Acute lymphoblastic leukemia secondary to myeloproliferative neoplasms or after lenalidomide exposure

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Key Clinical Message
Philadelphia-negative (Ph-) myeloproliferative neoplasms (MPN) do rarely transform to acute lymphoblastic leukemia (ALL). While causality is difficult to establish, a few cases of ALL arising after exposure to lenalidomide for registered indications (multiple myeloma, myelodysplastic syndrome with 5q deletion) have been described in the literature.

Keywords
Acute lymphoblastic leukemia, JAK2 V617F mutation, lenalidomide, myeloproliferative neoplasm.

Introduction
The classic Philadelphia chromosome-negative (Ph-) myeloproliferative neoplasms (MPN), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) share in common the activating Janus-associated kinase 2 (JAK2) V617F mutation in approximately 95, 60, and 60% of cases, respectively [1], and universal activation of the JAK-STAT (signal transducer and activator of transcription) pathway [2]. The JAK2 V617F mutation is specific to myeloid malignancies [3] and is not found in patients with “Ph-like” acute lymphoblastic leukemia (ALL) who, however, have been shown to have other alterations involving JAK2, including both fusions and point mutations [4]. Differences in mutant allele burden, STAT1 signaling, order of mutation acquisition, and clonal heterogeneity have been invoked as potential explanations of how the same driver mutation can result in substantially different clinicopathologic entities [1].

Both PV and ET may progress to myelofibrosis (post-PV MF (PPV-MF) or post-ET MF (PET-MF)) which, as well as PMF itself, may represent an “accelerated phase” in the spectrum of progression of MPN to acute myeloid leukemia (AML) [5, 6]. Considerable evidence supports the accumulation of a variety of genetic lesions during leukemic transformation (LT) of MPNs [7]. JAK2 V617F-induced genomic instability may lead ultimately to LT [5]. However, JAK2 V617F+ MPNs often transform to JAK2-wild-type AML [8]; in this situation, the chronic and leukemic phases could either be clonally related, arising from a shared pre-JAK2V617F clone, or clonally unrelated, reflecting transformation of independent stem cells [5].

The immunomodulatory agent lenalidomide is an analog of thalidomide that is approved for the treatment of
multiple myeloma (MM) [9, 10], myelodysplastic syndrome (MDS) with 5q deletion [11], and mantle cell lymphoma [12]. It is used most widely in MM, as part of two- [9, 10, 13] and three- [14–17] drug induction regimens, in both the frontline and relapsed/refractory settings, as well as in maintenance [18–20], usually as a single agent. Second primary malignancies have emerged as an issue of significant concern with this agent [21]. In general, these tend to be myeloid neoplasms and solid tumors, occurring mostly in the context of melphalan exposure [22].

Case Report

A 66-year-old Caucasian female with a nearly eleven-year history of MPN presented to the MD Anderson Cancer Center (MDACC) in January 2016 with a recent diagnosis (December 2015) of B-ALL. The patient had presented initially with anemia and leukopenia. She had no active infection or bleeding. She also did not have splenomegaly, either by clinical or ultrasonographic evaluation. The diagnosis was confirmed by the finding of 88% blasts in a 95% cellular bone marrow (BM, Fig. 1), all of which expressed the B-cell antigens CD19, CD20, and CD22. There was no evidence of MPN. Cytogenetics revealed a complex, monosomal karyotype. Targeted next-generation sequencing using a validated 28-gene myeloid panel [23] revealed only the JAK2 V617F mutation. Additionally, testing for calreticulin (CALR) mutations was negative. Treatment with chemoimmunotherapy (Cyclophosphamide, Vincristine, dexamethasone, Rituximab, and Inotuzumab Ozogamicin) was begun. Unfortunately, soon after completing her rituximab infusion on day 2 of therapy, the patient developed severe headache, hypertension, and became increasingly obtunded. Imaging disclosed extensive subarachnoid and intraventricular hemorrhage. Comfort measures were adopted given her very poor prognosis in the setting of severe thrombocytopenia, and she passed away the following day. No inotuzumab ozogamicin was administered. Cyclophosphamide and vincristine were the only cytotoxic drugs the patient received.

The patient had been diagnosed with an MPN, variously described as ET or PMF, in January 2005. JAK2 mutation status at diagnosis was not available. Initial management had been with anagrelide for thrombocyto-sis, which was changed to lenalidomide and prednisone in January 2012 because of anemia. She responded well to this regimen in terms of symptomatic improvement, platelet count control, and red cell transfusion independence. BM from 2012 was >90% cellular with grade 2–3 reticulin staining, compatible with PMF, and not significantly changed since June 2009. Repeat BM in May 2013 showed apparent improvement in terms of cellularity (50%) and fibrosis grade (focal, grade 1/3). Interestingly, no JAK2 (or MPL) mutation was detected. CALR mutations were not tested for at this stage. In March 2014, lenalidomide was discontinued due to symptomatic disease in the form of B symptoms and therapy with ruxolitinib begun, which the patient remained on until her presentation to MDACC.

