Case Presentation

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History

• 60 year-old man presented with anemia and thrombocytopenia. Hb 9.6, MCV 106 fl; WBC 26.7 x10⁹/L. (2% blasts); Plts. 92 x10⁹/L

• No relevant medical history

• No hepatosplenomegaly (confirmed by abdominal ultrasound)

• Treated with decitabine with control of leukocytosis
WBC 26,700 /dl (Neut 48%, Bands 2%, Meta 10%, Myelo 6%, Promyelo 1%, Blasts 2%, Eos 1%, Baso < 1%, Mono 4%, Lymph 16%)
8% blasts
MPX: confirms the high M:E ratio
Reticulin MF-0 to MF-1
CD34: approx. 5% pos. cells.)
- **Morphology**: Hypercellular (>90%) BM with M:E ratio 6:1 due to increased granulopoiesis predominantly neutrophilic. 8% blasts. Decreased erythropoiesis. Active megakaryopoiesis with at least 10% dysplastic forms.

- **Reticulin stain**: fibrosis 1-2 (on 0-4 scale); up to MF-1

- **Flow cytometry**: 4% CD45 dim blasts positive with CD34, CD13, CD33, and partially CD15.

- **IHC**: CD34 positive cells accounting for 5%. CD14: only rare positive monocytes.

- **Cytogenetics**: 46, XY. FISH negative for abnormalities of chromosome 5, 7, 20, and 8. FISH for PDGFRA and PDGFRB rearrangement negative.

- **Molecular analysis**: BCR-ABL1 neg., JAK2 neg., KIT neg.
Diagnosis

• An example of MDS/MPN
• The absence of monocytosis excludes a diagnosis of CMML
• The presence of immature myeloid cells in association with dysgranulopoietic neutrophils, dysmegakaryopoiesis MDS-type, the increased number of blasts and the absence of MPN-associated genetic abnormalities support a diagnosis of atypical CML (BCR/ABL1 neg.)

• **Diagnosis: MDS/MPN, aCML**
Atypical CML (BCR/ABL1 neg.)

- Rare, <2% of CML t(9;22)/BCR/ABL1 pos.
- Patients are older than in CML
- Variable splenomegaly
- Anemia and variable thrombocytopenia
- Neutrophilic leukocytosis (WBC $\geq 13 \times 10^9$/L)
  - $\geq 10\%$ immature myeloid cells
  - Dysgranulopoiesis (abnormal chromatin clumping)
- No or minimal basophilia (<2% of WBC)
- No or minimal monocytosis (<10% of WBC)
- Hypercellular BM with granulocytic proliferation displaying dysgranulopoiesis; variable dysplasia in the other lineages
- Cytogenetics: +8, +13, del(20q), del(12p)
aCML: Recent Bone Marrow Pathology Group Study authored by Sa Wang et al. Blood. 2014 Apr 24;123(17):2645-51

Subclassification of aCML and MDS/MPN by presence of leukocytosis (≥13x 10^9/L), PB myeloid precursors (≥10%), and dysgranulopoiesis (≥10%)
Additional molecular genetics findings in this case:

• *SETBP1* mutation detected
• *CSF3R* mutations not detected
Main distinction is with CNL
Both aCML and CNL are \textit{BCR-ABL1} negative neutrophilic neoplasms.
**Chronic Neutrophilic Leukemia (CNL)**

- Rare MPN with only ~250 pts reported
- In 20% published cases associated with M-spike (MGUS or myeloma)
- Neutrophilic leukocytosis, WBC $\geq 25 \times 10^9$/L
  - Neutrophils and bands $>80\%$
  - Promyelocytes + myelocytes + metamyelocytes $<10\%$; Blasts $<1\%$
  - Monocytes $<1 \times 10^9$/L
- Hypercellular bone marrow:
  - Neutrophilic proliferation
  - Neutrophilic maturation normal
  - Blasts $<5\%$ of marrow cells
  - Megakaryocytes normal
- Hepatosplenomegaly

Note toxic granulations
Bone marrow histology largely overlaps

**aCML**

Dysmegakaryopoiesis


**CNL**

Less significant dysmegakaryopoiesis

CSF3R mutations

IgG-like

FNIII-like Repeats

Membrane Proximal Mutations

T615A
T618I

Q741X
Q752X
D771fs
S783fs
W791X

Truncation Mutations
## CSF3R Frequency in aCML

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>All CSF3R</th>
<th>T618I CSF3R</th>
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<tbody>
<tr>
<td>Maxson et al, NEJM, 2013</td>
<td>8/20 (40%)</td>
<td>5/20 (25%)</td>
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<tr>
<td>Pardanani et al, Leukemia, 2013</td>
<td>0/19 (0%)</td>
<td>0%</td>
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<tr>
<td>Meggendorfer et al, Haematologica, 2014</td>
<td>2/60 (3%)</td>
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<tr>
<td>Piazza et al, Nat Genet, 2013</td>
<td>8/65 (12%)</td>
<td>4/65 (6%)</td>
</tr>
<tr>
<td>Wang et al, Blood, 2014</td>
<td>0/27 (0%)</td>
<td>0%</td>
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CSF3R and SETBP1 Mutations

Membrane proximal mutation:
Empirical trial with JAK1/2 inhibitors (ruxolitinib)

Truncation mutation(s):
Empirical trial with SRC inhibitors (dasatinib)


aCML: the presence of SETBP1 and ETNK1 mutation

**SETBP1**

**ETNK1**
CNL vs. aCML

**CNL**
- Neutrophilia with bands and toxic changes

**aCML**
- Neutrophilia with immature myeloid cells and dysplasia

**CSF3R** (90%)
- additional **SETBP1** +/- (50%)

**SETBP1** (15-32%)
- **ETNK1** (9%); in one third of these, coexists with **SETBP1**
- **CSF3R** (<10%)
Atypical CML $BCR-ABL1$ neg. becomes a better defined entity

- It has its own molecular profile:
  - $SETBP1$ mutations in 15-32% and $ETNK1$ mutations in 9%.
    $ETNK1$ coexistent with $SETBP1$ in 33%
  - $JAK2$, $CALR$ mutations rare or absent
  - $CSF3R$ mutations absent or very rare
- Can be separated from other MDS/MPN subtypes and from MPN (e.g., CNL, cases of MPN in AP)
- aCML has poorer survival than other MDS/MPN or MPN; novel targeted approaches much needed

Thank you for your attention