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Intraocular medulloepithelioma: A rare but important mimicker of retinoblastoma

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Short title: Medulloepitheliomas masquerading as retinoblastoma

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Keywords: medulloepithelioma, retinoblastoma, *DICER1*

Abstract
Introduction: Medulloepithelioma is a rare tumor arising from the primitive medullary epithelium affecting predominantly children.
Case presentations: We present two patients with ocular medulloepithelioma presenting in the first two years of life with strabismus, leukocoria and a large ocular mass occupying the globe. The clinical presentation and imaging initially raised suspicion for retinoblastoma and enucleation was performed. Histopathology confirmed the diagnosis of teratoid medulloepithelioma in both cases and genetic testing found a germline *DICER1* mutation in one of them.
Conclusion: These cases highlight the importance of considering medulloepithelioma in the differential diagnosis of intraocular tumors and underscore the value of genetic evaluation for underlying DICER1 mutations.

Introduction

Ocular medulloepithelioma is a rare embryonal tumor that originates from the primitive medullary epithelium and is most often located in the ciliary body but has rarely been described as originating from the optic nerve [1]. It was initially termed a "teratoneuroma" due to the heteroplastic tissues discerned within the tumor, or subsequently a "diktyoma" due to the interlacing bands of neuroepithelial cells and network of medullary epithelial cords. The term medulloepithelioma is currently used, based on the tumor's histological similarity to the medullary epithelium of the embryonic neural tube [2-3].

Medulloepithelioma typically presents as a slow growing mass in the ciliary body between 2 and 10 years of age [7]. The tumor is usually diagnosed when it is either large enough to be seen through the pupil or when it causes secondary visual effects such as through cataract or glaucoma [7]. It is often associated with a lengthy lag time due to the slow growth. The tumor can be cystic, may contain hyperechoic cartilage, and can seed into the anterior chamber. Retinoblastoma, in contrast, typically presents between birth and 3 years of age, is rapidly growing, arises from retina rather than ciliary body and presents most commonly with leukocoria and/or strabismus. The lag time is less with retinoblastoma. It is usually calcified, rarely with cyst-like formations, and can seed into the anterior chamber [8]. With clinical examination under anaesthetic and imaging (ultrasound/magnetic resonance imaging) it is normally straightforward to distinguish between medulloepithelioma and retinoblastoma.

Herein, we present two cases where eyes were enucleated with a presumptive diagnosis of advanced retinoblastoma but histopathological testing of the enucleated globes demonstrated medulloepithelioma. We describe the clinical, imaging and histopathological characteristics of these eyes.

Case presentation

Case 1

An 11-month-old male presented with a one-month history of an ingoing squint and absent red reflex in the left eye. He had no past medical or family history of note and dilated examination of his parents was normal. Examination under anaesthetic demonstrated a white, vascularized tumor infiltrating the lens, making it impossible to distinguish between lens and tumor, and occupying the posterior segment of his left eye (shown in Fig. 1A). There was no neovascularization of the iris (NVI) nor anterior chamber seeding. His intraocular pressure was normal and corneal diameters were 12mm in both eyes.

Ultrasound (US) showed a mass involving the whole globe and lens, with areas of internal hyperechogenicity suggestive of calcification, measuring 13mm in elevation and 16 x 17 mm in base (shown in Fig. 2A).

Magnetic resonance imaging (MRI) revealed an heterogenous, solid and cystic mass filling the left globe, with infiltration of the ciliary body and reduced depth of the anterior chamber (shown in Fig. 3A). The globe was small, and the lens was not visualised. The T1-weighted image showed mild central hyperintensity suggesting haemorrhage. After contrast administration there was strong, homogenous enhancement. The choroid was infiltrated by tumor and therefore not visualised (as opposed to the contralateral eye). Restricted diffusion, seen in cellular tumors, was mild on the Apparent Diffusion Coefficient (ADC) map (shown in Fig. 3C) with mean ADC values measuring 1371 x 10^{-6} mm^2/s (vs retinoblastoma with ADC values typically below 800 x 10^{-6} mm^2/s).

