Case #073

Extramedullary Acute Myeloid Leukemia/Monoblastic Sarcoma

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Case Presentation

• A 58-year-old Caucasian female presented with 1-month duration of vague abdominal pain, low grade fever, and fatigue.

• Initial workups, including CBC with automated differential, were essentially within normal limits.
Case Presentation

• Two months later, she presented to a local ER with fever, nausea, vomiting, abdominal pain, headache, and double vision.

• Her WBC 222 x 10^9/L.
• Physical examination revealed gingival hypertrophy and bleeding, diffuse lymphadenopathy, and right upper quadrant tenderness with a positive Murphy’s sign.
• A CT scan of her abdomen showed common bile duct dilatation with thickening of the gallbladder wall but no evidence of cholelithiasis.
• A HIDA scan (hepatic immunodiacetic acid scan) showed no visualization of the gallbladder, suggesting acute cholecystitis.
Peripheral blood

- Her CBC: WBC $229.7 \times 10^9$/L (85% blasts, 1% neutrophils, 11% lymphocytes, and 3% monocytes); Hgb 5.8 g/dL; Hct 18.2%; platelets $13 \times 10^9$/L.
- A peripheral blood smear showed many blasts with monocytic features.
- Flow cytometry revealed the blasts to be CD13+(dim), CD33+, CD14+, CD64+, CD11c+, CD38+, HLA-DR+, and MPO+. These cells were negative for CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD19, CD20, CD34, CD56 or TdT.
Genetic studies

• Cytogenetics demonstrated trisomy 8.

• Molecular studies detected the Fms-like receptor tyrosine kinase 3 internal tandem duplication (FLT3 ITD) mutation.
Diagnosis

• Acute monoblastic leukemia (AML-M5).
Clinical management

• The patient received induction chemotherapy and achieved complete remission by marrow examination.

• A percutaneous cholecystostomy tube was placed for her “acute cholecystitis”.

• However, shortly after her peripheral blood count recovery, the patient complained of abdominal pain and low grade fever again.

• A cholecystectomy was performed to eliminate the possible source of the patient’s gram-negative bacteremia.
Gallbladder, cholecystectomy
Extramedullary AML of gallbladder
The neoplastic cells are also CD163+ and cytoplasmic NPM1+.
Diagnosis

Gallbladder, cholecystectomy:

- Extramedullary acute myeloid leukemia/monoblastic sarcoma.
Cytogenetics
Follow up

• Eleven days after the cholecystectomy, her peripheral blood smear showed 4% circulating blasts. Repeated marrow biopsy confirmed the AML relapse.

• The patient received reinduction chemotherapy and achieved complete remission 6 weeks later.

• She underwent ASCT from an HLA-matched sibling.

• However, her AML relapsed 2 months later and the patient died of the disease 4 months later.
Why is this case interesting?

- First presentation as cholecystitis
- Gallbladder as a sanctuary for leukemic cells
- Recurrence of AML in gallbladder
- Genetic abnormalities: +8, +13 and FLT-3 ITD mutation
- Poor prognosis
Discussion

1. Extramedullary AML involving gallbladder is uncommon.

Table 1. Extramedullary Myeloid Neoplasms (Myeloid Sarcomas)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Site</th>
<th>Cytogenetics</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25/M</td>
<td>Scrotum</td>
<td>46,XY</td>
<td>Uninvolved</td>
</tr>
<tr>
<td>2</td>
<td>66/M</td>
<td>Kidney</td>
<td>47,XY,+21</td>
<td>RAEB-2*</td>
</tr>
<tr>
<td>3</td>
<td>27/M</td>
<td>Testis</td>
<td>46,XY,del(8)(q24.2)</td>
<td>AML, M2</td>
</tr>
<tr>
<td>4</td>
<td>54/F</td>
<td>Colon, LN</td>
<td>Not done</td>
<td>AML, M2</td>
</tr>
<tr>
<td>5</td>
<td>58/M</td>
<td>Orbit</td>
<td>46,XX</td>
<td>Uninvolved</td>
</tr>
<tr>
<td>6</td>
<td>72/M</td>
<td>Skin</td>
<td>46,XY</td>
<td>Uninvolved</td>
</tr>
<tr>
<td>7</td>
<td>46/F</td>
<td>Lymph Node</td>
<td>46,XX</td>
<td>Uninvolved</td>
</tr>
<tr>
<td>8</td>
<td>62/F</td>
<td>Gingiva</td>
<td>Not done</td>
<td>Myelofibrosis</td>
</tr>
<tr>
<td>9</td>
<td>36/F</td>
<td>Vagina</td>
<td>46,XX</td>
<td>AML, M1</td>
</tr>
<tr>
<td>10</td>
<td>38/M</td>
<td>T5, T7</td>
<td>47,XY,+8,t(9;22)</td>
<td>CML-BP**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(q34;q11.2)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>58/F</td>
<td>Gallbladder</td>
<td>48,XX,+8,+13</td>
<td>AML, M5</td>
</tr>
<tr>
<td>12</td>
<td>40/F</td>
<td>Breast</td>
<td>47,XX,t(4;7)</td>
<td>AML, M1</td>
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<tr>
<td></td>
<td></td>
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<td>(p12;p11.2)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>38/F</td>
<td>Skin</td>
<td>46,XX,inv(16)</td>
<td>AML, M2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p13.1q22)</td>
<td></td>
</tr>
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</table>
2. The role of trisomy 13 (+13) in the extramedullary disease is unknown.
Congenital Trisomy 13 (Patau syndrome)
Acquired trisomy 13 in leukemia

• Case 073:
  – 48,XX,+8,+13

• Case 129:
  – Complex cytogenetic abnormalities with +13.

• Case 160:
  – 47,XX,+13
Trisomy 13 is strongly associated with AML1/RUNX1 mutations and increased FLT3 expression in acute myeloid leukemia.

AML1/RUNX1 is implicated in leukemogenesis on the basis of the AML1-ETO fusion transcript as well as somatic mutations in its DNA-binding domain. Somatic mutations in RUNX1 are preferentially detected in acute myeloid leukemia (AML) M0, myeloid malignancies with acquired trisomy 21, and certain myelodysplastic syndrome (MDS) cases. By correlating the presence of RUNX1 mutations with cytogenetic and molecular aberration in a large cohort of AML M0 (N = 90) at diagnosis, we detected RUNX1 mutations in 46% of cases, with all trisomy 13 cases (n = 18) being affected. No mutations of NRAS or KIT were detected in the RUNX1-mutated group and FLT3 mutations were equally distributed between RUNX1-mutated and unmutated samples. Likewise, a high incidence of RUNX1 mutations (80%) was detected in cases with trisomy 13 from other French-American-British (FAB) subgroups (n = 20). As FLT3 is localized on chromosome 13, we hypothesized that RUNX1 mutations might cooperate with trisomy 13 in leukemogenesis by increasing FLT3 transcript levels. Quantitation of FLT3 transcript levels revealed a highly significant (P < .001) about 5-fold increase in AML with RUNX1 mutations and trisomy 13 compared with samples without trisomy 13. The results of the present study indicate that in the absence of FLT3 mutations, FLT3 overexpression might be a mechanism for FLT3 activation, which cooperates with RUNX1 mutations in leukemogenesis.

Thank you?