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Retinal astrocytoma in a young male with PTEN hamartoma tumor syndrome

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We present the novel finding of retinal astrocytoma in a 15-year-old boy with phosphatase and tensin homologue hamartoma tumor syndrome, confirmed by genetic testing.

Case Report

A 15-year-old boy with a history of phosphatase and tensin homologue (PTEN) hamartoma syndrome and type 1 myotonic dystrophy without significant ocular history was referred to pediatric ophthalmology at Rhode Island Hospital. Known systemic manifestations of his disease included autism, macrocephaly, gastrointestinal juvenile polyps, and penile freckling. PTEN hamartoma tumor syndrome (PHTS) was suspected when he passed a polyp with histology showing juvenile polyp. Sequencing and deletion/duplication analysis of the *PTEN* gene showed a heterozygous deletion of the entire gene, leading to the diagnosis. Small nucleotide polymorphism microarray was performed subsequently to determine the breakpoints and revealed a 151 Kb deletion at 10q23.2q23.31 [chr10: 89,480,314-89,631,525; GRCh37/hg19] overlapping *PTEN* and Killin (*KLLN*) genes. Given normal physical examination findings of both parents, the deletion was deemed to be de novo, and parental genetic testing was deferred. In the setting of known myotonic dystrophy, which had been diagnosed prenatally due to the family history in the mother, he was referred to pediatric ophthalmology to rule out presence of cataracts.

Ocular examination revealed 20/20 vision in both eyes, normal intraocular pressure, and no afferent pupillary defect. Anterior segment examination was unremarkable. Retinal examination of the right eye revealed blurred disk margins and a golden, mulberry-like retinal lesion approximately 1 disk diameter in size overlying the inferotemporal vasculature (Figure 1). Fundus examination of the left eye was unremarkable.

He was referred to a pediatric retina specialist. Macular ocular coherence tomography (OCT) showed moderate parafoveal thickening, with normal foveal contour in both eyes (Figure 2A). B-scan ultrasonography revealed hyperechogenicity of the lesion (Figure 2B). Given the lesion's appearance, the diagnosis of retinal astrocytoma was made. Ocular examination remained unchanged 2 years later.

Discussion

PTEN is a tumor suppressor protein in the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway, encoded by the *PTEN* gene that, when mutated, overactivates the AKT pathway, promotes cell growth, and predisposes individuals to a spectrum of abnormalities collectively referred to as PHTS. Subdivisions of this disorder include Cowden and Bannayan-Riley-Ruvalcaba syndromes. Numerous systemic abnormalities are associated with PHTS, including macrocephaly, autism and developmental delay, benign and malignant tumors of the skin, thyroid, breast/endometrium, and gastrointestinal tract, penile freckling, and arteriovenous malformations/hemangiomas.[1] Identification of a heterozygous mutation of the *PTEN* gene establishes the diagnosis.[1]

Reported ophthalmic manifestations include: amblyopia, strabismus, myopia, downward-slanting palpebral fissures, corneal nerve hypertrophy, prominent Schwalbe lines, cataract, pseudopapilledema, angioid streaks, and retinal hemangioma. These manifestations are not specifically found to demonstrate a genetic subcategory within PHTS but rather were isolated findings among PHTS patients. This demonstrates the variety of pathology that can

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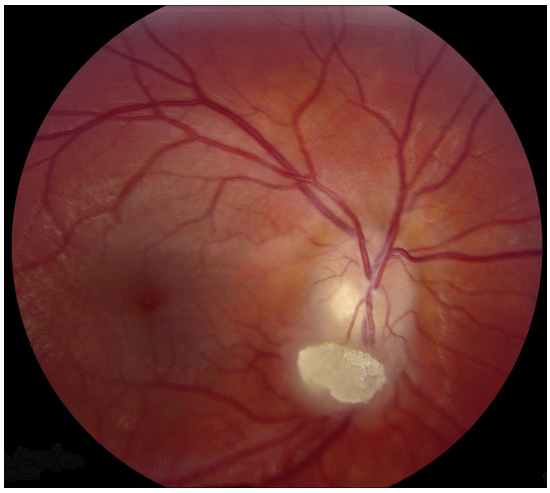

FIG 1. Fundus photograph, right eye. Magnified view showing details of astrocytoma with associated optic disk edema.

