SH2017-0299: Acute Myeloid Leukemia with BCR-ABL1

Ashley Vogel, Xi-Zuan Wang, Jinglan Liu, Guldeep Uppal & Jerald Gong
Thomas Jefferson University Hospital
Philadelphia, PA
Case Presentation

• 60 yo male with no past medical history
• Fatigue x 2 weeks
• Weight loss
• No history of hematologic abnormality
• No hepatosplenomegaly
## Admission Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Blood Count &amp; Differential</strong></td>
<td></td>
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<tr>
<td>WBC 9.2 B/L</td>
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<tr>
<td>RBC 2.69 T/L</td>
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<tr>
<td>Hemoglobin 8.1 g/dL</td>
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<tr>
<td>Hematocrit 24.2%</td>
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<tr>
<td>MCV 90 fL</td>
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<tr>
<td>MCH 30.1 pg</td>
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<tr>
<td>MCHC 33.5 g/dL</td>
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<tr>
<td>RDW 16</td>
<td></td>
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<tr>
<td>Platelets 11 B/L</td>
<td></td>
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<tr>
<td><strong>Neutrophils</strong> 35%</td>
<td></td>
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<tr>
<td><strong>Lymphocytes</strong> 23%</td>
<td></td>
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<tr>
<td><strong>Monocytes</strong> 2%</td>
<td></td>
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<tr>
<td><strong>Eosinophils</strong> 13%</td>
<td></td>
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<tr>
<td><strong>Basophils</strong> 1%</td>
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<tr>
<td><strong>Bands</strong> 4%</td>
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<tr>
<td><strong>Blasts</strong> 22%</td>
<td></td>
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<tr>
<td><strong>Fibrinogen</strong> 793 mg/dL</td>
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<tr>
<td><strong>LD</strong> 3400 IU/L</td>
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<tr>
<td><strong>D-Dimer</strong> 1261 ng/mL</td>
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</tbody>
</table>

**Peripheral blood smear:** Many circulating blasts.
Bone marrow core biopsy & aspirate smears
Flow Cytometry

- CD11c
- CD13
- CD11b
- CD33
- CD117
- CD5
- CD7
- CD20
- CD19
- CD34
- HLA-DR
- cCD79a
- cMPO
- cCD22
- cCD3
- cCD2
- Dual 22/3
Cytogenetic Findings

51-69,XY, +Y,+1,+2,+3,+6,i(6)(p10),+8,
t(9;22)(q34;q11.2),+10,+11,+12,+13,
del(13)(q12q14),+14,+15,+16,+18,+19,+20,
+der(22)t(9;22) [cp4] /46,XY [10]
Molecular Genetic Findings

RT PCR Results
- **p190 BCR-ABL1** fusion transcript detected
  - 30.103%
- **p210 BCR-ABL1** fusions transcripts e13/a2 and e14/a2 not detected

NGS 48-Gene Panel
**Illumina TruSight™ myeloid sequencing panel (MiSeq)**
- **TP53** mutation detected
  - Nucleotide change: c.548C>G
  - Amino acid change: p.S183*
  - Altered allele freq: 61.6%
- Remaining 47 genes tested negative, including ABL kinase mutation
Diagnosis:
Acute myeloid leukemia with BCR-ABL1

• t(9;22)(q34.1;q11.2) results in the formation of the Philadelphia (Ph) chromosome and the chimeric BCR-ABL1 fusion gene
  • CML
  • Ph+ ALL
  • <1% of AML cases
• Provisional entity in the 2016 WHO classification
  • Must be distinguished from myeloid blast crisis of CML
  • Exclude mixed phenotype acute leukemia with BCR-ABL1
• Poor risk group
AML with \textit{BCR-ABL1}: An emerging entity

- Proliferation of \textit{BCR-ABL1}-positive blasts on presentation creates a diagnostic dilemma
- Soupir et al 2007 - 16 cases of Ph+ AML
  - Morphologic and phenotypic overlap with CML
    - Ph+ AML presented less often with splenomegaly, lacked basophilia, lower bone marrow cellularity
- Nacheva et al 2010 and 2013 - 6 cases of Ph+ AML
  - Searched for specific genomic profiles using aCGH
    - \textit{BCR-ABL1}+ AML displays characteristics of lymphoid disease
- Neuendorff et al 2016 - 126 cases of Ph+ AML since 1975
  - Presented common clinical and molecular features
    - p190 and p210 are nearly equally distributed
    - Provided clinical algorithm
Differentiating CML in myeloid blast crisis from AML with *BCR-ABL1*

<table>
<thead>
<tr>
<th>CML in MBC</th>
<th>AML with <em>BCR-ABL1</em></th>
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<tbody>
<tr>
<td>Antecedent blood disorder, unexplained leukocytosis</td>
<td>No antecedent blood disorder</td>
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<tr>
<td>Splenomegaly</td>
<td>Absence of splenomegaly</td>
</tr>
<tr>
<td>Basophilia ≥ 2%</td>
<td>No basophilia</td>
</tr>
<tr>
<td>Near 100% marrow cellularity</td>
<td>&lt;100% marrow cellularity; median 80%</td>
</tr>
<tr>
<td>Typical AML blast crisis phenotype</td>
<td>Aberrant CD19, CD7 and TdT more common</td>
</tr>
<tr>
<td>Ph+ in near 100% of cells</td>
<td>Ph+ in &lt;100% of cells</td>
</tr>
<tr>
<td>p210 transcript in &gt;99% of cases</td>
<td>p190 and p210 detected in nearly equal distribution</td>
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<tr>
<td></td>
<td>Loss of <em>IKZFI</em> and <em>CDKN2A</em> and cryptic deletions within <em>IGH</em> and <em>TCR</em> genes</td>
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AML with \textit{BCR-ABL1} Carries Unique Genome Imbalances

- Nacheva et al used aCGH to perform a comparative study between several \textit{BCR-ABL1}+ entities
  - Findings similar to Ph+ ALL and lymphoid blast crisis of CML
    - Loss of \textit{IKZF1} and/or \textit{CDKN2A} genes were recurrent findings in AML with \textit{BCR-ABL1}
    - Accompanied by cryptic deletions within the \textit{IGH} and \textit{TRG@} genes
      - Ch14:105,405.050-105,415,455
    - Aberrations found to be \textbf{absent in myeloid blast crisis} of CML
- Unique loss provides a test to enable differentiation
- Further evidence for a unique biology

Deletion Detected at CDKN2A by OncoScan
Patient Follow-Up

• Induction chemotherapy and sirolimus plus dasatinib
• Induction failure
  • Repeat biopsy at day 30 revealed persistent AML
• Died <45 days following initial diagnosis
• Contribution of TP53 mutation?
Final Panel Diagnosis:
Acute Myeloid Leukemia with \textit{BCR-ABL1}

- Provisional entity in the 2016 WHO classification
- Diagnostic challenge with potential therapeutic implications
  - Our diagnosis is supported by:
    - Aggressive clinical course, absence of splenomegaly or basophilia, Ph+ in <100\% of cells, and presence of p190 transcript
- Array CGH has identified recurrent genome features similar to Ph+ lymphoid disease
  - May allow distinction from CML in myeloid blast crisis