HEMATOPOIETIC AND LYMPHORETICULAR SYSTEMS

White Blood Cell Disorders
Outline

- Hematopoiesis
- Cell Review
- Leukemia
  - Acute Leukemia
  - Chronic Leukemia
  - Myeloproliferative Disorders
- Lymphoma
  - Non-Hodgkin Lymphoma
  - Hodgkin Lymphoma
- Plasma Cell Disorders and Langerhans Cell Histiocytosis
  - Multiple Myeloma
  - Langerhans Cell Histiocytosis
- Extras: Leukocytosis DDx, Leukopenia DDx, Infectious Mononucleosis
Hematopoiesis

- Stepwise maturation of CD34+ stem cells
- Cells form and mature in bone marrow
- Normal count 5,000-10,000/µL
  - Leukopenia <5,000/µL
  - Leukocytosis >10,000/µL
- Altered count due to one cell type
Hematopoiesis

Hematopoietic CD34+ Stem Cell

Myeloid Stem Cell
- Erythroblast
  - RBC
- Myeloblast
- Monoblast
- Megakaryoblast
- Granulocyte
- Monocyte
- Megakaryocyte

Lymphoid Stem Cell
- B Lymphoblast
- Naïve B Cell
  - Plasma Cell
- T Lymphoblast
- Naïve T Cell
  - CD4+ T Cell
  - CD8+ T Cell
Leukemia and Lymphoma

- Leukemia
  - Malignancy of blood cells and bone marrow
  - Symptoms based on cytopenias

- Lymphoma
  - Mass-forming malignancy (-oma)
  - Often in lymph nodes

- Leukemias can become lymphomas when lymph nodes are seeded
Leukemias and Lymphomas

Hematopoietic CD34+ Stem Cell

Myeloid Stem Cell

- Acute Myeloid Leukemia, Acute Promyelocytic Leukemia
- Chronic Myeloid Leukemia

Langerhans Cell Histiocytosis

Polycythemia Vera

Acute Lymphoblastic Leukemia

- Acute Monocytic Leukemia
- Acute Megakaryoblastic Leukemia
- Essential thrombocytopenia, Myelofibrosis

- B-ALL
- Chronic Lymphocytic Leukemia, Hairy Cell Leukemia

B-ALL

T-ALL

Non-Hodgkin: Follicular, Mantle Cell, Maringal Zone, Burkitt, Diffuse Large B Cell Lymphomas
Hodgkin Lymphoma
Multiple Myeloma

Adult T Cell Lymphoma, Mycosis Fungiodes
LEUKEMIAS
Acute Leukemia

- Disruption of ability of cells to mature
- >20% blasts, neoplastic proliferation
- Leukocytosis
- Blasts crowd normal hematopoiesis
  - Anemia, thrombocytopenia, neutropenia
- AML or ALL based on phenotype of blasts
  1. Large cell
  2. Low cytoplasm
  3. Punched-out nucleolus
Acute Lymphoblastic Leukemia- ALL

- >20% lymphoblasts in bone marrow
  - TdT stain indicates lymphoblasts
- Children <15y
  - 80% of acute leukemias in children are ALL
  - Association with Down Syndrome after 5 years
- Sub-classified into B-ALL and T-ALL
- Clinically:
  - Abrupt onset
  - Mass effect (bone pain)
  - CNS effects
  - Sx related to BM suppression
B-ALL

- Common
- TdT+, CD10, CD19, CD20
- Excellent chemotherapy response
  - Prophylaxis to CSF and scrotum (barriers)
- Cytogenetic abnormalities
  - t(12;21) - good prognosis in kids
    - TEL/AML1
  - t(9;22) - poor prognosis in adults
    - BCR/ABL
    - Also in CML
T-ALL

- TdT+
- May be CD2, CD3, CD4, CD7, CD8
- Blasts do not express CD10 (v. B-ALL)
- Usually in teenagers
  - Mediastinal thymic mass
  - Called Acute Lymphoblastic Lymphoma
Leukemias and Lymphomas

- Hematopoietic CD34+ Stem Cell
  - Myeloid Stem Cell
    - Erythroblast
    - Myeloblast
    - Monoblast
    - Megakaryoblast
  - Lymphoid Stem Cell
    - B Lymphoblast
      - CD10
      - CD19
      - CD20
    - T Lymphoblast
      - CD2-8

- ALL
  - t(12;21)
  - t(9;22)
- Down Syndrome >5y

- RBC
- Granulocyte
- Monocyte
- Megakaryocyte
- Naïve B Cell
- Naïve T Cell
- Plasma Cell
- CD4+ T Cell
- CD8+ T Cell
Acute Myeloid Leukemia- AML

- >20% myeloblasts in bone marrow
- MPO staining in cytoplasm
  - Auer rods
- Presents 50-60 years of age
  - 80% of acute leukemias in adults are AML
- Sub-classified using cytogenetic abnormalities, lineage, or surface markers
  - Promyelocytic, monocytic, megakaryoblastic
- Can arise from pre-existing dysplasias
Acute Promyelocytic Leukemia- APL

- $t(15;17)$
  - PML/RARa
  - Translocation of retinoic acid receptor (RAR) from chromosome 17 to 15
  - RAR disruption blocks maturation

- Increased risk of DIC
  - Abnormal promyelocytes contain primary granules

- Treat with all-trans retinoic acid (ATRA)
  - Vitamin A derivative
  - Binds receptor, blasts mature
Acute Monocytic Leukemia

- Monoblasts
- No MPO
- Usually infiltrate gums
Acute Megakaryoblastic Leukemia

- Megakaryoblasts
- No MPO
- Association with Down Syndrome **before** 5 years
Leukemias and Lymphomas

Hematopoietic CD34+ Stem Cell

Myeloid Stem Cell

Myeloblast

Granulocyte

Erythroblast

RBC

MPO

Monoblast

Monocyte

Megakaryoblast

Megakaryocyte

B Lymphoblast

Naïve B Cell

Plasma Cell

T Lymphoblast

Naïve T Cell

CD4+ T Cell

CD8+ T Cell

AML

Down Syndrome <5y

APL- t(15;17)
Chronic Leukemia

- Neoplastic proliferation of mature lymphocytes
- Circulating
- Insidious
  - May live a long time with disease
- Older adults
- CLL, Hairy Cell, Adult T-Cell, Mycosis Fungiodes
Chronic Lymphocytic Leukemia - CLL

- Most common, adults >60y
- Naïve B cell proliferation
  - CD5, CD20
- Lymphocytosis, smudge cells
- Lymphadenopathy → Small Lymphocytic Lymphoma
- Complications
  - Hypogammaglobulinemia
  - Autoimmune hemolytic anemia
  - Richter transformation
Hairy Cell Leukemia

