Blastic Plasmacytoid Dendritic Cell Neoplasm with $\textit{DNMT3A}$ and $\textit{TET2}$ mutations (SH2017-0314)

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Clinical Presentation

• 71 year old man presented in June, 2015 with skin rash.

• Bone marrow core biopsy, aspirate smears, and skin biopsy were initially diagnosed as acute myeloid leukemia (AML).
  – Cytogenetic studies showed normal male karyotype, 46, XY[11].
  – FISH was negative for CBFB/MYH1 rearrangement.
  – Real-time PCR was negative for PML-RARA and RUNX1-RUNX1T1 fusion transcripts.
  – PCR was negative for FLT3-ITD, FLT3-D835, or NPM1 mutations.
Clinical Presentation

• Patient received multiple AML-based chemotherapy regimens
  – 7+3 induction chemotherapy (Daunorubicin and Cytarabine) with remission
  – Azacitidine, Pioglitazone, ATRA
  – Cytarabine
  – FLAG-IDA (Fludarabine, Cytarabine, Idarubicin and G-CSF)

• Patient received radiation for skin lesions.

• He was referred to our institution in June, 2016 for further treatment options.
SKIN LESIONS
Immunophenotypic profile of skin lesions

• Positive:
  – TCF4, CD123, CD43, CD7, and TdT (partial)

• Negative:
  – CD3, MPO, CD117, CD34, CD15, CD33, lysozyme, and CD56
Cytogenetic/FISH Studies

46,XY,t(6;8)(p21;q24.3)[5]/47,idem,+18[11]/46,XY[4]

MYC rearrangement detected in 90% of the cells
### Molecular Studies

<table>
<thead>
<tr>
<th>Gene</th>
<th>Exon</th>
<th>Nucleotide change</th>
<th>Amino acid change</th>
<th>Mutation</th>
<th>VAF(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNMT3A</td>
<td>23</td>
<td>c.2645G&gt;A</td>
<td>p.R882H</td>
<td>Missense</td>
<td>38.1</td>
</tr>
<tr>
<td>TET2</td>
<td>11</td>
<td>c.4893T&gt;G</td>
<td>p.Y1631</td>
<td>Nonsense</td>
<td>35.8</td>
</tr>
</tbody>
</table>
Proposed and Panel Diagnosis

Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
Treatment and Follow-up

• Patient treated with cobimetinib and venetoclax.

• End of cycle bone marrow was not done since patient developed tumor lysis syndrome and sepsis, and missed multiple doses.

• He died after 6 weeks from his admission.
Discussion

- Mutational spectrum of BPDCN
- Genetic abnormalities of BPDCN vs AML
<table>
<thead>
<tr>
<th>Pathway</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromatin Remodeling</td>
<td><strong>ASXL1</strong>, <strong>ATRX</strong>, <strong>EZH2</strong></td>
</tr>
<tr>
<td>DNA Methylation</td>
<td><strong>TET2</strong>, <strong>DNMT3A</strong>, <strong>IDH2</strong>, <strong>IDH1</strong>, <strong>TET1</strong></td>
</tr>
<tr>
<td>Transcript Factor</td>
<td><strong>ZEB2</strong>, <strong>ETV6</strong>, <strong>IKZF3</strong>, <strong>HOXB9</strong>, <strong>IKZF1</strong>, <strong>IKZF2</strong>, <strong>RUNX</strong></td>
</tr>
<tr>
<td>Splicing</td>
<td><strong>SF3B1</strong>, <strong>SRSF2</strong>, <strong>U2AF1</strong>, <strong>ZRSR2</strong></td>
</tr>
<tr>
<td>RAS/MAPK</td>
<td><strong>NRAS</strong>, <strong>KRAS</strong>, <strong>BRAF</strong></td>
</tr>
<tr>
<td>Nucleophosmin</td>
<td><strong>NPM1</strong></td>
</tr>
<tr>
<td>Protein Kinase</td>
<td><strong>MET</strong>, <strong>KIT</strong>, <strong>RET</strong>, <strong>FLT3</strong>, <strong>FLT3-ITD</strong>, <strong>JAK2</strong></td>
</tr>
<tr>
<td>Tumor Suppressor</td>
<td><strong>CDKN2A</strong>, <strong>TP53</strong>, <strong>APC</strong>, <strong>RB1</strong>, <strong>RB1</strong>, <strong>TP53</strong>, <strong>PTEN</strong>, <strong>VHL</strong></td>
</tr>
<tr>
<td>Ubiquitination</td>
<td><strong>CBLB</strong>, <strong>CBLC</strong>, <strong>UBE2G2</strong></td>
</tr>
<tr>
<td>DNA Damage Response</td>
<td><strong>ATM</strong>, <strong>MLH1</strong></td>
</tr>
</tbody>
</table>

