A rare case of Philadelphia-positive (P210BCR-ABL1) T-cell acute lymphoblastic leukemia/lymphoma associated with minimal residual disease persistence after intensive chemotherapeutic approaches

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ABSTRACT

T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) is a rare and aggressive leukemia. Philadelphia chromosome-positive cytogenetic abnormality is most common in CML. It is difficult to differentiate between de novo Ph+ T-ALL/LBL and T-cell lymphoblastic crises of CML. We present a case of adult Ph+ T-ALL/LBL with a likely history of antecedent CML. Initially thought to be a case of chronic-phase CML, a diagnostic quandary led to the pursuit of a lymph node biopsy that established the diagnosis of Ph+ T-LBL or T lymphoblastic blast crisis of CML, a clinical presentation extremely rare and only the second of its kind from our review of the literature. The patient was treated with an intensive chemotherapy regimen for over a year due to persistent minimal residual disease (MRD) positivity indicating aggressive disease.

Clinical Practice Points

Intensive pediatric regimen plus TKI for AYAs with Ph+ T- ALL/LBL is feasible and helps achieve complete remission (CR) at the end of induction.

Despite early CR, the kinetic pattern of measurable residual disease (MRD) response showed a slow pattern of disease regression in our patient. The sluggish MRD regression persisted despite use of second line agent Nelarabine and third generation TKI ponatinib.

New developments in understanding Ph+ T-ALL/LBL biology and their potential implications for future therapy are currently an unmet need, especially to facilitate MRD negative status for resistant cases.

1. Introduction

The Philadelphia chromosome (Ph+) is the most known cytogenetic abnormality in human leukemias and can be detected in more than 95 % of patients with CML and 20–40 % of patients with ALL [1]. The Philadelphia chromosome results from a translocation between the breakpoint (BCR) gene on chromosome 9 and the ABL proto-oncogene (ABL1) gene on chromosome 22. BCR-ABL1 is an active tyrosine kinase that promotes the development of leukemia [2]. The presence of the Philadelphia chromosome in T-cell ALL/LBL is rare. Ph+ malignancies have been distinguished by an aggressive presentation and a poor prognosis, especially in T-lineage disorders [2]. Here we present an extremely rare case of Ph+ T-cell ALL/LBL with p210 BCR-ABL1 cytogenetic abnormality that exhibited persistent minimal residual disease (MRD) positivity even after over a year of intensive chemotherapy.

2. Case report

A 33-year-old woman with no significant past medical history presented with a fall without loss of consciousness secondary to generalized

weakness for a few days. She also endorsed abdominal swelling, intermittent fevers, night sweats, and unintentional weight loss spanning over two years. She had also noticed facial and neck swelling during the two days preceding the presentation to the emergency department (ED). She carried a family history of non-Hodgkin's lymphoma in her father.

After the initial presentation to ED in April 2022, she was admitted to the medical ICU. The patient was tachycardic to a heart rate of 120 and was diaphoretic, however, afebrile. She appeared cachectic. Physical examination revealed bilateral diffuse non-tender cervical and inguinal lymphadenopathy and hepatosplenomegaly with spleen extending beyond the midline. Laboratory values revealed a white blood cell (WBC) count of 561 × 10^3 /uL with 2–3 % blasts in the periphery and increased mature cell lineages with predominant increases in neutrophils, monocytes, eosinophils, and basophils with a Hgb of 6.9 g/dL and a platelet count of 245 × 10^3 /uL. The metabolic panel was consistent with tumor lysis syndrome (TLS) [hyperkalemia (10), hyperphosphatemia (9.5), hyperuricemia (14), and hypocalcemia (6.9)]. Computed tomography (CT) of the chest, abdomen, and pelvis revealed cardiomegaly with a moderate-sized pericardial effusion, diffuse intra-abdominal lymphadenopathy, hepatosplenomegaly, portal hypertension with varices, and moderate ascites. Vascular ultrasound of all four extremities was negative for acute DVT.

The patient was initially admitted to the medical intensive care unit (MICU) to manage acute hypoxic respiratory failure requiring high-flow oxygen. She was started on hydroxyurea 2 g every 6 h, maintenance IV fluids, and allopurinol 300 mg bid for treatment of TLS. Hypoxia gradually resolved as leukocytosis resolved, suggesting the possible role of leukostasis.

