

# Hematopoietic and Lymphoid Systems

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February 6, 2008

## Outline

- Red Blood Disorders
- Bleeding Disorders/ Hemorrhagic Diatheses
- White Cell Disorders
- Disorders of Thymus and Spleen

## Red Blood Cell Disorders

### Anemias

- Anemia of Blood Loss: Acute vs. Chronic
- Anemia of ↓ Erythropoiesis
  - Iron deficiency anemia
  - Megaloblastic anemia
  - Anemia of chronic disease
  - Aplastic anemia
- Hemolytic Anemias
  - Hereditary Spherocytosis
  - Sickle Cell Disease
  - Immuno-hemolytic Anemia
  - Thalassemia
  - Paroxysmal Nocturnal Hemoglobinuria
  - HA from mechanical trauma to RBCs

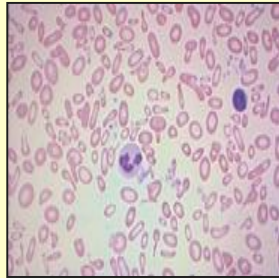
### Polycythemia

## Iron deficiency Anemia

- Most common form of nutritional anemia
  - Iron balance is maintained by regulation of absorption of dietary iron
  - ↑ Fe needs/erythropoiesis: absorbed iron transferred to plasma transferrin with ↓ iron loss through mucosal ferritin
- Negative iron balance/anemia
  - ↓ stored Fe (serum ferritin) and BM stainable Fe → ↓ serum iron and ↑ in serum transferrin iron-binding capacity (TIBC)
- Etiology: low dietary intake, malabsorption (gastrectomy), blood loss, ↑ demand (pregnancy)
- Laboratory:
  - low Hb/Hct, MCV, serum ferritin/iron
  - high TIBC
  - hypochromic microcytic RBCs

## Iron deficiency Anemia

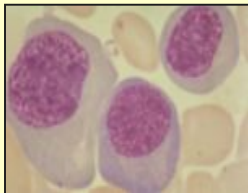
- Clinical:
  - Asymptomatic
  - Nonspecific: weakness, pallor, listlessness
  - “spooning of fingernails”
  - “pica” compulsion to eat dirt or clay
- **Smear:** microcytic hypochromic RBCs, anisocytosis, poikilocytosis



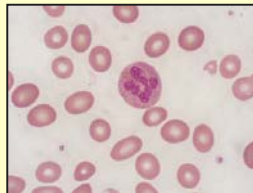
## Megaloblastic Anemia

- **Folate Deficiency**
- **Vitamin B12 (Cobalamin) Deficiency (*pernicious anemia*)**
  - Both are involved in DNA synthesis
  - All 3 cell lines affected:
    - RBC: megaloblasts
    - WBC: giant metamyelocytes, hypersegmented neutrophils
    - PLTs: bizarre multilobed megakaryocytes

## Megaloblastic Anemia



Megaloblastic erythroid precursors in BM



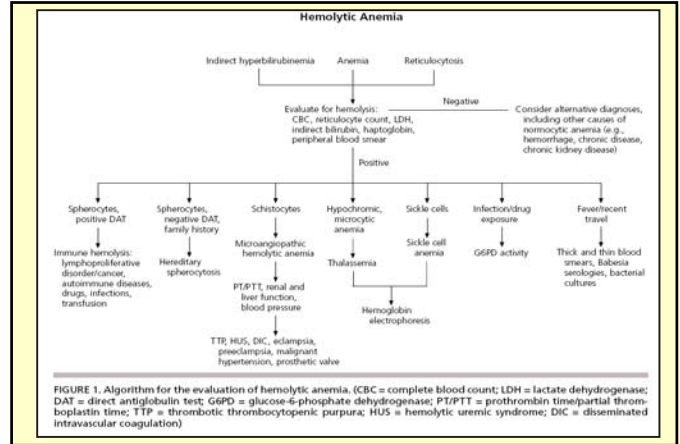
Macroovalocytes (>110 fl)  
Hypersegmented PMN in peripheral smear

## Aplastic Anemia

- Suppression of multipotent myeloid stem cells:
  - Anemia, neutropenia, thrombocytopenia
- Etiology: idiopathic, irradiation, myelotoxic drugs, chemicals, viruses
- Idiosyncratic reaction: chloramphenicol, sulfonamides
- BM: hypocellular with fat replacement
- No splenomegaly (not AA, if + splenomegaly)
- No reticulocytosis
- Treatment:
  - stop drug
  - BMT (< 40 y/o) for idiopathic
  - immunosuppression for older patients (w/o donors)