Methods

The unique features of this case prompted us to conduct a literature search for published cases of MPN transforming to ALL. In addition, we were intrigued by our patient’s prior exposure to lenalidomide and wondered whether the latter might have contributed to her LT in some way. We searched MEDLINE using PubMed in order to identify reports of patients who developed ALL after an MPN, or in the setting of lenalidomide therapy, using the following keywords: “acute lymphoblastic leukemia” AND “myeloproliferative neoplasm” OR “essential thrombocytemia” OR “essential thrombocytosis” OR “polycythemia vera” OR “myelofibrosis”; and “acute lymphoblastic leukemia” AND “lenalidomide” OR “multiple myeloma” OR “myelodysplastic syndrome” OR “5q syndrome,” respectively. A total of sixty-two articles were retrieved by these searches. The titles and abstracts of these articles were reviewed to select thirteen relevant case reports/series. Further, the reference lists of these articles were reviewed in an effort to find additional articles.

Discussion

Transformation of MPN to ALL is rare, with only seventeen cases reported in the literature (Table 1). Median time to progression to ALL was 10 years (range 2–25). Transformation carried a very poor prognosis, with 80% mortality reported in the published cases. Most ALLs arising in this context had a B-cell phenotype. Only a few of these are molecularly annotated. Czader and Orazi reported on disease progression of Ph− MPN and chronic myeloid leukemia at the session on LT of MPN at the Society for Hematopathology/European Association for Haematopathology workshop held in Houston, Texas, from October 24 through 26, 2013; two otherwise unpublished cases of progression of Ph− MPN, one ET and one PET-MF, to JAK2 V617F+ B-ALL were described in this article [24]. Ohanian et al. from our group reported a case of PPV-MF that progressed to B-ALL with a JAK2 exon 12 mutation [25]. Nagai et al. reported on a patient with JAK2 V617F+ ET who later developed Ph+ B-ALL, but in this case, the JAK2 V617F mutation was found only in the CD34+ hematopoietic stem and progenitor cells (HSPCs).
and not in the CD34<sup>+</sup>CD19<sup>+</sup> Ph<sup>+</sup> B-ALL cells, indicating that the two neoplasms were clonally distinct [26].

Delhommeau and colleagues studied the presence of the JAK2 V617F mutation in circulating B-, T-, and natural killer (NK) cells of patients with PV and PMF, and detected it in B- and NK cells from approximately half their patients with PMF and a minority of those with PV [27]. Furthermore, a few patients with PMF also carried the mutation in their peripheral T cells. The mutation was subsequently detected in B/NK/myeloid precursors from PV and PMF patients, as well as in T-cell fractions derived from CD34<sup>+</sup> cells, thus showing that MPN originates in a true myeloid/lymphoid progenitor cell, although the proliferative advantage conferred by the driver mutation appears to be limited to the myeloid lineage [27]. This would be consistent with the two-hit theory of leukemogenesis, suggesting that other genetic lesions are also involved in MPN pathogenesis. Indeed, it has been suggested that JAK2<sup>V617F</sup> only confers a weak proliferative advantage on the hematopoietic stem cell (HSC), such that on its own, it would cause an MPN with a very long latency; thus, JAK2<sup>V617F</sup>-bearing HSCs may remain harmless for a long time, until genetic or environmental changes such as hematopoietic stress or aging allow clonal dominance and MPN emergence [6].

![Figure 1.](image-url)
Only eight cases of ALL, all with a B-cell phenotype, arising as a second malignancy in lenalidomide-treated patients, have been reported in the literature. Median duration of lenalidomide therapy in the reported cases (Table 2) was 3 years (range 2–7). Most patients were receiving the drug for MM; two cases were reported in patients who were on the immunomodulatory agent for MDS with a 5q deletion [28]. Different doses and schedules were reported, and the patients with MM received lenalidomide during induction or as maintenance therapy, or both (Table 2). In contrast, the increased risk of myeloid neoplasms and solid tumors has been well described in the setting of prolonged lenalidomide maintenance therapy of MM, mainly in the context of prior exposure to high-dose melphalan conditioning [22]. Indeed, in the three large randomized controlled trials evaluating maintenance therapy with lenalidomide in a total of 690 patients with MM, only five cases of ALL were reported, four of them in the post-transplant maintenance setting [18–20].

The mechanisms of action of lenalidomide in MM [29] and MDS with del5q [30], involving the cereblon-
dependent destruction of Ikaros family transcription factors and casein kinase 1A1, respectively, have only recently been elucidated, and how the drug may affect an MPN clone over time remains largely unknown. Although not specifically approved for this indication, lenalidomide, with or without prednisone, is often used for the treatment of myelofibrosis [31–33], particularly for the amelioration of anemia, which does not usually improve significantly with ruxolitinib. However, simultaneous administration of lenalidomide and ruxolitinib is difficult [34]. Some experts reserve lenalidomide for patients with del5q given the potential for myelosuppression and thrombosis with this agent [35], although this particular cytogenetic abnormality is extremely rare in myelofibrosis [36].

Conclusion

Our case illustrates the pluripotency of the JAK2V617F+ stem/progenitor cell, as do a few others reported in the literature. The incidence of ALL occurring in the context of lenalidomide therapy is very low, precluding definitive conclusions.

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Authorship

AA and PB wrote the manuscript and AA performed literature searches. PB and SV reviewed the paper for important intellectual content. AA, PB, KN and CH provided clinical care to the patient. YOH performed hematopathologic evaluation of the cases and provided the bone marrow morphology and flow cytometry images.

Conflict of Interest

None declared.

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