Case Reports and Reviews

Case Report

Dual Hematologic Malignancies at Presentation: Concurrent T-Lymphoblastic Lymphoma and Chronic Myeloid Leukemia

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Abstract

Background: *Chronic Myeloid Leukemia (CML) is driven by the BCR::ABL1 fusion and typically progresses through a chronic phase before evolving into blast phase, most commonly of myeloid or B-lymphoblastic lineage. T-cell lymphoblastic transformation is exceedingly rare, particularly when presenting as an isolated extramedullary process at initial diagnosis.*

Case Presentation: *A middle-aged man presented with marked leukocytosis, anemia, thrombocytopenia, markedly elevated LDH, massive splenomegaly, and generalized lymphadenopathy. Peripheral blood smear and bone marrow findings were consistent with CML with a very small population of myeloblasts and lymphoblasts. This was confirmed by demonstrating BCR::ABL1 fusion using polymerase chain reaction (PCR). Axillary lymph node core biopsy revealed diffuse infiltration by blastoid T-lineage cells with expression of CD3, CD7, CD43, CD99, Tdt, and partial CD34, with a high proliferative index. Flow cytometry of peripheral blood demonstrated an aberrant T-lymphoblastic population comprising 62% of lymphocytes. FGFR1 rearrangement was not detected by FISH. Overall findings support concurrent CML with extramedullary T-lymphoblastic transformation.*

Discussion: *Extramedullary T-cell lymphoblastic crisis is a rare and diagnostically challenging form of CML progression and may present with minimal or absent marrow involvement. Differentiation from de novo T-lymphoblastic leukemia/lymphoma requires a high index of suspicion with clinical information, underscoring the importance of obtaining adequate tissue such as excisional lymph node biopsies, at presentation. To exclude entities with overlapping clinical and morphologic features, targeted evaluation for FGFR1 and related kinase fusions is essential, particularly to rule out 8p11 myeloid/lymphoid neoplasms, which may present with a similar phenotype.*

Conclusion: *This case represents a highly unusual presentation of synchronous CML and extramedullary T-lymphoblastic transformation. Comprehensive and adequately triaged sampling is critical to achieve diagnostic accuracy, guide risk stratification, and inform optimal management in atypical and aggressive forms of CML progression.*

Introduction

Chronic myeloid leukemia (CML) is a malignant myeloid proliferation driven by the BCR-ABL1 fusion gene, which generates a constitutively active, aberrant tyrosine kinase [1]. Like other chronic leukemias, CML typically follows a prolonged clinical course. In the absence of treatment, most patients progress from the chronic phase to more advanced disease within a few years of diagnosis. This transition is marked by increase in immature blood cells, declining functional status, constitutional symptoms such as fever and weight loss, and manifestations of severe anemia, thrombocytopenia, leukocytosis, and splenomegaly [2].

The natural history of untreated CML before the introduction of the targeted tyrosine kinase inhibitor (TKI) was biphasic or triphasic: an initial indolent CP followed by an accelerated phase (AP) and/or the blastic phase (BP). The WHO 2022 guidelines has, however, removed CML-AP as a diagnostic category and replaced it with the concept of "high-risk chronic phase" CML. This is because it may be identified at presentation or during the course of the disease while the patient is on TKI therapy [3].

CML is characterized by an increased number of myeloid precursors from the different stages of maturation in the peripheral blood with the blastic phase defined as >20% blasts [4]. At this point, most cases are myeloid blasts (70-80%),

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while 20 –30% are of lymphoid origin, predominantly B-cell phenotype. Extramedullary B-lymphoblast crisis presenting as soft tissue or nodal masses is uncommon, said to occur in 15-20% of blastic phase cases and often precedes or is discordant from marrow involvement [5]. A few cases, like ours, however, report a T-cell extramedullary transformation, from CML.

