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-ABL1 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 emergence 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-ABL1 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.

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. Cyto genetic 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 assess 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 V617F 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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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].

**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] | PVa JAK2         | CML                      | Add BCR/ABL      | Two clones by cytogenetics.     |
| Hummel et al, 2012 [6]   | ET JAK2          | MF                       | Add BCR/ABL      | BCR/ABL controlled with TKI.    |
| Zhou et al, 2015 [5]    | PV JAK2          | CML                      | Add BCR/ABL      | Two clones by progenitor colonies genotyping. Treatment: dasatinib and ruxolitinib. |
| Swaminathan et al, 2018 [11] | PV JAK2 exon12b | CML                      | Add BCR/ABL (b3a3) | BCR/ABL controlled with TKI.    |
| Ursuleac et al, 2013 [12] | PV JAK2         | CML                      | Add BCR/ABL      | BCR/ABL controlled with TKI.    |
| Iallades et al, 2008 [13] | PMF JAK2       | CML                      | Add BCR/ABL      | BCR/ABL absent in first sample. BCR/ABL controlled with TKI. Persistent JAK2 with same ratio. |
| Pingali et al, 2009 [14] | PV JAK2          | CML                      | Add BCR/ABL      | PV-JAK2 re-emerge when BCR/ABL controlled.                                    |
| Bocchia et al, 2007 [7]  | PV t(9;18)       | CML                      | Add BCR/ABL      | 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. |
| Mirza et al, 2007 [16]   | PV JAK2          | CML                      | Add BCR/ABL      | -                                                                             |
| Hussein et al, 2008 [17] | PV JAK2, BCR/ABL | CML                      | Add BCR/ABL      | BCR/ABL controlled with TKI. Blast crisis of JAK2 clone.                     |

Additional high WBC/thrombocytosis/erythrocytosis. bIn-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.
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 coexistence 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 ASXL1/2, IDH2, SRSF2, and GNAS at different frequencies (1-47%). Some patients harbored oncogenic mutations in K/RAS, 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 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. |
| Pagnan et al, 2016 [19] | CML | BCR/ABL | ET | JAK2 | BCR/ABL controlled with TKI. |
| Hussein et al, 2008 [17] | CML | BCR/ABL | MF | Add JAK2 | - |
| | | | | Add JAK2 | BCR/ABL not evaluated. |
| | | | | 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. |
| | | | | 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.
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<sup>a</sup>    | 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<sup>a</sup>    | 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]| Neutrophil leukocytosis, basophilia and thrombocytosis | JAK2 and BCR/ABL | No               | -               | Treated with TKI.                                |
| Park et al, 2013 [29]   | ET                | JAK2 and BCR/ABL         | None             | -               | Poor response with hydroxyurea.                  |
| 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.|
| Conchon et al, 2008 [35] | MF                | BCR/ABL and JAK2         | -                | -               | JAK2 positive when BCR/ABL controlled with TKI.  |
| Inami et al, 2007 [36]  | CML<sup>a</sup>   | 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.               |

<sup>a</sup>Additional high WBC/thrombocytosis/erythrocytosis. <sup>b</sup>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 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 Ph+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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