Hematologic Malignancies
White Cell Basics

You are now at the beginning of the WBC Basics study section.

Leukocytes or WBCs are found in a thin gray layer known as the buffy coat in centrifuged blood. Above the leukocytes lie the platelets.

Leukocytes are primarily defensive, but also have important sanitation and recycling duties.

Before reviewing the origin and development of WBCs let us first look at the mature WBC population normally found in the peripheral blood (buffy coat), including neutrophils, eosinophils, basophils, monocytes, and lymphocytes.

**Neutrophils** The mature neutrophil (12-15u dia) is characterized by segmentation into 2-5 lobes. The chromatin is dense and clumped with distinct lighter areas of parachromatin.

The cytoplasm is lightly eosinophilic with variable numbers of light staining "neutral" granules and a few and a few azurophilic 1 granules, persistent from earlier stages.

Neutrophils are important in the inflammatory process (as phagocytes and mediators of inflammatory reactions).
Bone Marrow
Hemopoiesis: The Blood Cell Lineage
“Blast” Forms

- “Blast” forms – immature cells, undifferentiated
- Blasts – CD34 Ag
- Percentage of “blasts” often determines label
Pluripotential Stem Cell

- Red Blood Cells (transport hemoglobin)
- Granular Cells (derive from myelocytes)
- Megakaryocytes - platelets
- Lymphocytes, Monocytes
Leukocytes - Granulocytes

Leukocytes – engulf and kill bacteria & viruses

- a.k.a. WBCs – 5 types
- Granulocytes & Agranulocytes
- Granulocytes
  - neutrophils
  - eosinophils
  - Basophils
Leukocytes - Agranulocytes

Lymphocytes - in blood, also spleen, lymph nodes

- “B” – plasma cell – multiple myeloma, macroglobulinemia
- “T” – thymus

Monocytes
**Eosinophils** The large orange granules of the eosinophil make the eosinophil the most readily recognizable cell in the blood. The eosinophil (12-15μ diameter has chromatin similar to that of a neutrophil, but usually fewer (2-3) lobes.

Normally 0-6% eosinophils are found in the peripheral blood.

The eosinophil specific granules contain rhomboid crystals by EM. This core contains Major Basic Protein (MBP), known to be toxic to several parasites (helminths, microfilariae; schistosomiasis), and some mammalian cells.

Compare the granules of the neutrophil (at left) with those of the eosinophil (at right).
Lymphocytes vary greatly in size (7-20m dia) and in nuclear and cytoplasmic character. The small lymphocyte (7-12m dia) has a round-oval nucleus with dense clumped "smudgy" chromatin; no visible nucleolus. Scanty light blue cytoplasm, while usually agranular, may contain a few small red granules. Contrast the chromatin of the lymphocyte and neutrophil. The lymphocyte at right is 15-18m dia.

Normal peripheral blood lymphocyte percentages vary from 15-60%.

Lymphocytes with peripherally clumped chromatin and often deep blue cytoplasm similar to plasma cells are termed plasmacytoid lymphocytes.
Leukemia

Definition:
“An uncontrolled production of white blood cells, which is caused by cancerous mutation of myelogenous or lymphogenous cells”

Leukemias: Classification

Acutes → Leukemias → Chronics

Lymphocytic (ALL)

Myelocytic (AML)

Lymphocytic (CLL)

Myelocytic (CML)
# Features of Major Leukemias

<table>
<thead>
<tr>
<th>Feature</th>
<th>Acute Lymphoblastic</th>
<th>Acute Myelogenous</th>
<th>Chronic Lymphocytic</th>
<th>Chronic Myelocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age of incidence</td>
<td>Childhood</td>
<td>Any age</td>
<td>Middle and old age</td>
<td>Young adulthood</td>
</tr>
<tr>
<td>WBC concentration</td>
<td>H in 50% N or L in 50%</td>
<td>H in 60% N or L in 40%</td>
<td>H in 98% N or L in 2%</td>
<td>H in 100%</td>
</tr>
<tr>
<td>Differential WBC count</td>
<td>Many lymphoblasts</td>
<td>Many myeloblasts</td>
<td>Small lymphocytes</td>
<td>Entire myeloid series</td>
</tr>
<tr>
<td>Anemia</td>
<td>In &gt; 90%, severe</td>
<td>In &gt; 90%, severe</td>
<td>In about 50%, mild</td>
<td>In 80%, but mild</td>
</tr>
<tr>
<td>Platelets</td>
<td>L in &gt; 80%</td>
<td>L in &gt; 90%</td>
<td>L in 20–30%</td>
<td>H in 60%; L in 10%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Commonly seen</td>
<td>Occasionally seen</td>
<td>Commonly seen</td>
<td>Infrequently seen</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>60%</td>
<td>50%</td>
<td>Usual and moderate</td>
<td>Usual and severe</td>
</tr>
<tr>
<td>Other features</td>
<td>50% CNS occurrence after 1 yr</td>
<td>Rare CNS occurrence; Auer rods may be seen in myeloblasts</td>
<td>Occasional hemolytic anemia and hypogammaglobulinemia</td>
<td>Leukocyte alkaline phosphatase low; Philadelphia chromosome positive in 85%</td>
</tr>
</tbody>
</table>

L = low; N = normal; H = high.
Further Classified by:

- Cell types
- Chromosomal abnormalities
- Molecular & Immunologic Markers
Conceptual Organization of Hematologic Malignancies

