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

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## 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 2008 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 MAG22, RUNX1 and MLL2 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><strong>Phenotyped therapy x 1 cycle</strong></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>5.0</td>
<td>3</td>
<td>Left: 6; Right: 3</td>
<td>Intermediate</td>
<td>40-100%</td>
<td><strong>ANBL0523 x 4 cycles (PR)</strong></td>
<td>Died 23 months after dx</td>
</tr>
<tr>
<td>3</td>
<td>16 years; female</td>
<td>Retropertioneal mass</td>
<td>20</td>
<td>4</td>
<td>Left adrenal: poorly differentiated Right adrenal: IGN</td>
<td>Low</td>
<td>90-100%</td>
<td><strong>ANBL0523 + x 4 cycles + Resection + radiation (SD)</strong></td>
<td>Alive with disease</td>
</tr>
<tr>
<td>4</td>
<td>12 years; male</td>
<td>Presacral mass; BM metastasis</td>
<td>6.4</td>
<td>4</td>
<td>Poorly differentiated</td>
<td>Low</td>
<td>40-50% in primary tumor. Neg in BM mets</td>
<td><strong>ANBL0523 + resection + ASC</strong></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>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial chr gains</td>
<td>2p</td>
<td>1p, 1q, 11q, 17q, 19p, 19q, Xp</td>
<td>2p, 2q, 3q, 3p, 6q, 7q, 17q, 17p, 22q, Xp</td>
<td></td>
</tr>
<tr>
<td>Partial chr Losses</td>
<td>19p, 2q, 2q</td>
<td>19p</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>-</td>
<td>-</td>
<td>2, 4, 9, 10, 11q, 19p, 22</td>
</tr>
</tbody>
</table>

| Fish Results | Tumor | Gain of MYCN and ALK | Gain of MYCN and ALK, AF3, and FOXO1 | Gain of MYCN, AF3, chromosome 2 centromere and chromosome 18 centromere |
|--------------|-------|----------------------|-----------------------------------|-------------------------------------------------
| Bone marrow  | Loss of one copy of SMARCB1 and NF2 | Gain of MYCN and ALK | MYCN amplification and non-amplified MYCN gains. Gain of chromosome 2 centromere |

<table>
<thead>
<tr>
<th>Exome Sequencing Variants</th>
<th>MAG22 - R564Q</th>
<th>RUNX1 - R201Q</th>
<th>ALK-F1245V, MLL2-ES80, &amp; TERT-promoter 124C&gt;T</th>
<th>ALK - F1174</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>617,-7,+1,add(2)(p21)x2, der(2;19)(p23)</td>
<td>add(3)(p21)x2, der(2;19)(p23)</td>
<td>ALK-F1245V, MLL2-ES80, &amp; TERT-promoter 124C&gt;T</td>
<td>ALK - F1174</td>
</tr>
</tbody>
</table>

## 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.
- MAG22, RUNX1, and MLL2 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: intermixed ganglioneuroblastoma; MKI: mitotic-karyorrhectic index; NR: no response; Dx: diagnosis; ASC: autologous stem cell transplant; PD: progressive disease; PR: partial response; Chr: chromosome