



The diagnostic challenges and clinical course of a myeloid/lymphoid neoplasm with eosinophilia and *ZBTB20-JAK2* gene fusion presenting as B-lymphoblastic leukemia

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Abstract We report the diagnostic challenges and the clinical course of a patient with an extraordinary presentation of B-lymphoblastic leukemia (B-ALL) with eosinophilia. We identified a novel *ZBTB20-JAK2* gene fusion as a chimeric RNA transcript using the Archer platform. This gene fusion from the same patient was recently identified by Peterson et al. (2019) at the genomic level using a different sequencing technology platform. The configuration of this gene fusion predicts the production of a kinase-activating JAK2 fusion protein, which would normally lead to a diagnosis of Philadelphia chromosome-like B-ALL (Ph-like B-ALL). However, the unusual presentation of eosinophilia led us to demonstrate the presence of this gene fusion in nonlymphoid hematopoietic cells by fluorescence in situ hybridization (FISH) studies with morphologic correlation. Therefore, we believe this disease, in fact, represents blast crisis arising from an underlying myeloid neoplasm with *JAK2* rearrangements. This case illustrates the difficulty in differentiating Ph-like B-ALL and myeloid/lymphoid neoplasm with eosinophilia and gene rearrangements (MLN-EGR) in blast crisis. As currently defined, the diagnosis of MLN-EGR relies on the hematologic presentations and the identification of marker gene fusions (including *PCM1-JAK2*, *ETV6-JAK2*, and *BCR-JAK2*). However, these same gene fusions, when limited to B-lymphoblasts, also define Ph-like B-ALL. Yet, our case does not conform to either condition. Therefore, the assessment for lineage restriction of gene rearrangements to reflect the pathophysiologic difference between B-ALL and MLN-EGR in blast crisis is likely a more robust diagnostic approach and allows the inclusion of MLN-EGR with novel gene fusions.

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INTRODUCTION

Kinase-activating JAK2 fusion proteins derived from gene rearrangements are increasingly recognized in hematopoietic neoplasms. These chimeric proteins, composed of a JAK2 kinase domain and the dimerization domain of a fusion partner, are the hallmarks of a subset of Philadelphia chromosome-like B-precursor acute lymphoblastic lymphoma/leukemia

(Ph-like B-ALL) and myeloid/lymphoid neoplasms with *PCM1-JAK2* (MLN-PJ) (Reiter et al. 2005; Adélaïde et al. 2006; Ehrentraut et al. 2013; Patterer et al. 2013; Bain and Ahmad 2014; Roberts et al. 2014, 2017). Ph-like B-ALLs lack *BCR-ABL1* fusion but share a similar gene expression profile and unfavorable clinical behavior to *BCR-ABL1*-positive B-ALL (Roberts et al. 2014, 2017). Although only 7% of Ph-like B-ALLs harbor *JAK2* rearrangements, at least 19 fusion partners have been described. Some of the fusions, including *PCM1-JAK2* and variants, are also present in MLN-PJ (Tasian et al. 2017). MLN-PJ, a provisional entity under the broader category of myeloid/lymphoid neoplasm with eosinophilia and gene rearrangements (MLN-EGR), was established using *PCM1-JAK2* as the index genetic abnormality and recently expanded to include *ETV6-JAK2* and *BCR-JAK2* as variants (Bain and Ahmad 2014; Swerdlow et al. 2017). The hematologic presentations, often with eosinophilia and features of myeloproliferative, myelodysplastic, or overlapping neoplasms, are distinct from B-ALLs. However, transformed B-ALL in MLN-PJ can occur (Reiter et al. 2005; Bain and Ahmad 2014; Tang et al. 2018). Therefore, separating these two entities can be difficult, especially in cases without a history of myeloid neoplasm. This report highlights an extraordinary case of a B-ALL with eosinophilia that harbors a novel *JAK2* fusion and may have arisen from an underlying myeloid neoplasm.

