Case 0148

Acute myeloid leukemia with myelodysplasia-related changes and cryptic t(8;16)(p11;p13); KAT6A/CREBBP

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Clinical presentation

• 24 year-old male with one month history of right-sided low back pain and right leg swelling

• Past and social history:
  – Non-smoker; social alcohol consumption
  – No significant medical or surgical history

• Review of systems:
  – Weight loss (40 lbs over two months, unintentional)
  – Generalized fatigue, dyspnea on exertion and chills

• Laboratory findings:
  – Hb 12.9 g/dl (13.5- 16 g/dl), Hct 38.4 (37- 47%), WBC count 3.2 x 10^9/L (3.5- 11 x 10^9/L), rare circulating blasts (0.8%) and platelet count 157 x 10^9/L (150- 400 x 10^9/L)
  – Serum LDH 739 IU/L (100- 220 IU/L)
  – D-dimer 696 ng/ml (0- 230 ng/ml)
Radiology

- Right Lower Extremity U/S:
  - No deep venous thrombosis
  - Diminished respiratory phasicity within right common femoral vein

- Abdomen and pelvis CAT:
  - Bulky retroperitoneal and inguinal adenopathy
  - Ill-defined soft tissue thickening of right psoas muscle with areas of hypoattenuation
  - Compression of right external iliac vein
  - Enlargement of paraspinal soft tissues at T11

- Testicular U/S:
  - No testicular lesions
Immunophenotype

• Positive markers
  CD45, MPO, Lysozyme, CD4, CD99, c-MYC, BCL-6

• Negative markers
  CD34, TdT, CD20, CD79a, Pax-5, CD138, MUM-1, CD10, BCL-2, CD5, and CD30

Final diagnosis
Myeloid neoplasm, consistent with myeloid sarcoma
Right iliac crest bone marrow

Blasts: 73.4%  
Giemsa 1000x
Flow cytometry
CD45 bright blasts (46% of all white blood cells) with unusually high side scatter

Immunophenotype

- Flow cytometry:
  - Positive for CD13, CD33, CD14, CD15, CD36, CD64, CD56, CD71, CD4, CD9 and HLA-DR
  - Negative for CD34, CD2, CD3, CD7, CD19, CD10, CD22, CD235a, CD11b, CD61, CD41 and CD24

- Immunohistochemistry:
  - Positive for CD68 and MPO

- Cytochemistry:
  - Positive for alpha-naphthyl butyrate esterase
Molecular and cytogenetic analyses

- **Karyotype**
  - 46,XY,add(1)(q21),t(6;13)(p23;q32),del(7)(q22q32),del(8)(p11),del(9)(p13p22),der(16)t(1;16)(q21;p13.3)[6]/47,idem,+mar[6]/46,XY[8]

- **Molecular**
  - *FLT3* ITD and TKD mutation – not detected
  - *CEBPA* mutation – not detected
  - *NPM* mutation, cell based – not detected

- **FISH**
  - nuc ish (*CBFBx2*)[200]
  - nuc ish (*MLLx2*)[200]
Final diagnosis

Acute myeloid leukemia with myelodysplasia-related changes

- Monocytic differentiation
  - CD34 negative blasts with monocytic markers (CD4, CD14, CD64 and CD68)
  - Extramedullary involvement

**Unique features**

- Prominent erythrophagocytosis
- Strong alpha-naphthyl butyrate esterase positivity and myeloperoxidase positivity
- High side scatter and bright CD45 by flow cytometry
- Evidence of disseminated intravascular coagulation
AML with t(8;16)(p11;p13)

First described in 1983 in an infant with AML associated hemophagocytosis

- **KAT6A (MYST3 or MOZ)** on 8p11
  - Monocytic leukemia zinc finger protein (histone acetyltransferase- activates AML1 transcription factor complex)

