TP53 mutation in a patient with paroxysmal nocturnal hemoglobinuria

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Clinical History

74M in overall good health, found to have anemia and thrombocytopenia

Past Medical History
  ◦ Hypertension

Family History
  ◦ CAD (multiple family members)
  ◦ No malignancies or hematologic disorders

Social History
  ◦ Prior smoker (quit 40 years ago)
  ◦ 1x glass red wine per night
Clinical History

Medications
- Irbesartan (BP)
- Aspirin
- Folate
- Glucosamine
- Fish oil
- Vitamin C

Allergies: NKDA
Clinical History

November 2016 (OSH)
- Routine blood work revealed new onset anemia and thrombocytopenia
- Coombs negative
- Normal iron, B12, folate
- No evidence of kidney disease
- No hypothyroidism
- Flow cytometry: paroxysmal nocturnal hemoglobinuria (per report)
  - 58% granulocytes (loss of GPI)
  - 52% monocytes (loss of GPI)
  - 0.3% red blood cells (type II)
  - 15% red blood cells (type III)
Clinical History

## January 2017
- Asymptomatic
- Labs drawn
- Bone marrow biopsy
- Molecular studies (NGS)

<table>
<thead>
<tr>
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<th>1/6/17</th>
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<tbody>
<tr>
<td>WBC (K/uL)</td>
<td>5.10</td>
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<tr>
<td>Hgb (g/dL)</td>
<td>9.6</td>
</tr>
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<td>HCT (%)</td>
<td>27.4</td>
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<tr>
<td>MCV (fL)</td>
<td>111.4</td>
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<tr>
<td>PLT (K/uL)</td>
<td>96</td>
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<tr>
<td>Retics (%)</td>
<td>6.2</td>
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<tr>
<td>LDH (U/L)</td>
<td>1229</td>
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<td>T-Bili (mg/dL)</td>
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Bone Marrow Biopsy

FINAL DIAGNOSIS:

Moderately hypercellular marrow with maturing trilineage hematopoiesis and slight erythroid hyperplasia.

Note: Diagnostic features of MDS are not recognized and there is no evidence of an aplastic process.
Flow (March 2017)

Granulocytes 82.8%

Monocytes 79.6%

RBC II: 0.6%, III: 16.8%
Additional Testing

Cytogenetics:
- 45,X,-Y[15]/46,XY[5]
- Loss of the Y chromosome is commonly seen in older men and although it may reflect a clonal process, and is not considered sufficient to diagnose MDS in a cytopenic patient

SNaPshot @ MGH (1/12/17)
- **TP53** ENSP00000269305.4:p.Tyr163Cys (ENST00000269305.4:c.488A>G)
- 73% variant allelic frequency
- Subsequent NGS
  - Rapid Heme Panel @ BWH (6/2/2017) – 51% VAF
  - SNaPshot @ MGH (8/8/2017) – 63% VAF
Bone Marrow Biopsy, p53
Patient Follow-Up

Progressive anemia resulting in 4U RBC transfusions in 2017

Started on eculizumab in March
- Marked decrease in LDH, but no response in Hgb/Hct
- Lab evidence of an autoimmune hemolytic anemia (DAT+)

Started on steroids
- Side effects not tolerated

Multiple heme-onc consults
- Increased dose of eculizumab
- Consider EPO
- No clear clinical trajectory for controlling hemolysis/symptoms
Discussion

PNH

- Non-malignant clonal disease of hematopoietic stem cells associated with hemolysis, marrow failure and thrombophilia
- Monogenic disease due to somatic mutation in PIGA (required for synthesis of GPI-anchored proteins)
  - Confers growth advantage
  - Leaves cells susceptible to complement destruction (loss of CD55 and CD59)
  - Hemolytic anemia
Discussion

No PIGA mutation!
- Whole exome sequencing of PNH identified multiple other genes with mutations arising as either subclones of PIGA or prior to PIGA (Shen et al, 2014)
  - Similarities to MDS: clonal hematopoiesis, persistent aberrant stem cell clone

Unexpected *TP53* mutation
- Positive strong IHC staining suggestive that mutation is pathogenic
- Associated with aggressive myeloid neoplasms; concerning for evolution to MDS
- No prior reports of *TP53* mutation in PNH
- Primarily reported as a somatic mutation (lung, breast, ovary, GI)
- One report of germline mutation in pediatric patient with osteosarcoma and family history of malignancies (McIntyre 1994)
Discussion

Further workup

- Given high variant allelic frequency, is the mutation germline?
  - No personal or family history of malignancies
- Is the mutation confined to the PNH clone?
  - Attempt at NGS on PNH+ vs. PNH- populations failed (not enough cells sorted)
Panel Diagnosis

Proposed: Paroxysmal nocturnal hemoglobinuria with a pathogenic TP53 mutation (clonal hematopoiesis of indeterminate potential, CHIP)
Acknowledgements

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