Adenocarcinoma Arising From Congenital Hypertrophy of Retinal Pigment Epithelium

Jerry A. Shields, MD; Carol L. Shields, MD; Ralph C. Eagle, Jr, MD; Arun D. Singh, MD

Congenital hypertrophy of the retinal pigment epithelium (CHRPE), traditionally regarded as a benign stationary condition, has recently been shown in 5 cases to give rise to an elevated, solid tumor. However, the histopathologic nature of the tumor that arises from CHRPE has not been previously determined. A 65-year-old woman developed a progressively enlarging peripheral fundus tumor that arose from a focus of classic CHRPE. The tumor produced a localized exudative retinal detachment, cystoid macular edema, and surface-wrinkling retinopathy. The mass was removed by local resection, and histopathologic examination revealed a low-grade adenocarcinoma of the retinal pigment epithelium, apparently arising from CHRPE. Although CHRPE is usually a benign nonprogressive lesion, it can give rise to a malignant tumor. Congenital hypertrophy of the retinal pigment epithelium should be observed periodically for development of a neoplasm.


REPORT OF A CASE

In January 1997, a 63-year-old woman with a 2-year history of slightly blurred vision in the right eye was found to have an ipsilateral fundus mass. She was referred to the Oncology Service at Wills Eye Hospital for management of a possible choroidal melanoma. She had undergone mastectomy for breast cancer 14 years earlier, with no local or systemic recurrence.

Her unaffected left eye had a visual acuity of 20/20 and was entirely normal. Her right eye had a visual acuity of 20/40 and normal intraocular pressure. Slitlamp biomicroscopy demonstrated a small, central posterior subcapsular cataract, and trace flare and trace cells in the anterior vitreous cavity. Fundus examination of the right eye disclosed a 12 × 10-mm, flat area of black pigmentation located between the ora serrata and the equator superiorly.
intrinsic pigmentation, and contain fine corkscrew vessels. Sparse vitreous cells were evident above the mass, and surface-wrinkling retinopathy with mild cystoid macular edema accounted for the patient’s vision loss.

Transcleral transillumination showed a moderate shadow measuring 12 × 10 mm in diameter, corresponding to the area of CHRPE. Within that shadow was a darker, distinct shadow measuring 7 × 7 mm, corresponding to the nodule seen clinically. With fluorescein angiography, the mass showed early hyperfluorescence and late staining, with leakage of fluorescein dye into the adjacent vitreous cavity (Figure 2). B-scan ultrasonography revealed a solid, dome-shaped mass that measured 3.0 mm in thickness (Figure 3A).

Our initial differential diagnoses included retinal vasoproliferative tumor and neoplasm of the pigment epithelium. Choroidal melanoma and metastasis were believed to be less likely.

It was decided that we observe the lesion at 6-month intervals. During the next 36 months, the mass gradually enlarged in thick-
ness (Figure 3B) and diameter (Figure 4), the visual acuity slowly worsened, the retinal feeder vessels became more dilated, and localized retinal exudation and secondary retinal detachment developed. The surface-wrinkling retinopathy and cystoid foveal edema became more pronounced. In addition, the smooth surface of the tumor disappeared because the tumor cells were diffusely infiltrating the overlying vitreous. Ultrasonography revealed that the thickness of the mass increased to 4.5 mm (Figure 3B).

The patient was informed that the enlarging tumor was likely to cause further vision loss secondary to vitreal seeding, retinal detachment, surface-wrinkling retinopathy, and vitreous hemorrhage. The options of diagnostic fine-needle aspiration biopsy, cryotherapy, irradiation, and tumor removal were discussed, and the patient elected to have tumor removal. After prophylactic laser photocoagulation posterior to the mass, the tumor was removed by a modified eye-wall resection.21 Postoperatively, the patient developed peripheral hemorrhagic retinal detachment and underwent pars plana vitrectomy, air/fluid exchange, vitreous instillation of sulfur hexafluoride gas, and cryotherapy. In February 2000, visual acuity was 20/400, and the retina was flat. There was pigment motting in the fovea, and the area of the original tumor appeared as a flat yellow scar.

