CASE REPORT

Acute Lymphoblastic Leukemia Transformation in Polycythemia Vera: A Rare Phenomenon

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Abstract Leukemic transformation in patients diagnosed with polycythemia vera (PV) is associated with poor prognosis and median survival not exceeding 3 months. To date only a few cases of post-PV acute lymphoblastic leukemia (ALL) have been reported. A 64-year-old female patient developed ALL 4 years after she had met PV criteria. At PV diagnosis a molecular study was positive for the *JAK2V617F* mutation. Due to high risk features (history of deep vein thrombosis) she was treated with hydroxyurea (HU) with moderate efficacy. She became anemic and thrombocytopenic with mild leukocytosis while still on HU. Blood and bone marrow smears revealed 40 and 100 % of blast cells, respectively. The immunophenotyping of blasts was consistent with a diagnosis of early precursor B cell ALL. She was found to be positive for the *JAK2V617F* mutation. Patient received an ALL induction regimen and achieved complete remission with negative minimal residual disease by flow cytometry. The post-chemotherapy study for the *JAK2V617F* mutation was positive. Patient has remained in remission for 4 months. A suitable donor searching was initiated. Post-PV ALL is an extremely rare phenomenon. Due to poor prognosis, an allogeneic stem cell transplantation should be considered in fit patients who achieved remission.

Keywords Polycythemia vera · Acute lymphoblastic leukemia · Leukemic transformation · *JAK2V617F* mutation

Introduction

Polycythemia vera (PV) is a Philadelphia-negative (Ph) classical myeloproliferative neoplasm (MPN) characterized by increased red blood cell (RBC) production and the presence of gain-of-function mutation of the Janus 2 kinase gene: *JAK2V617F* (95 %) or functionally similar *JAK2* mutation (5 %). The presence of *JAK2* mutation leads to uncontrolled proliferation of erythroid as well as myeloid and megakaryocytic lines causing panmyelosis [1]. The annual incidence of PV varies from 1.0 to 2.5 per 100,000 and it occurs at the median age of 61 years; patients younger than 20 years are rarely observed. The median survival is reported to be from 10.9 to 27.8 years since diagnosis [2]. Thrombosis or hemorrhage remains the main cause of death in this patient population [3]. PV may transform to myelofibrosis or acute myeloid leukemia (AML) with the range of reported frequencies to be between 6–14 and 5.5–18.7 % at 15 years, respectively. The risk factors for post-PV AML were postulated and included both clinical (age, leukocytosis, reticulin fibrosis, splenomegaly) and genetic factors (abnormal karyotype, TP53 and RUNX1 mutations). The mechanism underlying the leukemic progression remains unknown and it is likely multifactorial [4]. The transformation of PV into acute lymphoblastic leukemia (ALL) remains an extremely rare entity and only a few cases have been reported so far [5, 6].

Herein we report on a female patient with a short history of hydroxyurea (HU)-treated PV progressing to early precursor B-cell ALL.

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Case Presentation

A 64-year-old female was admitted to Hematology Unit in September 2015 with a suspicion of post-PV leukemic transformation (LT). She was diagnosed with PV in May 2010. At initial presentation her complete blood count (CBC) was as follows: hemoglobin (Hgb): 17 g/dl, RBC count: $6.58 \times 10^{12}/l$, hematocrit (HCT): (52.6 %), white blood cell (WBC) count: ($6.73 \times 10^9/l$) and platelet count (PLT): $626 \times 10^9/l$. Repeated blood tests were comparable. Blood smear revealed a predominance of segmented cells (68 %) with no immature shift. Serum iron and ferritin levels were normal. On biochemistry no abnormalities have been found. Physical examination detected a mild splenomegaly that was confirmed by abdominal ultrasound (14.5 cm). Serum erythropoietin (EPO) level was low (1.7 IU/l). Her serum vitamin B12 and uric acid levels were within normal range. Bone marrow biopsy was not performed. The *JAK2V617F* mutation was positive and she was diagnosed with PV. Patient had a history of deep vein thrombosis and HU was commenced at a daily dose of 2 g. She refused phlebotomy. She had been taking HU for 4 years moderate efficacy. No side effects of HU were present. In June 2015 an abdominal ultrasound revealed moderate splenomegaly (16 cm). Two months later she developed hyperleukocytosis ($16.4 \times 10^9/l$) and her general condition began to deteriorate. She was referred to our Unit. On admission CBC detected hyperleukocytosis ($13.6 \times 10^9/l$), anemia (Hgb 8 g/dl) and thrombocytopenia (PLT $78 \times 10^9/l$). Blood smear revealed a predominance of blast cells (40 %) with the presence of segmented cells (26 %), lymphocytes (21 %), erythroblasts (6 %), promyelocytes (4 %), myelocytes (2 %) and basophilic erythroblasts (1 %). Bone marrow aspiration was infiltrated by blast cells in 100 %. The bone marrow immunophenotyping was as follows: CD45(+) CD19(+) CD22(+) cyCD79a(+) CD20(–) CD52(+) CD10(–) CD58(+) Tdt(+) CD34(+) CD38(+) skappa(–), slambda(–) sIgM(–) cyIgM(–) with co-expression of CD33 and that was consistent with the diagnosis of early precursor B-cell ALL. Cytogenetic assay was negative for Philadelphia chromosome. Karyotype was normal. Molecular studies detected the *JAK2V617F* mutation but were negative for *MLL/AFF1*, *BCR/ABL p190* and *BCR/ABL p210*. Trephine biopsy revealed intertrabecular spaces to be filled with bone marrow cells in 90 % of which 90 % consisted of lymphoblasts. Fibrosis was not present. Patient started with the induction treatment according to Polish Adult Leukemia Group (PALG) protocol for ALL. Initially, she received dexamethasone (dex) as a pretreatment. Dex was then given on days 1–7 and 15–21, daunorubicin and vincristine on days 1, 8, 15 and pegylated asparaginase on day