- Neoplastic B cell proliferation
  - Hairy cytoplasmic processes
- TRAP+
  - Tartrate-resistant acid phosphatase
- Splenomegaly
  - Hairy cells accumulate in red pulp
- “Dry tap” on bone marrow aspiration
  - Marrow fibrosis
- Treat with cladribine
  - Adenosine deaminase inhibitor
Adult T Cell Leukemia/Lymphoma- ATLL

- Neoplastic proliferation of CD4+ T Cells
- HTLV-1 association
  - Japan, Caribbean, West Africa
- **Rash**
- Hepatosplenomegaly, lymphadenopathy, lytic bone lesions, hypercalcemia, cutaneous lesions
- Aggressive
Mycosis Fungiodes

- Proliferation of CD4+ T cells invading skin
  - Localized skin rash, plaques, nodules
  - Pautrier microabscesses in epidermis

- Spread to blood
  - Sezary syndrome
  - Lymphoblasts with cerebriform nuclei - Sezary cells
Leukemias and Lymphomas

Hematopoietic CD34+ Stem Cell

Myeloid Stem Cell
- Erythroblast
- Myeloblast
- Monoblast
- Megakaryoblast
- Megakaryocyte

Lymphoid Stem Cell
- B Lymphoblast
- T Lymphoblast
- Naïve B Cell
- Plasma Cell
- CD5, CD20
- Naïve T Cell
- CD4+ T Cell
- CD8+ T Cell
- CLL

OR

TRAP+
Myeloproliferative Disorders

- Neoplastic proliferation of mature myeloid cells
- 50-60 years
- High WBC count/Hypercellular BM
  - All cell lines increased
  - Classified by dominant cell
    - CML
    - Polycythemia Vera
    - Essential Thrombocythemia
    - Myelofibrosis

- Complications
  - Hyperuricemia, gout
  - Marrow fibrosis → Acute leukemia
Chronic Myeloid Leukemia - CML

- Neoplastic proliferation of mature granulocytes
- Basophilia
- t(9;22) BCR-ABL
  - Increased tyrosine kinase activity
  - Imatinib
- Splenomegaly
  - Accelerated phase, transforms to acute leukemia
  - AML > ALL because mutation in pluripotent stem cell
- Leukocyte alkaline phosphatase (-)
Polycythemia Vera

- Neoplastic proliferation of mature RBCs
  - Granulocytes, platelets
- JAK2 kinase mutation
- Hyperviscosity of blood
  - High RBC mass and volume
- Tx phlebotomy, hydroxyurea
- Death
- Reactive polycythemia
  - High EPO
Essential Thrombocytethemia

- Neoplastic proliferation of mature platelets
- JAK2 kinase mutation
- Increased bleeding/clotting
  - Under-functioning or over-functioning platelets
- Few complications
Myelofibrosis

- Neoplastic proliferation of mature megakaryocytes
- JAK2 kinase mutation
- Excess platelet-derived growth factor
  - Marrow fibrosis
- Extramedullarly hematopoiesis
  - Splenomegaly
  - Leukoerythroblastic smear
  - Infection, thrombosis, bleeding
Leukemias and Lymphomas

Hematopoietic CD34+ Stem Cell

Myeloid Stem Cell
- Erythroblast
- Myeloblast
- Monoblast
- Megakaryoblast

Lymphoid Stem Cell
- B Lymphoblast
- T Lymphoblast
- Naïve B Cell
- Naïve T Cell
- CD4+ T Cell
- CD8+ T Cell

CML
- JAK2 kinase
- t(9;22) BCR/ABL

IMATINIB
Lymphoma

- Neoplastic proliferation of lymphoid cells
- Mass (-oma)
- Non-Hodgkin (60%)
  - Small (Follicular, Mantle, Marginal)
  - Intermediate (Burkitt)
  - Large (Diffuse large B cell)
- Hodgkin (40%)
## Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>Non-Hodgkin</th>
<th>Hodgkin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Frequency</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Malignant cells</td>
<td>Lymphoid cells</td>
<td>Reed-Sternberg cells</td>
</tr>
<tr>
<td>Composition of mass</td>
<td>Lymphoid cells</td>
<td>Predominantly reactive cells</td>
</tr>
<tr>
<td>Clinical</td>
<td>Painless lymphadenopathy in late adulthood</td>
<td>Painless lymphadenopathy with B symptoms in young adults</td>
</tr>
<tr>
<td>Spread</td>
<td>Diffuse, extranodal</td>
<td>Contiguous, rarely extranodal</td>
</tr>
<tr>
<td>Staging</td>
<td>Limited importance</td>
<td>Guides therapy, radiation useful</td>
</tr>
<tr>
<td>Leukemia phase</td>
<td>Occurs</td>
<td>Does not occur</td>
</tr>
</tbody>
</table>

From Pathoma
Follicular Lymphoma

- Small B cells (CD20+)
- Follicle-like nodules
- Painless lymphadenopathy
- Late adulthood
- t(14;18) BCL2 inhibits apoptosis
  - Tx Rituximab
- Progression to diffuse large B cell lymphoma
Mantle Cell Lymphoma

- Small B cells (CD20+) expand mantle zone
  - CD5+
- Late adulthood
- Painless lymphadenopathy
- t(11;14) Cyclin D1
  - Promotes G1/S transition in cell cycle
Marginal Cell Lymphoma

- Small B cells (CD20+) expand the marginal zone
- Chronic inflammatory states
  - Hashimoto thyroiditis
  - Sjogren syndrome
  - H pylori gastritis
- Marginal zone formed by activation
Burkitt Lymphoma

- Intermediate B cells (CD20+)
- EBV association
- Extranodal mass in children/adolescents
  - African form in jaw
  - Sporadic form in abdomen
- $t(8;14)$ c-myc
- Starry sky
Diffuse Large B Cell Lymphoma

- Large B cells (CD20+)
  - May be mature T cells
- Diffuse growth in sheets
- Common
- Aggressive
- Sporadic
  - From low-grade lymphoma
    - Complication of Follicular Lymphoma
  - Late adulthood
# Hodgkin Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>Non-Hodgkin</th>
<th>Hodgkin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Frequency</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Malignant cells</td>
<td>Lymphoid cells</td>
<td>Reed-Sternberg cells</td>
</tr>
<tr>
<td>Composition of mass</td>
<td>Lymphoid cells</td>
<td>Predominantly reactive cells</td>
</tr>
<tr>
<td>Clinical</td>
<td>Painless lymphadenopathy in late adulthood</td>
<td>Painless lymphadenopathy with B symptoms in young adults</td>
</tr>
<tr>
<td>Spread</td>
<td>Diffuse, extranodal</td>
<td>Contiguous, rarely extranodal</td>
</tr>
<tr>
<td>Staging</td>
<td>Limited importance</td>
<td>Guides therapy, radiation useful</td>
</tr>
<tr>
<td>Leukemia phase</td>
<td>Occurs</td>
<td>Does not occur</td>
</tr>
</tbody>
</table>
Hodgkin Lymphoma

