Case Report

Transformation of an Unclassified Myeloproliferative Neoplasm with a Rare BCR-JAK2 Fusion Transcript Resulting from the Translocation (9;22)(p24;q11)

A. N. Chamseddine,1,2 P. Etancelin,3 D. Penther,3,4 F. Parmentier,3,4 C. Kuadjovi,3 V. Camus,1,2 N. Contentin,1,2 P. Lenain,1,2 C. Bastard,3,4 H. Tilly,1,2,4 and F. Jardin1,2,4

1Department of Clinical Hematology, Henri Becquerel Cancer Center, 1 rue d’Amiens, 76038 Rouen, France
2Blood and Marrow Transplant Unit, Henri Becquerel Cancer Center, 1 rue d’Amiens, 76038 Rouen, France
3Molecular and Genetic Laboratory Department, Henri Becquerel Cancer Center, 1 rue d’Amiens, 76038 Rouen, France
4INSERM U918 Unit, Henri Becquerel Cancer Center, 1 rue d’Amiens, 76038 Rouen, France

Correspondence should be addressed to A. N. Chamseddine; alichamseddine@hotmail.com and P. Etancelin; pascaline.etancelin@chb.unicancer.fr

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1. Introduction

Some myeloproliferative neoplasms (MPNs) are Philadelphia- (Ph-) negative, lacking the reciprocal t(9;22)(q34;q11) and its resultant BCR-ABL1 fusion gene. Currently, the most frequent genomic abnormality observed in Ph-negative MPN is a dominant gain-of-function V617F mutation in the JH2 kinase-like domain of JAK2 [1]. However, there are rare additional mechanisms described in Ph-negative MPNs that activate JAK2, such as chromosomal translocations that cause constitutive dimerization through the replacement of amino terminal sequences with a fusion partner [2, 3]. Indeed six different fusion partners have been associated with JAK2 (RPN1, SSBP2, PAX5, PCMI, BCR, and ETV6).

Here, we report a rare case of unclassified MPN (MPN-U) with a t(9;22)(p24;q11) leading to a 5’ BCR/3’ JAK2 fusion gene producing a fusion transcript that juxtaposed BCR exon 13 and JAK2 exon 17 and subsequently rapidly transformed into a myeloid granulocytic sarcoma. We also describe, 35 months after diagnosis and ~24 months after ASCT, a prolonged and sustained complete clinical, hematologic, and cytogenetic remission after undergoing allogeneic stem cell transplantation (ASCT).

2. Case Presentation

We report a case of a 49-year-old man with no significant medical history. The patient was referred to our center in
October 2011. The blood count was abnormal with anemia (Hb 11.2 g/dL) and a platelet count of 78000/mm³. The white blood cell count was 11500/mm³ with 30% lymphocytes, 2% monocytes, 2% eosinophils, 0% basophils, 29% neutrophils, and 37% promyelocytes, myelocytes, and metamyelocytes. Clinical examination was unremarkable. The bone marrow aspiration and biopsy associated with initial molecular blood and medullary analyses led to diagnose an MPN-U. It did not reveal any BCR-ABL1 rearrangement neither V617F JAK2 mutation. In February 2012, the patient presented to the emergency room with a sudden onset of pyramidal tract deficiency syndrome and with an increase of leukocytosis and blood myeloid precursors. The MRI scan revealed a thoracic spinal epidural compression extending from T4 to T10. Emergent laminectomy was done. Histological analysis was performed on the laminectomy specimen and demonstrated the presence of a granulocytic (myeloid) sarcoma. Radiation therapy was then performed. Cytogenetic examination of the bone marrow aspiration of the patient was performed on two unstimulated short-term cultures (24 hrs and 48 hrs). The karyotype was obtained by conventional R-banding analysis [4]. Chromosome analysis (Figure 1) showed t(9;22)(p24;q11) as the sole abnormality in 60% of the analyzed metaphases (12/20). In 10% of the analyzed metaphases (2/20), it showed the latter translocation in addition to der(22) t(9;22)(q24;q11). The last 30% of the analyzed metaphases (6/20) were normal. Mutations of exons 12, 13, and 14 and, in particular, the V617F JAK2 gene mutation were not found. Considering the t(9;22)(p24;q11), that the exons 12, 13, and 14 and the V617F JAK2 mutations were absent, and that JAK2 had previously been shown to fuse with BCR in MPN-like patients, the best fusion gene candidates were JAK2 in 9p24 and BCR in 22q11. 

