# Alveolar Rhabdomyosarcoma Masquerading as Embryonal Subtype: The Value of Modern Molecular Diagnostic Testing

*Kian Eftekhari, M.D.*, Christopher B. Chambers, M.D.†, Scott M. Goldstein, M.D.‡, William R. Katowitz, M.D.*‡, and James A. Katowitz, M.D.*‡*

***Abstract:*** **A 3-year-old child presented with a history of conjunctivitis in her OS. She had hyperglobus of the OS and a palpable mass in the left inferior orbit. An urgent MRI revealed an enhancing mass in the left orbit. The patient underwent an incisional biopsy with pathologic assessment most consistent with embryonal rhabdomyosarcoma. However, subsequent molecular genetic testing of the biopsy specimen was positive for the PAX3/PAX7-FKHR chimeric gene, indicating the tumor was actually an alveolar rhabdomyosarcoma. The patient received a more intensive chemotherapy regimen and also was treated with proton-beam radiotherapy. After chemotherapy and proton irradiation, the patient's tumor shrank considerably, and she remained in remission at over 3 years of follow up. This patient illustrates the new tools at the disposal of the orbital specialist including molecular genetic testing and proton-beam irradiation to diagnose and treat orbital rhabdomyosarcoma.**

Rhabdomyosarcoma is a rare but important tumor in the pediatric population, accounting for approximately 5% of all childhood cancers. There are approximately 250 newly diagnosed cases per year in the United States of which roughly 15% arise in the orbit.[1] Histologically, it has been classified into 4 subtypes including embryonal, alveolar, pleomorphic, and botyroid. These subtypes can sometimes be difficult to classify, but the distinction is important as it can influence the overall prognosis of the child. Alveolar subtype traditionally carries the worse prognosis for survival, with embryonal being much less aggressive and—fortunately for the ophthalmologist—the most common to present in the orbit. However, as molecular diagnostic techniques have advanced forward in the past 2 decades, there have been advances in the field of pathologic study showing that many embryonal rhabdomyosarcomas carry genetic mutations that cause them to behave as the more aggressive, alveolar phenotype. We report here a case of a rare presentation of rhabdomyosarcoma initially diagnosed as embryonal subtype, but—after testing revealed a genetic mutation in the tumor cells—the tumor was eventually classified as alveolar that subsequently changed the management of the child's malignancy.

## METHODS

**Interventional Case Report.** Oral informed consent was obtained from the study participant, and the study was Health Insurance Portability and Accountability Act complaint.

## CASE DESCRIPTION

A 30-month-old child initially presented to the Children's Hospital of Philadelphia with intermittent left lower eyelid swelling and tearing for 5 months. She had been treated with topical antibiotic ointment and steroids in the past without improvement. On initial examination, her visual acuity was central, steady, and maintained, and external examination revealed hyperglobus of the OS with a palpable mass in the inferonasal orbit.

An urgent orbital MRI revealed a heterogeneously enhancing, extraconal mass in the left inferior orbit with displacement of the globe (Fig. 1). In addition, the MRI exhibited mild enhancement of the lacrimal gland bilaterally. The patient underwent an incisional biopsy via transconjunctival approach, and initial pathologic diagnosis was consistent with embryonal rhabdomyosarcoma based on the small, round tumor cells and absence of most alveolar elements within the tumor sample (Fig. 2). A CT of the chest revealed a lung nodule

