• Letter to the Editor •

Intraocular medulloepithelioma in children: clinicopathologic features itself hardly differentiate it from retinoblastoma

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Dear Editor,

I am Dr. Jinho Lee from the Department of Ophthalmology, Seoul National University Hospital, Seoul, Korea. I am writing to present five case series of intraocular medulloepithelioma. Medulloepitheliomas are the second most common type of pediatric intraocular tumors. They display clinical characteristics similar to retinoblastomas, such as leukocorias and intraocular endophytic masses, and are extremely difficult to clinically differentiate from retinoblastomas. Recently, immunohistochemical and molecular biologic analyses have been actively performed to identify the unique features of medulloepithelioma[1-5]. This case series described the clinical, radiological, and pathological (including immunohistochemistry) features of intraocular medulloepithelioma. This study was approved by local ethical committee of Seoul National University Hospital. Written consents were obtained from the parents of each child.

All patients were diagnosed between January 2008 and December 2015 at the Seoul National University Hospital and the Seoul Metropolitan Government-Seoul National University Boramae Medical Center. Two patients underwent surgery in our hospital and were followed up regularly afterwards. The other three patients were referred to our clinic shortly after visits to the local clinics (2, 4d, and 2wk later). The median age at initial diagnosis was 3y (range, 8mo to 12y) and boys were predominant (ratio, male to female=4:1) in the study cohort. Case 2 has already been reported by our group in Korean[6]. All cases were unilateral. Tumor mass appeared as typically hypervascular with white or red coloration. Computed tomography (CT) imaging revealed calcification, similar to that seen in retinoblastomas, in three patients (Cases 1, 2, and 3).

All five children underwent enucleation. During the follow-up period (median, 5.3y; range, 1.1-10y), two children developed metastases in their ipsilateral parotid gland. Microscopically, primitive neuroepithelial cell nests were surrounded by mesenchymal tissue rich in hyaluronic acid. Under higher magnification, neuroepithelial cells were arranged in anastomosing cords and tubules. Undifferentiated neuroblastic cells resembling cells from retinoblastomas were observed adjacent to neuroepithelial rosettes (Figure 1). In teratoid medulloepitheliomas, heterotopic tissue also was present, most of which was mature hyaline cartilage.

There were no specific immunohistochemical markers to help differentiate medulloepithelioma from retinoblastoma. The primitive neuroepithelial components were intensely immunoreactive for nestin and vimentin. The neuronal markers, including synaptophysin, neuron specific enolase and CD56, were variably positive. The neuroepithelium might show patchy expression of cytokeratins, which possibly are helpful for diagnosis of medulloepithelioma, but which were not observed in the retinoblastoma (Figure 2). The detailed clinical findings and results of immunohistochemical staining are provided in Table 1. Also, the detailed clinical and radiological features of the tumor are summarized in Table 2.

Case 1 A 3-year-old boy was admitted due to a corneal discoloration in his left eye with an unknown onset period. He had been diagnosed with persistent pupillary membrane (PPM) of the left eye and undergone pupilloplasty and posterior synechiolysis at the age of 14mo. Two years later,

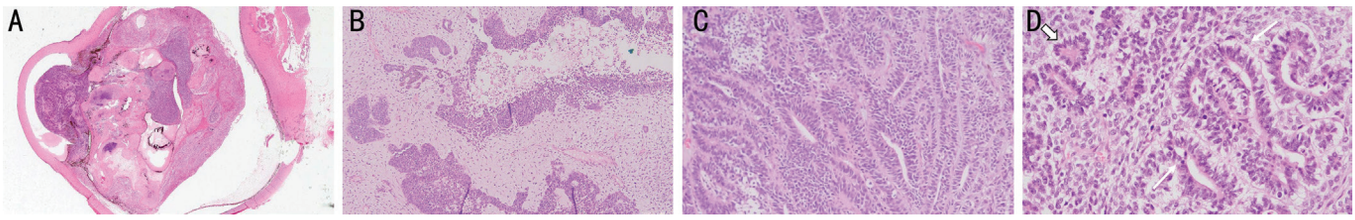

Figure 1 H&E staining of teratoid medulloepithelioma (Case 1) A: A 1.8×1.8×1.6-cm^3-sized endophytic mass is shown without extraocular involvement (×10); B: Primitive neuroepithelial cell nests are surrounded by mesenchymal tissue rich in hyaluronic acid; C: Neoplastic pseudostratified neuroepithelial cells are arranged in tubular and trabecular patterns (×200); D: Both Homer Wright (thick arrow) and Flexner-Wintersteiner rosettes (thin arrow) are observed (×400).

