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CASE REPORT

TBL1XR1-JAK2: a novel fusion in a pediatric T cell acute lymphoblastic leukemia patient with increased absolute eosinophil count

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Abstract

T-lymphoblastic leukemia/lymphoma (T-ALL/LBL) with any *JAK2* gene fusion is rarely reported. Here, we report a case of T-ALL with a novel *TBL1XR1-JAK2* gene fusion in a 5-year-old boy. His lab showed a high white blood cell count, mild anemia, moderate thrombocytopenia, and concurrently increased eosinophils (absolute eosinophil count: 4 × 10^9/L). Peripheral blood and bone marrow aspirate smears showed > 90% mononucleated blasts. Flow cytometry on peripheral blood revealed a large blast population positive for CD2, surface CD3 (< 25%), CD10 (50%), CD5, CD7, CD4, CD8, TdT, CD1a (60%), and CD45. Conventional karyotype analysis showed t(3;9)(q26;p24) and t(11;14)(p13;q11.2)/*TCRD-LMO2*. Next-generation sequencing (NGS) identified a novel *TBL1XR1-JAK2* gene fusion in a sequencing depth of 180 × by RNAseq, *FBXW7 R465H* mutation, and loss of exons 2–3 of *CDKN2A/B* by DNAseq. Follow-up bone marrow aspirate on day-28 post-induction therapy revealed no morphologic evidence of residual leukemia. We believe that the *TBL1XR1-JAK2* fusion may behave in a similar functional manner to the *PCM1-JAK2* fusion gene and constitutes a new variant of this family and a potential target of tyrosine kinase inhibitor (TKI) therapy.

Keywords T-ALL/LBL · *TBL1XR1-JAK2* gene fusion · Tyrosine kinase inhibitor

Introduction

T cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) is an aggressive malignancy of early T cell progenitors, involving bone marrow and blood (T-ALL) or presenting with primary involvement in the thymus, lymph node, or extranodal site (T-LBL). It accounts for about 10–15% pediatric ALL cases with a predominance in male adolescents [1]. T-ALL/LBL in childhood is generally considered a higher-risk disease for presenting with high-risk features at diagnosis, such as older age and higher white blood cell count [2].

Common genomic alterations in T-ALL/LBL include the activating mutation of the *NOTCH1* signaling pathway, inactivating mutation of *FBXW7* signaling, and deletion or methylation of *CDKN2A* and *CDKN2B* [3]. Constitutional activation of *JAK-STAT* results from an activating mutation of *JAK1* and *JAK3* and is found in 10% of T-ALL/LBL patients [3].

JAK2 gene fusions have been reported in pediatric T-ALL/LBL cases (see Table 1). To date, more than thirty *JAK2* fusion variants affecting *TEL(ETV6)*, *PCM1*, *TPM3*, *CD99*, *MYH9*, *BCR*, *SSBP2*, *STRN3*, *PAX5*, and others have been described [9]. Among these variants, the WHO 2016 proposed a provisional entity, specifically myeloid/lymphoid neoplasms with *PCM1-JAK2* in myeloid/lymphoid neoplasms with eosinophilia and rearrangement of certain fusion genes category [10, 11]. The diseases in this category can present in different ways, as myeloproliferative neoplasms (MPN), myelodysplastic/myeloproliferative neoplasm (MDS/MPN), or lymphoid, as in our case. In this article, we present the *TBL1XR1* gene as a novel *JAK2* fusion partner gene in a pediatric patient with T-ALL/LBL.

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Table 1 Literature study of *JAK2* fusion partner genes in T-ALL/LBL

Fusion gene	Chromosomal translocation	Journal	Year	Reference
TEL (*ETV6*)	t(9;12)(p24;p13)	*Science*	1997	Lacronique et al. [4]
PCM1	t(8;9)(p22;p24)	*Leukemia*	2006	Adelaide J. et al. [5]
TPM3	N/A	*PLOS Genetics*	2013	Atak ZK. et al. [6]
PCM1	N/A	*Nat Genet*	2017	Liu Y. et al. [7]
CD99	N/A	*Nat Genet*	2017	Liu Y. et al. [7]
MYH9	N/A	*PNAS*	2018	Chen B. et al. [8]

