Progression of a JAK2 V617F-Positive Essential Thrombocythemia (ET) to a JAK2 V617F-Negative Post-ET Myelofibrosis in Accelerated Phase with Chronic Myelomonocytic Leukemia-like Monocytosis

Anna S. Nam, MD & Wayne Tam, MD, PhD

Division of Hematopathology, Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY.

Society of Hematopathology 2017 Workshop
Clinical History

• 69 year old man with a history of multiple sclerosis, tx interferon β1a
• Found to have thrombocytosis in 2005
• CBC:

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<thead>
<tr>
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<th>Value</th>
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<tbody>
<tr>
<td>WBC</td>
<td>8.6K/uL</td>
<td>Neutrophils</td>
<td>67%</td>
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<tr>
<td>Hgb</td>
<td>15.3 g/dL</td>
<td>Lymphocytes</td>
<td>23%</td>
</tr>
<tr>
<td>Hct</td>
<td>44.5%</td>
<td>Monocytes</td>
<td>7%</td>
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<tr>
<td>MCV</td>
<td>89.5 fL</td>
<td>Eosinophils</td>
<td>2%</td>
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<tr>
<td>Platelets</td>
<td>903K/uL</td>
<td>Basophils</td>
<td>1%</td>
</tr>
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Ancillary studies

• Karyotype 46,XY[20]

• NGS of myeloid panel of 2006 PB (retrospective):
  • JAK2 V617F VAF 30%
  • ASXL1 Q877* VAF 18%
Diagnosis

Myeloproliferative neoplasm, most consistent with essential thrombocythemia
2005-2014

• Managed with anagrelide
• Asymptomatic, no splenomegaly, normal LDH, no leukoerythroblastosis

• CBC 2014:

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<tr>
<td>WBC</td>
<td>15.1K/uL</td>
<td>Neutrophils</td>
<td>53%</td>
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<tr>
<td>Hgb</td>
<td>13.0 g/dL</td>
<td>Bands</td>
<td>4%</td>
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<tr>
<td>Hct</td>
<td>39.6%</td>
<td>Lymphocytes</td>
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<tr>
<td>MCV</td>
<td>89.5 fL</td>
<td>Monocytes</td>
<td>11%</td>
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<tr>
<td>Platelets</td>
<td>366K/uL</td>
<td>Eosinophils</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Basophils</td>
<td>4%</td>
</tr>
</tbody>
</table>
Ancillary studies

- NGS of myeloid panel (PB):
  - JAK2 V617F VAF 12%
  - ASXL1 Q877* VAF 12%
  - ASXL1 G646fs VAF 21%
  - PHF6 G10fs VAF 30%
  - TET2 V1999A VAF 2%
Diagnosis

Essential thrombocythemia with increased fibrosis, in progression to post-ET myelofibrosis.
2014-2017

- Managed with hydroxyurea
- Progressive leukocytosis
- Splenomegaly, elevated LDH, leukoerythroblastosis

**CBC 2017:**

<table>
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<tr>
<td>Hgb</td>
<td>9.4 g/dL</td>
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<tr>
<td>Hct</td>
<td>29.8%</td>
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<tr>
<td>MCV</td>
<td>95.4 fL</td>
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<tr>
<td>Platelets</td>
<td>203K/uL</td>
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</table>

| Neutrophils   | 14% |
| Bands         | 10% |
| Metamyelo     | 5%  |
| Myelocyte     | 6%  |
| Promyelocyte  | 2%  |
| Blasts        | 5%  |

| Lymphocytes   | 18% |
| Monocytes     | 24% |
| Eosinophils   | 5%  |
| Basophils     | 11% |

[BLASTS 5%]
Summary of Bone Marrow Findings

- Increased blasts (12%) and monocytes (16%) on aspicular bone marrow smear
- Increased M:E ratio (5.5)

Ancillary studies

- Karyotype (PB): 45,XY,-7[14]
- NGS of myeloid panel (PB):
  - **ASXL1** G646fs  VAF 30%
  - **PHF6** G10fs  VAF 74%
  - **CBL** Y371H  VAF 2%
  - **KDM6A** S900P  VAF 5%
Final Panel Diagnosis

Post-essential thrombocythemia myelofibrosis in accelerated phase with chronic myelomonocytic leukemia-like monocytosis
Summary

**JAK2** V617F VAF 30%
**ASXL1** Q877* VAF 18%
**ASXL1** G646fs VAF 21%
**PHF6** G10fs VAF 30%
**TET2** V1999A VAF 2%

2005
- **ET**

2014
- **ET in progression to post-ET MF**

2017
- **Post-ET MF in AP with CMML-like monocytosis**

**CBL** Y371H VAF 2%
**KDM6A** S900P VAF 5%
**Monosomy 7**
CMML-like progression of PMF indicates an accelerated phase of disease

• After development of monocytosis, death in 5 of 10 patients and transfusion dependence in 2 of 10.

• Monocytosis associated with leukocytosis, anemia, decreased platelet count, circulating blasts

• No change in JAK2 mutational status or cytogenetic evolution

Boiocchi et al., Mod Pathol 26(2):204-12, 2013.
Leukemic progression of MPNs frequently associated with loss of $JAK2$ mutation

- In 12 of 21 patients with $JAK2$ V617F+ MPN that progressed to blast phase, $JAK2$ V617F was negative in the acute leukemia.

Role of therapy on selecting divergent clone

• Uncertain how hydroxyurea or anagrelide may have played a role in selecting clone

• Hydroxyurea has been shown to cause genomic instability

Conclusions

• This case demonstrates the evolution of an MPN from ET (2005), to ET in progression to post-ET MF (2014), and finally to post-ET MF, in accelerated phase, with CMML-like features (2017).

• The molecular findings suggest that disease progression from ET to accelerated phase of post-ET MF in this case may have occurred via clonal selection and expansion of a divergent or separate clone rather than a simple direct evolution.
Thank you!
Final Panel Diagnosis

Post-essential thrombocythemia myelofibrosis in accelerated phase with chronic myelomonocytic leukemia-like monocytosis