T–cell Acute Lymphoblastic Leukemia in a Patient with Pre–existing Essential Thrombocythemia: A Case Report and Literature Review

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A B S T R A C T

The occurrence of T–cell acute lymphoblastic leukemia (T–ALL), on a background of preexisting Philadelphia–negative Myeloproliferative neoplasm is rare. Among the few reported cases where no deep molecular sequencing was performed, it was difficult to ascertain whether these leukemia's occurred de-novo or were due to the clonal progression of underlying MPN. We present a case of a 49–year-old man with a history of essential thrombocythemia who subsequently developed T–ALL. By utilizing next generation sequencing we were able to determine that these two entities originated from two distinct clones and were likely random events. We report the outcome and review the literature.

1. Introduction

In the past few years, advancement in research has helped to better understand the pathogenesis of Philadelphia-negative myeloproliferative neoplasm (PN–MPN) and their leukemic/myelofibrotic transformation on a molecular level. Using next generation sequencing (NGS), we are now able to identify several somatic mutations that play a pivotal role in clonal evolution of these neoplasms and allowed us to establish a more precise prognostic classification[1]. The development of a lymphoid malignancy after a PN–MPN is an uncommon, unexplored phenomenon, limited to few case reports and case series, none of which rely on deep molecular sequencing to elucidate a possible clonal association. Herein, we report a case of T–cell acute lymphoblastic leukemia (T–ALL) occurring in a patient with pre-existing essential thrombocythemia (ET) utilizing the NGS findings to parse this out more clearly. We discuss the risk factors of PN-MPN progression to acute myeloid leukemia (AML) and compare them to what is known so far about the risk of developing a lymphoid malignancy after PN–MPN.

2. Case report

A 49–year-old man with past medical history of JAK2/CALR–negative ET diagnosed in 2010 (MPL mutational status not available) presented in December 2020 with a 5–day history of drenching night sweats and exertional dyspnea. For the past few months, he has had worsening fatigue, loss of appetite, early satiety, and unintentional weight loss of 7 lbs. He had been on Hydroxyurea and Aspirin for the past 10 years. On admission, CBC showed a WBC 67.7 K/μL, hemoglobin 10.7 g/dL, platelets 46 K/μL . A full body CT scan showed 7.3 × 3.5 × 4.1 cm anterior mediastinal homogenous mass and diffuse cervical and axillary lymphadenopathy. A bone marrow (BM) biopsy showed hypercellular marrow involved by T–lymphoblastic leukemia (T–ALL) (Fig. A). Karyotype analysis showed an abnormal near diploid, biclonal male karyotype (46,XY,−10,14,+2mar[6]/49~56, XY,+5,+15,+16,+19,+20,+20[cp2]/46,XY[12]). Flow cytometry identified 93% lymphoblasts expressing cytoplasmic CD3, TdT, CD38, CD2, CD4, CD5, CD8 (partial), and CD10 but lacking surface CD3, CD19, CD16, CD20, MPO, HLA-DR., CD56, CD19, CD20 and CD34 suggestive of T–ALL . A B–lymphoblastic leukemia–specific set FISH analysis was negative for t (9;22) BCR–ABL1 fusion and other abnormalities. A 23–panel lymphoid NGS (NeoTYPE Analysis™) was unremarkable while a 62–panel myeloid NGS (NeoTYPE Analysis™) showed 2 mutations: NOTCH1 (L1678P) (variant allele frequency (VAF) 49.9%, read depth 1887) and PHF6 (splice site c.374+1G > A) (VAF 95.8%, read depth 742). The patient was initiated on chemotherapy with the Hyper–CVAD protocol. A repeat BM biopsy after cycle 1A showed no residual acute leukemia but persistent involvement by the previously diagnosed MPN (megakaryocytic hyperplasia). A flow

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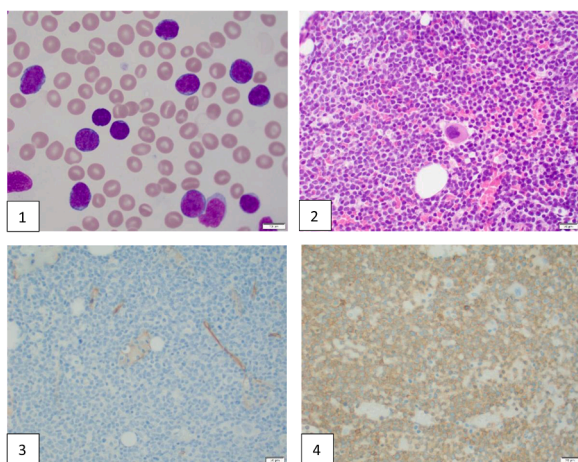 *E-mail address:* kapil.meleveedu@chartercare.org (K. Meleveedu).