FISH analysis (Figure 2) using dual fusion probes for BCR (22q11.2) and ABL1 (9q34) regions (LSI BCR/ABL ES Dual Color Translocation Probe, Abbott Molecular; Vysis, Des Plaines, IL, USA) excluded the BCR-ABL1 fusion and showed an extra signal of the BCR probe, suggestive of an extra chromosome 22 or additional chromosome material containing the 22q11.2 region: two intense green signals were on the normal chr22 (green arrows, BCR probe) and one reduced intensity green signal was localized on the derivative chr22 and on the short arm of derivative chr9 (dotted green arrow, telomeric part of the BCR probe). Notice that one of the derivative chromosome signals was too feint to be seen in some nuclei.
(Life Technologies, Carlsbad, CA, USA) identified an in-frame fusion of the last nucleotide of BCR exon 13 with the first nucleotide of JAK2 exon 17 (Figure 3). There was no loss or insertion of a base at these breakpoints.

To follow up the minimal residual disease, a specific primer-probe assay was designed. Real time quantitative PCR (QPCR) using TaqMan chemistry was performed on an Applied 7500 (Life Technologies, Carlsbad, CA, USA) with the following sequences: forward primer 5'-GCT GAC CAA CTC GTG TGT GAA-3', reverse primer 5'-TCA GGT GGT ACC CAT GGT ATT CT-3' and the probe FAM 5'-CAG CAT TCC GCT GAC CAT CAA TAA GGA-3'. QPCR expression levels of BCR-JAK2 were carried out relative to the expression of the housekeeping gene ABL1. Molecular monitoring was able to detect low levels of disease. Hence, the assay was >4 logs more sensitive than conventional cytogenetic, detecting one copy of BCR-JAK2 to 10000 copies of ABL1 (0.0001%) and allowing us to follow up the effectiveness of treatment. The patient underwent acute myeloid leukemia-like chemotherapy induction and consolidation achieving a chronic phase in May 2012. An ASCT from a matched human leukocyte antigen- (HLA-) unrelated donor (MUD) was then undertaken in August 2012 with a TBI-Endoxan regimen conditioning and without any Graft-versus-host disease complications. The QPCR follow-up of BCR-JAK2 expression in both the bone marrow and peripheral blood mononuclear cells showed complete hematological and molecular (<0.0001%) remission 3 months later. With 35-month follow-up, the patient remains alive without detectable BCR-JAK2 transcript levels in the blood and no transplant-related complications (Figure 4).

3. Discussion

We have described the presence of a BCR-JAK2 fusion gene in a patient with a rapid blast evolution. This fusion gene is the result of a reciprocal translocation between chr9 and chr22, implying the possible occurrence of a double break on chr9. A fragment of the 3’ end of exon 17 of the JAK2 on chr9 translocated to exon 13 of chr22 in the proper orientation to generate an in-frame fusion transcript with the 5’ end of the BCR gene. The resultant encoded 1330-amino-acid chimeric protein contained the N-terminal coiled-coil dimerization domain of BCR and the C-terminal tyrosine kinase domain JH2 of JAK2. The constitutive activation of this chimeric protein is mediated by oligomerization through the coiled-coil domain of BCR and by disruption of the autoinhibitory role of the inhibitory regions (IR) of the pseudo-kinase domain JH2 of JAK2. In fact, there are three inhibitory regions (IR1, -2, and -3) within JH2. IR3, at the C terminus of JH2, directly inhibits JH1. IR2, in the C-terminal lobe of JH2, and IR1, extending from the N-terminal to the C-terminal lobe, enhance the IR3-mediated inhibition of JH1. Hence, the disruption of IR by mutation, deletion, or translocation increases basal JAK2 activity. Consequently, the BCR-JAK2 chimeric protein is entirely or partially deprived of IR1, which may result in the upregulation of JAK2 activity [5]. Preclinical studies implied a possible role of c-ABL1 in Jak2 activation in various Ph-negative myeloid malignancies [6] and demonstrated that the BCR-JAK2 fusion gene induces STAT5 activation and inhibits BCRxL gene expression, thereby promoting tumorigenic properties and increasing cell survival [7].

