RELA Fusion-Positive Ependymoma in a Child with Down Syndrome

Julie Chan, MD, PhD*; Alon Kashanian, BS*; Serguei I. Bannykh, MD, PhD; Fataneh Majlessipour, MD; Joshua Breunig, PhD**; Moise DanieLPour, MD**

* Denotes equal contribution as first author; ** Denotes equal contribution as senior author

Cedars-Sinai Medical Center
Los Angeles, California
Disclosures

There are no disclosures for this study or abstract.
Introduction

• Down syndrome (DS) is the most common of the multiple malformation syndromes in humans and is associated with an increased risk of childhood malignancy, particularly leukemia.¹⁻⁵

• Although ependymomas are the third most common pediatric brain tumor, only a few cases of ependymoma have been reported in children with DS.⁶⁻⁸

• We report the first case of a RELA fusion-positive ependymoma in a 3-year-old boy with DS.
A 3-year-old boy with Down syndrome and otherwise unremarkable past medical history presented with two weeks of progressive left-sided weakness.

Initial imaging demonstrated an 8 cm right frontal-parietal minimally-enhancing mass with significant midline shift and hemorrhage.

Pre-operative T1 post-contrast (A) and FLAIR (B) imaging demonstrating a large heterogeneous mass with a minimal contrast enhancing portion.
Case Presentation

- We performed a right parietal craniotomy for gross total image-complete resection. Intraoperatively, the lesion appeared necrotic with hemorrhagic components. Samples were sent for pathology and molecular studies.

Post-operative T1 post-contrast (C) and FLAIR (D) sequences demonstrate good image-complete resection.
Case Presentation

• **Histologic evaluation (Fig. A-B)**
  Negative: Synaptophysin, GFAP, TP53, IDH1-R132H, L1CAM, BRAF V600E
  Positive: Olig2 (~90%), INI1, ATRX

• **Electron Microscopy (Fig. C-E)**
  Showed abortive ependymal differentiation

• **Molecular Studies**
  Showed no amplifications of PDGFRA, MET or EGFR, but detected rearrangement of C11orf95 and RELA consistent with fusion.

H&E (A) stain shows minimal evidence of perivascular pseudorosettes with diffuse strong positivity for Olig2 (B). Electron microscopy demonstrates abortive ependymal differentiation (Fig. 2 C-E) with focally developed junctional complexes (black arrows), basal membrane deposition (white arrowheads), microlumena (asterisk), and polar bodies (white arrows). Scale bars: 100 µ (A & B), 1000 µ (C-E).
Case Presentation

- On post-operative day 28, he was transferred to another facility for inpatient rehabilitation.

- Three months after discharge, routine repeat imaging demonstrated intracranial recurrence. We performed a second craniotomy with gross total resection. The final pathology was once again positive for ependymoma.

### Grading of Ependymal Tumors According to 2016 WHO

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subependymoma</td>
<td>I</td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td>I</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>II</td>
</tr>
<tr>
<td>Ependymoma, RELA fusion-positive</td>
<td>II or III</td>
</tr>
<tr>
<td>Anaplastic ependymoma</td>
<td>III</td>
</tr>
</tbody>
</table>
Case Presentation

• We began treatment with proton beam therapy. Treatment appeared successful without radiographic evidence of local recurrence.

• However, shortly after completion of proton therapy, spinal imaging was suggestive of drop metastases and leptomeningeal spread.

• Despite two successful resections and maximum proton therapy, the patient passed away one month after the discovery of drop metastases, approximately one year after his first craniotomy.

T1-weighted spinal MRI with single nodule (arrow) at L2-3 suspicious for drop metastasis less than one year after initial diagnosis
• The incidence of solid tumors in patients with DS is significantly decreased when compared to individuals without the disorder.\(^2\text{-}^5\)

  • Literature review revealed two reports of ependymoma in patients with DS: medullary ependymoma found incidentally in an electively terminated 19-week fetus and an L1-5 intramedullary tumor in a 13-year-old girl.\(^7\text{-}^8\)

• Recent studies suggest that trisomy of chromosome 21 permits overexpression of tumor suppressors or growth factors and may be protective against the formation of tumors.

  • Baek et al. describe overexpression of DSCR1 which reduces vascular endothelial growth factor, inhibiting angiogenesis and subsequent solid tumorigenesis.\(^10\)
Discussion - OLIG2 Positivity in Ependymoma

• OLIG2 is a basic helix-loop-helix transcriptional repressor protein, located within chromosome 21. Under normal physiological conditions, OLIG2 plays a critical role in the development of astrocytes, neural progenitors, and oligodendrocytes.\textsuperscript{11-14}

• In brain tumor cells it appears that OLIG2- cells utilize neovascularity while OLIG2+ cells utilize normal vasculature for blood supply, suggesting OLIG2+ tumors may be resistant to traditional antiangiogenic therapy.\textsuperscript{11}

• OLIG2 is also expressed in other cancers of the CNS including 100% of diffuse gliomas. However, OLIG2 expression is typically absent or minimally expressed in ependymomas and other non-diffuse gliomas.\textsuperscript{15}

• Our patient's tumor showed OLIG2 positivity in up to 90% of tumor nuclei.
Discussion- OLIG2 Positivity in Ependymoma

• The role of OLIG2 in glioma tumorigenesis, progression, and resistance to therapy is not well understood.

• One theorized mechanism of action in tumors is an oppositional relationship between OLIG2 and p53. Mehta et al. demonstrated that OLIG2 exerts some of its downstream biological function by suppressing p53 acetylation [68]. The interaction between a duplicated OLIG2 locus and suppressing p53 acetylation would theoretically result in a more aggressive tumor with greater genomic instability and a higher risk of recurrence.\textsuperscript{16}

• Given that OLIG2 and OLIG1 both reside on chromosome 21 and are duplicated in children with Down syndrome, the transcriptional networks regulated by these transcription factors may play a direct role in the aggressive nature of solid tumors found in this case. Further studies are required to investigate their role in DS.
Conclusion

• At this time, extent of surgical resection appears to be the only consistent clinical prognostic marker associated with survival.\textsuperscript{17}

• Here, we emphasize that OLIG2 positivity should not exclude the diagnosis of ependymoma from consideration.

• Finally, we highlight the importance of investigating genetic markers and display here their utility in ependymoma classification. Testing for RELA fusion-positivity was critical in both the diagnosis and management of our patient's health condition.
Study Contributors

Dr. Julie Chan  
Alon Kashanian  
Dr. Serguei Bannykh  
Dr. Fataneh Majlessipour  
Dr. Joshua Breunig  
Dr. Moise Danielpour
References