**PATHOLOGICAL FEATURES**

The specimen was fixed in formaldehyde and submitted for routine processing. Gross inspection showed an ovoid mass with a thin strip of sclera at its base. The superficial portion of the tumor was nonpigmented, and the deeper portion was pigmented. Microscopic examination revealed a segment of choroid and a partially pigmented moundlike tumor that rested on the denuded inner surface of Bruch’s membrane. The sensory retina and the choroid were infiltrated with amelanotic tumor cells (Figure 5). The pigmented cells were arranged in a tubuloacinar configuration and contained large round melanosomes. The more superficial portion of the tumor that replaced the retina was composed of similar epithelial cells, except that they had minimal cytoplasmic pigmentation (Figure 6). Some of the nuclei contained prominent nucleoli, and rare mitotic figures were identified. The apical part of the neoplasm directly invaded the vitreous cavity, where it was topped by a layer of fibrinous exudate. There was extensive choroidal invasion by sheets and tongues of similar amelanotic tumor cells. Conspicuous foci of chronic inflammatory cells, including mature plasma cells with scattered Russell bodies, were present within the tumor and

**Figure 4.** A, Fundus drawing in late 1999 showing a fleshy yellow mass arising in the area of CHRPE and invading the overlying vitreous, producing subretinal exudation. B, Fundus photograph taken at the same time as Figure 4A. Note that the tumor has enlarged in diameter and thickness and is producing subretinal exudation.

**Figure 5.** Low-magnification photomicrograph of the tumor showing junction between basal pigmented cells and more superficial nonpigmented cells. The tumor has diffusely replaced the choroid (below) and the sensory retina (above) (hematoxylin-eosin, original magnification ×15).
the underlying choroid. In some areas, the tumor cells formed cords and bands that rested on prominent periodic acid-Schiff–positive connective tissue septa, most likely representing basement membrane (Figure 7). Short segments of tall, heavily pigmented RPE cells consistent with residual CHRPE were present on Bruch’s membrane at the base of the tumor (Figure 8).

The tumor cells showed moderately intense immunoreactivity for vimentin, moderate diffuse and focally intense immunoreactivity for cytokeratin marker CAM 5.2, and trace to mild diffuse immunoreactivity for S100 protein. Scattered tumor cells showed intense immunoreactivity for cytokeratin marker AE1. Melanoma-specific antigen HMB-45 was non-reactive.

The tumor was classified as a low-grade adenocarcinoma of the RPE based on the local invasion of the choroid, retina, and vitreous, and the presence of nuclear pleomorphism with prominent nucleoli and occasional mitotic figures. The final diagnosis was low-grade adenocarcinoma arising from CHRPE.

Until recently, CHRPE was generally considered to be a stationary lesion with no known tendency to enlarge or spawn solid neoplasms. In recent years, however, solitary CHRPE has been observed on several occasions to increase in basal dimensions, and histopathologic studies have shown evidence of associated RPE hyperplasia in CHRPE lesions. Our group recently reported clinical observations on 5 cases of elevated, solid tumors that apparently arose from typical CHRPE. From our observations on those 5 cases, it seems that tumors arising from CHRPE slowly enlarge, invade the sensory retina, and develop a retinal blood supply. Eventually, they can cause intraretinal exudation, which can lead to an exudative retinal detachment, similar to that seen with retinal capillary hemangioma and Coats disease. Preretinal macular fibrosis and cystoid foveal edema are also common complications.

We believe that the tumors that arise from CHRPE have clinical and histopathological features similar to other neoplasms of the pigment epithelium. Such tumors are usually dark gray to black, invade the sensory retina, acquire a retinal blood supply, and produce exudative retinopathy. Although they are usually located in the peripheral fundus, they are frequently associated with preretinal gliosis and cystoid edema in the macular area. Based on our clinical observations of 5 cases and the histopathologic findings on the 1 case reported here, it seems that true neoplasms of the RPE can arise from CHRPE. In our case, the tumor proved histopathologically to be a low-grade adenocarcinoma of the RPE arising from a focus of CHRPE.