Fig. A. 1,2: Bone marrow aspirate/biopsy showing hypercellular marrow mostly composed of immature lymphoid cells with clumped chromatin and scant to moderate cytoplasm that account for > 95% of all cells. 3,4: Immunohistochemistry stains showing lesional cells lacking CD34 (3) (CD117 and CD20 not illustrated) but diffusely expressing CD5 (4).

cytometry was normal and a myeloid NGS panel now showed MPL (W515K) mutation (VAF of 21.8%, read depth 1101). He sustained complete remission (CR) after 4 cycles and successfully underwent an allogeneic transplant with a fully matched unrelated donor at the time of this report.

3. Discussion

3.1. Incidence and characteristics of T-ALL after PN-MPN

The usual evolution of polycythemia vera (PV) and ET would be a progression to Myelofibrosis (MF) or AML. The occurrence of a lymphoid malignancy, specifically T–cell ALL, after PN–MPN is rarely described in the literature. In their case series, Alhuraiji et al. reported 17 cases of ALL after PV/ET/MF until 2019, only 1 being T–ALL that dates back to 1986[2,3]. In 2020, Burns et al. reported 1 case of T–ALL after primary MF and 2 cases of angioimmunoblastic lymphoma developing after ET[4]. In addition to that, we found a case of T–ALL after ET reported by Berkahn et al. in 1996[5].

Thus, including the case presented here, only 4 cases of T–ALL after PN–MPN are described so far with median age of 55.5 years (range: 20–87 years), median time to progression of 6.5 years (range: 2 months-10 years), and a male to female ratio of 3:1 (Table A). A complex karyotype is present in 2 out of these 4 cases. JAK-2 was mutated in 1 case, wild-type in our case and not analyzed in 2 cases as they date back to the period before JAK-2 testing. Hydroxyurea was used in 2 out of 4 cases including our case. Unlike ours, an NGS analysis was not performed in any of the other cases. Initial NGS in our case revealed mutations in NOTCH1 and PHF6 whereas NGS after remission showed MPL mutation. The outcome was poor in the other 3 reported cases with death occurring in less than 6 months. At the time of this submission, our patient successfully completed an allogenic transplant after his 4th month of CR.

3.2. Risk factors for the development of acute leukemia (myeloid versus lymphoid) after PN-MPN

3.2.1. Clinical

In general, the risk factors for myeloid leukemic transformation in PN–MPN include advanced age, increase in WBC and previous exposure to high dose myelosuppressive therapy. Specifically, for ET, Gangat et al. concluded that platelet count > 1 million/μL, age > 60 years and hemoglobin < 12 g/dL (for female) and < 13.5 g/dL (for males) are considered independent risk factors[6].

Concerning the occurrence of lymphoid malignancies after PN–MPN, Vannucchi et al. found an increased risk with male gender and MPN duration of > 5 years[7]. However, the cases were limited to chronic lymphocytic leukemia, non–Hodgkin lymphoma and plasma cell disorders.

3.2.2. Molecular

3.2.2.1. *JAK2V617F mutation.* Before the era of NGS, several studies found that JAK2 mutated MPN can either evolve into a JAK2-negative AML or less frequently into a JAK2-positive AML suggesting a possible evolution from the same clone, a different clone or a pre–JAK2 clone[8]. In ET, the presence of JAK2 has not been shown to be associated with myelofibrotic progression or clonal evolution whereas the data seems to be contradictory with PMF[8].

Contrariwise, in both ET and PV, JAK2V617F mutation seems to carry a significant risk of development of certain lymphoid malignancies as demonstrated by Vannucchi et al.[7]. Worth to mention that the only

Table A
Characteristics of cases of T–ALL occurring after MPN.