Advanced retinoblastoma was suspected and enucleation performed a week after the initial presentation. Pathological analysis demonstrated an expansile tumor effacing the posterior segment with pushing borders compressing the anterior segment and distorting the globe. The tumor appeared to arise from the ciliary epithelium of the pars plicata and was formed of large irregular and coalescing islands of neoplastic hyaline cartilage with intervening hypocellular mesenchyme and variable myxoid stroma (shown in Fig.4A). There were foci of cords, tubules and irregular cysts formed by pseudostratified neuroepithelium with occasional rosettes and areas with pigmented neuroepithelium (shown in Fig. 4B). There were microscopic foci showing sarcomatous change with overlapping spindle cells, pleiomorphic nuclei and numerous mitoses and apoptotic bodies (shown in Fig. 4C). There was no invasion of the optic nerve or the subarachnoid space. The optic nerve resection was free from tumor. Focally, there was suggestion of choroidal invasion, consistent with MRI findings, with tumor pushing towards and touching the sclera in one region. Nevertheless, artefact could not be entirely excluded. The tumour was partly enveloping and destroying the lens. Central haemorrhage, suspected on MRI, was not visualised histopathologically. Based on the above, the diagnosis of malignant teratoid medulloepithelioma was established. Supplementary treatment with 4 cycles of chemotherapy (vincristine, etoposide and carboplatin) was given.

Case 2

A 17-month-old boy presented with a two-month history of leukocoria and strabismus in the right eye. He had no past medical nor family history of note and dilated examination of his parents was normal. Examination under anaesthetic demonstrated neovascularization of the iris (NVI) but normal intraocular pressures. Corneal diameters were 12.25mm in the right eye and 11.5mm in the left eye. Fundoscopy showed a total retinal detachment with underlying white, vascularized tumor (shown in Fig. 1B). Ultrasound showed a tumor occupying the vitreous cavity measuring 12.5mm in elevation and 16.57 x 16.76 mm in diameter with areas of internal hyperechogenicity, suggestive of calcification (shown in Fig. 2B). MRI showed a right-sided heterogenous intraocular mass occupying most of the globe, arising more posteriorly than in patient 1 (shown in Fig 3B). There was a small area of enhancement at the level of the optic nerve, suspicious of post-laminar invasion. In contrast to patient 1, there was more restricted diffusion on the ADC map with mean ADC values measuring 898 x 10^{-6} mm^2/s (shown in Fig 3D). Due to suspected retinoblastoma, the patient underwent enucleation of the right eye.

Histopathology demonstrated, the tumor was formed of tubules, cords and bands of polarized neuro-epithelial cells. There were intratumoral cysts, pools of loose mesenchymal stroma and mucin (neoplastic intra-tumoral vitreous) and areas with a 'fish-net ' like architecture (shown in Fig. 4D). There were poorly differentiated retinoblastoma-like areas and scattered Flexner-Wintersteiner rosettes, but most of the rosettes were larger and multi-layered (shown in Fig. 4E). There were numerous mitoses. An area of cartilage was present (shown in Fig. 4F). There was multifocal, full thickness choroidal invasion with the tumor abutting the sclera. There was no optic nerve involvement and the optic nerve section margin was free of tumor. The tumor seemed to arise from the retina. There were no invasion of the lens and no ciliary body involvement. Based on the above, the patient was diagnosed with a malignant teratoid medulloepithelioma and supplementary treatment with 4 cycles of chemotherapy (vincristine, etoposide and carboplatin) was given. He also had gene testing which identified *DICER1* germline mutation. He was referred for further screening and follow up, including pulmonary, thyroid and renal surveillance, in accordance with recent surveillance recommendations for *DICER1* carriers [24]. To date, no evidence of systemic involvement has been detected.

Discussion

We have presented two children (aged 11 and 17 months) presenting with leukocoria and strabismus who had clinical and radiological examinations highly suggestive of retinoblastoma which led to treatment by enucleation. Histopathology confirmed the diagnosis of a malignant teratoid medulloepithelioma.

The classical similarities and differences between medulloepithelioma and retinoblastoma that are described in the literature are shown in Table 1 [1,3 -14]. Medulloepithelioma typically presents as a ciliary body mass with intratumoral cysts, which can be visualized with ultrasound and MRI. The cysts might dislodge from the tumor and float in the anterior chamber or the vitreous. Secondary effects of the ciliary body mass include secondary glaucoma, lens changes, pupillary mass and extraocular extension. Medulloepithelioma tends to create a retrolental neoplastic cyclitic membrane, the presence of which can help differentiate medulloepithelioma from retinoblastoma and Coats' disease [7].

