Case Report

Histopathology of Intraocular Medulloepithelioma following Iodine-125 Plaque Brachytherapy

Sukriti Mohan a  William Steven Gange a  Jonathan Kim a  Maria Elena Sibug Saber a, b

a Department of Ophthalmology, Keck School of Medicine of University of Southern California, Los Angeles, CA, USA; b Department of Pathology, Keck School of Medicine of University of Southern California, Los Angeles, CA, USA

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Abstract
We report the case of a 15-year-old female with a medulloepithelioma who underwent enucleation following plaque brachytherapy. To our knowledge, this is the first report of the histopathological findings of medulloepithelioma following brachytherapy. Histopathology revealed radiation-related changes such as hyalinized vessels, photoreceptor atrophy, degenerative changes of the retina, and preretinal fibrous tissue. Additionally, the retinal nerve fiber layer showed signs of cystoid edema. Subretinal fluid, not commonly associated with medulloepithelioma, was also noted on histology; interestingly, it was seen adjacent to the tumor on B scan prior to brachytherapy. After enucleation, hyaline cartilage was also present on histology, although neuroepithelium was absent. Although we do not have pathological confirmation that neuroepithelium was present prior to brachytherapy, it is possible that brachytherapy preferentially affected neuroepithelium, leading to decrease in tumor size.

Introduction
Intraocular medulloepithelioma is a rare embryonal tumor derived from the nonpigmented ciliary body epithelium [1, 2]. Microscopically, its appearance is similar to the primitive retina and medullary epithelium of brain tissue [1, 3]. Although there are rare cases of
this neoplasm manifesting in adulthood, it commonly presents in children aged between 2 and 10 years old. Given that small tumors do not usually cause functional visual changes, patients are usually initially asymptomatic. Tumors are often detected when they grow large enough to be visualized through the pupil or when they begin causing symptoms [1, 4–6], which include vision loss due to retinal detachment, lens subluxation or cataract formation, leukocoria, pain due to neovascular glaucoma, or changes in the eye’s appearance [1]. Misdiagnosis or delay in diagnosis is common. Kaliki et al. [5] found that 88% of cases in their study were initially misdiagnosed. Broughton and Zimmerman [1] found that most cases had a delay in surgical therapy of at least 1 year after signs or symptoms presented. Of 10 cases that Shields et al. [4] described, 6 had a delay in diagnosis.

Management options for medulloepithelioma have traditionally included enucleation and observation, though treatment options are evolving. Enucleation is the most frequent surgical treatment, given these tumors often cannot be safely resected and have a high recurrence rate [1]. Plaque brachytherapy has also been shown to be effective for small- to medium-sized tumors without extraocular extension in several small case series [5, 7–10]. Although the histopathology of medulloepithelioma has been well-described, to date there have been no histopathological findings reported on tumors treated with plaque brachytherapy. Here, we describe the case of a patient with medulloepithelioma who underwent enucleation following plaque brachytherapy.

Case Presentation

A 15-year-old female presented with 3 months of progressively blurry vision in the left eye. Visual acuity was 20/150–2, and intraocular pressure was normal. On confrontational visual fields, the patient was noted to have an inferonasal field cut in the left eye. Slit-lamp exam was remarkable for a temporal cataract and a large adjacent ciliary body tumor (shown in Fig. 1a). The tumor was whitish in appearance and associated with a shallow exudative retinal detachment involving the macula (shown in Fig. 1b), but no vitreous seeding or retinal infiltrative lesions were noted. B scan showed a 13.9 mm (transverse) × 7.8 mm (longitudinal) × 9.4 mm (height) ciliary body tumor with adjacent subretinal fluid and no internal calcifications (shown in Fig. 1c). A scan demonstrated moderate to high internal reflectivity throughout the tumor (shown in Fig. 1d). Exam of the right eye was unremarkable. MRI of the orbit showed a heterogeneously enhancing lobulated irregular mass centered along the posterior aspect of the ciliary body, without evidence of extrascleral extension or optic nerve involvement.

Given the clinical appearance of the tumor and ultrasound findings, medulloepithelioma was the leading diagnosis. While atypical retinoblastoma was a consideration, the lack of vitreous seeding and calcifications, as well as the patient’s age, made retinoblastoma a less likely diagnosis. Leiomyoma was also considered, although these are typically dome-shaped tumors with low to moderate internal reflectivity. Biopsy was deferred, given the risk of extraocular seeding should this tumor have been malignant, and surgical excision was not recommended, given the large size of the tumor. Given the patient’s fairly good visual potential, the patient preferred a trial of plaque brachytherapy to enucleation.

