Case SH2017-0281

Acute Myeloid Leukemia with RUNX1 and Several Co-mutations

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Chief Complaint: 72 year old man presented with worsening dyspnea, poor appetite and weight loss.

Past Medical History: Hypertension, Diverticulosis
Social History: Retired mill worker, non-smoker, occasional drinks
Family History: Father- heart disease, Mother- gastric cancer
Physical exam: No lymphadenopathy, no hepatosplenomegally
**Peripheral Smear:**

<table>
<thead>
<tr>
<th>CBC</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>119 K/uL</td>
</tr>
<tr>
<td>Hgb</td>
<td>6.7 g/dL</td>
</tr>
<tr>
<td>Hct</td>
<td>20%</td>
</tr>
<tr>
<td>Plt</td>
<td>102 K/uL</td>
</tr>
<tr>
<td>Neut</td>
<td>1190/uL</td>
</tr>
<tr>
<td>Lymph</td>
<td>8340/uL</td>
</tr>
<tr>
<td>Mono</td>
<td>2380/uL</td>
</tr>
<tr>
<td>Blast</td>
<td>107190/uL</td>
</tr>
</tbody>
</table>
Bone Marrow Aspirate
Flow Cytometry:

CD45 dim blasts comprise 90% of the nucleated cells. The blasts express CD34, CD117, CD33, and dim TdT. A subset of blasts show a monocytic phenotype with expression of CD11b, CD14, bright CD64, CD33 and dim CD34 without CD117.
Cytogenetics/FISH:

Karyotype:
46~47, XY, add(4)(q21), inc[2]/46, XY[15]

FISH for CBFB rearrangement in 16q22 was negative
Illumina based Targeted NGS (ARUP Myeloid Malignancies Mutation Panel):

Tier 1 Variants:
1. RUNX1  c.601C>T,  p.Arg201* (NM_001754.4)  VAF: 91.1%
2. U2AF1  c.101C>T,  p.Ser34Phe  (NM_006758.2)  VAF: 45.9%
3. WT1  c.1138delinsGG,  p.arg380fs  (NM_024426.4)  VAF: 34.7%
4. PHF6  c.903delinsGT,  p.TYR301* (NM_001015877.1)  VAF: 7.8%
5. FLT3  c.2039C>T,  p.Ala680Val  (NM_004119.2)  VAF: 31.3%

Tier 2 Variants:  None detected
Tier 3 Variants:  None detected
Final Diagnosis:

- AML with mutated RUNX1
  
  (provisional entity, WHO acute leukemia classification 2016 revision)
Runx1 Biology

• Transcription factor essential for hematopoiesis
• 261 kb gene on the long arm of chromosome 21
• Most point mutations within the 2 major functional domains:
  • Runt-homology domain (RHC, RUNT)- DNA binding, interaction with CBFβ
  • Transactivation domain (TAD)

Recurrent chromosomal translocations:

- t(8;21)(q22;q22) RUNX1-RUNX1T1
- t(3;21)(q26.2;q22) MCOM(EVI1)-RUNX1
- t(12;21)(p13;q22) ETV6-RUNX1

Point mutations:

- Missense
- Nonsense
- Frameshift

Point mutations are associated with:

- AML
- MDS
- Therapy-related MDS/AML
- CMML
- T-lymphoblastic leukemia
- Congenital bone marrow failure syndromes (Fanconi anemia and congenital neutropenia)
- Familial platelet disorder with associated myeloid malignancy
RUNX1 Point Mutations in AML

- RUNX1 point mutations found in 10% of patients with AML
  - 9% in de novo AML and 24% in secondary AML
- AML with RUNX1 point mutations were almost exclusive of AML with recurrent genetic abnormalities
- Associated with older age, male sex, and secondary AML evolving from MDS
- Predominantly inactivating mutations in the RHD domain

Gaidzik VI et al. Leukemia 2016;30:2160-2168
• RUNX1 mutated AML are associated with inferior overall survival
• RUNX1 mutated secondary AML (AML from MDS) had inferior outcome compared to RUNX1 mutated de novo AML
RUNX1 Mutations in MDS

• RUNX1 mutations can be found in up to 20% of MDS cases including:
  • Primary MDS
  • MDS arising from congenital bone marrow failure syndromes
    • Fanconi anemia, 20%
    • Congenital neutropenia, 68%
  • Therapy-related MDS/AML
    • Frequently associated with monosomy 7/del 7q
  • AML arising from progression of MDS
    • AML with myelodysplasia related changes

Harada H et al Blood 2004;103:2316-2324
Christiansen DH et al Blood 2004;104:1474-1481
Quentin S et al Blood 2011;117:e161-e170
Skokowa J et al Blood 2014;123:2229-2237
### Cytogenetic abnormalities sufficient to diagnose AML with MRC

<table>
<thead>
<tr>
<th>Complex karyotype (3 or more abnormalities)</th>
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</thead>
<tbody>
<tr>
<td>Unbalanced abnormalities</td>
</tr>
<tr>
<td>-7/del(7q)</td>
</tr>
<tr>
<td>del(5q)/t(5q)</td>
</tr>
<tr>
<td>i(17q)/t(17p)</td>
</tr>
<tr>
<td>-13/del(13q)</td>
</tr>
<tr>
<td>del(11q)</td>
</tr>
<tr>
<td>del(12p)/t(12p)</td>
</tr>
<tr>
<td>idic(X)(q13)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Balanced abnormalities</th>
</tr>
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<tbody>
<tr>
<td>t(11;16)(q23.3;p13.3)</td>
</tr>
<tr>
<td>t(3;21)(p26.3;q21.2)</td>
</tr>
<tr>
<td>t(1;3)(p36.3;q21.2)</td>
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<tr>
<td>t(2;11)(p21;q23.3)</td>
</tr>
<tr>
<td>t(5;12)(q32;p13.2)</td>
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<tr>
<td>t(5;7)(q32;q11.2)</td>
</tr>
<tr>
<td>t(5;17)(q32;p13.2)</td>
</tr>
<tr>
<td>t(5;10)(q32;q21.2)</td>
</tr>
<tr>
<td>t(3;5)(q25.3;q35.1)</td>
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</tbody>
</table>

- Morphologic detection of dysplasia in at least 50% of cells in 2 lineages
- History of MDS
- Presence of MDS-related cytogenetic abnormality
Familial platelet disorder with predisposition to acute myeloid leukemia

• Rare autosomal dominant disorder with germline RUNX1 mutation
• Clinical symptoms:
  • Mild to moderate thrombocytopenia
  • Platelet dysfunction
  • Bleeding propensity
  • 40% lifetime risk for development of MDS and AML, average age of onset 33 years
• Over 70 families identified, most with unique RUNX1 mutations
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RUNX1 somatic mutations in AML: Biallelic mutations and co-mutations

- Over 50% of RUNX1 mutations in undifferentiated AML (M0) are biallelic
- RUNX1 mutations co-occur with:
  - Epigenetic modifiers (ASXL1, IDH2, KMT2A, EZH2)
  - Spliceosome components (SRSF2, SF3B1)
  - FLT3-ITD and FLT3-TKD
  - STAG2, PHF6, and BCOR
- Some co-mutations (ASXL1, SRSF2, PHF6) are associated with inferior prognosis

Osato M. Oncogene 2004;23:4284-4296
Gaidzik VI et al. Leukemia 2016;30:2160-2168