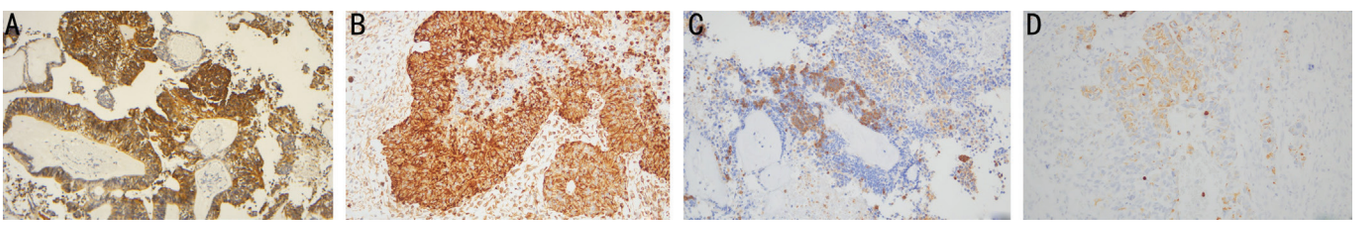

Figure 2 Representative images of various immunohistochemical markers Tumor cells are diffusely positive for CD56 staining (A) and nestin (B). There are some patchy expressions of synaptophysin (C) and cytokeratin (D).

Table 1 Clinical and immunohistochemical features of the patients in our case series

Case	Age/sex	Eye	Clinical findings	Final diagnosis	Positive IHC markers
1	3y/M	OS	Vascular mass in anterior chamber	Teratoid medulloepithelioma	Vimentin; nestin; CD56; cytokeratin; myogenin (teratoid); desmin (teratoid)
2	9y/M	OS	Retinal hypervascular mass	Teratoid medulloepithelioma	Vimentin; NSE; CD56; S-100
3	12y/M	OD	Protruding mass through cornea	Teratoid medulloepithelioma	Vimentin; nestin; CD56; NSE; S-100; GFAP; synaptophysin
4	8mo/M	OS	Funnel-shaped retinal detachment	Nonteratoid medulloepithelioma	Vimentin; nestin; CD56; cytokeratin; synaptophysin
5	8mo/F	OD	Posterior synechiae	Nonteratoid medulloepithelioma	Nestin; CD56; cytokeratin; synaptophysin (weak)

M: Male; F: Female; OS: Left eye; OD: Right eye; IHC: Immunohistochemical; NSE: Neuron specific enolase; GFAP: Glial fibrillary acidic protein.

Table 2 Clinical characteristics of the tumor in our series

Feature	Data
Anterior segment, *n* (%)	
Episcleral feeder vessels	2 (40)
Iris heterochromia	1 (20)
Iris neovascularization	1 (20)
Corectopia	2 (40)
Ectropion uveae	0
Cataract	1 (20)[a]
Lens subluxation or dislocation	1 (20)
Secondary neovascular glaucoma	1 (20)
Posterior segment, *n* (%)	
Retrolental membrane	2 (40)
Vitreous opacity	3 (60)
Retinal detachment	3 (60)
Extraocular tumor extension, *n* (%)	2 (40)
Intratumoral calcification, *n* (%)	3 (60)
Intratumoral cysts, *n* (%)	0
Largest basal dimension, mm (range)	
Median	12 (4.38-17)
Tumor thickness, mm (range)	
Median	10 (1.69-16)

[a]One patient had already undergone lensectomy for primary misdiagnosis.

a highly vascularized mass was observed through the cornea (Figure 3). The B-scan ultrasonography (US) examination showed a diffuse heterogeneous echogenic vitreous opacity containing multiple small highly echoic lesions without any visible contours of the intraocular mass. On a CT scan, a 1.6×1.7×1.6 cm^3 irregular intraocular mass was found with multifocal small calcifications. The patient underwent enucleation and was diagnosed with a malignant teratoid medulloepithelioma. Fourteen months later, the patient developed a metastatic tumor in his left parotid gland and underwent total parotidectomy with a lymph node dissection. He was then treated with chemotherapy, followed by autologous peripheral blood stem cell transplants. During the five-year follow-up period, there were no signs of recurrence.

