Hematologic Disease in Internal Medicine with an Emphasis on the Elderly

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Hematological Disease in the Elderly

• Anemia
• Clonal Disorders of Hematopoiesis
• Hematologic Malignancies
  - Leukemia
  - Lymphoma
  - Plasma Cell Dyscrasias
Clinical Features of Anemia

- **Symptoms** - Fatigue, Syncope, Dyspnea, Headache, Palpitations, Confusion, Angina
- **Signs** - Pallor, Icterus, Tachycardia, High-Output Heart Failure, Ascites
- **Laboratories** - CBC, Reticulocyte Count, MCV, Erythropoietin Level, LDH, Peripheral Blood Smear
Reticulocyte Count

First Correction = \( \frac{\text{\% reticulocytes}}{\text{Hemoglobin Count}} \)  

Second Correction = First Correction \( \frac{\text{Hemoglobin Patient}}{2} \)  
(if nRBCs are present)
Anemia - A Diagnostic Approach

• Definition
  - Hgb < 13 g/dl in males
  - Hgb < 11.5 g/dl in females

Hypoproliferative  Ineffective  Compensatory
(Compensatory) (Hemolytic)

Reticulocytopenic Anemias
Reticulocytopenic Anemias

Hypoproliferative  Ineffective
(MCV - normal or low)  (MCV - high)
ERC
→
PRONORMOBLAST
→
×2
BASOPHILIC
NORMOBLAST
→
×2
POLYCHROMATOPHILIC
NORMOBLAST
→
×2
EOSINOPHILIC
NORMOBLAST
→
×2
NUCLEATED
RED CELL
→
RETICULOCYTE
Hypoproliferative Anemia

- Deficiency of Iron
  - Chronic blood loss
  - Dietary or Impaired Absorption
  - Urinary Loss
  - Hemodialysis
- Hemoglobinopathies
Hypoproliferative Anemia (cont.)

- Disorders of Heme Synthesis
  - Lead intoxication
  - INH, Pyrazinamide
- Sideroblastic
- Anemia of Chronic Disease
Causes of Iron Deficiency

• Blood Loss
• Gastrointestinal (varices, peptic ulcer, nonsteroidal agent, angiodysplasia, neoplasia, inflammatory bowel disease, parasites)
• Renal
• Pulmonary
• Phlebotomy
• Malabsorptive (gastritis, intestinal disease, gastric surgery)
# Malignancies in Elderly Patients

(from Scott R. Comprehensive Therapy 20: 575-579; 1994)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>740</td>
<td>0</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>4.3</td>
<td>403</td>
</tr>
<tr>
<td>Lung</td>
<td>502</td>
<td>174</td>
</tr>
<tr>
<td>Colon / Rectum</td>
<td>418</td>
<td>288</td>
</tr>
<tr>
<td>Hematologic</td>
<td>184</td>
<td>118</td>
</tr>
<tr>
<td>Stomach</td>
<td>80</td>
<td>36</td>
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Fe Deficiency vs. Anemia of Chronic Disease

• 70 - 75% of Anemia of the Elderly
• Chronic Disease Consists of Chronic Inflammation
  - Neoplasia
  - Infection
  - Rheumatologic Disease
• Both Conditions May Co-Exist in a Patient
The Case For/Against Parenteral Iron

• Deficiency Despite Oral Therapy

• Poor Tolerance

  Dose of Fe dextran =
  \[0.0476 \times \text{wt in kg} \times (14.8-\text{hemoglobin})\]
  +6 in women
  +4 in men
  given in IM in small doses or
  given in IV in single infusion

• Ascorbate
Other Hypoproliferative Microcytic Disorders

• Aplastic Anemia
• Thalassemia
• Sideroblastic Anemia
• Anemia of Chronic Disease
• Marrow Infiltrative Disorders
Disorders of Ineffective Hematopoiesis

- Reticulocytopenia with Elevated MCV
- Differential Diagnosis
  - Deficiency of B12 or Folic Acid
    - Dietary, Drugs, Malabsorption, Parasites, Intrinsic Factor insufficiency, Increased requirement, impaired metabolism
  - Drug-induced
  - Inborn errors of metabolism
  - Myelodysplasia
  - Other – Vitamin C, B6, thiamine deficiency
  - Endocrinopathy
Characteristic Features of Megaloblastic Anemia

• Signs – jaundice, vitiligo, glossitis, cheilosis, neurologic dysfunction

• Laboratory – Red Blood Cell Folate, Hemocysteine, Methylmalonic Acid
Compensatory (Hemolytic) Anemias

- Vasculopathy
  - Macroangiopathic
  - Microangiopathic
- Plasma Factors
  - Envenomation
  - Tocins
- Membraneopathy
  - Congenital
  - Acquired
    - Immune
    - Infections
    - Collagen-Vascular
    - Drug-Related
    - Neoplastic
    - Physical Agents
Compensatory (Hemolytic) Anemias (cont.)