Peripheral blood smear revealed severe leukocytosis with increased amounts of peripheral metamyelocytes, promyelocytes, and mature myeloid cells, basophilia, and eosinophilia. Blood PCR testing was remarkable for positive BCR/ABL1 p210 (e13a2e/14a2) isoform at % IS of 11.1986. Bone marrow (BM) evaluation revealed hypercellular marrow (95 %) with left-shifted granulocytic hyperplasia and 7 % blasts. These findings initially suggested chronic phase CML. However, clinical presentation and peripheral blood flow cytometry findings of a subclonal population of T lymphoblasts (abnormal, immature T-cell population representing 11 % of white cells with abnormal expression of cytoplasmic CD3, decreased CD5, increased CD7, low CD8, small subset CD34, with normal expression of CD45 without CD4, CD16 or CD56) raised concern for underlying lymphomatous process. This prompted further work-up with a right axillary lymph node excisional biopsy, which confirmed the diagnosis of Philadelphia positive T cell ALL/LBL consistent with T lymphoblastic blast crisis of CML (CML-BP), a clinical presentation extremely rare and only the second of its kind from our review of the literature. Immunohistochemical staining was positive for CD3-TdT and cleaved NOTCH1 and negative for CD20 and MPO. Ki-67 expression was high (90 %). Immunophenotype was remarkable for CD45-positive (63 %) lymphoblasts. In addition, the cells expressed CD5 and CD8, making the Early T cell precursor phenotype less likely [3–5]. The A fluorescence in situ hybridization (FISH) testing revealed t(9;22) BCR-ABL1 (76 %, with a predominant 3F1R1G pattern). PET/CT scan showed generalized lymphadenopathy with increased FDG uptake (Maximum SUV:2.4). ECHO showed moderate pericardial effusion with no evidence of tamponade. CSF analysis was negative for blast cells. Cytogenetic analysis with G-banding showed abnormal female karyotype: 46, XX,t(9;22)(q34;q11.2) [4]/48, idem,+19,+der(22)t(9;22) [6]. Acute leukemia next-generation sequencing (NGS) panel revealed a variant of strong clinical significance in the *ASXL1* (p.Q748Hfs*24, VAF: 36.1 %) gene (Table 1). Relevant genomic tests are outlined in Table 2. T cell receptor rearrangements studies were not obtained at initial presentation.

The patient received TKI nilotinib 400 mg per oral twice daily starting day 8 of induction therapy with C10403 regimen: vincristine 2 mg intravenous days 1,8,15, 22; daunorubicin (37.75 mg injection) 25 mg/m^2 IV on days 1,8,15,22; pegaspargase 2500 IU/m^2 IV on day 4;

Table 1
In-house targeted next generation sequencing panel.

Date	Genes	Clinical significance (CS)
04/13/2022	**ASXL1** p.Q748Hfs*24, c.2244delA VAF: 36.1 %	Potential CS
05/09/2023	**ASXL1** p.Q748Hfs*24, NM_015338.5, c.2244delA VAF: 39.4 %	Strong CS
05/09/2023	**BCR-ABL1** t(9;22)(q34.1;q11.23) BCR: exon 14 (NM_004327.3) ABL1: exon 2 (NM_005157.5)	Strong CS
06/21/2023	**ASXL1** p.Q748Hfs*24, NM_015338.5, c.2244delA VAF: 24.1 %	Strong CS
06/21/2023	**BCR::ABL1** t(9;22)(q34.12;q11.23) BCR: exon 14 (NM_004327.4) ABL1: exon 2 (NM_005157.6)	Strong CS

Table 2
Broader commercial 700 gene panel (04/15/2022).

Gene	Protein alteration	DNA alteration	Variant frequency%	Variant interpretation
ABL1	BCR-ABL1	–	-	Pathogenic Fusion
ASXL1	p.Q/48fs	c.2244delA	38	Pathogenic variant
ATM	p.L2330V	c.6988C > G	46	Variant of Uncertain Significance
RAD51D	p.T328I	c.983C > T	51	Variant of Uncertain Significance

prednisone 45 mg bid on days 1–28. Nilotinib was preferred over dasatinib in the presence of pleural, pericardial effusions, and ascites. CNS prophylaxis with intrathecal therapy was done per treatment protocol. Hematological remission was achieved post-induction, and the patient demonstrated significant clinical improvement. However, cytogenetic remission was not achieved. RT-PCR (peripheral blood) was still positive for BCR-ABL1 p210 transcript, and flow cytometry-based MRD analysis (obtained 8 weeks after initial BM evaluation) identified 0.7 % abnormal, immature T cell population of the total white cells. She was continued on the C10403 regimen for consolidation and nilotinib 200 mg bid (dose reduced due to liver toxicity). Meanwhile, the allogeneic hematopoietic stem cell transplantation (HSCT) team was consulted for a curative intent HSCT. C10403 was eventually discontinued because of intolerability and persistent MRD positivity deep into her C10403 treatment course. The patient's entire treatment course is listed in Table 3.

