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

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

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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>• Neuroblastoma therapy x 1 cycle</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>6.7</td>
<td>3</td>
<td>Right adrenal: poorly differentiated</td>
<td>Intermediate</td>
<td>40-50%</td>
<td>• ANBLS32 x 4 cycles (FR)</td>
<td>Died 23 months after dx</td>
</tr>
<tr>
<td>3</td>
<td>16 years; female</td>
<td>Retropertitoneal mass</td>
<td>6.4</td>
<td>3</td>
<td>Right adrenal: not evaluable</td>
<td>Low</td>
<td>90-100%</td>
<td>• ANBLS32 + resect</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>4</td>
<td>12 years; male</td>
<td>Presacral mass; BM metastasis</td>
<td>4</td>
<td>4</td>
<td>Right adrenal: not evaluable</td>
<td>Low</td>
<td>40-50% in primary tumor: HG in BM mets</td>
<td>• ALK [Bcr-Abl]</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, 4q, 11q, 17q, 19p, 19q, Xp</td>
<td>2p, 3q, 4q, 6q, 6q, 7q, 17q, 22q, Xp</td>
<td>3q, 7q, 9p, 15q, Xp</td>
</tr>
<tr>
<td>Partial chr Losses</td>
<td>19p, 22q</td>
<td>19p</td>
<td>-</td>
<td>1, 4, 5, 8, 10, 12, 13, 18, 20</td>
</tr>
<tr>
<td>Whole chr gains</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1, 6, 7, 10, 12, 13, 14, 15, 16, 18, 20</td>
</tr>
<tr>
<td>Whole chr Losses</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2, 4, 9, 11, 19p, 22</td>
</tr>
</tbody>
</table>

Discussion

• Resistance to chemotherapeutic agents such as vincristine, cisplatin, and cyclophosphamide may be due to genetic mutations that are found with higher frequency in this age group.
• Our exome sequencing studies revealed ALK mutations in a number of the cases, which suggests that tumor progression may be associated with ALK inhibitors.
• Overall genotypic changes in the cases are quite diverse. However, deletion of 19p was found in 3/4 cases (the other case had overlapping 19p LOH), suggesting a possible role of this tumor in the development of NB in older patients.

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 if they have 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; IG: intermedullary ganglionneuroblastoma; MKI: mitotic-karyorrhectic index; NR: no response; Dx: diagnosis; ASCT: autologous stem cell transplant; PD: progressive disease; PR: partial response; Chr: chromosome

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, RUNXI 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.