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Acute promyelocytic leukemia co-existing with JAK2 V617F positive myeloproliferative neoplasm: a case report

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Abstract: The V617F mutation of Janus-associated kinase 2 (JAK2) is commonly seen in myeloproliferative neoplasms (MPN). Transformation of JAK2 positive MPNs to acute leukemia has been reported. We here report a case of acute promyelocytic leukemia which was later confirmed to have a co-existing JAK2 V617F positive MPN. In addition, the patient was found to have FLT3-TKD mutation, which, together with PML/RARa, could play a role in the MPN transformation to APL.

Keywords: Acute myelogenous leukemia (APL); myeloproliferative neoplasms (MPN); PML/RARa; Janus-associated kinase 2 (JAK2)

Introduction

The Janus-associated kinase 2 (JAK2) V617F mutation is detected in over 95% of patients with polycythemia vera (PV) and in about 50% of cases of essential thrombocythemia (ET) and primary myelofibrosis (PMF) (1-3). Transformation of myeloproliferative neoplasms (MPN) into acute myelogenous leukemia (AML) is a well-studied and reported phenomenon (2,4,5). Both transformation of ET to AML (6,7), as well as a JAK2 V617F mutation in de novo AML are very rare (8). Amongst all subtypes of AML originating from MPN, acute promyelocytic leukemia (APL) is extremely rare. In the English literature there have been only 9 such cases reported to date (1,7,9-14). In the same literature search we have not found any case of APL with concurrent diagnosis of MPN. Herein, we present the case of a young male with new onset APL and JAK2 positive MPN.

Case presentation

A young male (<40 years old) was referred to our hospital for gingival bleeding, pancytopenia and fever. The patient had previously presented with fever, sore throat, and tonsillar enlargement and had been treated empirically for pharyngitis with antibiotics. He also reported gingival bleeding and several episodes of epistaxis as well as dark stools in the few weeks preceding admission. Physical examination was significant for gingival bleeding and enlarged tonsils. Abdominal ultrasonography revealed splenomegaly with longest diameter of 14.3 cm. A complete blood count on admission was remarkable for a white blood count (WBC) of 2.1×10⁹/L, hemoglobin (Hgb) of 9.8 g/dL, and platelet count of 11×10⁹/L. The peripheral blood smear revealed 10% blasts and 42% promyelocytes. Bone marrow biopsy done on admission showed sheets of immature atypical myeloid cells, comprising more than 90% of the marrow cellularity. Those cells showed moderate to abundant cytoplasm, irregular nuclei (some of which were indented or bilobed), smudged chromatin and prominent nucleoli. Maturing myeloid elements including segmented neutrophils were not seen; megakaryocytes and erythroid precursors were markedly decreased. No reticulin fibrosis...
was seen. Karyotyping revealed t(15;17)(q24;q21) in all 20 metaphases analyzed. Molecular studies were positive for PML/RARA, FLT3 TKD and JAK2 V617F mutations (Table 1). Additional molecular studies for genes associated with MPN, MDS, and AML were negative (Table 2) (15). The patient was immediately started on all-trans retinoic acid (ATRA). Arsenic trioxide (ATO) was added on day 10 according to the reported regimen for clinically low-risk APL (16). The hospital course was complicated by differentiation syndrome with a high WBC (Figure 1A) and pleural and pericardial effusions for which a short course of dexamethasone was given. Surprisingly, a rapid increase in platelet count was observed during count recovery, with values reaching as high as 1,700×10^9/L (Figure 1B). Bone marrow biopsy at this point showed increased reticulin fibrosis, a left shift in myeloid lineage cells with dysplastic and an increased number of megakaryocytes. The morphology overall was reported to be consistent with MPN (PMF/ET). A FISH panel for myelodysplasia was negative and a chromosome study revealed a normal karyotype: 46 XY. Molecular studies were negative for the FLT3 TKD, but remained positive for the JAK2 V617F mutation. The PML/RARA was still detectable by PCR post-induction therapy with ATRA and ATO. The patient was started on consolidation chemotherapy with cytarabine and idarubicin for a total of two cycles. He continued ATRA throughout consolidation. The patient became PCR negative for PML/RARA after completion of two cycles of consolidation chemotherapy, however the JAK2 mutation remained positive (Table 1). At that point the patient had a normal WBC but a high platelet count, with platelets as high as 949×10^9/L. Since the patient presented with leukemia transformation, peak counts of platelets were higher than 1,500×10^9/L, and bone marrow biopsy revealed dysplastic megakaryocytes as well as reticulin fibrosis, we believe that this patient might more likely have PMF than ET, and had high risk PMF/ET, even though he was younger than 40 (17). Therefore, low dose aspirin (81 mg) and hydroxyurea 1,000 mg daily were given for the PMF/ET. Interferon and ruxolitinib were discussed but clinically impractical at the time. The patient was also placed on maintenance treatment for APL with ATRA every 3 months.