About nine months after the initial presentation, ALL T cell MRD analysis demonstrated 0.07 % (Table 4) on BM aspirate by flow cytometry; therefore, nelarabine was prescribed with a plan of near-future HSCT. The patient underwent 3 cycles of nelarabine 1500 mg/m2 IV on days 1,3 and 5. Two months later (March 2023), the BM aspirate was positive for MRD at 0.03 % (at which time venetoclax was added), and in May 2023, MRD was positive 0.013 % (assay detection limit <0.01 %). RT PCR remained positive for BCR-ABL1 p210 transcript. She remained on ponatinib 30 mg once daily during this time.

The patient underwent one cycle of the modified Pullarkat regimen (without navitoclax). Most recent bone marrow aspirates remained positive at low MRD levels around 0.034 % (Table 4). She proceeded to HSCT in MRD+ state and at the time of this report is within the first fourteen days of HSCT without complications.

Table 3
Treatment regimen charted against corresponding lab values.

Month	Treatment	Hb (g/dL)	WBC (per uL)	Platelet (per uL)	T-cell ALL MRD
Early April 2022 (on presentation)	Hydroxyurea + Nilotinib	6.9	638,000	242,000	
Late April 2022	AYA C10403 (ALL) (<40) Induction regimen + Nilotinib	7.3	2410	14,000	11 %
Early June 2022	AYA C10403 Consolidation + Nilotinib	7.6	49,630	366,000	0.7 %
Early August 2022	AYA C10403 Interim Maintenance + Nilotinib	9.9	2920	191,000	1.8 %
Early October 2022 to Late November 2022	AYA C10403 Delayed Intensification + Ponatinib	11	1480	93,000	0.33 %
AYA C10403 Discontinued Due To Intolerability. Only on Dasatinib in December 2022.					
Early January 2023	Nelarabine cycle 1 + Dasatinib	11.7	3430	96,000	
Late January 2023	Nelarabine cycle 2 + Venetoclax cycle 1 + Ponatinib	12.9	5340	95,000	0.07 %
February 2023	Nelarabine cycle 3 + Venetoclax cycle 2 + Ponatinib	13.5	5030	688,000	0.05 %
March 2023	Venetoclax cycle 3 + Ponatinib	12.1	7720	1,728,000	0.03 %
April 2023 to	Modified Pullarkat +	10.2	13,990	2,808,000	0.013 %
June 2023	Venetoclax + Ponatinib	11.4	1560	58,000	0.034 %
August 2023		11.2	1950	77,000	0.04 %

Hb- Hemoglobin, WBC- White Blood Cell, MRD- Minimal residual disease

Table 4
BCR ABL MR, IS and NCN corresponded with TKI treatment.

Date	TKI	BCR/ABL1 P210 MR	BCR/ABL1 P210 % IS	BCR/ABL1 P190 NCN (%BCR/ABL1:ABL1)
4/11/22		0.95	11.1986	–
4/16	Nilotinib 400 mg bid	–	–	0.0129
7/5	Nilotinib 200 mg bid	0.43	37.4604	–
09/19	Ponatinib 30 mg qd	<0.3	>50	–
11/30	Ponatinib 45 mg qd	<0.3	>50	0.0307
12/6	Dasatinib 100 mg qd			
2/9/23	Ponatinib 30 mg qd	<0.3	>50	0.0172
3/3/23	Ponatinib 30 mg qd	<0.3	>50	0.0225
5/8/23	Ponatinib 30 mg qd	<0.3	>50	0.0088
6/21/23	Ponatinib 30 mg qd	0.35	44.6691	0.0062
8/3/23	Ponatinib 30 mg qd	0.56	27.5461	0.0048

TKI - Tyrosine Kinase Inhibitor, MR- Molecular Response, IS- international scale, NCN- normalized copy number

3. Discussion

In this report, we detail an exceptionally rare case of Philadelphia chromosome-positive T-cell acute lymphoblastic leukemia/lymphoma (Ph+ T-ALL/LBL) in a young adult female. The patient's initial presentation included widespread lymph node swelling, liver and spleen enlargement, anemia, profound leukocytosis, and tumor lysis syndrome. Initial blood and bone marrow tests indicated chronic myeloid leukemia (CML), however, further analysis with peripheral blood flow cytometry and lymph node biopsy established a diagnosis of CML in blast phase (CML-BP), overall, diagnosis consistent with secondary Ph+ T-ALL/LBL (i.e. arising out of prior CML).