On MRI, medulloepitheliomas typically appear as heterogeneous retrolental masses composed of both solid and cystic components. Small tumors might lack the cystic component and appear as a dense solid mass [5]. The solid component is usually isointense to mildly hyperintense to vitreous on T1-weighted and hypointense on T2-weighted images and shows enhancement after contrast administration [4,5]. Intratumoral calcification is less frequently seen in medulloepitheliomas than in retinoblastomas. However, about 30% of teratoid medulloepitheliomas contain cartilage, that may undergo dystrophic calcification [4,11]. Apparent Diffusion Coefficient (ADC) values tend to be higher in medulloepitheliomas compared to more cellular retinoblastomas [9].

As demonstrated by these cases, histopathology plays a crucial role in the diagnosis of medulloepithelioma. However, distinguishing between poorly differentiated malignant medulloepithelioma and retinoblastoma can be challenging as they can morphologically resemble one another. Tumor origin is a useful distinguishing feature, with medulloepitheliomas tending to arise from the non-pigmented ciliary epithelium. Medulloepitheliomas are generally comprised of cords of primitive neuroepithelial cells surrounded by

hyaluronic acid-rich hypocellular stroma. The space between the anastomosing cords of neuroepithelial cells may be filled in with sheets of undifferentiated neuroblasts, indistinguishable by light microscopy from retinoblastoma cells. Flexner-Wintersteiner and Homer Wright rosettes can be found among the undifferentiated neuroblasts but compared with those in retinoblastoma, they are often larger, more cellular and multilayered. Other features more specific to medulloepithelioma are neuroepithelial tubules, the presence of neuropil-like material, microcystic architecture and absence of calcification (unless cartilage is present) [1, 12]. Immunohistochemical staining can be useful with diffuse positivity of PAX8 and LIN28A normally seen in medulloepithelioma but not retinoblastoma [13, 14].

Based on histopathology, medulloepithelioma is classified as nonteratoid and teratoid and benign or malignant. Nonteratoid medulloepithelioma consists only of primitive medullary epithelium, while teratoid medulloepithelioma will present heteroplastic elements, like cartilage, neuroglial tissue or rhabdomyoblasts. Hyaline cartilage is the most common heteroplastic element found in teratoid medulloepitheliomas. Malignant medulloepithelioma is diagnosed based on four features, including retinoblastoma-like elements (sheets of neuroblastic cells among the cords) with or without rosettes, sarcoma-like elements, pleomorphism and high mitotic activity, and invasion into adjacent tissues [1,3,6,7]. Management of patients with malignant medulloepithelioma with no extrascleral extension is controversial. Our current practice, based on previously published good results, is to treat these patients with adjuvant systemic chemotherapy [15]. Metastatic disease from medulloepithelioma is rare, but no cases have been reported in the literature in tumours without extrascleral extension or without prior invasive procedures that might cause extraocular spread [1,3,6,7,16]. Verdijk has therefore proposed reducing the two classification entities above into one and introducing a histopathology-based grading system to improve consistency in pathological reporting and facilitate clinical management [17].

A relatively new development that may help with distinguishing between retinoblastoma and medulloepithelioma in the future is cell-free DNA (cfDNA) analysis of aqueous humour [18]. Absence of a RB1 mutation in aqueous humour DNA would make the diagnosis of medulloepithelioma more likely. Moreover, medulloepitheliomas may have a distinct somatic copy number alteration (SCNA) profile enabling distinction between medulloepitheliomas and other masquerading conditions such as Coat's disease. So far, loss of chromosomes 1p, 4, and 16p, and gain of chromosome 8 are the most frequently reported SCNAs in intraocular medulloepithelioma [19,23].

DICER1 is a widely expressed gene encoding ribonuclease III, which is essential in the production of microRNAs [20]. Germline *DICER1* mutation is associated with Pleuropulmonary Blastoma Family Tumor and Dysplasia Syndrome (PPB-FTDS), a familial cancer syndrome which includes a wide range of tumors that typically affect children. Previous studies found that only a minority of patients with DICER-1 germline mutation or PPB-FTDS develop an intraocular medulloepithelioma [20-22]. Somatic DICER-1 mutations have also been noted in sporadic cases with intraocular medulloepithelioma, suggesting the existence of distinct molecular variants of intraocular medulloepithelioma [23].

