Idiopathic Reactive Hyperplasia of the Retinal Pigment Epithelium

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Objectives: To present and discuss 2 patients with acquired peripapillary pigmented lesions.

Methods: We reviewed the patients’ clinical records and histopathologic findings.

Results: The first patient was diagnosed with a pigmented papillary lesion that was followed up for 38 years. The second patient was a child with neurofibromatosis type 1 who developed a pigmented peripapillary lesion following excision of an optic nerve glioma. Histologic findings in both cases demonstrated hyperplasia of the retinal pigment epithelium with associated findings.

Conclusions: The lesions presented an idiopathic reactive hyperplasia of the retinal pigment epithelium. The clinical and histopathologic findings resemble findings reported with the combined hamartoma. We suggest that such lesions are reactive in nature, rather than hamartomatous.

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PERIPAPILLARY pigmented lesions that involve the optic nerve and adjacent retina may represent choroidal melanoma, choroidal nevus, melanocytoma, congenital hypertrophy of the retinal pigment epithelium, adenomatous lesions, idiopathic reactive hyperplasia of the retinal pigment epithelium, or combined hamartoma. Two cases of an acquired pigmented peripapillary lesion with histopathologic findings are reported and discussed.

CASE 1

A 53-year-old white, asymptomatic woman underwent an ocular examination and refraction in 1959 after breaking her eyeglasses. Findings from previous ocular examinations were normal. She had no history of ocular trauma. Visual acuity was 20/15 OU and intraocular pressure was 24 mm Hg OD, and 26 mm Hg OS. Ophthalmoscopic examination of the left eye revealed a stellate-shaped, pigmented lesion on the optic disc with an adjacent flame-shaped, peripapillary hemorrhage. The lesion was photographed in 1963 (Figure 1). The patient was treated for open-angle glaucoma in both eyes. By 1971, the pigmented lesion of the left optic nerve had enlarged slightly (Figure 2). Visual acuity was 20/40 OU. In 1982, the patient developed a central retinal vein occlusion of the right eye, and the visual acuity was 20/200 OD and 20/70 OS. Laser trabeculoplasty was performed on both eyes in 1985. Visual acuity declined to 20/400 OD and 20/200 OS in 1986. Cataract surgery was performed in both eyes in 1986, with only a modest improvement in visual acuity. The pigmented lesion of the left eye continued to enlarge in a stellate pattern with development of an overlying whitish fibrotic material (Figure 3, A). Fluorescein angiography was performed in 1987 (Figure 3, B and C). Fundus photography in 1994 demonstrated slight enlargement of the pigmented lesion with an adjacent intraretinal hemorrhage. Visual acuity declined to no light perception; the eye became painful and was enucleated in 1997.

PATHOLOGIC FINDINGS

The gross specimen contained a stellate-shaped, pigmented lesion involving the optic nerve head and adjacent retina. Microscopic examination of this area (Figure 4) demonstrated pigmented cells organized in isolated cords and rosettes extending into the optic disc and into the optic nerve...
beyond the level of the lamina cribrosa. Calcification and osteoid formation were present within the optic nerve. There was marked hyperplasia of the retinal pigment epithelium (RPE) adjacent to the disc forming a layer of fibrous metaplasia overlying the neural retina. The retina surrounding the disc and underlying the layer of fibrous metaplasia was disorganized and gliotic. A profound loss of ganglion cells in the periphery and cystoid change were seen. Numerous thick-walled vessels were present in the superficial optic disc (Figure 5). Other areas of dense fibrous metaplasia overlying the retina with gliosis and disorganization occurred adjacent to the disc (Figure 6). Areas of periodic acid–Schiff–positive basement membrane proliferation were adjacent to the areas of RPE proliferation. There was marked thickening of the walls of the short posterior ciliary arteries (Figure 7).

CASE 2

In March 1991, a 2-year-old boy was referred to the Children’s Hospital of Philadelphia, Philadelphia, Pa, with a diagnosis of neurofibromatosis 1 and a left optic nerve glioma. His visual acuity was 20/100 OD and 20/150 OS. The left optic disc was swollen. Magnetic resonance imaging showed a fusiform optic nerve tumor that enhanced with gadolinium and extended from the globe through the canal, but did not reach the optic chiasm.
In September 1991, visual acuity of the left eye had decreased, and a left optic nerve decompression was performed in an attempt to preserve vision. By May 1992, the proptosis increased. Magnetic resonance imaging showed that the tumor had increased in size and extended to the chiasm, with some suggestion that the right optic nerve was enlarging. Because of poor vision and substantial exophthalmos, the optic nerve tumor was excised from the globe to the chiasm using a transfrontal approach. Postoperatively, the patient developed a dural leak of cerebrospinal fluid into the periorbit, with increasing proptosis, corneal ulceration, and enucleation.

**PATHOLOGIC FINDINGS**

Gross examination of the specimens showed a normalized globe and an enlarged optic nerve. Microscopic examination of the optic nerve showed a pilocytic astrocytoma with a surrounding cuff of arachnoid gliomatosis. The gross view of the opened eye showed a retinal detachment and a tan mass lesion anterior to the optic disc (Figure 8). The retina was detached, thrown into folds, and drawn into a funnel by a band of proliferative tissue. In the area of the retina adjacent to the optic nerve and extending into the disc and optic nerve, proliferative RPE was arranged in cords and acinarlike structures (Figure 9). Surrounding these structures, a periodic acid–Schiff stain showed basement membrane material. Pigment epithelial cell proliferation also extended forward into an area of glial proliferation ante-
rior to the disc. The optic canal was otherwise completely obliterated by fibrous connective tissue.