- Reed-Sternberg cells
  - Large B cells, owl-eyed nuclei
  - CD15, CD30 (No CD20!)
- Secrete cytokines
  - Attract other cells to form mass
- Classical subtypes
  - Nodular sclerosis (70%)
  - Lymphocyte-rich (best prognosis)
  - Mixed cellularity (IL-5 & eosinophils)
  - Lymphocyte-poor (worst prognosis)
Leukemias and Lymphomas

Hematopoietic CD34+ Stem Cell

Myeloid Stem Cell
- Erythroblast
  - RBC
- Myeloblast
- Monoblast
- Megakaryoblast
- Megakaryocyte

Lymphoid Stem Cell
- B Lymphoblast
  - Naïve B Cell
  - Plasma Cell
- T Lymphoblast
  - Naïve T Cell
  - CD4+ T Cell
  - CD8+ T Cell

RITUXIMAB

Follicular: t(14;18) BCL2, CD20+
Mantle: t(11;14) Cyclin D1, CD20+, CD5+
Marginal: CD20+
Burkitt: t(8;14) c-myc, CD20+
Diffuse large: CD20+
Hodgkin: CD15+, CD30+

Diffuse large: T cells
Adult T Cell: CD4+
PLASMA CELL DISORDERS AND LANGERHANS CELL HISTIOCYTOSIS
**Multiple Myeloma**

- Malignant plasma cell proliferation
  - IL-6
- Bone pain & hypercalcemia
  - Lytic axial lesions
- M spike
- Increased infection risk
- Rouleaux formation
- Primary AL amyloidosis
- Proteinuria

---

MGUS a precursor?
Distinguish from Waldenstrom macroglobulinemia (see supplemental)
Langerhans Cell Histiocytosis

- Langerhans cells- specialized dendritic cells in skin
  - Birbeck (tennis racket) granules on EM
  - S-100
- Letterer-Siwe Disease
  - Malignant, skin rash
- Eosinophilic Granuloma
  - Benign, pathologic fracture
- Hand-Schuller-Christian Disease
  - Malignant, scalp rash
PLASMA CELL DISORDERS AND LANGERHANS CELL HISTIOCYTOSIS

Hematopoietic CD34+ Stem Cell

Myeloid Stem Cell
- Erythroblast
- Myeloblast
- Monoblast
- Megakaryoblast
- Granulocyte
- Monocyte
- Megakaryocyte

Lymphoid Stem Cell
- B Lymphoblast
- T Lymphoblast
- Naïve B Cell
- Naïve T Cell
- CD4+ T Cell
- CD8+ T Cell

Langerhans Cell (DC)
- S-100

Plasma Cell
- IL-6
Leukopenia DDx

- **Neutropenia**
  - Chemotherapy (drug toxicity)
  - Infection moves neutrophils to tissues

- **Lymphopenia**
  - Immunodeficiency (DiGeorge, HIV)
  - High cortisol (exogenous, Cushing’s)
    - Lymphocyte apoptosis
  - Autoimmune (SLE)
  - Whole body radiation
Leukocytosis DDx

- **Neutrophilia**
  - Bacterial infection/tissue necrosis
  - High cortisol (stress!)

- **Monocytosis**
  - Chronic inflammation and malignancy (Bacterial endocarditis, IBD, Collagen vascular dz)

- **Eosinophilia**
  - Allergy (type I hypersensitivity)
  - Parasite
  - Hodgkin Lymphoma (IL-5 chemotactic for eosinophils)
  - Asthma
  - Collagen vascular disease

- **Basophilia**
  - Chronic Myeloid Leukemia
  - Allergic reaction

- **Lymphocytosis**
  - Viral infection (CD8+)
  - Bordetella Pertussis (lymphocytosis promoting factor prevents lymphocytes from leaving blood)
## Chromosomal Translocations

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Associated Disorder</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(9;22)</td>
<td>CML, B-ALL (poor prognosis)</td>
<td>BCR/ABL tyrosine kinase</td>
</tr>
<tr>
<td>t(8;14)</td>
<td>Burkitt Lymphoma</td>
<td>C-myc</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Mantle Cell Lymphoma</td>
<td>Cyclin D1</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>Follicular Lymphoma</td>
<td>BCL2</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>APL (subset of AML)</td>
<td>PML/RARA</td>
</tr>
</tbody>
</table>

From First Aid
Infectious Mononucleosis-EBV

- Saliva transmission
- Lymphocytic leukocytosis (CD8+)
  - Lymphadenopathy- T cell hyperplasia in lymph node paracortex
  - Splenomegaly- T cell hyperplasia in PALS
  - Atypical lymphocytes- reactive CD8+
- Pharyngitis, hepatitis, latent in B cells
- Monospot, serology
- Splenic rupture, rash with ampicillin, recurrence, B cell lymphoma
Monoclonal Gammopathy of Undetermined Significance - MGUS

- Monoclonal expansion of plasma cells
- Common in elderly
- M spike
- Asymptomatic
  - No lytic bone lesions, hypercalcemia, AL amyloid, Bence Jones proteinuria
- Multiple Myeloma precursor
  - 1-2% per year develop MM
Waldenstrom Macroglobulinemia

- **B-cell lymphoma**
  - Monoclonal IgM production (pentamers are big!)

- **Clinical**
  - Lymphadenopathy
  - NO lytic bone lesions (distinguish from MM)
  - Visual/neuro deficits
  - Bleeding

- **M spike** (IgM, not IgG/IgA of MM)

- **Tx** plasmapheresis
  - Removes IgM
PRACTICE QUESTIONS

From Robbins Review of Pathology, available through library
A 12 year-old boy is taken to the physician because he has had increasing abdominal distension and pain for the past 3 days. Physical examination shows lower abdominal tenderness, and the abdomen is tympanic with reduced bowel sounds. An abdominal CT scan shows a 7-cm mass involving the region of the ileocecal valve. Surgery is performed to remove the mass. Histologic examination of the mass shows sheets of intermediate-sized lymphoid cells, with nuclei having coarse chromatin, several nucleoli, and many mitoses. A bone marrow biopsy sample is negative for this cell population. Cytogenetic analysis of the cells from the mass shows a t(8;14) karyotype. Flow cytometric analysis reveals 40% of the cells are in S phase. The tumor shrinks dramatically in size after a course of chemotherapy. Which of the following is the most likely diagnosis?

A. Diffuse large B-cell lymphoma
B. Follicular lymphoma
C. Acute lymphoblastic leukemia
D. Plasmacytoma
E. Burkitt lymphoma
A 9 year-old boy is taken to his pediatrician because of a generalized seborrheic skin eruption and fever. He has been diagnosed and treated for otitis media several times in the past year. On physical examination, he has mild lymphadenopathy, hepatomegaly, and splenomegaly. The electron micrograph show in the figure was taken from a mass lesion involving the mastoid bone. What is the most likely diagnosis?

