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Case Report

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Emergence of *BCR-ABL1* Chronic Myeloid Leukemia in a *JAK2*-V617F Polycythemia Vera

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Abstract

Emergence of a new chronic myeloid neoplasm in the setting of a previous one, or their concomitant appearance seems to be a rare event, but plenty of cases have been reported. We describe the case of a patient with *JAK2*-V617F polycythemia vera, which looses *JAK2* clone and develops overt *BCR-ABL1* chronic myeloid leukemia after 6 years. Once treatment with tyrosine kinase inhibitors controls *BCR-ABL*1 clone, *JAK2* clone arises again. In this report, we review the literature and discuss the clonal relationship of this event in light of the new molecular data.

Keywords: Chronic myeloid leukemia; Chronic myeloproliferative neoplasm; *BCR-ABL1*; *JAK2*-V617F

Introduction

Myeloproliferative neoplasms (MPNs) include a heterogeneous group of disorders. The most frequent are chronic myelogenous leukemia (CML), essential thrombocytosis (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). CML is characterized by Philadelphia chromosome translocation between the long arms of chromosome 9 and 22, leading to the *BCR-ABL1* fusion gene. Philadelphia negative disorders (Ph-MPN) are associated with driver mutations, such as *JAK2*, *CALR*, and *MPL*. *JAK2*-V617F mutation is present in more than 90% of patients with PV (or exon 12 mutation in V617F negative), and more than 50% of patients with ET or PMF [1]. *CALR* mutation is present in 20-25% of TE and PMF, and *MPL* mutation is found in 3% of TE and 7% of PMF. The rest of MPNs are "triple negative", but a minority present somatic mutations in other genes [2].

Classically, *BCR-ABL1* and *JAK2* were considered mutually exclusive driver genetic lesions [3, 4]. Here we describe a case of emergence of *BCR-ABL1* CML in the setting of *JAK2*-V617F PV.

Case Report

In 2012 a 70-year-old female was admitted with hematocrit of 63.9%, hemoglobin 22 g/dL, normal platelets, and white blood cell (WBC) of 15.97 × 10^9/L with neutrophilia without spleen enlarge. Her smear showed absence of leukoerythroblastic picture and presence of mature granulocytes.

Bone marrow aspirate showed granular hyperplasia without blast excess; and biopsy was not performed at that time. Molecular testing revealed V617F mutation in *JAK2* gene. *JAK2*-PV was diagnosed and she was treated with phlebotomies, acetylsalicylic acid (ASA) and hydroxyurea. Her disease was controlled, without thrombotic or hemorrhagic complications.

Six years later, progressive leukocytosis and spleen enlargement were observed. Her WBC was 80 × 10^9/L with normal hemoglobin and platelets counts. There was concern of progression to acute leukemia so she was re-evaluated. Her smear showed leukoerythroblastosis with no blasts excess. Bone marrow smear showed no leukemic progression and biopsy informed granulocyte hyperplasia, absence of fibrosis, and 5% of cluster of differentiation (CD)34/CD117 progenitors. Cytogenetic analysis had no evaluable metaphases, and fluorescence *in situ* hybridization (FISH) for *BCR-ABL1* was positive in 99% of nucleus. Conventional reverse transcription polymerase chain reaction (RT-PCR) showed b2a2 *BCR-ABL1* fusion gene.

At this point we had a patient with *JAK2*-PV who evolved to chronic phase of *BCR-ABL1* CML. In order to asses if this was a progression of the same clone or was a second myeloproliferative clone, we performed *JAK2* by allele specific oligonucleotide (ASO)-PCR (ASO-PCR) for V61F mutation, which was negative, suggesting two different clones. We also assessed the presence of *BCR-ABL1* by FISH in marrow sample of her diagnosis in 2012, but it was not an evaluable sample.

She started imatinib 400 mg QD and ASA, and stopped hydroxyurea, achieving complete hematologic remission at the first month of treatment. Cutaneous and hematologic toxicity was detected required dose reduction to 300 mg QD. She achieved cytogenetic complete remission at 3 months despite dose adjustment, but minor molecular response at 6 months.