Case study

A middle-aged male presented at his family doctor with a 2-month history of night sweats and unintentional weight loss and on blood testing, was found to have peripheral blood leucocyte count of 400 x 109/L, hemoglobin of 91 x 109/L, platelet count of 52 x 109/L and LDH of close to 1500 U/L and was subsequently referred to the hospital hematology team for review. Physical examination revealed massive splenomegaly (exceeded 20 cm in craniocaudal dimension) and left cervical and axillary lymphadenopathy. Peripheral blood film demonstrated significant leukocytosis, with a neutrophilic left shift, showing predominantly immature granulocytes (myelocytes and metamyelocytes), and accompanied by eosinophilia and basophilia without dysplasia. These findings suggested a myeloproliferative neoplasm, specifically chronic myelogenous leukemia (CML). He was subsequently started on hydroxyurea and allopurinol while other results were pending.

Bone marrow aspiration showed a hypercellular marrow with marked myelopoietic expansion and a myeloid-to-erythroid ratio of 20:1, with preservation of all maturation stages. Megakaryopoiesis was decreased, lymphoblasts comprised 4%, myeloblasts 4%, and the remaining cell populations were unremarkable. Subsequent PCR testing confirmed the presence of the BCR::ABL1 fusion, with karyotype t(9;22)(q34;q11), supporting a diagnosis of CML. At this stage, classification of the disease was challenging using both ICC and WHO criteria. The patient was initiated on dasatinib 100 mg daily.

Imaging demonstrated splenomegaly and generalized lymphadenopathy involving the mesenteric, para-aortic, iliac chain, and bilateral inguinal nodes. Core biopsy of the left axillary lymph node confirmed a diffuse effacement of nodal architecture by atypical lymphoid cells. (Figure1). These