- A. Acute lymphoblast leukemia
- B. Multiple myeloma
- C. Hodgkin lymphoma, mixed cellularity
- D. Langerhans cell histiocytosis
- E. Disseminated tuberculosis
A 53 year-old man comes to his physician because he felt a lump near his shoulder 1 week ago. On physical examination, there is an enlarged, nontender, supraclavicular lymph node and enlargement of the Waldeyer ring of oropharyngeal lymphoid tissue. There is no hepatosplenomegaly. CBC is normal except for findings of mild anemia. A lymph node biopsy specimen shows replacement by a monomorphous population of large lymphoid cells with enlarged nuclei and prominent nucleoli. Immunohistochemical staining and flow cytometry of the node indicates that most lymphoid cells are CD19+, CD10+, CD3-, CD15-, and terminal deoxynucleotidyl transferase negative (TdT-). Which of the following is the most likely diagnosis?

- A. Chronic lymphadenitis
- B. Diffuse large B-cell lymphoma
- C. Hodgkin lymphoma
- D. Lymphoblastic lymphoma
- E. Small lymphocytic lymphoma
A 50 year-old man has had headache, dizziness, and fatigue for the past 3 months. His friends have been commenting about his increasingly ruddy complexion. He also has experienced generalized and severe pruritus, particularly when showering. He notes that his stools are dark. On physical examination, he is afebrile, and his blood pressure is 165/90. There is no hepatosplenomegaly or lymphadenopathy. A stool sample is positive for occult blood. CBC shows hemoglobin 22.3g/dL (high), hematocrit 67.1% (high), MCV 94 (nl), platelet count 453,000 (high), and WBC count 7800 (high). The serum erythropoietin level is very low. What is the most likely diagnosis?

- A. Myelodysplastic syndrome
- B. Essential thrombocytosis
- C. Chronic myelogenous leukemia
- D. Erythroleukemia
- E. Polycythemia vera
A 61-year-old man reports a history of back pain for 5 months. He has recently developed a cough that is productive of yellow sputum. On physical examination, he is febrile, and diffuse rales are heard on auscultation of the lungs. He has no lymphadenopathy or splenomegaly. Laboratory studies include a sputum culture that grew *Streptococcus pneumoniae*. The serum creatinine level is 3.7 mg/dL, and the urea nitrogen level is 35 mg/dL. The figure shows a skull radiograph. During his hospitalization, a bone marrow biopsy is performed. Which of the following is the biopsy specimen most likely to show?

- A. Scattered small granulomas
- B. Numerous plasma cells
- C. Nodules of small mature lymphocytes
- D. Occasional Reed-Sternberg cells
- E. Hypercellularity with many blasts
References

- Pathoma
- First Aid for the USMLE Step 1
- Robbins Pathologic Basis of Disease 8th Ed.
- Dr. Foucar’s Lectures
- Questions from Robbins Review of Pathology 3rd Ed.
Hematopoietic and Lymphoreticular Systems 2: White Blood Cell Disorders

1. Hematopoiesis
   a. Stepwise maturation of CD34+ stem cells
   b. Cells form and mature in bone marrow
   c. Normal count 5,000-10,000 per microL
      i. Leukopenia <5,000 per microL
      ii. Leukocytosis >5,000 per microL
   d. Usually an altered count is due to one cell type

2. Blood Cell Review
   a. RBC
      i. Anucleate, biconcave discs
      ii. Lifespan 120 days
      iii. Uses glucose for energy through glycolysis
   b. Granulocytes
      i. Neutrophils (60-70% of WBC in blood)
         1. Multilobed nucleus
         2. Phagocytic, increased in bacterial infection (first responder)
         3. Granules: alkaline phosphatase, collagenase, lysozyme, lactoferrin, acid phosphatase, peroxidase, B-glucuronidase
         4. Lifespan 6 hours
      ii. Basophils (<1%)
         1. Bilobed nucleus
         2. Densely basophilic granules: heparin, histamine, leukotrienes
         3. Mediates allergic reaction
      iii. Eosinophils (2-4%)
         1. Bilobed nucleus
         2. Brink pink granules: histaminase, aroylsulfatase
         3. Defense against helminthes, remove foreign bodies bound to IgE
   c. Monocytes (2-8%)
      i. Large kidney-bean nucleus
      ii. Abundant “frosted glass” cytoplasm
      iii. Monocyte in blood, macrophage in tissue
   d. Megakaryocytes
      i. Form platelets from cytoplasmic fragments
      ii. Function in primary hemostasis
      iii. Lifespan 8-10 days
   e. Lymphocytes (25-30%)
      i. Round, large, densely-staining nucleus
      ii. Limited pale cytoplasm
      iii. Adaptive immunity (become T and B cells)
         1. T>B cells
         2. T cells: CD3+, CD4+/CD8+
         3. B cells: CD19+, CD20+

3. Leukemia v. Lymphoma
   a. Leukemia
      i. Malignancy of blood cells and bone marrow
      ii. Symptoms based on cytopenias
   b. Lymphoma
      i. Mass-forming malignancy (indicated by –oma)
      ii. Often in lymph nodes
c. Leukemias can become lymphomas when they grow as a mass in tissues.