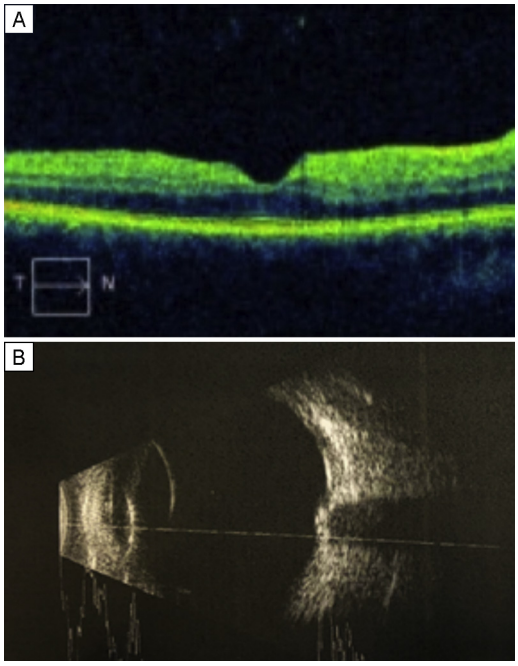

FIG 2. A, Optical coherence tomography of the affected right macula showing parafoveal thickening. B, B-scan of the right eye showing a sessile, hyperechogenic lesion inferior to the optic nerve, with associated high A spike.

manifest within this disorder. Given the small number of cases reported, it is unclear whether specific ocular abnormalities are associated with the various subcategories within PHTS. Although classically associated with a systemic syndrome, retinal astrocytomas can occur in isolation. Retinal astrocytoma has not previously been described in association with PHTS.[1-3]

Heterozygous mutations in other genes in the PI3K/PTEN/AKT/TSC/mTORC1-signaling pathway are also known to cause segmental overgrowth, hamartomas, and malignant tumors. This includes tuberous sclerosis (TS) caused by a heterozygous mutation in the *TSC1* or *TSC2* gene. This suggests the possibility of shared clinical manifestations of hamartomas (ie, retinal astrocytoma) between PHTS and TS patients. Retinal astrocytoma is a well-known ocular manifestation of TS.[3] The presence of retinal astrocytoma in our patient may function as evidence that PHTS and TS can be linked through a common pathway.[1,3-5]

The degree of morbidity from retinal astrocytic hamartoma depends on lesion size, location, associated exudation, and presence of retinal detachment and/or neovascular glaucoma; the presence of the retinal hamartoma may not necessarily cause ocular morbidity. Generally, patients who have one or more retinal astrocytomas tend to have no visual symptoms, unless the tumor involves the macula. If the lesion is associated with an exudative retinal detachment, the macula may also be involved, thus affecting visual acuity. Treatment also depends on the characteristics of the lesion. More peripheral and small lesions may be followed periodically, whereas those concerning for growth may warrant treatments such as laser photocoagulation or cryotherapy.[1,3-6]

Various ocular imaging studies are also useful during assessment of retinal glial lesions. Shields et al describe the distinctive characteristics between astrocytic hamartomas and retinal astrocytic proliferation when imaged with spectral domain OCT. Characteristics of retinal astrocytomas include origin within the nerve fiber layer with moth-eaten calcific nodules. This differs from retinal astrocytic proliferation, which originates from deeper retinal layers, including the retinal pigmented epithelium. Differences in appearance on both fluorescein angiography and sonography may also be of benefit if the diagnosis remains questionable.[6]

Considering the numerous ocular abnormalities that occur with PHTS, we suggest patients diagnosed with PHTS undergo complete baseline ophthalmic examination to reduce ocular morbidity secondary to undiagnosed findings. Lifelong, multidisciplinary care is also essential, given their increased risk for systemic malignancy and developmental comorbidities.

Literature Search

PubMed was searched without date restriction using the following terms: *PTEN*, *PTEN hamartoma syndrome* AND *tuberous sclerosis*, *ophthalmic manifestations* AND *PTEN*.

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