Myeloid neoplasm with del(5q) and SF3B1 and MPL gene mutations

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Memorial Sloan Kettering Cancer Center
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Patient Y.K.

77 year old male

Past Medical History:
Paroxysmal A fib
Diabetes
HTN
HLD
GERD

Social History:
Emigrated from South Korea in 1973
Retired architectural engineer
Former smoker
No exposures

Family History:
No hematologic disease

Medications:
Atorvastatin
Lisinopril-hydrochlorothiazide
Aspirin
Metformin-sitagliptin
Esomeprazole
Multivitamin
Fish oil
Probiotic
Elevated platelets

WBC: 7 k/μL
Hgb: 10.8 g/dL
MCV: 95
Plt: 1,486 k/μL
Neutrophils 55%
Monocytes 9%
Eosinophils 1%
Basophils 1%

Normal splenic U/S

Karyotype: 46XY
FISH: Del(5q31)
Negative: BCR-ABL1, JAK2 V617F, MPL515, CALR

WBC: 10.2 k/μL
Hgb: 8.4 g/dL
Plt: 444 k/μL

Mild fatigue

Lenalidomide

Hypercellular BM
Erythroid dysplasia (>10%)
Increased atypical megs
Ring sideroblasts (>50%)
No reticulin fibrosis
Blasts not increased

WBC: 11.3 k/μL
Hgb: 8.6 g/dL
MCV: 80
Plt: 562 k/μL
ANC: 6.9 k/μL
ALC: 3.3 k/μL
AMC: 0.3 k/μL
AEC: 0.6 k/μL
ABC: 0.1 k/μL

Worsening fatigue

Anagrelide


Lenalidomide

MSKCC for second opinion

46,XY,del(5)(q31q31)[9]/46,XY[11]

Deletion of 5q31 (83% of the cells)

Molecular Analysis

SF3B1
p.K666Q
(c.1996A>C)
VAF 46%

MPL
p.W515S
(c.1544G>C)
VAF 39%
Expert Panel Proposed Diagnosis

Myeloid neoplasm with features of both myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis and myelodysplastic syndrome with isolated del(5q)
MDS with Isolated Del(5q)

- Erythroid hypoplasia
- Hypolobated megs
- Myeloid/erythroid dysplasia uncommon

- Del(5q) + 1 cytogenetic abnormality (except -7 or del(7q))

MDS/MPN-RS-T

- Anemia
- Thrombocytosis
- Hypercellular BM

- Erythroid hyperplasia
- Large, atypical megs
- Dyserythropoiesis + >15% ring sideroblasts
- +/- Myeloid dysplasia

- SF3B1 (~85%)
- JAK2 V617F (~50%), MPL (<10%), CALR exon 9 (<10%)
- ~50% SF3B1 and JAK2 V617F
- Isolated del(5q) excluded
<table>
<thead>
<tr>
<th></th>
<th>MDS with Isolated Del(5q)</th>
<th>MDS/MPN-RS-T</th>
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<tbody>
<tr>
<td>Median age</td>
<td>67</td>
<td>71-75</td>
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<tr>
<td>Median OS</td>
<td>145 mo (<em>WHO, 2008</em>)</td>
<td>76 mo (<em>Broseus et al, 2012</em>)</td>
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<tr>
<td>AML transformation</td>
<td>&lt;10% (<em>WHO, 2008</em>)</td>
<td>1.8/100 patients/year (<em>Broseus et al, 2012</em>)</td>
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<td>2% (<em>Patnaik et al, 2011</em>)</td>
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<tr>
<td>Complications</td>
<td>Transfusion-dependent anemia</td>
<td>Transfusion-dependent anemia</td>
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<td></td>
<td></td>
<td>Thrombosis</td>
</tr>
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<td></td>
<td>- 3.6/100 patients/year (<em>Broseus et al, 2012</em>)</td>
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<td>- 20% (<em>Patnaik et al, 2011</em>)</td>
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<td>- Risk of vasomotor symptoms</td>
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<tr>
<td>Treatment</td>
<td>Transfusion/ESA Lenalidomide</td>
<td>Transfusion/ESA</td>
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<td></td>
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<td>Aspirin/Anti-platelet agents</td>
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<td>Cytoreductive agents (Hydroxyurea)</td>
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<td>Lenalidomide</td>
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</tbody>
</table>
69 yo Male
Generalized weakness
Pallor, splenomegaly

CBC
WBC: 19.1 k/μL
Hgb: 9.3 g/dL
MCV: 67
Plt: 650 k/μL
PB: Mild left shift

Bone Marrow Biopsy
90% cellular
Erythroid hypoplasia
Increased atypical megs
35% ring sideroblasts
<5% blasts
2-3/4 fibrosis

