RARE CASE OF B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA WITH T(14;14)(q11.2;q32)

Linnea Banker, MD, Christine Sholy, M3, Lakshmi Chelapareddy, MD, Richard D. Hammer, MD

Department of Pathology & Anatomical Sciences, University of Missouri, Columbia, MO 65212, USA

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Introduction

A 53-year-old female with no significant medical history presented to University Hospital with fatigue & abnormalities on complete blood count at an outside institution. White blood cell count (WBC) was 36.19x10^9/L with a differential including 66% blasts, hemoglobin was 6.2g/dL, & platelet count was 12.4x10^9/L A peripheral blood smear (PBS) & bone marrow (BM) aspirate & biopsy were obtained for analysis.

Methods

Flow Cytometric Analysis

Flow cytometric (FC) analysis was performed on the BM at the University of Missouri Hospital (1 Hospital Drive, Columbia, MO 65212).

Chromosome Analysis

Chromosome analysis was performed on the BM at Mayo Clinic Laboratories – Rochester Main Campus (200 First Street SW, Rochester, MN 55905) using the culture without mitogens method.

Fluorescent In-Situ Hybridization

Fluorescent in-situ hybridization (FISH) was performed on the BM at Mayo Clinic Laboratories – Rochester Main Campus (200 First Street SW, Rochester, MN 55905). Probe strategies involved dual color, double fusion, break apart probe, & region gain & loss.

Next Generation Sequencing

Next generation sequencing (NGS) was performed on the BM at Foundation Medicine (150 Second St, 1st Floor. Cambridge, MA 02141). The assay utilized DNA sequencing to interrogate 406 genes as well as selected introns of 31 genes involved in rearrangements. RNA sequencing of 265 genes was also included.

Minimal Residual Disease Analysis

Minimal residual disease (MRD) analysis was performed on the BM using the Clonoseq assay at Adaptive Biotechnologies Corporation (1551 Eastlake Avenue East, Suite 200, Seattle, WA 98102). The Clonoseq assay utilizes multiplex polymerase chain reaction (PCR) & NGS to identify & characterize a dominant clonotype. MRD analysis was also conducted with FC on the BM at the University of Missouri Hospital (1 Hospital Drive, Columbia, MO 65212).

Case & Results

- FC analysis performed on the PBS confirmed B-cell acute lymphoblastic leukemia/lymphoma (B-ALL). Blasts were 72.8% with aberrant expression of bright CD10, CD24 & CD123; moderate CD19, HLA-DR, CD38 & cTdT; & dim surface CD22 & CD45. Blasts were negative for surface immunoglobulin light chain, CD20, cCD22, CD34, & all related myeloid & T-cell antigens & did not show overexpression of CRLF2.
- BM demonstrated B-ALL. Chromosome analysis was significant for 46,XX,t(14;14)(q11.2;q32)[4]/46,XX[5]. B-ALL FISH indicated 84% of nuclei had the *IgH* rearrangement. *BCR/ABL1* qualitative RT-PCR was negative. NGS revealed alternations in *NRAS* & *IGH* with variant allele frequencies of 43.99% & 36.40%, respectively, & *IGH-CEBPE* rearrangement. Loss of *CDKN2A* & *CDKN2B* & multiple variants of unknown significance were detected as well.
- Cerebrospinal fluid was negative for disease involvement. The patient started Hyper-CVAD Part A. Rituxan & tyrosine kinase inhibitors were omitted as blasts were CD20 negative & *BCR/ABL1* testing was negative, respectively. The patient completed hyper-CVAD Part A without complications.
- Repeat BM biopsy performed prior to initiation of hyper-CVAD Part B showed no evidence of B-ALL. FC demonstrated 1.5% blasts, & the patient's previously immunophenotyped leukemic blasts were not detected. Cytogenetic testing demonstrated 46,XX[20]. B-ALL FISH was normal, & 0 residual clonal cells were detected for MRD. Thus, the findings were consistent with complete remission (CR). The patient completed hyper-CVAD part B & was placed POMP maintenance regimen. Unfortunately, the patient passed away shortly afterwards due to acute infectious complications.

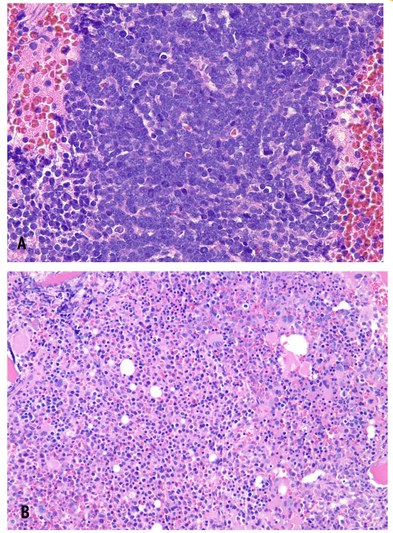

Figure 1 H&E diagnostic BM. (A) Initial BM demonstrates numerous blasts consistent with B-ALL (200x). (B) BM obtained post-therapy is negative for B-ALL.

Table 1: Summary of reported findings in B-ALL patients with t(14;14)(q11;q32).

