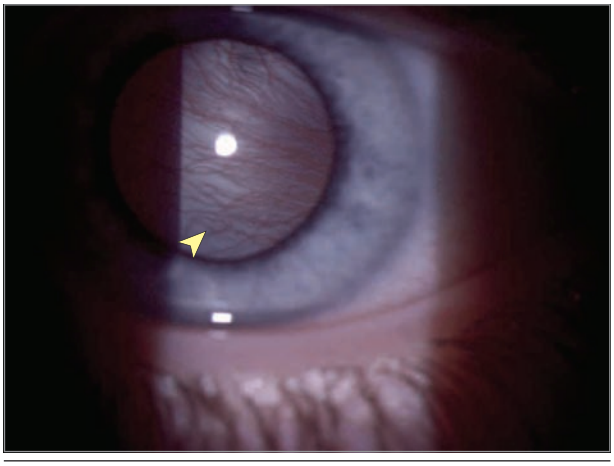
DICER1 Syndrome Discovered Through an Eye Tumor

Medulloepithelioma of the ciliary body (MECB) is a rare tumor that could be associated with DICER1 tumor predisposition syndrome. Understanding this link may aid with genetic counseling or surveillance of affected individuals, potentially contributing to improved management and outcomes. Here is a case of MECB subsequently diagnosed as DICER1 syndrome.

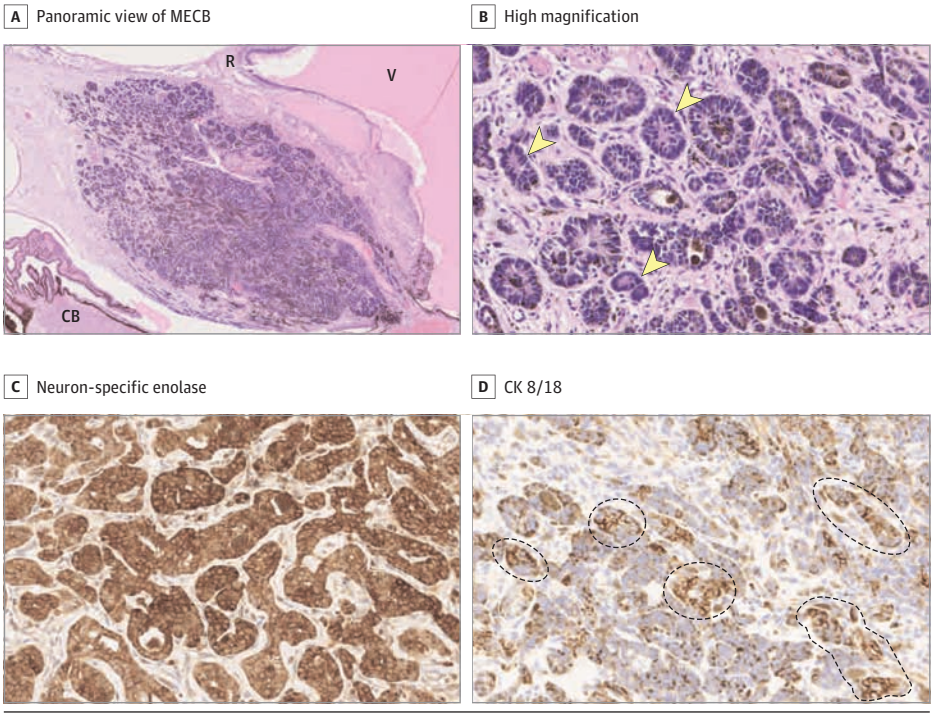
Report of a Case | A 9-year-old boy had vision impairment in his left eye. Examination of the left eye included visual acuity of questionable light perception, microphthalmos, and a retrolental cyclitic membrane (**Figure 1**). Examination showed a fleshy, whitish-pink ciliary body mass. B-scan ultrasound confirmed a ciliary body mass with intralesional cysts and total retinal detachment. The right eye had visual acuity of 20/20 and otherwise was unremarkable. Orbital magnetic resonance imaging showed inhomogeneous posterior chamber signals with diffuse, marked, and irregular circumferential thickening of the inner choroid and retinal layer. The left ciliary body was thickened associated with a hypervascular lesion, 7 × 5 × 2.7 mm^3 with intense and anomalous enhancement. The clinical and imaging findings were consistent with MECB. Therefore, left eye enucleation was performed. Histological examination showed neoplastic proliferation involving the inner surface of the ciliary body. The neoplasm also had cells with poorly differentiated neuroblastic morphology, arranged in rosettes with increased mitotic activity (**Figure 2**A and B). Immunohistochemical stains showed positivity for neuron-specific enolase (Figure 2C), MNF116 cytokeratins, CK 8/18 (Figure 2D), weak and focal reactivity for S100, and negativity for acidic glial fibrillar protein. There were no areas of heterologous differentiation nor invasion of the iris, cornea, or sclera. The real-time polymerase chain reaction conducted on formalin-fixed paraffin-embedded samples of tumor tissue revealed presence of a mutation in exon 25 (p.E1813D) of the *DICER1* gene associated with a diagnosis of malignant MECB. The ultrasound examination of the head and neck lymph nodes revealed an enlarged thyroid with an inhomogeneous echogenicity, consisting of various mixed solid-cystic and iso-hyperechoic nodules. Fine-needle aspi-

Figure 1. Slitlamp Examination of the Anterior Segment Revealing a Retrolental Cyclitic Membrane With Haphazard Blood Vessels



The arrowhead is pointing to the blood vessels.