**Discussion**

Both ET and PV may progress to myelofibrosis, and all MPNs may evolve into AML. The most common to transform in this way is PMF, occurring in about 15%
of cases (1,18). Such transformation happens even less frequently in patients with ET (6,7). In the majority of PV cases there are clones homozygous for \( \text{JAK2} \) \( V617F \) mutations, which are rarely found in ET (19,20). \( \text{JAK2} \) \( V617F \) mutations are very rare in de novo AML (8).

Amongst all subtypes of AML originating from MPNs, APL has been reported the least frequently. Only 2 of the early case reports had molecularly documented \( \text{PML/RARa} \) mutation (7,12) (Table 3). The \( \text{JAK2} \) \( V617F \) mutation status was unknown in 8 of the cases (1), as they were reported prior to the 2005 discovery of the \( \text{JAK2} \) mutation (21,22). The association between APL and MPNs was thought to be due to promyelocytic blastic crisis of MPN, APL secondary to cytoreductive therapy, and de novo APL (7). Braun et al. recently reported a case of APL with \( \text{PML/RARa} \) and \( \text{JAK2} \) \( V617F \) mutation (1). The authors postulated that the inflammatory response resulting from the chemokine release (CLL-2 and IL-8) from ATRA-treated APL cells was accentuated by inflammatory downstream signalling from the \( \text{JAK-2} \) mutation and that this led to severe differentiation syndrome. JAK-2 inhibition by ruxolitinib in the in vitro studies on NB-4 APL cells treated with ATRA did not affect CLL-2 and IL-8 levels, supporting the importance of \( \text{JAK2} \) in downstream activation as previously described (1,2). However, the role of JAK-2 inhibition in the management of differentiation syndrome has not been

**Table 3** Case reports on transformation of myeloproliferative neoplasms to acute promyelocytic leukemia

<table>
<thead>
<tr>
<th>Underlying MPN</th>
<th>Prior treatment</th>
<th>Years since diagnosis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET→PMF</td>
<td>Hydroxyurea, aspirin, ruxolitinib</td>
<td>16.0→2.0</td>
<td>(1)</td>
</tr>
<tr>
<td>ET</td>
<td>None</td>
<td>9.3</td>
<td>(7)</td>
</tr>
<tr>
<td>ET</td>
<td>Uracil, mustard</td>
<td>3.9</td>
<td>(13)</td>
</tr>
<tr>
<td>ET</td>
<td>Busulfan</td>
<td>5.2</td>
<td>(14)</td>
</tr>
<tr>
<td>ET</td>
<td>Hydroxyurea</td>
<td>1.7</td>
<td>(11)</td>
</tr>
<tr>
<td>ET</td>
<td>Hydroxyurea, warfarin</td>
<td>4.0</td>
<td>(12)</td>
</tr>
<tr>
<td>PV</td>
<td>Phlebotomy</td>
<td>2.0</td>
<td>(12)</td>
</tr>
<tr>
<td>PV</td>
<td>Phlebotomy</td>
<td>9.3</td>
<td>(10)</td>
</tr>
<tr>
<td>PMF</td>
<td>Hydroxyurea</td>
<td>6.8</td>
<td>(9)</td>
</tr>
</tbody>
</table>

MPN, myeloproliferative neoplasm; ET, essential thrombocythemia; PMF, primary myelofibrosis; PV, polycythemia vera.

**Figure 1** White blood counts and platelet counts during induction and consolidation chemotherapy. (A) The high WBC was observed during ATRA induction therapy. (B) Rapid increases in platelet count were seen during the recovery phase post chemotherapy.
clinically proven. In the patient presented by Braun et al, the diagnosis of MPN predated the diagnosis of APL. Our report presents for the first time a case of APL diagnosed concurrently with a MPN. It is highly possible that the APL clone remained dominant and masked the phenotype of MPN at the time of diagnosis. The MPN clone became dominant after the APL clone was suppressed. It remains unknown whether the APL clone arose from the MPN clone since we were not able to perform single cell genome analysis prior to the initiation of the APL therapy like in those cases reported in the literature (23-25). Since splenomegaly and FLT3-TKD were also present at the time of diagnosis, we hypothesize that the JAK2 V617F mutated MPN clone (likely PMF) was present first and that additional mutations like FLT3 and PML/RARA took place later and then led to the development of APL (26-32). It is of interest to point out that the case of APL transformed from a known diagnosis of ET with fibrosis also was found to have FLT3-TKD (D835 mutation) in addition to JAK2 V617F mutation (1). These two cases of APL transformation from ET /PMF containing FLT3-TKD mutation make it likely that FLT3-TKD mutation plays a driver role for this transformation process involving PML/RARA.

Conclusions

This is the first case with molecular data showing co-existence of PML/RARA, FLT3-TKD, and a JAK2 V617F mutation at the time of APL diagnosis. We hypothesize that the JAK2 V617F mutated MPN clone was present first, and that additional mutations like FLT3 and PML/RARA took place later and then led to the development of APL.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Unfortunately due to special circumstance in this case, consent could not be obtained for publication. The authors ensured that there was no identifiable information in the case (i.e., no race and age were reported). We believe this case has scientific value and is important for clinical literature.

References