Ph+ T-ALL/LBL is exceedingly rare clinical entity. A comprehensive review of the literature identified only 31 cases of de novo and transformed or secondary Ph+ T-ALL/LBL [7]. Differentiating between de novo T-ALL/LBL and T-cell CML-BP (Table 5) presents significant clinical and diagnostic challenges. Characteristically, a prior history of CML, advanced age, prolonged symptom duration, the presence of extramedullary disease, significant splenomegaly, elevated counts of granulocytic precursors, eosinophils, and basophils, presence of non-e1a2 BCR-ABL1 isoform as the major BCR-ABL breakpoint transcript, and the absence of lymphoblastic leukemia in bone marrow, are indicative of T-cell lymphoid blast crisis in CML (or T-cell CML-BP) [8]. These cases typically respond to multi-agent chemotherapy and TKIs. In contrast, indicators such as younger age, male gender, extensive bone marrow blast involvement, and TCR gene rearrangement mutations suggest a diagnosis of de novo T-ALL/LBL [2,7,9,10]. In the case under discussion, the patient's extensive symptom history, blood and bone marrow analyses, and lymph node biopsy findings pointed towards T-cell CML-BP or transformed Ph+ T-ALL/LBL. However, certain features such as non-sustained response to 2nd and 3rd generation TKI-based therapy and a markedly high white blood cell count were more suggestive of primary Ph+ T-ALL/LBL.

Previously, Monma et al. have hypothesized that leukemic progenitor cells in the T-cell lineage harboring del(7) and t(9;22) chromosomal abnormalities might differentiate into the myeloid lineage, potentially elucidating the occurrence of Ph+ acute bilineage leukemia, T-ALL, and acute myelomonocytic leukemia within a single patient [11]. This theory might also apply to our patient, indicating a potential bilineage differentiation process. Padhi et al. reported a similar case of a middle-aged man with generalized lymphadenopathy diagnosed with CML in the chronic phase on peripheral blood and bone marrow examination. Lymph node biopsy revealed T-cell ALL/LBL. The patient was treated with induction chemotherapy (hyper-CVAD regimen) and dasatinib for 3 cycles, followed by allo-HSCT. He was on maintenance dasatinib and had measurable residual disease (MRD) positivity, similar to our case [12].

Li et al.'s review of 31 Ph+ T-ALL/LBL cases reported Ph+ T-ALL/

Table 5
General differentiators between de novo T-ALL/LBL and T-cell lymphoid blast crisis of CML.

Characteristic	de novo T-ALL/LBL	T-cell lymphoid blast crisis of CML
Prior history of CML	Absent	Present
Longer duration of symptoms	Absent	Present
Age	Younger	Older
Extramedullary disease	Absent	Present
Splenomegaly	Absent	Often present
Major BCR-ABL breakpoint transcript	May be present	Often present
Sex	Male preponderance	Not specific
Bone marrow involvement by blasts	Always present	May be present or absent
Increased circulating granulocytic precursors, basophils, eosinophils	Absent	Often present
Response to chemotherapy with TKIs	Poor	Excellent

LBL to be male-predominant, with 26 males and 5 females. Eighteen cases presented with minor breakpoint transcripts of the BCR-ABL1 fusion gene. Following induction therapy, most patients achieved complete remission (CR) [7]. Unlike this series, our patient was female, presented with a less common breakpoint transcript and had the unique manifestation of tumor lysis syndrome (TLS), likely linked to her profound leukocytosis. Furthermore, her complex cytogenetics suggested clonal evolution and aggressive disease phenotype that might explain persistent MRD positivity. It is also interesting to note that while immunohistochemical staining suggested the presence of the NOTCH1 gene alteration, the NGS did not. Previous studies have highlighted the prognostic significance of molecular abnormalities like NOTCH and FBXW7 in T-cell ALL, underscoring the complexity of diagnosing and treating this condition [10].

Xu et al. reported a case in 2012 of BCR-ABL positive T-cell ALL in a 6-year-old girl with leukocytosis and splenomegaly who had multiple relapses of acute leukemia but never demonstrated any morphologic features of CML. She underwent a stem cell transplant in 2007 and stayed in molecular remission since [13]. In another study (2014), Xu et al. discussed two cases of T-cell ALL presenting as CML-BP. The first case was of a 24-year-old female with leukocytosis (32 % T lymphoblasts), BCR-ABL1 rearrangement, and morphologic features of CML on diagnostic bone marrow biopsy. She was started on TKI (imatinib) and underwent a stem cell transplant; three months after the transplant, she relapsed and died. Her remission and relapse bone marrow biopsies did not show any CML features, again highlighting the challenges associated with treating this disease. The second case was of a 66-year-old man with diffuse lymphadenopathy and B symptoms, showing T-cell ALL in the lymph node (T-cell lymphoid blast crisis of CML) and concurrent CML-CP in his bone marrow. He was treated appropriately but, he was lost to follow-up [14].