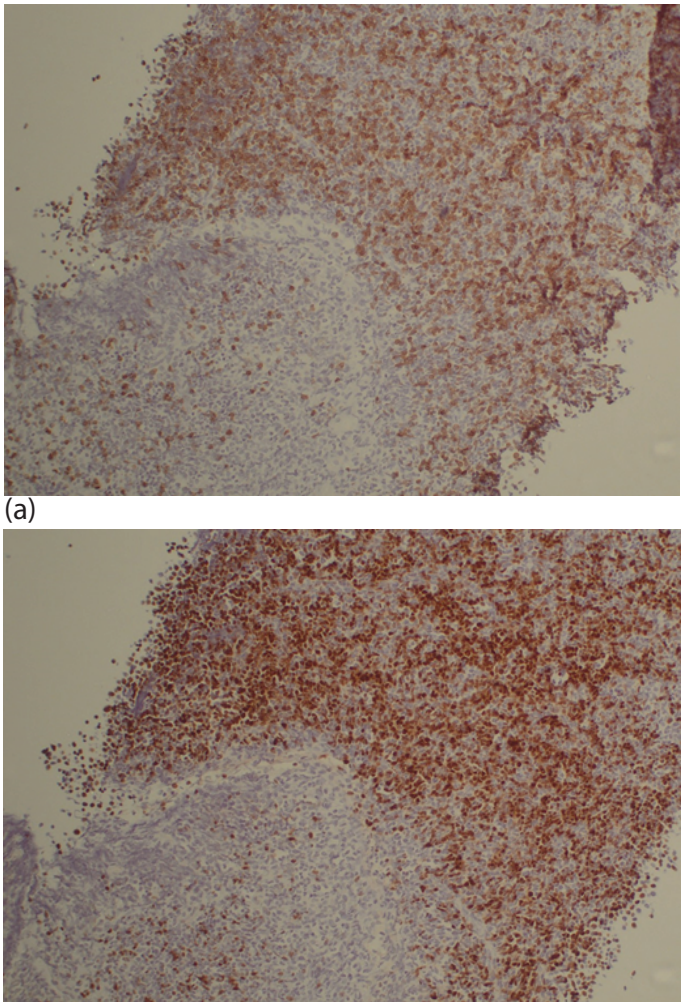


Figure 2. *T lymphoblasts at 10x highlighted by CD3 (a) and Tdt (b)*

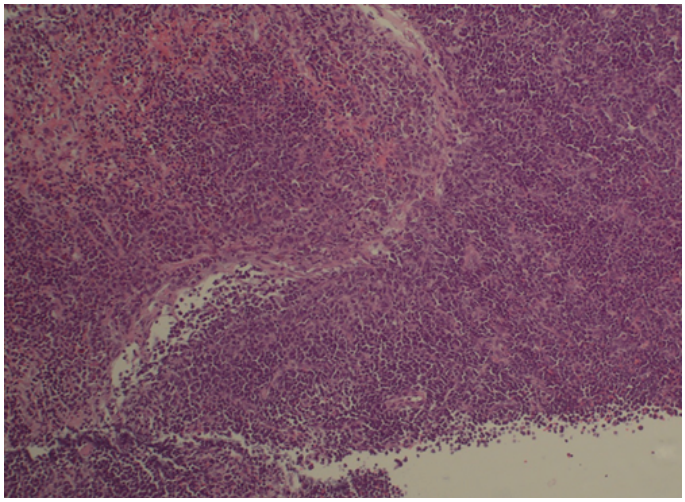


Figure 1. *Hematoxylin and Eosin stained lymph node biopsy at 10x showing both populations of myeloid and lymphoid blasts, vaguely separated by a cleft. Cells are medium to large sized with fine nuclei chromatin and prominent nucleoli.*

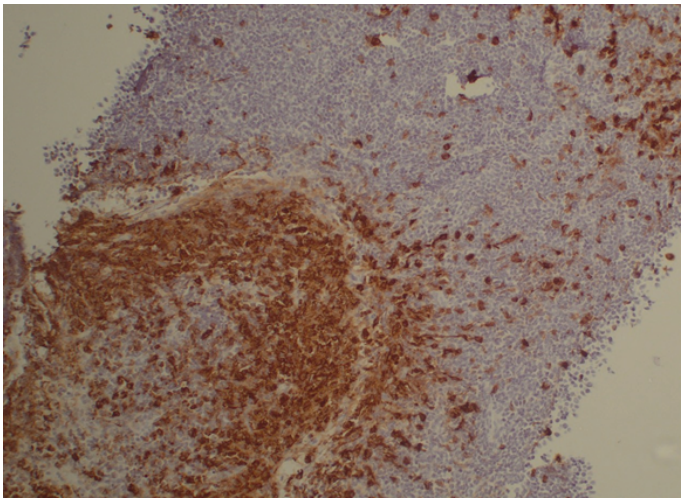
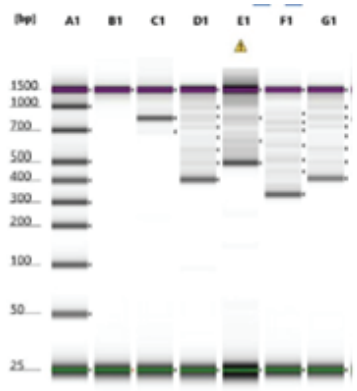


Figure 3. *Myeloid blasts are highlighted by myeloperoxidase at X10 magnification in the same lymph node biopsy as above.*



Sample Info

Well	Conc. [ng/µl]	Sample Description	Observations
A1	18,0	Ladder	Ladder
B1		BCR-ABL_PCR,25-BCR15_BLANK	OK
C1	2,21	BCR-ABL_PCR,25-BCR15_NEGATIVE	OK
D1	4,57	BCR-ABL_PCR,25-BCR15_POS_B3A2	OK
E1	2,75	BCR-ABL_PCR,25-BCR15_POS_E1A2	OK
F1	5,77	BCR-ABL_PCR,25-BCR15_POS_B2A2	OK
G1	4,04	BCR-ABL_PCR,25-BCR15_253HG-MO1028	B3A2 POSITIVE