Size of font, relative proportion of the mutations; blue font, recurrent mutations; black font, genetic alterations occurred once; underline: deletions

Discussion

- Mutational spectrum of BPDCN
- Genetic abnormalities of BPDCN vs AML
Recurrent chromosomal/copy number changes in BPDCN

<table>
<thead>
<tr>
<th>Chromosome region</th>
<th>Change</th>
<th>Candidate genes (proteins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9p21.3</td>
<td>Loss</td>
<td><strong>CDKN2A</strong>*(p16\textsuperscript{INK4a}, p14\textsuperscript{ARF}), CDKN2B (p15\textsuperscript{INK4b}),** MTAP</td>
</tr>
<tr>
<td>9q12-9q34.3</td>
<td>Loss</td>
<td><strong>CDCC14B, DBC1, SYK</strong></td>
</tr>
<tr>
<td>12p13.2-p13.1</td>
<td>Loss</td>
<td><strong>CDKN1B</strong>*(p27\textsuperscript{KIP1}), ETV6**</td>
</tr>
<tr>
<td>13q11-31.1</td>
<td>Loss</td>
<td><strong>RB1, LATS2, KPNA3</strong></td>
</tr>
<tr>
<td>15q11.2–q26.3</td>
<td>Loss</td>
<td>*</td>
</tr>
<tr>
<td>7p12.2</td>
<td>Loss</td>
<td><strong>IKZF1</strong></td>
</tr>
<tr>
<td>17p</td>
<td>Loss</td>
<td><strong>TP53</strong></td>
</tr>
<tr>
<td>4q34.1-4q34.2</td>
<td>Loss</td>
<td>*</td>
</tr>
<tr>
<td>5q21, 5q32–q35.2</td>
<td>Loss</td>
<td><strong>SMAD5, MSH3</strong></td>
</tr>
<tr>
<td>6q23.3–q27</td>
<td>Loss</td>
<td><strong>PARK2</strong></td>
</tr>
<tr>
<td>19p13.3–p13.4</td>
<td>Loss</td>
<td>*</td>
</tr>
<tr>
<td>3p22.2–p21.1</td>
<td>Loss</td>
<td><strong>PTPN23</strong></td>
</tr>
<tr>
<td>7p22.3–p22.1</td>
<td>Loss</td>
<td><strong>MAD1L1</strong></td>
</tr>
<tr>
<td>21q22.3</td>
<td>Loss</td>
<td>*</td>
</tr>
</tbody>
</table>

*Candidate genes are not mentioned, because losses included large parts of chromosomes and hundreds of genes. Blue font, most frequent genetic alterations.

ATRX1, EZH2, SF3B1, SRSF2, U2AF1, ZRSR2, IKZF1-3, ATM, MET, RB1, ZEB2, APC, CDKN2A

9p21.3(CDKN2A/CDKN2B)
13q13.1-q14.3 (RB1),
12p13.2-p13.1 (CDKN1B),
13q11-q12 (LATS2)
7p12.2 (IKZF1)
17p (TP53)

MYC

NPM1, ASXL1
TET2, NRAS, DNMT3A
IDH2, KIT, TP53
t(11;19) (q23;p13.3)
(KMT2A-MLLT1)

FLT3-ITD
FLT3, CEBPA, RUNX1, KMT2A

t(8;21)(q22;q22)
inv(16)(p13.1q22) or t(16;16)(p13.1;q22)
t(15;17)(q22;q12)
t(9;11)(p22;q23)
t(6;9)(p23;q34)
inv(3)(q21q26.2) or t(3;3)(q21;q26.2)
t(1;22)(p13;q13)

AML

BPDCN

13q13.1-q14.3 (RB1),
12p13.2-p13.1 (CDKN1B),
13q11-q12 (LATS2)
7p12.2 (IKZF1)
17p (TP53)

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MYC
Thank You!

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