CASE REPORT

Intraocular medulloepithelioma: an unusual and challenging entity in paediatric population

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Abstract

Intraocular medulloepithelioma is a rare, congenital tumour of the non-pigmented ciliary epithelium. It most frequently arises from the ciliary body but can also have its origin from the retina, iris and optic nerve. The age when lesion first appears is typically around 2-10 years. Nearly 50-60% of patients having this lesion may also have secondary features such as cataract and neovascular glaucoma. Those with extrascleral medulloepithelioma are at risk for metastasis. Systemic correlation of the tumour with pleuropulmonary blastoma/DICER1 gene is reported in the literature.

Here, we report a case of a 15 years old boy with one year history of right eye proptosis and painful red right eye along with decreased vision for one week. He was assessed and operated for cataract elsewhere three years back. The ophthalmology team managed him for endophthalmitis with intravenous antibiotics, followed by 2 sessions of cryotherapy and finally an enucleation of right eye was performed due to severe pain and no vision in the involved eye. His left eye, general physical examination and systemic evaluation were normal. Histopathology revealed the diagnosis of 'malignant teratoid medulloepithelioma'. Therefore, evaluation of systemic associations for DICER1 gene mutations was performed by the oncology team. For high risk feature of scleral invasion on histopathology, he was treated with chemotherapy. Since the tumour is of rare occurrence; an international expert team with vast research experience in PPB/DICER1 associated tumours was also contacted. He was registered in International PPB/DICER1 registry where a detailed central radiology and pathology review was performed. Genetic counseling and surveillance plan was also suggested by the international registry.

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Introduction

Medulloepitheliomas are the second most prevalent type of paediatric intraocular tumours. They arise from the ciliary body from the non-pigmented ciliary epithelium, and rarely from the iris, retina, or optic nerve head. Age of presentation is typically amid 2 and 10 years with 75% to 90% of tumours revealing in the first ten years of life.1 Its systemic correlation with pleuropulmonary blastoma (PPB) family tumour and dysplasia syndrome and DICER1 gene has been documented in literature.[1]

DICER 1 gene mutation manifests as a familial cancer syndrome. Reported tumours with this mutation include pleuropulmonary blastoma, cystic nephroma, ovarian Sertoli Leydig cell tumour, thyroid hyperplasia or goiter, medulloblastoma, rhabdomyosarcoma, colon cancer, Wilm's tumour etc. This syndrome should be considered in the existence of related family history or another PPB-related tumour. As the tumour is very rare with a variable and often delayed presentation, this case report highlights the challenges faced by physicians of various subspecialty especially the oncology team in diagnosis and patient management.

Case Report

A 15 years old boy presented at Al Ibrahim Eye Hospital Karachi in August 2021 with proptosis of right eyeball for past one year. A week prior to the ophthalmologist consult he developed painful red right eye with loss of vision. At the age of 12, he was operated on for a cataract in the right eye. Patient did not have the family history of ocular or PPB-FTDS related neither tumours nor the stigmata of the DICER1 syndrome.

Based on clinical and radiologic assessments; he was initially managed for endophthalmitis. With no response to intravenous antibiotic and no vision in the right eye, a EUGA was performed that revealed right eye congestion and swelling with uveal prolapse at 12^{o} clock near the

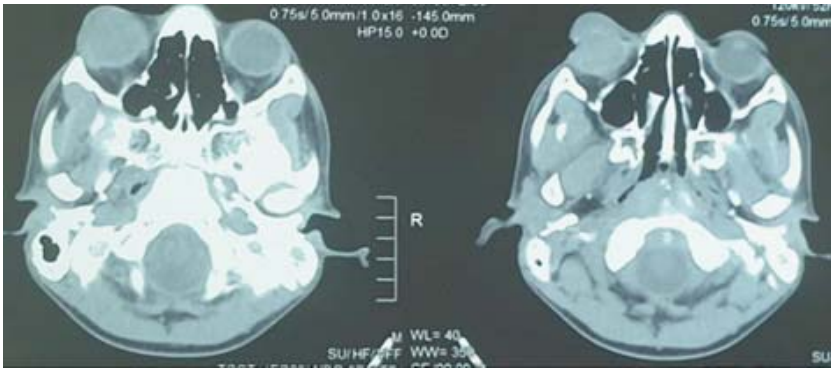

Figure-1: CT scan objectified an exophytic intraocular mass, causing deformation of the right eyeball, with no calcifications.