Genetics
Del(5q31) [30]
(-): JAK2, BCR-ABL1,
ETV6-PDGFRB

Proposed Diagnosis
RARS-T with superimposed 5q-syndrome

Hydroxyurea + Lenalidomide
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>IPSS Score</th>
<th>Hematological Findings</th>
<th>Cytogenetic Abnormality</th>
<th>Treatment</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szpurka et al, Blood, 2006</td>
<td>70 yo</td>
<td>Splenomegaly 0.5 IPSS score</td>
<td>Hgb 10.2 g/dL, Plt 691 k/μL, MCV 106, ANC 2.3 k/μL, AMC 0.4 k/μL</td>
<td>20% cellularity, 2% BM blasts, Megs unremarkable, 51% ring sideroblasts, No reticulin fibrosis</td>
<td>(+) JAK2 V617F (+) Del(5q)</td>
<td>RARS-T</td>
</tr>
<tr>
<td>Patnaik et al, Am J Hematol, 2016</td>
<td>12/82 (15%) patients with RARS-T had abnormal karyotype</td>
<td>One with Del(5q31)</td>
<td>Cytogenetic abnormality associated with worse overall survival</td>
<td>Lenalidomide</td>
<td>RARS-T</td>
<td></td>
</tr>
<tr>
<td>Woll et al, Cancer Cell, 2014</td>
<td>83 yo M</td>
<td>Low IPSS score</td>
<td>WBC 22 k/μL, Hgb 8.7 g/dL, Plt 877 k/μL, ANC 16 k/μL</td>
<td>&lt;5% BM blasts, No ring sideroblasts</td>
<td>(+) SF3B1 (VAF 18-37%) (+) JAK2 V617F (VAF 18-33%) (+) Del(5) (q21q34) [25]</td>
<td>Transfusion-independent with lenalidomide, MDS/MPN</td>
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JAK2 V617F: Janus kinase 2 variant 617F
Del(5q): Deletion of chromosome 5q
SF3B1: Splicing factor 3B subunit 1
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<tr>
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<th>Patient 1</th>
<th>Patient 2</th>
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<tbody>
<tr>
<td>Date of Diagnosis</td>
<td>11/15/2010</td>
<td>12/22/2011</td>
</tr>
<tr>
<td>Age/Sex</td>
<td>62M</td>
<td>71M</td>
</tr>
<tr>
<td>Original Diagnosis</td>
<td>MDS/MPN</td>
<td>MPN</td>
</tr>
<tr>
<td>CBC</td>
<td>WBC nl, Hgb 10.1, Plt 783</td>
<td>WBC 9.0, Hgb 12.1, Plt 1,400</td>
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<tr>
<td>BM Findings*</td>
<td>• &gt;95% cellular</td>
<td>• &gt;90% cellular</td>
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<tr>
<td></td>
<td>• Increased left-shifted myeloid precursors</td>
<td>• Mild granulocytic dysplasia</td>
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<tr>
<td></td>
<td>• Meg hyperplasia and dysplasia</td>
<td>• Meg hyperplasia and dysplasia</td>
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<tr>
<td></td>
<td>• Reported ring sideroblasts</td>
<td>• 5% ring sideroblasts (suboptimal)</td>
</tr>
<tr>
<td></td>
<td>• 2-3+ reticulin fibrosis</td>
<td>• 2+ reticulin fibrosis</td>
</tr>
<tr>
<td>Molecular Alterations</td>
<td>• Normal karyotype</td>
<td>• 46,XY,del(5)(q22q35)[17]/46, idem,del(20)(q11.2)[3]</td>
</tr>
<tr>
<td></td>
<td>• FISH: del(5q) (10%), del(17p13) (10%)</td>
<td>• FISH: del(5q31) (92%), del(20q) (15%)</td>
</tr>
<tr>
<td></td>
<td>• *MPL W515L</td>
<td>• *SF3B1 K666N (VAF 42%)</td>
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<td></td>
<td></td>
<td>• *MPL W515L (VAF 45%)</td>
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<td>• *IDH1 R132C (VAF 9%)</td>
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*Bone marrow findings based on follow-up biopsies reviewed at MSKCC
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</thead>
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<tr>
<td><strong>Complications</strong></td>
<td>TIA, DVT, HSM Transfusion dependent</td>
<td>Retinal vein occlusion, SM Transfusion dependent</td>
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<tr>
<td><strong>Symptoms</strong></td>
<td>Bone pain, fever, night sweats, fatigue, early satiety, weight loss</td>
<td>Fatigue</td>
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<tr>
<td><strong>Therapies</strong></td>
<td>1. Lenalidomide and hydroxyurea</td>
<td>Hydroxyurea Lenalidomide trial</td>
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<td></td>
<td>2. Hydroxyurea only and darbepoetin prn</td>
<td>Darbepoetin added</td>
</tr>
<tr>
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<td>3. Ruxolitinib</td>
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<tr>
<td><strong>Outcome</strong></td>
<td>Progressive anemia and leukocytosis DOD</td>
<td>Progressive anemia Progressed to AML-MRC DOD</td>
</tr>
<tr>
<td><strong>Time to Death</strong></td>
<td>63 mo</td>
<td>64 mo</td>
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Patient Y.K. Follow-Up

•Received pRBC transfusions
  – Anemia (Hgb 8.2 g/dL), fatigue and atrial fibrillation

• Restarted on low dose lenalidomide

• Alive at 18 months
Conclusions

• Biology unclear
  – Belong in one defined category?
  – Overlap disease?
  – Two concurrent processes?

• Order of genetic alterations?
  – Relatively high VAF of SF3B1 and JAK2/MPL mutations and percentage of cells with del(5q) by FISH

• MDS with isolated del(5q)?
  – Mixed response to lenalidomide
  – Possible increased thrombotic risk
  – Possible worse outcomes
Conclusions

- Myeloid neoplasms with features overlapping between MDS/MPN-RS-T and MDS with isolated del(5q) are rare and poorly understood.
- Classification and treatment planning may be difficult.
- Descriptive diagnosis.
Expert Panel Proposed Diagnosis

Myeloid neoplasm with features of both myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis and myelodysplastic syndrome with isolated del(5q)