

Adenocarcinoma of Retinal Pigment Epithelium Clinically Diagnosed as Malignant Melanoma; A Case Report with Unsystematic Review of Literature

Fahimeh Asadi-Amoli, MD,¹ Hedyeh Moradi, MD²
Mohammad-Taher Rajabi, MD,³ Mohammad Riazi-Esfahani, MD⁴

Abstract

Purpose: True neoplasm (adenocarcinoma) of retinal pigment epithelium (RPE) is very rare; since it can be misdiagnosed as intraocular malignant melanoma it is of importance to know the clinical and pathologic aspects of this neoplasm. Here, we report a case of adenocarcinoma of RPE.

Methods: Case report.

Results: A 60-year-old man with progressive loss of the vision of the right eye was enucleated with a clinical diagnosis of malignant melanoma. Grossly, a solid well-circumscribed mass occupying the posterior section of the globe near the optic disc was observed. In histological evaluation, the tumor was composed of cells having large, pleomorphic, and hyperchromatic nuclei and prominent nucleoli with occasional pigmentation. Tumor cells were mostly arranged in a papillary pattern. To differentiate it from melanoma, immunohistochemistry was performed. Epithelial membrane antigen (EMA) was strongly positive and HMB45 was negative; this is consistent with the diagnosis of adenocarcinoma of RPE. On systemic evaluation no metastases was found.

Conclusion: Adenocarcinoma of RPE is very rare but it should be considered in the differential diagnosis of malignant melanoma of the eye.

Keywords: retinal pigment epithelium, malignant melanoma, adenocarcinoma

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1. Associate Prof. of Pathology, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences
2. Resident in Pathology, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences
3. Ophthalmologist, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences
4. Associate Prof. of Ophthalmology, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences

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Correspondence to:
Mohammad-Taher Rajabi, MD
Eye Research Center
Farabi Eye Hospital
Tel: 55414941-6
Email: mt_rajabi@yahoo.com

Introduction

In contrast to reactive hyperplasia of retinal pigment epithelium (RPE), the true neoplastic lesions of RPE are rare,^{1,2} Differentiating hyperplasia from true neoplasia may be difficult because neoplastic lesions are so rare and both types of proliferations show variable clinical and histological characteristics.¹ In addition, true neoplastic proliferation can develop from reactive hyperplasia.^{1,3-5}

Because of the rarity of RPE adenocarcinoma and the importance of differential diagnosis with malignant melanoma (a common pigmented neoplasm in eye), we report a rare case of RPE adenocarcinoma in a patient that was enucleated with a clinical diagnosis of malignant melanoma.

Case Report

A 60-year-old man presented with complaint of progressive visual loss in the right eye from 5 months prior to presentation. His past ocular and systemic history was unremarkable.

Ophthalmologic examination revealed exudative retinal detachment and small, slightly elevated fleshy mass on the nasal side of the right optic nerve. Visual acuity of the right eye was hand motion. Anterior segment evaluation of the right eye showed only mild cataract. Intraocular pressure was 14 mm Hg. According to the above findings malignant melanoma was proposed.

Systemic evaluation did not show any abnormal finding. B-scan ultrasonography of the right eye showed retinal detachment and dome-shaped peripapillary retinal mass nasal to the optic nerve head with a high reflective anterior border, acoustic solidity and no posterior shadowing (Figure 1). A-scan ultrasonography revealed a lesion with initial high-amplitude echoes and high to moderate internal reflectivity. Neither funduscopy nor ultrasonographic findings was suggestive of special diagnosis. Because the patient had a progressively enlarging mass over the optic disc associated with progressive visual loss, diagnosis of choroidal melanoma was suggested by two retinal specialists, and enucleation was performed.



Figure 1. B-scan ultrasonogram demonstrating an abruptly elevated dome-shaped mass at the posterior pole with acoustic solidity and secondary retinal detachment

Pathology report

In cut sections of the enucleated globe, a well-circumscribed, tan-white mass with dark brown spots was seen, measured 1.8 cm in diameter. The mass was near to the optic nerve head (Figure 2).



Figure 2. Gross photograph of paraffin block of the sectioned globe showing an elevated mass at the posterior pole near the optic nerve; note the extensive yellow brown exudation throughout a wide area of the fundus.