It was difficult to define the best therapy. JAK2 inhibitors alone or in combination with chemotherapy may not be effective against the BCR-JAK2 fusion gene malignancies [7, 8]. Compared with JAK2 mutations, JAK2 fusions are probably associated with more aggressive diseases such as

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**Figure 3:** Mechanism of BCR-JAK2 fusion and breakpoints direct sequencing. Sanger sequencing alignment of the RT-PCR product revealed a break at nucleotide 3458 of exon 13 of BCR (nucleotides highlighted in red) and at nucleotide 1 of exon 17 of JAK2 (nucleotides highlighted in blue). Amino acids of the respective fusion gene BCR-JAK2 reveal a new valine residue (V) that has been created at the fusion junction.

**Figure 4:** Quantitative real time PCR expression levels of BCR-JAK2 follow-up. BCR-JAK2 follow-up carried out relative to the expression of the housekeeping gene ABL1, in the bone marrow and the peripheral blood, after allogeneic stem-cell transplantation (black arrow). It revealed one of the longest sustained complete hematologic and cytogenetic remissions at 35 months of follow-up in a BCR-JAK2 fusion MPN-U.
Table 1: Characteristics of cases reported in the literature with BCR-JAK2 fusion gene.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Translocation</th>
<th>Isoform</th>
<th>Clinical presentation</th>
<th>Treatment</th>
<th>Follow-up (FU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griesinger et al. [11]</td>
<td>2005</td>
<td>63</td>
<td>F</td>
<td>t(9;22) (p24;q11.2)</td>
<td>BCR exon 1 fused to JAK2 exon 19</td>
<td>aCML</td>
<td>Hy; Cy; Mit</td>
<td>Death from blast crisis</td>
</tr>
<tr>
<td>Cirmena et al. [12]</td>
<td>2008</td>
<td>67</td>
<td>F</td>
<td>t(9;22) (p24;q11)</td>
<td>BCR exon 14 fused to JAK2 exon 11</td>
<td>AML</td>
<td>HD + ASCT (MSD)</td>
<td>Death from disease relapse</td>
</tr>
<tr>
<td>Lane et al. [13]</td>
<td>2008</td>
<td>44</td>
<td>M</td>
<td>t(9;22) (p24;q11.2)</td>
<td>BCR exon 1 fused to JAK2 exon 17</td>
<td>aCML</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Elmagar et al. [14]</td>
<td>2012</td>
<td>84</td>
<td>M</td>
<td>t(9;22) (p24;q11.2)</td>
<td>BCR exon 1 fused to JAK2 exon 19</td>
<td>aCML</td>
<td>Hy; IM</td>
<td>ND</td>
</tr>
<tr>
<td>Tirado et al. [15]</td>
<td>2010</td>
<td>14</td>
<td>M</td>
<td>t(9;22) (p24;q11.2)</td>
<td>ND</td>
<td>ALL</td>
<td>Polychemotherapy, ASCT (MSD)</td>
<td>CHR at 6-month FU</td>
</tr>
<tr>
<td>Bellesso et al. [16]</td>
<td>2013</td>
<td>54</td>
<td>M</td>
<td>t(9;22) (p24;q11.2)</td>
<td>ND</td>
<td>aCML</td>
<td>Hy + INF α</td>
<td>Death from aGVHD</td>
</tr>
<tr>
<td>Xu et al. [17]</td>
<td>2013</td>
<td>28</td>
<td>M</td>
<td>ins(22;9) (q11p13p24)</td>
<td>BCR exon 1 fused to JAK2 exon 19</td>
<td>aCML</td>
<td>IM, DAS + Hy, ASCT (MSD)</td>
<td>CHR at 27-month FU</td>
</tr>
<tr>
<td>Impera et al. [18]</td>
<td>2011</td>
<td>84</td>
<td>M</td>
<td>t(9;22) (p24;q11.2)</td>
<td>BCR exon 1 fused to JAK2 exon 15</td>
<td>MPN-U</td>
<td>IM, DAS, INF α</td>
<td>CHR at 21-month FU</td>
</tr>
<tr>
<td>Schwaab et al. [8]</td>
<td>2015</td>
<td>ND</td>
<td>M</td>
<td>t(9;18) (p24;q12)*</td>
<td>BCR exon 1 fused to JAK2 exon 17</td>
<td>aCML</td>
<td>Jak2 inh</td>
<td>Relapse at 18-month FU</td>
</tr>
<tr>
<td>Cuesta-Dominguez et al. [7]</td>
<td>2012</td>
<td>58</td>
<td>M</td>
<td>49, XY, +X, +2, +4, +9, +11, +19, add(19)</td>
<td>BCR exon 1 fused to JAK2 exon 15</td>
<td>ALL</td>
<td>High-risk ALL protocol, ASCT, INF α</td>
<td>&gt;6 years</td>
</tr>
<tr>
<td>Roberts et al. [19]</td>
<td>2012</td>
<td>2.7</td>
<td>M</td>
<td>t(3;22) (p12;q11;2;p24)</td>
<td>BCR exon 1 fused to JAK2 exon 15</td>
<td>ALL</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Angelova et al. [20]</td>
<td>2011</td>
<td>53</td>
<td>M</td>
<td>t(9;22) (p24;q11)</td>
<td>ND</td>
<td>MPN-U</td>
<td>No treatment</td>
<td>Death from blast crisis</td>
</tr>
</tbody>
</table>

