Hyperleukocytosis:
A Medical Emergency

Denise Rokitka, MD, MPH

Objectives

- To understand the meaning of hyperleukocytosis
- To understand the pathophysiology of leukostasis
- To recognize the risk factors associated with the complications of hyperleukocytosis
- To know management of patients with hyperleukocytosis

Case Presentation

- 14 year old male with a one week history of cough, sore throat, intermittent fevers, and occasional joint pains.
- His joint pains were self resolved.
- He was seen by his PMD 4 days prior to arrival in the ED and was diagnosed with Strep Throat and started on Amoxicillin. However, he continued to have fevers.
- On the day of admission, he awoke with weakness, numbness, and tingling of his left side and was brought to the Emergency Department.
- He also complained of vomiting and photophobia.

Physical Exam

- Alert but very confused, not oriented to place or time but he did seem to be oriented to person
- Hepatosplenomegaly
- Diffuse Lymphadenopathy
- Lungs clear, Heart tachycardia
- Neurological- decreased tone and weakness in left arm and leg, unable to follow commands

Imaging
### Laboratories

- **Blistas**: 92%
- **PT**: 27.1
- **PTT**: 39.7
- **INR**: 2.5
- **Fibrinogen**: 84
- **LDH**: 4764
- **Uric Acid**: 13.2
- **BUN/Cr**: 13/1.5
- **Total Bilirubin**: 1.8
- **AST**: 131
- **ALT**: 28
- **ESR**: 2

### Timeline

- **3:00 PM**: Called for consult in ER, Neurosurgery consulted. Blood culture was drawn and Vancomycin and Ceftazidime were given.
- **4:30 PM**: Surgery consulted for pheresis catheter placement and FFP ordered. Fosphenytoin load given.
- **5:00 PM**: Patient to CT scanner for CT spine.
- **6:00 PM**: Patient transferred to PICU and rasburicase and hydroxurea given and CVL placed.
- **7:30 PM**: Patient transferred to MRI suite and FFP infusion started.
- **8:00 PM**: Decision to electively intubate for MRI due to inability to remain still for MRI.
- **8:30 PM**: MRI begins.

### Autopsy

- **Acute monoblastic leukemia**: M5a by FAB classifications
- **Diffuse lymphadenopathy** involving neck, axillary, pulmonary hilas, mesentery, small and large intestines and inguinal regions.
- **Parenchymal hemorrhage** and diffuse blast infiltrate of the left upper lung.
- **Splenomegaly (720 g)** with diffusely parenchymal and focal infarction.
Autopsy

- Hepatomegaly (2700 g) with acute passive congestion.
- Focal erosion of gastric mucosa, stomach.
- Shock kidneys.
- Focal infarction, right and left kidneys.
- Heart showed evidence of acute ischemic change with extensive leukostasis and patchy parenchymal infiltrate by monoblasts
- Multiple foci of intracerebral hemorrhage, bihemispheric

Leukocytosis

- WBC>100,000/µL
- Incidence: 6-15% with ALL; 12-25% with ANLL
- Higher incidence of symptomatic Hyperleukocytosis with AML/ANLL versus ALL
- Mortality: One week mortality rate is 20-40%; with major causes due to pulmonary and intracerebral complications

Associated Factors for Hyperleuk.

<table>
<thead>
<tr>
<th>AML</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 1 year</td>
<td>Age &lt; 1 year</td>
</tr>
<tr>
<td>FAB M4, M5</td>
<td>Male sex</td>
</tr>
<tr>
<td>APL microgranular variant (M3v)</td>
<td>T-cell phenotype</td>
</tr>
<tr>
<td>Chromosome 6 abnormalities</td>
<td>Leukemic cell ploidy&lt;50 ch.</td>
</tr>
<tr>
<td>Inv(16)(p13q22)</td>
<td>CNS involvement</td>
</tr>
<tr>
<td>11q23 rearrangements</td>
<td>11q23 rearrangements</td>
</tr>
<tr>
<td>Expression of lung resistance protein (LRP)</td>
<td>Ph- positive ALL</td>
</tr>
<tr>
<td>Loss of p16 expression</td>
<td></td>
</tr>
</tbody>
</table>

Leukostasis

- “The morphological evidence of intravascular accumulation of leukemic blasts occupying most or all of the vascular lumen, with or without the presence of fibrin.”

How does leukostasis happen?

- Proposed theories:
  - Increased blood viscosity in the microcirculation, and in vitro studies show that flow in capillary glass tubes is severely impaired at high concentrations of leukemic cells.
  - Myeloblasts have an even larger MCV compared to lymphoblasts, therefore increasing leucocrit further.

How does leukostasis happen?