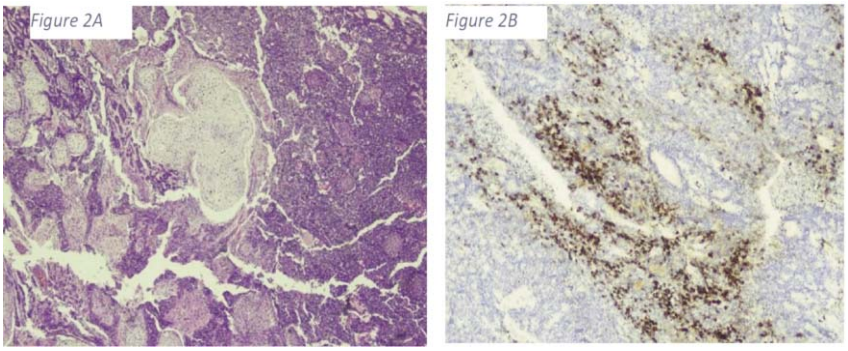

Figure-2 (A-B): Tumour with heterologous component (cartilage).

limbus. His general physical examination and systemic evaluation were unremarkable.

CT Scan orbits revealed an exoplanetic intraocular mass casuing deformity of the right eyeball with no calcification (Fig-1).

Performance of B- Scan ultrasonography (US) established a heterogeneous ciliary body mass with no calcifications.

Although rare for the age, with the suspicion of retinoblastoma and no vision in involved eye, the patient underwent enucleation of right eye and the specimen was submitted for histological examination. Patient was then followed up at oncology department, National Institute of Child Health, Karachi for further management.

Macroscopic description: The enucleated eye measured 3.5cm x 2.5cm x 2.0 cm. A pale white lesion measuring 3cm x 2cm involving the anterior chamber and reaching the cornea and lens was identified.

Microscopic description: Infiltrating lesion arranged in the form of ribbons and tubules composed of partly differentiated neuroectodermal cells. Individual cells show pleomorphic to hyperchromatic nuclei with increased nuclear to cytoplasmic ratio. Differentiation into Homer-Wright rosettes and Flexner–Wintersteiner rosettes were present. The tumour infiltrated the sclera, retina, sub-retinal space, and choroid (fig. 2A and 2B). This neoplastic lesion also exhibits heterologous elements comprising of cartilage. Mitotic activity was also noted. Immunohistochemical analyses of the sample revealed positive staining for CD56, CD99 and synaptophysin. The diagnosis of malignant teratoid medulloepithelioma was made.

Contrast enhanced Magnetic Resonance (MR) imaging of brain and orbit was performed with dedicated orbital protocol four weeks after surgery in which abnormal soft tissue thickening measuring 2.7cm x 1.4cm x 2.6cm was appreciated along anterior, lateral superior aspect abutting the lateral rectus muscle. Other extraocular muscles appeared normal with homogenous postcontrast enhancement.

As the patient had high risk histology features including scleral invasion and radiologic finding of suspicious extra-ocular involvement, he was discussed in the intracity multidisciplinary tumour board, to discuss further management options. Patient has also been registered in International PPB/DICER1 registry. Central.