Figure 4. *Detection of BCR-ABL fusion transcripts by PCR analysis. PCR-based analysis demonstrating detection of BCR-ABL fusion transcripts. A molecular weight ladder (A1), blank (B1), and negative control (C1) show no specific amplification, while positive control samples (D1–F1) demonstrate amplification at the expected fragment sizes for known BCR-ABL transcript variants. The patient sample (G1) shows a distinct amplification band corresponding to the B3A2 (e14a2) BCR-ABL transcript, consistent with a p210 BCR-ABL fusion. Courtesy of Dr. Darci Butcher.*

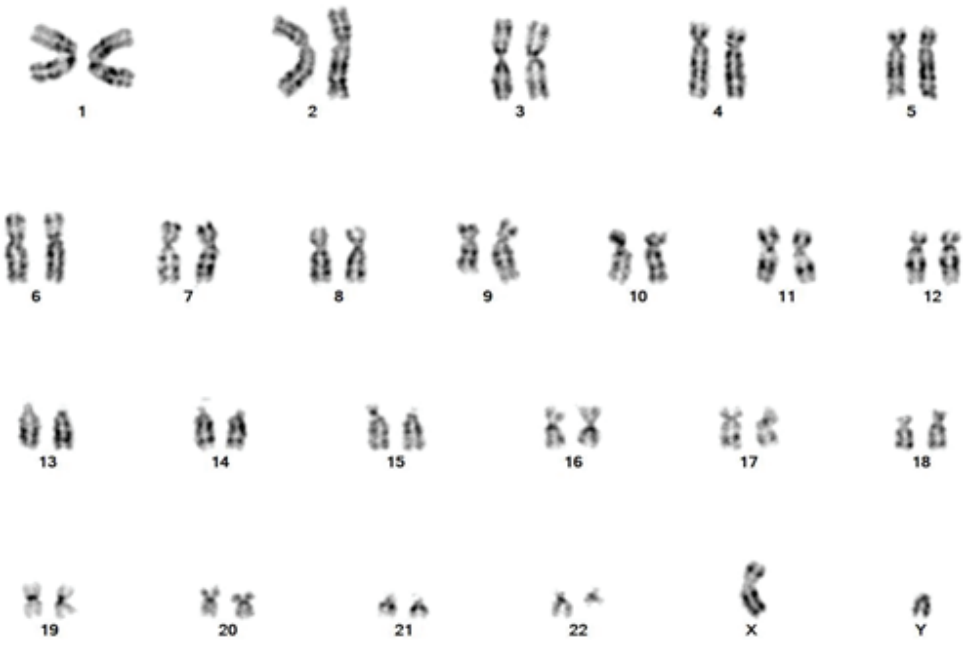


Figure 5. *Conventional cytogenetic analysis. G-banded metaphase karyotype arranged in standard order. Cytogenetic analysis was performed to assess for chromosomal abnormalities, including rearrangements involving chromosomes 9 and 22. Courtesy of Dr. Darci Butcher.*

cells looked blastoid, pleomorphic, with irregular nuclear contour and scanty cytoplasm. Frequent mitotic and apoptotic figures, as well as eosinophilia and eosinophil precursors were seen. By immunocytochemistry (IHC), (Figures 2 and 3) the neoplastic cells were positive for CD7, CD43, CD99, CD5, CD3 (membranous and cytoplasmic), Tdt and Bcl2; partially positive for CD34 and focally positive for CD1a. The malignant cells were negative for CD2, MUM1, CD20, PAX5, BCL6 and CD56. CD23 showed a disrupted follicular dendritic meshwork, confirming a diffuse pattern, while CD68 highlighted background histiocytes. CD4 and CD8 highlighted some scattered, reactive T cells. Sparse, reactive B cells were highlighted by CD20 and PAX5. Ki67 proliferation index was high (85-90%). CD117 highlighted only a small subset of cells, while myeloperoxidase stained numerous cells, predominantly in a perivascular distribution. Molecular testing for the BCR-ABL1 gene was carried out on the bone marrow aspiration sample (Figure 4), but could not be performed on the lymph node due to insufficient fresh tissue, and FISH for BCR-ABL1 on formalin-fixed paraffin-embedded (FFPE) tissue was unsuccessful.

