Familial Acute Myeloid Leukemia with Germline CEBPA Mutation

SH/EAHP Workshop 2017
Case #SH2017-0283

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Clinical History

19 year-old man with no significant past medical history presented with one-month history of bruising, petechiae, rib and shoulder pain, and night sweats

PMH: Asthma
PSH: Fracture surgery
FH: No history of leukemia

Chest XRAY demonstrated small pleural effusions and atelectasis
CBC showed marked leukocytosis to 119,000/uL comprising mostly immature cells
Peripheral Smear and Bone Marrow Aspirate Smears Showed Numerous Blasts
Bone Marrow Flow Cytometry Demonstrated Increased Myeloblasts and Monocytic Cells

- Blasts: CD7 (subset), CD13 (dim), CD33 (bright), CD34 (bright), CD38 (bright), CD56 (subset), CD117, HLA-DR (subset), icMPO

- Monocytic cells: CD14 (heterogeneous), CD36 (heterogeneous), CD56 (subset)
Bone Marrow Biopsy Showed Sheets of Blasts

Final Diagnosis:
Acute myeloid leukemia

Conventional cytogenetics:
Normal male karyotype, 46,XY[20]

FISH:
No evidence of AML1/ETO1, BCR-ABL1, CBFB, EV1, MLL, or PML-RARA rearrangement
Sanger Sequencing Studies Identified Two CEBPA Mutations

Fragment 1
N-terminus c.169G>T (p. Glu57*)

Fragment 2
C-terminus c.909_941dup (p. Lys304_Val314dup)
Next-Generation Sequencing Studies Identified Additional Mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>COSMIC ID</th>
<th>Mutation Location</th>
<th>Mutant Allele Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEBPA</td>
<td>c.169G&gt;T (p.E57*)</td>
<td>COSM42116</td>
<td>Exon 1</td>
<td>48%</td>
</tr>
<tr>
<td>CEBPA</td>
<td>c.909_941dup (p.K304_V314dup)</td>
<td>NA</td>
<td>Exon 1</td>
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</table>
Next-Generation Sequencing Studies Identified Additional Mutations

**CLINICALLY SIGNIFICANT MUTATIONS**

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<td>NA</td>
<td>Exon 1</td>
<td>NA</td>
</tr>
<tr>
<td>GATA2</td>
<td>c.953C&gt;T (p.A318V)</td>
<td>COSM255084</td>
<td>Exon 4</td>
<td>46%</td>
</tr>
<tr>
<td>NRAS</td>
<td>c.38G&gt;A (p.G13D)</td>
<td>COSM573</td>
<td>Exon 2</td>
<td>42%</td>
</tr>
</tbody>
</table>

**MUTATION OF UNDETERMINED CLINICAL SIGNIFICANCE**

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<tr>
<td>NRAS</td>
<td>c.35G&gt;A (p.G12D)</td>
<td>COSM564</td>
<td>Exon 2</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Final Diagnosis:** Acute myeloid leukemia with (likely) biallelic mutations of *CEBPA*
Clinical Course

AML with biallelic $CEBPA$
$CEBPA$ c.169G>T (p.E57*)
$CEBPA$ c.909_941dup (p.K304_V314dup)
$GATA2$ c.953C>T (p.A318V)
$NRAS$ c.38G>A (p.G13D)
$NRAS$ c.35G>A (p.G12D)

Day 1
Diagnosis

Day 14
Bone Marrow
No excess blasts

Day 30
Bone Marrow
Day 30 Bone Marrow Showed 15-20% Blasts

(H&E, B5, 40X)

(CD34, 40X)
Next Generation Sequencing and Sanger Sequencing Demonstrated Persistence of the N-terminus CEBPA Mutation Without Other Mutations

**Fragment 1**
Positive for N-terminus c.169G>T (p. Glu57*)

**Fragment 2**
No Mutations Detected
Clinical Course

Day 1
Diagnosis
AML with biallelic CEBPA
CEBPA c.169G>T (p.E57*)
CEBPA c.909_941dup (p.K304_V314dup)
GATA2 c.953C>T (p.A318V)
NRAS c.38G>A (p.G13D)
NRAS c.35G>A (p.G12D)