Microscopic examination of the posterior segment mass revealed, a neoplastic tissue composed of epithelioid tumor cells having large pleomorphic, hyperchromatic nuclei and prominent nucleoli. Occasionally brown pigmentation could be seen in stroma and between tumor cells. Tumor cells had been arranged in tubular nests mostly in papillary pattern. Rarely mitosis was apparent, but no necrosis was seen. Tumor involved retina, choroids and head of the optic nerve but was confined to the sclera and did not extend

beyond it. In cut sections of optic nerve, no tumoral involvement was seen (Figures 3-5).

According to histopathological findings three differential diagnoses are proposed; 1) adenocarcinoma of retinal pigmented epithelium; 2) malignant melanoma; and 3) metastatic adenocarcinoma.

Malignant melanoma can also show papillary pattern, epithelioid appearance and brown pigmentation. Therefore immunohistochemistry (IHC) was mandatory for definite diagnosis; HMB45 was negative, EMA strongly positive (Figures 6, 7). IHC findings ruled out malignant melanoma. For excluding metastatic carcinoma, complete systemic survey was performed that did not show any tumoral involvement. Finally, diagnosis of true adenocarcinoma of RPE was confirmed.

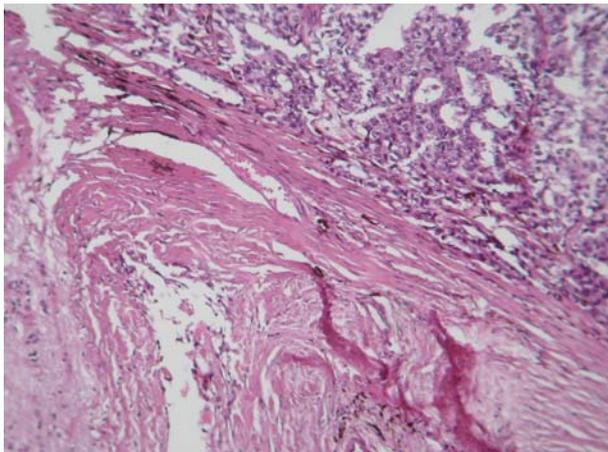


Figure 3. Photomicrograph showing adenocarcinoma of RPE involving choroid and head of the optic nerve (hematoxylin-eosin, original magnification $\times 200$)

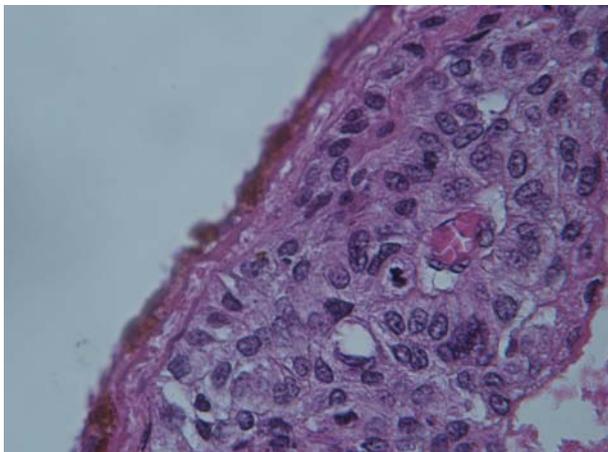


Figure 4. Photomicrograph of adenocarcinoma of RPE showing epithelioid tumor cells with mild to moderate pleomorphism, some mitotic figures, large vesicular nuclei, and prominent nucleoli (hematoxylin-eosin, original magnification $\times 400$)

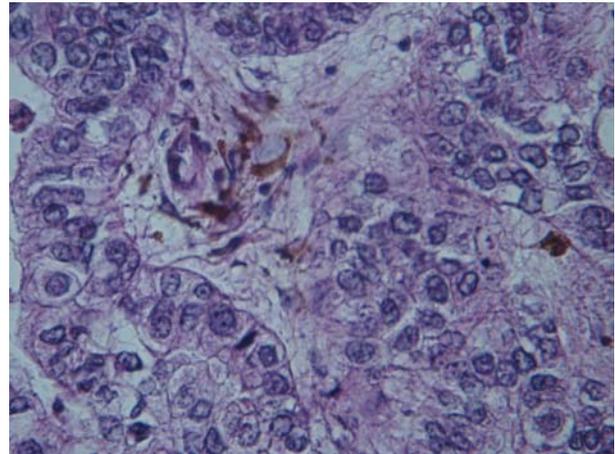


Figure 5. Photomicrograph of adenocarcinoma of RPE showing brown pigmentation in stroma and among tumor cells (hematoxylin-eosin, original magnification $\times 400$)