Flow cytometry of the lymph node biopsy revealed that approximately two-thirds of the total white cells were lymphocytes. These cells demonstrated the following immunophenotype: dim CD45+, membranous CD3-, cytoplasmic CD3+, CD4-, CD8-, CD19-, CD5+, CD2-, CD7+, partial CD34+, Tdt-, and partial CD1a+. The remaining population consisted of T cells with either helper or suppressor phenotypes, polyclonal B cells, and a notable proportion of granulocytes. Given the morphological resemblance to 8p11 myeloid/lymphoid proliferative syndrome, FISH analysis using FGFR1 break-apart probes was performed on peripheral blood, which yielded negative results. Subsequent cerebrospinal fluid examination confirmed central nervous system involvement by malignant cells.

Overall, the identification of T-cell lymphoblastic lymphoma within the lymph node, together with concurrent myeloid precursor and T-cell lymphoma involvement in the bone marrow, and negative FGFR1 testing, establishes the diagnosis of extramedullary blastic phase of chronic myeloid leukemia (CML).

Discussion

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with a yearly incidence of 1-2/100000 with a slight male predominance.(Statistics Canada.) It is characterized by the presence of the Philadelphia chromosome in approximately 95% of cases, resulting from reciprocal (t(9;22)(q34;q11)) translocation that fuses BCR on chromosome 22 with ABL on chromosome 9 [4]. The remaining cases carry either variant or cryptic rearrangements involving the same loci, detectable only by FISH or molecular testing [7]. BCR::ABL1's constitutive tyrosine kinase activity is the central pathogenic driver of chronic-phase CML, activating key signaling pathways including JAK/STAT, PI3K/AKT, and RAS/MEK/MAPK, promoting uncontrolled growth and impaired apoptosis [5]. The natural history of CML until the introduction of tyrosine kinase inhibitors (TKI) included a chronic phase, which is usually asymptomatic followed by an accelerated progression and later a blastic phase. The accelerated phase is now called the 'high risk chronic phase' as it is now encountered on presentation or while the patient is on TKI treatment [9].

Progression to blastic phase (BP) is strongly associated with additional chromosomal abnormalities such as 3q26.2 (MECOM) rearrangements, monosomy 7, isochromosome 17q, and complex karyotypes which predict a higher likelihood of progression. Other abnormalities such as trisomy 8/19/21, a second Ph chromosome, or 11q23 involvement may also confer risk. Other common gene alterations seen in advanced disease include TP53, RB1, MYC, CDKN2A, RUNX1 and TET2 [10].

T-lymphoblastic leukemia/lymphoma (T-ALL), especially extramedullary T-cell lymphoblastic transformation presenting with a peripheral blood picture of CML is quite rare, with fewer than a dozen cases documented in the literature and occurring predominantly in adult males [11]. Immunophenotypically, T-lymphoblastic leukemia/lymphoma may express markers reflective of the various stages of T cell maturation, including the pro-T, pre-T, cortical T, and medullary T cell stages [12]. Our patient's neoplastic cells were diffusely positive for CD7, CD43, CD99, predominantly positive for CD5, CD3 (membranous and cytoplasmic), partially positive for CD34, focally positive for CD1a and CD10. This report confirms a T-lymphoblastic leukemia/lymphoma, matches, to a large extent, the pre-T stage.