The tumor was treated with $^{125}$I plaque brachytherapy, 45 Gy over 5 days. Over the following year, there was minimal tumor regression (shown in Fig. 1e) to a size of 13.3 mm (transverse) × 7.7 mm (longitudinal) × 8.7 mm (height). While the subretinal fluid was stable initially postoperatively, by 1 year following brachytherapy, the subretinal fluid had increased (shown in Fig. 1f) despite stable tumor dimensions. Additionally, while the visual acuity improved transiently to 20/100+1, at 1 year following brachytherapy, the vision declined to 20/800+2. Given that tumor dimensions were stable, continued observation was recom-
mended. However, 14 months after brachytherapy, the patient elected to proceed with enucleation, due to persistence of the retinal detachment and poor vision.

Grossly, the left globe measured 23.5 (AP) × 24 (H) × 25 (V) mm with 9 mm of optic nerve attached. The optic nerve diameter with sheath was 4.5 mm. The cornea and sclera were unremarkable. The pupil was round and centered. Transillumination showed a weak and vague 5.5 (H) × 11 (V) mm shadow from approximately 1:00 to 4:00.

The eye was opened horizontally. The cornea, anterior chamber angles, and iris were unremarkable. The iris was not involved by tumor. The lens was minimally displaced nasally.

**Fig. 1.** Clinical appearance of medulloepithelioma prior to and following plaque brachytherapy. **a** Slit-lamp photo of the left eye demonstrating a large whitish ciliary body tumor. **b** Fundus photo of the left eye demonstrating the large medulloepithelioma temporally with adjacent subretinal fluid involving the macula. **c** Transverse B scan at 3:00 demonstrating the medulloepithelioma with adjacent exudative retinal detachment (arrowhead). **d** Scan showing moderate to high internal reflectivity throughout the tumor. **e** Slit-lamp photo showing stable appearance of the medulloepithelioma 1 year following brachytherapy. **f** Longitudinal B scan at 3:00 demonstrating interval worsening of the subretinal fluid (asterisk) adjacent to the tumor.
There was a white elongated firm tumor in the temporal ciliary body corresponding to the location of the shadow seen on transillumination (shown in Fig. 2a). The tumor basal diameter was 6 mm, and the height (thickness) was 5.5–6 mm. There was focal increased pigmentation along the tumor base. The posterior and inferior portions of the vitreous cavity were partially filled with cobweb-like whitish membranes. The retina was diffusely detached secondary to a large gelatinous subretinal exudate. The sclera was not involved by tumor.

H&E-stained sections revealed a tumor located in the temporal ciliary body, in the pars plana and extending minimally or overhanging the peripheral retina (shown in Fig. 2b). The tumor on the slides measured 5 mm in basal diameter and 7 mm in thickness. The tumor seemed to originate from the nonpigmented ciliary epithelium. The tumor was elongated (taller than wide) and was composed only of heteroplastic elements, namely cartilage admixed with small amounts of loose, myxoid stroma, containing few bland spindled and stellate cells (shown in Fig. 2c). Eosinophilic hyalinized tissue surrounded the cartilage and myxoid stroma. Toward the posterior base of this tumor and adjacent to peripheral retina, there was reactive proliferation of pigmented epithelium admixed with small fragments of disorganized neural retina with cystoid change (shown in Fig. 2d). No recognizable neoplastic neuroepithelium was identified.

Extensive eosinophilic subretinal exudate was present. The neural retina showed varying degrees of photoreceptor degeneration throughout. Immediately posterior to the tumor base, the peripheral temporal retina was thinner and demonstrated some hyalinization presumably around blood vessels and microcystic changes (shown in Fig. 3a). The nasal peripheral retina
also displayed cystic changes. Focally, a cuff of small lymphocytes surrounded two peripheral temporal retinal arterioles. Nasally, there was focal hyalinization in the outer retina. The remaining neural retina showed patchy edema of the nerve fiber layer and mild dilatation of vascular channels (shown in Fig. 3c). Focal subneural retinal fibrous membranes were seen sometimes admixed with pigmented cells. Preretinal fibrocellular membranes with or without tiny blood vessels were also present within the vitreous cavity (shown in Fig. 3d). These histopathological features in the retina were likely radiation-related.

**Discussion**

Medulloepithelioma is typically nonpigmented and appears irregularly gray-white to pink in color [1, 2]. Microscopically, it is composed of multilayered sheets and cords of pseudostratified, poorly differentiated neuroepithelial cells surrounded by hypocellular stroma rich in hyaluronic acid [1, 3]. In more than half of cases, multiple cysts are present within the tumor [1, 4, 5]. These cysts can detach from the tumor and relocate into the anterior chamber or vitreous cavity [4].

