Case Report

P190^{BCR-ABL1} in a Patient with Philadelphia Chromosome Positive T-Cell Acute Lymphoblastic Leukemia: A Rare Case Report and Review of Literature

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Keywords

T-cell-acute lymphoblastic leukemia · Philadelphia positive acute leukemia · Acute leukemia · T-blastic phase of CML · De novo T-ALL · P190^{BCR-ABL1} positive acute leukemia

Abstract

T-acute lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/LBL) is rare and aggressive leukemia. Philadelphia chromosome positive (Ph+) is the most common cytogenetic abnormality in chronic myeloid leukemia (CML) and B-acute lymphoblastic leukemia (B-ALL). Ph+ T-ALL is exceeding rare and has a therapeutic and prognostic significance. The incidence and outcome of Ph+ T-ALL are unknown. Differentiation between Ph+ T-ALL/LBL and T-cell lymphoblastic crises of CML may be difficult. We report a rare case of adult de novo T-ALL with significant monocytosis, having Ph+ with (P190 *BCR-ABL1*) as a cytogenetic abnormality. He was treated with ALL induction chemotherapy and imatinib and achieved complete remission, then relapsed twice and expired shortly after the last CNS relapse.

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Introduction

Ph positivity is the most frequent cytogenetic abnormality in chronic myeloid leukemia (CML) cases that occurs in (95%). It occurs as well in (30–40%) of adult B-acute lymphoblastic leukemia (B-ALL) cases [1, 2], in (2–5%) of children with B-ALL and acute myeloid leukemia (AML), and rare cases of B-cell lymphoma [3, 4]. It has a prognostic significance, which is associated with a high rate of relapse and short-term of complete remission (CR) [3] with the need for upfront stem cell transplants in CR1 [5].

It was reported that Ph+ malignancies were distinguished by an aggressive presentation and a poor prognosis especially in T-lineage disorders [5]. Ph+ T-ALL/lymphoblastic lymphoma (LBL) is very rare and only a few cases are reported in literature [6–8]. A total of 31 cases of de novo Ph+ T-ALL and Ph+ T-ALL in a blastic phase of CML have been reported to date [3].

In addition, the clinical course and prognosis of this subtype are also unidentified. T-cell lymphoid blast crises in CML are continuously a close differential diagnosis with Ph+ T-ALL. The frequency of different BCR-ABL1 isoforms differs between the diseases, and p210 BCR-ABL1 is found in 95% of CML patients, while p190 is present in 70% of Ph+ B-ALL cases [9]. The presence of P190 of Ph+ T-ALL patients is exceeding rare.

Here, we presented an exceptionally rare case of Ph+ T-ALL/LBL with de novo P190 BCR-ABL1 as cytogenetic abnormality and associated with a significant monocytosis. As T-ALL associated with Philadelphia chromosome positive (Ph+) is a rare incident, in which the clinical relevance, prognosis, and the role of this cytogenetic abnormality in leukemogenesis are presently indeterminate. In this article, we make a review of the reported cases of Ph+ T-ALL.

Case Report

It is a case of a 66-year-old Palestinian male patient, a heavy smoker with multiple comorbidities including hypertension, Type 2 diabetes mellitus, and renal impairment. He was presented with a 2 months history of progressively increasing neck swelling and left ear pain associated with hearing loss and difficulty speaking that worsened the last 3 days before admission. The patient has a previous history of stroke with sequelae of left-sided weakness.

The patient appeared pale with ecchymosis patches over both arms. Clinical examination was significant for multiple enlarged submental, submandibular, periauricular lymph nodes (LNs) described as fixed, firm, and not tender with no overlying skin redness. No hepatosplenomegaly appreciated. No focal neurological deficit apart from sensorineural hearing loss. Complete blood count revealed marked leukocytosis with white blood cell count (WBC) $66 \times 10^3/\mu\text{L}$ (4–10), moderate macrocytic anemia with hemoglobin 9.0 g/dL (13–17), and mild thrombocytopenia with platelets $138 \times 10^3/\mu\text{L}$ (150–400).

