UNC MEDICAL CENTER
UNC HEALTH CARE

Caring For Patients With Leukemias, Lymphomas and Myeloma

What are these Diseases?

What Problems Do These Patients Have?

How You Can Help

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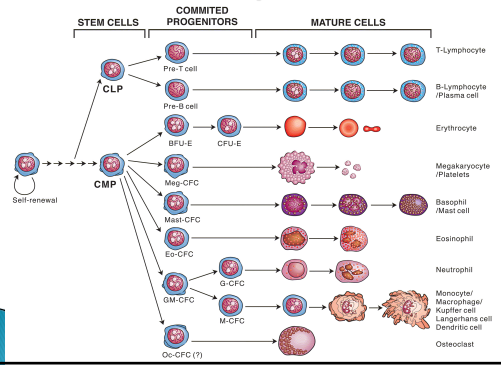
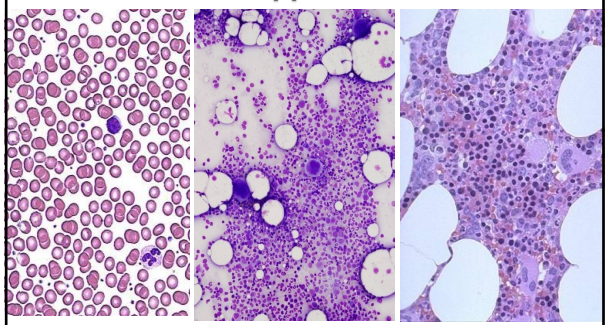
Normal Blood Cell Growth or Hematopoeisis



Normal Marrow Appearance

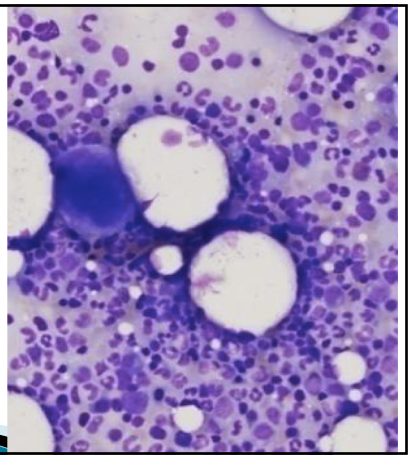


Peripheral Blood:
-The first look
-Cells in suspension
-Can be diagnostic

Bone Marrow Aspirate:
-Cytology
-Differential
-Cells in suspension

Bone Marrow Biopsy:
-Architecture
-Pattern of involvement

Normal Marrow appearance demonstrates great diversity



Leukemias

The Leukemias: An Overview

- **Leukemias** are ***cancers of hematopoietic cells***.
  - Significant ***peripheral blood and bone marrow involvement***.
- They are composed of malignant cells that are predominantly of **myeloid** origin (AML, CML), or **lymphoid** origin (ALL, CLL).
- They can manifest clinically over months to years…
  - **Chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), OR**
- They can manifest clinically over weeks to months…
  - **Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL).**

CML: Epidemiology

- Incidence: 1 to 2 / 100,000
  - 4830 new cases in US in 2008.
  - 450 deaths.
- Median age at diagnosis: 66 yrs.
- Male/Female ratio: 1.4 / 1
- Risk Factors
  - Ionizing radiation exposure

Jemal A, et al. *CA Cancer J Clin.* 2008 Mar-Apr;58(2):71-96.

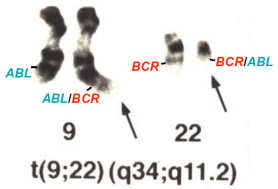
Clinical Presentation of CML

- **Common Symptoms**
  - Fatigue, sweats, fevers
  - Weight loss/anorexia
  - Abdominal fullness, early satiety
- **Physical Exam Findings**
  - Splenomegaly
  - Hepatomegaly
- **Common Laboratory Findings**
  - **Leukocytosis** (high WBC count)
    - **Neutrophilia**
    - **Basophilia**
    - **Eosinophilia**
  - Anemia
  - Thrombocytosis

***20-40% of patients are asymptomatic and the diagnosis is made by an abnormal blood count**

Pathogenesis: The Philadelphia Chromosome

- t(9;22) present in 95% of CML cases by conventional cytogenetics.
- 5% of CML cases harbor "cryptic" translocations that can be detected by FISH.
- t(9;22) required for a diagnosis of CML.