Even though the tumor in our patient arose from the CHRPE, it appeared clinically to be amelanotic. However, the deeper part of the tumor was pigmented histopathologically. This finding accounted for the dark shadow produced by transillumination of the seemingly amelanotic tumor. It
seems that as these tumors proliferate, some of them lose pigmentation. We have seen another case of histopathologically proven adenocarcinoma of the RPE that was nonpigmented.\textsuperscript{22} In that case, the lesion presumably arose from a juxtapapillary hyperplasia of the RPE in an eye with ocular histoplasmosis.\textsuperscript{22}

The pathogenesis of the tumor described here is uncertain. Tumors of the RPE may occur as reactive hyperplasia, benign adenoma, or malignant adenocarcinoma. It is tempting to speculate that other reported neoplasms of the RPE may have originated from foci of CHRPE, which underwent reactive hyperplasia and subsequent neoplasia.\textsuperscript{20,23} However, the stimulus for such change remains unknown. In a sense, such transformation of CHRPE into a neoplasm of the RPE may be analogous to the malignant transformation of a choroidal nevus into a malignant melanoma.

The diagnosis of an RPE neoplasm arising from CHRPE is best made by indirect ophthalmoscopy with recognition of a pigmented or nonpigmented mass arising from typical CHRPE with minimally dilated retinal feeding and draining blood vessels. It is possible that such tumors may clinically obscure the underlying CHRPE. If so, clinically the lesion is like other RPE tumors reported in the literature.\textsuperscript{20} Fluorescein angiography generally accentuates the feeder vessels and shows moderately intense hyperfluorescence of the mass. Ultrasonography shows an abruptly elevated mass with medium to high internal reflectivity, but the ultrasonographic findings alone may be insufficient to consistently differentiate a neoplasm of the RPE from choroidal melanoma.

The management of neoplasms arising from CHRPE should be similar to that of other tumors of the RPE.\textsuperscript{20} The ultimate treatment has not yet been determined, but it seems advisable to do fundus photography and examine the lesion periodically if it is small and asymptomatic. The other 4 patients we previously reported are currently being managed by observation only. However, the patient reported here required active treatment because the tumor was enlarging and was producing vision-threatening complications. Although the best treatment for symptomatic cases is unknown, options include treating the macular edema medically or with grid laser photocoagulation, or treating the tumor with laser photocoagulation, cryotherapy, plaque brachytherapy, or local resection. Local resection was performed in our patient with the hope that removing the tumor completely would stabilize the progressive complications.

The visual prognosis varies for patients with neoplasms arising from CHRPE. Most tumors are relatively small and show little change in the early stages. With time, however, there is slow enlargement of the mass and progressive exudative retinopathy, often with preretinal macular gliosis and cystoid macular edema causing visual loss. The systemic prognosis is excellent. To our knowledge, no adenocarcinoma of the RPE has exhibited distant metastasis.

In summary, we have documented a progressive, low-grade adenocarcinoma that appeared clinically and histopathologically to arise from CHRPE. We recommend that patients with CHRPE be followed up periodically for evolution of the lesion into a neoplasm.

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Corresponding author and reprints: Jerry A. Shields, MD, Oncology Service, Wills Eye Hospital, 900 Walnut St, Philadelphia, PA 19107.

REFERENCES


Archives Web Quiz Winner

Congratulations to the winner of our December quiz, James A. Kimble, MD, of the University of Alabama at Birmingham. The correct answer to our December challenge was melanocytoma and associated combined retinal vein and artery occlusion. For a complete discussion of this case, see the Clinicopathologic Report section in the January Archives (Shields JA, Shields CL, Shah P, Sivalingam V. Partial lamellar sclerouvectomy for ciliary body and choroidal tumors. Ophthalmology. 1991;98:971-983). Be sure to visit the Archives of Ophthalmology World Wide Web site (http://www.archophthalmol.com) and try your hand at our Clinical Challenge Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of the book One Hundred Years of JAMA Landmark Articles.

Figure 1. Fundus photograph showing pigmented mass over optic disc.