A variety of stimuli can produce proliferation of the RPE. In case 1, the underlying cause of the RPE proliferation is unknown. The lesion enlarged over the 38 years of observation, and the pattern of growth followed the retinal vasculature. The overlying gliosis seemed to follow the migration of pigmented cells as a reactive phenomenon. The periodic intraretinal hemorrhages may have been due to either RPE hyperplasia or glaucoma.

In case 2, the patient had neurofibromatosis type 1 and developed a peripapillary mass lesion following resection of an optic nerve glioma. The only prior ophthalmoscopic finding in the eye was optic disc edema. The RPE proliferation could have been caused by a secondary effect of the tumor, the surgical trauma during excision of the glioma, ischemia produced by amputation of the nerve and surrounding blood supply, or other unknown stimuli. In a similar case, Hrisomalos et al\textsuperscript{1} presented clinical photographs of a "pseudo" combined hamartoma following papilledema in an 11-year-old boy with the following clinical description: "...a mildly elevated grayish lesion extending from the optic disc ... retinal vascular tortuosity and prominent epiretinal membrane formation over the surface of the lesion ... all of the characteristics of a combined hamartoma. ..." It is possible that swelling of the optic disc caused by various stimuli can stimulate RPE hyperplasia.

Histologically, the lesions of these 2 patients resemble a combined hamartoma of the retina and RPE. Cardell and Starbuck\textsuperscript{2} first used the term "hamartoma" and indicated that the histologic changes seen were "clearly a hamartoma" based on structural grounds. Histologically, the juxtapapillary lesion consisted of a mixture of glia, RPE, and capillaries, with some hyalinization and calcification of the stroma. In 1969, Vogel et al\textsuperscript{3} described the histopathologic findings of a similar lesion that consisted of marked disorganization of the optic nerve head and retina. They noted severe degeneration, gliosis, and proliferation of RPE into and through the retina with the formation of cords, strands, and sheets of pigment epithelium. In 1973, Gass\textsuperscript{4} proposed the term "hamartoma of the pigment epithelium and retina" and reported 7 cases without histologic information, indicating that the hamartomatous malformation involved the pigment epithelium, retina, retinal blood vessels, and overlying vitreous. In a later classification of focal congenital anomalies of the RPE, Gass\textsuperscript{5} described combined RPE and retinal hamartomas as sessile, pigmented, dysplastic tumors that involve the sensory retina and vitreoretinal interface, as well as the RPE. In 1979, Laqua and Wessing\textsuperscript{6} described 6 patients with "congenital retinopigment epithelial malformation, previously described as hamartoma." Histopathologic findings were provided in 1 case that demonstrated RPE hyperpigmentation and hypertrophy with malformation and thickening of the overlying sensory retina. They concluded that such lesions only simulated tumors or hamartomas.

Two large series in the literature have been published that discuss the entity commonly referred to as "combined hamartoma." The first was presented at the 1983 American Academy of Ophthalmology and later published in 1984 by Schachat et al\textsuperscript{7} The members of the Macula Society contributed 60 cases that met enrollment criteria, including "...an endophytic tumor at the level of the sensory retina and RPE, which was variably pigmented, contained abnormal-appearing retinal blood vessels, and which was associated with some degree of traction at the vitreoretinal interface, producing clinically obvious traction on the sensory retina." They found that all lesions were solitary and
unilateral, and most presented with painless loss of vision. Gass, in an accompanying editorial, concluded that the lesions were hamartomas. He based the conclusion on the association of these lesions with incontinuity pigmenti, bilateral colobomas of the optic disc, congenital pit of the optic nerve head, sex-linked juvenile retinoschisis, multiple cleft-au-lait spots, small facial hemangiomas, and, in 1 patient, the presence of 2 combined hamartomas in 1 eye. Other reports have strengthened the association with neurofibromatosis types 1 and 2.9-18 Additionally, Font et al19 summarized the condition of 54 eyes of 53 patients in a series of combined hamartomas and found that 76% were juxtapapillary and that some lesions demonstrated growth.

It is difficult to determine if the origin of a lesion is developmental in nature, consistent with a hamartoma, or is simply a reactive hyperplasia reaction of the RPE to an unknown stimulus. Case 1 suggests that idiopathic reactive hyperplasia of the RPE can look both clinically and histologically similar to lesions described as combined hamartomas. Histopathologic findings of the second case seem similar to cases of combined hamartoma. This lesion was acquired and represents an accelerated proliferation of the RPE in response to a perioperative or tumor-related stimulus. The clinical histories and histopathologic findings of our patients suggest that idiopathic reactive hyperplasia of the RPE may be responsible for such lesions and it is still unclear whether similar lesions represent true hamartomas.

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From the Archives of the Archives

A look at the past . . .

SCHWEIGER reports on 450 cases of retinal hemorrhage collected from the histories of 45,000 patients seen by his father in private practice. In an exhaustive and comprehensive way, everything is said which can be said on the subject. Some figures may be noticed. Pure retinal hemorrhage was found in 300 patients, i.e., 6.6 to the thousand; the remainder showing inflammatory symptoms. As regards the well-known white patches, he states that in 300 eyes with hemorrhages, these patches were found 100 times. One fifth of the patients suffered from diabetes, 1/10 from albuminuria, and 1/20 from both affections at once. The number of diabetic patients with hemorrhages, but without retinitis, was three times as large as of those with both hemorrhages and retinitis. In nephritic cases, the number of patients with bilateral albuminuric retinitis was in the ratio of 8:1 as regards those with hemorrhagic retinitis. In 10 cases the well-known disc-shaped hemorrhage at the macula was noted. In favorable cases, complete resorption took place in from four to six months.