RESULTS

Clinical Presentation

The patient is a 33-yr-old woman who was referred to our institution with complaints of malaise, dyspnea, and fatigue for 3 wk. Initial laboratory studies revealed a leukocytosis (WBC = 42.9 K/ μ L) with 45% circulating blasts and absolute eosinophilia (2.6 K/ μ L), anemia (hemoglobin = 6.2 g/dL), and thrombocytopenia (platelets = 12 K/ μ L) (Fig. 1A). A computed tomography scan revealed nonspecific diffuse lymphadenopathy and mild splenomegaly. A bone marrow aspirate and biopsy demonstrated increased blasts (60.4%) and increased eosinophil fraction (16%) (Fig. 1B,C). Flow cytometry analysis detected increased abnormal B-lymphoblasts, positive for CD19, CD20 (partial), CD10, TdT, and CD34, consistent with a pre-B-ALL.

Genomic Analysis

The presentation of B-ALL with eosinophilia elicits a differential diagnosis that includes B-ALL (including subsets with interleukin-3 gene fusions [Meeker et al. 1990]) and MLN-EGR in blast crisis. A *JAK2* rearrangement (*JAK2-R*) was detected as a balanced translocation between Chromosomes 3q13 and 9p24 by karyotype analysis (Fig. 2A) and confirmed with a fluorescence in situ hybridization (FISH) study using *JAK2* break-apart probes. Cells with bean-shaped/bilobed nuclei (likely maturing myeloid elements) are positive for *JAK2-R* (72% of 53 nuclei) (Fig. 2B). The cell fractions with *JAK2-R* were higher than the blast fractions at diagnosis (80% *JAK2-R* nuclei vs. 41% blasts by marrow aspirate smear differential) and after the first induction (21.5% *JAK2-R* nuclei vs. 2.6% blasts by marrow aspirate smear differential or 6% blasts of viable cells by MRD-flow cytometry). Following reinduction, the blast fraction (0.4% by aspirate smear differential) decreased further, but the *JAK2-R* was not detected by FISH studies despite persistent minimal residual disease (MRD) (0.19% of viable cells by MRD flow cytometry). This discordance in neoplastic cell fractions and the presentation of eosinophilia led us to confirm the presence of *JAK2-R* in erythroid precursors using FISH assay with morphologic correlation, performed on destained Wright–Giemsa-stained marrow aspirate smears (Fig. 2C). Break-apart signals in myeloid elements, although present, were obscured by autofluorescent granules precluding

