Hamartomas of the Iris and Ciliary Epithelium in Tuberous Sclerosis Complex

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Astrocytic hamartomas of the retina are the principal ocular manifestation of tuberous sclerosis complex. Iris abnormalities are rare in tuberous sclerosis complex and include focal areas of stromal depigmentation and atypical colobomata. We describe 2 patients who were found on histopathological examination to have lesions consistent with hamartomas of the iris pigment epithelium and ciliary body epithelium. Iris abnormalities, including pupillary irregularities, were noted on clinical examination prior to the development of iris neovascularization in both patients. These observations suggest that iris abnormalities, including atypical colobomas, may be caused by hamartomas of the iris pigment epithelium and ciliary epithelium in some patients with tuberous sclerosis complex. To our knowledge, hamartomas of tissues derived from the anterior part of the neuroectodermal optic cup have not been reported in cases of tuberous sclerosis complex.

REPORT OF CASES

CASE 1

A Jordanian boy was noted to have an abnormal right pupil at age 2 months. He was born by cesarean delivery at 36 weeks owing to breech presentation, weighed 3 kg, and was active at birth. Respiratory distress syndrome complicated by spontaneous pneumothorax that developed 1 day postpartum. Findings from examination with anesthesia at age 3 months disclosed no fundus abnormalities. At that time, the right eye was noted to be “weak” and drifting. After the child developed seizures at age 1.5 years, magnetic resonance imaging studies revealed occipital infarctions and multiple small nodules consistent with heterotopias in the wall of the lateral ventricles. Ultrasonography showed mild enlargement of the kidneys and renal cysts. No unequivocal skin lesions were noted. The family history was negative for cancer, ocular disease, retinoblastoma, and seizures. He had 3 healthy sisters.

At age 37 months, the patient developed a red irritated right eye and was referred to the Oncology Service at Wills Eye Hospital, Philadelphia, Pa, for a second opinion regarding diagnosis and management. The referring physician thought that the child had TSC. Findings from examination disclosed an irritated right eye with hyperemia that did not fix on or follow objects. There was florid iris neovascularization, and the intraocular pressure was 43
Ophthalmoscopy disclosed a total retinal detachment and a yellow-white mass that overhung the optic disc. The tumor was estimated to be about 12.0 mm in basal diameter and 8.8 mm in thickness. Two smaller astrocytic hamartomas were found in the left eye. They were located nasally at the disc and inferonasally at the equator and measured 1.75 × 1.50 × 0.25 mm and 3.0 × 1.5 × 0.5 mm, respectively. After discussion with the family, the blind, painful, glaucomatous right eye was enucleated and fixed in formaldehyde. The preoperative diagnosis was large aggressive, astrocytic hamartoma in association with TSC.

OPHTHALMIC PATHOLOGY

The 22-mm-diameter right globe was opened obliquely to include a 7-mm-diameter transillumination shadow in the inferonasal quadrant. Ectropion iridis and angle closure were noted grossly. Nasally, a smooth, salmon-colored nodule that measured about 8 × 7 mm arose from the posterior part of the totally detached retina, filling the subretinal space and locally abutting the retinal pigment epithelium. Serial sections were prepared.

Findings from histopathologic examination disclosed an extensively necrotic, multilobular retinal tumor consistent with a giant cell astrocytoma. Anterior segment findings included a florid fibrovascular membrane that flattened the anterior iridic surface and produced ectropion of the IPE and sphincter muscle (Figure 1). The angle was occluded by peripheral anterior synchiae. One iris leaflet was otherwise normal. The other leaflet was shorter and had striking abnormalities of the IPE, characterized by a multilayer of variably pigmented cells whose abundant cytoplasm was relatively nonpigmented compared with normal IPE (Figure 1 and Figure 2). Some of the more heavily pigmented cells contained large round melanin granules. The placoid cellular hamartoma was 5 or 6 cells in thickness. The neighboring iris stroma contained a few islands of similar cells. Much of the hamartomatous process appeared to arise from the anterior layer of the IPE and was lined posteriorly by a mildly attenuated layer of pigmented epithelium. In some sections, the hamartomatous plaque was confined to the pupillary part of the affected iris leaflet where it had replaced most of the sphincter muscle. Only a minute focus of anteriorly displaced muscular tissue was observed near the pupillary margin. In other areas, the cellular plaque involved the entire posterior aspect of the iris and was continuous with an identical process that involved the CBE, affecting both layers in some places.