Case 2 A 9-year-old boy presented with a prolonged conjunctival injection and decreased visual acuity to hand motion, which was incidentally found in his left eye two days before visiting the emergency room. His visual acuity was 20/20 at a routine examination five months ago. Slit-lamp examination revealed a protruding ciliary body touching the cornea, and a neovascular retrolental membrane. Funduscopic examination showed a hypervascular mass and a diffuse

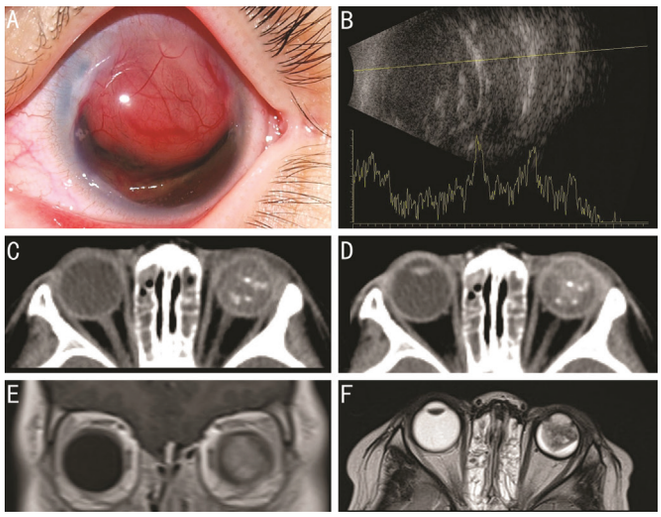

Figure 3 Clinical and radiological images of a 3-year-old boy (Case 1) A: A reddish highly vascularized mass is identified superior to the cornea; B: B-scan ultrasound images show a diffuse heterogeneous echogenic vitreous change without any definite evidence of intraocular mass or cyst. Multiple small highly echoic lesions were included. C, D: A CT scan shows a 16×17×16-mm^3-sized irregular intraocular mass. C: The mass including its multifocal stippling calcifications is well-visualized on the pre-contrast image; D: The tumor shows marked enhancement on the post-contrast image; E: Magnetic resonance imaging (MRI) reveals the presence of a heterogeneous intraocular tumor in the T1-weighted image with Gadolinium enhancement; F: A seagull-like hyperintense signal abnormality is observed in the T2-weighted image, consistent with retinal detachment.

proliferative vitreoretinopathy with retinal detachment. CT scan revealed a calcified mass. MRI showed a T1-hyperintense and a T2-hypointense solid mass arising between the inferonasal iris and lens, along with diffuse subretinal fluid. The patient underwent enucleation under suspicion of retinoblastoma. The pathological findings were consistent with a benign teratoid medulloepithelioma. No post-enucleation recurrence or metastasis was observed during the ten-year follow-up period.

Case 3 A 12-year-old boy was admitted with painful blindness in his right eye that had developed after a trauma. At the age of five, the patient had been diagnosed with persistent fetal vasculature (PFV) and had undergone lensectomy and pupilloplasty. A red round mass protruded from the right eyeball (Figure 4). A CT scan revealed intratumoral calcification with marked enhancement of the mass and the adjacent orbital tissue, indicating an extraocular extension. The patient underwent enucleation of his right eyeball and was then diagnosed with a malignant teratoid medulloepithelioma. Five months after the surgery, a metastasis was found in the right parotid gland and he underwent total parotidectomy. Despite additional adjunctive chemotherapy with local radiotherapy, a new metastasis occurred at the right temporal fossa.

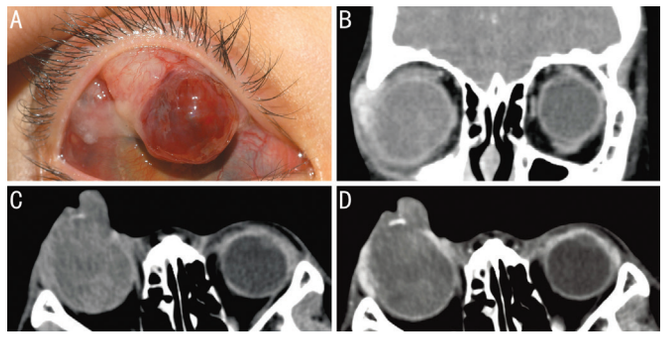

Figure 4 Clinical and radiological images of a 12-year-old boy (Case 3) A: A red flesh lobulated mass with a stalk protruding from the right eyeball; B: In the coronal CT image, the mass is destructing and protruding through the right temporal fossa. The pre-contrast (C) and post-contrast (D) axial CT images reveal a protruding mass in the right eye. D: A superolateral orbital enhancement is found, consistent with the orbital extension.

