Adenocarcinoma of the Retinal Pigment Epithelium

Malignant neoplasms of the retinal pigment epithelium (RPE) are rare. Only a few well-documented cases have been described in the last decades. Some of these tumors developed in association with choroidal neovascularization, which is the most common cause of blindness in the world. The neovascularization is often related to age-related macular degeneration, but it can also be caused by other conditions such as diabetic retinopathy, sickle cell retinopathy, and age-related macular degeneration (AMD). AMD is a leading cause of blindness in the Western world, and it is estimated that 7 million people in the U.S. are affected by this condition. AMD is a degenerative disease of the macula that leads to the development of new blood vessels in the retina, which can cause bleeding and scarring, resulting in vision loss.AMD is a major cause of blindness in the Western world, and it is estimated that 7 million people in the U.S. are affected by this condition. AMD is a degenerative disease of the macula that leads to the development of new blood vessels in the retina, which can cause bleeding and scarring, resulting in vision loss.

Report of a Case. A 37-year-old man was referred to our clinic in 1980 for a progressive loss of vision in his right eye during the preceding months. His visual acuity was counting fingers OD and 20/20 OS. Funduscopy showed a subfoveal hemorrhagic lesion in the right eye, several atrophic choriretinal scars nasal to the optic disc, and peripapillary atrophy (Figure 1A). Fluorescein angiography revealed a subfoveal neovascular membrane (Figure 1B). We assumed that a histoplasmosis-like lesion (pseudo–presumed ocular histoplasmosis syndrome) had caused the observed changes. No specific therapy was recommended. The left eye was normal.

Seventeen years later, in 1997, the patient (then 54 years old) developed a slowly progressive additional loss of his central visual field in the right eye. The visual acuity was reduced to hand motions OD, and funduscopy showed a prominent, nonpigmented subretinal mass in the macular region overlying the optic disc (Figure 2A). The surrounding retina was detached. Subretinal strands and yellowish exudates were visible. Simultaneous fluorescein and indocyanine green angiography revealed a vascularized tumor with parts of the blood supply coming from the retinal vasculature (Figure 2B and 2C). Ultrasound A- and B-scan echography revealed a solid, dome-shaped (no collar-button configuration) tumor with a prominence of 3.4 mm and 30% to 70% reflectivity.

A thorough medical examination was performed including computed tomography of the cranium, thorax, abdomen, and pelvis; bronchoscopy; panendoscopy; sonography of the abdomen; and endosonography. The results of all examinations were normal. Clinically, an amelanotic choroidal melanoma was suspected, and enucleation was performed. Five years after enucleation, the patient is doing well with no signs of malignancy.

Macroscopically, the sectioned globe showed a dome-shaped, gray-yellow subretinal mass occupying the region anterior to the optic disc. The tumor was 8 × 5 mm at the base and 3 mm thick. It was surrounded by yellowish subretinal exudates and a shallow retinal detachment. Histologically (Figure 3A-D), the tumor was composed mainly of nonpigmented cuboidal epithelial cells arranged in a glandulotubular pattern. Other parts exhibited a solid or trabecular growth. A few cells...
contained small melanin granules. Mitotic figures were observed in only 1 of 50 high-power fields. The MIB-1 labeling index indicated that the cellular proliferation was 4%, which is in agreement with a low-grade adenocarcinoma.

The tumor was widely infiltrating the retina and focally the choroid and prelaminary optic nerve. At the base of the tumor, reactive RPE proliferations merged into it continuously.

Immunohistochemical stains (Figure 4) of the tumor cells were positive for cytokeratins 1, 5, 10, and 14; 7, 8, and 19; and Lu5 (panepithelial marker); epithelial membrane antigen; and vimentin. These stains were weakly positive for carbohydrate antigen 19-9 and neuron-specific enolase. Tumor cells were negative for S100 protein (calcium binding protein), HMB-45 antigen (antimelanoma), and carcinoembryonic antigen.

Because of the morphologic characteristics, immunohistochemical phenotype, and presence of melanin granules in some of the tumor cells, the patient was diagnosed as having adenocarcinoma of the RPE.

Comment. Proliferative conditions of the RPE include reactive hyperplasia, benign adenoma, and malignant adenocarcinoma. The differentiation between these lesions is often difficult, even histologically.9,10 Most

Figure 2. Color fundus photography (A) and simultaneous fluorescein (B) and indocyanine green (C) angiography of the right eye in 1997, showing a nonpigmented vascularized tumor overlying the macula and optic disc.

Figure 3. Results of a histological stain showing the flat-based tumor (A) (hematoxylin-eosin, original magnification ×50); glandulotubular, trabecular, and partly solid architecture (B) (hematoxylin-eosin, original magnification ×100); a higher magnification of this architecture (C) (hematoxylin-eosin, original magnification ×200); and cytologic details with pale, medium pleomorphic nuclei, partly prominent nuclei, and focal fine intracytoplasmic melanin granules (D) (hematoxylin-eosin, original magnification ×400).
cases of RPE carcinoma have been clinically misdiagnosed as choroidal melanoma. Currently, most subretinal tumors assumed to be choroidal melanomas are treated with radiotherapy without histological confirmation. The diagnosis of an RPE carcinoma may therefore be missed.

Finger et al described a darkly pigmented subretinal tumor accompanied by inflammation that was suspected of being an adenocarcinoma of the RPE. In several published cases, RPE carcinomas were darkly pigmented, but in others, including our case, they were clinically nonpigmented and did not exhibit significant uveitis. Tumors have been located at the posterior pole, as well as anterior to the equator. Other clinical features appear to be more useful for the differential diagnosis, including a retinal blood supply of the tumor and extensive yellowish exudates. Both features are rare in choroidal melanoma.

The cellular pattern in this case was that of a highly differentiated adenoid tumor. Invasive growth was the criterion for malignancy. There was no evidence of extracocular spread or metastasis. In fact, metastasis has been absent in all well-documented cases. Extracocular extension has been described by Loeffler et al. To our knowledge, this was the only case that showed no adenoid differentiation but randomly oriented spindle-shaped cells with several mitotic figures. This may represent a more aggressive and invasive form of RPE carcinoma.

Tso and Albert as well as Shields et al found that neoplastic RPE proliferations usually develop in otherwise normal eyes. However, in a large proportion of the recently published cases, an RPE carcinoma arose from a juxta-papillary histoplasmosis scar, from a congenital hypertrophy of the RPE, in an eye with phthisis, or in our case from a chorioretinal scar following a subfoveal neovascular membrane. Therefore, it appears likely that reactive proliferation of the RPE plays a role in the pathogenesis of these rare tumors.

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