A battery of special immunohistochemical stains was performed (Figure 3). The placoid IPE hamartoma was intensely immunoreactive for vimentin (+4) and smooth-muscle actin (+3) and moderately immunoreactive for neuron-specific enolase (+2). Findings for glial fibrillary acidic protein and S100 protein were trace positive; for desmin, muscle-specific actin, and cytokeratin marker CAM 5.2, negative to trace positive. The normal iris sphincter muscle was intensely immunoreactive for smooth-muscle actin and desmin (+4) and moder-
ately immunoreactive for muscle-specific actin (+2). The nonpigmented ciliary epithelium stained moderately intensely for vimentin, neuron-specific enolase, and cytokeratin CAM 5.2 (+2 to +3) and was trace positive for S100 protein. Diagnoses included TSC by history; aggressive, extensively necrotic astrocytic hamartoma/astrocytoma of the posterior retina; total retinal detachment; iris neovascularization and secondary closed-angle glaucoma; and findings consistent with a hamartoma of the IPE and CBE.

CASE 2

The right eye of a 2 1/2-year-old Hispanic boy with known TSC was enucleated when it developed a total retinal detachment and painful neovascular glaucoma. The patient had been followed up by one of us (M.G.W.) since age 6 months when a giant retinal hamartoma was seen measuring 3 to 4 disc diameters and obscuring the optic disc. The involved right eye was mildly “microphthalmic” and had an atypical inferior iris coloboma. The coloboma was not photographed but was described as an area of stromal thinning, increased pigmentation, and displacement of the pupillary margin toward the inferior limbus. The eye was fixed in neutral-buffered formaldehyde.

OPHTHALMIC PATHOLOGY

Broad peripheral anterior synechiae occluded the anterior chamber angle of the soft, 21-mm-diameter right eye. Extensive ectropion iridis rimmed the 8-mm diameter pupil. The eye was opened vertically. Macroscopically, the inferior iris leaflet was shorter. The retina was totally detached in a funnel configuration. Posteriorly, the subretinal space contained a bilobed, cream-colored tumor that was contiguous with the retina. The tumor was 14 mm in largest diameter and 7 mm in elevation.

Findings from microscopic examination disclosed a giant cell astrocytoma of the retina that was approximately 80% necrotic. Anteriorly, a florid fibrovascular membrane flattened the heavily pigmented iris, and the angle was closed by broad peripheral anterior synechiae. In the region of the inferior coloboma, a multilayered plaque of large, unusual, relatively amelanotic pigment epithelial cells appeared to arise from the anterior layer of the IPE. The plaque and its constituent cells appeared remarkably similar to those found in case 1. The adjacent ciliary processes were indistinct, and the ciliary epithelium was abnormal, also composed of variably pigmented cells with abundant cytoplasm. An area of abrupt transition between the normal and abnormal ciliary epithelium was observed on the pars plana (Figure 4). In the affected area, both inner and outer layers were involved. On the inner surface of the ciliary body, the abnormal pigmented epithelium was reduplicated and formed cords and tubules (Figure 5). The hamartomatous process also involved the nonpigmented ciliary epithelium, which formed cysts and cellular plaques.

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Figure 3. Case 1. Immunohistochemistry, iris hamartoma. Posterior placoid part and intrastromal islands of hamartoma show intense immunoreactivity for (A) vimentin (VIM) and (B) smooth-muscle actin (SMA) and (C) moderately intense staining for neuron-specific enolase (NSE). Findings for (D) glial fibrillary acidic protein (GFAP) are trace positive (peroxidase-antiperoxidase, original magnification ×50).
crotic astrocytic hamartoma/astrocytoma of the posterior retina; total retinal detachment; iris neovascularization and secondary closed-angle glaucoma; and findings consistent with a hamartoma of the IPE and CBE.