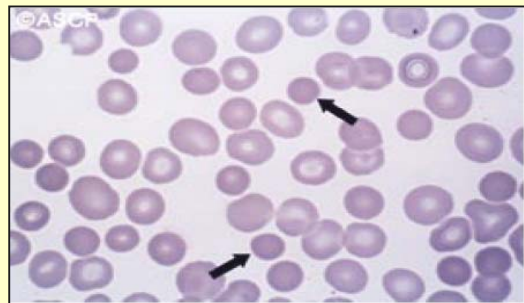
## Hemolytic Anemia

- ↑ RBC destruction
  - ↑ Erythropoiesis:
    - reticulocytosis
  - Iron accumulation:
    - hemosiderosis
  - Etiology:
    - Intravascular: heat, Clostridia toxin, trauma, complement fixation
    - Extravascular (RES)
- Intravascular:
    - hemoglobinemia
    - hemoglobinuria
    - hemosiderinuria
    - ↓ haptoglobin
  - Extravascular
    - No hemoglobinemia or hemoglobinuria
    - Normal haptoglobin
    - Microspherocytes



## Hemolytic Anemia: Hereditary Spherocytosis

- Abnormal RBC skeletal/membrane proteins (ie. Ankyrin)
- RBCs with reduced membrane stability → lose membrane fragments, assume a "sphere"
- Clinical: anemia, splenomegaly, jaundice
- Lab: ↑ osmotic fragility
  - Upon exposure to hypotonic salt solution, spheroidal shape limits volume of expansion.
- RBCs shortened lifespan
- Treatment: splenectomy to alleviate anemia
  - patient continues to have spherocytes



**FIGURE 2.** Spherocytes (arrows), characterized by a lack of central pallor, occur in both autoimmune hemolytic anemia and hereditary spherocytosis.

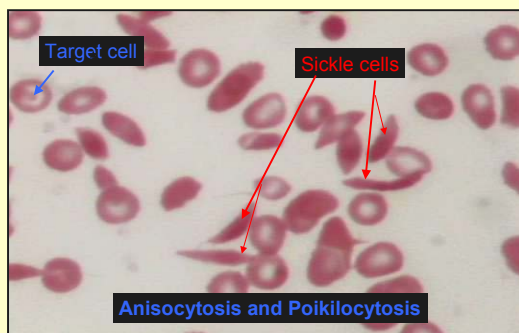
## Immuno-hemolytic Anemias

- Caused by antibodies reacting against normal or altered RBC membranes
  - Autoimmune, drugs, neoplasms, infections
  - Antigen that stimulates antibody or complement-mediated destruction of RBCs
- Classification:
  1. Warm antibody: Idiopathic, B-cell Neoplasms (CLL/SLL), SLE, Drugs (aldomet, PCN, Quinidine)
  2. Cold antibody: M. pneumoniae. Infectious mono.
- Laboratory:
  - + DAT (detects anti-RBC antibodies)
  - Microspherocytes on peripheral smear

## Hemolytic Anemia: Sickle Cell Anemia

- Most prevalent hemoglobinopathy caused by mutations of the  $\beta$ -globin chain  $\rightarrow$  sickle Hb (HbS)
  - 8% of American blacks (1:600)
  - 30% of African blacks (protective effect of HbS against malaria)
- Single AA substitution in the globin chain (val for glu)
- Normal adult: 96% *HbA*, 3% *HbA<sub>2</sub>*, 1% *HbF*
- On deoxygenation: *HbS* polymerize (*gelation/crystallization*)
  - Change in physical state cause RBC distortion "sickle/crescents"
  - Reversible sickling  $\rightarrow$  irreversible sickling despite adequate O<sub>2</sub>
  - RBC hemolysis (anemia), capillary stasis (ischemia/thrombosis)