In summary, both cases presented with strabismus, leukocoria and a mass in the posterior segment of the eyeball, raising suspicion for retinoblastoma. Enucleation was performed and histopathology made the diagnosis of a malignant teratoid medulloepithelioma. Ophthalmologists should be aware of this diagnosis and include this rare tumor in their differential of patients with a similar presentation.

Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from patients' parents/legal guardians for publication of the details of their 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

GM: data gathering and data analysis, writing, editing and revising the manuscript. AV: Data gathering and data analysis, editing and revising the manuscript. UL, PG, VB, HC, CD, TC: Imaging review, editing and revising the manuscript. MSS: Editing and revising the manuscript, and supervision. MAR: Editing and revising the manuscript, and supervision. GN: conceptualization, data gathering and data analysis, editing and revising the manuscript, and supervision.

Data Availability Statement

Relevant data that are included in this article are not publicly available to protect the confidentiality of the included patients but may be requested from the corresponding author (GM) upon reasonable request.

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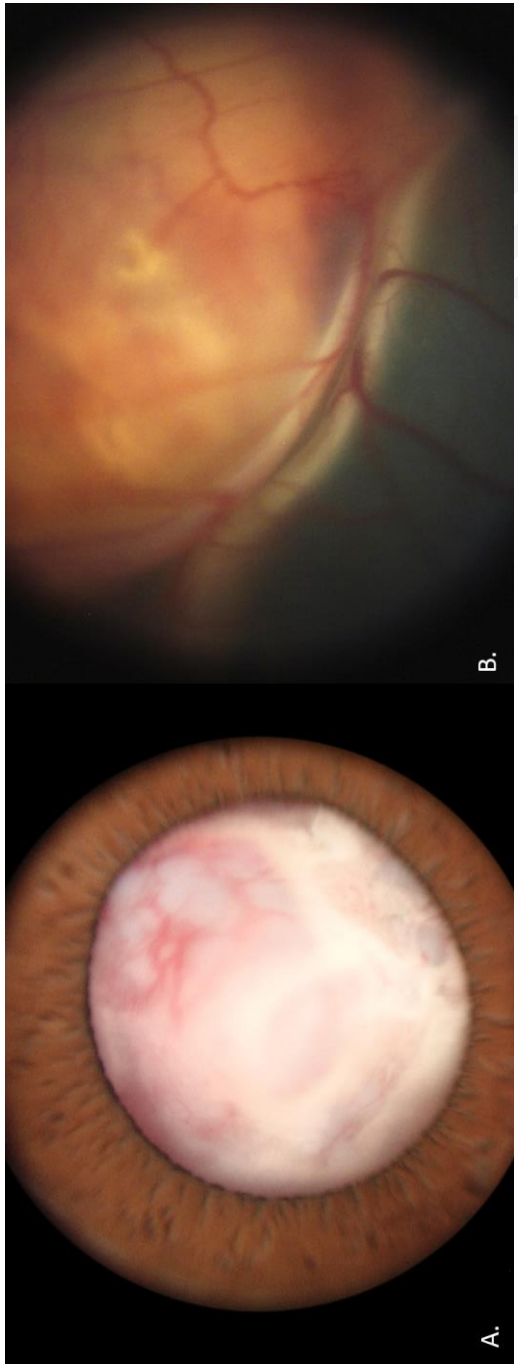
Figure Legends

