Case SH2017-238

Leonardo Boiocchi, MD

September 8, 2017
SH/EAHP Workshop
Chicago, IL
Clinical history

- 64 year-old man
- Incidental thrombocytosis noted on annual physical

CBC at presentation:
- WBC 11.49 x 10^9/L (normal range: 4 - 10 x 10^9/L)
- HGB 12.7 g/L (normal range: 11.5 - 16.4 g/L)
- HCT 40.0%; MCV 81.0 fL
- **PLT 1106 x 10^9/L**;  
- Normal differential

- No splenomegaly
Bone marrow aspirate:

- Normal maturation of myeloid and erythroid lineage
- No dysplasia
Cytogenetics

- Normal karyotype, 46,XY[20]

Molecular results

Next generation sequencing (NGS)-based assay (54 gene panel, Trusight Myeloid Sequencing Panel, Illumina)

- JAK2 V617F (allele burden 43%)
- SF3B1 L666A (hot spot mutation; allele burden 46%)
Ring sideroblasts: 18% of all erythroid forms
Diagnostic considerations

• The morphological and molecular features (JAK2+) associated with leukocytosis $\geq 11 \times 10^9$/L fulfill WHO 2016 criteria for the diagnosis of early (pre-fibrotic) primary myelofibrosis

• SF3B1 mutation was associated with numerous RS

• Absence of dysplasia and lack of anemia (Hb<10) excluded MDS/MPN-RS-T
Diagnosis

Proposed Diagnosis:
Myeloproliferative neoplasm consistent with pre-fibrotic primary myelofibrosis (PMF-0), with ring sideroblasts

Panel Diagnosis:
Pre-fibrotic primary myelofibrosis (with ring sideroblasts and SF3B1 mutation)
SF3B1 mutations in MPNs

- Mutations of splicing genes (SF3B1, SRSF2 and U2AF1) are overall rare in MPNs: <10% of cases

- Splicing genes more frequently mutated in PMF > ET > PV (Delic et al.)

- SF3B1 mutations described in 6.5% of PMF cases (Lasho et al.):
  - Clinical features similar between SF3B1-mutated and WT PMF
  - Mutation associated with RS in marrow
  - No prognostic value

Our experience: a joint study between MGH and BWH

151 MPNs patients (2014-2017):
• 54 (36%) PMF
• 6 (4%) of secondary MF (3 post-PV MF, 3 post-ET MF)
• 29 (19%) PV
• 39 (26%) ET
• 23 (15%) MPN-U

SF3B1 mutations in 15 cases (10%):
• 12 (80%) MF
  • 8 PMF (53%)
  • 2 of post-ET MF
  • 2 post-PV MF
• 1 PV (7%)
• 2 MPN-U (13%)

Median allele burden: 34.7% (range: 1.8-54.8%)
Clinico-pathologic features

• Similar morphology to wild-type cases
• SF3B1-mutated cases showed no significant dysplasia and <5% blasts

• WBC, Hgb, platelet count similar in mutated and SF3B1-WT cases (p>0.8 for all)

• 9 SF3B1-mutated cases stained with iron:
  • RS in 5 cases (55%) (median: 17%; range: 8-40% of erythroid precursors)
  • no RS in SF3B1-WT MPN cases (n=36)
Conclusions

- SF3B1 mutations present in approximately 10% of MPNs
- More common in MF cases
- Only morphologic difference with WT MPNs is the presence of RS
- No clinical difference with WT cases
- **Important to exclude MDS/MPN-RS-T**
- 2 out of 4 post-PV/ET cases had very low SF3B1 mutation burden (1.8% and 3.6%): SF3B1 mutation might represent a late sub-clonal event in PV or ET
- All PMF cases showed higher SF3B1 mutation burden: SF3B1 mutation might represent an earlier event in PMF
Acknowledgements

Massachusetts General Hospital:
• Valentina Nardi, MD
• Robert Hasserjian, MD
• Gabriela Hobbs, MD

Brigham and Women’s Hospital:
• Olga Pozdnyakova, MD PhD
• Waihay J Wong, MD PhD
Case SH2017-238

Panel Diagnosis

Pre-fibrotic primary myelofibrosis (with ring sideroblasts and SF3B1 mutation)