- Hematologic malignancies
  - Lymphoid disorders
    - Acute lymphocytic leukemia
      - Lymphoma
        - Hodgkin's disease
        - Non-Hodgkin's lymphoma
          - T cell chronic lymphoid leukemias
          - B cell chronic lymphoid leukemias
    - Other lymphoproliferative disorders
      - Myeloma
      - Chronic lymphoid leukemias
  - Myeloid disorders
    - Chronic myeloid disorders
      - Chronic myeloproliferative disorders
        - Polycythemia vera
        - Essential thrombocythemia
        - Myelofibrosis with myeloid metaplasia
    - Acute myeloid leukemia
      - Myelodysplastic syndrome
      - Chronic myelogenous leukemia
      - Atypical chronic myeloid disorders
      - Atypical CML
      - Chronic neutrophilic leukemia
      - Mast cell disease
      - Chronic eosinophilic leukemia
Hematopoietic Disease

Lymphoid Disorders

Myeloid Disorders
Myeloid Disorders

- Acute Myeloid Leukemia (AML)
- Chronic Myeloid Disorders
- Myeloproliferative Disorders
- Myelodysplastic Syndrome (MDS)
Myelodysplastic Syndromes (MDS)

- Bone Marrow Dysfunction
- Impaired production and maturation
- a.k.a. pre-leukemia, sub-acute leukemia, smoldering leukemia, refractory anemia
MDS

- Neoplastic clonal stem cell disorder
- Results in ineffective hematopoiesis; Cells destroyed before leave BM: cytopenia
  - Refractory anemia, neutropenia, thrombocytopenia
  - May precede acute leukemia (AML) or BM failure
  - Often follows chemo/radiation therapy
  - Dx often made in retrospect
MDS

Some are “unclassifiable” or “atypical”
Myeloproliferative Disorders

- Essential Thrombocytosis
- Polycythemia Rubra Vera
- Agnogenic Myeloid Metaplasia/Myelofibrosis
- Chronic Myelogenous Leukemia
MyeloProliferative Disorders

- Abnormal proliferation of one or more cell lines.
- CML - granulocytosis
- Polycythemia vera - RBC
- Essential thrombocythemia - thrombocytosis
- Myelofibrosis –aka myeloid metaplasia
- Mastocytosis
- See Bulletins 3-11, 3-32
Lymphomas

- Diverse group of tumors arising from immune cells (solid, lymphoid lineage)
  - Neoplastic proliferation of lymphoid cells that disseminate thru body
  - “lymphoproliferative disorder”
  - aka reticulosarcoma (old term)
Hodgkin’s vs. Non-Hodgkin’s Lymphoma (NHL)

<table>
<thead>
<tr>
<th>Hodgkin’s</th>
<th>Non-Hodgkin’s Lymphoma (NHL)</th>
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</thead>
<tbody>
<tr>
<td>Reed Sternberg cell</td>
<td>Disseminated</td>
</tr>
<tr>
<td>Localized to specific nodes</td>
<td>Rapid spread, non-contiguous</td>
</tr>
<tr>
<td>Spreads orderly and contiguous</td>
<td>Rapid spread, non-contiguous</td>
</tr>
<tr>
<td>Diagnoses – usually early stage</td>
<td>Usually later stage</td>
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</table>
Hodgkin lymphoma is a neoplastic proliferation of lymphoid cells predominantly involving lymphoid tissues. The malignant cell is the Reed-Sternberg cell. Reed-Sternberg (R-S) cells are essential to the diagnosis of Hodgkin lymphoma. The presence of R-S cells is necessary, but as R-S cells are not unique to HD, R-S cells alone are not sufficient for the diagnosis.

The Reed-Sternberg cell is a lymphoid cell and in most cases, is a B cell, and clonal. R-S cells are very large with abundant pale cytoplasm and two or more oval lobulated nuclei containing large nucleoli (red on H & E).

Hodgkin lymphoma was first described by Thomas Hodgkin in an 1832 series of tumors of the absorbent (lymph) glands. The characteristic Reed-Sternberg cell was decribed by Carl Sternberg (1898) and Dorothy Reed (1902).

Hodgkin lymphoma represents about 30% of all lymphoma or almost 10,000 cases per year (2-3 /100,000/year) in the United States.

Hodgkin lymphoma is separated from non-Hodgkin lymphoma not only by a unique histologic appearance, but also because the systemic manifestations (such as fever) and the clinical presentation are distinctive.

Hodgkin lymphoma generally presents as regional enlargement of a single group of peripheral lymph nodes, as opposed to non-Hodgkin lymphoma in which nodal involvement is more widely disseminated.
Bulletin 3-11

Define the following as primary cancers of the bone

- Myelofibrosis w/myeloid metaplasia
- Polycythemia vera (p vera)
- P vera with leukocytosis and thrombocytosis
- Myelodysplastic Syndrome
- Carcinoid tumors (except of appendix)
Bulletins 3-32

- Brain cancer: cerebrum, cerebellum, brain stem and diencephalon (thalamus, pituitary, pineal)
- Cancer of pleura is distinct from lung cancer
- Urethral – consider as bladder
- P vera and variants – consider bone cancer
- Essential thrombocytosis or thrombocythemia – consider as bone cancer
DMC Referral

- These are often very complicated conditions to classify with overlapping clinical and pathologic features (NCI lists 52 types).

- If the diagnosis is not clear: request an opinion from DMC who is a hematologist/oncologist.
What we have learned

- Blood Cell Lineage
- Types of granulocytes and agranulocytes
- 4 basic types of leukemias
- Current conceptual classification of hematologic malignancies
What we have learned

- Distinction between myelodysplastic syndrome and myeloproliferative disorders
- Some distinctions between Hodgkins and non-Hodgkins lymphomas
- Need for a hematologist/oncologist DMC opinion if the diagnosis is unclear
Questions