## Hemolytic Anemia: Sickle Cell Anemia

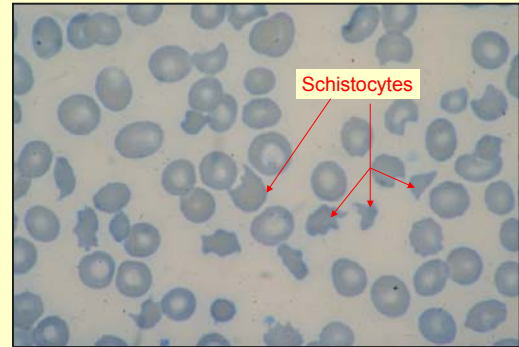


## Hemolytic Anemia: Sickle Cell Anemia

- Clinical: anemia + complications:
  - acute chest syndrome, strokes, acute pain crisis, priapism, leg ulcers, *Salmonella* osteomyelitis
- Treatment:
  - Hydroxyurea
    - Increases HbF = retards sickling by inhibiting polymer formation
  - RBC transfusions
  - RBC exchanges during acute crises

## Hemolytic Anemia from Mechanical Trauma to RBCs

- Etiology
  - Cardiac valves: mechanical/porcine
    - RBCs damaged by shear stress from turbulent blood flow
  - Microangiopathic hemolytic anemia:
    - RBCs damaged as they squeeze through abnormal narrow BV
    - Malignant HTN, SLE, TTP/HUS



Schistocytes in Mechanical Hemolysis

## Bleeding Disorders: Hemorrhagic Diatheses

- Bleeding disorders from BV wall abnormalities
- Disseminated Intravascular Coagulation
- Bleeding from thrombocytopenia
  - ITP
  - Drug-induced thrombocytopenia
  - HIV associated thrombocytopenia
  - Thrombotic microangiopathies: TTP / HUS
- Bleeding related to CF abnormalities
  - Deficiency of Factor VIII-vWF Complex
  - Von Willebrand Disease
  - Hemophilia A (FVIII deficiency)
  - Hemophilia B (FIX deficiency)

## Laboratory Tests for Bleeding Diathesis

- Bleeding Time (2-9 minutes)
  - In vivo assessment of PLT response to injury
  - Abnormal with PLT dysfunction or deficiency
- Platelet counts ( $150-450 \times 10^3/\text{mm}^3$ )
- Prothrombin Time (PT)
  - Check extrinsic/common pathway (CF 1, 2, 5, 8, 7, 10)
- Partial Thromboplastin Time (PTT)
  - Check intrinsic/common pathway (all CF except 7)
  - Acquired inhibitors (antibody)

## Disseminated Intravascular Coagulation

- Acute, subacute, chronic
- Activation of both coagulation cascade and fibrinolysis
  - “paradox” *bleeding in the presence of widespread coagulation (fibrin microthrombi)*
- Trigger: tissue factor in the circulation or EC injury
- Etiology: sepsis, OB complications, trauma malignancy
  - Acute DIC: OB complications (bleeding diathesis)
  - Chronic DIC: malignancy (thrombotic complications)

## Disseminated Intravascular Coagulation

- Bleeding diathesis
  - from PLT and CF consumption
  - release of plasminogen activators
    - Plasmin cleaves fibrin
    - Plasmin digests CF V / VIII
- Fibrinolysis leads to ↑ FDP
  - Inhibit PLT aggregation
  - Antithrombin activity
  - Impaired fibrin polymerization
- Management:
  - ✓ Treat underlying disorder
  - ✓ FFP/ CRYO
  - ✓ ?? Heparin
  - ✓ recombinant activated protein C (Xigris)

## Thrombocytopenia

- Spontaneous bleeding, ↑ BT, <100,000 PLTs, normal PT/PTT
- Bleeding from small BV: petechiae/ecchymoses
  - in the skin, mucous membranes, GIT/GU tracts
- Etiology:
  1. Splenic sequestration
  2. ↓ Production: BM failure (AA, Rx, tumor)
  3. ↑ Destruction (N or ↑ megakaryocytes in BM)
    - immune (anti PLT antibodies/ immune complexes)
    - nonimmune (TTP, DIC, heart valves)

*Example: HIV = suppression of megas, immune complex mediated injury of PLTs, autoantibodies*

## Drug Induced Thrombocytopenia

- Quinine, Rifampin, Bactrim, Interferon, Danazol, Carbamazepine, Vancomycin, Acetaminophen
- GP IIb-IIIa blocking drugs (Abciximab)
- Herbal remedies (Jui™)
- Dietary supplements, tahini (pulped sesame seeds)

