Late Presentation of Retinoblastoma in a Teen with Aicardi Syndrome

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Key Words

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Abstract

Background/Aims: Retinoblastoma (Rb) generally presents in children <8 years of age. Aicardi syndrome (AS) is a congenital, neurodevelopmental disorder that has been associated with various ophthalmic abnormalities, but no reports have related it to a delayed presentation of Rb. This report describes the late presentation of Rb in a teenage patient with AS and suggests modifications in ophthalmic screening to facilitate early detection. **Methods:** A chart review was conducted of a patient with AS. We examined the ophthalmic history, fundus images and B-scan ultrasonography. Histopathological analysis was conducted on globe sections. **Results:** The patient's ophthalmic history was consistent with normal findings of AS: fundus images and B-scan ultrasonography revealed chorioretinal lacunae and an area of retinal detachment, respectively. The patient presented with chronic irritation and mydriasis of the blind left eye. This was enucleated as treatment. Histopathology revealed a focally differentiated Rb. Immunohistochemistry demonstrated that the tumor cells were positive for synaptophysin and

negative for the wild-type Rb protein, and a high Ki-67 proliferation index was shown. **Conclusion:** Our patient was diagnosed with Rb at age 16. AS has been associated with numerous ophthalmic findings, but this is the first report relating it to a late Rb presentation. Meticulous ophthalmic examinations should be considered through the teenage years and early adulthood of AS patients.

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Case Report

A 13-year-old Caucasian girl with a history of Aicardi syndrome (AS) presented with left eye redness and pupillary mydriasis. The patient's prior ophthalmologic medical history was significant for chorioretinal lacunae (fig. 1a, b), consistent with AS. There was no family history of AS, retinoblastoma (Rb) or other eye abnormalities.

Visual acuity was no light perception in the left eye and estimated to be light perception in the right. Dilated funduscopic examination revealed limited visualization of the left fundus due to a dense cataract, suspected vitreous hemorrhaging and chronic retinal detachment. The retina of the right eye appeared flat but otherwise unremarkable. B-scan ultrasonography of the left eye revealed an area of retinal detachment (fig. 1c) with moderate vitreous debris. The patient was managed with serial examination and close observation.

Fig. 1. **a, b** Fundus images of the normal right eye demonstrate chorioretinal lacunae (**a**; arrow) characteristic of AS. The arrows in **b** point to macular atrophy. **c** B-scan ultrasonography of the affected left eye demonstrates retinal detachment (arrows) thought to be the sole cause of left eye blindness. **d** Subsequent imaging of the left eye illustrates a potential inferior mass (m).

Fig. 2. **a** Low-power view of the eye that shows a mass (m) filling the posterior segment, a cataractous lens (l) and a detached retina (arrows). Original magnification $\times 1.2$. **b** Histopathological photograph showing tumor infiltration behind the lens. The lens (l) shows cataractous changes (*). Original magnification $\times 4$. **c** Microphotograph exemplifying the presence of Homer Wright rosettes (arrow). Original magnification $\times 20$. **d** Histologic image illustrating a moderately differentiated Rb. Original magnification $\times 40$.

At age 16, the patient presented with two episodes of recurrent left eye irritation, which was treated with gentamicin and atropine drops. After 2 years of persistent left eye redness and irritation, the patient's guardian requested a therapeutic enucleation.

Gross examination revealed an intact cornea with visible pupil and irregular margins. The sclera was intact and normal aside from bright red focal congestion. The posterior cavity was filled with a red-brown clot, evidence of a vitreous hemorrhage, and the lens displayed abnormal positioning. The entire specimen was fixed for histopathology, with no fresh tumor recovered.

Histopathologic examination revealed a partially degenerated, cataractous lens that was displaced anteriorly (fig. 2a, b). The posterior segment showed a mass projecting into the vitreous, filling nearly the entire posterior cavity and a detached retina (fig. 2a, b). The mass showed a focally differentiated Rb with Homer Wright rosettes (fig. 2c, d). Immunohistochemistry demonstrated that the tumor cells were positive for synaptophysin and negative for the wild-type Rb protein, suggesting an *RB1* gene mutation, consistent with Rb (obtained from chart review). Tumor cells stained negative for GFAP, MAP2 and cytokeratin AE1/AE3 but expressed in-

Fig. 3. **a** Histopathological photograph demonstrating features of AS including the chorioretinal lacunae. These are composed of lakes of blood and proteinaceous material (arrows), surrounded by proliferated retinal pigment epithelium. Original magnification $\times 4$. **b** Microphotograph of the posterior pole with optic nerve hypoplasia (ON) accompanied by ectopic retinal pigment epithelium in the meninges and peripapillary area (arrows). Original magnification $\times 10$. **c** Histopathological image illustrating the choroid with lacunae (arrow) and subretinal exudate with cholesterol clefts (*), representing remote hemorrhage. Original magnification $\times 4$. **d** Histopathological photograph representing other characteristic Aicardi findings and tumor cells (arrow) in the lacunae but not in the choroid (CH). Notice the chronic inflammation in the choroid (*). Original magnification $\times 20$.

dicators of a high proliferation rate, with an increased labeling of Ki-67 (obtained from chart review).

