



Case report

Successful treatment of metastatic congenital intraocular medulloepithelioma with neoadjuvant chemotherapy, enucleation and superficial parotidectomy

Justin B. Hellman^a, George J. Harocopos^{b,c}, Lily Koo Lin^{a,*}^a Department of Ophthalmology and Vision Science, University of California at Davis, Sacramento, CA, USA^b Department of Ophthalmology and Visual Sciences, Washington University, St. Louis, MO, USA^c Department of Pathology and Immunology, Washington University, St. Louis, MO, USA

ARTICLE INFO

Keywords:

Medulloepithelioma
Enucleation
Chemotherapy
Pediatric
Metastases

ABSTRACT

Purpose: To report a case of metastatic intraocular medulloepithelioma successfully treated with neoadjuvant chemotherapy, superficial parotidectomy, and enucleation.

Observations: A 5-year-old male with history of cataract surgery, glaucoma drainage device, endocyclophotocoagulation, scleral patch grafting, and chronic posterior “inflammation” in a blind left eye presented with a rapidly enlarging painful mass under the left upper eyelid. Biopsy of the conjunctival mass and fine needle aspiration of an enlarged preauricular lymph node revealed medulloepithelioma, which was also seen in the left parotid gland on positron emission tomography (PET) scan. The patient's father refused exenteration, so the patient received 3 cycles of vincristine, cisplatin, cyclophosphamide, and etoposide per a retinoblastoma protocol. Repeat magnetic resonance imaging (MRI) showed regression of ocular extension, and an enucleation was performed, histologically confirming the diagnosis of malignant, non-teratoid medulloepithelioma. The child later underwent superficial parotidectomy and received an additional round of chemotherapy. There has been no evidence of recurrence for 9 years.

Conclusions and importance: There is no standard treatment for metastatic intraocular medulloepithelioma. The neoadjuvant chemotherapy regimen used in our patient led to regression of the extrascleral extension of the tumor, allowing for enucleation rather than a more disfiguring exenteration, as well as likely improving his prognosis. We believe that it is reasonable to consider neoadjuvant chemotherapy for patients with extrascleral and/or metastatic medulloepithelioma.

1. Introduction

Medulloepithelioma is a rare childhood embryonal tumor arising from primitive neuroepithelium lining the optic cup.¹ Within the eye it usually develops in the nonpigmented ciliary epithelium of the pars plicata, but it has also been noted to arise in the retina, iris, and optic nerve.^{2–6} It is thought to arise in utero and typically presents in childhood, with 78% of patients presenting in the first decade.⁷ Typical clinical presentations include unilateral neovascular glaucoma, cataract, anterior uveal cysts (sometimes free-floating cysts in the anterior chamber), staphyloma, and “uveitis.” It is not uncommon for intraocular medulloepithelioma to have a delay in diagnosis after patients have undergone ocular surgery for cataract or glaucoma, which can lead to extrascleral extension and metastasis.^{5–8} Cases confined to the eye can be successfully managed with enucleation, though cryotherapy

and plaque radiotherapy can be considered for small tumors. Extrascleral extension occurs in 10–19% of cases and is a poor prognostic factor which can lead to metastasis and death.^{6–9} Given the rare occurrence of metastatic medulloepithelioma, there is no standard treatment protocol. We present a patient with non-teratoid malignant medulloepithelioma with extrascleral extension and metastases to the preauricular lymph nodes and parotid gland who was successfully treated with chemotherapy (vincristine, cisplatin, cyclophosphamide, and etoposide), superficial parotidectomy, and enucleation with disease-free survival of 9 years.

2. Case report

A 5-year-old male with history of cataract in the left eye status post extraction at age 1, glaucoma of the left eye status post glaucoma

* Corresponding author. Department of Ophthalmology and Vision Science, University of California Davis Health, 4860 Y St, Suite 2400, Sacramento, CA, 95817, USA.
E-mail address: lklin@ucdavis.edu (L.K. Lin).