Peripheral blood (PB) smear showed moderate macrocytic anemia with some NRBCs. There was marked leukocytosis with (24%) blasts. Some were medium to large with abundant cytoplasm, irregular/convoluted nuclear borders, fine chromatin, prominent one or more nucleoli, and a few with cytoplasmic granules. Others appeared smaller with a very high N/C ratio and inconspicuous nucleoli. There was a marked shift to the left, different stages of maturation seen with basophilia. Monocytic cells were markedly increased and including some immature forms (promonocytes). Platelets were mildly reduced in number (Fig. 1). The differential count segmented neutrophils (15%), lymphocytes (7%), eosinophils (1%), basophils (2%), promyelocytes (2%), myelocytes (7%), metamyelocytes (3%), monocytes and promonocytes (39%), and blasts (24%).

Fig. 1. Peripheral blood smear (Wright stain). **a** Shows leukocytosis with neutrophilia, shift to left, all stages seen, basophilia, monocytosis, and 24% blasts ($\times 50$). **b** Higher power, highlights the blast, shift to left, and basophilia ($\times 100$).

Fig. 2. Bone marrow aspirate (Wright stain). **a, b** is infiltrated by 22% blasts with preserved trilineage hematopoietic cells, left-shifted granulocytic hyperplasia, showing different maturation stages with increased monocytic cells ($\times 50$).

Bone marrow (BM) examination was done. The aspirate was infiltrated with 22% blasts with preserved trilineage hematopoietic cells. The blasts have the same morphology as that of the PB with pseudopods, fine azurophilic granules, and or vacuoles. The monocytic component was significantly increased (26%). Granulopoiesis was hyperplastic, left-shifted, in different maturational stages with an increased M/E ratio (7.3), and relatively reduced erythropoiesis (Fig. 2). No significant dysplasia was noted. The trephine BM biopsy was mildly hypercellular for age (60–70%) and showed infiltration with many primitive cells with active granulopoiesis, increased eosinophils, markedly increased monocytic cells, decreased erythropoiesis, and preserved megakaryocytes (Fig. 3).

Immunohistochemical stains showed increased positivity for CD34, CD1a, TdT, and CD10. There was diffuse strong positivity for CD99 and lysozyme. CD163 and CD68 highlighted increased monocytic cells (Fig. 4).

Flowcytometry analysis performed on BM aspirate showed an abnormal population of blasts expressing cytoplasmic CD3 (20%) and including 2 subpopulations: one population

Fig. 3. Bone marrow biopsy (H&E) (inset) is mildly hypercellular for age (60–70%) shows infiltration with many primitive cells with primitive-looking chromatin, convoluted/intended nuclear borders, relatively abundant cytoplasm and prominent nucleoli with preserved granulopoiesis, increased eosinophils, markedly increased monocytic cells, decreased erythropoiesis and preserved megakaryocytes.

with dim CD45 (9%) and expressing CD34, CD7, CD5, CD33, and CD11b with aberrant partial cCD79 and negative for CD1a and another population with moderate CD45 (11%) and expressing cytoplasmic CD3, CD7, CD5, aberrant partial CD11b, and partial CD1a. These cells were negative for CD34, CD33, and cCD79a.

Both populations were negative for cMPO, CD117, CD13, CD15, CD64, CD14, HLADR, CD11c, CD36, GP, CD41, CD61, sCD3, CD2, CD4, CD8, TCR alpha/beta, TCR gamma/delta, CD19, CD20, CD10, CD56, and TdT. There was increase in the monocytic cells (28%) expressing (CD64 and CD14) (Fig. 5).

The fluorescence in situ hybridization (FISH) analysis was performed on interphase nuclei obtained from a BM sample. The analysis revealed dual fusion hybridization signal pattern for BCR and ABL1 probes on chromosomes 9 and 22, indicated $t(9;22)$ in 92%, which resulted in Ph+. Further, the iFISH analysis was performed using BCR/ABL1 dual fusion extra signal probe to discriminate between major and minor breakpoints (m-bcr). The analysis revealed a m-bcr associated with the p190 transcript (Fig. 6).