We report a rare case of a middle aged man diagnosed with extramedullary T lymphoblastic lymphoma and CML at the same time confirmed by PBF, BMA, flow cytometry and PCR and karyotype analysis. Extramedullary blast crisis in CML represents a rare clinicopathology complication distinct from intramedullary progression and presents as isolated masses in the lymph nodes, skin or sanctuary sites like the mediastinum or central nervous system [13]. In patients without a known history of CML, distinguishing between a CML blastic phase and de novo T-ALL can be challenging. In this case, confirmation with BCR-ABL1 testing was not possible because the formalin-fixed lymph node biopsy failed FISH analysis and there was insufficient fresh tissue for PCR. Nevertheless, based on the clinical presentation and the available laboratory findings, the diagnosis could be established.. This condition is not only rare, but quite aggressive as such patients are known to present suddenly, with no documented chronic phase [14]. In contrast to the more common myeloid or B-lymphoblastic transformations, extramedullary T-lymphoblastic crisis presents diagnostic challenges, especially when marrow findings are minimal or absent. In some patients, the blast crisis may occur entirely outside the marrow, as in our case, emphasizing the need for high clinical suspicion and integration of molecular findings. In this case, the patient presented with generalised lymphadenopathy showing T-lymphoblastic morphology and immunophenotype, consistent with a T-cell lymphoblastic crisis. According to the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias, the blastic phase is defined by the presence of more than 5% morphologically identifiable lymphoblasts [15]. In contrast, the WHO classification considers any extramedullary blast proliferation sufficient to establish blastic phase. In our case, the peripheral blood demonstrated 4% blasts, which does not meet the ICC threshold for blastic phase; however, under the WHO criteria, the presence of extramedullary blast involvement fulfills the definition. These divergent classification frameworks introduce diagnostic complexity and may significantly influence therapeutic and management decisions [16].

A bone marrow aspirate in conjunction with a lymph node biopsy generally provides the optimal specimen set for cytogenetic evaluation at initial presentation, allowing

for a comprehensive karyotypic assessment to differentiate blastic transformation of CML from a biologically distinct de novo malignancy. In this case, however, insufficient fresh tissue precluded PCR analysis, and FISH performed on FFPE material was unsuccessful due to lack of appropriate assay validation. This scenario highlights the critical importance of obtaining adequate diagnostic material to support thorough immunohistochemical, flow cytometric, and cytogenetic evaluation—particularly in extramedullary lesions that may first present as lymphoid or soft-tissue biopsies.

Ongoing molecular surveillance and vigilance for atypical patterns of disease evolution in CML remain essential. Transformation to an extramedullary T-cell lymphoblastic crisis may occur abruptly, underscoring the aggressive nature of clonal progression and the need for individualized management strategies.

Asides BCR-ABL translocation, rearrangements involving FGFR1, ETV6, or JAK2 have been implicated in aggressive T-lineage transformation and should be investigated using fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS) panels where available. FGFR1 rearrangements, in particular, are associated with the 8p11 myeloproliferative syndrome, a highly aggressive variant that may phenotypically overlap with CML blast crisis and requires targeted molecular confirmation [17]. It was not found in our case patient.

In summary, extramedullary T-cell lymphoblastic transformation of CML represents a rare but clinically consequential manifestation of disease progression. Accurate classification requires adequate and appropriately triaged specimens—including peripheral blood, bone marrow aspirate and core biopsy, and, when feasible, an excisional lymph node biopsy—to enable integrated assessment of morphology, immunophenotype, cytogenetic abnormalities, and molecular alterations.

Comprehensive ancillary testing, including targeted evaluation for FGFR1 rearrangements and other tyrosine kinase fusions, is critical to distinguish this entity from de novo T-lymphoblastic neoplasms, which may present with overlapping features. Such differentiation is essential for precise risk stratification and to guide optimal therapeutic decision-making in this high-risk clinical context.

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Dr. Darci Butcher, Clinical Laboratory Scientist at Hamilton Health Sciences, Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences and St Joseph's Healthcare. Hamilton, Ontario, Canada

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