<https://doi.org/10.1016/j.ajoc.2018.06.019>

Received 27 January 2018; Received in revised form 8 June 2018; Accepted 19 June 2018
Available online 21 June 2018

2451-9936/© 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

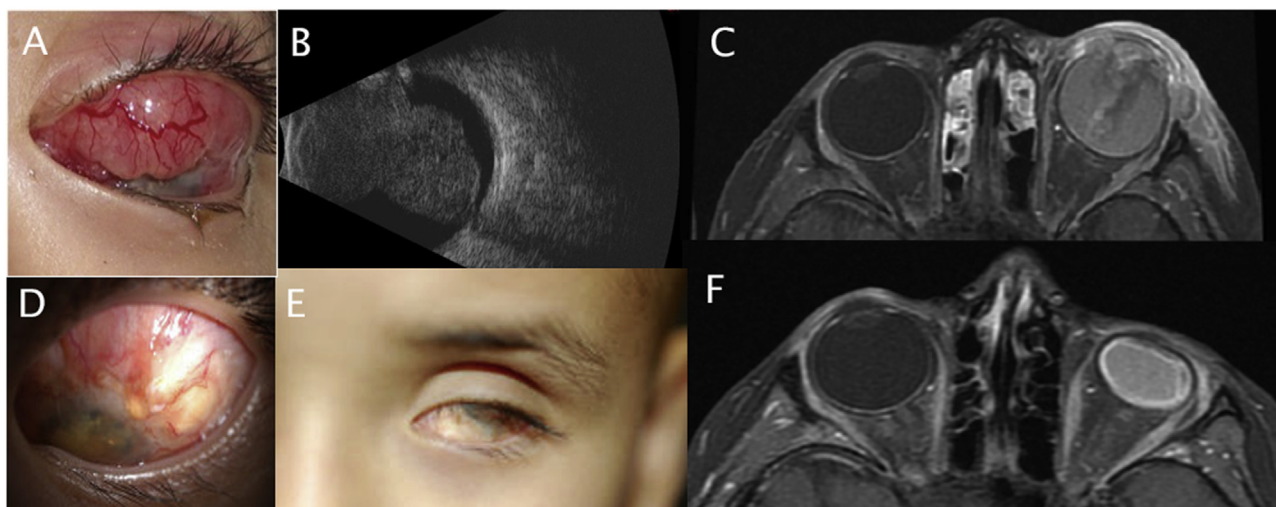


Fig. 1. (A) External photograph demonstrating extrascleral extension of the medulloepithelioma. (B) B-scan ultrasound demonstrating large intraocular mass with extrascleral extension. (C) Magnetic resonance imaging of the orbits reveals an intraocular mass of the left eye with extrascleral extension. (D–E) External photographs demonstrating clinical response after 3 cycles of chemotherapy. (F). Post-chemotherapy MRI showing regression of extrascleral extension.

drainage device and endocyclophotocoagulation at age 2, scleral patch grafting, and chronic posterior “inflammation” thought to be due to retained cortical material in a blind left eye was initially referred for enucleation at age 4, but upon oculoplastic examination was noted to have a painful mass under the left upper eyelid involving both the palpebral and bulbar conjunctiva (Fig. 1A). B-scan ultrasound (Fig. 1B) and magnetic resonance imaging (MRI; Fig. 1C) revealed a large intraocular mass of the left eye with extrascleral extension but without optic nerve extension. There was no calcification noted on the B-scan ultrasound. Biopsy of the conjunctival mass revealed sheets of poorly differentiated neuroepithelial cells, some in characteristic rosette-like structures, consistent with medulloepithelioma. A whole-body PET scan revealed metastasis in the left parotid gland. Retinoblastoma and metastatic neuroblastoma were also considered in the histologic differential diagnosis. With the histopathologic results, exenteration was recommended over enucleation. The patient’s father refused exenteration, so the patient was treated with 3 cycles of vincristine, cisplatin, cyclophosphamide and etoposide. He had an excellent response with regression of the eyelid mass (Fig. 1D–E), and repeat MRI showed regression of the extraocular extension (Fig. 1F).

Enucleation was performed along with multiple biopsies of the conjunctiva and surrounding orbital tissues. Histopathology of the enucleated globe revealed total anterior synechiae, with the anterior chamber and vitreous cavity obliterated by fibro-hyaline material, adherent posteriorly to totally detached (closed-funnel), gliotic retina, while the cornea exhibited decompensation, with calcific band keratopathy and stromal vascularization. Most notably, tumor cells were present in both the ciliary body and retina exhibiting hyperchromatic nuclei, scant cytoplasm, and nuclear molding, characteristic of the “round, blue cell,” neuroectodermal family of tumors. The tumor was more specifically categorized as malignant, non-teratoid medulloepithelioma (as opposed to retinoblastoma) based upon the tumor pattern and morphology. In the ciliary body, the “diktyoma” pattern characteristic of medulloepithelioma was appreciated, replacing a portion of the ciliary stroma (Fig. 2A). Some areas of “ghost” tumor cells were seen, along with foci of calcification and regions of fibrosis/hyalinization, and no mitotic figures were identified in the ciliary body portion of the tumor, consistent with partial tumor regression as a result of chemotherapy. However, there was an obvious cluster of tumor cells tracking through the sclera at the presumed site of the prior glaucoma drainage device (Fig. 2B), as evidenced by the presence of residual suture material, with microscopic extrascleral extension identified in that vicinity on some sections. Posteriorly, tumor was also seen