Cytogenetic analysis revealed abnormal complex Karyotype: 46, XY, $t(9;22)$ (q34;q11.2) [29]/46, idem, add (10) (q24) [11]/46, idem, der(7) $t(7;10)$ (q32;q22) [3]/46, and idem, add (16) (q?22) [2]. The G-banding chromosome analysis of 45 metaphase cells from the BM sample revealed an abnormal karyotype with 4 subclones. The main clone was with a reciprocal translocation between chromosome 9 at band q34 and chromosome 22 at band q11.2, which result was Ph+. Each of the subclones had additional nonrecurrent structural abnormalities involving chromosomes 7, 10, and 16.

PB and BM findings were consistent with T-ALL/LBL with $t(9;22)$; BCR-ABL1 (Ph+) However, the possibility of T-cell LBL/lymphoma blast phase of CML could not be ruled out as was suggested from morphology. The patient's neurological complaints raised suspicion for CNS involvement, but lumbar puncture was not feasible with such a poor patient's performance. CT Head showed no recent infarction or hemorrhage. MRI head and posterior fossa without contrast did not reveal any obvious sizable brain lesion or cerebellopontine angle mass.

Positron emission tomography showed mild-to-moderate fluorodeoxyglucose avid uptake present in multiple bilateral para jugular, jugulodigastric, posterior triangular, submental, and bilateral axillary LNs. Bilateral pleural fluid was noted. An irregular ground-glass opacity in the right upper lobe and in the apical segment of the lung with minimal uptake

Fig. 4. **a** IHC stain shows increased positivity for CD34, CD1a, TdT, and CD10, a diffuse strong positivity for CD99 and lysozyme. CD163 highlights increased monocytic cells. **b** CD1a (inset) shows scattered CD1a positive cells.

that might represent lung involvement. The liver and spleen were unremarkable with no obvious adenopathy in the abdomen or pelvis. The initial plan of the leukemia MDT meeting was to start the patient on GMALL chemotherapy protocol (adopted from German Multi-center Study Group for Adult ALL).

The patient was started on tumor lysis measures, imatinib, and steroids. He could not tolerate the chemotherapy (one dose of idarubicin, vincristine, and cyclophosphamide), therefore, given the patient's age, comorbidities, and overall poor prognosis of Ph+ T-ALL, he was considered not fit for aggressive chemotherapy and the best available treatment option for him would be TKIs, steroids +/- vincristine, along with antimicrobial prophylaxis.

He was started on Imatinib 600 mg daily but could not tolerate that dose due to fluid retention. Imatinib dose was reduced several times according to tolerance, which barely controlled his disease for few months.

Four months later, he attained complete hematological remission (CHR) but not molecular remission. BCR-ABL1 e1a2 rearrangement resulting in a p190 protein, the fusion transcript type commonly associated with de novo ALL, was detected in the blood (Fig. 7).

Two months later, he presented with high WBCs $36 \times 10^3/\mu\text{L}$. Flowcytometry analysis performed on the PB showed 32% blasts expressing cytoplasmic CD3 and including two

Fig. 5. Flowcytometry performed on bone marrow aspirate shows an abnormal population of blasts positive for cCD3 comprising (20%) and including 2 subpopulations: one population comprises (9%) (green colored) with dim CD45 and expressing CD34, cCD3, CD7, CD5, CD33, and CD11b. Negative for CD1a and another abnormal population comprises (11%) (red colored) with moderate CD45 and expressing cCD3, CD7, CD5, partial CD11b, and partial CD1a. These cells are negative for CD34 and CD33. Both populations were negative for cMPO, CD117, CD13, CD15, CD64, CD14, HLADR, CD11c, sCD3, CD2, CD4, CD8, TCR alpha/beta, TCR gamma/delta, CD19, CD20, CD10, and TdT. There are increase in the monocytic cells (28%) expressing CD64 and CD14.

subpopulations: one subpopulation with dim CD45 (9%) expressing CD34, cytoplasmic CD3, CD7, CD33, partial dim CD5, with aberrant cCD79a and negative for CD1a and another subpopulation with slightly brighter CD45 (23%) expressing cytoplasmic CD3, CD7, partial dim CD5, with partial aberrant cCD79a and partial CD1a and negative for CD34 and CD33. There were increased monocytic cells (20%) expressing (CD64 and CD14) which proved relapse by morphology and flow cytometry.