10. Intrathecally she was given methotrexate and liposomal cytarabine. She did not receive her fourth dose of daunorubicin/vincristine due to toxic effect of asparaginase. The liver function tests were as follows: total bilirubin: 0.19 mmol/l (normal: 0.003–0.017), ALP: 1273 IU/l (normal: 32–92), GGTP: 423 IU/l (normal: 5–24), AST 399 IU/l (normal: <31) and ALT 441 IU/l (normal: <34). Due to liver dysfunction, blood clotting tests were severely impaired and activated partial thromboplastin time and prothrombin time were unmeasurable. She was given symptomatic treatment with full recovery of liver function. During her next stay she was found to be in complete remission of her ALL with negative minimal residual disease by flow cytometry. Her *JAK2V617F* mutation remained positive. Currently, 4 months since her ALL diagnosis, she remains in complete remission searching a suitable unrelated donor for allogeneic stem cell transplantation.

Discussion

LT in patients diagnosed with Ph-negative MPN is associated with poor prognosis with a median survival not exceeding 3 months. The most common type of blast transformation in this patient setting remains AML whereas only single patients with ALL have been reported so far. It has demonstrated that most LT cases developed in patients who received prior chemo- or radiotherapy for their MPN with high-dose pipobroman (P^{32}) and alkylating agents being the commonest [7]. Numerous mutations have been detected in AML evolving from Ph-negative MPN but this genetic profile differs somehow from that observed for de novo AML. Some of these abnormalities may have a prognostic significance, nevertheless their role in LT remains unclear [8]. Of note is, that single patients were found to be negative for the *JAK2V617F* mutation at their LT, even though this mutation was detected at chronic phase of MPN which may suggest the co-existence of two independent clones [7]. Clinical characteristics of post-PV ALL is limited due to data paucity, but some preliminary conclusions can be made on single case series. The reported patients had time interval between PV and post-PV ALL between 3 and 25 years. All these patients received P^{32} and/or alkylating agents for their PV and survival after ALL diagnosis did not exceed several months. It should be underscored that none of the transformed patients received HU or phlebotomy alone. All but one ALL case was of B-cell origin [9]. Interestingly, only two patients with ALL arising in post-PV myelofibrosis have been reported in the literature so far [6, 10]. The Ohanian case [6] illustrates the genetic diversity of LT as

Table 1 Summary of patients with acute lymphoblastic leukemia following polycythemia vera (modified from [9])

Patient no.	Age (years)	Gender	PV treatment	PV-ALL interval (years)	Cytogenetics at ALL	ALL outcome at last contact	References
1	76	M	Phlebotomy, Bu	16	46, XY	Died	[5]
2	63	F	P ³² , HU	6	ND	Died	[9]
3	75	M	Phlebotomy, HU	3	46, XY	Alive	[11]
4	22	F	Phlebotomy	17	ND	Alive	[12]
5	77	M	P ³² , CHL	5	46,XY	Died	[13]
6	74	M	P ³² , Bu, CHL, nitrogen mustard	6	ND	Died	[14]
7	42	M	P ³² , Bu	10	47, XY; 6q–, +8	Died	[15]
8	20	M	Bu	10	46, XY	Died	[15]
9	68	F	P ³² , Bu, CHL	25	Complex	Died	[16]
10	54	F	P ³² , HU	13	ND	Alive	[17]
11	64	F	HU	4	46, XX	Alive	Present case

ALL acute lymphoblastic leukemia, Bu busulfan, CHL chlorambucil, F female, M male, ND no data, HU hydroxyurea, P³² pipobroman, PV polycythemia vera

this process was accompanied by a temporary disappearance of *JAK2*-exon 12 mutation and the emergence of an *NRAS* mutated clone. Of note is that the latter is not observed in adult patients with ALL. Overall, as far as we know, 11 cases of post-PV ALL have been reported [5, 9, 11–17], but only three patients including the present case received HU and/or phlebotomy alone for PV [11, 12]. Details were shown in Table 1.

Regarding our female patient, we should point out a relatively short time interval between PV and post-PV ALL (4 years). She received HU for her PV, however this agent used alone was not found to be leukemogenic [18]. When comparing single-agent therapy: HU versus P³², the cumulative incidence of LT evolving from PV was 16.6 and 49.4 % at 20 years, respectively. This finding seems to confirm the leukemogenicity of P³², however the rate of blast transformation after HU treatment was unexpectedly higher than previously reported [4, 19]. The association between the presence of the *JAK2*V617F mutation and LT in PV patients was not found [20]. The presence of the *JAK2*V617F mutation both before and after ALL occurrences may suggest the co-existence of PV and ALL. The pathogenic role of certain cytogenetic/molecular abnormalities in blast transformation remains under investigation [4]. Regarding the extremely poor prognosis of transforming patients, regardless of therapeutic approach, allogeneic stem cell transplantation after remission achieving, remains the only curative option [7].

The likely pathogenesis of post-PV ALL remains unexplained. The presence of two abnormal clones on cytogenetic studies has been detected: one of myeloid and one of lymphoid origin suggesting the co-existence of two independent clones [16]. The acquisition of a new

molecular event leading to transformation is also likely [6]. Moreover, one may not exclude that LT is induced by prior PV treatment as it was mentioned elsewhere [7] or that we have a coincidental occurrence of these two neoplasms. It seems that better understanding of genetic profile leading to transformation will identify patients with high-risk of LT thereby better management and treatment.

Compliance with Ethical Standards

Conflict of interest None.

Ethical Standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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