Approaching Pancytopenia

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Objectives

• Understand work up of Pancytopenia
• Present differential diagnosis of Pancytopenia
• Recognize “Not Miss” causes of Pancytopenia
• Most common indication for bone marrow biopsy
H&P

- Fever
- URI symptoms
- LAD
- Hepato or splenomegaly
- B symptoms
- Travel history
- Prescribed, non-prescribed and herbal medications
- ETOH
- Environmental and chemical exposure history
- Sexual history
Most Common Cause

• Chemotherapy
Congenital Bone Marrow Failure Syndromes

- Fanconi Anemia (Mitomycin C or Diepoxybutane test)
- Dyskeratosis Congenita (genetic testing)
- Shwachman-Diamond Syndrome (genetic testing, sweat chloride test normal)
- Congenital Amegakaryocytic Thrombocytopenia (genetic testing, elevated thrombopoietin level)
- Hemophagocytic Lymphohistiocytosis (hemophagocytosis, hypertriglyceridemia, hypofibrinogenemia, low/absent NK cell activity, elevated serum ferritin, soluble CD25 > 2,400 U/ml)
Paroxysmal Nocturnal Hemoglobinuria

- Hemolysis
- Pancytopenia
- Venous Thrombosis
- Flow Cytometry for PNH: CD CD55 and 59
Peripheral Destruction of Hematopoietic Cells

- Hemophagocytosis
- Prosthetic valves
- Splenomegaly
- Drugs
- Infection
Sequestration

• Splenomegaly
Acquired Bone Marrow Failure Syndromes

• Most often what is seen in adult population
Chemotherapy
Radiation
Autoimmune Disorders

- Aplastic Anemia
  - Idiopathic (if not caused by drugs, chemicals, radiation, virus, anorexia, pregnancy)
  - Distinguish from hypoplastic MDS (cytogenetics and FISH)
### Table 3

Cytogenetic Abnormalities Associated With MDS

<table>
<thead>
<tr>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>–7 or del(7q)</td>
</tr>
<tr>
<td>–5 or del(5q)</td>
</tr>
<tr>
<td>i(17q) or t(17p)</td>
</tr>
<tr>
<td>–13 or del(13q)</td>
</tr>
<tr>
<td>del(11q)</td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
</tr>
<tr>
<td>del(9q)</td>
</tr>
<tr>
<td>idic(X)(q13)</td>
</tr>
<tr>
<td>t(11;16)(q23;p13.3)</td>
</tr>
<tr>
<td>t(3;21)(q26.2;q22.1)</td>
</tr>
<tr>
<td>t(1;3)(p36.3;q21.2)</td>
</tr>
<tr>
<td>t(2;11)(p21;q23)</td>
</tr>
<tr>
<td>inv(3)(q21q26.2)</td>
</tr>
<tr>
<td>t(6;9)(p23;q34)</td>
</tr>
</tbody>
</table>

MDS, myelodysplastic syndrome.

*In the setting of persistent cytopenias of unknown etiology, these abnormalities are considered presumptive evidence of MDS. Adapted from Brunning et al.29*
Autoimmune Disorders

- Systemic Lupus Erythematosus
- Any other autoimmune disorder (or the treatment for it)
Marrow Space Occupying Lesions

- Heme malignancy
  - MDS/MPD
  - Leukemia
  - Lymphoma
  - Multiple Myeloma
- Metastatic malignancy
- Granulomatous disease
Infection

- Viral
- Fungal
- Bacterial
### Table 5
Infectious Etiologies Implicated in Acquired Aplastic Anemia

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus</td>
<td></td>
</tr>
<tr>
<td>Hepatitis&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>Others (dengue fever, leptospirosis, cytomegalovirus)</td>
<td></td>
</tr>
<tr>
<td>Parvovirus (aplastic crisis)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Not consistently associated with any of the known hepatitis viruses.