The case was discussed in the hematology department. The agreement was to shift to dasatinib along with steroids, with close follow-up. He was started on dasatinib 50 mg daily then increased to 100 and 140 mg daily once tolerated.

The patient was kept on dasatinib and again attained CHR. Unfortunately, he could not tolerate that TKI as well when developed a refractory cough and bilateral chest crepitations upon auscultation. ECHO showed pulmonary hypertension; RVSP of 44 mm Hg and high-resolution. CT chest showed bilateral subpleural ground-glass attenuation areas associated with interstitial thickening and reticular infiltration. Dasatinib was then changed to nilotinib 300 mg BID which was well tolerated for 2 months. The patient was kept in CHR. The patient developed QT prolongation so nilotinib was held for 2 weeks.

After another 5 months, the patient presented to the emergency with a history of sudden painless left monocular visual loss, associated with a fluctuation of the level of consciousness and irritability. MRI head displayed a subtle enhancing area in the pons associated with areas of meningeal thickening and enhancement, raising the possibility of leukemic involvement. MRI whole spine with contrast revealed subtle areas of meningeal thickening and enhancement in the cervical, dorsal, and lumbar regions raising the suspicion of meningeal leukemic deposits.

Fig. 6. **a** Interphase FISH analysis using BCR and ABL1, dual fusion probes. The image shows 1 green, 1 red, and 2 yellow signals a result of fusion of red and green. The fusion indicates BCR/ABL1 rearrangement, $t(9;22)$. **b** Interphase FISH analysis using BCR and ABL1, extra signal probes to determine if it is major break point or minor. The image shows 1 green, 1 red, and 2 yellow signals a result of fusion which indicates minor break point for BCR/ABL1 rearrangement. FISH, fluorescence in situ hybridization.

The patient had clinical and radiological CNS leukemic involvement despite maintained CHR. He was not fit for any kind of aggressive treatment, a family meeting was held, and agreed to keep the patient on best supportive care. He was shifted under palliative team and rendered Do Not Resuscitate (DNAR code), shortly after expired.

Discussion

T-ALL/LBL is an aggressive and rare leukemia that affects both children and adults. It frequently presents with a high WBC and/or bulky mediastinal mass [10]. Cytogenetic abnormalities are present in a substantial number of patients in T-cell ALL, but there are no recurrent disease-defining abnormalities unlike B-ALL or AML [11].

Ph results from a translocation between the breakpoint cluster region (*BCR*) gene on chromosome 9 and the ABL proto-oncogene 1 (*ABL1*) gene on chromosome 22. The reciprocal translocation between the 2 chromosomes, $t(9;22)$ (q34;q11), results in the formation of the atypically short chromosome 22, generally recognized as the (Ph). BCR-ABL1 is an active tyrosine kinase encoded by the fusion gene consisting of the breakpoint cluster region (*BCR*) and the ABL proto-oncogene 1 (*ABL1*) which promotes the development of leukemia [12].

It is a problematic and challenging to differentiate between Ph+ T-ALL/LBL and T-cell lymphoblastic (T-LB) crises of CML [13]. In CML, only a few cases of T-derived blastic crisis have been reported, which may be a diagnostic dilemma to distinguish those from Ph+ T-ALL/LBL [2].

The prevalence of Ph+ T-ALL is restricted to case reports and small case series with only a total of 31 cases reported in the literature, including de novo and transformed or secondary cases [3, 8]. The clinical behavior and prognostic relevance of this abnormality are currently not known [4].

