Evaluation of Bone Marrow Biopsies in Patients with Cytopenias

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Cytopenias

- The most common indication for non-staging bone marrow biopsy and aspiration
- May be incidental finding(s) from routine examination
- May be associated with symptoms
  - Fatigue
  - Fever
  - Weight loss

General Causes of Cytopenias

- Failure to produce
  - Marrow failure in one or more cell lines
  - Reduced normal marrow due to space occupying proliferation
    - Acute leukemia
    - Metastatic tumor
    - Fibrosis
- Peripheral destruction or loss
  - Hypersplenism
  - Bleeding
  - Drugs
- Infection-related
- (Auto)Immune mediated
  - Autoimmune disorders
  - Drugs
- Ineffective production
  - Myelodysplastic syndromes

Cytopenia Definitions

- Leukopenia (<4.0 x 10^9/L)
  - Neutropenia (<1.8 x 10^9/L)
    - <1.5 x 10^9/L
    - <1.0 x 10^9/L for African-Americans
  - Lymphopenia
    - <1.5 x 10^9/L in adults
    - <2.0 x 10^9/L in children
  - Monocytopenia
    - <0.2 x 10^9/L
- Anemia (<12.0 g/dL woman; <13.5 g/dL man)
  - <10.0 g/dL
- Thrombocytopenia (<150 x 10^9/L)
  - <100 x 10^9/L
Case 1

83-year-old man with neutropenia and macrocytic anemia

- WBC: 6.2 K/µL
- RBC: 2.82 MIL/µL
- HGB: 9.8 g/dL
- HCT: 29.1%
- MCV: 103 fL
- MCH: 34.5 pg
- MCHC: 33.5
- RDW: 30.9%
- PLT: 303 K/µL
- Neut 13.7%
- Lymph 82.5%
- Mono 3.7%
- Eos 0.1%
- ABS NEUTS: 0.85 K/µL
Peripheral Blood Flow Cytometry

- Predominance of T-cells
  - Predominance of CD8+ T-cells
  - CD57 expression on some T-cells
  - No definite loss of T-cell antigens
- No increase in NK- or B-cells
  - B-cells polytypic
Molecular Genetics of Peripheral Blood

Clonal T-cell receptor gamma chain gene rearrangement detected by PCR analysis

Case 1

Diagnosis: T-cell Large Granular Lymphocytic Leukemia
T-cell Large Granular Lymphocytic Leukemia

- Persistent LGLs in the blood (usually $2.0 \times 10^9/L$ or greater)
- Middle age or older adults with no sex predilection
- Complete blood count
  - Neutropenia +++
  - Anemia +/-
  - Thrombocytopenia --
- Association with sustained immune stimulation/rheumatoid arthritis
- CD8+ T-cells that are usually clonal and express CD57, but may lose CD5
- Indolent clinical course with morbidity due to infection

Causes of Acquired Neutropenia

- Drugs and Therapy
- Infections
  - EBV
  - Hepatitis
- (Auto)Immune
  - Rheumatoid arthritis
  - Chronic idiopathic neutropenia
- Complement Activation
  - Dialysis
  - Cardiac bypass surgery
- Nutritional deficiencies
  - B12, folate
  - Copper (gastric bypass surgery)
- Paraneoplastic
  - LGL leukemia
  - Hodgkin lymphoma
  - Wilms tumor
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Lymphopenia

- Infectious
  - HIV
- Drugs/Therapy
  - Corticosteroids
- Autoimmune disorders
- Congenital
- Physiologic stress
  - Extreme exercise
  - Myocardial infarction
  - Stroke

Monocytopenia

- Hairy cell leukemia
- Chronic lymphocytic leukemia
- Aplastic anemia
- Severe burns
- Autoimmune disorders
- HIV infection
- Drugs/Therapy
  - Glucocorticoids
  - Radiation exposure
  - Hemodialysis
Case 2

A 45-year-old man status post kidney and pancreatic transplant 8 months earlier, now with anemia and transferred with a diagnosis of myelodysplastic syndrome. A bone marrow was performed to confirm the diagnosis and evaluate blast percentage.

CBC Data

WBC: 6.4 K/uL
RBC: 2.73 mil/uL
HGB: 8.2 g/dL
HCT: 23.3 %
MCV: 85.4 fL
PLT: 374 K/uL
RDW: 14.0 %
ABS NEU: 4.10 K/uL
ABS LYM: 1.45 K/uL
Case 2

Diagnosis: Parvovirus B19 infection
Parvovirus B19 Infection
- Small non-enveloped DNA virus
- Most infections occur in childhood
- Causes “fifth disease” (erythema infectiosum) and polyarthropathy
- Acute infection usually causes self-limited RBC aplasia for 4-8 days
- Patients with pre-existing RBC abnormalities, such as SS disease develop aplastic crisis
- Chronic infection occurs with immunosuppression

Causes of Red Cell Aplasia
- Congenital or seemingly congenital
  - Diamond-Blackfan anemia/syndrome
  - Fetal red cell aplasia (non-immune hydrops fetalis)
  - In utero Parvovirus B19 infection
- Acquired
  - Transient erythroblastopenia of childhood
  - Transient pure red cell aplasia
  - Chronic pure red cell aplasia
  - Acute Parvovirus B19 infection
  - Drug induced
  - Immune mediated disorders
- Associated with another condition
  - Chronic lymphocytic leukemia
  - Large granular lymphocytosis
  - 5q-minus myelodysplasia
  - Parvovirus B19 infection associated with immunodeficiency
    - HIV
    - Transplantation
    - Thymoma
    - Pregnancy