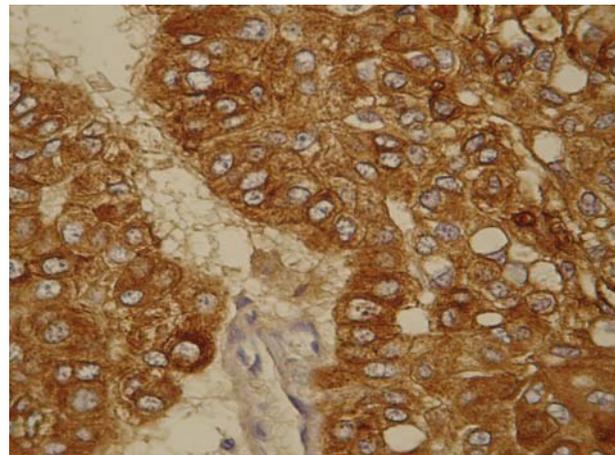


Figure 6. Immunohistochemical staining for epithelial membrane antigen (EMA) showing strong immunoreactivity in the tumor cells, original magnification $\times 400$

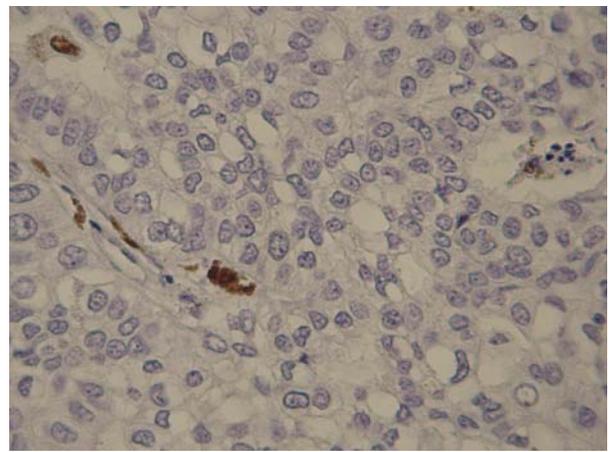


Figure 7. Immunohistochemical staining for HMB45 showing no immunoreactivity in the tumor cells; original magnification $\times 400$

Discussion

Neoplastic lesions that arise from RPE may be reactive hyperplasia, adenoma or adenocarcinoma. Reactive hyperplasia is generally present following trauma or inflammatory eye disease. Adenoma of RPE is a benign looking tumor with very slow rate of progression.¹ In addition adenomas arise most often from pigmented epithelium of iris and ciliary body rather than retina.^{6,7} Presence of anaplasia, hyperchromasia, pleomorphism and mitosis differentiate adenocarcinoma from adenoma.¹

Tso and *Albert* suggest criteria for differentiating reactive hyperplasia from adenocarcinoma of RPE. Typically reactive hyperplasia occurs in patient with a history or pathologic evidence of trauma or eye disease, whereas neoplastic lesions tend to be discrete tumors in otherwise normal eye.¹ However cases of adenocarcinoma following blind eye staphyloma³ and histoplasmosis scar are reported.⁴ In addition, the median age for neoplastic lesion is somewhat younger (fifth decade) than that for reactive hyperplasia (seventh decade).¹ In pathological evaluation mitosis is commoner and pleomorphism more evident in neoplastic lesions than in hyperplastic ones.

True adenocarcinoma of RPE is very rare but they are of great importance because of its more resemblance, to malignant melanoma, both in clinical and pathological characteristics.

Malignant melanoma is the most common primary neoplasm in posterior segment in adulthood, it can induce retinal detachment and in pathology may be pigmented, epithelioid appearance with papillary pattern; all these findings may also be present in adenocarcinoma of RPE.^{5,8}

The other probable differential diagnosis of RPE adenocarcinoma is metastatic carcinoma. To rule out this possibility a complete systemic work up of internal organs (for example GI tract, kidney, and liver) must be performed.