- **CREBBP (CBP)** on 16p13
  - Binds cAMP response element-binding protein (CREB) (nuclear transcriptional coactivator with intrinsic histone acetyltransferase activity)

- Fusion transcript of unknown significance
  - Many variants (KAT6A exon 15 or 16 to CREBBP exon 2-8; both in and out of frame)

Karyotype

- 46,XY,add(1)(q21),t(6;13)(p23;?q32),del(7)(q22q32),del(8)(p11),del(9)(p13p22),der(16)t(1;16)(q21;p13.3)[6]/47,idem,+mar[6]/46,XY[8]
FISH for KAT6A/CREBBP

KAT6A[8p11.2](R)/CREBBP[16p13.3](G)

KAT6A/CREBBP fusion in 77.8% of nuclei evaluated
Amended karyotype

46,XY,t(1;16;8)(q21;p13;p11),t(6;13)(p23;?q32),del(7)(q22q32),del(9)(p13p22)[6]/47,ide
m,+mar[6] /46,XY[8]

Three way translocation resulted in 1q material on 16p; 16p material (CREBBP) on 8p
(KAT6A) with resultant KAT6A/CREBBP fusion; and 8p material (KAT6A) on 1q
Revised final diagnosis

Acute myeloid leukemia with myelodysplasia-related changes and cryptic t(8;16)(p11;p13); KAT6A/CREBBP

Despite distinct phenotypic findings, t(8;16)(p11;p13); KAT6A/CREBBP is not recognized as a recurrent genetic abnormality for the purposes of AML classification

- Frequent association with complex karyotype and/or prior therapy
- Reported marked difference in outcome of pediatric versus adult cases
- Other translocation partners also associated with similar phenotypic abnormalities
- Distinct gene expression (close to MLL-rearranged AML) and microRNA profile
# AML with t(8;16)(p11;p13)

<table>
<thead>
<tr>
<th>Series</th>
<th>Total cases</th>
<th>t-AML cases</th>
<th>Pediatric cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gervais 2008</td>
<td>29</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Haferlach 2009</td>
<td>13</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Boyd 2009</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Brown 2012</td>
<td>13</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diab 2013</td>
<td>18</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Coenen 2013</td>
<td>62</td>
<td>1</td>
<td>62</td>
</tr>
<tr>
<td>Gupta 2014</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Blieden 2014</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chakroborty 2014</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Andrade 2016</td>
<td>5</td>
<td>0</td>
<td>5 (all &lt;24 mo)</td>
</tr>
<tr>
<td>Hanada 2016</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Barrett 2017</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hoshino 2017</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>172</strong></td>
<td><strong>43 (25%)</strong></td>
<td><strong>77 (45%)</strong></td>
</tr>
</tbody>
</table>

- At least 172 reported cases
- 0.2-0.4% of AML; 1.6% of t-AML
- Female predominance (64%)
- Median age at diagnosis
  - Adults: 63 yrs (19-92 yrs)
  - Pediatric: 1.2 yrs (>50% younger than 2 yrs; 30% in first month)
- Monocytic differentiation (93%)
- Parallel MPO and NSE positivity (96%)
- Erythrophagocytosis (70%)
- Disseminated Intravascular Coagulation (40%)
- Extramedullary involvement (54%)
  - Leukemia cutis - more in adults
  - Granulocytic sarcoma - more in pediatric
  - CNS involvement - more in pediatric
Cytogenetic aberrations

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Isolated t(8;16)</th>
<th>Additional karyotypic aberrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Single</td>
</tr>
<tr>
<td>All cases</td>
<td>169</td>
<td>99 (59%)</td>
<td>29 (17%)</td>
</tr>
<tr>
<td>Pediatric</td>
<td>74</td>
<td>50 (68%)</td>
<td>15 (20%)</td>
</tr>
<tr>
<td>t-AML</td>
<td>35</td>
<td>15 (43%)</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>de novo adult</td>
<td>39</td>
<td>23 (59%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