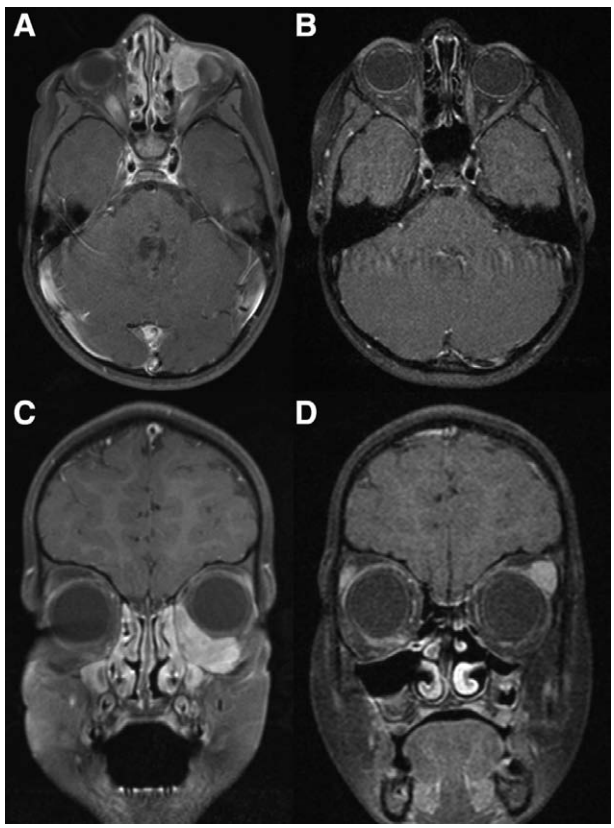


**FIG. 1.** Initial MRI at the time of diagnosis showing a large enhancing mass in the inferomedial left orbit (**A** and **C**). Subsequent MRI showing resolution following orbital proton radiotherapy and chemotherapy (**B** and **D**).

*Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; †Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; and ‡Department of Ophthalmology, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

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Address correspondence and reprint requests to William R. Katowitz, M.D., Department of Ophthalmology, Children's Hospital of Philadelphia, 34th St., and Civic Center Boulevard, Philadelphia, PA 19104-4399. E-mail: katowitzw@email.chop.edu

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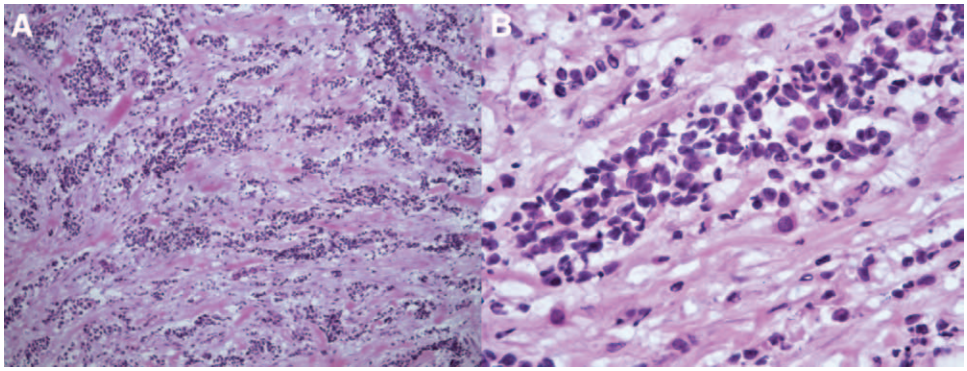


**FIG. 2.** Biopsy specimen of the orbital mass with hematoxylin and eosin staining in low power (**A**) and high power (**B**) showing small, round tumor cells.

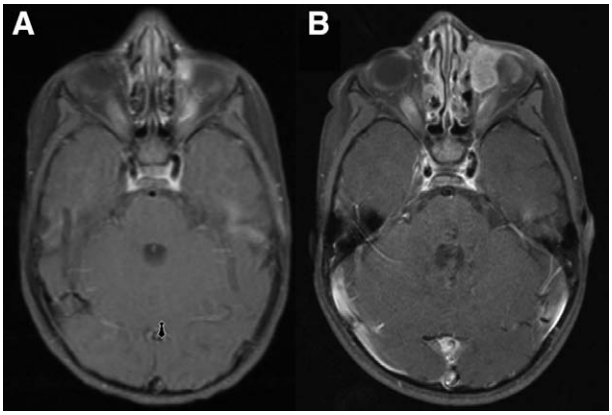


**FIG. 3.** **A**, MRI of the orbit 6 months prior to presentation showing a small mass in the inferomedial left orbit. **B**, Compared with the MRI image at the time of the orbital mass biopsy.

that was biopsied and found to be negative for malignancy. A systemic workup including PET/CT along with a bone scan, lumbar puncture, and bone marrow aspirate did not reveal evidence of metastatic disease. She was initially placed in the Children's Oncology Group (COG) low-risk protocol for rhabdomyosarcoma that includes an accelerated course of vincristine, actinomycin D, and cyclophosphamide chemotherapy and local radiation therapy. The patient began chemotherapy postoperatively.

