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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 *MAGI2*, *RUNX1* and *MLL* 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

	Case 1	Case 2	Case 3	Case 4
<b>Age and gender</b>	11 years; female	13 years; male	16 years; female	12 years; male
<b>Clinical presentation</b>	Left adrenal mass; BM metastasis	Bilateral adrenal masses; LN metastasis	Retroperitoneal mass	Presacral mass; BM metastasis
<b>Tumor size (cm)</b>	10.5	Left: 6.7 Right: 3	20	6.4
<b>INSS stage</b>	4	3	3	4
<b>Tumor histology</b>	Poorly differentiated; pheochromocytoma-like morphology	Left adrenal: poorly differentiated Right adrenal: IGN	Poorly differentiated	Poorly differentiated
<b>MKI</b>	Low	Intermediate	Low	Low
<b>ATRX staining</b>	90-100%	90-100%	90-100%	40-50% in primary tumor. Neg in BM mets
<b>Treatment (Response)</b>	<ul style="list-style-type: none"> <li>Pheochromocytoma therapy x 1 cycle</li> <li>ANBL0532 x 4 cycles (NR)</li> <li>ANBL1221 x 4 cycles (NR)</li> <li>MIBG therapy</li> </ul>	<ul style="list-style-type: none"> <li>Complete resection (relapsed 4 months later with mets)</li> <li>ANBL0532 with ASCT + radiation (PD)</li> <li>Temodar, irinotecan, Dinutuximab (PD)</li> <li>Compassionate Lorlatinib</li> </ul>	<ul style="list-style-type: none"> <li>ANBL0532 x 4 cycles (PR)</li> <li>Resection + radiation (SD)</li> <li>Alectinib x 6 months (PD)</li> <li>Lorlatinib</li> </ul>	<ul style="list-style-type: none"> <li>ANBL0532 + resection + ASCT followed by radiation and resection of residual tumor</li> <li>Relapsed prior to starting maintenance phase: received Temodar, irinotecan (PD)</li> <li>Palliative Cytoxan and topotecan</li> </ul>
<b>Outcome</b>	Died 21 months after dx	Died 23 months after dx	Alive with disease	Died 18 months after dx

### Table 2. Genetic Findings in Tumor and BM Samples

	Case 1	Case 2	Case 3	Case 4	
<b>Microarray results – Tumor</b>	Partial chr gains	-	2p	1p, 1q, 11p, 11q, 17p, 17q, 19p, 19q, Xp	
	Partial chr Losses	19p, 22q	19p	-	
	Whole chr gains	-	-	2, 4, 5, 6, 7, 10, 12, 13, 14, 15, 16, 18, 20	
	Whole chr losses	-	-	-	Y
	cnLOH	-	-	2, 4, 9, 10, 11, 19p, 22	16p
<b>Fish Results</b>	Tumor	Loss of one copy of SMARCB1 and NF2	Gain of MYCN and ALK	Gain of MYCN, AFF3, chromosome 2 centromere and chromosome 18 centromere	
	Bone marrow	Loss of one copy of SMARCB1 and NF2	Normal MYCN and ALK	MYCN amplification and non-amplified MYCN gains. Gain of chromosome 2 centromere	
<b>Chr results</b>	Tumor	46,XX[20]	46,XY,der(19)t(2;19)(p21;p13.2)[8]/46,XY[13]	46,XX[20]	
	Bone marrow	46,XX[20]	-	46,XX[20]	
<b>Exome Sequencing Variants</b>	MAGI2 - R564Q RUNX1 - R201Q	ALK-F1245V, MLL2-E550, & TERT-promoter 124C>T	ALK - F1174L	61,Y,-X,+1,add(2)(q37)x2,+der(2)add(p23)add(q33),add(3)(q12),+der(4)t(4;12)(q27;q12),+add(5)(q13),add(7)(q33),+i(7)(q10),+8,add(9)(p21),+12,+13,+13,+14,-15,+16,+18,19,+20,+5mar[4]/65,sl,+add(3)(p23),+5,add(11)(p15),+18,-21,+2mar[3]/66,sl1,add(16)(q24),+mar[6]/46,XY[7]	

## 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.
- MAGI2*, *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; ASCT: autologous stem cell transplant; PD: progressive disease; PR: partial response; Chr: chromosome