Acute Myeloid Leukemia (Promyelocytic) with Novel IRF2BP2-RARA Fusion SH2017-0180

Keyur P. Patel, MD, PhD


Department of Hematopathology
University of Texas MD Anderson Cancer Center

No relevant financial relationships to disclose
Clinical History

- 19-year-old female
- Presented with ecchymoses and epistaxis
- Outside workup suggested leukemia vs storage disorder
- CBC: WBC 4.5 K/uL, Hgb 9.1 g/dL, platelet 29 K/uL
- Coagulation
  - PT: 19.6 sec (ref 12.7-15.0 sec)
  - aPTT: 46.3 sec (ref 24.7-35.9 sec)
  - D-Dimer: >20 mcg/mL (ref 0.00-0.40 mcg/mL)
  - Fibrinogen: 60 mg/dL (ref 202-450 mg/dL)
Morphologic Findings

Abnormal Cells: 60%  No obvious Auer rods
Special Stains

Myeloperoxidase (MPO)

PML Oncogenic Domain (POD) Immunofluorescence
Flow Cytometry

Aberrant promyelocytic immunophenotype

• **Positive:** CD13, CD15, CD11a (dim partial), CD18 (dim partial), CD33, CD38, CD45 (dim), CD117 (partial), CD123, and MPO (uniform strong)

• **Negative:** CD10, CD14, CD34, CD36, CD41, CD56, CD64, HLA-DR, TdT, B-cell and T-cell markers
Cytogenetic Findings

- 46,XX[20]

- **PML-RARA FISH:**
  - *PML-RARA* Fusion Probe: No fusions
  - *RARA* Breakaport probe: No RARA rearrangement
Molecular Diagnostics

Leukemia Translocation Panel: Negative for
- t(8;21)(q22;q22); RUNX1-RUNX1T,
- inv(16)(p13.1q22) CBFB-MYH11 variants A, D, E
- t(15;17)(q22;q12); PML-RARA long form, short form, alternate form
- t(9;22)(q34;q11.2); BCR-ABL1 e1a2, e13a2, e14a2
- t(12;21)(p13;q22); ETV6-RUNX1
- t(1;19)(q23;p13.3); E2A-PBX1
- t(4;11)(q21;q23); MLL-AF4
- t(6;9)(p23;q34); DEK-NUP214.

Oligonucleotide microarray: Negative for
- t(15;17)(q22;q21)/PML-RARA
- t(5;17)(q35;q21)/NPM1-RARA
- t(11;17)(q13;q21)/NUMA1-RARA
- t(11;17)(q23;q21)/ZBTB16-RARA

Mutation Profile:
NM_002524(NRAS): c.35G>A p.G13D, (<5%)
Diagnosis and Treatment

- BM morphologic findings and the presence of DIC suggested acute promyelocytic leukemia
- Induction:
  - ATRA, arsenic trioxide (day 2) and Gemtuzumab (day 6)
- Remission: 5 weeks after diagnosis
- Consolidation (8 months): ATRA, arsenic trioxide
- Relapsed: 2 months after end of consolidation (10 months after first induction)
- Salvage Therapy:
  - ATRA, arsenic trioxide and idarubicin
  - Haploidentical SCT
Additional Molecular Studies (Research)

• RNAseq:
  – Fusion reads involving,
    • Interferon regulatory factor 2 binding protein 2 (IRF2BP2) exon 2
    • RARA exon 3
• Confirmed by PCR (M13-tagged primers):
  – cDNA (RT-PCR)
  – gDNA (PCR):
    • IRF2BP2 breakpoint (exon 2); chr1:234742961
    • RARA breakpoint (intron 2); chr17:38502042
• Sanger Sequencing
Our Diagnosis
Acute Myeloid Leukemia (Promyelocytic), with Novel
IRF2BP2-RARA Fusion

Final Consensus Diagnosis
Acute Promyelocytic Leukemia with Variant RARA
Rearrangement, IRF2BP2-RARA
2nd Case of APL with IRF2BP2-RARA Fusion

- 68 year old female
- Pancytopenia, but, no DIC
- No response to ATRA monotherapy
- Remission with Idarubicin+cytarabine+GO
- Multiple relapses
- Died 27 months after diagnosis

Shimomura et al. Cancer Science 2016
### RARA Translocations in APL

- Commonly involved t(15;17)(q24.1;q21.2)/PML-RARA
- Associated with response to ATRA and good outcomes
- Variant RARA fusions are uncommon, but, create significant diagnostic and therapeutic challenges