The left enucleated eye showed background changes of AS, including multiple areas of chorioretinal lacunae, composed of lakes of blood and proteinaceous material surrounded by proliferation of the retinal pigment epithelium and a lack of true vessel formation (fig. 3a). Some of the lacunae contained nests of tumor cells (fig. 3a, c, d). The eye also demonstrated hypoplasia of the optic nerve, ectopic retinal pigment epithelium in the meninges and a peripapillary coloboma (fig. 3b). The choroid demonstrated a normal appearance with alternating areas of vascular dilation and stromal nongranulomatous inflammation (fig. 3d). There were no features of tumor invasion. The eye showed retinal detachment and gliosis with fibrovascular proliferation forming subretinal, cyclitic and anterior chamber membranes.

Thirty-six months following her procedure, the patient remains free of tumor recurrence.

Discussion

The majority of Rbs present in patients <4 years of age, with a median age of 2 years, and the diagnosis of Rb beyond age 8 is rare [1]. This patient presented with initial symptoms at age 13. Since Rbs grow rapidly and can be fatal if untreated [1], it is not likely that the tumor had been consistently growing from early childhood. A more probable explanation is malignant transformation of a retinocytoma disguised by the background of retinal anomalies seen in this patient at adolescence.

AS is a rare, X-linked neurodevelopmental disorder diagnosed in infancy and is characterized by agenesis of the corpus callosum, the presence of chorioretinal lacunae and infantile seizures [2, 3]. A clinical investigation of the frequency of ophthalmologic findings in patients diagnosed with AS reported that over one third of the eyes presented with coloboma, a finding that was associated with chorioretinal lacunae and presence of a cataract [2, 3]. These findings have not been associated with the diagnosis of Rb and other ocular malignancies. This patient presented with chorioretinal lacunae, a cataract and coloboma. Patients with coloboma have an increased risk of retinal detachment, a finding in this patient that initially disguised the presence of a mass. Histopathological analysis of the patient's affected eye revealed a host of findings that effectively confirmed tumor growth.

Rbs may develop in eyes with preexisting abnormalities obscuring diagnosis [4]. Our patient presented with chorioretinal lacunae, a dense cataract and retinal detachment, impeding visualization of the retina. Retinal detachment was thought to be the cause of her left eye blindness and limited intraocular visualization. Chronic irritation of the blind eye led to a therapeutic enucleation. Gross and histopathological evaluations revealed a tumor-filled eye and supported a diagnosis of Rb.

Rb and AS have not been directly linked but each can be associated with congenital colobomas [2, 4]. Colobo-

mas have been associated with chromosomal abnormalities involving chromosomes X and 13 [4, 5], both of which have been implicated in mechanisms of Rb tumorigenesis [6, 7]. While no gene has been identified for AS, the syndrome is presumably inherited in an X-linked dominant fashion [2]. Due to the presentation of a wide range of phenotypes and severities, X-chromosome inactivation (XCI) has been proposed as a probable cause of AS [2]. Several cases of XCI and 13q inactivation due to X:13 translocations have been reported in cases of Rb [6, 8–10]. Thus, it would be interesting to determine if a combination of XCI and X:13 translocation could serve as a possible link between the Rb and AS. Due to the absence of a viable tumor at diagnosis, it was not possible to perform Rb (RB1) gene analysis.

There have been several cases associating Rb with coloboma and others associating coloboma with AS, but this is the first report of unilateral Rb in a teenager with AS. Challenges associated with the developmental delay in patients diagnosed with AS suggest that as these children are followed for visual abnormalities, they should be observed meticulously for the possible late development of Rb. Ophthalmologists should carefully examine changes in intraocular pressure and ultrasound images to detect

elevations and enhancements that could signify tumor growth, especially if the patient presents with retinal detachment. Early diagnosis of Rb is vital to the survival of the patient, as these rapidly growing tumors prove fatal when left untreated. In patients with AS, an early Rb diagnosis could be impeded by (1) the presence of other ophthalmologic findings that obscure the retina and (2) the inability to perform adequate examinations when developmental delay limits patient cooperation. Physicians should consider, on a case-to-case basis, if performing periodic examinations under anesthesia is necessary for adequate observation of the globes of AS patients through their teenage years and possibly into early adulthood.

Statement of Ethics

The subject's guardian approved publication of this report. Single-patient case reports are exempt from IRB approval. This report is in compliance with HIPAA guidelines.

Disclosure Statement

There are no conflicts of interest to disclose.

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