replacing a portion of the retina, with no evidence of chemotherapy effects in this portion. The tumor extended up to (but not past) the lamina cribrosa of the atrophic optic nerve (Fig. 2C) and the cut edge was free of tumor. On higher magnification (Fig. 2D), frequent mitotic figures were identified in the retinal portion of tumor, and rosette structures were relatively more prevalent than in the ciliary body portion, with the rosettes exhibiting the multi-layering and cellular elongation characteristic of medulloepithelioma (as compared to the single-layered, non-elongated cells characteristic of the rosettes in retinoblastoma). The multiple biopsies of the orbit were all negative for tumor. The patient subsequently received one more round of chemotherapy and underwent superficial parotidectomy with clear margins and has had no evidence of recurrence for 9 years.

3. Discussion

Metastatic intraocular medulloepithelioma is a very rare disease, so there have been no clinical trials to elucidate evidence-based therapy. The earliest reported case in 1941 involved recurrence with metastases after enucleation. Another early case had extrascleral extension at presentation and the patient died 3 years later.¹

Andersen in 1962 reviewed 60 medulloepithelioma cases, half of which came from the Armed Forces Institute of Pathology (AFIP). He reported a delay in diagnosis from months to 9 years. He noted that for tumors confined “within the bulb”, the prognosis was “excellent” and patients “were safe”. The cases that “perforated the bulb” had a malignant course leading to death, often from intracranial disease.⁵

Broughton and Zimmerman observed extrascleral extension in 10 of 56 patients with 3 patients dying of metastatic disease within 5 years and 3 lost to follow-up. Of the surviving patients with extrascleral extension, one was treated with exenteration, one was treated with radiotherapy and systemic chemotherapy, and 2 were treated with enucleation alone with survival at 1–5 years.⁶

In Kaliki et al.’s series of 41 patients, 3 had extrascleral extension on presentation. Exenteration was performed on one patient, and the other 2 patients underwent enucleation. All 3 later developed metastases. Each patient received chemotherapy and radiation, though the specific regimens were not reported, and one of the patients died.⁷ One patient in a series of 10 patients reported by Shields et al. had extrascleral extension without metastasis and underwent exenteration.⁸ Canning et al. presented 16 patients, 3 with extrascleral extension without metastases and all were treated with enucleation, with one receiving adjuvant radiotherapy.⁹