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Partner</th>
<th>ATRA Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(5;17)(q23;q21)</td>
<td>Nucleophosmin (NPM1)</td>
<td>Sensitive</td>
</tr>
<tr>
<td>t(11;17)(q13;q21)</td>
<td>nuclear mitotic apparatus (NUMA1)</td>
<td>Sensitive</td>
</tr>
<tr>
<td>t(17;17)(q21;q24)</td>
<td>cAMP-dependent protein kinase type I alpha regulatory subunit (PRKAR1A)</td>
<td>Sensitive</td>
</tr>
<tr>
<td>t(4;17)(q12;q21)</td>
<td>FIP1-like 1 (FIP1L1)</td>
<td>Sensitive</td>
</tr>
<tr>
<td>t(X;17)(p11;q12)</td>
<td>BCL6 corepressor (BCOR)</td>
<td>Sensitive with relapses</td>
</tr>
<tr>
<td>der(17)(q21.3;q23)</td>
<td>signal transducer and activator of transcription 5b (STAT5B)</td>
<td>Resistant</td>
</tr>
<tr>
<td>t(11;17)(q23;q21)</td>
<td>zinc finger and BTB domain containing 16 (ZBTB16), previously promyelocytic leukemia zinc finger (PLZF)</td>
<td>Resistant</td>
</tr>
</tbody>
</table>
Synergistic Effect of Arsenic Trioxide and ATRA

Arsenic Trioxide (ATO) Actions on PML moiety

1. C212/213 oxidation / ATO binding
2. K160 SUMOylation (UBC9)
3. Relocalization to nuclear bodies
4. Polyubiquitination (RNF4)
5. Proteasomal degradation of PML and PML-RARA

Retinoic Acid (ATRA) Actions on RARA moiety

1. ATRA binding to LBD-AF2
2. LBD-AF2 conformational change
3. Transcriptional activation in RARE
4. Polyubiquitination
5. Proteasomal degradation of RARA and PML-RARA

PML-p53 Axis Drives Cure in APL

ATRA Resistance in Variant Translocations

- N-CoR/SMRT complex interaction with ZBTB16, STAT5b implicated in resistance
- IRF2BP2 is known to bind to N-CoR co-repressors

N-CoR: Nuclear Receptor Co-Repressor
SMRT: Silencing Mediator for Retinoid and Thyroid receptors

Interferon Regulatory Factor 2 Binding Protein 2 (IRF2BP2)

- Located at 1q42.3, contains 2 exons
- Encodes a nuclear protein that binds IRF2.
- IRF2BP2 overexpression inhibits apoptosis by impeding p53 function.
- Represses transactivation of nuclear factor of activated T cells (NFAT), which in turn regulates cell cycle, differentiation, apoptosis, angiogenesis.
- Rare reports of fusions with CDX1 (mesenchymal chondrosarcoma), NTRK1, CALM1, NEROD2
Interesting Features of This Case

• First reported case of novel *IRF2BP2-RARA* fusion, which expands the list of *RARA* partners.

• The patient initially responded well to ATRA, arsenic trioxide and Gemtuzumab.

• Early relapse suggests a more aggressive clinical course and/or require more intensive therapy.

• Highlights the importance of morphologic examination to establish the diagnosis of APL, especially in cases with variant *RARA* fusions.
Follow-Up

- In remission, 39 months after haploidentical SCT
- Recently gave birth to a healthy baby boy, 51 months after initial diagnosis
Thank You

Identification of a Novel Fusion Gene, \textit{IRF2BP2-RARA}, in Acute Promyelocytic Leukemia

C. Cameron Yin, MD, PhD\textsuperscript{a,\*}; Nitin Jain, MD\textsuperscript{b,\*}; Meenakshi Mehrotra, PhD\textsuperscript{a,\*}; Jianhua Zhang, PhD\textsuperscript{c}; Alexei Protopopov, PhD\textsuperscript{c}; Zhuang Zuo, MD, PhD\textsuperscript{a}; Naveen Pemmaraju, MD\textsuperscript{b}; Courtney DiNardo, MD\textsuperscript{b}; Cheryl Hirsch-Ginsberg, MD\textsuperscript{d}; Sa A. Wang, MD\textsuperscript{a}; L. Jeffrey Medeiros, MD\textsuperscript{a}; Lynda Chin, MD\textsuperscript{c}; Keyur P. Patel, MD, PhD\textsuperscript{a}; Farhad Ravandi, MD\textsuperscript{b}; Andrew Futreal, PhD\textsuperscript{c}; and Carlos E. Bueso-Ramos, MD, PhD\textsuperscript{a}

Yin et al, J NCCN, 2015;13; 19-22