Histology review substantiated the diagnosis of ciliary body medulloepithelioma with heterologous differentiation Figure-2(A-B). There were features which had parallels with pleuropulmonary blastoma as well as some of primitive central nervous system tumours in the DICER 1 setting. Based on tumor board consensus, adjuvant chemotherapy was started. 6 cycles of CEV protocol (Carboplatin, Etoposide, Vincristine) were given at 3 weekly interval. End of therapy assessment showed only post-surgical changes.

Discussion

Ocular medulloepithelioma is a rare embryonal tumour emerging from the primitive medullary epithelium. The tumour is archetypally unilateral, and there are no acknowledged risk factors with no gender or racial partialities. It has been designated formerly by various names such as teratoneuroma and diktyoma. However, Grinker created the medulloepithelioma term first but included all the adult and embryonal tumour of the ciliary body under one umbrella.[2] It was not until 1980 when

Zimmerman and Sobin restricted the use of the term to refer exclusively to congenital tumours arising from embryonal fragments of the ciliary body medullary epithelium.[3]

Although most occur sporadically, an association of intraocular medulloepithelioma with PPB and DICER 1 has been reported in literature.[1]

DICER 1 gene is an autosomal dominant trait located at 14q32.13 and manifests as a familial cancer syndrome, known as Pleuropulmonary Blastoma Family Tumour and Dysplasia Syndrome (PPB-FTDS). Through the work of Kaliki S et al[4] in which, they analyzed 41 cases of ciliary body epithelioma, it was found that < 5% of patients with medulloepithelioma have a history of PPB. For this reason, we registered our patient in the International PPB Registry; and the registry confirmed the histologic features in our patient which has parallels with pleuropulmonary blastoma as well as DICER 1.

Clinical suspicion of tumour is often unnoticed and most patients are treated for secondary complications of the tumour before it is learnt that there is an underlying mass causing problems. Most common presenting symptoms include loss of vision (27%), leucocoria (20%), and painful red eye (20%). As the tumour is rare, symptoms are often overlooked, patients are often treated for secondary complications like cataract or glaucoma before the underlying tumour is identified.[5] In our case report, the patient had a cataract and later presented with painful red eye, before the diagnosis was finally established.

The diagnosis of medulloepithelioma is to be made by clinical assessment with utilization of imaging modalities and more importantly by ocular examination findings. However, histopathology remains the hallmark for definitive diagnosis. The imaging modalities include Ultrasound B-scan, Fluorescein angiography and Magnetic resonance imaging (MRI).

Ultrasound B-scan will demonstrate cysts, areas of cartilage and is also an efficient way to dig out the location and size of the tumour. MRI is considered as superior imaging modality due to its higher resolution for pre-operative planning to see the extent and characterization of the lesion. Masses appear hypointense signals on T1 weighted and hyperintense on T2 weighted images respectively. Intra-tumoural cysts are considered as pathognomonic feature readily picked by MRI Furthermore, any extra-ocular or extra-scleral invasion of tumor can be caught on this imaging modality.[6]

Differential diagnosis of medulloepithelioma includes other ocular tumours such as retinoblastoma, malignant melanoma, or secondary involvement of orbit in Ewing sarcoma, Rhabdomyosarcoma, and Neuroblastoma.

Histologically, medulloepithelioma is classified into teratoid and nonteratoid types. Teratoid variety, which represents 40% of all medulloepithelioma, is distinguished by the presence of heterologous elements, such as cartilage, skeletal muscle, and brain tissue, whereas nonteratoid medulloepithelioma is a pure proliferation of cells of the medullary epithelium.[7] Our patient's histologic specimen also showed the presence of cartilage. Features of malignancy include the presence of sarcoma-like elements or undifferentiated neuroblastic cells, nuclear pleomorphism, mitotic index and invasion of uvea, cornea, or sclera; 1 we too, have found scleral involvement in our patient.

