Adenocarcinoma of the Retinal Pigment Epithelium Arising in Conjunction with Late Recurrence and Systemic Metastasis of Retinoblastoma

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Established Facts

- Intraocular recurrence and/or systemic metastasis of retinoblastoma typically occur within 2 years of the initial diagnosis.
- Adenocarcinoma of the retinal pigment epithelium is a very uncommon intraocular tumor which is most frequently found incidentally when a phthisical eye is enucleated for other reasons.

Novel Insights

- To the best of our knowledge, this case documents by far the latest recurrence of retinoblastoma with systemic metastasis. This highlights the importance of continued clinical observation and appropriate long-term follow-up.
- This is the first published case of retinal pigment epithelium adenocarcinoma occurring concurrently with retinoblastoma, illustrating the importance of considering a second primary intraocular tumor in the differential diagnosis.

Keywords

Retinoblastoma · Metastasis of retinoblastoma · Late recurrence of retinoblastoma · Retinal pigment epithelium adenocarcinoma · Phthisical eye

Abstract

In 1974, an 8-month-old male was diagnosed with bilateral retinoblastoma. His left eye was enucleated, while the right eye was salvaged with a combination of external beam radiotherapy (4,000 cGy total, divided in 20 fractions) and reti-

nal laser treatment. Thirty-nine years later, he developed intraocular recurrence of retinoblastoma with extrascleral spread. Histopathological examination also identified a second distinct malignancy, retinal pigment epithelium adenocarcinoma, arising in continuity with the retinoblastoma. Further investigation revealed foci of metastatic retinoblastoma in his parotid gland. He was subsequently treated with a combination of orbital exenteration, extensive neck dissection, and resection of metastatic foci, followed by a high-dose ablative chemotherapeutic regimen consisting of cisplatin, vincristine, and cyclophosphamide. Although very

rare, late recurrence of retinoblastoma with systemic metastasis is possible, and continued clinical observation and appropriate long-term follow-up should be considered. Additionally, it is important to consider a second primary intraocular tumor in the differential diagnosis, especially in a patient with heritable retinoblastoma who has undergone radiation therapy.

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Introduction

Retinoblastoma accounts for approximately 4% of all pediatric malignancies and is the most common primary intraocular malignancy in children with one-third of those affected having bilateral involvement [1]. In salvageable eyes, intraocular recurrence of retinoblastoma is almost always detected within the first 1–2 years following initial chemoreduction [2].

Metastasis from retinoblastoma also typically occurs within 1 year of the initial diagnosis [3]; moreover, late recurrence and systemic metastasis are so rare that, if there is no metastatic disease present 5 years after treatment, the patient is typically considered cured [4].

We report a case of intraocular recurrence of retinoblastoma 39 years after the initial diagnosis associated both with systemic metastasis and concurrent development of a contiguous adenocarcinoma of the retinal pigment epithelium (RPE).

Case Report

In 1974, an 8-month-old male was diagnosed with bilateral retinoblastoma. His left eye was enucleated, while his right eye was salvaged with a combination of external beam radiotherapy and retinal laser treatment. A total of 4,000 cGy was delivered in 20 fractions through anterior and 2-wedged lateral fields. From the completion of treatment in June 1974, he maintained approximately 20/40 best corrected visual acuity for many years.

He was eventually lost to follow-up but later re-presented in 2009 with corneal neovascularization and neovascular glaucoma secondary to presumed proliferative radiation retinopathy. He subsequently received numerous intravitreal anti-VEGF injections, panretinal photocoagulation, and cyclophotocoagulation; however, his intraocular pressures remained labile.

In September 2012, he developed a nonclearing vitreous hemorrhage requiring vitrectomy. The vitreous fluid was sent for pathology. Fragmented cellular and nuclear debris with disintegrated inflammatory cells were seen, but there was no definitive evidence of a neoplasm.

By April 2013, he had developed a blind, painful eye as a result of uncontrollable intraocular pressure. Additionally, on examination, he was found to have an abnormal, fixed perilimbal conjunc-

tival plaque. There was no longer any view of the posterior segment as a result of significant corneal scarring. The patient was referred to the ocular oncology service, and his remaining right eye was promptly enucleated 39 years after the initial diagnosis of retinoblastoma.