Clinical presentations of adenocarcinoma of RPE are variable; including vitreous hemorrhage, fibrosis, exudative retinal detachment, and nonspecific choroiditis. Visual acuity may range between $20/20$ to no light perception.

Most reported cases of RPE neoplasm are clinically diagnosed as malignant melanoma. Since the former has no or at least little potential for metastasis, it would be desirable to have some criteria for differentiating them from malignant melanoma.^{5,9} Tumors of RPE appear as an abruptly elevated mass that arises perpendicularly from RPE and lacks the adjacent base of pigmented choroidal tumor that is seen with most melanoma. Although tumors of the RPE can be abruptly elevated or pedunculated, they occur internal to the Bruch's membrane and therefore do not produce a classic mushroom configuration that characterizes some melanomas. Prominent blood vessels which are commonly observed with choroidal melanoma are not seen in RPE tumors. Tumors of RPE are more likely to produce vitreous seedings and hemorrhages, because they arise internal to Bruch's membrane.⁵

The RPE tumor is very likely to produce yellow intraretinal and subretinal exudation, often leading to an exudative retinal detachment, similar to a retinal capillary hemangioma. However, subretinal exudation seen in choroidal melanoma that frequently produces retinal detachment is serous in nature, and an appreciable yellow retinal or subretinal exudation is extremely rare in a similar sized melanoma. Another distinguishing feature of RPE is the development of a retinal blood supply. An RPE tumor is most likely to exhibit a feeding retinal artery and a draining vein. Although a melanoma can rarely invade the retina and cause dilated tortuous retinal vessels, it is usually only the vein, and not the artery, that becomes dilated.⁵

There are no proven cases of adenocarcinoma of RPE that have metastasis to other sites.² However some authors believed that in presence of extra-scleral extension, metastasis are possible.¹⁰

These RPE tumors have various histological patterns: mosaic, tubular, papillary, vacuolated, and anaplastic. Tumors with mosaic pattern are graded as the best differentiated and those with anaplastic pattern, the least differentiated. The others are in the middle spectrum.¹

Adenoma of RPE is one of the differential diagnoses of adenocarcinoma of RPE.

Histopathologically, many patterns are seen in adenoma. The cells may proliferate in an oval or hexagonal array with no fibrovascular matrix, or the cells may have vacuolated appearance. The pigment granules retain their large oval configuration.¹ In addition, adenoma most often arises from pigmented epithelium of iris and ciliary body region and less often from RPE.^{6,11} Adenocarcinoma of RPE shows anaplasia, pleomorphism and increased mitotic activity, as well as tendency toward local invasion of choroids and optic nerve head. Tumor cells showing hyperchromasia, prominent nucleoli and mitotic activity.¹

Fine needle aspiration biopsy (FNAB) is one of the best procedures that can assist in diagnosis of RPE carcinoma. The tumor of RPE demonstrate deeply pigmented, plump, round cells with large melanosomes, compared the spindle cells and smaller melanosomes in malignant melanoma.^{5,12}

Immunohistochemical studies in RPE adenocarcinoma show immunoreactivity for low molecular weight cytokeratin (CK), vimentin and also S₁₀₀, suggesting the neuroectodermal origin of tumor.³ The best way to differentiate melanoma from adenocarcinoma of RPE is immunohistochemistry for HMB₄₅ (as a

melanocytic marker) and EMA/CK (as epithelial markers). In our case HMB₄₅ was negative thus melanoma was excluded, EMA and CK were strongly positive that suggest epithelial origin of the tumor. S₁₀₀ was also weakly positive in favor of neuroectodermal origin of tumor cells. The presence of pleomorphism, anaplasia, mitosis, and local invasion, suggest malignant characteristic or carcinoma, and the presence of tubular and papillary pattern, suggest adenocarcinoma. Extracellular pigmented granules suggest RPE adenocarcinoma, and absence of any systemic metastasis as primary origin of the tumor ruled out metastatic adenocarcinoma.

Conclusion

The rare neoplasm of adenocarcinoma of RPE must be considered in the differential diagnosis of a more common malignancy such as choroidal melanoma. Tumors of RPE are generally considered to have a benign course with a weak tendency for metastasis in contrast to malignant melanomas. In addition to reporting a case of RPE adenocarcinoma, we provided a review on clinical features and differential diagnosis of tumors of RPE,

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