FUSION PROTEIN WITH CONSTITUTIVE TYROSINE KINASE ACTIVITY

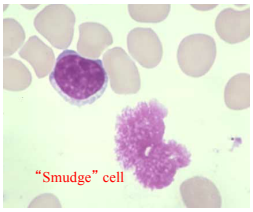
Therapeutic Options

- **Abl tyrosine kinase inhibitors**
  - Imatinib mesylate (Gleevec)
  - Second or third generation Abl inhibitors
    - Nilotinib
    - Dasatinib
    - Bosutinib
    - Ponatinib
- **Allogeneic stem cell transplantation** (SCT)

Chronic Lymphocytic Leukemia

CLL: Epidemiology

- **The most common adult leukemia**
  - 15,110 new US cases in 2008
  - 4,390 deaths from CLL
- **Median age at diagnosis: 72**
- Risk Factors
  - Familial
    - Family members at 2 – 7X increased risk of developing disease **RARE**
  - Environmental
    - Agent Orange



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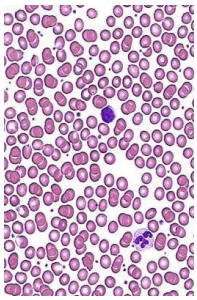
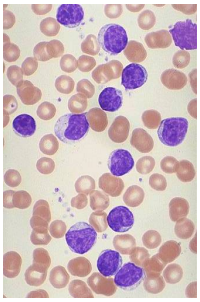
Morphology

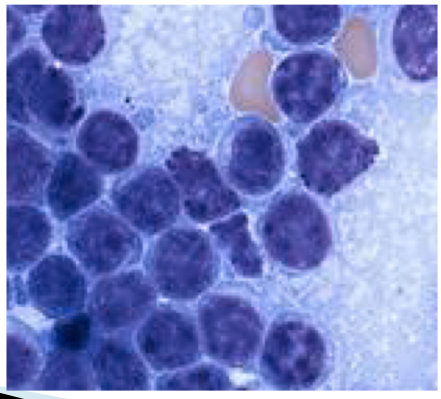


Normal blood:
-mostly neutrophils
-scattered lymphs



Peripheral blood: CLL
-usually diagnostic
-lymphocytosis

In contrast to a normal marrow, there is homogeneity, not diversity in malignancies



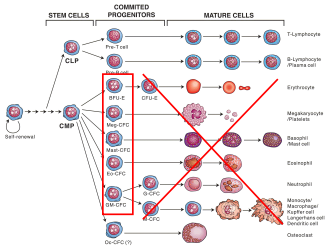
Clinical Presentation of CLL

- **Common Symptoms**
  - Fatigue, sweats, fevers
  - Weight loss/anorexia
  - Abdominal fullness, early satiety
  - Frequent infections
    - Respiratory infections
    - Encapsulated organisms
  - **Incidental lab finding in ~20%**
- **Common Physical Exam Findings**
  - Lymphadenopathy
  - Splenomegaly
  - Hepatomegaly
- **Common Laboratory Findings**
  - Leukocytosis (high WBC count)
    - **Lymphocytosis**
  - Anemia
  - Thrombocytopenia
  - **Hypogammaglobulinemia**
- **Common Therapies**
  - Ibrutinib
  - Bendamustene
  - Rituximab
  - Fludarabine
- **Difficult to cure, but most patients live for 10-15 years**

Acute Myeloid Leukemia

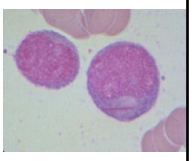
Origins of AML

- AML is a malignancy of a ***committed myeloid progenitor cell***.
- In AML, the malignant cells largely ***lose the ability to differentiate***.
  - **Morphologically homogeneous** population of myeloblasts.