On pathological examination, the enucleated eye measured 20 × 34 × 20 mm with 7 mm of optic nerve attached and a nodule of fat and apparent scar tissue adjacent to the nerve (Fig. 1a). The cornea was moderately opaque with a rough surface, and a clear view of the pupil and iris could not be obtained. The eye was opened horizontally, and the posterior chamber was filled with yellowish-white material. The lens and retina could not be clearly visualized.

Although, on microscopic examination, the globe was filled with largely necrotic tumor, there were several foci of viable tumor cells consistent with retinoblastoma (Fig. 1b). These cells expressed synaptophysin and CD56, but definite rosettes could not be seen. The limbal nodule was confirmed to be retinoblastoma (Fig. 1c), and there was a suggestion of lymphatic permeation. Much of the posterior aspect of the scarred cornea was lined by retinoblastoma cells (Fig. 1d), and necrotic tumor was present in the ciliary body. The choroid was extensively infiltrated by retinoblastoma cells. The retina was largely replaced by tumor, although some gliotic retina could be identified at the periphery.

An unexpected finding was the patchy replacement of ciliary epithelium in both the pars plicata and pars plana by both retinoblastoma cells and a population of cuboidal epithelial cells. There was also focal replacement of normal RPE by the cuboidal cells, which generally lacked pigment and had pink, mildly vacuolated cytoplasm. The choroid was thickened in places by this epithelial proliferation, and, adjacent to the optic nerve head, there was perineural infiltration through the sclera with formation of a 5.5-mm juxtapapillary nodule on the episcleral surface (Fig. 1e). Nuclei were large and moderately pleomorphic with small nucleoli (Fig. 1f); mitotic figures were readily identifiable. The cells expressed cytokeratins (AE1/AE3 but not CK7 or CK8/18) as well as CD56 and S-100 protein (Fig. 1g). There was no expression of synaptophysin (Fig. 1h). In keeping with an RPE origin, the cells formed tubules, nests, and lamellae within an abundant hyaline, periodic acid-Schiff-positive matrix.

The optic nerve head was cupped, and both the retinoblastoma and malignant RPE cells extended into the retrolaminar optic nerve but not to the resection margin of the nerve. Neither tumor was present in the subdural space.

In light of the extrascleral involvement, the patient was taken back to the operating room for a right eyelid-sparing exenteration in July 2013. A bone marrow biopsy, bone scan, and lumbar puncture were all within normal limits. An MRI of the brain revealed 2 lesions in the inferior frontal lobe of uncertain significance. With serial observation, the intracranial lesions have remained stable. A CT scan of the neck showed 3 nodules in the right parotid gland. Fine-needle aspiration biopsy of these masses revealed a malignant small blue-cell tumor in keeping with metastatic retinoblastoma. An extensive right neck dissection with right total parotidectomy was undertaken in September 2013. Histopathologic examination of a supraclavicular lymph node removed during this dissection showed a nodule of poorly differentiated malignancy with small round blue-cell morphology. Although surgical margins from this resection were negative, by April 2014, a repeat PET scan showed recurrence, and a second neck dissection was planned. However,

Fig. 1. **a** Whole mount photograph of the enucleated globe showing an intraocular mass with necrosis, perlimbal conjunctival plaque, and juxtapapillary nodule on the episcleral surface. HE. **b** High-power view of viable retinoblastoma. HE. $\times 400$. **c** Limbal nodule of retinoblastoma. HE. $\times 200$. **d** Retinoblastoma lining the posterior aspect of the cornea. HE. $\times 100$. **e** Perineural infiltration through the sclera by the RPE adenocarcinoma. HE. $\times 200$. **f** High-power view of the RPE adenocarcinoma. HE. $\times 400$. **g** Periodic acid-Schiff-positive matrix surrounding the nests of RPE adenocarcinoma. **h** RPE cells express cytokeratin, but retinoblastoma cells do not. **i** Positive immunostaining for S-100 protein in RPE adenocarcinoma (right) and absent staining in retinoblastoma (left). $\times 200$. **j** Absent immunostaining for synaptophysin in RPE adenocarcinoma (bottom) and positive staining in retinoblastoma (top). $\times 200$. RPE, retinal pigment epithelium.

at the time of surgery, the tumor was more extensive than initially suspected, and the wound was closed without additional surgical excision. Subsequently, 4 cycles of a high-dose ablative chemotherapeutic regimen, consisting of cisplatin, vincristine, and cyclophosphamide, were administered systemically.