Day 14
Bone Marrow
No excess blasts

Day 30
Bone Marrow
15-20% blasts
CEBPA c.169G>T (p.E57*) 51%
Clinical Course

Day 1
Diagnosis
AML with biallelic CEBPA
CEBPA c.169G>T (p.E57*)
CEBPA c.909_941dup (p.K304_V314dup)
GATA2 c.953C>T (p.A318V)
NRAS c.38G>A (p.G13D)
NRAS c.35G>A (p.G12D)

Day 14
Bone Marrow
No excess blasts

Day 30
Bone Marrow
15-20% blasts
CEBPA c.169G>T (p.E57*) 51%

Buccal Swab
MEC
Sanger Sequencing of Buccal Swab Identified N-terminus CEBPA Mutation

Fragment 1
Positive for N-terminus c.169G>T (p. Glu57*)

Final Diagnosis: Acute myeloid leukemia with germline CEBPA mutation
Clinical Course

**Day 1**
Diagnosis
AML with biallelic CEBPA
*CEBPA* c.169G>T (p.E57*)
*CEBPA* c.909_941dup (p.K304_V314dup)
*GATA2* c.953C>T (p.A318V)
*NRAS* c.38G>A (p.G13D)
*NRAS* c.35G>A (p.G12D)

**Day 14**
Bone Marrow
No excess blasts

**Day 30**
Bone Marrow
15-20% blasts
*CEBPA* c.169G>T (p.E57*) 51%

**Day 14**
Buccal Swab

**Day 30**
Bone Marrow

**7+3**

**MEC**

No excess blasts
*CEBPA* c.169G>T (p.E57*) 50%
Clinical Course

- Patient received allogeneic hematopoietic stem cell transplant 9 months after initial diagnosis
- Genetic counseling was provided
- Parental blood samples were submitted for germline $CEBPA$ testing
Sanger Sequencing of Parental Samples Demonstrated Absence of Germline CEBPA Mutation

Final Diagnosis: Acute myeloid leukemia with *de novo* germline CEBPA mutation
CCAAT/Enhancer Binding Protein Alpha (CEBPA) Encodes a Transcription Factor

Alternative start sites can give rise to different isoforms

Recognizes the CCAAT promoter motif, and forms homodimers and heterodimers

(Adapted from Green, CL et al, JCO, 2010)
Somatic CEBPA Mutations Occur in the N- and C-terminus

Adapted from Green, CL et al, JCO, 2010
Somatic Bi-allelic CEBPA Mutations Are Associated With a Favorable Prognosis in AML

(Green, CL et al, JCO, 2010)
(Dufour A, et al, JCO, 2009)
Familial AML with Germline CEBPA Mutations Are Autosomal Dominant

- Early-onset primary AML
- Often M1 or M2 with aberrant CD7
- Median age 24.5 years (1.75 to 46 years)

- Penetrance is high with rare unaffected carriers
Germline CEBPA Mutations Occur in the N-terminus

Familial AML with Germline CEBPA Mutations Demonstrates Favorable Prognosis

Case Summary

• 19 year-old man with primary AML with two *CEBPA* mutations
• Found to have one *de novo* germline N-terminus *CEBPA* mutation with a somatic C-terminus *CEBPA* mutation
• Allogeneic stem-cell transplant was pursued for refractory disease and germline predisposition to AML
• Familial AML with *CEBPA* mutations are autosomal dominant with high penetrance
• Overall survival is superior to survival in somatic *CEBPA*-mutated AML
Final Panel Diagnosis:
Acute myeloid leukemia with biallelic mutations of *CEBPA* (one germline, one somatic)


Acknowledgement

Department of Pathology and Lab Medicine
Thomas D. Lee
Sureni Mullegama
Sophie Song
Sheeja Pullarkat
Dinesh Rao

Department of Medicine, Hematology Oncology
Hyung Suh
Gary Schiller
Thank you. Questions?