	Our case	Burns et al. [4]	Aitchison et al. [3]	Berkahn et al. [5]
Age / Gender	49 / Male	62 / Male	20 / Male	87 / Female
MPN type	ET	PMF	PV	ET
Mutation	JAK2 V617F / CALR - Negative	JAK2 V617F	N/A	N/A
Treatment of MPN	Hydroxyurea	Erythropoietin	Phlebotomy and busulfan	Hydroxyurea
Time to LP	10 years	3 years	10 years	2 months
Karyotype at progression	46,XY,−10,−14,+2mar[6]/49~ 56, XY,+5,+15,+16, +19,+20,+20[cp2]/46, XY[12]**	46,XY,i(17)(q10)/46,idem,del(20) (q11.2q13.1)	Unknown	46, XX
Flow cytometry / IHC	CD3, TdT, CD38, CD2, CD4, CD5, CD8 (partial), and CD10 (Flow cytometry)	TdT, CD1a, CD2, CD7 and cytoplasmic CD3, CD33 and CD34 (Flow cytometry)	unknown	CD2, CD5, CD7 and cytoplasmic CD3. Rearrangement of TCR β and γ (IHC)
NGS	-Lymphoid: negative -Myeloid: mutations in **NOTCH1** (L1678P), **PHF6** (splice site c.374+1G > A)	Unknown	N/A	N/A
Treatment of ALL	Hyper-CVAD (4 cycles), followed by HSCT	Hyper-CVAD, Nelarabine, Clofarabine and Cytarabine	vincristine, prednisolone, daunorubicin then prednisolone and mercaptopurine	Supportive care
Outcome	In the 4th month of remission	Relapse in 2 months then death	Death after 5 months	Rapid deterioration and death

** 6 cells analyzed show monosomies 10 and 14 and gain of 2 marker chromosomes of C– and G–group size. 2 cells show trisomies 5,15,16 and 19 and tetrasomy 20 without structural anomalies. The remaining cells are cytogenetically normal.
LP: Leukemic progression, IHC: immunohistochemistry, NGS: Next Generation Sequencing, N/A: not applicable, HSCT: Hematopoietic stem cell transplant.

potential molecular link between MPN and lymphoid malignancy would be the JAK-STAT pathway. Nevertheless, in our case as others, there continues to be reports of lymphoid malignancies developing after a JAK2-negative PN-MPN[4].

3.2.2.2. *Other somatic mutations.* The use of NGS has allowed the identification of several other mutations with additional prognostic parameters in PN–MPN. For instance, ASXL1, SRSF2, and IDH2 in PV and SH2B3, SF3B1, U2AF1, TP53, IDH2, and EZH2 in ET, are considered "adverse variants/mutations" as they are associated with inferior survival and myeloid leukemic/fibrotic progression[1].

In contrast, mutational studies guiding the progression to lymphoid malignancies are vastly lacking. However, few studies has shown that some mutations can be shared by Early T–cell Precursor ALL and myeloid neoplasms such as SH2B3, FLT3, RUNX1 and EZH2[9].

3.3. The benefit of NGS in the current case

It is well known that constitutive activation of NOTCH1 signaling (along with other recurrent genetic aberrations including PHF6) results in the malignant transformation of hematopoietic progenitors primed towards T cell development to an oncogenic-ALL clone[10]. On the other hand, MPL mutation which activates JAK–STAT signal transduction independently of ligand binding affects the behavior of hematopoietic stem cells at later stages of development much beyond lineage commitment. Whether these mutations were truly implicated in the pathogenesis of ET transformation to T–ALL in our case remains unknown, but such a lineage switch seems highly unlikely. Furthermore, the presence of MPL (W515K) mutation on remission and its absence in the leukemic cells in our patient reinforces that the T–ALL originated from a different and distinct clone entirely not related to ET (de novo). It is possible that the patient's ET could have had an MPL mutation initially itself at quantities lower than the detection limit of our panel or it might be that this clone evolved due to the selective pressure from ongoing chemotherapy. Our major limitation is the unavailability of the MPL mutational status at the diagnosis of ET.

4. Conclusion

Deep molecular sequencing is of great value in the setting of development of lymphoid malignancies after PN–MPN as it may reveal whether this phenomenon is an independent, random event or true clonal progression of MPN and may assist in uncovering putative new molecular pathways or novel disease initiation mechanisms. Despite being a rare entity, clinicians should maintain a high index of suspicion for the occurrence of such malignancies in any PN–MPNs who presents with clinical symptoms and signs suggestive of an acute leukemia.

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Declaration of Competing Interest

None

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