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Giant Cell Astrocytoma of the Retina in One Month Old Infant

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Abstract
A 4-week-old boy with subependymal lesions consistent with tuberous sclerosis was evaluated for a large intraocular tumor in the left eye. The eye was enucleated and examination showed a retinal giant cell astrocytoma composed of giant, round cells and spindle-shaped cells, with associated aggregates of mononuclear inflammatory cells.

Introduction
Tuberous sclerosis was first described in 1880 by the French neurologist Désiré-Magloire Bourneville when he described the brain lesions found postmortem in a 15-year-old who suffered seizures since infancy. Tuberous sclerosis is a congenital neurocutaneous syndrome characterized by widespread hamartomas in the skin, brain, eye and visceral organs. In 1998, the National Institutes of Health standardized the diagnostic criteria for tuberous sclerosis complex (TSC). The retinal tumors associated with TSC consist mostly of astrocytes, but a few cases of larger tumors, so-called giant cell astrocytomas, with more aggressive behavior, have been described in patients with TSC ranging in age 1 to 14 years. We report a case of a one-month old male with a giant cell astrocytoma of the retina without calcification or necrosis that have been associated in all previously described cases.

History
This one-month old twin male was found to have a left intraocular tumor on fundus examination. The prenatal and family histories were noncontributory. Examination showed several flat, depigmented skin lesions. Ophthalmic examination revealed normal anterior segments and a large, white tumor involving the macula and temporal half of the fundus in the left eye, with associated subretinal fluid (Figure 1A). The right fundus was normal. B-scan ultrasonography showed a left intraocular tumor, with no calcification (Figure 1B). An MRI and a CT showed subependymal lesions consistent with tuberous sclerosis. Enucleation of the left eye was performed.

Pathologic Findings
A 10 × 9mm white tumor was present 2mm temporal to the optic nerve head (Figure 2A). Microscopic examination showed a temporal exophytic tumor arising in the macula. The tumor was composed of giant, round cells with abundant, glassy, eosinophilic cytoplasm, displaced nuclei, and prominent nucleoli (Figure 2B). It also contained spindle-shaped cells with fusiform nuclei and prominent nucleoli (Figure 2C). There were no mitotic figures noted. The tumor contained vascular channels and scattered aggregates of mononuclear inflammatory cells. There were no areas of necrosis or calciospherites. A separate, 0.5 ×
0.5 mm, focal proliferation of spindle shaped cells was present in the nerve fiber layer of the nasal retina. The central retinal artery and vein were dilated. Immunohistochemical stains were positive for neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), S100 protein (S100) in both cell types (Figure 2D,E). CD3 and CD68 staining were positive in the mononuclear inflammatory cells. Ultrastructurally, the giant tumor cells demonstrated abundant smooth and rough endoplasmic reticulum while spindle-shaped tumor cells revealed collections of complex interdigitations on electron microscopy (Figure 3A–D). The diagnosis was giant cell astrocytoma of the retina.

**Discussion**

TSC is caused by loss-of-function in one of two genes, TSC1 located on human chromosome 9q34 or TSC2, located on 16p13. The proteins encoded by TSC1 and TSC2 are called “hamartin” and “tuberin”, respectively. Close phenotypic similarities between the features associated with TSC1 and TSC2 mutations suggest that TSC is a disease characterized by locus heterogeneity.4–6 Hamartin and tuberin, the cellular proteins encoded by TSC1 and TSC2, are now known to interact to suppress the P13K signal transduction pathway. TSC1 and TSC2 likely represent tumor suppressor genes.

The proteins hamartin and tuberin bind to one another inside the cytoplasm to form a molecular complex that serves as a gate to control cell growth and survival signals conveyed through the P13K signal transduction pathway. Hamartin and tuberin, by regulating mTOR, integrate two important signals governing cell growth: growth factors and nutrients. Additionally, experiments with Tsc2+/− and Pten+/− mice have shown that benign tumors arise in Tsc2+/− mice and more aggressive tumors arise in Tsc2+/− Pten+/− mice, thus suggesting that loss of Tsc2 creates an inhibitor feedback loop, in which mTOR or one of its downstream effectors suppresses Akt, which is overcome with loss of Pten.1 This may explain why malignant tumors rarely occur in patients with TSC.