Fig. 7. T-ALL with a BCR-ABL1 e1a2 transcript type (p190 fusion). Positive for an e1a2 *BCR-ABL1* gene fusion by single-step RT-PCR. A PCR product corresponding in size to that expected from an e1a2 *BCR-ABL1* gene fusion was amplified from this blood by single-step RT-PCR. Single-step RT-PCR is performed using primers which amplify across the breakpoints of the chimeric *BCR-ABL1* gene rearrangement associated with ALL and should detect more than 1 in 1,000 cells. RT-qPCR using standardized EAC primer/probes has been used to quantitate the number of *BCR-ABL1* p190 transcripts and reference gene transcripts (*ABL1*). ALL, acute lymphoblastic leukemia; RT-qPCR, quantitative reverse transcription PCR; EAC, Europe against Cancer.

Padhi et al. [14] in 2018 described a man with generalized lymphadenopathy, who was diagnosed with CML in chronic phase on PB and BM. LN biopsy revealed a T-cell LBL/lymphoma (T-ALL). This was an extraordinary presentation of blastic crisis of CML. The patient was treated with induction chemotherapy (hyper-CVAD regimen) plus dasatinib for 3 cycles followed by allogeneic stem cell transplant (allo-HSCT) and was on maintenance dasatinib and had a minimal residual disease.

Alshomar and El Fakih [8] in 2020 reviewed and summarized the reported cases including case series of Ph-positive T-ALL. They supposed that these cases are principally adults, affecting males more than females, recurrently concomitant with extramedullary involvement, with the majority having 210 transcript size and normal karyotype. De novo cases were almost represented equally to secondary cases, and although the majority were consolidated with allogeneic BM transplant, the outcomes considered generally poor.

In addition, Li et al. [3] in 2021 reported a very rare case of Ph+ T-cell LBL. The patient was 46 years male who presented with lymphadenopathy and positron emission tomography suggesting lymphoma infiltration. LN biopsy revealed diffuse infiltration with TdT-positive T lymphoblasts. The patient complete blood count was normal. BM aspiration and flow cytometry analysis revealed a 15.5 and 22% infiltration of immature T-LBs, respectively. Cytogenetic analysis revealed translocation of 9q34 (ABL1) to 22q11 (BCR) (ph+) with e1a2 BCR-ABL1 fusion transcript by PCR. T-cell LBL stage IV diagnosis was made. The patient

received initial induction with hyper-CVAD regimen and TKI followed by HSCT. The patient kept alive in continuous CMR 2 years after allo-HSCT.

Li et al. [3] did as well literature review with a total of 31 cases. They concluded that Ph+ T-ALL/LBL cases were more common in males with 26 males and 5 females. 18 cases were adults with a median age of 47 years (range from 18 to 72), while 13 cases were children with a median age of 8 years (range from 5 to 17). Anterior mediastinal mass was presented in 7 cases. Almost all cases were having Ph+ at the initial diagnosis except for 3 cases, which the Ph+ evolved during relapse. 18 cases were having (m-bcr) BCR-ABL1 fusion gene. There was one patient who presented with 2 types of BCR-ABL1 transcripts. Following induction chemotherapy, the majority of patients achieved CR. A combination of chemotherapy and TKIs was given to 6 patients. 11 patients underwent HSCT with or without CR1. Ten patients were alive until the last follow-up, while 15 patients were dead with a median survival of 7 months (range from 0.1 to 60). The overall prognosis was poor; however, some patients may show prolonged CR duration and survival induction chemotherapy with a combination of hyper-CVAD and TKIs [3].

The BCR/ABL fusion oncogene, the product of the *t*(9;22) Ph is known to have existed in 3 main forms (P190, P210, and P230) that emerge from distinct breakpoints in the BCR gene on chromosome 22, resulting in translocation of BCR exon 1, exons 1–12/13, or exons 1–19, respectively, to the c-ABL gene on chromosome 9. These distinctive oncogenes give rise to 3 different fusion proteins of molecular mass 190, 210, and 230 kD, which contain the same portion of the c-ABL tyrosine kinase but different amounts of BCR sequence [15].

The P210 form of BCR/ABL is found in patients with CML, and in acute lymphoid and myeloid leukemias, although some patients with acute leukemia and P210 are likely to be cases of CML diagnosed in blast crisis. In contrast, the P190 form of BCR/ABL is commonly found in Ph+ B-ALL and occasionally in AML but is rarely if ever observed in CML [7], and it is usually associate with monocytosis and the proportion of monocytes is usually >3% and often mimic chronic myelomonocytic leukemia [16].