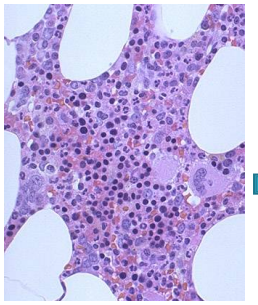
Acute Myeloid Leukemia

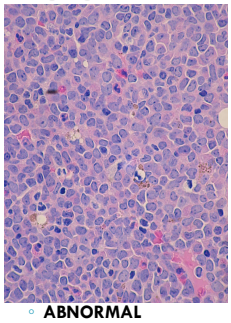
Clonal expansion of myeloid blasts



- **Classification requires:**
  - Morphology
    - ***≥20% of blood or bone marrow blasts***
    - ***Auer rods are seen only in a subset of (but if you see one – it's most likely AML)***
- **Can arise *de novo* or as a consequence of underlying disorder (such as: MDS, MPD)**
- **Primarily seen in adults with peak incidence at age 65**
- **Treatment requires intensive chemotherapy with or without stem cell transplant and is cured about 40% of the time in adults**

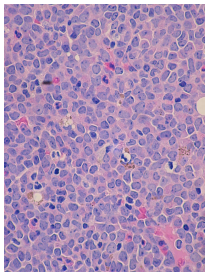
Bone Marrow Biopsy

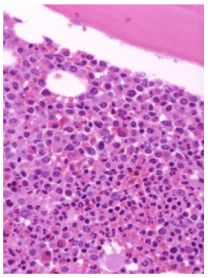




- NORMAL
  - Trilineage hematopoiesis
- ABNORMAL
  - Monotonous population of mononuclear cells

Bone Marrow Biopsy: AML vs. CML



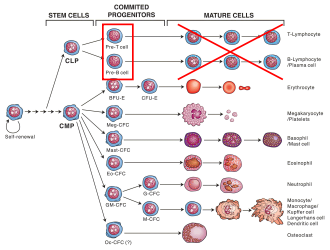


- ABNORMAL:AML
  - Monotonous population
- ABNORMAL:CML
  - Maturing granulocytes-**too much of a good thing!**

Acute Lymphoblastic Leukemia

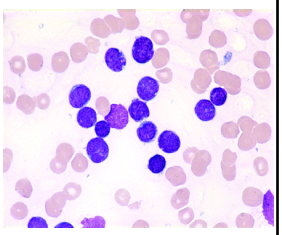
Origins of ALL

- ALL is a malignancy of a ***committed lymphoid progenitor cell (pre-T or –B cell)***.
- In ALL, the malignant cells largely ***lose the ability to differentiate***.
  - **Morphologically homogeneous** population of lymphoblasts.



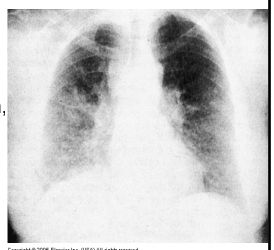
ALL: Epidemiology

- **Acute Lymphoblastic Leukemia**
  - 5,430 new cases in the US in 2008.
  - 1,460 deaths.
  - Median age at diagnosis: **11**.
  - **Most common cancer in children**.
    - Peak incidence in ages 2 to 5.
  - Risk factors
    - Prior **radiation**
    - Prior **chemotherapy**
      - Alkylating agents
      - Topoisomerase II inhibitors
    - **Familial syndromes**
      - Down syndrome
      - Neurofibromatosis



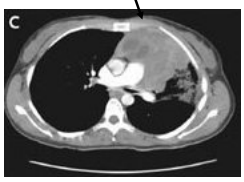
Clinical Manifestations

- **Anemia -- severe**
  - Fatigue, dyspnea
- **Neutropenia -- severe**
  - Opportunistic infections (staph, gram negatives, fungal)
- **Thrombocytopenia -- severe**
  - Ecchymoses, petechiae, mucocutaneous bleeding
- **Hepatosplenomegaly**
  - Abdominal pain, early satiety



Clinical Manifestations

* Mediastinal mass in a patient with precursor T-cell ALL.



- **Lymph node involvement**
  - Less common in AML.
- **Mediastinal mass**
  - Esp. precursor T-cell ALL
- CNS involvement
  - Prevention of CNS relapse a cornerstone of treatment.
    - Intrathecal chemotherapy.
    - Cranial radiation.
- Testicular involvement
  - A strong predictor of CNS involvement/relapse in males.