At his most recent follow-up in April 2016, the patient was doing well clinically, and all imaging studies demonstrated stability with no evidence of tumor progression.

Discussion

While intraocular recurrence with systemic metastasis of retinoblastoma typically occurs within 1–2 years after the initial diagnosis [3], our case dramatically illustrates that this is not an absolute rule. Advances in retinoblastoma treatment have resulted in survival rates upwards of 96% in some countries [5], and current management strategies place greater emphasis not only on saving the life but also on salvaging the globe. In fact, survival rates have risen enough that second systemic primary malignancies have now become the leading cause of death in retinoblastoma survivors, particularly those with germline Rb-1 mutations [6]. Not only are retinoblastoma survivors with Rb-1 gene mutations at a significant risk for second primary *systemic* malignancies, but those whose globes are salvaged are also at risk for second primary *intraocular* malignancies, such as RPE adenocarcinoma. Our case highlights the importance of considering second primary intraocular tumors, especially in a patient with heritable retinoblastoma who has undergone radiation therapy.

While aberrations of the RPE, including congenital hypertrophy of the RPE, combined hamartomas, or reactive hyperplasia, are frequently observed, malignant neoplasia of the RPE is exceedingly rare. RPE adenocarcinomas are most often found incidentally when a phthisical eye is enucleated for other reasons [7], including the presumptive diagnosis of uveal melanoma [8]. Moreover, the line between abnormal reactive and neoplastic RPE proliferations has been postulated to shift over time, as malignant transformation of a congenital hypertrophy of the RPE into an adenocarcinoma of the RPE has been reported [9].

In the case we have reported here, it is possible that the earlier treatment of retinoblastoma induced a reactive proliferation of the RPE, which subsequently underwent malignant transformation. A similar hypothesis was proposed by Shields et al. [10] in a case of RPE adenocarcinoma arising from a peripapillary histoplasmosis scar. However, the combination of genetic predisposition coupled with radiation exposure provides an alternative ex-

planation for the development of RPE adenocarcinoma within the context of recurrent retinoblastoma, since both tumors originate from the same embryonic tissue. It is possible that both tumors arose from reactivation of a common cancer stem cell or that changes in the microenvironment related to the development of the RPE adenocarcinoma permitted exit from dormancy of a retinoblastoma cancer stem cell. Despite the common use of external beam radiation in hereditary retinoblastoma in the past, to the best of our knowledge there have been no reports of RPE adenocarcinoma as a second primary malignancy in a patient with retinoblastoma.

While external beam radiotherapy is no longer commonly used to treat retinoblastoma, many novel therapeutic strategies, such as the injection of intra-arterial chemotherapeutic agents directly into the ophthalmic artery, aim to decrease the necessity for enucleation. Consequently, in our modern-day era of retinoblastoma treatment, some eyes classified as group D and E by the International Classification of Retinoblastoma, which would have previously been enucleated, are now salvaged. However, by not being able to perform a histopathological examination on the specimen, high-risk patients may not be as reliably identified. The importance of this limitation is currently very controversial – while metastatic retinoblastoma occurs in less than 10% of patients in developed countries, this risk can be stratified based on histopathological risk factors.

High-risk histopathological factors, such as invasion of the tumor beyond the lamina cribrosa or into the orbit [11], and clinical factors, including bilateral disease, increase the risk of developing metastases. Eyes that meet criteria for high-risk retinoblastoma have a 24% chance of developing metastatic disease, which is subsequently reduced to 4% if treated appropriately with systemic chemotherapy [12]. Therefore, the ability to thoroughly, and accurately, identify patients with high-risk retinoblastoma is thought by some care providers to be of critical importance. It remains to be seen whether the contemporary treatment algorithms prioritizing salvage of high-grade eyes result in more substantial rates of late recurrence in the decades to come.