Treatment options like local resection, plaque radiation therapy and cryotherapy are reserved for small lesions or recurrent tumours. Enucleation is the treatment of choice for large size and invasive tumours in the absence of extra-ocular spread. Hellman et al[8] gave a successful trial of 3 cycles of neoadjuvant chemotherapy using retinoblastoma protocol in intraocular medulloepithelioma, and post-chemotherapy imaging showed regression of ocular extension of tumour. Similarly, another case report revealed complete regression of ciliary body medulloepithelioma with intravitreal and intracameral melphalan injections.[9] Systemic prognosis is favourable, but those with extraocular extension and orbital involvement demonstrate risk for local recurrence and metastasis. Follow-up is therefore, mandatory. KA Schultz et al[10] has recently published recommendations for the genetic testing and surveillance strategies for DICER 1 associated tumours. Our patient is now off therapy for the last six months and is in remission.

Conclusion

Medulloepithelioma of ciliary body is a very rare entity; specifically teratoid variety that is our case. Its management is also challenging as the condition is often misdiagnosed. Imaging is often inconclusive due to multiple mimics but plays an important role for pre-operative road mapping. Enucleation is a standard treatment for advanced intraocular tumour. The role of systemic chemotherapy has been documented in the literature for advanced disease; owing to its ability of decreasing tumour size. A multi-disciplinary approach and genetic testing is therefore recommended as there is still no standard of care for this tumour.

Consent: Informed consent of the guardians for publishing this case was taken.

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Conflict of Interest: None.

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References

1. Tadepalli SH, Shields CL, Shields JA, Honavar SG. Intraocular medulloepithelioma - A review of clinical features, DICER 1 mutation, and management. Indian J Ophthalmol 2019;67:755-62. doi: 10.4103/ijo.IJO_845_19.
2. Grinker RR. Gliomas of the retina: including the results of studies with silver impregnations. Arch Ophthalmol 1931;5:920-35. doi:10.1001/archopht.1931.00820060088009.
3. Campbell RJ. Histological Typing of Tumours of the Eye and Its Adnexa, 2nd ed. Heidelberg, Germany: Springer Berlin, 1998; pp 115.
4. Kaliki S, Shields CL, Eagle RC Jr, Vemuganti GK, Almeida A, Manjandavida FP, et al. Ciliary body medulloepithelioma: analysis of 41 cases. Ophthalmology 2013;120:2552-9. doi: 10.1016/j.ophtha.2013.05.015.
5. Yazicioglu T, Yavuzer D, Şimşek Ş. Intraocular medulloepithelioma: case series. Ophthalmol J 2021;6:27–30. doi: 10.5603/oj.2021.0002
6. Ashour OZ, Stalling M, Ramsey J, Straka DG, Pierson CR, Martin LC. Intraocular Medulloepithelioma: AIRP Best Cases in Radiologic-Pathologic Correlation. Radiographics 2018;38:194-9. doi: 10.1148/rg.2018170160.
7. Saunders T, Margo CE. Intraocular medulloepithelioma. Arch Pathol Lab Med 2012;136:212-6. doi: 10.5858/arpa.2010-0669-RS.
8. Hellman JB, Harocopos GJ, Lin LK. Successful treatment of metastatic congenital intraocular medulloepithelioma with neoadjuvant chemotherapy, enucleation and superficial parotidectomy. Am J Ophthalmol Case Rep 2018;11:124-7. doi: 10.1016/j.ajoc.2018.06.019.
9. Stathopoulos C, Gaillard MC, Schneider J, Munier FL. Successful treatment of ciliary body medulloepithelioma with intraocular melphalan chemotherapy: a case report. BMC Ophthalmol 2020;20:239. doi: 10.1186/s12886-020-01512-y.
10. Schultz KAP, Williams GM, Kamihara J, Stewart DR, Harris AK, Bauer AJ, et al. DICER1 and Associated Conditions: Identification of At-risk Individuals and Recommended Surveillance Strategies. Clin Cancer Res 2018;24:2251-61. doi: 10.1158/1078-0432.CCR-17-3089.