Treatment; intensive chemotherapy with cure rates of 90% in children and 20-50% in adults

Lymphomas

Lymphoma Types: WHO Classification

Non-Hodgkin

- B-cell (85% of North-American lymphomas)
- T-cell (15% of North-American lymphomas)
- **Working Formulation**
  - Low Grade
    - Small lymphocytic lymphoma
    - Follicular small cleaved lymphoma
  - Intermediate Grade
    - Diffuse large cell lymphoma
  - High Grade
    - Burkitt lymphoma
    - Lymphoblastic lymphoma

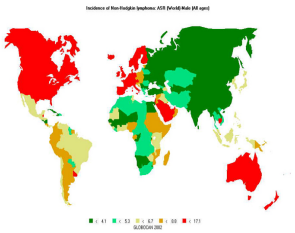
Hodgkin Lymphoma

Lymphoma Epidemiology

- Lymphoma definition: malignant neoplasm of lymphocytes associated with a solid mass or infiltrate
- 6th most common cancer in America
- Approximately 74,000 new lymphoma cases diagnosed a year in US
  - 65,000 Non-Hodgkin
  - 9,000 Hodgkin; peak incidence in teens and again in pts over 55
- Approximately 21,000 deaths a year in US due to lymphoma
- Approximately 1,000 people worldwide are diagnosed with lymphoma every day.

Non-Hodgkin Lymphoma Incidence & Risk Factors

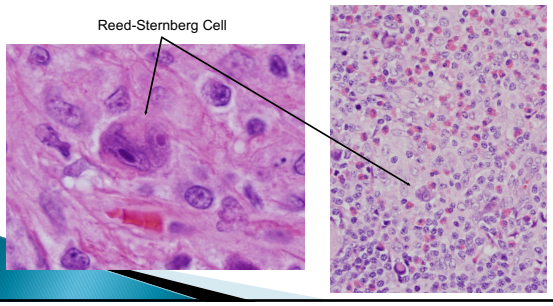
- Highest incidence in the United Sates, Australia, New Zealand and Europe
- Incidence is rising
- Risk factors
  - **Age: more frequent w advancing age**
  - Infections
  - Immune disorders
  - Toxins-agent orange
  - **New Immune therapi for diseases like RA, S MS**



Hodgkin Lymphoma

- Malignant lymphoma characterized by a distinctive cell: the **Reed-Sternberg cell**
- Reed-Sternberg cell is an **activated B-cell**
- EBV genome is present about 40% of cases
- **peak incidence in 20's, smaller peak at age >50 yrs**
- extranodal involvement in 20 of cases at presentation
- spreads along contiguous or adjacent lymph nodes

Hodgkin Lymphoma
R-S cells and background



Lymphoma "Ann Arbor" Staging

Stage†	Criteria
IA or IB	A single nodal region or a single extra-nodal site (IE)
IIA or IIB	Two or more nodal regions or an extra-nodal site and regional nodal involvement (IIE) on the same side of the diaphragm
IIIA or IIIB	Lymphatic involvement on both sides of the diaphragm
IVA or IVB	Liver or bone marrow involvement or extensive involvement of another extralymphatic organ

→ Radiographic studies
Bone Marrow Bx

*Data obtained from Carbone et al.[17]

†A denotes the absence of fever, night sweats, or a 10 percent weight loss, and B the presence of fever, night sweats, or a 10 percent weight loss.

Armitage, JO. N Engl J Med 328:1023-1030, 1993.

The Working Formulation

	Presentation	Treatment
Low Grade (Follicular, Small lymphocytic)	Often asymptomatic	Treat symptoms
Intermediate Grade (Diffuse Large B-Cell)	Sometimes asymptomatic	R-CHOP +/- XRT
High Grade (Burkitt, Lymphoblastic)	Usually symptomatic	Treat similar to lymphoblastic leukemia

Hodgkin's Disease is treated with ABVD +/- XRT

These are very treatable and usually CURABLE with chemo +/- XRT

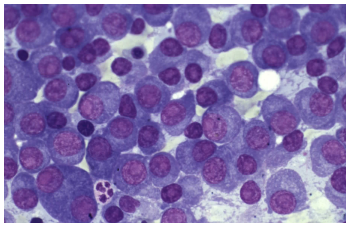
Plasma Cell Diseases

What are Plasma Cell Dyscrasias?