4. Leukemia
   a. Acute
      i. Disruption of ability of cells to mature
      ii. Indicated by neoplastic proliferation of >20% blasts
         1. Large cell
         2. Low cytoplasm
         3. Punched-out nucleolus
      iii. Leukocytosis
      iv. Crowd out normal hematopoiesis
         1. Anemia (fatigue, hypoxia)
         2. Thrombocytopenia (bleeding)
         3. Neutropenia (infection)
      v. Differentiate myeloid v. lymphoid phenotypically as they appear identical on histology
   b. Acute Lymphoblastic Leukemia (ALL)
      i. Most common cancer of children <15 years
      ii. Association with Down Syndrome after 5 years of age
      iii. TdT+
         1. DNA polymerase stains in the nucleus of lymphoblasts only
            a. No myeloblasts
            b. No mature lymphocytes
            c. B-ALL and T-ALL are TdT+
      iv. Clinically they present similar to AML with:
         1. Abrupt “stormy” onset in days to weeks
         2. Mass effect (bone pain, lymphadenopathy, splenomegaly)
         3. CNS effects (headache, vomiting, nerve palsies)
         4. Symptoms relating to bone marrow suppression
      v. B-ALL
         1. Most common form of ALL
         2. Characterized by TdT+, CD10+, CD19+, CD20+
         3. Good response to chemotherapy
            a. CSF, scrotum require prophylaxis because of barriers
      iv. Cytogenetics
         a. t(12;21) in children, good prognosis
            i. TEL/AML1
         b. t(9;22) Philadelphia chromosome, adults, poor prognosis
            i. BCR/ABL
            ii. Usually seen in CML
   vi. T-ALL
      1. TdT+, any of CD2+, CD3+, CD4+, CD7+, CD8+
      2. Do not express CD10 like B-ALL
      3. Presents in teenagers as mediastinal thymic mass
         a. Mass → Acute Lymphoblastic Lymphoma
   c. Acute Myeloid Leukemia (AML)
      i. Malignant accumulation of >20% immature myeloid cells in the bone marrow
      ii. Positive cytoplasmic staining of MPO (myeloperoxidase)
         1. MPO used by granulocytes to kill phagocytized particles
         2. Crystallizes to form Auer rods
      iii. Older adults between 50 and 60 years
      iv. Sub-classified using recurring cytogenetic abnormalities, or lineage and surface markers
1. Acute Promyelocytic Leukemia
2. Acute Monocytic Leukemia
3. Acute Megakaryoblastic Leukemia
v. May also arise from pre-existing dysplasias or myelodysplastic syndromes
   1. Previous exposure to alkylating agents in chemotherapy, radiotherapy
vi. Many patients die of other causes (infection, bleeding) before they can be diagnosed with AML
vii. Acute Promyelocytic Leukemia (APL) is a type of AML (myeloid lineage)
   1. t(15;17) moving the retinoic acid receptor on chromosome 17 to chromosome 15
   2. Blocks the maturation of promyelocytes, causes an accumulation of blasts/promyelocytes
viii. Abnormal promyelocytes contain primary granules,
   1. Granulocytes
   2. May cause DIC (emergency!)
i. Tx: ATRA (all trans retinoic acid)
a. Vitamin A derivative that binds the broken RAR, allowing the blasts to mature and eventually die
d. Acute Monocytic Leukemia
i. Malignant proliferation of monoblasts
ii. No cytoplasmic MPO staining (not a granulocyte)
iii. Characteristically infiltrate gums
e. Acute Megakaryoblastic Leukemia
i. Malignant proliferation of megakaryoblasts
ii. No MPO
   1. No O2-dependent killing
iii. Association with Down Syndrome before 5 years of age
f. Chronic Leukemia
i. Neoplastic proliferation of mature, circulating lymphocytes
ii. Insidious onset in older adults
   1. Can live a long time with the disease
iii. Chronic Lymphocytic Leukemia (CLL)
   1. Proliferation of neoplastic naïve B cells
      a. Co-express CD5 and CD20
      b. CD5 is usually a T-cell marker
   2. Most common leukemia over all
   3. Smear:
      a. Smudge cells- on normal CBC, more frequently with CLL due to fragile membrane
      b. Lymphocytosis
   4. CLL in lymph nodes can become small lymphocytic lymphoma
      a. Now forming a mass
5. Complications:
   a. Hypogammaglobulinemia causing infection: can’t produce Ig, common cause of death
   b. Autoimmune hemolytic anemia (cells attempt to make Ig and instead make an antibody against their own RBC)
c. Transformation into diffuse large B cell lymphoma (Richter transformation)
i. Clinically manifested by enlarging lymph nodes or spleen (like SLL but more mutations)

iv. Hairy Cell Leukemia
   1. Neoplastic proliferation of mature B cells with hairy cytoplasmic inclusions
   2. TRAP +
   3. Splenomegaly:
      a. hairy cells accumulate in red pulp of the spleen (usually would expect white pulp)
   4. No sample of aspiration of bone marrow because of fibrosis of the marrow
   5. No lymphadenopathy
   6. Tx: Cladribine, an adenosine deaminase inhibitor.
      a. Blocking part of the purine degradation pathway that leads to toxic buildup of adenosine in the malignant B cells

v. Adult T-Cell Leukemia/Lymphoma
   1. Neoplastic proliferation of CD4+ T cells
   2. Associated with HTLV-1
      a. Japan, Caribbean, West Africa
   3. Rash (differentiates from Multiple Myeloma)
   4. Hepatosplenomegaly, lymphadenopathy, lytic bone lesions, hypercalcemia, cutaneous lesions
   5. Aggressive

vi. Mycosis Fungiodes
   1. Neoplastic proliferation of CD4+ T cells that infiltrate the skin
      a. Form localized skin rashes, plaques, or nodules
      b. Pautrier microabscesses: aggregates in the epidermis
   2. Spread to blood: Sezary syndrome with sezary cells on smear
      a. Cerebriform nuclei

Sezary syndrome: Sezary syndrome is a type of cutaneous T-cell lymphoma (CTCL), which belongs to a larger group of disorders known as non-Hodgkin’s lymphomas. Sezary syndrome is characterized by a widespread red rash that may cover most of the body, the presence of specific malignant cells (Sezary cells) in the blood, and abnormally enlarged lymph nodes. Other signs and symptoms may include intense itchiness, scaling and peeling of the skin; fever; weight loss; hair loss; outward turning of the eyelids (ectropion); palmoplantar keratoderma; malformation of the nails; and hepatosplenomegaly.

http://rarediseases.info.nih.gov/gard/7629/sezary-syndrome/resources/1

5. Myeloproliferative Disorders
   a. Malignant proliferations of mature myeloid cells
   b. Disease of late adulthood (50-60 years)
   c. Subcategorized by dominant cell type
      i. BUT usually all lineages are increased
         1. Leukocytosis
         2. Hypercellular bone marrow
   d. Complications
      i. Hyperuricemia/gout: high cell turnover and purine degradation to dipose of nuclear material
      ii. “Burnt out” fibrotic marrow
      iii. Mutation progression may lead to acute leukemia
   e. Chronic Myeloid Leukemia (CML)
      i. Neoplastic proliferation of mature myeloid cells (granulocytes)
ii. Highly associated with basophilia
   1. Distinguish from leukemoid reaction of infection

iii. Philadelphia chromosome t(9;22)
   1. BCR-ABL fusion with increased tyrosine kinase activity
   2. Tx: imatinib blocks tyrosine kinase activity

iv. Commonly associated with splenomegaly
   1. Indicates accelerated disease phase
   2. Can become acute leukemia after acceleration

v. Leukocyte alkaline phosphatase (LAP) negative
   1. Granulocytes don’t have secondary granules needed to clear infection
   2. Would be positive in leukemoid reaction due to infection

f. Polycythemia Vera
   i. Neoplastic proliferation of mature RBCs
      1. May also have increased granulocytes and platelets
   ii. JAK2 kinase mutation
   iii. Clinical symptoms associated to hyperviscosity of blood
      1. Blurry vision, headache
      2. Increased VTE- Budd-Chiari syndrome (thrombosis in hepatic vein causing liver infarction)
      3. Flushed face
      4. Itching after bathing (also an increase in mast cells that release histamine)
   iv. Tx with phlebotomy or hydroxyurea
      1. Death in 1 year without Tx
   v. Distinguish from reactive polycythemia
      1. Low EPO levels and normal SaO2