Case	Age (yr)/sex	WBC x10^9/L	BM blast (%)	Immunophenotype	Karyotype	FISH	CR (Y/N)	Reference
1	5.6/F	38.7	N/A	B-cell lineage	45,XX,-7,t(14;14)(q11;q32)[14]/46,XX[2]	N/A	Y	1
2	7/F	171	85	CD10+, CD19+, CD38+	46,XX,t(14;14)(q11;q32)[13]/46,XX[1]	Breakpoints located telomeric to TCRα/δ & IGH loci	Y	2
3	36/F	41.1	85	CD10+, CD19+, CD38+, CD22+	46,XX,del(6)(q22),t(14;14)(q11;q32)[20]	IGH involvement	Y	3
4	44/M	73.6	92.5	CD9+, CD10+, CD19+, CD20+, CD22+, CD38+	47,XY,t(14;14)(q11;q32),+mar[15]/46,XY[5]	IGH involvement	NT	3
5	45/M	1	N/A	CD10+, CD19+, CD34+, CD38+	45,XY,dup(5)(q14q21),-7,t(14;14)(q11;q32)[17]	IGH & CEBPE involvement	N/A	4
6	39/F	3.6	88.5	CD10+, CD19+, cCD79a+, HLA-DR+	47,XX,+4,t(14;14)(q11;q32)[20](07.11.19)	IGH & CEBPE involvement	Y	5
7	5/F	3.9	90	CD10+, CD19+, CD22+, CD33+, CD34+, CD38+, CD45+, CD79b+, HLA-DR+	46,XX,del(9)(p21), t(9;14;14)(p12;q11;q32)[20]	IGH & CEBPE (PAX5 & CDKN2A deletion) involvement	Y	6
8	53/F	36.19	93.6	CD10+, C19+, CD22+, CD24+, CD38+, CD123+, HLA-DR+	46,XX,t(14;14) (q11.2;q32)[4]/46,XX[5]	IGH & CEBPE involvement	Y	Present case

Abbreviations: F, female; M, male; N/A, not available; Y, yes; NT, no treatment

Discussion

To date, there have been seven reported cases of B-ALL with t(14;14)(q11;q32), making this case the eighth. This translocation is often associated ataxia-telangiectasia[3] & is frequently observed in T-cell lineage neoplasms. It has been shown to involve the TCRA gene on 14q11, a commonly involved locus in T-cell leukemias. As in our case, previous reports of B-ALL with t(14;14)(q11;q32) have not involved the TCRA gene but have instead involved the *IGH* gene.[3,5] *IGH* is frequently involved in B-cell neoplasms & is partnered with a variety of oncogenes. The *IGH* gene is part of the hallmark of translocations for many B-cell neoplasms. For example, t(11;14)(q24;q32) is often associated with mantle cell lymphoma, multiple myeloma, & chronic lymphocytic leukemia, & t(8;14)(q24;q32) is frequently seen in Burkitt lymphoma & ALL L3 type.[3]

In the present case, the patient's BM following chemotherapy initiation was negative for residual clones by both molecular techniques & FC. This clinical picture aligns with previously reported cases in which B-ALL patients with t(14;14)(q11;q32) achieved CR following treatment.[1-6]

Conclusion

Together with previously reported cases, this case demonstrates that t(14;14)(q11;q32) in B-ALL may be associated with a more favorable prognosis. This specific translocation may be its own entity in the diagnosis of B-ALL. This cytogenetic abnormality is a rare finding, and more data is required before definitive conclusions can be made about its prognostic indications.

References

1.Raimondi SC, Zhou Y, Mathew S, et al. Reassessment of the prognostic significance of hypodiploidy in pediatric patients with acute lymphoblastic leukemia. Cancer. 2003;98(12):2715-2722. doi:10.1002/cncr.11841

2.Berger R, Busson M, Daniel MT. B-cell acute lymphoblastic leukemia with tandem t(14;14)(q11;q32). Cancer Genet Cytogenet. 2001;130(1):84-86. doi:10.1016/s0165-4608(01)00459-9

3.Liu S, Bo L, Liu X, Li C, Qin S, Wang J. IGH gene involvement in two cases of acute lymphoblastic leukemia with t(14;14)(q11;q32) identified by sequential R-banding and fluorescence in situ hybridization. Cancer Genet Cytogenet. 2004;152(2):141-145. doi:10.1016/j.cancergencyto.2003.11.008

4.Akasaka T, Balasas T, Russell LJ, et al. Five members of the CEBP transcription factor family are targeted by recurrent IGH translocations in B-cell precursor acute lymphoblastic leukemia (BCP-ALL). Blood. 2006;109(8):3451-3461. doi:10.1182/blood-2006-08-041012

5.Han Y, Xue Y, Zhang J, et al. Translocation (14;14)(q11;q32) with simultaneous involvement of the IGH and CEBPE genes in B-lineage acute lymphoblastic leukemia. Cancer Genetics and Cytogenetics. 2008;187(2):125-129. doi:10.1016/j.cancergencyto.2008.08.008

6.Zerrouki R, Benhassine T, Bensaada M, Lauzon P, Trabzi A. The complex translocation (9;14;14) involving IGH and CEBPE genes suggests a new subgroup in B-lineage acute lymphoblastic leukemia. Genet Mol Biol. 2016;39(1):7-13. doi:10.1590/S1415-475738420140368