- PCD are diseases associated with a monoclonal proliferation of **immunoglobulin producing plasma cells**
- PCDs are diseases of adults and include the following:
  - **Multiple Myeloma (MM)**
  - **Smoldering Multiple (asymptomatic) Myeloma**
  - **Monoclonal Gammopathy of Uncertain Significance (MGUS)**
  - **Waldenström's Macroglobulinemia**
  - **Amyloidosis**

Bone Marrow Clonal Plasmacytosis

Monotonous proliferation of ONE TYPE of Cell



Multiple Myeloma: Epidemiology

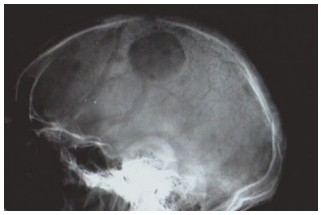
- Approximately 1% of all malignancies
- Approximately 10% of hematological malignancies
- Approximately 20,000 cases a year
- Primarily incurable, but survival has increased from 2–3 years to 10 years or more in the past decade

Findings associated with abnormal proliferation of plasma cells in the bone marrow

- Impaired hematopoiesis (anemia, neutropenia)
- Hypogammaglobulinemia (decreased levels of normal serum immunoglobulins)
- Bone disease
  - Lytic lesions/pathologic fractures
  - Hypercalcemia
- Nerve root compression (radiculopathy)

Lytic Skull Lesion

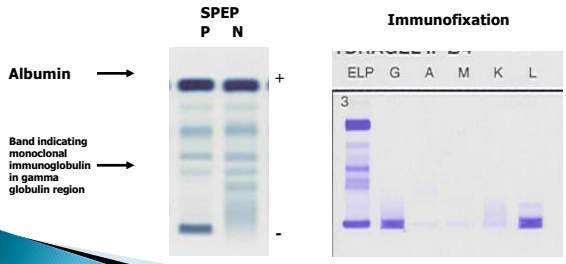
Lytic lesions see on skeletal survey, but not bone scans



Bone pain is presenting symptom in 70% of patients

- Pathologic fractures including vertebral compression fractures
- Neurological pain
  - Radiculopathy and paraparesis associated with vertebral compression fractures
- Commonly involved bones include: **Myeloma Survey**
  - Vertebral column
  - Ribs
  - Skull
  - Pelvis
  - Femurs
  - Clavicles
  - Scapulae

Serum protein electrophoresis and immunofixation – IgG λ "M-spike"



Findings associated with abnormal immunoglobulins and other factors secreted by malignant plasma cells

- Renal Disease
- Rouleaux
- Amyloid
- Hyperviscosity
- Cryoglobulins
- Coagulation abnormalities

Issues for Care

- Fear and Anxiety
  - Death
  - Pain; mouth sores, multiple IVs, procedures
  - Loss and dependence on others
  - Uncertainties about treatments–which ones and will they work?
- Depression
  - Disfigurement
  - Help with self-care

Issues for Care

- Fatigue
  - Anemia
  - Metabolic effects of treatment
- Cytopenias or Low Blood Counts
  - Infections
    - Fever, Shortness of breath, need for antibiotics
  - Need for transfusions
- Weight loss
  - Loss of appetite
  - Nausea from treatment
  - Diarrhea from effects of chemotherapy or infection

Issues for Care

- Costs
  - Loss of income
  - Continued living expenses
  - Expensive medications
  - Transportation
  - Child care
- Emotional Support
  - Isolation
  - Fear of death and disabilities
  - Pain
- Housing when care is away from home

Issues for Care

- **Available Resources**
- UNC Cancer Center Support Program, http://unclineberger.org/patientcare/support/ccsp/documents/unc-cancer-resource-list-list-October 2016
- Leukemia and Lymphoma Society (L&LS)
- Multiple Myeloma Research Fund (MMRF)
- American Cancer Society (ACS)