BCR exon 19/ABL exon 2 (e19/a2) junction characteristic of P230 form represent a distinctive clinical entity named neutrophilic CML, with a much more benign course than that combined with the traditional b2/a2 or b3/a2 P210 BCR/ABL fusion. These observations raise the question of whether different forms of BCR/ABL protein have intrinsically different leukemogenic activity in hematopoietic cells [17]. Our case represents P190 form of BCR/ABL indicating (Ph+) (ALL), along with T cells, not B cells as usual.

According to our literature review, cases of (Ph+) T-ALL and cases of the T-cell blastic crisis of CML were reported. Differences between the 2 entities could help in establishing a diagnosis of (Ph+) T-cell blastic crisis of CML versus (Ph+) T-ALL. Presence of history of CML (long duration of symptoms, old age, and massive splenomegaly), presence of an increased number of residual circulating granulocytic precursors, eosinophils, and basophils, and presence of major BCR-ABL breakpoint transcript favors T-LB crises of CML. None of the CML cases in T-LB crises showed minor bcr-abl breakpoint transcript by RT-PCR. On the other hand younger age, BM involvement by numerous blasts, and presence of minor bcr-abl transcript favors de novo Ph+ T-ALL.

Our patient is an adult male who presented with a very high WBCs and infiltration of PB and BM with T-lymphoid blast with no previous history of CML. The PB smear and BM showed granulocytic left shift with increased eosinophils and basophils which give the morphological impression of the background of undiagnosed CML. Also, there was a significant monocytosis in PB with increased monocytic cells in the BM.

He was (Ph+) with a P190 transcript with no history of CML that favors de novo T-ALL but at the same time, the morphological findings raise a possibility of the blastic phase of

undiagnosed CML. The P190 transcript was not reported in cases of T-LB crises of CML. And up to our knowledge, our case is the first case reported ph+ T-ALL with P190 transcript associated with increased monocytic cells which is a consistent finding in CML with P190 transcript.

Male sex and younger age were predominant in T-ALL. Medullary involvement with LB leukemia was present in all cases of T-ALL but only in about half of the cases of CML blastic crisis. Combined morphologic, molecular, and FISH analysis can help to differentiate between the 2 entities. Although both diseases present a poor prognosis, differentiating them might have clinical importance [1]. The treatment plan for these patients is not well recognized due to the scarcity of this entity and advance studies are required to better recognize this subgroup [5, 18].

Allo-HSCT remains the standard of care for achieving long-term disease-free survival in Ph+ ALL, there are a substantial number of patients who are incapable to undergo the procedure and therefore treated with combining TKIs with chemotherapy effectively [6].

Conclusion

Ph+ T-ALL is a rare entity. Worldwide a limited number of cases have been reported. Clinical relevance, prognostic value, and treatment strategy are not well defined for these patients. Differentiation between Ph+ T-ALL/LBL and T-LB crisis of CML was difficult because it is diagnosed with no prior history of CML although it has morphological suspension of background of CML. The presence of p190 transcript with the increased monocytic component was exceeding rare in Ph+ T-ALL. Outcomes of these patients are generally poor; however, induction with a combination of HCVAD and second-generation TKI's may achieve prolonged remission in some patients.

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Statement of Ethics

The authors have no ethical conflicts to disclose. The case report was conducted ethically in accordance with the guideline of the Medical Research Center of Hamad Medical Corporation, and after obtaining their approval. Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no relevant financial interests.

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Author Contributions

Dr. Samah Kohla wrote the manuscript and did the literature review. Dr. Sarah EL Kourashy wrote and edited the clinical part of the manuscript. Dr. Zafar Nawaz edited the cytogenetic/molecular part of the manuscript. Dr. Ahmad Al-Sabbagh aided in the diagnosis. Dr. Feryal A Ibrahim performed the flow cytometry analysis. Dr. Reda Youssef reviewed and edited the radiological part of the manuscript.

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