RBC aplasia secondary to thymoma
Parvovirus B19 Infection

- Differential diagnosis of red cell aplasia
- Differential diagnosis of myelodysplasia
  - Especially with a history of immunosuppression

Thrombocytopenia

- Artifactual
  - EDTA-clumping
  - Satellitism
- Decreased production
  - Hereditary
  - Acquired (MDS)
- Increased destruction
  - Immune
    - Idiopathic
    - Infectious
    - Drugs
    - Pregnancy
  - DIC, TTP, HUS
  - Hypersplenism
  - Hemophagocytic syndromes
- Abnormal distribution
  - Splenomegaly
  - Hypothermia
  - Dilution
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  - EDTA-clumping
  - Satellite
- Decreased production
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  - Acquired (MDS)
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    - Pregnancy
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  - Hemophagocytic syndromes
- Abnormal distribution
  - Splenomegaly
  - Hypothermia
  - Dilution

Case 3

75-year-old man with pancytopenia and splenomegaly without adenopathy. A prior bone marrow at another hospital reportedly detected bone marrow involvement by follicular lymphoma. A bone marrow was performed to confirm the diagnosis. No marrow aspirate could be obtained.
CBC Data

WBC: 1.4 K/μL
RBC: 3.16 MIL/μL
HGB: 9.6 g/dL
HCT: 28.3%
MCV: 89.7 fL
RDW: 20.1%
PLT: 61 K/μL
AUTO DIFF: NEU: 10.7%; LYM: 81.1%;
MONO: 7.4%; EOS: 0.7%; BASO: 0.1%
Kappa monotypic B cells expressing CD10, CD25 and CD103
Case 3

Diagnosis: Hairy Cell Leukemia

Hairy Cell Leukemia

- A rare clonal, mature B cell neoplasm that is CD5 negative and usually CD10 negative
  - Approximately 600 new cases in US each year
- Occurs primarily in middle aged men
- Characteristically involves blood, marrow and splenic red pulp without lymphadenopathy
- Patients typically present with pancytopenia with monocytopenia

Hairy Cell Leukemia

- Often hard to find the cells in blood
- Marrow infiltrate is interstitial and subtle, especially early in the disease
- Can be missed by flow cytometry if the monocyte or large lymphoid gate is not analyzed

Hairy Cell Leukemia Gating

HCL  SMZL
Hairy Cell Leukemia Immunophenotype

- Flow cytometry
  - CD19 and CD20 positive and light chain restricted
  - CD5 negative
  - CD10 positive in 10-25%
  - CD25 positive
  - CD11c positive
  - CD103 positive
- Immunohistochemistry
  - TRAP and DBA.44 positive
  - Annexin A1 positive
  - T-bet positive
  - Cyclin D1 weak positive
Hairy Cell Leukemia Variants

- Immunophenotypic variants
  - Expression of CD10 and/or CD23, or lack of bright CD11c, CD25 or CD103 may occur and does not appear to be clinically significant (Am J Clin Pathol 125:251, 2006)
- Morphologic variant
  - Prominent nucleoli and higher white blood cell counts
  - Some cases represent splenic marginal zone lymphoma or mantle cell lymphoma
  - True cases rare and appear distinct for typical hairy cell leukemia

Pancytopenia at Stanford

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Adults</th>
<th>Children</th>
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<tbody>
<tr>
<td>Acute myeloid leukemia</td>
<td>14%</td>
<td>5%</td>
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<tr>
<td>Lymphoblastic leukemia</td>
<td>6%</td>
<td>83%</td>
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<tr>
<td>Mixed phenotype acute leukemia</td>
<td>2%</td>
<td>2%</td>
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<tr>
<td>Myelodysplastic syndrome</td>
<td>43%</td>
<td>2%</td>
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<tr>
<td>Chronic myelomonocytic leukemia</td>
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</tr>
<tr>
<td>Myeloproliferative myelofibrosis</td>
<td>5%</td>
<td>--</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>2.5%</td>
<td>--</td>
</tr>
<tr>
<td>B-cell lymphoma</td>
<td>7%</td>
<td>--</td>
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<tr>
<td>Langerhans cell histiocytosis</td>
<td>2%</td>
<td>--</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>2%</td>
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Non-neoplastic causes of pancytopenia in adult and pediatric patients at Stanford

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Adults</th>
<th>Children</th>
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</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>-</td>
<td>12.5%</td>
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<tr>
<td>Nonspecific findings*</td>
<td>77%</td>
<td>62.5%</td>
</tr>
<tr>
<td>Drug related</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Infection</td>
<td>8.5%</td>
<td>12%</td>
</tr>
<tr>
<td>Multifactorial/systemic disease</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td>Hypersplenism</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Other autoimmune</td>
<td>-</td>
<td>6%</td>
</tr>
<tr>
<td>Congenital disorders</td>
<td>-</td>
<td>6%</td>
</tr>
<tr>
<td>Unknown</td>
<td>15.5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

* etiology determined, when possible, based on non-bone marrow findings


Summary

- A variety of disorders result in cytopenias
- Clinical and drug history can clarify many causes
  - Autoimmune disorders
  - Viral and other infectious diseases
  - Drug reactions
- Bone marrow evaluation is helpful when the above have been excluded
- Neoplastic disorders are the most common cause of pancytopenia

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Thank you for your attention