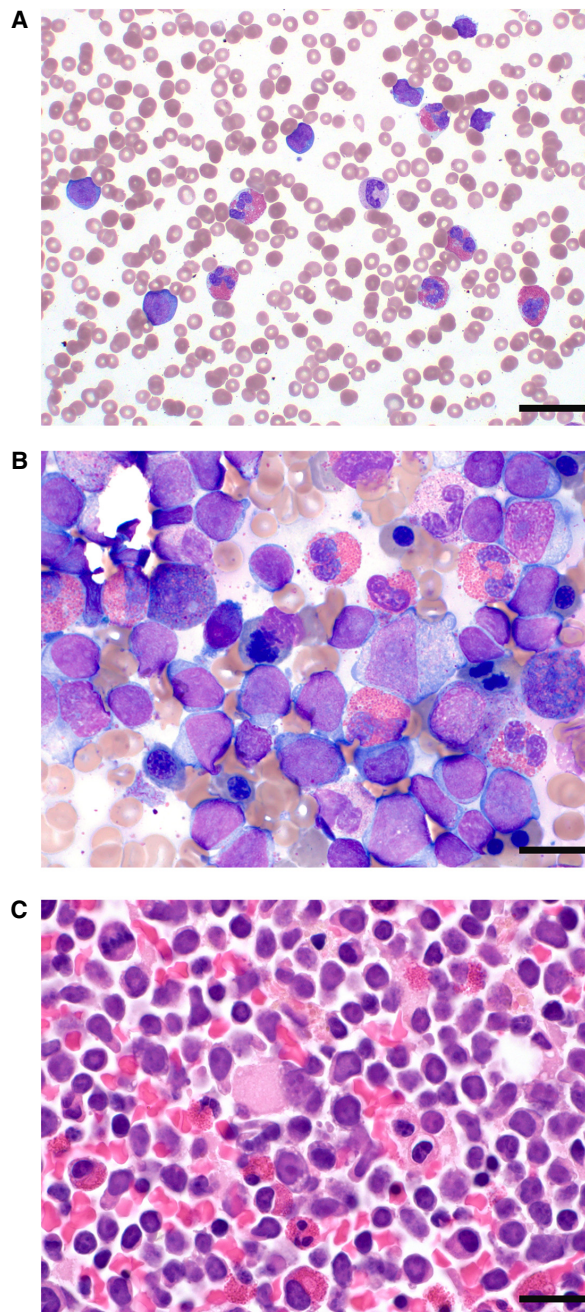


Figure 1. B-lymphoblastic leukemia/lymphoma and absolute eosinophilia. (A) A Wright–Giemsa-stained peripheral blood smear demonstrates increased circulating blasts and increased mature eosinophils (original magnification, 500 \times). Increased blasts and immature eosinophils in bone marrow are seen on the Wright–Giemsa-stained bone marrow aspirate smear (B) (original magnification, 10000 \times) and in the hematoxylin and eosin–stained section of the bone marrow core biopsy (C) (original magnification, 1000 \times). Scale bars, (A) 20 μ m; (B,C) 10 μ m.

quantification (Fig. 2C). The detection of *JAK2-R* in multiple hematopoietic lineages indicates a defect at the level of pluripotent hematopoietic stem cells (HSCs), consistent with an underlying MLN-EGR.