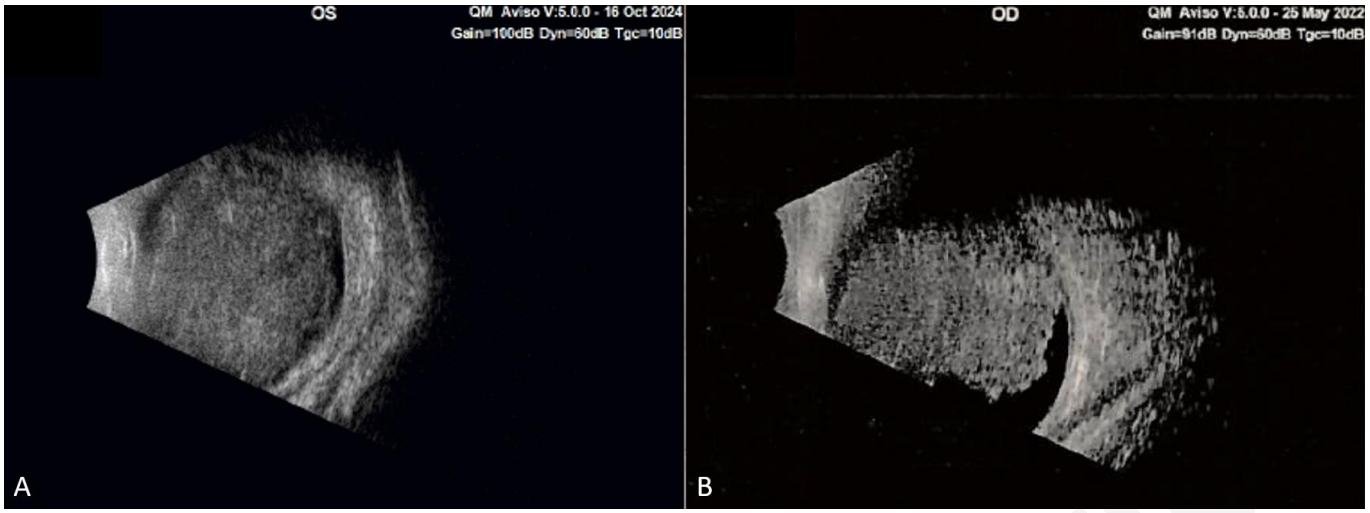
Fig.1. (**A**) Clinical examination of the left eye in case 1 showed a white, vascularized tumor infiltrating the lens and occupying the posterior segment. (**B**) Fundus photos of case 2 revealed a retinal detachment with white subretinal mass present.

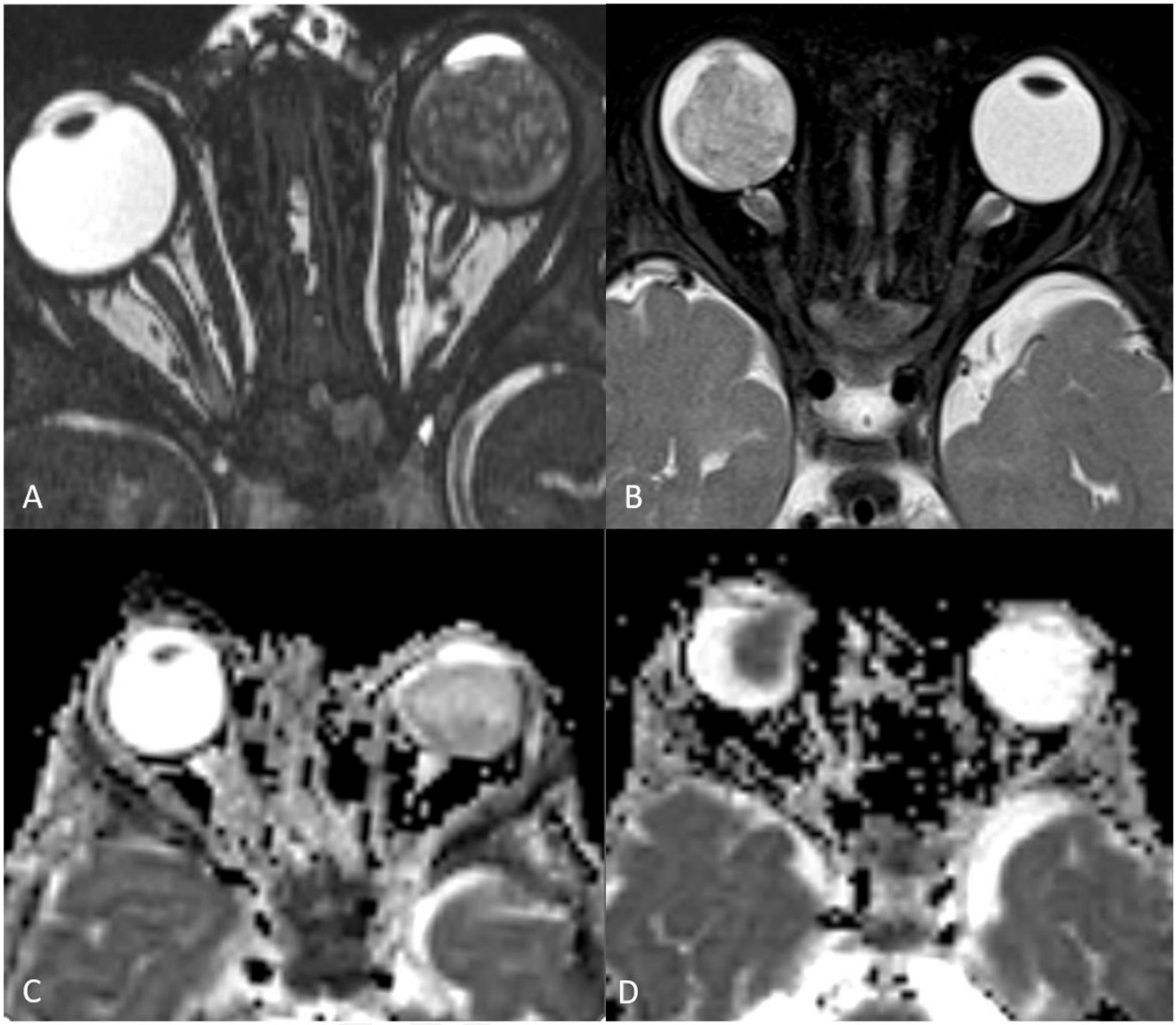
Fig.2. B-scan ultrasound. (**A**) B-scan ultrasound of case 1 shows a diffuse echogenic mass filling the vitreous cavity, measuring 16 x 17 mm in base. (**B**) B-scan ultrasound of case 2 shows a mass occupying the vitreous cavity, measuring 16.57 x 16.76 mm.