## Idiopathic Thrombocytopenic Purpura

- Acute (children)
- Chronic (20-40 y/o women)
- Primary or secondary (Lymphoma, SLE)
- Etiology: autoimmune
  - Anti-PLT antibodies against GP IIb/IIIa or Ib/IX complexes
- Spleen – site of antibody synthesis and destruction of IgG-coated PLTs
- Clinical: symptoms after minor trauma
- Diagnosis: by exclusion, clinical, BM

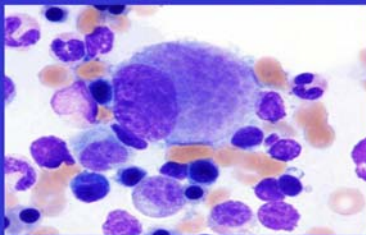


A 43 year old woman presented to her physician with the complaint of easy bruising. Physical examination showed multiple petechiae and a large ecchymotic area in the thigh following minor trauma

Lazarchick, J. ASH Image Bank 2001;2001:100177

## Bone Marrow in ITP

Figure 6.



Bone marrow showing an immature megakaryocyte with cytoplasmic budding. Young megakaryocytes are seen in increased numbers in ITP

## Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

- Pentad of TTP:
  - Fever, ↓ PLTs, microangiopathic hemolysis, CNS and renal Sx
  - D/D Hemolytic uremic syndrome
    - Renal > CNS, childhood onset, follows E. coli O157:H7 infection that produces Shiga-like toxin that damages endothelial cells
- Common finding: *fibrin microthrombi* in the microcirculation resulting in microangiopathic hemolysis (*schistocytes*)
- TTP: *deficiency of vWF cleaving protease*
  - Familial/genetic
  - Autoantibody
- Treatment:
  - Therapeutic plasma exchange + Immunosuppressants

### Heparin Induced Thrombocytopenia with Thromboses (HITT)

- Drug induced thrombocytopenia
- 5% of patients treated with unfractionated heparin by any route
- Etiology: acquired antibodies against PF4/heparin complexes on PLT surface
- Venous or arterial thromboses (rarely bleed) even in severe thrombocytopenia resulting ischemia
- Treatment: D/C heparin, use alternative anticoagulants (ie. Argatroban®)

### Coagulation Disorders

- Acquired coagulation disorders
  - Liver disease
- Hereditary Deficiencies
  - Hemophilia A (X-linked)
  - Hemophilia B /Christmas Disease (X-linked)
  - vonWillebrand Disease (Autosomal dominant)

### Deficiencies of Factor VIII/VWF Complex

- Hemophilia A
- vonWillebrand Disease
  - Factor VIII bound to VWF by non-covalent bonds
  - 99% of the complex is vWF made up of HMW multimers, produced by EC and megakaryocytes, for *PLT adhesion*

### Von Willebrand Disease

- Most common inherited bleeding disorder
  - Autosomal dominant, variants are recessive
- Prolonged BT, normal PLT counts
- Spontaneous bleeding from mucous membranes, excessive bleeding from wounds, menorrhagia
- Types:
  - Type I (most common) - ↓ vWF
  - Type IIA - no intermediate /HMW multimers
  - Type IIB - abnormal HMW multimers
  - Type III - absence to nondetectable multimers

## Hemophilia A

- Most common hereditary disease associated with serious bleeding
- X-linked : males or homozygous females
  - 30% from mutations so not familial
- Reduced amount or activity of Factor VIII
- Clinical: easy bruising, massive hge post surgery or trauma, spontaneous hemorrhage (hemearthroses)
- Normal PT and PLT counts, but ↑ PTT corrected by mixing studies (add plasma)
- Diagnosis: Factor VIII assay
- Treatment: recombinant Factor VIII

## WHITE CELL DISORDERS

- Leukopenia
- Leukocytosis:
  - Reactive
    - Neutrophilic: bacterial infection, burns, MI
    - Eosinophilic: asthma, hay fever, allergy, parasites, drug reactions, Hodgkin
    - Basophilic: rare, myeloproliferative disorder
    - Lymphocytosis: viral infection, *B. pertussis*
  - Neoplastic

## Non-Neoplastic Disorders of WBCs Infectious Mononucleosis

Acute self-limited disease of adolescents/young adults

- B-lymphocytotropic EBV
- Fever, sore throat, generalized adenitis
- ↑ atypical lymphocytes (60%), humoral antibody response, hepatitis, febrile rash,
- Lab: + Heterophil reaction (monospot test), + specific antibodies for EBV (EBNA, VCA, EA)
- EBV potent transforming virus: B-cell lymphomas, especially immunosuppressed organ and BMT recipients