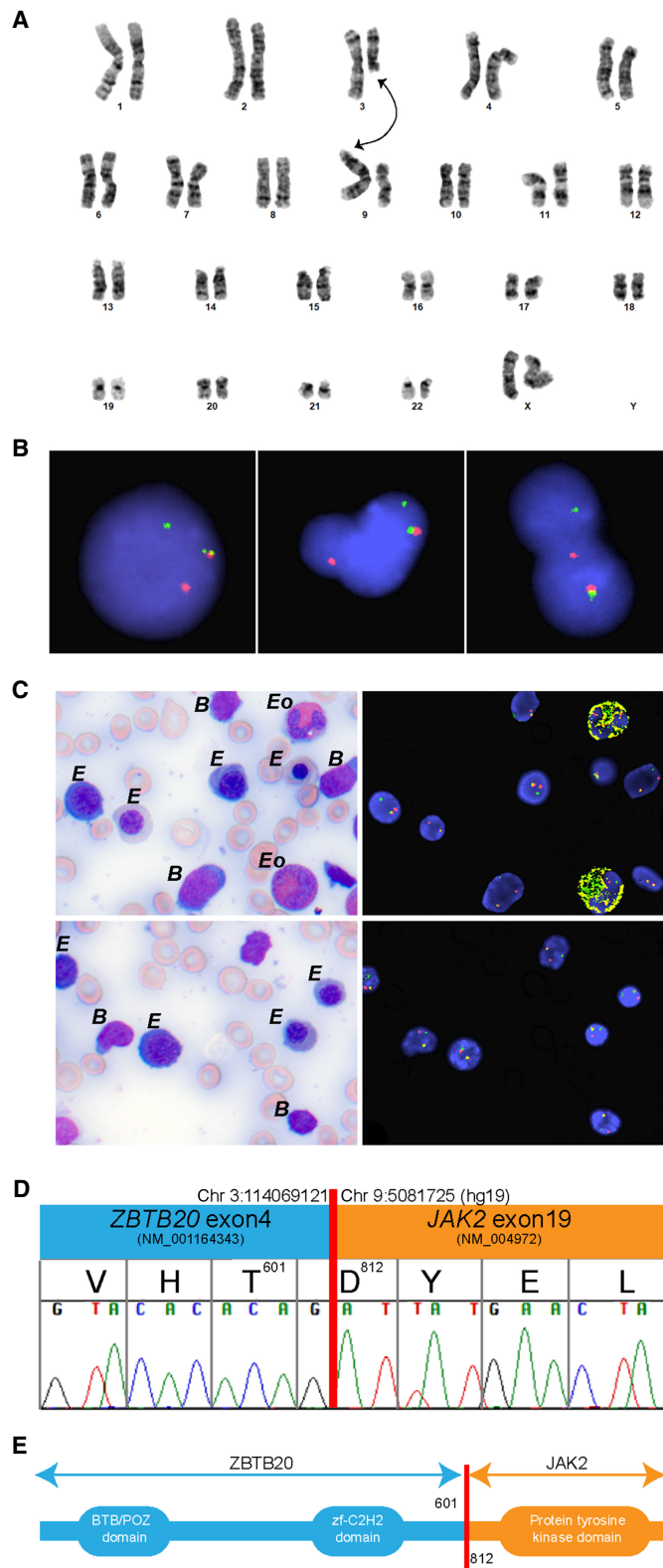


Figure 2. See legend on following page.

An in-frame fusion between ZBTB20 exon 4 as the 5' partner (ZBTB20:NM_00116342 [exon:4] Chr 3:114069121) and JAK2 exon19 as the 3' partner (JAK2:NM_004972 [exon:19] Chr 9:5081725) was identified using the Archer next-generation sequencing (NGS) assay and analysis based on human genome assembly version hg19 (see Table 1). ZBTB20 is reportedly expressed in germinal center B cells, plasma cells, and neuronal tissues, but the expression in myeloid/erythroid precursors remains unknown (Chevrier et al. 2014; Wang and Bhattacharya 2014; Maeda 2016; Zhu et al. 2018). Expression of ZBTB20-JAK2 RNA chimeric transcripts was confirmed by Sanger sequencing on cDNA amplicons (Fig. 2D). The predicted chimeric protein contains one dimerizing BTB/POZ domain and one zinc-finger-C2H2 domain of ZBTB20 at the amino terminus fused with the JAK2-tyrosine-kinase domain (Fig. 2E), allowing for constitutive activation of ZBTB20-JAK2 fusion protein through partner-mediated oligomerization, similar to other known kinase-activating JAK2 gene fusions (Roberts et al. 2014; Maeda 2016; Zhu et al. 2018). Furthermore, the cytogenomic array identified a deep 107-kB deletion at Chromosome 7p12, consistent with a homozygous *IKZF1* deletion (data not shown). *IKZF1* deletion is a frequent genetic event in Ph-like B-ALL but has also been reported in B-ALL transformed from myeloproliferative neoplasms (Mullighan et al. 2008; van der Veer et al. 2013; Tasian et al. 2017). These findings are consistent with B-ALL arising from an underlying myeloid neoplasm.

Treatment Course

The patient was initiated with induction chemotherapy with CALGB 8811 plus rituximab (R-Larson protocol). Notably, the patient's eosinophil count continued to rise rapidly (it peaked at 8K/ μ L), but dropped precipitously along with the blast count after initiation of chemotherapy. A bone marrow aspirate and biopsy at day 30 with normalization of blood cell counts was morphologically negative but positive for MRD (6% of viable cells and 8.5% of mononuclear cells by flow cytometry). Following reinduction with the B-arm of hyper-CVAD, she continued to be in a morphologic remission, but MRD persisted (0.19% of viable cells and 3.1% of mononuclear cells by flow cytometry). Given her persistent MRD level of disease, one cycle of blinatumomab was given, and she then underwent an 8/8 matched unrelated donor transplant. A bone marrow aspiration and biopsy performed on post-transplant day 104 demonstrated a morphologic remission with no evidence of minimal residual disease by flow cytometry. The patient remains in remission now at 200 d post-transplant.