Xia et al. reported a case of a 28-year-old woman who developed T-ALL co-expressing both p210 and p190 BCR-ABL transcripts five years after the initial diagnosis of CML in the chronic phase. At initial presentation, she was treated with hydroxyurea and TKI (imatinib initially, followed by dasatinib) over the years. She eventually stopped treatment, developed CML blast crisis, and died about eight years after being first diagnosed. Their study provided molecular evidence to support the presence of minor breakpoint transcript and chromosome 11p15 - crucial for developing T-LBL/ALL from the blast crisis of CML [15].

Current evidences suggest that in younger patients with a fully matched donor and no significant comorbid conditions, allo-HSCT continues to be beneficial [16]. Daver et al., as well as Cazzaniga et al., recommended regular monitoring of MRD to optimize the use of TKIs and for early consideration of allo-HSCT [17,18].

At the time of writing this case report, our patient was able to attain a complete hematological response (CHR). However, molecular response (MR) was never achieved (Table 1). We assessed the trajectory of BCR-ABL transcripts with different dosing/schedules of 2nd/3rd generation TKI therapies. Between April-November 2022, the patient was treated with 2nd generation TKI (nilotinib) based therapy, and the percentage of BCR/ABL1 P190 transcripts increased slightly (0. 0129–0.0307). Between late January and June 2023, with 3rd generation TKI (ponatinib) based therapy, the percentage of BCR/ABL1 P190 transcripts decreased one-log from 0.0225 to 0.0048. The % IS for BCR/ABL1 P210 was 11.19 at presentation, and 27.54 at the time of last evaluation. (Supplementary Table 2). The T-cell MRD trend showed a decline from 11 % to 0.04 %; however, never became undetectable per assay limit (<0.01 %), suggesting aggressive disease in our patient. Our patient proceeded to HSCT in MRD positive state as this confers the best chance of long-term cure.

Our case aligns with the observations made by Jain et al., where Ph+ T-cell lymphoid leukemias exhibit aggressive clinical features and challenging treatment courses. The varied immunophenotypes, and the overall poor prognosis associated with Ph+ T-cell lymphoid leukemias, resonate with the clinical trajectory observed in our patient. Moreover, the discussion of potential lineage differentiation in Ph+ leukemic stem cells as explored in their study provides a deeper understanding of the biological underpinnings that might have influenced the disease progression in our case [19].

Our patient's persistent MRD positivity reflects the critical role MRD plays in the prognosis of T-ALL/LBL. In pediatric T-ALL, MRD levels at the end of induction (day 33) and after induction-consolidation (day 78) are the most powerful prognostic factor for relapse. The 7-year-EFS rates were 91.1 %, vs 80.6 %, vs 49.8 %, for patients who attained sustained MRD negativity at day 33, vs low ($\leq 10^{-3}$) detectable levels- vs high ($\geq 10^{-3}$) detectable levels- of MRD at day 78, respectively.

This insight, while derived from pediatric cases, underscores the potential impact of MRD dynamics in adult T-ALL/LBL management and prognosis, suggesting that similar MRD-based stratification could be beneficial in adult patients as well [6].

4. Conclusion

In summary, the major highlights of our case include the regular trending of the MRD status, persistent positivity suggesting aggressive disease, and the use of different chemotherapeutic drugs and TKIs that kept the patient in remission before proceeding to allo-HSCT from a matched unrelated donor. Our report emphasizes a pressing need for advancements in our understanding of Ph+ T-ALL/LBL as well as the exploration of new treatment strategies to counter persistent disease states. Our report advocates for continued research into MRD dynamics in adult T-ALL/LBL to refine therapeutic approaches and improve patient outcomes, drawing parallels to the established prognostic significance of MRD in pediatric T-ALL [6]. New developments in understanding Ph+ T-ALL/LBL biology and their potential implications for future therapy are currently an unmet need, especially to facilitate MRD negative status in resistant cases.

CRediT authorship contribution statement

Shruti Shah: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rupayan Kundu:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Rahul Mishra:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Sudipto Mukherjee:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Abhay Singh:** Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2024.100456.

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