Present case 2011 49 M t(9;22) (p24;q11) BCR exon 13 fused to JAK2 exon 17 MPN-U/GS 3 + 7, ASCT (MUD) CMR at 35-month FU

F: female; M: male; aCML: atypical chronic myeloid leukemia; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; MPN-U: unclassified myeloproliferative neoplasm; GS: granulocytic sarcoma; Hy: hydroxyurea; Cy: cytarabine; Mit: mitoxantrone; HD: High-dose chemotherapy; ASCT: allogeneic stem cell transplantation; ND: not described; MSD: matched sibling donor; MUD: matched unrelated donor; IM: imatinib; DAS: dasatinib; Jak2 inh: Jak2/JAK2 inhibitor ruxolitinib; aGVHD: acute graft-versus-host disease; CHR: complete hematological response; CMR: complete molecular remission. *The RNA sequencing indicated the presence of a BCR-JAK2 fusion gene. The BCR-JAK2 fusion was subsequently confirmed by RT-PCR and PCR from genomic DNA. BCR-JAK2 in this case is therefore likely to be the result of a small insertion of BCR into the JAK2 locus on the der(18).

4. Conclusion

We described a rare Ph-negative case of MPN with a BCR-JAK2 transcript and a reciprocal t(9;22)(q34;q11) that was detected juxtaposing BCR exon 13 and JAK2 exon 17. This rare entity underlies often an aggressive clinical course with rapid progression to blast phase within the first 2 years after diagnosis (Table 1). To the best of our knowledge, this is the thirteenth case reported worldwide. Furthermore we report here the first described isoform fusion transcript juxtaposing BCR exon 13 and JAK2 exon 17. It revealed one of the longest sustained complete clinical, hematologic and cytogenetic remissions in a BCR-JAK2 fusion MPN-U. These rare BCR-JAK2 fusions suggest common pathways between JAK2 activation and the natural history of lympho/myeloproliferative hematologic malignancies. One should take into consideration JAK2 fusions when investigating Ph-negative MPN patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.
References