Figure 2. Identification and characterization of a novel ZBTB20-JAK2 gene rearrangement. (A) A balanced t(3;9)(q13;p24), as indicated by the arrows, is detected by conventional G-banding karyotype analysis. (B) JAK2 gene rearrangement is confirmed by using a break-apart FISH probe set in interphase nuclei (original magnification, 1000 \times). The red signals are 5' JAK2 probes and the green signals are 3' JAK2 probes. The yellow signals and the red and green signals in close tandem represent overlapping red and green signals, consistent with intact JAK2 loci. Positive break-apart signals, consistent with JAK2 rearrangements, are present in cells with bean-shaped nuclei and bilobed nuclei, possibly representing immature and mature eosinophils. (C) JAK2 rearrangements in erythroid elements (E) and blasts (B) are confirmed by comparing a Wright-Giemsa-stained bone marrow aspirate smear (original magnification, 400 \times , with digital magnification, 2.5 \times) and the JAK2 break-apart FISH assay (original magnification, 1000 \times) performed after destaining. Although break-apart signals can be seen in maturing eosinophils (Eo), autofluorescence of cytoplasmic granules preclude definitive assessment. (D) A modified DNA chromatogram derived from Sanger sequencing summarizes the breakpoints in ZBTB20 and JAK2 genes (genomic coordinates provided on top), the site of fusion (red line), the resultant DNA sequence, and the corresponding amino acid (with the amino acid residue positions of each protein partner listed as superscripts). (E) The resultant fusion protein is predicted to contain the BTB/POZ (dimerization) domain and a zf-C2H2 domain from ZBTB20 and the protein tyrosine kinase domain from JAK2.

Table 1. Gene fusion identified from sequencing using Archer Dx FusionPlex

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect (substitution, deletion, etc.)	dbSNP/dbVar ID	Genotype (heterozygous/homozygous)	ClinVar ID (optional)	Parent of origin (optional)	Observed effect (if shown to be different from predicted effect) (optional)	Comments (optional)
ZBTB20	3	Chr 3: 114069121		Fusion	NM_00116342: c.1_1804::	n/a	n/a	SCV001190540	n/a		Somatic
JAK2	9	Chr 9: 5081725			NM_004972: c.2324_* (p.T601::p.D812)						

DISCUSSION

This case illustrates the difficulty in differentiating Ph-like B-ALL and MLN-EGR in blast crisis. The key distinction is the ability of the gene fusions to drive neoplastic HSCs in MLN-EGR, sustaining multilineage hematopoietic differentiation, whereas the effect in Ph-B-ALL is restricted to the lymphoid lineage. Per the current World Health Organization (WHO) classification, the diagnosis of MLN-EGR relies on the hematologic presentations and the identification of “known” gene fusions, many of which are shared with Ph-like B-ALL. Our case does not conform to either condition. Eosinophilia, although helpful in this case, is not universally present in MLN-EGR. Two cases of B-ALLs without eosinophilia were retrospectively found to harbor *PCM1-JAK2* in multiple lineages using FISH studies with morphologic correlation, consistent with MLN-PJ in blast crisis (Tang et al. 2018). Therefore, assessment for lineage restriction of gene rearrangements to reflect the pathophysiologic difference between B-ALL and MLN-EGR in blast crisis is likely a more robust diagnostic approach and allows the inclusion of MLN-EGR with novel gene fusions. FISH study with morphologic correlation represents a tractable way to routinely assess lineage restriction of gene rearrangements.

Although it is not known whether eosinophilia was present in this patient prior to the presentation of B-ALL, a subclinical myeloid neoplasm with *JAK2* rearrangement likely preceded the onset of B-ALL in our patient. In MLN-PJ that manifests as chronic eosinophilic leukemia, remission following treatment with *JAK2* inhibitors has been reported (Bain and Ahmad 2014; Schwaab et al. 2015; Lierman et al. 2012; Rumi et al. 2015, 2013; Reiter et al. 2005). It is tantalizing to speculate whether the blast crisis was preceded by a subclinical prodromal state that may serve as a window of opportunity for *JAK* inhibitor treatment. However, because of its rarity, there is a lack of knowledge about robust clinical features of the prodromal state. Therefore, only by consistently making a diagnostic distinction between Ph-like B-ALL and B-ALL arising from MLN-EGR can we accumulate evidence and experience with this unique disease.

A different group has reported the detection of *ZBTB20-JAK2* fusion from the same patient using mate-pair sequencing (Peterson et al. 2019). Their report offers a different level of information and nicely complements our findings. They identified the breakpoints and the site of fusion to be within intron 4 of *ZBTB20* and intron 18 of *JAK2* at the genomic level and deduced a productive rearrangement based on the genomic configuration. In their report, they speculated on the possibility of MLN-EGR but did not offer additional evidence. Furthermore, their reports focused on the initial presentation without providing a detailed clinical course. In contrast, our approach using the Archer platform characterizes the chimeric RNA transcript by sequencing the complementary DNA, providing evidence for active transcription of the gene fusion. Importantly, we demonstrated *JAK2-R* in nonlymphoid lineage

cells, supporting the possibility of underlying MLN-EGR, and presented a detailed clinical course as described above.