Unlike retinoblastoma, it is generally believed that RPE adenocarcinoma does not metastasize; however, there has been 1 documented case with metastatic foci found in the parietal lobe and cerebellopontine angle [13]. Despite this, RPE adenocarcinoma is too rare, and reports regarding the degree of aggressive behavior are too heterogeneous to draw accurate conclusions regarding prognosis.

While late recurrence of retinoblastoma is also rare, Goto et al. [14] reported a case of recurrent retinoblastoma 12 years following brachytherapy, and, more recently, Choi et al. [15] published a case of extraocular recurrence with systemic metastasis occurring 13 years and 8 months after the initial diagnosis. Taken in concert with the case we have described above, it is clear that, while uncommon, late recurrence with systemic metastasis of retinoblastoma is possible.

Another unusual feature in our case is the development of corneal neovascularization and neovascular glaucoma poorly responsive to anti-VEGF therapy, approximately 4 years before the recurrence of the retinoblastoma was recognized. Proliferative retinopathy resulting from radiation treatment given 35 years earlier is very atypical. They may rather be manifestations of tumor-induced angiogenesis, either from the recurrent retinoblastoma or the RPE adenocarcinoma.

Summary

Continued long-term follow-up should be considered, and clinicians must stay keenly aware of the possibility of atypical presentations of recurrent disease, regardless of the duration from initial diagnosis.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

- Shields C, Shields J: Basic understanding of current classification and management of retinoblastoma. *Curr Opin Ophthalmol* 2006; 17:228–234.
- Shields C, et al: Chemoreduction for retinoblastoma. Analysis of tumor control and risk for recurrence in 457 tumors. *Am J Ophthalmol* 2004;138:329–337.
- MacKay C, Abramson D, Ellsworth R: Metastatic patterns of retinoblastoma. *Arch Ophthalmol* 1984;102:391–396.
- Kaliki S, et al: High-risk retinoblastoma based on International Classification of Retinoblastoma: analysis of 519 enucleated eyes. *Ophthalmology* 2013;120:997–1003.
- Shields C, Shields J: Retinoblastoma management: advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. *Curr Opin Ophthalmol* 2010;21: 203–212.
- Kleinerman RA, Tucker MA, Tarone RE, et al: Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol* 2005;23:2272–2279.
- Saeed M, et al: Diagnostic surprise in an evisceration specimen. *Orbit* 2007;26:129–131.
- Finger P, et al: Adenocarcinoma of the retinal pigment epithelium: a diagnostic and therapeutic challenge. *Graefes Arch Clin Exp Ophthalmol* 1996;234:22–27.
- Shields J, et al: Adenocarcinoma arising from congenital hypertrophy of retinal pigment epithelium. *Arch Ophthalmol* 2001;119:597–602.
- Shields J, et al: Adenocarcinoma of retinal pigment epithelium arising from a juxtapapillary histoplasmosis scar. *Arch Ophthalmol* 1994;112:650–653.
- Kopelman J, McLean I, Rosenberg S: Multivariate analysis of risk factors for metastasis in retinoblastoma treated by enucleation. *Ophthalmology* 1987;94:371–377.
- Ghassemi F, Khodabande A: Risk definition and management strategies in retinoblastoma: current perspectives. *Clin Ophthalmol* 2015;9:985–994.
- Heindl L, et al: Aggressive metastasizing adenocarcinoma of the retinal pigment epithelium with trisomy 21. *Br J Ophthalmol* 2008; 92:389–391.
- Goto H, et al: Recurrence of retinoblastoma 12 years after brachytherapy. *Am J Ophthalmol* 2002;134:773–775.
- Choi J, Kang HJ, Lee JW, et al: Very late relapse of bilateral retinoblastoma. *J Pediatr Hematol Oncol* 2015;37:264–267.