Neuroblastoma in Adolescents and Children Older than 10 Years: Unusual Clinicopathologic and Biologic Features

Laura McCarthy
*Children's Mercy Hospital*, lcmccarthy@cmh.edu

Katherine Chastain
*Children's Mercy Hospital*

Terrie Flatt
*Children's Mercy Hospital*, tgflatt@cmh.edu

Eugenio Taboada
*Children's Mercy Hospital*, etaboada@cmh.edu

Robert E. Garola
*Children's Mercy Hospital*, regarola@cmh.edu

*See next page for additional authors*

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Authors
Laura McCarthy, Katherine Chastain, Terrie Flatt, Eugenio Taboada, Robert E. Garola, John Herriges, Linda D. Cooley, and Atif Ahmed

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Neuroblastoma in Adolescents and Children Older than 10 Years: Unusual Clinicopathologic and Biologic Features

Laura McCarthy DO1, Katherine Chastain MD1, Terrie Flatt MD1, Eugenio Taboada MD2, Robert Garola MD1, John Herriges PhD2, Linda Cooley MD2, Atif Ahmed MD2

1. Division of Hematology/Oncology/Bone Marrow Transplant, Children’s Mercy Kansas City 2. Department of Pathology and Laboratory Medicine, Children’s Mercy Kansas City

Background

- Neuroblastoma (NB) occurrence in children > 10 years is rare; older patients have poorer outcomes. Exome sequencing, which provides information regarding genetic mutation burden of NB is more often being utilized to plan targeted therapy.

Objective

- Describe 4 cases of NB diagnosed since 2006 in children > 10 years and present their clinical, histologic and biologic features, emphasizing unusual clinicopathologic characteristics and the role of DNA microarray analysis and Next Generation Sequencing in their management.

Summary of Cases

- All tumors presented with extensive visceral involvement, large size, and lymph node involvement or distant metastasis and high clinical stage.
- Other unusual features: presence of bilateral tumors (case 2) and pheochromocytoma-like morphology (case 1)
- Complex chromosomal gains and 19p deletions were common (table 2)
- Exome sequencing revealed ALK variants in two cases and previously unreported MAG2, RUNX1 and ML2 mutations (table 2)
- All patients received standard chemotherapy and two patients received ALK-targeted trial therapy. Most patients seemed to have chemotherapy-resistance and an ultimately fatal course.
- Three patients died of disease, ranging 18-23 months after diagnosis. One patient has active disease and is receiving trial therapy.

Table 1. Clinical and Histologic Findings of Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age and gender</th>
<th>Clinical presentation</th>
<th>Tumor size (cm)</th>
<th>INSS stage</th>
<th>Tumor histology</th>
<th>MKI</th>
<th>ATRX staining</th>
<th>Treatment (Response)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11 years; female</td>
<td>Left adrenal mass; BM metastasis</td>
<td>10.5</td>
<td>4</td>
<td>Poorly differentiated; pheochromocytoma-like morphology</td>
<td>Low</td>
<td>90-100%</td>
<td>(case 2)</td>
<td>Died 21 months after dx</td>
</tr>
<tr>
<td>2</td>
<td>13 years; male</td>
<td>Bilateral adrenal masses; LN metastasis</td>
<td>Left: 6.7, Right: 3</td>
<td>3</td>
<td>Left adrenal: poorly differentiated</td>
<td>Low</td>
<td>40-100%</td>
<td>(case 3)</td>
<td>Died 23 months after dx</td>
</tr>
<tr>
<td>3</td>
<td>16 years; female</td>
<td>Retropertitoneal mass</td>
<td>10.5</td>
<td>3</td>
<td>Poorly differentiated</td>
<td>Low</td>
<td>40-100%</td>
<td>(case 4)</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>4</td>
<td>12 years; male</td>
<td>Presacral mass; BM metastasis</td>
<td>10.5</td>
<td>4</td>
<td>Poorly differentiated</td>
<td>Low</td>
<td>40-100%</td>
<td>(case 1)</td>
<td>Died 18 months after dx</td>
</tr>
</tbody>
</table>

Table 2. Genetic Findings in Tumor and BM Samples

<table>
<thead>
<tr>
<th>Microarray results – Tumor</th>
<th>Fish Results</th>
<th>Bone marrow</th>
<th>Chr results</th>
<th>Exome Sequencing Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case 1</strong></td>
<td><strong>Case 2</strong></td>
<td><strong>Case 3</strong></td>
<td><strong>Case 4</strong></td>
<td><strong>MAG2</strong></td>
</tr>
<tr>
<td>Partial chr gains</td>
<td>-</td>
<td>2p</td>
<td>1p, 1q, 11p, 17q, 17p, 19p, Xp</td>
<td>2p, 2q, 3q, 4q, 6q, 7q, 17q, 17p, Xp</td>
</tr>
<tr>
<td>Partial chr Losses</td>
<td>15p, 22q</td>
<td>15p</td>
<td>-</td>
<td>3q, 7p, 9p, 15q, 19p</td>
</tr>
<tr>
<td>Whole chr gains</td>
<td>-</td>
<td>2, 4, 5, 6, 7, 10, 12, 13, 14, 15, 16, 18, 20</td>
<td>1, 4, 5, 8, 10, 12, 13, 18, 20</td>
<td></td>
</tr>
<tr>
<td>Whole chr losses</td>
<td>-</td>
<td>2, 4, 9, 10, 11p, 22</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>chrCNV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14p</td>
</tr>
<tr>
<td>Tumor</td>
<td>Loss of one copy of SMARCB1 and NF2</td>
<td>Gain of MYCN and ALK</td>
<td>Gain of MYCN, ALK, and FOK1</td>
<td>Gain of MYCN, ALK, and RUNX1</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Loss of one copy of SMARCB1 and NF2</td>
<td>Normal MYCN and ALK</td>
<td>MYCN amplification and non-amplified MYCN gains</td>
<td>MYCN amplification and non-amplified MYCN gains</td>
</tr>
</tbody>
</table>

Exome Sequencing Variants

- MAG2: R564Q
- RUNX1: R301Q
- ALK-P1245V, ML2-E550, & TERT-promoter 124C>T
- ALK - F1174

Discussion

- Resistance to chemo and poor prognosis may be due to genetic mutations that are found with higher frequency in this age group.
- Our exome sequencing studies revealed ALK mutations as the most common genetic abnormality, which is associated with poor survival in high- and intermediate-risk disease, but also provides opportunity for targeted therapy with ALK inhibitors.
- Overall genomic profiles of our cases are very diverse. However, deletion of 19p was found in 3/4 cases (the other case had overlapping 19p cn-LOH, suggesting this tumor previously had a loss of one copy of 19p). This suggests that loss of 19p may be significant to the development of NB in older patients.
- MAG2, RUNX1, and ML2 variants have not been previously reported in neuroblastoma.

Conclusion

- NB in children > 10 years may exhibit unusual clinicopathologic features with large tumors, bilateral adrenal disease, pheochromocytoma-like features, complex DNA microarray results and rare genetic profiles.
- Older patients behave as having high risk disease despite absence of usual poor-prognostic factors.
- Although next generation sequencing and targeted therapy may offer hope, patients could still have a dismal outcome.

Abbreviations

- BM: bone marrow; LN: lymph node; IGN: intermedullary ganglioneuroblastoma; MKI: mitotic-karyorrhectic index; NR: no response; Dx: diagnosis; ASCT: autologous stem cell transplant; PD: progressive disease; PR: partial response; Chr: chromosome