This case is the first report of a ZBTB20-JAK2 fusion defining a case of MLN-EGR presenting as B-ALL. Although remission following treatment of MLN-PJ with JAK2 inhibitors has been reported (Lierman et al. 2012; Rumi et al. 2013, 2015; Bain and Ahmad 2014; Schwaab et al. 2015; Reiter and Gotlib 2017), there is a near-complete absence of reported responses to these therapies targeting JAK mutations and/or fusion genes in B-ALLs, including Ph-like ALLs (Roberts et al. 2014; Reinert et al. 2018). This patient's case was appropriately initially classified as a B-ALL, and therapy was selected based on this diagnosis. Given the paucity of data for targeted therapy in this disease state, we chose a guideline-based clinical approach to primary refractory B-ALL, which is largely driven by application of additional cytotoxic chemotherapy. Given her persistent MRD status after two cycles of therapy, blinatumomab, a targeted bispecific T-cell engager (BiTE) treatment was delivered as a third-line therapy based on the current labeled indication. This clinical approach ultimately led to her successful transplant and MRD-negative complete remission now at 200 d post-transplant. This case further highlights the need for trial-based assessments of mutation/fusion-directed agents in acute lymphoid and myeloid leukemias.

METHODS

Karyotype analysis and FISH studies using JAK2 break-apart probes (Empire Genomics) were performed and analyzed according to routine laboratory protocols. Cytoscan HD array (Thermo Fisher) was performed according to the manufacturer's instruction and analyzed using the Chromosome Analysis Suite.

B-ALL MRD status was assessed by flow cytometry, as described by the report from Children's Oncology Group study AALL0232 (Borowitz et al. 2015).

To identify the 5'-JAK2 fusion partner, the analysis was carried out using the NGS customized FusionPlex Pan-Heme kit (Archer Dx) performed at Nationwide Children's Hospital, Columbus, Ohio. This assay utilizes unidirectional primers specific for known kinase targets (GSPs) at the 3' end to amplify targeted cDNA fragments that are ligated at the 5' end with molecular barcodes and universal primers, enabling the identification of both known and novel fusions involving targeted genes (as listed in Supplemental Material 1). Sequencing was performed using an Illumina sequencer. The sequencing run statistics are shown in Table 2. Downstream analysis identified the gene fusion using the proprietary Archer Analysis Pipeline v5.1 provided by the manufacturer. Confirmatory Sanger sequencing was performed on targeted cDNA amplicon using the following M13-tailed custom-designed primers:

Forward Primer CAGCAGACCCAGTTTGTGAC

Reverse Primer ATTTTGGGAGTGTGGAGATGTGCCG

Table 2. Sequencing run statistics

	RNA reads (count)
All fragments	2,301,160
Unique fragments	1,466,751
Unique start sites	185,499
RNA median fragment length	187
Target fusion supporting reads	109
Target fusion unique start sites	62

ADDITIONAL INFORMATION

Data Deposition and Access

The variants reported in this study have been submitted to ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) under accession number SCV001190540.

Ethics Statement

The patient has given oral consent for the preparation and publication of this case report. The use of the clinical record and data in this report is in accordance with University of Michigan Internal Review Board Protocol (HUM00160360), which allows for retrospective analysis of deidentified data and clinical record for research purposes. The protocol HUM0016360 has been approved for a waiver of informed consent as the research involves no more than the minimal risk to the participants.

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Author Contributions

W.Y.L, R.B.P., L.S., S.M.C., D.L.B., and R.J.H.R. conceptualized the study and analyzed data. W.Y.L, L.S., J.Y., H.X., E.M.P., and R.B.P. generated figures and analyzed data. W.Y.L. and L.S. drafted the manuscript. All authors reviewed and edited the manuscript.

Competing Interest Statement

The authors have declared no competing interest.

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