Clinical history

The patient is a 5-year-old boy, with an unremarkable past medical history, who presented with new onset of a neck mass for 3 or 4 days, decreased appetite, abdominal pain, and mild fever (99.9 degrees F) for 1 day. His laboratory evaluation revealed mild anemia (hemoglobin 9.3 g/dL), high white blood cell count (404.3 × 10^9/L), increased eosinophils (absolute eosinophil count: 4 × 10^9/L), moderate thrombocytopenia (platelet count 66 × 10^11/L), and high LDH (4800 units/L). Ultrasonographic study of the neck mass suggested it was composed of multiple enlarged lymph nodes. Peripheral blood and bone marrow aspirate smears showed > 90% mononucleated blasts with variably sized immature nuclei (see Fig. 1A and B).

Flow cytometry of peripheral blood revealed a large blast population positive for CD2, surface CD3 (< 25%), CD10 (50%), CD5, CD7, CD4, CD8, TdT, CD1a (60%), and CD45 and negative for CD34, CD117, CD13, CD33, CD14, CD64, CD11b, CD11c, HLD-DR, CD19, and CD20 (see Fig. 1C and D). By immunohistochemistry, blasts were negative for MPO on the bone marrow clot section. This immunophenotypic profile is a characteristic of T cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL).

Conventional karyotype analysis showed male karyotype (46,XY) and translocations t(3;9)(q26;p24) and t(11;14)(p13;q11.2)/*TCRD-LMO2* in 7 of 20 metaphase cells examined (see Fig. 2). The FISH analysis showed deletion of the *CDKN2A* gene on the short arm of chromosome 9 at p21