Six months after the diagnosis of *BCR-ABL1* CML, the hematocrit rose to 48%, suggesting *JAK2*-PV clone recurrence, and indeed *JAK2*-V617F was confirmed by molecular testing,

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Table 1. Clinical and Genetic Characteristics of Published Cases Including Initial Molecular Lesion *JAK2* in Combination With Molecular Change of *JAK2*, *BCR*/*ABL* or *JAK2* and *BCR*/*ABL*

Reference	Initial phenotype	Initial molecular lesion	Phenotype change	Molecular change	Observations
Siricilla et al, 2017 [10]	PV[a]	*JAK2*	CML	Add *BCR*/*ABL* Retain *JAK2*	Two clones by cytogenetics.
Hummel et al, 2012 [6]	ET	*JAK2*	MF	Add *BCR*/*ABL* Retain *JAK2*	*BCR*/*ABL* controlled with TKI.
Zhou et al, 2015 [5]	PV	*JAK2*	CML	Add *BCR*/*ABL* Retain *JAK2*	Two clones proved by progenitor colonies genotyping. Treatment: dasatinib and ruxolitinib.
Swaminathan et al, 2018 [11]	PV	*JAK2* exon12[b]	CML	Add *BCR*/*ABL* (b3a3) Retain *JAK2*	*BCR*/*ABL* controlled with TKI.
Ursuleac et al, 2013 [12]	PV[a]	*JAK2*	CML	Add *BCR*/*ABL* Retain *JAK2*	*BCR*/*ABL* controlled with TKI.
Jallades et al, 2008 [13]	PMF	*JAK2*	CML	Add *BCR*/*ABL* Retain *JAK2*	*BCR*/*ABL* absent in first sample. *BCR*/*ABL* controlled with TKI. Persistent *JAK2* with same ratio.
Pingali et al, 2009 [14]	PV	*JAK2*	CML	*BCR*/*ABL*	PV-*JAK2* re-emerge when *BCR*/*ABL* controlled.
Bocchia et al, 2007 [7]	PV	t(9;18)	CML	Add *BCR*/*ABL* Retain t(9;18) *JAK2*	*JAK2* positive tested in deferred in first sample.
Yamada et al, 2014 [15]	PMF	*JAK2*	CML	Add *BCR*/*ABL*	*BCR*/*ABL* secondary event proved by progenitor colonies analysis.
Wang et al, 2015 [9]	PV	*JAK2*	CML	Add *BCR*/*ABL*	*BCR*/*ABL* secondary event on *JAK2* cells proved by progenitor colonies genotyping.
	PV	*JAK2*	CML	Add *BCR*/*ABL*	*BCR*/*ABL* secondary event on JAK2 cells proved by progenitor colonies genotyping.
Mirza et al, 2007 [16]	PV	*JAK2*	CML	Add *BCR*/*ABL*	-
	PV	*JAK2*	CML	Add *BCR*/*ABL*	-
Hussein et al, 2008 [17]	PV	*JAK2*, *BCR*/*ABL* negative	CML	Add *BCR*/*ABL*	*BCR*/*ABL* controlled with TKI. Blast crisis of *JAK2* clone.

[a]Additional high WBC/thrombocytosis/erythrocytosis. [b]In-frame deletion of six nucleotides (c.1620_1627delinsGA). PV: polycythemia vera; PMF: primary myelofibrosis; ET: essential thrombocytosis; CML: chronic myelogenous leukemia; TKI: tyrosine kinase inhibitor.

so phlebotomies were added in order to control both clones. Because of poor response and toxicities to imatinib, dasatinib was started at 9 months of *BCR-ABL1* CML diagnosis achieving major molecular response. She stopped ASA for 1 month and developed a deep vein thrombosis, but with normal hematocrit.

Discussion

Concomitance or emergence of a new chronic myeloid neoplasm is a rare event; however plenty of evidence is published. Tables 1, 2 and 3 [5-37] show the latest reports on the matter.

The presence of driver mutations with concomitant phenotypes (CML and Ph-MPN) at the beginning of the disease has been reported. Treatment of this scenario is challenging, but concomitant ruxolitinib and tyrosine kinase inhibitor (TKI) were successfully used [5].

Coexistence of *JAK2*-V617F and *BCR-ABL1* from the beginning in first blood sample of six patients studied for MPN was described in our country previously [38]. Additionally,

Table 2. Clinical and Genetic Characteristics of Published Cases Including Initial Molecular Lesion *BCR/ABL* in Combination With Molecular Change of *JAK2*, *BCR/ABL* or *JAK2* and *BCR/ABL*

