Double-Hit Ph-Negative Adult B-ALL with *MYC* and *BCL2* Rearrangements and *CDKN2A* Genetic Abnormalities Have Poor Clinical Outcomes: Report of Two Cases

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Background and Design:

While much research has focused on the features and poorer prognosis of double/triple-hit diffuse large B-cell lymphoma patients, little is known about the impact of concomitant *MYC* and *BCL2* gene rearrangements on the outcomes of adult B-acute lymphoblastic leukemia (B-ALL) patients.

Two rare cases of *MYC*+/*BCL2*+ double hit B-ALL were identified: one de novo and one likely dedifferentiated from a follicular lymphoma. Clinical characteristics, lab findings, and outcomes were analyzed along with tissue evaluation and cytogenetic studies. Bone marrows were subjected to next generation sequencing to identify gene mutations which may modify prognosis in these double hit acute leukemia patients.

Results: Clinical Presentation

	Patient 1	Patient 2
Age at diagnosis / Gender	57/M	50/M
Chief complaint	Unilateral neck mass, groin pain/edema	Abdominal bloating, anorexia, 12 lb wt loss
"B" symptoms	Yes	Yes
Initial WBC count (k/uL)	26.1	8.09
Peripheral blasts	1%	7%
Hemoglobin (g/dL)	15.3	8.9
Platelets (k/uL)	58	66
Serum LDH (U/L)	12,910	1,695
Uric acid (mg/dL)	15.5	18.8
Marrow blasts	60%	85%
Lymphadenopathy	Yes, diffuse	No
Splenomegaly	Yes	Yes
Extramedullary masses	Yes	Yes

	Patient 1	Patient 2
Initial BM karyotype	N/A, partial dry tap, not performed	N/A, near complete dry tap, no dividing cells in 48 hours
Important non-BM findings	LN: <i>BCL2</i> / <i>IGH</i> , <i>BCL2</i> gains; NEG for t(11;14)	N/A, testicular masses not biopsied
Initial BM FISH	<i>MYC</i> rearrangement, <i>BCL2</i> / <i>IGH</i> , <i>BCL2</i> gains, <i>CDKN2A</i> deletion, abnormal <i>BCL6</i> signals	Negative ALL FISH: No <i>MYB</i> or <i>CDKN2A</i> deletions, t(9;22), <i>KMT2A-R</i> or <i>IGH-R</i> , or <i>ETV6</i> / <i>RUNX1</i>
Initial BM NGS	<i>CDKN2A</i> c.325G>A; p.Ala109Thr	Not performed

Patient 1: High Grade Follicular Lymphoma & Double-Hit B-Acute Lymphoblastic Leukemia

- 3 week h/o left-sided neck swelling and fatigue, previously treated as infectious
- New onset right scrotal and lower extremity edema and pain
- CT scan: Extensive lymphadenopathy and right hydronephrosis due to mass effect
- Initial concern for undiagnosed CLL/SLL with Richter transformation; Clonal CD5+ B cells
- Inguinal lymph node with grade 3A follicular lymphoma and microfocal B-ALL
- Bone marrow involvement with B-ALL
- No remission; died 9 months after his initial diagnosis

Patient 2: Double-Hit B-Acute Lymphoblastic Leukemia with Extramedullary Masses

- 2 week h/o abdominal bloating, anorexia, 12 lb weight loss, previously treated as infectious
- Bone marrow involvement with de novo B-ALL and extramedullary masses
- Bilateral testicular masses; h/o undescended right testicle status post-orchiopey at age 10
- 3 month remission and new onset pararenal mass; transferred for clinical trial
- CD20-positive chest wall mass; died 6 months after his initial diagnosis

	Patient 2
Induction	HyperCVAD A/B
Post-induction CR (BM)	Yes, 3 months
Post-induction BM Cytogenetics	46,XY[20]; normal ALL FISH
Relapse BM karyotype	Complex: 46,XY,t(2;8)(p12;q24.1),del(13)(q12;q14),der(14),t(14;18)(q32;q21.3),t(14;18)[19]/46,XY[1]
Relapse BM FISH	<i>IGH</i> rearrangement
Relapse BM NGS	<i>CDKN2A</i> : c.296G>A; p.Arg99Gln

Pictures courtesy of Dr. Yang O. Huh, MD (MD Anderson Cancer Center)

Discussion

Patient 1:

- t(14;18) subclone likely acquired t(8;14) in the bone marrow where it transformed to B-ALL
- Significance of the clonal CD5-positive B cells in the blood, marrow, and lymph node is unclear
- CDKN2A* exon 2 missense mutation prior to induction
- CDKN2A* deletion and *KIT*, *ATRX*, and *STAG2* missense mutations post-induction

Patient 2:

- t(2;8) and biallelic t(14;18)
- Pararenal mass with B-ALL/B-LBL morphology
- Prior to death, developed a CD20-positive chest wall mass

Both patients had *CDKN2A* exon 2 missense mutations which may result in p16 inactivation. This may also result in responsiveness to the novel use of cdk4/cdk6 inhibitors which are currently employed in breast cancer treatment. *CDKN2A* and *MYC* deregulation have also been associated with transformation.

Conclusion

- FISH for *MYC*, *BCL2*, and/or *BCL6* translocations is not generally performed for leukemia but may help identify poor prognosis double/triple-hit patients
- CDKN2A* exon 2 missense mutations and/or *CDKN2A* deletions may contribute to HyperCVAD refractory disease or rapid relapse in these patients
- It is imperative that we identify additional prognostic and/or predictive biomarkers which may impact disease outcome in adult Ph- B-ALL patients