- 59% of all cases and 43% of t-AML cases have t(8;16)(p11;p13) as isolated cytogenetic abnormality at initial presentation
- 20% of t-AML cases and at least 13% of adult de novo cases presented with complex karyotype
- Additional abnormalities are more likely in t-AML and adults
- Cytogenetic complexity does not correlate with morphological features or clinical presentation
Prognosis in adults

- Median overall survival - 4.7 to 8.8 months (t-AML- 6 months; not statistically significant)
- 50% mortality in first 10 months
- CR rate similar to other AMLs
- Short duration of remission; median DFS - 3.5 months
- Degree of cytogenetic complexity did not correlate with OS

Prognosis in pediatric population

- 60% 5-year survival
  - Similar to other pediatric AML
Spontaneous Regression

- 12 reported pediatric (9 cases < 1 month; congenital) cases
  - t(8;16) the sole detected abnormality at initial presentation in all cases
  - EMD present in all cases (leukemia cutis in all except one)
  - Erythrophagocytosis and disseminated intravascular coagulopathy reported in one case each

- Hoshino, et al 2017: First reported adult case of spontaneous regression
  - t(8;16) the sole detected abnormality
Key points

• AML with t(8;16) has unique phenotypic attributes
  – Enables identification of cryptic translocations

• Increased incidence in perinatal and post-chemotherapy populations

• In majority of cases t(8;16) was only cytogenetic abnormality
  – Additional mutations more likely in older population or at recurrence

• t-AML and *de novo* cases exhibit similar phenotypic and prognostic features
  – Slight increased frequency of additional cytogenetic mutations in t-AML

• Available survival data reproducibly suggest adult cases behave poorly
  – Many potential confounders including age of studies, high initial mortality rate at presentation, etc.

• Spontaneous regression associated with absence of other cytogenetic abnormalities, DIC and erythrophagocytosis
  – Recently reported adult case suggests differences between adult and pediatric population may reflect therapeutic decisions not biology
Clinical course

- Developed pulmonary embolism (started on rivaroxaban)
- Initiated on 7 + 3 chemotherapy
- Morphological and cytogenetic remission in Day 21 bone marrow
- Received mismatched related allogenic stem cell transplant
- Chronic GVHD of liver and GIT
- In remission 14 months after BMT
Final panel diagnosis

Acute myeloid leukemia with myelodysplasia-related changes [with t(1;16;8)(q21;p13;p11) KAT6A-CREBBP]
Distinct gene expression profile; close to MLL-rearranged AML

t(11q23)/MLL and t(8;16)(p11;p13) - selective activation of HOXA genes (without HOXB)

Haferlach et al., Leukemia. 2009;23(5):934-43
Distinct microRNA signature targeting RET proto-oncogene

Fusion partner promiscuity

• Fusion partners independently involved in AML-associated abnormalities:
  – *KAT6A* - t(8;19)(p11;q13), t(6;8)(q27;p11), t(8;22)(p11;q13) and inv(8)(p11q13)
  – *CREBBP* - t(10;16)(q22;p13) and t(11;16)(q23;p13)

• Erythrophagocytosis in AML seen in other scenarios
  – inv(8)(p11q13) – fusion partner for *KAT6A* is *NCOA2* (nuclear receptor coactivator 2, alias *TIF2*)

• Translocation not unique to leukemia, also reported in:
  – chordoma, breast papillomas, salivary adenoid cystic carcinoma, alveolar rhabdomyosarcoma & dysplastic nevi, mature T/NK cell neoplasm, CLL & Burkitt lymphoma
Acknowledgements

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  - Sunita Singh, Ph.D., FACMG
References

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• https://cgap.nci.nih.gov/Chromosomes/Mitelman (Total cases reported till July 2017)
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• Wu X. et. al. Pediatr Blood Cancer 2011;56:331–332
Circulating blasts- 0.8%