Reference	Initial phenotype	Initial molecular lesion	Phenotype change	Molecular change	Observations
Hummel et al, 2012 [6]	CML	*BCR/ABL*	MF	Add *JAK2*	*BCR/ABL* controlled with TKI. JAK2 low allele burden.
Darling et al, 2017 [18]	CML	*BCR/ABL*	ET	Add *JAK2*	*BCR/ABL* controlled with TKI.
Pagnanol et al, 2016 [19]	CML[a]	*BCR/ABL*	ET	*JAK2*	*BCR/ABL* controlled with TKI.
Hussein et al, 2008 [17]	CML[a]	*BCR/ABL*	MF	Add *JAK2*	-
	CML	Ph	MF	Add *JAK2*	*BCR/ABL* not evaluated.
Bader et al, 2019 [21]	CML[a]	*BCR/ABL*	MF[a]	*JAK2*	*BCR/ABL* controlled with TKI.
Curtin et al, 2005 [22]	ET	-	CML	*BCR/ABL*	Before *JAK2* description, *BCR/ABL* positive in first sample.
Tefferi et al, 2010 [23]	CML	*BCR/ABL*	PV	Add *JAK2*	*JAK2* positive when *BCR/ABL* controlled with TKI.
Kim et al, 2006 [20]	CML	*BCR/ABL*	MF	*JAK2*	*JAK2* remain positive when *BCR/ABL* controlled with TKI.
	AP CML	*BCR/ABL*	-	*JAK2*	*JAK2* remain positive when *BCR/ABL* controlled with TKI.

[a]Additional high WBC/thrombocytosis/erythrocytosis. PV: polycythemia vera; MF: myelofibrosis; ET: essential thrombocytosis; CML: chronic myelogenous leukemia; TKI: tyrosine kinase inhibitor; AP: accelerated phase; Ph: Philadelphia positive chromosome.

Tabassum et al reported a surprisingly high frequency (44%) of *JAK2*-V617F and *BCR-ABL1* in 25 CML patients in Pakistan [39].

JAK2 and *BCR-ABL1* concomitance with a predominant phenotype has also been reported [40]. In fact, the presence of very low levels of *BCR-ABL1* in Phi-MPN and even its disappearance without treatment could represent a clonal hematopoiesis of indeterminate potential (CHIP) abnormality [41].

There are also reports on transforming phenotypes with second genetic mutations. The appearance of *JAK2* Phi-MPN phenotype in the course of a CML treated with TKI was observed [6, 23, 42]; and a diagnosis of CML in the course of a Phi-MPN like our patient was also described [5, 42]. This could represent a previous masked clone, or a new one because of selective pressure.

Whether these scenarios are a consequence of a single clone that acquires a "second hit" or emergence of a second clone, it is not well known. There are some reports that address this issue by progenitor colonies genotyping. Bocchia et al observed that *JAK2*-V617F and *BCR-ABL1* transcript can co-exist in an early (erythroid-myeloid-committed) progenitor cell, but few colonies showed *JAK2*-V617F mutation alone, whereas none showed *BCR-ABL1* transcript alone. Treatment with imatinib caused disappearance of *BCR-ABL1* remaining *JAK2* in most of colonies, suggesting that a subclone of pre-existing *JAK2*-V617F mutant hemopoietic progenitors at a certain point acquired *BCR-ABL1* translocation [7]. Bornhauser reported concurrent *JAK2-BCR-ABL1* in only two of 16 granulocytic colonies but in none of 15 erythroid colonies, suggesting that *BCR-ABL1* occurred at a later stage of myelopoiesis [8]. Zhou described a patient with concurrent PV and CML where the majority of the myeloid colonies have *JAK2*-V617F or *BCR-ABL1*, but not both, confirming that the two disorders arose within distinct clones [5].

Wang et al observed in two patients with features like the one in this report, that the acquisition of *BCR-ABL1* occurred after *JAK2* mutation, and that the development of CML is a secondary event that may occur in either heterozygous or homozygous *JAK2*-V617F hematopoietic progenitor cells [9].

Molecular landscape of MPN is rapidly evolving, and many driver and secondary mutations are arising with next-generation sequencing (NGS). Some epigenetic regulators mutations or oncogenic mutations described in myelodysplastic syndromes and acute myeloid leukemia are common in myeloproliferative diseases [2]. Kandarpa et al recently described the molecular characteristics of eight patients with combined phenotypes (CML and MF) by exome/transcriptome sequencing. They found the presence of mutations in epigenetic regulators such as *TET2*, *ASXL1/2*, *SRSF2*, and *IDH2* at different frequencies (1-47%). Some patients harbored oncogenic mutations in *N/KRAS*, *TP53*, *BRAF*, *EZH2*, and *GNAS* at low frequencies (0.5-39%). Subclonal frequencies of these mutations might indicate clonal evolution of the disease. Genomic instability might be a result of mutation in epigenetic regulators and probably hematopoietic stem cells accumulate multiple genetic variants with clonal dominance. Findings in this study suggest that CML in those patients might be a secondary disease arising from underlying genetic instability [43].