• Hemoglobinopathy

• Enzymopathy

• Infections
Hematological Diseases- A Spectrum of the Benign and the Malignant

• Cytopenias

• Clonal Disorders of Hematopoiesis

• Hematologic Malignancies
  - Leukemia
  - Lymphoma
  - Plasma Cell Dyscrasias
  - Coagulopathies- Hemorrhagic and Prothrombotic
Cytopenias

• Clinical manifestations depend on the cell that is missing

• The workup can be via a pathophysiologic or “kinetic” approach:
  • Disorders of Diminished Production
  • Disorders of Ineffective Production
  • Disorders of Consumption
Disorders of “too much”- Cytoses

• Primary- due to a disorder of cell growth and regulation in the marrow- usually clonal and characterized by distinct cytogenetic or molecular features (some, as yet, undiscovered)

• Secondary- due to an extramedullary stimulus, typically polyclonal. Also called “reactive”
Clonal Disorders of Hematopoiesis

Myelodysplasia

Myeloproliferative Syndromes

Acute Myelogenous Leukemia

Aplastic Anemia

P.N.H.
Chronic Myeloproliferative Disorders

• Characterized by:
  • Hepatosplenomegaly
  • Hypermetabolism
  • Clonal increase in numbers of one or more circulating mature blood cell types
  • Clonal hematopoiesis without dysplasia
  • Predisposition to evolution to acute leukemia
Mechanisms of Oncogenesis

Constitutive activation of bcr-abl tyrosine kinase
-Intracellular signaling pathway activation

Altered proliferation, adhesion, survival
Mechanism of Action of Imatinib Mesylate

POLYCYTHEMIA VERA

DEFINITION: Hematopoietic Stem Cell Disorder- JAK2 V617F in 95%
  Sustained Erythrocytosis
  Increased RBC Mass
  Cellular Proliferation

PREVALENCE: 0.5-2.6 per 100,000
AGE: Peak Onset Age 50-60
SEX: Male > Female

Ethnic Predisposition: Less common in Asians, more common in Ashkenazi Jews
Myelodysplasia

- Oligoclonal Disorder of Hematopoiesis
- Progressive Cytopenias
- Variable Risk of Evolution to Acute Leukemia - R-IPSS Risk Stratification on-line

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<thead>
<tr>
<th>Type</th>
<th>Risk of Transformation</th>
<th>Median Survival</th>
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<tbody>
<tr>
<td>RA</td>
<td>11-26%</td>
<td>17-64 mos</td>
</tr>
<tr>
<td>RARS</td>
<td>5-39%</td>
<td>16-52 mos</td>
</tr>
<tr>
<td>RAEB</td>
<td>27-66%</td>
<td>9-17 mos</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>50-81%</td>
<td>5-10 mos</td>
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Diagnosis of Myelodysplasia

• Laboratory Features – (Macrocytic) Anemia with or without leukopenia, thrombocytopenia, monocytosis dysplasia of the marrow elements, abnormal cytogenetics
Management of Myelodysplasia

• Supportive – Antibiotics, Transfusion, Hematopoietins

• Remittive – Differentiating Agents, Cytotoxics
Acute Myelogenous Leukemia - EPIDEMIOLOGY

1) Incidence – 2.5 per 100,000; 
   ? Rising Incidence Over Time

2) Age-Related Increase 
   (Approximately 20 per 100,000 Over Age 80)

3) Increase Male:Female 
   (Approximately 2:1 in the Age Group Over 65)

4) Geographic Distribution

5) Ethnic Differences
MYELOMA
CLONAL PROLIFERATION OF PLASMA CELLS

“CROWDING OUT” OF NORMAL MARROW CELLS
PANCYTOPENIA, ANEMIA, INFECTIONS, BLEEDING
BONE LESIONS
TUMOR GROWTH + BONE RESORPTION
CELLS MAKE IL-1 & OTHER BONE RESORBING FACTORS
“PUNCHED OUT” OSTEOLYTIC LESION ON XRAY
(NO OSTEOBLASTIC COMPONENT)
BONE PAIN, PATHOLOGIC FX, HYPERCALCEMIA
INCREASED CELL TURNOVER
URIC ACID & CALCIUM PHOSPHATE DEPOSITS
MYELOMA
CLINICAL FINDINGS

PATHOLOGIC FRACTURES
PANCYTOPENIAS
INCREASED INFECTIONS
RENAL FAILURE
HYPERVISCOSITY
LYMPHOID-PLASMACYTOID CELLS IN MARROW +/- BLOOD
CLONAL PRODUCTION OF IGM
IGM PENTAMERS, HYPERVISCOSITY
SYMPTOMS FROM HYPERVISCOSITY
FATIGUE, MALAISE, SOB, NEUROL, BLEEDING, HEADACHE, VISION
NO BONE LESIONS

WALDENSTROMS MACROGLOBULINEMIA
CHRONIC LYMPHOCYTIC LEUKEMIA

CLINICAL FEATURES

Lymphocytosis
Lymphadenopathy,
Hepatosplenomegaly
Frequent infections
Immunologic abnormalities
  hypogammaglobulinemia
  immune cytopenias,
  Paraproteinemias
Histologic transformation
Secondary malignancies
CHRONIC LYMPHOCYTIC LEUKEMIA

LABORATORY FINDINGS

Lymphocytosis with morphologically Mature b cells
MONOCLONAL LYMPHOCYTES (κ or λ Ig)
Coexpression of CD5 (a T cell marker) with CD19 & 20 (B cell markers)
Anemia, thrombocytopenia (marrow replacement or immune-related)
Hypogammaglobulinemia (paraproteins)
Marrow infiltration with cll cells
Lymph nodes (diffuse small cell lymphoma)
Responsive but not curative with standard rx

Treat only if symptomatic
   Alkylators, fludarabine, combination chemo
   Steroids (immune cytopenias)
   Monoclonal antibody therapy
   Ibrutinib, Idelalisib
   Treat infections and other complications

   High dose therapy with blood or marrow transplant
   In younger patients with an allo- donor

Median survival varies with stage of disease
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