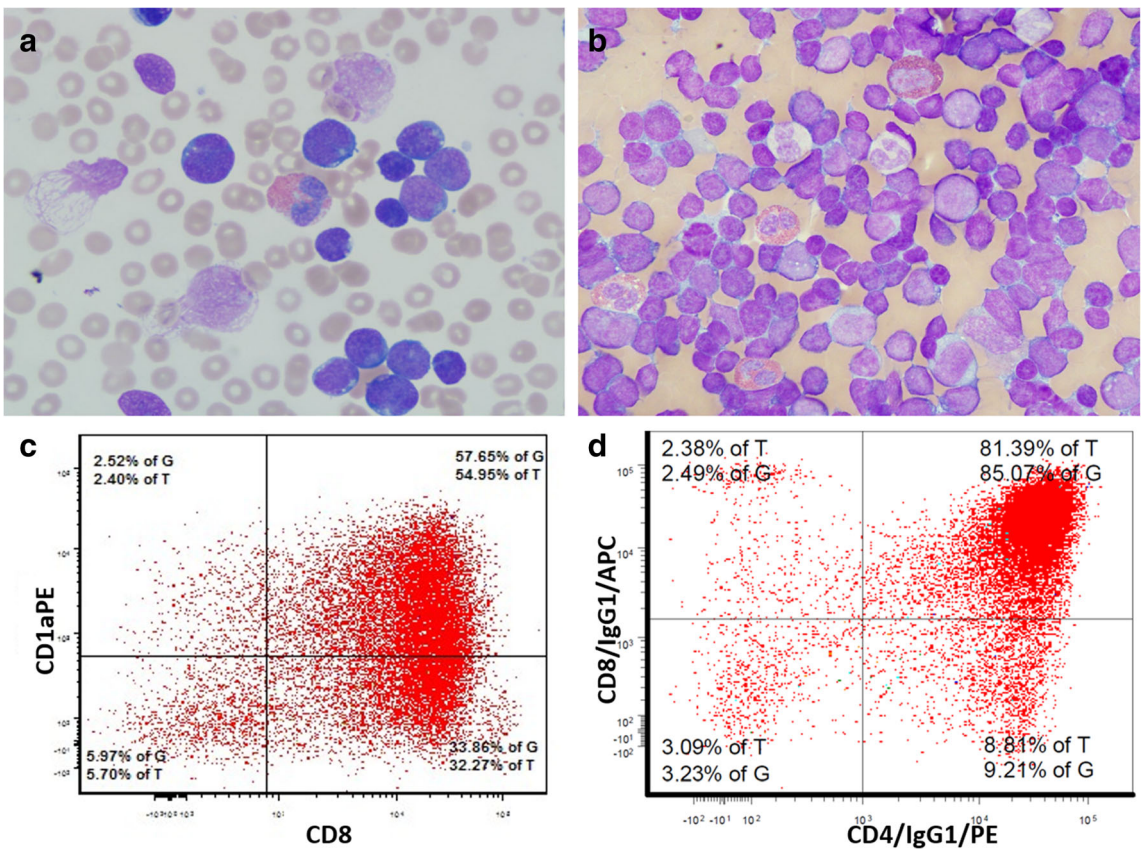

Fig. 1 Peripheral blood smear (A), bone marrow aspirate smear (B), and flow cytometry (C and D). (A and B) Wright stain, × 100 objective; (C and D) flow cytometry on peripheral blood, dot plot CD1a vs CD8 (C) and CD8 vs CD4 (D); blasts are positive for CD4, CD8, and CD1a (60%)

but was negative for *BCR-ABL1*, *KMT2A* (*MLL*), and *ETV6-RUNX1* gene rearrangements. NGS was performed on peripheral blood and found to have a novel gene fusion (*TBL1XR1-JAK2).* This *TBL1XR1-JAK2* fusion was identified to a sequencing depth of 180 × by RNAseq. Additionally, *FBXW7 R465H* mutation and loss of exons 2–3 of *CDKN2A/B* were also noted in DNAseq, which are the most common genomic alterations in T-ALL/LBL [3].

The patient was started on induction therapy with cytarabine, vincristine, daunorubicin, and prednisolone. Follow-up bone marrow aspirate on day 28 post-induction revealed no morphologic evidence of residual leukemia. Peripheral blood count improved, with WBC (4 × 10^9/L) and platelet count (254 × 10^11/L); however, mild anemia (9.1 g/dl) persisted. The patient did obtain complete remission after one cycle of induction therapy.

Methods

Wright stain was used for peripheral blood and bone marrow aspirate smears on Sysmex Automated Hematology Analyzer (Sysmex America, Inc., Lincolnshire, IL), model NX-9000, or manually. All sequencing samples and runs were prepared and completed by FoundationOne Heme, a comprehensive genomic profiling by NGS method by Foundation Medicine (Morrisville, NC, and Cambridge, MA). Flow cytometric analysis and conventional karyotyping with the GTW banding technique and banding resolution at 450 were completed by Integrated Oncology Esoterix Genetic Laboratories (Shelton, CT).

Discussion

Our case is a typical cortical T cell ALL with a novel gene fusion of *TXL1XR1-JAK2* and a concurrent increase of absolute eosinophil count in peripheral blood. It shows some features similar to the myeloid/lymphoid neoplasm with *PCM1-JAK2*, a newly proposed provisional entity with a *JAK2* fusion and concurrent eosinophilia in the 2016 WHO. The neoplasms reported in this provisional entity are most often seen in myeloid lineage; in only rare cases has this fusion been described in B-ALL/T-ALL [10, 11]. Clinical presentation of this provisional entity varies from myeloproliferative disorder to acute leukemia. Any *JAK2* fusion gene in T-ALL/