g. Essential Thrombocythemia
   i. Neoplastic proliferation of mature platelets
   ii. JAK2 kinase mutation
   iii. Increased bleeding/clotting due to under/over functioning platelets
   iv. Rarely progresses to marrow fibrosis or acute leukemia
   v. No risk for hyperuricemia/gout
      1. Platelets from megakaryocyte, no nuclear material

h. Myelofibrosis
   i. Neoplastic proliferation of mature megakaryocytes
   ii. 50% associated with JAK2 kinase mutation
   iii. Produce excess platelet-derived growth factor (PDGF)
      1. Marrow fibrosis
   iv. Clinical features due to fibrosis
      1. Extramedullary hemaotpoiesis- splenomegaly
      2. Leukoerythroblastic smear
         a. Tear drop RBs escaped from fibrotic marrow
         b. Nucleated RBCs and immature granulocytes
      3. Increased infection, thrombosis, bleeding because spleen can’t make adequate cells
6. **Lymphoma**
   a. Neoplastic proliferation of lymphoid cells forming a mass
   b. Origin in lymph node or extranodal tissue
   c. Non-Hodgkin Lymphoma (60%)
      i. Characteristics:
         1. Divided by cell type (B or T), cell size, pattern of growth, expression of surface markers, cytogenetic translocations
         2. Multiple peripheral nodes
         3. Common extranodal involvement
         4. Noncontiguous spread
         5. Mostly B cells involved
         6. Peak incidence 20-40 years
         7. Association with HIV/immunosuppression
         8. Fewer constitutional symptoms
   ii. **Follicular Lymphoma**
      1. Neoplastic proliferation of small B cells (CD20+)
      2. Form follicle-like nodules
      3. Late adulthood, painless lymphadenopathy
      4. Driven by t(14;18) → BCL2 inhibits apoptosis
         a. B cell chromosome 14 is the location of Ig heavy chain, highly active in B cells
         b. When translocations include chromosome 14 they result in over-activation of whatever ends up on chromosome 14
         c. BCL2 inhibits apoptosis, required in follicle because B cells undergo somatic hypermutation and many are the wrong cell type and need to die
      5. Tx: low dose chemo or rituximab (anti-CD20)
      6. Progress to diffuse large B cell lymphoma to additional mutations and present as an enlarging lymph node
      7. Distinguished from reactive follicular hyperplasia due to infection by
         a. Disruption of normal LN architecture
         b. Lack of tingible body macrophages, indicating that they’re not around to phagocytose the B cells that fail somatic hypermutation
         c. monoclonal
   iii. **Mantle Cell Lymphoma**
      1. Neoplastic proliferation of small B cells, CD20+
      2. Expand mantle zone of normal lymph node
      3. Late adulthood, painless lymphadenopathy
      4. t(11;14)
         a. Cyclin D1, cell cycle regulator, increased expression
         b. Pushes cells through G1/S transition
   iv. **Marginal Cell Lymphoma**
      1. Neoplastic proliferation of small B cells, CD20+
      2. Expand the marginal zone of the normal lymph node
         a. Marginal zone doesn’t exist without activation
         b. Lymphoma associated with chronic inflammation
   v. **Burkitt Lymphoma**
      1. Neoplastic proliferation of intermediate-sized B cells, CD20+
      2. Highly associated with EBV (latent in B cells)
3. Presentation as extranodal mass in children/young adults
   a. African form - jaw
   b. Sporadic form - abdomen
4. t(8;14), C-MYC
   a. Promotes cell growth
5. High mitotic index and starry sky appearance
   a. B cells with interspersed macrophages
vi. Diffuse Large B-Cell Lymphoma
   1. Neoplastic proliferation of large B-cells, CD20+
      a. May also be mature T cells
   2. Diffuse
      a. Malignant, aggressive, no follicular definition
   3. Common and aggressive
   4. Arises sporadically from the transformation of low-grade lymphoma (like Follicular)
   5. Presents late adulthood with enlarging lympho node/extradonal mass
d. Hodgkin Lymphoma (40%)
i. Characteristics:
   1. Localized, single group of lymph nodes
   2. Extranodal involvement is rare
   3. Contiguous spread
   4. Bimodal distribution- young adults, >55 years adults
   5. 50% cases associated with EBV
   6. Constitutional B symptoms
      a. Low grade fever
      b. Weight loss
      c. Night sweats
ii. Neoplastic proliferation of Reed-Sternberg cells
   1. Large B cells (germinal center or post-germinal center)
   2. Multi-lobed nuclei with prominent nucleoli
      a. “Owl eyes”
   3. CD15+, CD30+, no CD20
   4. Secrete cytokines- form a mass
      a. Cause of B symptoms (above)
      b. Attract reactive lymphocytes, plasma cells, macrophages, eosinophils
      c. Fibrosis
iii. Subtypes
   1. Nodular sclerosis (65-70%)
      a. Most common, enlarging cervical/mediastinal lymph node in young females
   2. Lymphocyte-rich
      a. Best prognosis
   3. Mixed-cellularity (20-25%)
      a. IL-5, attracts eosinophils
   4. Lymphocyte-poor
      a. Aggressive
      b. Worst prognosis
      c. Elderly HIV+
7. Plasma Cell Disorders and Langerhans Cell Histiocytosis
   a. Multiple Myeloma
      i. Most common PRIMARY malignancy of bone
         1. Metastatic cancer is the most common malignant bone lesion over all
      ii. Malignant proliferation of plasma cells in the bone marrow, stimulated by IL-6
         1. Clock fase chromatin
         2. Ig cytoplasmic inclusions
      iii. Cell of origin is post-germinal center B cell that homes to bone marrow and has
differentiated into a plasma cell
   iv. Clinical features:
      1. Bone pain, hypercalcemia
         a. Activation of RANK receptor on osteoclasts leading to bone degradation,
hypercalcemia, increased fracture risk
      2. Elevated serum protein because neoplastic plasma cells produce
immunoglobulins
         a. M spike on serum protein electrophoresis (SPEP) due to increased IgG
> IgA
      3. Increased infection risk because monoclonal antibody can’t prevent infection
         a. Common cause of death
   v. Rouleaux formation of RBCs on blood smear
      1. Decreased charge between RBCs cause them to stack on smear
   vi. Primary AL amyloidosis
      1. Light chain overproduction: free light chains circulating in serum and depositing
in tissues, also called primary amyloidosis
         a. Proteinuria
         b. Excreted in urine as Bence-Jones protein
         c. Deposit in kidney tubule and leads to risk for renal failure
   vii. MGUS may be a precursor
   viii. Important to distinguish from Waldenstrom macroglobulinemia
   b. Langerhans Cell Histiocytosis
      i. Neoplastic proliferation of langerhans cells, a specialized type of dendritic cell present in
the skin
         1. Derived from monocytes
         2. Present antigen to naïve T cells
      ii. Characterisitic Birbeck granules (look like tennis racekts) on EM
      iii. CD1a+, S100+ (from neural crest origin)
      iv. Pathoma’s rule for categorizing:
         1. > 2 names = malignant, have a skin rash
         2. 2 names in individuals <2 years old
         3. 3 names in individuals >3 years old
      v. Letterer-Siwe Disease (>2 names)
         1. Skin rash
         2. Cystic skeletal defects in children <2 years old
         3. Malignant, rapidly fatal
      vi. Eosinophilic granuloma (0 names)
         1. Benign proliferation of Langerhans cells
         2. DDx for pathologic fracture in adolescent
         3. No skin involvement
         4. Langerhans cells with eosinophils on biopsy
vii. Hand-Schuller-Christian Disease (3 names)
   1. Malignant, skin rash on scalp
   2. Lytic skull defects, diabetes insipidus
   3. Exophthalmos in child >3y

