sclerosis complex. These tumors also stain positive for both neuronal and glial markers. Unlike our case, these astrocytomas occur in a juxtapapillary location and contain broad areas of necrosis. Where our patient has morphologically recognizable ganglion cells, these tuberous sclerosis complex–related astrocytomas contain atypical cells resembling those seen in cortical tubers and subependymal giant cell astrocytoma. Glioneuromas composed of admixed glial and neuronal cells have also been reported in patients without a diagnosis of NF1.5

To our knowledge, this is the first report of a retinal glioneuronal hamartoma in NF1. While ocular findings such as iris Lisch nodules, ciliary body and diffuse choroidal neurofibromas, optic nerve gliomas, sphenoid bone dysplasia, and eyelid plexiform neuromas have frequently been noted in patients with NF1,6-8 retinal tumors have rarely been described. Many retinal tumors have been reported in association with NF1, but most without pathologic descriptions.9-11 There are few reports detailing the histopathologic findings of large astrocytic hamartomas.12-14 Patients with NF1 can also show diffuse hyperplasia or benign neoplasia of the connective tissue, meningeal, and glial elements in the central or peripheral nervous system.15

In conclusion, our case is best classified as a glioneuronal hamartoma and suggests that the CHRRPE may be an incorrect clinical diagnosis in the absence of pathologic analysis. Absent proliferative activity argues for a hamartomatous etiology over a neoplasm such as a ganglioneuroma.

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Surgical Removal of an Atypical Macular Epiretinal Membrane in Neurofibromatosis Type 2: Clinicopathologic Correlation and Visual Outcome

M acular epiretinal membranes (ERMs) are common manifestations in children with neurofibromatosis type 2 (NF2).1 The ERMs in NF2 have been speculated to be hamartomatic in nature. Immunohistological techniques have rarely been used to characterize these ERMs.2 The following case describes the clinical and histologic characteristics of a dense ERM in a case of NF2.

Report of a Case. During a dilated fundus examination, a 2-year-old girl with confirmed NF2 and a history of esotropia and amblyopia in the left eye was noted to have a depigmented macular lesion in her left eye. The patient was undergoing patching therapy for amblyopia and was otherwise healthy. Family history was significant for neurofibromatosis affecting her father and paternal grandmother, the latter of whom had neoplasms of the brain, eyes, and auditory nerves that led to deafness, blindness, and death by age 34 years. On genetic testing, the child and her father were confirmed to have deletion of the NF2 promoter and exon 1, described as c.-8547_45 del.

Visual acuity was central, steady, and maintained in the right eye and central, steady, and unmaintained in the left eye. There was no afferent pupillary defect. Ocular versions were full with a left esotropia of 30 to 40 prism dipters. Cycloplegic refraction was +3.00 sphere OD and +2.00 sphere OS. Slitlamp examination showed normal anterior segments without cataracts or Lisich iris nodules. Fundus examination of the left eye revealed a gray, flat, macular lesion occupying an area of 2 × 2.5 disc diameters, partially obscuring underlying retinal and perifoveal vasculature (Figure 1A). A clinical diagnosis of a dense macular ERM in the left eye, possibly hamartomatic in etiology and possibly visually significant, was made. A small gray inner retinal opacity was also noted in the perifoveal region of the right eye (not shown). Magnetic resonance imaging of the brain and spine revealed no tumors.

Examination under anesthesia was performed. Spectral-domain optical coherence tomography (Biopigen, Inc) of the left eye demonstrated a thickened ERM and underlying neurosensory retina with evidence of vitreous attachment to the membrane that caused slight elevation at its edges (video, http://www.archophthalmol.com). Fluorescein angiography showed apparent absence of a foveal avascular zone due to perifoveal hypervascularity that crossed the horizontal raphe centrally (Figure 1B). The macular ERM showed no intrinsic vascularity. The patient underwent pars plana vitrectomy and ERM striping in the left eye. The membrane was noted to be densely adherent to the macula but with a definite anatomic plane between the membrane and retina. As the membrane separated, so did a continuous posterior vitreous membrane, presumably a layer of the posterior cortical vitreous. The membrane was submitted for histologic studies. Light microscopy showed a highly cellular membrane with up to 4 layers of cells in some areas. There was weak staining for glial fibrillary acidic protein (Figure 2). There was insufficient specimen for adequate evaluation of periodic acid–Schiff or S-100 protein staining. The cells were of indeterminate origin; no astrocytes were identified in the limited amount of tissue available. Visual acuity was 20/20 OD and 20/125 OS 6 months after vitrectomy and continued refractive and amblyopia management that consisted of part-time occlusion of the right eye. The retinal vasculature in the left macula remained unchanged in appearance without recurrence of ERM.

Video available online at www.archophthalmol.com

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