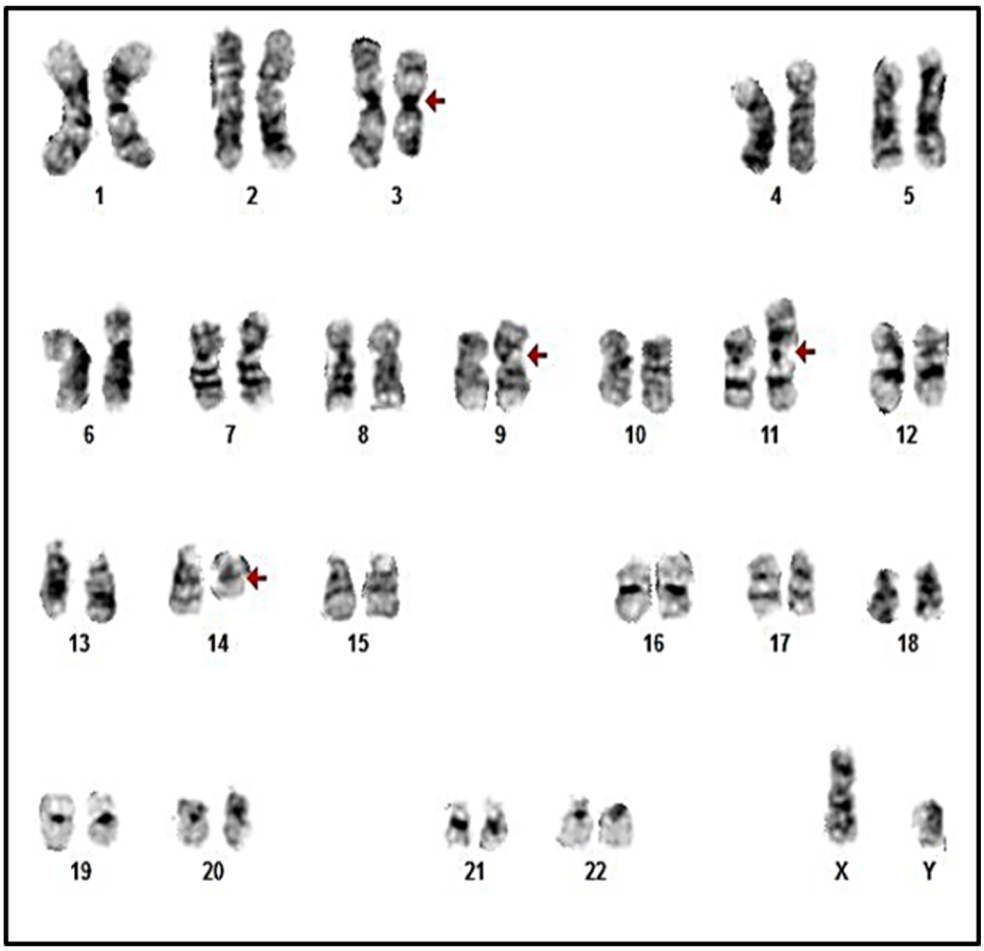

Fig. 2 Conventional karyotype. Representative conventional Karyogram showing translocations t(3;9)(q26;p24) and t(11;14)(p13;q11.2) in 7 of 20 metaphase cells examined

LBL is extremely rare; only six cases have been reported (see Table 1). Its role in prognosis remains unknown.

NGS data identified that the *TBL1XR1-JAK2* fusion gene and breakpoints are located at chr3:176750806-176750846 in *TBL1XR1* (ENSG00000177565) and chr9:5073715-5073755 in *JAK2* (ENSG00000096968) in this patient. *TBL1XR1-JAK2* gene fusion causes a hybrid protein that combines the N-terminal portion of the *TBL1XR1* and kinase portion of *JAK2* (Fig. 3). Because the cytogenetic location of the *TBL1XR1* gene is 3q26.32 (https://ghr.nlm.nih.gov/gene/TBL1XR1), this fusion gene is consistent with the cytogenetic finding of t(3;9)(q26;p24) translocation. We hypothesize that *TBL1XR1-JAK2* gene fusion functions like all other *JAK2* chimeric fusions, such as *PCM1-JAK2* and *TEL-JAK2* [4, 12]. These hybrid proteins cause constitutive activation of the *JAK-STAT5* and *PI3K* signaling pathways, which can regulate cell survival, growth, and differentiation.

TBL1XR1 (transducin-beta-like 1X-related protein 1), also known as *TBLR1*, is an F-box/WD40-repeat-containing protein that was originally isolated as gene transcript that is preferentially expressed in human $CD34^{+}/CD38^{-}$ earliest human hematopoietic progenitor cells [13]. It is an intrinsic component of the *SMRT/NCoR* corepressor complexes and is also required for transcriptional activation by nuclear receptors and other regulated transcriptional factors and is also important for the activation of intracellular signaling pathways, such as *Wnt/β*-catenin, *NF-κB*, and *Notch* [14].

Loss of *TBL1XR1* is associated with resistance to glucocorticoids in B-lymphoblastic leukemia (B-ALL) [14]. Recurrent mutations of *TBL1XR1* are found in high-risk B-ALL [15]. The *TBL1XR1* gene has been reported as a recurrent fusion partner of *RARA* and *RARB* in acute promyelocytic leukemia [16–18] and of *TP63* in 5% of de novo diffuse large B cell lymphoma (DLBCL) of the germinal center B cell-like subtype (GCB) [19]. *TBL1XR1-ROS1* in juvenile myelomonocytic leukemia (JMML) and *TBL1XR1-PDGFRB* in acute myeloid leukemia (AML) with eosinophilia are also reported [20, 21]. The significance of the *TBL1XR1* gene alteration in T-ALL/LBL is unknown.