About 6 weeks after initiating her 22-week course of chemotherapy, molecular genetic studies of the tumor cells revealed a chimeric fusion of the PAX3/PAX7-FKHR genes. This finding indicated that the tumor was actually an alveolar rhabdomyosarcoma and thus conferred a worse prognosis. The patient was reclassified into the COG intermediate-risk protocol and subsequently received an additional 20 weeks of the same chemotherapeutic agents. Subsequent MRI imaging of the orbits and clinical examination showed regression of the tumor and remission of the symptoms of tearing, conjunctival injection, and left lower eyelid swelling.

On review of her records at the time of her initial orbital MRI, it was noted that the patient had a brain MRI about 6 months prior to presentation as part of a workup for failure to thrive. Although the cuts were not as thin as an orbital MRI, it was noted that there was a small, enhancing mass in the inferomedial left orbit (Fig. 3).

Given the tumor location and the patient's age, the patient received orbital proton-beam radiation therapy instead of traditional external-beam radiation therapy. After chemotherapy and proton irradiation, the patient's tumor shrank considerably, and she achieved a complete remission. She received regular clinical examinations by the oculoplastic specialist and pediatric oncologist in addition to an MRI of the orbits every 3 months for the first 15 months after diagnosis, then twice a year. At 4-year follow up, the patient's tumor has not recurred.

## DISCUSSION

Classically, orbital rhabdomyosarcoma has been described as a tumor that presents aggressively with the alveolar subtype, carrying a poor prognosis.[1] This case was atypical because the patient presented subacutely with an orbital mass that was eventually diagnosed as alveolar rhabdomyosarcoma, a diagnosis only made after molecular genetic testing confirmed the tumor's genetic identity.

Other authors have commented on a variant presentation of orbital rhabdomyosarcoma that presented somewhat indolently.[2] In our case, the tumor was initially diagnosed as embryonal subtype. Genetic testing of the biopsy sample revealed that the tumor was positive for a chimeric fusion of the PAX3/PAX7-FKHR genes.[3] This genetic translocation has been associated specifically with alveolar rhabdomyosarcoma and—in studies of rhabdomyosarcoma elsewhere in the body—to confer a worse prognosis.[4,5] Central pathologic review of the specimen along with genetic testing reclassified the patient's tumor as alveolar rhabdomyosarcoma. The molecular test was conducted as part of the central pathologic review of the specimen in accordance with the recommendations of the Soft Tissue Sarcoma Committee guidelines within the Children's Oncology Group.

The patient went on to receive proton-beam orbital radiation for her disease. Proton-beam radiation has been shown to have a more precise entrance and exit dose without delivering as much radiation to adjacent vital structures. Had the patient received external-beam radiation therapy, there would have been a modest amount of radiation delivered to the brain. With proton-beam therapy, the dose delivered to structures behind the tumor including the brain is much lower because of its improved exit-dose profile.[6]

An additional peculiar aspect of this case is that the patient had coincidentally gotten a brain MRI 6 months prior to her presentation of rhabdomyosarcoma which—on further review—had shown a small mass in the orbit corresponding to the location of her subsequent biopsy-proven rhabdomyosarcoma. Whether this mass was actually rhabdomyosarcoma at the time of that MRI or whether it was a mass that underwent malignant transformation is unknown. It does,

however, call in question the traditional assumption that rhabdomyosarcoma presents acutely. In an era where orbital imaging will only become more common, more asymptomatic orbital masses may be discovered and perhaps question traditional dogma.

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