*X-linked lymphoproliferative disorder-inability to mount an immune response to EBV, boys with SH2D1A gene mutation.*

## Non-Neoplastic Disorders of WBCs Cat Scratch Disease

Acute self-limited lymphadenitis of childhood (<18 y/o)

- Caused by *Bartonella henselae* (related to *rickettsiae*)
- Axillary and neck adenopathy occurs 2 weeks after a feline scratch / splinter or thorn injury that regresses in 2-4 months
- Raised inflammatory nodule/vesicle/eschar
- Biopsy: sarcoid-like “stellate” granulomas/microabscess with central necrosis filled with PMNs
- Skin test: + CSD skin antigen test
- Treatment: Antibiotics ???
  - Useful in immunocompromised patients (i.e. doxycycline, erythromycin)

## Neoplastic Proliferations of WBCs

- Lymphoid Neoplasms
  - NHL, Hodgkin's Lymphoma, Lymphocytic leukemias, Plasma cell dyscrasias
- Myeloid Neoplasms
  - AML
  - Chronic myeloproliferative disorders
  - Myelodysplastic syndromes
- Histiocytic Neoplasms

## Lymphoid Neoplasms

- Vary in clinical presentation/behavior
  - Leukemias: arise from the BM and circulate peripherally
  - Lymphomas: tumor masses in LN and organs
  - Plasma cell dyscrasias: bone mass with systemic Sx related to inappropriate production of complete/partial monoclonal Ig polypeptide
- Spread to LN, spleen, liver and BM
- Involve the peripheral blood – "leukemia"
- Controversial classification: clinical, morphologic, phenotypic and genotypic

## Lymphoid Neoplasms

- Derived from a SINGLE transformed cell ("*Monoclonal*")
- Disrupt N immune regulation:
  - Immunodeficiency
  - Autoimmunity
- B-cell origin (80-85%) : CD10, CD19, CD20 & sIg
- T-cell origin (15%) : CD2, CD3, CD4, CD7 & CD8
- NK tumors rare: CD15 & CD56
- Points:
  - Tdt - immature T/B cells (lymphoblasts)
  - CD13, CD14, CD15, CD64 – myeloid cells
  - CD34 - stem cells, early myeloid and lymphoid progenitor cells

## Hodgkin vs. Non-Hodgkin Lymphoma

### HL

- Localized to single axial group of LN
- Orderly spread by contiguity
- Rare mesenteric & Waldeyer ring
- Extranodal uncommon

### NHL

- Multiple peripheral LN
- Noncontiguous spread
- Common mesenteric & Waldeyer ring
- Extranodal common

## Lymphoid Neoplasms

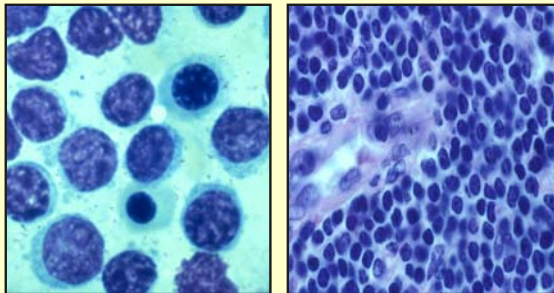
- Precursor B-cell Neoplasms
- Peripheral B-cell Neoplasms
  - B-cell CLL/SLL
  - Mantle cell lymphoma
  - Follicular Lymphoma
  - Malt Lymphoma
  - Plasma cell myeloma
  - Burkitt Lymphoma
- Precursor T-cell Neoplasms
- Peripheral T/NK Cell Neoplasms
  - Mycosis fungoides/Sezary syndrome
- Hodgkin's Lymphoma
  - Nodular Sclerosis
  - Mixed cellularity