The first case of constitutive activation of *JAK2* signaling due to *JAK2* fusion with partner *TEL* (*ETV6*) in T-ALL/LBL was reported in 1997 [4]. Similarly, a novel *ZBTB20-JAK2* fusion was recently reported in a young adult with a newly diagnosed B-ALL with eosinophilia [12]. Our case is a *JAK2* fusion with a novel partner *TBL1XR1* in a T-ALL/LBL patient with a significant increase in the absolute count of eosinophils. We predict that *TBL1XR1-JAK2* may have a similar function as the *PCM1-JAK2* fusion gene and could be a new variant in this family. Furthermore, this fusion may potentially be a target of TKI therapy.

In summary, the *TBL1XR1-JAK2* gene fusion has not been reported before in the published literature. Its significance in T-ALL/LBL remains unclear. Additionally, a common chromosome alteration t(11;14)(p13;q11.2)/*TCRD-LMO2* was detected in our patient. This arises from a T cell receptor delta *TCRD* V(D)J recombination and leads to *LMO2* activation which is suggestive of favorable prognosis [22, 23]. Additional genetic abnormalities are also identified in this case, such as loss of *p14* and *p16* and mutation of *FBXW7*, which cause a loss in the control of cell cycle, *c-Myc*, and *PI3K* signaling activation [3]. *JAK2* fusions are associated with an aggressive phenotype [24]. Overall, our case is suggestive of a high-risk T-ALL with limited options for therapies. The introduction of TKI may show an improved outcome. Unfortunately, no study on TKI use in lymphoid neoplasms with *JAK2* fusion and only a limited number of studies in myeloid neoplasms with *PCM1-JAK2* have been reported. *Schwaab J* and *Naumann N* group recently reported a study on the treatment of *JAK2* fusion-positive myeloid neoplasms (*PCM1-JAK2* and *BCR-JAK2*) in 9 patients using the TKI ruxolitinib [24]. A frequent but transient remission was found in their study. Considering this initial study in a small number of patients, future studies are needed to investigate the potentials of TKI therapeutics in *JAK2* fusion-positive myeloid/lymphoid neoplasms.

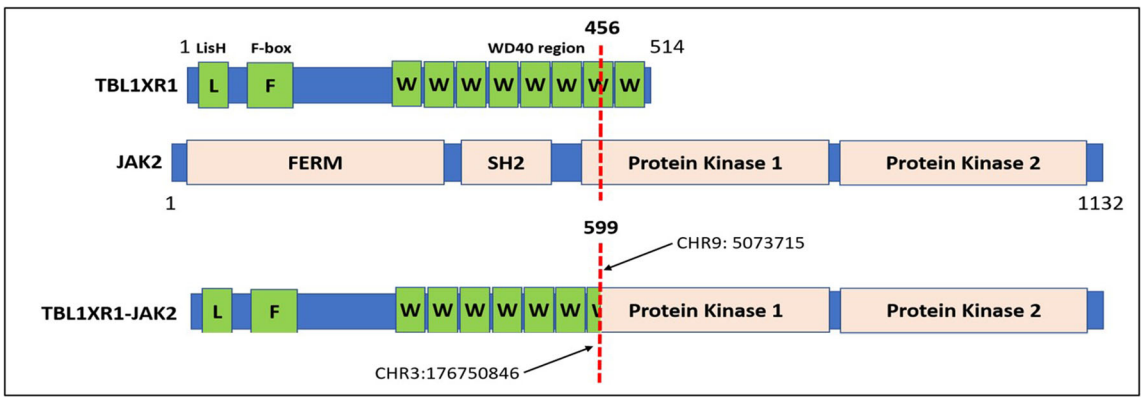

Fig. 3 *TBL1XR1-JAK2* chimeric protein structure. *TBL1XR1-JAK2* hybrid protein structure demonstrating RNAseq results in a sequencing depth of 180 ×. Breakpoints are located at chr3:176750806-176750846 in *TBL1XR1* (ENSG00000177565) and chr9:5073715-5073755 in *JAK2* (ENSG00000096968)

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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