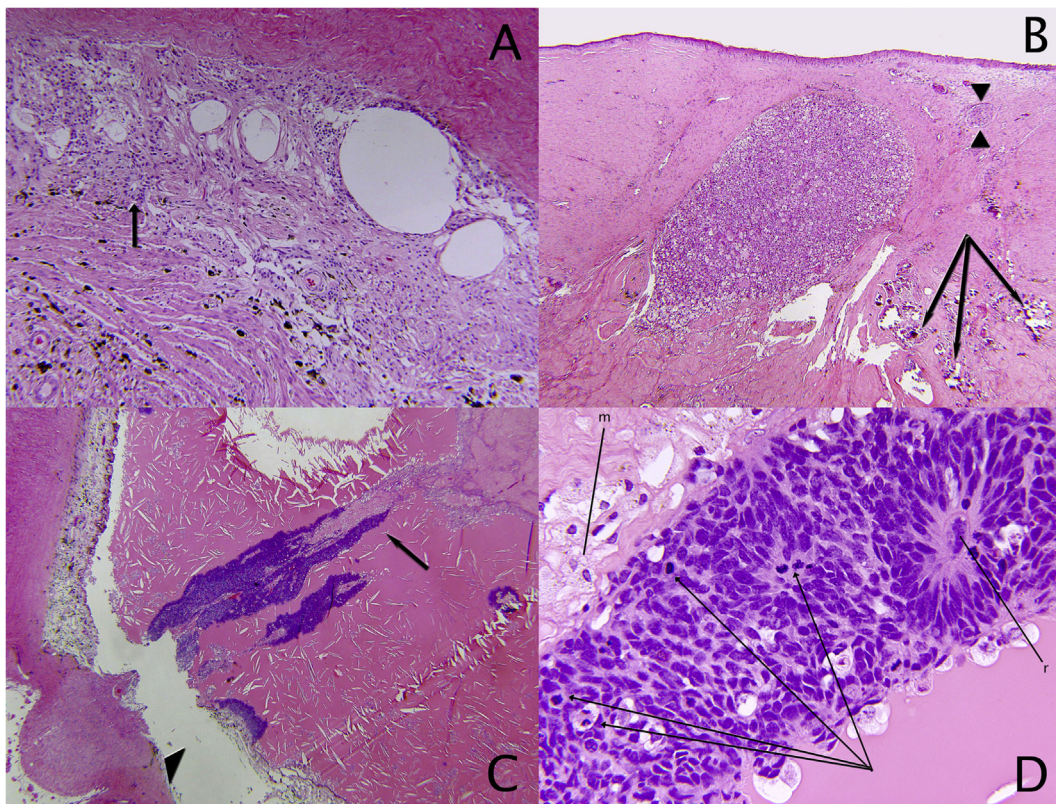


Fig. 2. Histopathology of the enucleated globe (H&E stain). (A) In the ciliary body, tumor is present in the stroma exhibiting the “diktyoma” pattern (with cystoid spaces) characteristic of medulloepithelioma. The tumor cells appear rather loosely arranged, with intervening bands of fibrosis/hyalinization, consistent with prior chemotherapy. A rosette structure (arrow) is identified (original magnification, $\times 100$). (B) In the intercalary region of the sclera, a large clump of tumor cells is seen tracking through a path consistent with the location of the prior glaucoma seton, and microscopic extrascleral extension (covered by conjunctiva) is appreciated (arrowheads). Foci of calcification (arrows) are seen adjacent to the tumor cluster (original magnification, $\times 40$). (C) Posteriorly, tumor is also seen replacing a portion of the retina, with the arrow indicating the transition zone between tumor on the lower left and totally detached, gliotic retina on the upper right. The subretinal space is filled with proteinaceous exudate containing cholesterol clefts along with several tumor cell clusters. The atrophic optic nerve is seen in the lower left corner of the frame, and the tumor extends up to (but not past) the level of the lamina cribrosa (arrowhead). Note: the band of empty space to the right of the optic nerve is artifactual (original magnification, $\times 20$). (D) Higher magnification of the retinal portion of the tumor shows densely packed tumor cells with hyperchromatic nuclei, scant cytoplasm, and nuclear molding, with multiple mitotic figures (arrows) and with a rosette structure (r) identified, exhibiting the cellular elongation and multi-layering characteristic of medulloepithelioma. Lipid-laden macrophages (m) are incidentally noted in the subretinal space (original magnification, $\times 400$).

Viswanathan et al. reported 3 cases of metastatic medulloepithelioma. All 3 patients underwent exenteration with adjuvant radiotherapy, and 1 patient received salvage chemotherapy.¹⁰ Sosinska-Mielcarek et al. presented a case of orbital recurrence with intracranial involvement after enucleation. Notably the patient did not respond to 2 rounds of bleomycin, etoposide, and cisplatin and ultimately died within 6 months.¹¹

There are only 2 prior reports of neoadjuvant chemotherapy for the treatment of metastatic medulloepithelioma. Meel et al. reported a patient with a history of left eye enucleation for intraocular medulloepithelioma and extraocular extension noted on histopathology. The patient was lost to follow-up and returned with a large left orbital medulloepithelioma with metastases to the preauricular and cervical lymph nodes. He was noted to have remission after 3 cycles of vincristine, carboplatin, and etoposide, ultimately receiving 6 cycles as well as radiotherapy to the left orbit, preauricular, and upper neck region with no recurrence of disease at 15 months.¹² Meel et al. described their case as neoadjuvant chemotherapy as it avoided exenteration and radical neck dissection. One could also argue that this was adjuvant chemotherapy as the patient had previously been enucleated before he was lost to follow-up. The second case describes a patient with an extensive 15 \times 10 cm exophytic mass of the right orbit with metastases to the preauricular, submandibular, cervical and parotid lymph nodes. Three cycles of ifosfamide, cisplatin, and etoposide were administered

with no improvement. Exenteration with excision of a temporal fossa mass, total parotidectomy, and modified neck dissection were performed along with adjuvant radiotherapy, and the patient was disease-free 3 years later.¹³

4. Conclusions

Congenital intraocular medulloepithelioma when confined to the globe is often treated successfully with a favorable prognosis. Unfortunately the diagnosis is not uncommonly delayed months or even years, often following ocular surgeries, which can lead to extrascleral extension, possibly metastatic disease and tumor-related death.^{5–8} This case highlights, as have other previously reported cases of medulloepithelioma with diagnostic delay, the importance of maintaining a high clinical index of suspicion for an intraocular tumor in cases of unilateral infantile/pediatric glaucoma or in cases of unilateral infantile/pediatric white cataract.