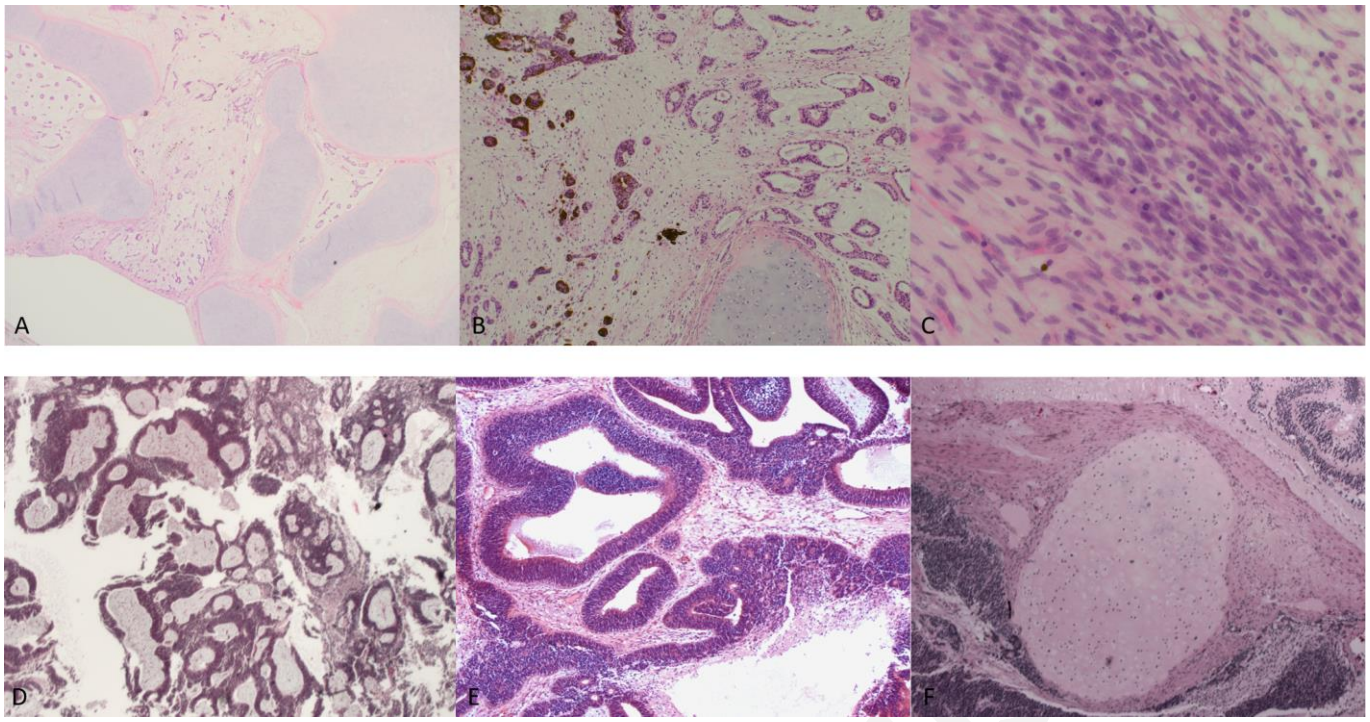
Fig.3 Magnetic resonance imaging.
T2-weighted imaging: **(A)** case 1: an inhomogeneous mass fills the left globe. The ciliary body and lens are predominantly involved; the tumor appears to fill the intraocular cavity and contains multiple small T2 hyperintense cysts. **(B)** case 2: a hypointense mass lesion positioned more posteriorly and appearing to arise from the retina.
ADC maps: **(C)** case 1**:** restricted diffusion is present (dark appearance) suggestive of a cellular tumor. **(D)** case 2: increased restricted diffusion (darker appearance) than in case 1 more in keeping with retinoblastoma than medulloepithelioma.