Table 3. Clinical and Genetic Characteristics of Published Cases Including Initial Molecular Lesion *JAK2* and *BCR/ABL* in Combination With Molecular Change of *JAK2*, *BCR/ABL* or *JAK2* and *BCR/ABL*

Reference	Initial phenotype	Initial molecular lesion	Phenotype change	Molecular change	Observations
Bee et al, 2010 [24]	PV[a]	*JAK2* and *BCR/ABL*	CML	*JAK2* present when *BCR/ABL* is treated, and *vice versa*.	Two clones with clonal dominance.
Payande et al, 2011 [25]	ET[a]	*JAK2* and *BCR/ABL*	No	No	-
Hummel et al, 2012 [6]	CML	*JAK2* and *BCR/ABL*	PV	High *JAK2* allele burden when PV phenotype.	PV phenotype when treated with imatinib.
Darling et al, 2017 [18]	Neutrophilic leukocytosis, basophilia and thrombocytosis	*JAK2* and *BCR/ABL*	No	-	Treated with TKI.
Xu et al, 2014 [26]	CML	*BCR/ABL* and *JAK2*	No	-	Two clones? CMR with TKI, persistent JAK2.
Hassan et al, 2015 [27]	CML/MF	*BCR/ABL* and *JAK2*	No	-	*JAK2* tested in deferred in first sample. Poor control of *BCR/ABL* with TKI.
Hussein et al, 2008 [17]	CML[b]	*BCR/ABL* and *JAK2*	No	-	Concurrent lesions at the beginning.
Toogeh et al, 2011[28]	PV	*JAK2* homozygous *BCR/ABL*	-	-	-
Park et al, 2013 [29]	ET	*JAK2* and *BCR/ABL*	None	-	Poor response with hydroxyurea.
	PMF	*JAK2* and *BCR/ABL*	-	-	*BCR/ABL* controlled with TKI.
Qin et al, 2014 [30]	ET	*JAK2* and *BCR/ABL*	-	-	Diagnosis during pregnancy.
Kramer et al, 2007 [31]	CML	*BCR/ABL*	MF	*JAK2*	*JAK2* positive tested in deferred in first sample.
Bornhauser et al, 2007 [8]	MF	-	-	*BCR/ABL JAK2*	*BCR/ABL* secondary event proved by progenitor colonies analysis.
Campiotti et al, 2009 [32]	CML	*BCR/ABL* and *JAK2*	-	-	*JAK2* and *BCR/ABL* controlled with TKI.
Pastore et al, 2013 [33]	CML	*BCR/ABL*	TE	*JAK2*	*JAK2* positive tested in deferred in first sample.
Cambier et al, 2008 [34]	PV	*BCR/ABL* and *JAK2*	-	-	Two clones proved by progenitor colonies analysis.
	CML				
Conchon et al, 2008 [35]	MF	*BCR/ABL* and *JAK2*	-	-	*JAK2* positive when *BCR/ABL* controlled with TKI.
	CML				
Inami et al, 2007 [36]	CML[a]	*BCR/ABL*	PV	*JAK2*	*JAK2* positive tested in deferred in first sample.
Gattenlohner et al, 2009 [37]	CML	*BCR/ABL*	MDS/MPN	*JAK2*	*JAK2* positive since the beginning.

[a]Additional high WBC/thrombocytosis/erythrocytosis. [b]Bone marrow findings of other MPN. WBC: white blood cell; PV: polycythemia vera; PMF: primary myelofibrosis; ET: essential thrombocytosis; CML: chronic myelogenous leukemia; TKI: tyrosine kinase inhibitor; MPN: myeloproliferative neoplasm; MDS: myelodysplastic syndrome; CMR: Complete molecular response.

There is no enough information about which patients harbor both genetic mutations or will develop a second myeloproliferative disease, but at least those who have mixed phenotype or change phenotype and/or bone marrow histopathology are candidates for molecular testing. Recent reports of the concomitance of *BCR-ABL1* and *CALR* in patients with CML and PMF suggest testing *CALR* in *JAK2*-negative patients [44].

Management of these cases could be complicated, especially if two phenotypes are expressed, but CML treatment with TKIs and Phi-MPN control with hydroxyurea and/or phlebotomies in case of PV in association with ASA has been used, like in our patient. Ruxolitinib and TKIs, either given together or in alternating schedule, have been successfully used with no major adverse events [5, 43].

In conclusion, we described a patient with *JAK2*-PV who developed a *BCR-ABL1* CML, but with absence of *JAK2*-V617F at the time of switching. Then PV phenotype and *JAK2* mutation reappeared during CML treatment with TKI. These could be a result of two clones with clonal predominance.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

Mariana Lorenzo is the manuscript author; Sofia Grille and Mariana Stevenazzi are the reviewers.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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