Tumors are classified as nonteratoid or teratoid, as well as benign or malignant [1, 11]. Nonteratoid tumors comprise only primitive medullary epithelium, which is usually positive for vimentin and neuron-specific enolase [9, 12–14]. Teratoid tumors also exhibit heteroplastic elements such as mature hyaline cartilage, striated muscle, and brain tissue [1]. Features that help distinguish medulloepithelioma from retinoblastoma, which the poorly differentiated cells may resemble, include neuroepithelial tubules and lack of calcification [3]. In addition, Flexner-Wintersteiner and Homer-Wright rosettes can be seen, but they are usually larger and more cellular compared to those seen in retinoblastoma [1, 3].

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**Fig. 3.** a Peripheral retina immediately adjacent to tumor showing occluded hyalinized vessels, degenerative changes in retina, photoreceptor atrophy, subretinal exudeate, and preretinal fibrous tissue (asterisk) (×10). b Fibrous bands (arrowhead) attached to the disc (×4). c RNFL with cystoid change/edema (×10). d Preretinal fibrocellular membrane (×20).
There are several reports of successful plaque brachytherapy treatment with $^{125}$I and $^{106}$Ru as primary treatment, especially for small- or medium-sized tumors [5, 7–10]. Ang et al. [7] described 5 cases in which $^{125}$I plaque was used; in 4 of 5 cases, the tumors regressed, and there was no recurrence or metastases at follow-up, which varied from 12 months to 17 years. Poon et al. [8] described the use of $^{106}$Ru for 5 patients with tumors less than 5 mm in height. Eighty percent regressed, and none relapsed or required enucleation at 26 months of follow-up [8]. Kaliki et al. [5] described the use of plaque brachytherapy as primary treatment in 3 tumor cases, followed by slow regression and no recurrence after 1 year.

Although the pool of literature on the use of brachytherapy as primary treatment for medulloepithelioma is relatively small, our findings show that this modality can achieve limited success. In this case, the tumor's basal diameter decreased from 20 mm as assessed by ultrasound to 6 mm at enucleation, approximately 13 months after the procedure. Height of the mass decreased from 9.4 mm to between 5.5 and 6 mm. Additionally, vision improved as assessed by confrontational visual fields by the second follow-up visit, approximately 7 months after the procedure. Visual acuity of the eye also improved from 20/200−2 preoperatively to 20/100+1 at the second follow-up visit. However, due to persistent subretinal fluid and retinal detachment leading to poor vision, the eye was eventually enucleated.

Subretinal fluid is not commonly associated with medulloepithelioma. Ang et al. [7] cited the presence of subretinal fluid as an adverse effect after treatment with brachytherapy in the case of a 10 month-old female. Lee et al. [15] also described diffuse subretinal fluid as visualized by MRI of benign teratoid medulloepithelioma in the case of a 9-year-old male; in this case, however, primary treatment was enucleation. In our case, the subretinal fluid was present prior to brachytherapy and was probably secondary to the tumor, although its persistence could be related to radiation-related complications.

Brachytherapy is associated with a number of ophthalmic complications, including radiation retinopathy. The risk of developing radiation retinopathy depends on factors such as total dose, fraction size, and comorbid conditions. Histological findings include subretinal fibrosis, capillary occlusion and dilatation, and changes to the retinal pigment epithelium [16]. Success in long-term suppression of radiation maculopathy has been noted with intravitreal anti-vascular endothelial growth factor and triamcinolone acetonide injections [17, 18]. In cases of suspected radiation retinopathy following brachytherapy, timely intravitreal injections may be an important therapeutic option to consider for preservation of vision.

To our knowledge, this is the first description of the histopathological findings of medulloepithelioma after brachytherapy. Significant findings, which were likely radiation-related, included hyalinized vessels, degenerative changes in the retina, preretinal fibrous tissue, and subretinal fluid. Interestingly, although hyaline cartilage was present on histology as determined after enucleation, neuroepithelium was absent. It is possible that brachytherapy preferentially affected the neuroepithelium, leading to reduction in size of the mass. One important caveat however is that the diagnosis of medulloepithelioma was made clinically due to risk of extraocular seeding. Therefore, we do not have pathological confirmation of the presence or extent of neuroepithelium prior to brachytherapy.

**Statement of Ethics**

Approval by the Institutional Review Board at the University of Southern California was waived for this retrospective case report study. The study was performed in accordance with HIPAA guidelines and in compliance with the tenets of Declaration of Helsinki. Written informed consent was obtained from the patient, who is now over 18 years old, for publication of the details of her medical case and any accompanying images.
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors made substantial contributions to the conception or design of this work, as well as drafting and revision of the manuscript, and provided final approval for the version to be published. Ms. Sukriti Mohan and Dr. William Gange drafted the manuscript and developed associated figures. Dr. Jonathan Kim provided his surgical expertise on the case and assisted in revising the article for important intellectual content. Dr. Maria Sibug Saber provided integral histopathology slides and interpretation of them.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author Dr. Maria Sibug Saber.

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