Case 4 An 8-month-old boy with a 4-day history of a "brownish pupil" in his left eye was referred to the emergency room. Funduscopy examination showed a total-funnel shaped serous retinal detachment with marked retinal vessel engorgement. US examination showed a heterogeneous echogenic lesion attached to the retina. An MRI scan showed a T1-hyperintense and T2-hypointense lobulated mass. Under the suspicion of a retinoblastoma, the patient underwent enucleation of the left eyeball. He was diagnosed with a malignant nonteratoid medulloepithelioma. During the five-year post-enucleation period, there have been no signs of recurrence.

Case 5 An 8-month-old girl visited our clinic due to an enlarged right eyeball for two weeks. She could not fixate and follow near objects and her intraocular pressure was measured at 25 mm Hg OD. CT and MRI scans revealed no definite evidence of an intraocular mass or calcification, but US examination showed a tubule-shaped irregular echogenic lesion. The patient was initially diagnosed with either a PFV or a retinoblastoma, followed by secondary glaucoma. One month later, a follow-up US examination showed the presence of an irregular diffuse echogenic mass filling the vitreous cavity. A T1-weighted MRI showed a high signal of intraocular content, suggesting hemorrhagic content. Due to suspected malignancy, the patient underwent enucleation of the right eyeball and was diagnosed with a malignant medulloepithelioma. She was offered chemotherapy for eight months post-operation. Three years later, there were no signs of recurrence.

DISCUSSION

We found that the clinical and radiological findings were very similar to those observed for retinoblastomas. Immunohistochemical analyses of the samples revealed positive staining for nestin, vimentin, CD56, and myogenin, similar to that observed for retinoblastomas.

In our study cohort, three cases (60%) were of the teratoid variant and their major heteroplastic tissues were hyaline cartilage islands and rhabdomyoblastic elements, consistent with previous reports[7]. In this study, four cases (80%) were pathologically malignant, which was similar to the frequency of malignancy in previous reports[7-8].

The most common intraocular tumors in children are retinoblastomas; therefore, intraocular medulloepitheliomas should be differentiated from retinoblastomas, as the two disease-causing entities are very different in their management and prognosis. Several parameters capable of differentiating medulloepitheliomas from retinoblastomas have been reported[9-11]. In our study, the mean age was consistent with that seen in previous studies. Also, intraocular cystic changes are much more common in medulloepitheliomas than in retinoblastomas[12]. However, in our examined cases, we observed no cystic changes in our patients. In addition, medulloepitheliomas are located in a more anterior position, such as the ciliary body or iris, compared to retinoblastomas that typically originate from within the retina. This pattern was reflected in our study, as majority of tumors originated from the ciliary body. The tumors showed marked enhancement on both CT and MRI scans, which is consistent with previous reports[13]. Intratumoral calcification is also suggested to be a good differential and is less observed in medulloepitheliomas than in retinoblastomas[10,14]. However, three cases (60%) showed calcifications in our study. Based on these considerations, there appear to be no absolute clinical differential diagnostic factors and, thus, histopathology is mandatory.

Intraocular medulloepithelioma may have many manifestations other than retinoblastoma, which could lead to misdiagnosis and treatment delay. Two patients (Cases 1 and 3) were originally misdiagnosed with PPM and PFV. In another patient (Case 5), we postponed the enucleation for one month because of the uncertainty of the diagnosis. In the literature, about 20% of intraocular medulloepithelioma manifested signs of PFV[7,15]. Finally, despite no histopathologic signs of extraocular or optic nerve invasion after enucleation, one patient (Case 1) developed a metastasis at his left parotid gland 14mo later. Therefore, clinicians should be aware of the complexity of clinical manifestations and prognosis of intraocular medulloepithelioma for proper management.

In conclusion, we reported on five medulloepithelioma cases that were difficult to differentiate from retinoblastomas. It is essential that medulloepitheliomas are included in the differential diagnosis of a pediatric intraocular mass.

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