Blood and Bone Marrow
Diagnosis: A Challenge at Any Patient Age

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Objectives

• Appreciate age-based normal lymphocyte parameters

• Identify clues to unique blood and bone marrow disorders in children and adults

• Review pancytopenia causes and clues to diagnosis based on age
Age-Related Variations in Blood Lymphocytes

• Lymphocytes predominate in blood by 2-3 weeks of age

• Sustained lymphocyte predominance in blood throughout childhood

• Neutrophils predominate by late childhood, early adolescence
Absolute Lymphocyte Count 9,000

3 yr old—normal
65 yr old—CLL
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Lymphocytosis</th>
<th>Lymphopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>&gt; 10,000</td>
<td>&lt; 2,500</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>&gt; 9,000</td>
<td>&lt; 4,000</td>
</tr>
<tr>
<td>Child</td>
<td>&gt; 7,000</td>
<td>&lt; 2,800</td>
</tr>
<tr>
<td>Adult</td>
<td>&gt; 4,000</td>
<td>&lt; 1,500</td>
</tr>
</tbody>
</table>

*Conventional units per µL*
Age, Clinical Features Key

Morphology: Non-Activated
Non-Activated Lymphs: CD4’s predominate

Age, Clinical Features Key

Child-Pertussis
Adult- Leuk/Lymphoma
Lymphs: Child vs. Adult

Blood: 10-month-old male; “Kiddie Lymphs”
Lymphs in Young Child: Distinct Vacuoles/Granules

Sialic Acid/Storage Disease
Vacuolated Lymphocytes in Adult

Mantle Cell Lymphoma
Discrete vacuoles in lymphocytes as a subtle clue to mantle cell lymphoma

Ref: Lynch DT, Foucar K. Blood 2016; 127: 3292
Lymphocytosis: Key Tips

• Dramatic age-related variations in normal
• Assess lymphocytes: morphologic heterogeneity (viral infection) vs. homogeneity (possible neoplasm); “kiddie” lymphs, pertussis
• Assess other lineages
• Sustained lymphocytosis in adult often neoplastic
• Isolated lymphocytosis in child more likely non-neoplastic
• Flow cytometric IP valuable on a limited basis (Flow may be misleading)
### Lymphocytes in Normal BM

<table>
<thead>
<tr>
<th></th>
<th>Neonates, Infants, Young Children</th>
<th>Children (&gt;4 years)</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Lymphocytes</strong></td>
<td>May exceed 40%</td>
<td>~ 15-20%</td>
<td>&lt; 5-15%</td>
</tr>
<tr>
<td><strong>Morphology of lymphocytes</strong></td>
<td>Hematogones may be abundant</td>
<td>Variable proportion of hematogones</td>
<td>Usually mature</td>
</tr>
<tr>
<td><strong>Distribution of lymphocytes</strong></td>
<td>Diffuse, small clusters</td>
<td>Diffuse, small clusters</td>
<td>Diffuse, small clusters</td>
</tr>
<tr>
<td><strong>IP of lymphocytes</strong></td>
<td>B’s predominate (HG’s)</td>
<td>Variable</td>
<td>T’s predominate</td>
</tr>
</tbody>
</table>
BMA in 2 year old with thrombocytopenia

Marked increase in lymphocytes > 50%
Morphology

Hematogones vs. Lymphs
Hematogones

- Benign B-cell precursors showing spectrum of maturation
- Key morphologic feature: homogeneous, dense chromatin
- Diffuse, small clusters on biopsy, clot section
- Spectrum of maturation confirmed by flow cytometry, IHC
- Key clinical settings: young patient (variety of pediatric conditions), BM recovery
Bone Marrow: Hematogones

- **CD45** Range in CD45
- **CD10** Range in CD10
- **CD20** Spectrum of maturation
Hematogone-like ALL
ALL, Precursor B
Cytopenias

• Single, bicytopenia, pancytopenia

• “Explained” vs “Unexplained”
# Age-Based Approach to Pancytopenia

<table>
<thead>
<tr>
<th>Age</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate:</td>
<td>Infection, germline disorder, maternal therapy/underlying illness</td>
</tr>
<tr>
<td>Infant:</td>
<td>Infection, nutritional deficiency, neoplasm, germline disorder</td>
</tr>
<tr>
<td>Child:</td>
<td>Infection, systemic illness, nutritional deficiency, neoplasm</td>
</tr>
<tr>
<td>Adult:</td>
<td>Infection, systemic illness, medications, nutritional def., neoplasms, homeopathic remedies</td>
</tr>
</tbody>
</table>
Case: Pancreatitis

History:

83 year old female with fatigue and bruising

CBC:

WBC 5.5  
MCV 98

H/H 9.4/27  
Plt 10
Blood

70% abnormal cells
Blood: Pancytopenia

- Absolute Neutrophil ct.: $0.1 \times 10^9 /L$
- Platelet Count: $10 \times 10^9 /L$
- Moderate N/N Anemia