8. Supplemental
   a. Leukopenia DDx
      i. Neutropenia
         1. Chemotherapy/drug toxicity
         2. Infection moves neutrophils to tissues
      ii. Lymphopenia
         1. Immunodeficiency (DiGeorge, HIV)
         2. High cortisol (exogenous, Cushing’s)
            a. Lymphocyte apoptosis
         3. Autoimmune (SLE)
         4. Whole body radiation
   b. Leukocytosis DDx
      i. Neutrophilia
         1. Bacterial infection/tissue necrosis
         2. High cortisol (as in stress)
            a. Both cause release of the margined pool of neutrophils and release of immature neutrophils (left shift)
               i. Characterized by decreased Fc receptors and decreased CD16
      ii. Monocytosis
         1. Chronic inflammation and malignancy
            a. Bacterial endocarditis
            b. IBD
            c. Collagen vascular disease
      iii. Eosinophilia
         1. Allergy (type I hypersensitivity)
         2. Parasite
         3. Hodgkin lymphoma (IL-5 chemotactic for eosinophils)
         4. Asthma
         5. Collagen vascular disease
      iv. Basophilia
         1. Chronic Myeloid Leukemia
         2. Allergic reaction
     v. Lymphocytosis
         1. Viral infection (CD8+)
         2. Bordatella Pertussis
            a. lymphocytosis promoting factor prevents lymphocytes from leaving blood
   c. Chromosomal translocations
      i. From First Aid

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Associated Disorder</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(9;22)</td>
<td>CML, B-ALL (poor prognosis)</td>
<td>BCR/ABL</td>
</tr>
<tr>
<td>t(8;14)</td>
<td>Burkitt Lymphoma</td>
<td>C-myc</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Mantle Cell Lymphoma</td>
<td>Cyclin D1</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>Follicular Lymphoma</td>
<td>BCL2</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>APL (subset of AML)</td>
<td>PML/RARa</td>
</tr>
</tbody>
</table>
d. Infectious Mononucleosis
   i. Most commonly caused by EBV (HHV-4)
      1. Less commonly by CMV (HHV-5)
   ii. Saliva transmission
      1. Kissing disease, common in teens
   iii. Causes a lymphocytic leukocytosis due to reactive CD8+ (viral infection)
      1. Lymphadenopathy (paracortex expands)
      2. Splenomegaly (PALS expands)
      3. Leukocytosis composed of atypical lymphocytes
         a. Large nucleus
         b. Abundant cytoplasm
         c. Originally thought to be monocytes (hence the name Infectious Mononucleosis)
   iv. Primary infection of oropharynx, liver, and B cells causing pharyngitis and hepatitis
   v. Diagnosed with monospot or serology
   vi. Complications
      1. Capsule of spleen is fragile when enlarged, may rupture
      2. Rash with ampicillin exposure
      3. Latency of virus in B cells
         a. May reactivate
         b. B cell lymphoma (immunodeficient)

e. Monoclonal Gammopathy of Undetermined Significance (MGUS)
   i. Monoclonal expansion of plasma cells common in elderly
   ii. Exhibits M spike
      1. DDx: Multiple Myeloma, Waldenstrom Macroglobulinemia
   iii. Asymptomatic
      1. No lytic bone lesions
      2. No hypercalcemia
      3. No AL amyloid or Bence Jones proteinuria
   iv. 1% of MGUS will develop Multiple Myeloma each year

f. Waldenstrom Macroglobulinemia
   i. B cell Lymphoma characterized by monoclonal IgM production
   ii. Features associated with IgM being a large pentamer
      1. Generalized lymphadenopathy
      2. Increased serum protein
      3. M spike made of IgM
         a. IgG>IgA in Multiple Myeloma
      4. Visual and neuro deficits due to high blood viscosity
         a. DDx: Polycythemia Vera
      5. Bleeding due to defective platelet aggregation
   iii. Tx: plasmapheresis
9. Practice questions- From Robbins Review of Pathology, available through library

1. A 12 year-old boy is taken to the physician because he has had increasing abdominal distension and pain for the past 3 days. Physical examination shows lower abdominal tenderness, and the abdomen is tympanic with reduced bowel sounds. An abdominal CT scan shows a 7-cm mass involving the region of the ileocecal valve. Surgery is performed to remove the mass. Histologic examination of the mass shows sheets of intermediate-sized lymphoid cells, with nuclei having coarse chromatin, several nucleoli, and many mitoses. A bone marrow biopsy sample is negative for this cell population. Cytogenetic analysis of the cells from the mass shows a t(8;14) karyotype. Flow cytometric analysis reveals 40% of the cells are in S phase. The tumor shrinks dramatically in size after a course of chemotherapy. Which of the following is the most likely diagnosis?

   A. Diffuse large B-cell lymphoma
   B. Follicular lymphoma
   C. Acute lymphoblastic leukemia
   D. Plasmacytoma
   E. Burkitt lymphoma

Answer: (E) Burkitt Lymphoma

Burkitt and Burkitt-like lymphomas can be seen sporadically (in young individuals), in an endemic form in Africa (in children), and in association with HIV infection. All forms are highly associated with translocations of the MYC gene on chromosome 8. In the African form and in HIV-infected patients, the cells are latently infected with EBV, but sporadic cases are negative for EBV. This form of lymphoma is typically extranodal. Diffuse large cell lymphomas are most common in adults, as are follicular lymphomas; they do not carry the t(8;14) translocation. Acute lymphoblastic lymphomas can be seen in boys this age, but the mass is in the mediastinum, and the lymphoid cells are T cells. Plasmacytomas appear in older adults and are unlikely to produce an abdominal mass. Because of the high growth fraction (40% in this case), Burkitt lymphomas respond very well to chemotherapy that includes cycle acting agents. By contrast, slow-growing tumors with a low growth fraction are more indolent and less responsive to chemotherapy.