Despite knowing that intraocular medulloepithelioma can be associated with a delay in diagnosis, it will likely to continue to occur, as it has been repeatedly reported in the literature, as early as 1962, throughout the decades, to this present case. Given that these cases of extrascleral extension from misguided ocular surgery can lead to tumor-related death, it is important to disseminate treatment strategies that may alter this malignant course. A review of the literature reveals

several potential treatments that can be used in combination including exenteration, dissection of involved lymph nodes, radiotherapy, and chemotherapy.

Our patient received neoadjuvant chemotherapy with vincristine, cisplatin, cyclophosphamide, and etoposide, prior to surgical excision, which significantly reduced the tumor burden from “extrascleral” to nearly “intraocular”, allowing for enucleation rather than a more disfiguring exenteration. This has likely altered his clinical course from a poor prognosis associated with extrascleral extension and metastasis, to a favorable prognosis associated with tumor confined to the globe. He has demonstrated disease-free survival of 9 years. Our case is one of the very few reports in the literature describing the use of neoadjuvant chemotherapy for extrascleral, metastatic, intraocular medulloepithelioma with the longest reported follow-up. We believe that it is reasonable to consider neoadjuvant chemotherapy in cases of extrascleral, metastatic medulloepithelioma, thereby potentially avoiding disfiguring surgery as well as improving prognosis.

Patient consent

Consent to publish the case report was obtained. This report does not contain any personal information that could lead to the identification of the patient.

Acknowledgements and disclosures

No funding or grant support. All authors attest that they meet the current ICMJE criteria for Authorship. Acknowledgements: None; Conflicts of Interest: None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ajoc.2018.06.019>.

References

1. Cardell BS, Starbuck MJ, Diktyoma. *Br J Ophthalmol*. 1959;43:217–224.
2. Morris AT, Garner A. Medulloepithelioma involving the iris. *Br J Ophthalmol*. 1975;59:276–278.
3. Takei H, Florez L, Moroz K, Bhattacharjee MB. Medulloepithelioma: two unusual locations. *Pathol Int*. 2007;57:91–95.
4. Vadmal M, Kahn E, Finger P, Teichberg S. Nonteratoid medulloepithelioma of the retina with electron microscopic and immunohistochemical characterization. *Pediatr Pathol Lab Med*. 1996;16:663–672.
5. Andersen SR. Medulloepithelioma of the retina. *Int Ophthalmol Clin*. 1962;2:483–506.
6. Broughton WL, Zimmerman LE. A clinicopathologic study of 56 cases of intraocular medulloepitheliomas. *Am J Ophthalmol*. 1978;85:407–418.
7. Kaliki S, Shields CL, Eagle Jr RC, et al. Ciliary body medulloepithelioma: analysis of 41 cases. *Ophthalmology*. 2013;120:2552–2559.
8. Shields JA, Eagle Jr RC, Shields CL, Potter PD. Congenital neoplasms of the non-pigmented ciliary epithelium (medulloepithelioma). *Ophthalmology*. 1996;103:1998–2006.
9. Canning CR, McCartney AC, Hungerford J. Medulloepithelioma (diktyoma). *Br J Ophthalmol*. 1988;72:764–767.
10. Viswanathan S, Muku D, Qureshi S, Ramadwar M, Arora B, Kane SV. Orbital medulloepitheliomas - with extensive local invasion and metastasis: a series of three cases with review of the literature. *Int J Pediatr Otorhinolaryngol*. 2008;72:971–975.
11. Sosinska-Mielcarek K, Senkus-Konefka E, Jaskiewicz K, Kordek R, Jassem J. Intraocular malignant teratoid medulloepithelioma in an adult: clinicopathological case report and review of the literature. *Acta Ophthalmol Scand*. 2006;84:259–262.
12. Meel R, Chawla B, Mohanti BK, Kashyap S, Bakhshi S. Ocular medulloepithelioma chemosensitivity. *Ophthalmology*. 2010;117:2440 e1–2.
13. Sajid Q. Colossal Malignant Nonteratoid medulloepithelioma of the eye with unusual metastases: the natural history. *Int J Head Neck Surg*. 2010;1:39–42.