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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
Age and gender	11 years; female	13 years; male	16 years; female	12 years; male
Clinical presentation	Left adrenal mass; BM metastasis	Bilateral adrenal masses; LN metastasis	Retroperitoneal mass	Presacral mass; BM metastasis
Tumor size (cm)	10.5	Left: 6.7 Right: 3	20	6.4
INSS stage	4	3	3	4
Tumor histology	Poorly differentiated; pheochromocytoma-like morphology	Left adrenal: poorly differentiated Right adrenal: IGN	Poorly differentiated	Poorly differentiated
MKI	Low	Intermediate	Low	Low
ATRX staining	90-100%	90-100%	90-100%	40-50% in primary tumor. Neg in BM mets
Treatment (Response)	• Pheochromocytoma therapy x 1 cycle • ANBL0532 x 4 cycles (NR) • ANBL1221 x 4 cycles (NR) • MIBG therapy	• Complete resection (relapsed 4 months later with mets) • ANBL0532 with ASCT + radiation (PD) • Temodar, irinotecan, Dinutuximab (PD) • Compassionate Lorlatinib	• ANBL0532 x 4 cycles (PR) • Resection + radiation (SD) • Alectinib x 6 months (PD) • Lorlatinib	• ANBL0532 + resection + ASCT followed by radiation and resection of residual tumor • Relapsed prior to starting maintenance phase: received Temodar, irinotecan (PD) • Palliative Cytoxan and topotecan
Outcome	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
Microarray results – Tumor	Partial chr gains	-	2p	1p, 1q, 11p, 11q, 17p, 17q, 19p, 19q, Xp	2p, 2q, 3p, 3q, 6p, 6q, 7q, 17p, 17q, 22q, Xp
	Partial chr Losses	19p, 22q	19p	-	3q, 7p, 9p, 15q, 19p
	Whole chr gains	-	-	2, 4, 5, 6, 7, 10, 12, 13, 14, 15, 16, 18, 20	1, 4, 5, 8, 10, 12, 13, 18, 20
	Whole chr losses	-	-	-	Y
	cnLOH	-	-	2, 4, 9, 10, 11, 19p, 22	16p
Fish Results	Tumor	Loss of one copy of SMARCB1 and NF2	Gain of MYCN and ALK	Gain of MYCN, AFF3, and FOXO1	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
Chr results	Tumor	46,XX[20]	46,XY,der(19)t(2;19)(p21;p13.2)[8]/46,XY[13]	46,XX[20]	46,XY,t(1;11)(q21;p11.2)[13]/46,XY[7]
	Bone marrow	46,XX[20]	-	46,XX[20]	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,sdl1,add(16)(q24),+mar[6]/46,XY[7]
Exome Sequencing Variants		MAGI2 - R564Q RUNX1 - R201Q	ALK-F1245V, MLL2-E550, & TERT-promoter 124C>T	ALK - F1174L	

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