Figure 2. Pathology Findings of Medulloepithelioma of Ciliary Body



A, The panoramic view shows a tumor involving the inner surface of the ciliary body (CB) with extension into the vitreous (V) cavity and posterior chamber. The detachment of the retina (R) was also evident (hematoxylin-eosin, original magnification ×25). Histologically the tumor consists of anastomosing cords and ribbons of polarized neuroepithelial cells that resemble embryonic medullary epithelium. Abundant pigment is also present. MECB indicates medulloepithelioma of the ciliary body. B, In this field, sheets of poorly differentiated neuroblastic cells and Homer Wright rosettes are evident (arrowheads) (hematoxylin-eosin, original magnification ×100). C and D, The tumor cells are strongly immunoreactive for neuron-specific enolase (C, immunoperoxidase, original magnification ×100), and focally positive for CK 8/18 (D, dashed circles) (immunoperoxidase, original magnification ×100).

ration revealed numerous aggregates of thyrocytes in a microfollicular arrangement with a mildly increased nucleus-cytoplasmic ratio, diagnosed as a multinodular goiter. Radiological examinations showed no masses or neoplasms in other organs. The coexistence of intraocular medulloepithelioma and thyroid disease raised suspicions of a genetic syndrome caused by a *DICER1* gene mutation. A germline heterozygous pathogenic *DICER1* mutation was identified (NM_177438.3: c.4465-4468dup p.(Gly1490Valfs*3)). The genetic variant, predicted to introduce a premature stop codon in the protein, is absent in population databases and is likely to be pathogenic (class 4 second American College of Medical Genetics).[1]

Discussion | MECB, a primitive neuroepithelial tumor, represents the most common congenital and early childhood neoplasm of the nonpigmented epithelium of the ciliary body.[2] It has been classified into nonteratoid and teratoid subtypes, based on absence or presence of heteroplastic elements, including hyaline cartilage, myoblast, and brainlike tissue. Pathologic prognostic factors include presence of poorly differentiated neuroepithelial morphology with or without rosettes, foci of sarcomatous differentiation, invasion of ocular structures, and extrascleral extension.[3] In about half of the cases, retrolental cyclitic membranes are present, representing migration of neoplastic tissue from the mass over the anterior hyaloid.[3] Most cases are sporadic, but the tumor rarely can occur within the DICER1 syndrome, a rare genetic disorder inherited in an autosomal dominant pattern, caused by mutations in the *DICER1* gene, involved in the processing of microRNAs. DICER1 syndrome, which is associated with an increased risk of various types of tumors such as pleuropulmonary blastoma, thyroid tumors, eye abnormalities, and others, has been linked to at least 7 cases of MECB associated with pleuropulmonary blastoma.[3-5] Among these cases, only 1 involved both germline and somatic mutations in the tumor tissue. Our case represents an MECB as the initial manifestation of a germline DICER1, highlighting the potential importance of this rare association and genetic consultation of these patients.

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COMMENT & RESPONSE

Acetylcholinesterase Inhibitors, AMD, and Alzheimer Disease

To the Editor We read with great interest the article by Sutton and colleagues[1] investigating the association between acetylcholinesterase inhibitors (AChEIs) and the incidence of age-related macular degeneration (AMD) among US veterans with Alzheimer disease (AD). The study shows a slight decrease in the incidence of AMD in patients with AD receiving AChEIs. While this study sheds light on the exciting therapeutic potential of AChEIs, some methodological issues should be assessed.

First, although the authors have considered many variables in the propensity score model (in their Table 3),[1] including all prior diagnoses recorded up to a year before the index, there are still factors that could serve as proxy information to address unmeasured confounding. These include, for example, prior use of AChEIs, socioeconomic and educational status,[2] and supplementation with antioxidant minerals or vitamins, such as zinc, vitamin C, and vitamin E.[3] We suggest also adjusting for AD severity to reduce patient heterogeneity, as AChEIs are primarily approved for mild to moderately severe AD.[4] The number of eye examination clinic visits per year is higher in the untreated group compared with the AChEI-treated group (median, 1.5 vs 1.32) after propensity score matching.[1] We recommend transforming the variable into quadratic or tertiary terms to try balancing between the cohorts.

The Kaplan-Meier curves in their Figure[1] showing the cumulative incidence of AMD over the study period for matched cohorts are questionable. Patients treated with AChEIs had fewer AMD events from baseline, indicating that the 2 patient groups could differ by nature. Possible reasons include residual confounding, unbalanced propensity score matching, and selection bias. Moreover, the propensity score–matched sample size decreased by half for the untreated group and nearly two-thirds for the treated group compared with the original sample size. These could lead to reduced internal and external validity and efficiency. The average treatment effect of AChEIs on the treated participants from the study might not