The Differential Diagnosis and Bone Marrow Evaluation of New-Onset Pancytopenia
Elizabeth P. Weinzierl, MD, PhD and Daniel A. Arber, MD *American Journal of Clinical Pathology*, 2013; 139, 9-29.
Hemophagocytosis

- Must have 5 of the following
  - Fever
  - Splenomegaly
  - Cytopenia involving 2 or more cell lines
  - Hypertriglyceridemia or hypofibrinogenemia
  - Hepatitis
  - Low or absent NK cell activity
  - Histiocyte activation
Ineffective Marrow Production

- Drugs
- ETOH
- Infiltration
- Deficiencies
Malignancy

• Any
  • Lung and Breast most common non heme malignancy
Drugs

• Most common cause for aplastic anemia
### Table 4
Drugs and Chemicals Associated With Acquired Aplastic Anemia

<table>
<thead>
<tr>
<th>Drugs and Chemicals</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Chloramphenicol, streptomycin, tetracycline, methicillin, mebendazole, sulfonamides, trimethoprim/sulfamethoxazole, flucytosine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Hydantoins, carbamazepine, phenacemide</td>
</tr>
<tr>
<td>Antidiabetes drugs</td>
<td>Tolbutamide, chlorpropamide</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Cimetidine, ranitidine, chlorpheniramine</td>
</tr>
<tr>
<td>Antiprotozoals</td>
<td>Quinacrine, chloroquine</td>
</tr>
<tr>
<td>Antithyroid drugs</td>
<td>Methimazole, methythiouracil, propylthiouracil</td>
</tr>
<tr>
<td>Benzene</td>
<td></td>
</tr>
<tr>
<td>Carbinazone</td>
<td></td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>Acetazolamide, methazolamide</td>
</tr>
<tr>
<td>Cytotoxic drugs used in cancer chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td></td>
</tr>
<tr>
<td>Gold</td>
<td></td>
</tr>
<tr>
<td>Insecticides</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
</tr>
<tr>
<td>Methylodopa</td>
<td></td>
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<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Phenybutazone, indomethacin, ibuprofen, sulindac, aspirin</td>
</tr>
<tr>
<td>O-penicillamine</td>
<td></td>
</tr>
<tr>
<td>Potassium perchlorate</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td>Chlorpromazine, prochlorperazine, piperacetazine, chlordiazepoxide, meprobamate, methyprylon</td>
</tr>
</tbody>
</table>

* Adapted from Shimamura and Guinan.37

The Differential Diagnosis and Bone Marrow Evaluation of New-Onset Pancytopenia
Elizabeth P. Weinzierl, MD, PhD and Daniel A. Arber, MD *American Journal of Clinical Pathology*, 2013; 139, 9-29.

Nutritional Deficiencies

- Copper
- Folate
- B12
- Anorexia Nervosa
A 29-year-old postpartum woman with new-onset pancytopenia. **A.** A peripheral blood smear demonstrated pancytopenia but was otherwise unremarkable (Wright, x60). **B.** The aspirate smear demonstrated mainly stromal cells, histiocytes, and plasma cells with a paucity of hematopoietic elements (Wright, x60). **C.** A core biopsy specimen demonstrated an extremely hypocellular marrow with an absence of hemapoietic elements (H&E, x40). Cytogenetic studies were normal. The patient was diagnosed with aplastic anemia and underwent bone marrow transplant.
A 71-year-old man with new-onset pancytopenia. 

**A**, A peripheral blood smear demonstrated hypogranular neutrophils and occasional circulating blasts. 

**B**, An aspirate smear demonstrated dysplastic megakaryocytes (arrow), megaloblastic erythroblasts, hypogranular myeloid cells, and numerous blasts. 

**C**, A core biopsy specimen demonstrated a hypercellular marrow largely replaced by blasts. On flow cytometry, the blasts expressed CD34, CD117, CD13, myeloperoxidase, and HLA-DR. Fluorescence in situ hybridization demonstrated trisomy 8. The patient was diagnosed with acute myeloid leukemia with myelodysplasia-related changes.
Work up

• H&P
  • Fever
  • URI symptoms
  • LAD
  • Hepato or splenomegaly
  • B symptoms
  • Travel history
  • Prescribed, non-prescribed and herbal medications
  • ETOH
  • Environmental and chemical exposure history
  • Sexual history

• CBC Diff
  • MCV

• Review of peripheral smear
  • blasts

• Bone Marrow Biopsy
  • Aspirate and Core
  • Flow Cytometry
  • Cytogenetics
  • FISH
  • PCR
  • *Talk to your pathologist
Not Miss

- MDS
  - Distinguish from AA
- Leukemia
  - Early treatment has better outcomes for the non elderly population
- HIV
  - I have been fooled!
- ETOH
  - I have been fooled!
Take Home Points

• H and P will lead you

• Listen to your patients but check for HIV and watch for ETOH withdrawal

• Don’t miss Leukemia (AML or ALL)

• Bone Marrow Biopsy
  • Talk to the pathologist
Thank You!!!!

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