2. A 9 year-old boy is taken to his pediatrician because of a generalized seborrheic skin eruption and fever. He has been diagnosed and treated for otitis media several times in the past year. On physical examination, he has mild lymphadenopathy, hepatomegaly, and splenomegaly. The electron micrograph show in the figure was taken from a mass lesion involving the mastoid bone. What is the most likely diagnosis?

   A. Acute lymphoblast leukemia
   B. Multiple myeloma
   C. Hodgkin lymphoma, mixed cellularity
   D. Langerhans cell histiocytosis
   E. Disseminated tuberculosis
Answer: (D) Langerhans cell histiocytosis

Shown here are the famous rod-like tubular Birbeck granules, with the characteristic periodicity seen in Langerhans cell proliferations. In this case, the skin eruptions, organomegaly, and lesion in the mastoid suggest infiltrates in multiple organs. The diagnosis is multifocal Langerhans cell histiocytosis, a disease most often seen in children. In half of these cases, exophthalmos occurs, and involvement of the hypothalamus and pituitary stalk leads to diabetes insipidus; these finds are called Hand-Schuller-Christian disease. Acute lymphoblastic leukemia in children can involve the marrow, but does not produce skin or bone lesions. Myeloma is a disease of adults that can produce lytic bone lesions, but not skin lesions. Hodgkin lymphoma is seen in young adults and does not produce skin lesions or bone lesions. Tuberculosis can produce granulomatous disease with bony destruction, but the macrophages present in the granulomas are epithelioid marchopages that do not have Birbeck granules.

3. A 53 year-old man comes to his physician because he felt a lump near his shoulder 1 week ago. On physical examination, there is an enlarged, nontender, supraclavicular lymph node and enlargement of the Waldeyer ring of oropharyngeal lymphoid tissue. There is no hepatosplenomegaly. CBC is normal except for findings of mild anemia. A lymph node biopsy specimen shows replacement by a monomorphous population of large lymphoid cells with enlarged nuclei and prominent nucleoli. Immunohistochemical staining and flow cytometry of the node indicates that most lymphoid cells are CD19+, CD10+, CD3-, CD15-, and terminal deoxynucleotidyl transferase negative (TdT-). Which of the following is the most likely diagnosis?

A. Chronic lymphadenitis
B. Diffuse large B-cell lymphoma
C. Hodgkin lymphoma
D. Lymphoblastic lymphoma
E. Small lymphocytic lymphoma

Answer: (B) Diffuse large B-cell Lymphoma

Diffuse large B-cell lymphoma occurs in older individuals and frequently manifests as localized disease with extranodal involvement, particularly of the Waldeyer ring. The staining pattern indicates a B-cell proliferation (CD19+, CD10+). T-cell (CD3) and monocytic (CD15) markers are absent. TdT can be expressed in B lineage cells at an earlier stage of maturation. Small lymphocytic lymphoma also is a B-cell neoplasm, but it manifests with widespread lymphadenopathy, liver and spleen enlargement, and lymphocytosis. Lymphoblastic lymphoma is a T-cell neoplasm that occurs typically in the mediastinum of children. Hodgkin lymphoma is characterized by Reed-Sternberg cells. In chronic lymphadenitis, the lymph node has many cell types- macrophages, lymphocytes, and plasma cells. A monomorphous infiltrate is typical of non-Hodgkin lymphomas.

4. A 50 year-old man has had headache, dizziness, and fatigue for the pat 3 months. His friends have been commenting about his increasingly ruddy complexion. He also has experienced generalized and severe pruritus, particularly when showering. He notes that his stools are dark. On physical examination, he is afebrile, and his blood pressure is 165/90. There is not hepatosplenomegaly or lymphadenopathy. A stool sample is positive for occult blood. CBC shows hemoglobin 22.3g/dL (high), hematocrit 67.1% (high), MCV 94 (nl), platelet count 453,000 (high), and WBC count 7800 (high). The serum erythropoietin level is very low. What is the most likely diagnosis?

A. Myelodysplastic syndrome
B. Essential thrombocytosis
C. Chronic myelogenous leukemia
D. Erythroleukemia
E. Polycythemia vera

Answer: (E) Polycythemia Vera
This patient has polycythemia vera, a myeloproliferative disorder characterized by an increased RBC mass, with hematocrit concentrations typically exceeding 60%. Although the increased RBC mass is responsible for most of the symptoms and signs, these patients also have thrombocytosis and granulocytosis. This occurs because, similar to other myeloproliferative disorders, PV results from transformation of a multipotent stem cell. The high hematocrit concentration causes an increase in blood volume and distension of the blood vessels. The neoplastic erythroid progenitor cells requires extremely small amounts of erythropoietin for survival and proliferation; the levels or erythropoietin are virtually undetectable in PV. When combined with abnormal platelet function, this condition predisposes the patient to bleeding. Abnormal platelet function also can predispose to thrombosis. The pruritus and peptic ulceration most likely are the result of the histamine release from basophils. In some patients, the disease “burns out” to myelofibrosis. A few patients “blast out” into acute myelogenous leukemia, and other patients develop chronic myelogenous leukemia. Myelodysplastic syndromes and myeloproliferative disorders, such as essential thrombocytosis, are not accompanied by such an increase in RBC mass. Erythroleukemia typically is not accompanied by such a high hematocrit concentration because leukemic erythroid progenitors do not differentiate into mature RBCs.

5. A 61-year-old man reports a history of back pain for 5 months. He has recently developed a cough that is productive of yellow sputum. On physical examination, he is febrile, and diffuse rales are heard on auscultation of the lungs. He has no lymphadenopathy or splenomegaly. Laboratory studies include a sputum culture that grew *Streptococcus pneumoniae*. The serum creatinine level is 3.7 mg/dL, and the urea nitrogen level is 35 mg/dL. The figure shows a skull radiograph. During his hospitalization, a bone marrow biopsy is performed. Which of the following is the biopsy specimen most likely to show?

A. Scattered small granulomas  
B. Numerous plasma cells  
C. Nodules of small mature lymphocytes  
D. Occasional Reed-Sternberg cells  
E. Hypercellularity with many blasts

Answer: (B) Numerous Plasma Cells

Multiple myeloma produces mass lesions of plasma cells in bone that lead to lysis and pain. The skull radiograph shows typical punched-out lytic lesions, produced by expanding masses of plasma cells. The Ig genes in myeloma cells always show evidence of somatic hypermutation. Bence Jones proteinuria can damage the tubules and give rise to renal failure. Multiple myeloma can be complicated by AL amyloid, which also can lead to renal failure. Patients with myeloma often have infections with encapsulated bacteria because of decreased production of IgG, required for opsonization. Granulomatous disease (which is not produced by pneumococcus) can involve the marrow, but usually it does not produce such sharply demarcated lytic lesions. Nodules of small lymphocytes suggest a small-cell lymphocytic leukemia/lymphoma, which is not likely to produce lytic lesions. Reed-Sternberg cells suggest Hodgkin lymphoma. Blasts suggest a leukemic process.