The benign brain hamartomas that occur in TSC include 1) cortical tubers, consisting of fascicles of neurons, astrocytes, and giant cells; 2) subependymal nodule (SEN), which resembles cortical tuber but has a higher cellular packing density; and 3) subependymal giant cell astrocytoma (SEGA), which contains cells with more prominent nuclei and abundant, glassy, eosinophilic cytoplasm. Immunohistochemical and ultrastructural studies have indicated that these giant cells arise from mixed glioneuronal precursors.

As described in the article by Shields JA et al7, the clinicopathologic features of retinal astrocytomas include a sessile or slightly elevated lesion that may be unilateral, bilateral, solitary, multifocal, transparent, opaque, noncalcified or calcified.8–9 In their study of four enucleated eyes from patients with TSC and aggressive retinal giant cell astrocytoma7, the patients ranged in age from 1 to 14 years. One eye had a solitary tumor and three had multiple tumors, with the large, aggressive tumors located posteriorly and the smaller, non-progressive tumors located anteriorly, similar to the current case. The aggressive tumors exhibited 50% to 95% necrosis, and all contained calciospherites.7 All eyes exhibited neovascularization of the iris (NVI).7 Interestingly, the tumor in the current case did not contain calciospherites, although there were foci of CD3+ and CD68+ inflammatory cells present. These represent T cells and macrophages, respectively. The age of the current patient was one month, and it is possible that the inflammatory infiltrates are precursors of areas of necrosis where dystrophic calcification in the form of calciospherites will eventually form. Additionally, NVI may have eventually developed in the current case. Therefore, the pathologic findings in the current case are consistent with early findings in aggressive retinal giant cell astrocytoma in a patient with TSC. Unlike Shields and coworkers7, the giant cells in the current case immunostained for both neuronal (NSE, S-100) and glial (GFAP)
markers, consistent with a neuronal/glial precursor cell of origin. There were also no hamartomas of the iris or ciliary body in the current case, as previously described.10

There have been eight reported cases of eyes enucleated with enlarging retinal astrocytomas in patients with evidence of TSC.7,11 All except one of these patients were 14 years old or younger at the time of enucleation. The one exception was a 27-year-old woman.11 Critical review of that case shows that the retinal tumor did not have the aggressive histopathologic features as outlined by Shields and coworkers7, thus leading to the speculation that the patient had a form furste or more benign clinical variant than those patients with aggressive giant cell astrocytomas.7 Conversely, there have been twelve reports describing the pathologic findings in patients without apparent TSC whose eyes were enucleated for enlarging retinal astrocytomas.7,12 Five of the cases occurred in children age 9 years or younger, including two in children age 1 year or less.12,13 It is possible that TSC was diagnosed at a later age in these young patients.

These findings suggest a two-hit genetic mechanism, with a retinal stromal cell origin in retinal giant cell astrocytoma, similar to the stromal cell origin of hemangioblastoma in von Hippel Lindau disease.14 In the latter case, hypoxia inducible factor (HIF) upregulated by tumor cells leads to angiogenesis in the tumor. The vascular channels leak serum, and lipid is imbibed by the tumor cells, hence yielding foamy tumor stromal cells.14 These cells have a mixed neuronal/glial phenotype, similar to the retinal giant cells in giant cell astrocytoma. Ultrastructural studies of retinal giant cell astrocytoma show prominent rough endoplasmic reticulum and intracytoplasmic lipid droplets.12 Other ultrastructural features leading to a hypothetical Müller cell origin have been elegantly described by Jakobiec and co-workers.12

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**References**

Figure 1.
A. The left eye contains a large tumor temporal to the optic nerve. There is associated subretinal fluid. B. B-scan ultrasonography of the left eye discloses a solid, intraocular tumor (7.8 × 11.8 × 11 mm) without calcospherites.
Figure 2.
A. A large white mass is present temporal to the optic nerve. B. The mass is composed of giant round cells with displaced nuclei and prominent nucleoli C. spindle-shaped cells with
fusiform nuclei and prominent nucleoli are also present. D. The spindle-shaped cells stained positively (arrows) for neuron-specific enolase (NSE). E. The giant cells stained positively (arrows) for glial fibrillary acidic protein (GFAP). (B. and C., hematoxylin and eosin, D. NSE, E. GFAP 100X)
Figure 3.