**COMMENT**

Tuberous sclerosis complex is a heritable disorder characterized by the development of benign tumors (hamartias and hamartomas) in multiple organ systems, including the brain, skin, and eye. One of Van der Hoeve’s 3 original phakomatoses, TSC now is thought to be caused by mutations in 1 of 2 tumor suppressor genes. About 60% of cases are sporadic. Although familial cases seem to be inherited in an autosomal dominant fashion, the disorder is thought to be recessive at the molecular level. Penetrance is high (approximately 95%) if careful clinical and radiological evaluation is performed to exclude formes frustes. About half of all families with TSC show linkage to chromosome 9q34, and about half to chromosome 16p13. The patchy distribution and focal nature of the hamartomas suggest that they might result from inactivation of a tumor suppressor gene by a “2-hit” process analogous to that operative in the molecular pathogenesis of retinoblastoma. Indeed, molecular genetic analysis of hamartomas from patients with TSC has shown loss of heterozygosity for the regions of chromosomes 9 and 16 known to harbor the TSC genes, consistent with the occurrence of somatic second-hit mutations. Constitutional deletions consistent with first-hit mutations have also been identified in the appropriate part of chromosome 16 (16p13.3). This led to the sequencing of the TSC2 gene on chromosome 16. Tuberin, the predicted protein product of the TSC2 gene, has an area of sequence homology with the GTPase activating protein rap1GAP, suggesting a possible mechanism for its role in regulating cellular growth. The protein product of the 9q34 TSC gene is called hamartin.

Retinal lesions, which usually are called astrocytic hamartomas, are the characteristic ocular manifestation of TSC. Astrocytic hamartomas are found in 50% or more of patients with TSC and occur bilaterally in about half. Rare iris abnormalities have been reported in patients with TSC and include focal areas of stromal depigmentation and atypical colobomata. The areas of stromal depigmentation have not been examined histopathologically but are thought to be analogous to the hypomelanotic cutaneous “ash leaf” spots, which are early clinical manifestations of TSC. They are reported not to show increased transillumination.

Both cases reported here were noted to have iris abnormalities, including pupillary irregularities on clinical examination prior to the development of iris neovascularization. Case 1 was said to have had an abnormal pupil at age 2 months, but specific information about the nature or location of the iris abnormalities is unavailable. Case 2 had an atypical coloboma in the inferior iris. The iris coloboma in a patient described by Welge-Luessen and Latta also was located inferiorly. Another eye, which had clinically apparent iris abnormalities and a large retinal astrocytoma, was presented by Lloyd at the 1999 meeting of the Verhoeff-Zimmerman Society.
Lloyd’s case contained a focal hamartoma of the IPE that had identical histopathologic features.

The 2 cases reported here had lesions of the IPE and CBE that are consistent with hamartomas. Abnormalities of the iris and pupil were evident on clinical examination in both patients. In case 2, the location of the iridociliary hamartoma corresponded to the location of an atypical coloboma that was noted clinically in the inferior iris. The retinal hamartomas of TSC affect tissue derived from the inner layer of the embryonic optic cup. In contrast, the iridociliary hamartomas described here appear to affect tissues derived from its outer layer or both the inner and outer layers. The hamartoma of the pars plana with the abrupt margin shown in Figure 4 is especially interesting because both contiguous inner and outer epithelial layers appear to be affected. These observations suggest that the formation of the hamartoma may have occurred after the inner and outer layers of the optic cup had fused to form the ciliary epithelium.

The demonstration of positive immunoreactivity for smooth-muscle actin in the iridal part of the hamartoma in case 1 (Figure 3) is not particularly unexpected because the hamartoma appeared to primarily affect the anterior layer of the IPE. The dilator muscle of the iris is comprised of cellular processes, with smooth-muscle differentiation arising from the anterior layer of the IPE.

The histopathologic findings reported here indicate that hamartomas of the IPE and ciliary epithelium occur in some patients with TSC and may be the cause of clinically apparent iris abnormalities. To our knowledge, hamartomas of tissues derived from the anterior part of the neuroectodermal optic cup have not been described previously in patients with TSC.

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