Hematopoietic Failure
Flow Cytometry

CD33
CD34
HLA-DR
CD13

SSC

CD11
7
Flow Cytometry Cytospin

Dx: ?
FISH for *PML-RARA*

PML (red) RARA (green)
Additional Studies

• Quantitative PCR for *PML-RARA*
  Positive – high copy number (typical at diagnosis)

• **Final Diagnosis:**
  Acute Promyelocytic Leukemia
  (confirmed molecularly)
Acute Promyelocytic Leukemia

• Rapid diagnosis essential
• Morphologic features are highly characteristic; rapid MPO cytochemical stain valuable
• Flow cytometry features are highly characteristic
• *PML-RARA* fusion gene may be cryptic by FISH (6% of cases)
• PCR can detect fusion gene in false negative FISH cases
Case: Bicytopenia

78-yr-old female with neutropenia, anemia and progressive functional decline.

**CBC:**
WBC 1.5, Hgb 9.1, Hct 28%, MCV 98 Fl, RDW 16.7%, Plt 177
Blood - Bicytopenia
BM Aspirate
BM Aspirate - Vacuoles
BM biopsy - Normocellular
Case: Diagnosis

Anemia and neutropenia secondary to zinc-induced copper deficiency
Case: Disease Course

- Searched EMR re dentures (found in Nurses notes)
- Alerted hematologist
- Additional history: patient never removed dentures even at night
- Serum zinc 166 (H)
- Serum copper < 10(L)
- Complete resolution of CBC and functional deficits after copper therapy
Features of Copper Deficiency

• Neurologic syndrome mimics subacute combined degeneration of cobalamin deficiency

• Patients may also have ataxic myelopathy

• Copper deficiency from zinc ingestion, prolonged parenteral nutrition, enteric feeding, following gastrectomy, liver disease (alcoholism) denture pastes (formerly)

• Cause of deficiency may not be apparent
Case: Pancytopenia

42-yr-old male with 2 week history SOB, gum bleeding, tingling sensation upper and lower extremities, weight loss, malaise, weakness.
<table>
<thead>
<tr>
<th>CBC</th>
<th>WBC</th>
<th>3.2 (↓ ANC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>Hgb</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Hct</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>RDW</td>
<td>30.7%</td>
<td></td>
</tr>
<tr>
<td>Plt</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Retic</td>
<td>5.9%</td>
<td></td>
</tr>
<tr>
<td>4 NRBC/100WBC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Blood-Pancytopenia
NRBC at Feather
Blood-Pancytopenia
Case: Diagnosis

Clinical dx: TTP

Blood smear dx: ?
Additional Labs

Absolute retic 0.07  N1

Haptoglobin < 8  ↓

LDH 1600  ↑

Vitamin B\textsubscript{12}  93  ↓
Case: Diagnosis

Megaloblastic anemia mimicking TTP

Reference
Follow Up Labs

ADAMTS13: 71 N1
MMA: 3.08 ↑
IF ab: positive
Shiga toxin: negative
Case: Key Tips

• Megaloblastic anemia can manifest with pancytopenia

• Oval macrocytes broken in spleen (frags, ↑ RDW)

• MCV 122 — not due to retics (Note MCV may be normal in Meg An)

• Retic % was elevated but not absolute retic count
Case: Pancytopenia

14-year-old African-American female with no past medical history; presents with emesis x 3 days, excessive fatigue, decreased appetite

**CBC:** WBC 1.9, RBC 1.4, Hgb 4.7, Hct 13.6%, MCV 99, MCHC 34.8, RDW 34%, Plt 67
Blood: 14-year-old girl
Blood: 14-year-old girl
Blood: 14-year-old girl
Bone Marrow Biopsy
Case: Differential Diagnosis

- Congenital dyserythropoietic anemia
- Other constitutional RBC disorder
- Myeloid neoplasm (pancytopenia, packed bone marrow)
- Megaloblastic anemia (?? normal MCV)
Case: Additional Lab Data

- Low serum cobalamin
- Increased homocysteine
- Increased methylmalonic acid
- Positive intrinsic factor
Case: Final Diagnosis

*Megaloblastic anemia,*  
*pernicious anemia*

Follow-up:  
Patient responded to cobalamin therapy
Megaloblastic Anemia Caveats

• Highly variable blood picture (normal MCV, lack of “classic” features)

• Risk of vitamin B$_{12}$ deficiency-associated neurologic impairment significant, especially in infants

• If cobalamin level is borderline but not below lower limit, still pursue other tests—MMA, IF ab, etc.
Summary

• Clinical information, CBC data, blood smear and bone marrow morphology essential

• Correlation with age-related normal parameters essential

• Appreciation of the full spectrum of findings in megaloblastic anemia and copper deficiency is key to distinction from a neoplasm or other condition

• Pancytopenia may have non-neoplastic or neoplastic cause