Fig.4. Pathology. Case 1 (A-C) and case 2 (D-F). (**A**)**.** Large irregular and coalescing islands of neoplastic hyaline cartilage with intervening hypocellular mesenchyme and variable myxoid stroma (hematoxylin & eosin, original magnification x20) (**B**) Foci of cords, tubules and irregular cysts formed by pseudostratified epithelium with occasional rosettes. There are areas of pigmented neuroepithelium (hematoxylin & eosin, original magnification x200). (**C**) Foci of sarcomatous change (hematoxylin & eosin, original magnification x400). (**D**) The tumor is composed of cords, tubules and cysts, with areas with 'fish-net'-like architecture. (**E**) Presence of retinoblastoma-like areas and scattered Flexner-Wintersteiner rosettes, with most of the rosettes appearing larger and multi-layered. (**F**) Area of cartilage within the tumor.









	Medulloepithelioma	**Retinoblastoma**
Origin	Non-pigmented ciliary epithelium (rarely in the iris, retina, or optic nerve head)	Retinal neuroblastic cells
Age at diagnosis	Children (usually <10 years)	Infants and young children (usually <5 years)
Clinical Presentation		
Clinical appearance	White, gray, or yellowish ciliary body mass; may appear whitish-pink with chalky or calcified opacities	White retinal mass, often with calcification
Lens changes	Lens coloboma, lens subluxation, cataract, retrolental cyclitic membrane	Not typical; may cause secondary cataract if advanced
Cysts	Commonly contains intratumoral cysts - cysts may float in anterior chamber or vitreous	Rare
Calcification	Rare	Common
Fluorescein angiography	Haphazard vessels emanating from the ciliary body across the hyaloid face	Regular, organized vessels emanating from the closed central funnel of the retinal detachment out toward the ciliary body region
Ultrasound	Heterogeneous mass with cysts, possible cartilage or rarely calcification	Mass with high internal reflectivity and calcification
MRI	Isointense to mildly hyperintense T1 and hypointense T2 retrolental mass with homogeneous or heterogeneous contrast enhancement (due to cysts), higher ADC values compared to retinoblastoma on diffusion-weighted imaging (DWI)	mildly hyperintense T1 and hypointense T2 retinal mass with signal voids indicating calcifications, heterogeneous contrast enhancement, restricted diffusion with low ADC values on diffusion-weighted imaging (DWI)
Pathology		
Heteroplastic Elements	May be present (teratoid variant: cartilage, rabdomyoblasts, neuroglial tissue, etc.)	Absent

Rosettes	May show rosettes, occasionally Homer-Wright and Flexner-Wintersteiner-like (often larger and more cellular than retinoblastoma)	Prominent Flexner-Wintersteiner and Homer Wright rosettes
Neuroepithelial tubules	Present	Absent
Immunohistochemical staining	Positive for PAX8 and Lin28A (intensity of Lin28A staining correlated with prognosis)	Negative for PAX8 and Lin28A
Genetic Mutation	Rarely associated with DICER-1 mutations (germline or somatic)	98% of non-heritable retinoblastomas have somatic *RB1* mutations, 2% have somatic amplification of the *MYCN* oncogene without a detectable *RB1* mutation
Metastasis	Rare, unless there is extraocular extension or central nervous system involvement	High risk in cases with adverse histopathology

Table 1. Differences between medulloepithelioma and retinoblastoma