- The leukemic blasts are highly active and associated with the release of cytokines which can exacerbate the local hypoxemia.
How does leukostasis happen?

- Leukemic blast-endothelial cell interactions lead to vascular wall disruption and bleeding, likely due to locally released cytokines such as TNF-alpha, IL-1, and IL-4.
- The up-regulation of adhesion receptors such as L-selectin and E-selectin which can promote adhesion to the vascular endothelium and therefore, lead to tissue invasion and poor flow through vessels.

Clinical Manifestations

- Respiratory distress, hypoxemia, diffuse interstitial or alveolar infiltrates.
- CNS
  - Confusion, somnolence, stupor, delirium, coma
  - Headache, dizziness, weakness, gait instability
  - Papilledema, retinal vein distention, retinal hemorrhages
- Coagulopathy/DIC
- Renal Failure

Laboratory Abnormalities

- Pancytopenia
- Increased PT/PTT
- Hyperuricemia
- Hyperphosphatemia
- Hypocalcemia
- Hyperkalemia
- Increased Lactate - evidence for poor tissue perfusion

Treatment

- Avoidance of transfusion of red blood cells when possible.
- Careful correction of coagulopathy with FFP and Platelets.
- Prevention of Tumor Lysis Syndrome
  - Hydration
  - Allopurinol/Rasburicase

Treatment

- Cytoreduction
  - Initiation of Induction Chemotherapy
  - Hydroxyurea - 50-100mg/kg/day PO q6hrs
  - Leukapheresis
Early death rates in 146 AML Patients anal initial WBC count >50 x 10^9/L - Pheresis versus non-Pheresis Groups

<table>
<thead>
<tr>
<th></th>
<th>Pheresis</th>
<th>No Pheresis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>71</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Death by end of wk 2</td>
<td>9 (13%)</td>
<td>17 (23%)</td>
<td>.174</td>
</tr>
<tr>
<td>Death by end of wk 4</td>
<td>16 (23%)</td>
<td>19 (25%)</td>
<td>.699</td>
</tr>
<tr>
<td>Death by end of wk 6</td>
<td>12 (24%)</td>
<td>21 (28%)</td>
<td>.583</td>
</tr>
</tbody>
</table>

Giles et al. Leukemia Lymphoma 2001; 42-67

Cox model for 2-week survival in 146 AML patients and initial WBC >50,000

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheresis</td>
<td>0.3</td>
<td>.0056</td>
</tr>
<tr>
<td>Increasing age</td>
<td>1.03</td>
<td>.014</td>
</tr>
<tr>
<td>Increasing WBC count</td>
<td>1.23</td>
<td>.0003</td>
</tr>
<tr>
<td>Performance status 0-2</td>
<td>0.11</td>
<td>.000006</td>
</tr>
</tbody>
</table>

Giles et al. Leukemia Lymphoma 2001; 42-67

Prognosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death within 1 week</th>
<th>Survival at 1 week</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial WBC to 10^9/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2,500</td>
<td>187</td>
<td>.009</td>
</tr>
<tr>
<td>Range</td>
<td>100-400</td>
<td>101-400</td>
<td></td>
</tr>
<tr>
<td>Initial Blasts to 10^9/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>267</td>
<td>140</td>
<td>.037</td>
</tr>
<tr>
<td>Range</td>
<td>62-475</td>
<td>45-157</td>
<td></td>
</tr>
<tr>
<td>Pheresis count to 10^9/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>86</td>
<td>58</td>
<td>.02</td>
</tr>
<tr>
<td>Range</td>
<td>16-450</td>
<td>10-260</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>14</td>
<td>.032</td>
</tr>
<tr>
<td>Female</td>
<td>19-77</td>
<td>9-79</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>21</td>
<td>.97</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>6 (28.6%)</td>
<td>3 (21.4%)</td>
<td>.02</td>
</tr>
<tr>
<td>Comorbidity (%) - Present</td>
<td>9 (45.4%)</td>
<td>6 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenic (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>14 (100%)</td>
<td>5 (14.7%)</td>
<td>.005</td>
</tr>
<tr>
<td>Neutropenic (%) - Present</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
<td></td>
</tr>
<tr>
<td>Neurological symptom (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>0 (0%)</td>
<td>1 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

Key Points

- Hyperleukocytosis is an Oncologic Emergency
- Standard of care at this time continues to be Leukophoresis and if not possible other modalities can be used.
- What could have been done differently in this case?

Treatment

- Cranial Irradiation
- Drugs to inhibit or down regulate cytokines production and adhesion molecules
- Dexamethasone inhibits up-regulation of CD18, L-selectins, and IL-8 receptors on myeloid leukemic cells

Dexamethasone inhibits up-regulation of CD18, L-selectins, and IL-8 receptors on myeloid leukemic cells