Probable Early Myelodysplastic Syndrome

Case Number: SH2017-269

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Clinical History

• 67-year-old man
• PMHx:
  – Sweet’s syndrome & knee pain 6 years ago (prednisone)
  – Progressed to polyarthritis (DMARDs)
  – Developed pulmonary histoplasmosis (prednisone)
  – Mild leukopenia for past 21 mths (MTX)
  – 6 mths ago developed acute pericarditis (colchicine)
• Mild microcytic anemia, neutropenia, & relative monocytosis → BM bx to r/o T-LGL
CBC

- Hgb 12.3 g/dL
- RBC 5.88 x 10^{12}/L
- MCV 69.2 fL ↓
- RDW 18.4% ↑
- WBC 3.3 x 10^9/L ↓
- PLT 172 x 10^9/L

WBC Differential (%)

- Neutrophils: 51 → ANC 1.7 x 10^9/L
- Lymphocytes: 24 → ALC 0.8 x 10^9/L
- Monocytes: 24 → AMC 0.8 x 10^9/L
- Basophils 1
PB Smear

- Rather unremarkable PB smear (A)
- While the majority of the circulating neutrophils were cytologically normal (B & C), occasional hypogranular (D) and Pseudo-Pelger-Hüet (E) neutrophils were present.
BM Aspirate

- Cellular with intact trilineage hematopoiesis
• Unremarkable erythroid maturation
• Majority of the granulocytic maturation unremarkable
• No increase in blasts
However, there were occasional areas with subtle hypogranular neutrophils (arrows) and a rare Pseudo-Pelger-Hüet form was identified (insert)
• Occasional hyperchromatic megakaryocyte
BM Biopsy

- Hypercellular bone marrow biopsy
BM Biopsy Con’t

- Panhyperplasia
- Aside from scattered hyperchromatic, bare megakaryocyte nuclei (arrow), trilineage hematopoiesis was morphologically unremarkable
Flow Cytometry

- Top panel (A) of histograms represents normal HLA-DR/CD13 pattern of expression on blasts (orange population) for reference.

- Bottom panel (B) of histograms reveals abnormal HLA-DR/CD13 pattern of expression on blasts (orange population) from the patient.
Flow Cytometry Con’t

• Top histogram (A) represents normal CD13/CD16 pattern on maturing granulocytes for reference

• Bottom histogram (B) reveals an equivocal CD13/CD16 pattern on maturing granulocytes from the patient
Special Studies

- Iron stain: Absent storage iron. No sideroblasts/ring sideroblasts.
- Butyrate esterase/chloroacetate esterase dual stain: No increase in monocytes. No dual esterase-positive cells.
- IHC: No abnormal infiltrates of CD3-positive T-cells (left) or CD20-positive B-cells (right)
- Conventional chromosome analysis: 46,XY[20]
OncoHeme Next Generation Sequencing

• 4 pathogenic mutations:
  1. **ASXL1**: c.1934dup; p.Gly646Trpfs*12 (36%)
  2. **IDH1**: c.395G>A; p.Arg132His (44%)
  3. **KRAS**: c.182A>G; p.Gln61Arg (41%)
  4. **SRSF2**: c.284C>A; p.Pro95His (44%)

• Final diagnosis: Hypercellular bone marrow with panhyperplasia, slight granulocytic and megakaryocytic atypia, and no increase in blasts. No morphologic features that are diagnostic of a myeloid neoplasm are identified.

- Median VAF was 0.09

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<tr>
<th>Risk of hematologic cancer</th>
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<td>Detectable mutation</td>
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<tr>
<td>VAF ≥0.10</td>
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Similar observations were made by Genovese et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 2014;371(26):2477-2487

<table>
<thead>
<tr>
<th></th>
<th>Traditional ICUS</th>
<th>CHIP</th>
<th>CCUS</th>
<th>Lower Risk MDS</th>
<th>Higher Risk MDS</th>
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<td>−</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Dysplasia</td>
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<tr>
<td>Cytopenias</td>
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<td>−</td>
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<td>BM Blast %</td>
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<td>Overall Risk</td>
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<td>Very Low</td>
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<td>Observations</td>
<td>Obs/BSC/GF IMiD/IST</td>
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<td>HMA/HCST</td>
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Clonal Cytopenias

- Mutations in **spliceosome genes** (*SF3B1, SRSF2, U2AF1, & ZRSR2*):
  - **Highest predictive value, irrespective of co-occurring mutations**
  - Detection of these mutations in patients with unexplained cytopenia should be considered highly predictive of myeloid neoplasm
- **Isolated** mutations in *DNMT3A, TET2, & ASXL1* had a lower predictive value

- Clonal cytopenia had a 14x higher probability of developing a myeloid neoplasm
- 95% 5-yr cumulative probability of developing a myeloid neoplasm if **highly predictive mutation pattern**:
  1. Spliceosome gene mutations
  2. Mutations in *DNMT3A*, *TET2*, or *ASXL1* with comutations in *RUNX1*, *EZH2*, *CBL*, *BCOR*, *NRAS*, *CUX1*, *TP53*, or *IDH1*/*IDH2*

- No significant difference in overall survival & risk of disease progression when comparing:
  - CCUS & highly specific mutation patterns (navy curve)
  - Myeloid neoplasm with myelodysplasia:
    - Without excess blasts (maroon curve)
    - Similar mutation patterns

- Underlying genetic lesions may provide presumptive evidence of MDS even in the absence of definitive morphologic features
Panel Diagnosis for Case Number: SH2017-269

• Clonal cytopenia of undetermined significance