## Summary of More Common Lymphoid Neoplasms

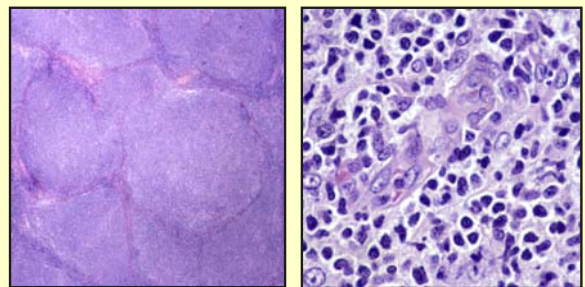
Entity	Frequency	Morphology	Comments	
<b>SLL/CLL</b>	3-4% of lymphomas 30% of leukemias	Diffuse pattern, Small lymphocytes	CD5 + Mature B cell Express <b>slg</b> *	Old age Indolent Gen. adenopathy
<b>Follicular lymphoma</b>	40% of adult lymphomas	Follicular pattern, Germinal center cells	CD10+, BCL2+ Mature B cells Express <b>slg</b>	Same as above t (14, 18) Difficult to cure
<b>Burkitt lymphoma</b>	<1% of lymphomas in the US	Intermediate size NUCLEOLI "starry sky"	CD 10+, <b>slg</b> Mature B cells	Endemic in Africa Rapid spread ↑ ImmunoSx Px
<b>Plasma cell myeloma</b>	Most common lymphoid neoplasm in adults	Plasma cells w/ nucleoli and Ig inclusions	Mature B cells with <b>clg</b> **	Bone lesions, ↑ Ca Plasmacytoma Renal insufficiency
<b>M. fungoides/Sezary syndrome</b>	Most common type of cutaneous lymphoma	Usually small cells with convoluted nuclei	CD4+, CD3+ Mature T cells	Local/generalized skin involvement Very indolent

\* **slg** – surface immunoglobulin \*\***clg** – cytoplasmic immunoglobulin

## Small Lymphocytic Lymphoma

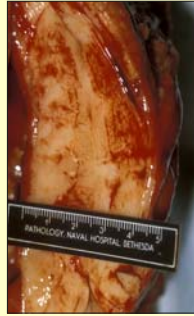


## Follicular Lymphoma

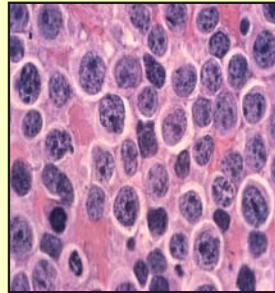




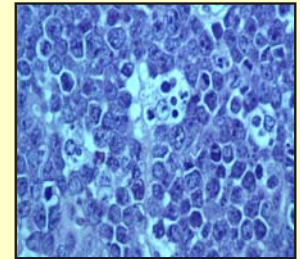
WHO Fascicle 2001



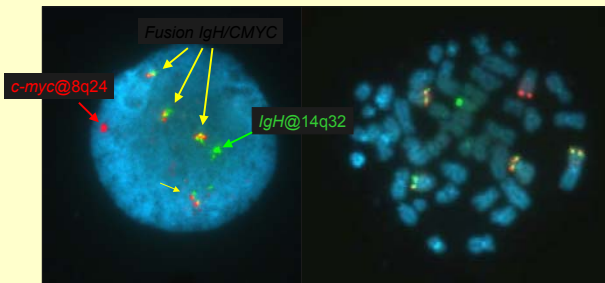
### Burkitt Lymphoma



"starry sky pattern"



### Molecular Diagnostics [FISH] Burkitt Lymphoma



### Precursor B- and T- Cell Lymphoblastic Leukemia/Lymphoma

- Aggressive tumors of children/young adults
- Composed of immature lymphocytes (lymphoblasts)
- Lymphoblastic tumors are indistinguishable morphologically with similar symptomatology
  - Pre-B: present as leukemias with extensive BM involvement
  - Pre-T: mediastinal masses involving the thymus progress rapidly to a leukemic phase or involve BM
  - Both pre-B/T lymphoblastic tumors have the clinical appearance of ALL at some time during their course
- ALLs comprise 80% of childhood leukemia (peaks at age 4) and are usually pre-B phenotype

### Acute Leukemias (AML/ALL)

- Block in differentiation – “blasts” w/ prolonged generation time
  - Accumulation of “blasts”
    - Result from a clonal expansion
    - Failure of maturation
    - Suppress normal hematopoiesis
- ↓
1. ↓ in normal RBCs, WBCs and PLTs
  2. Aim of TX is to reduce the leukemic clone to allow reconstitution with the progeny of remaining normal stem cells

### Acute Leukemias (AML/ALL)

#### Clinical Features

- Abrupt onset
- Symptoms related to BM depression
  - *Fatigue from anemia, fever from infection, bleeding from thrombocytopenia*
- Bone pain and tenderness
  - BM expansion with subperiosteal infiltration
- Generalized adenopathy, hepatosplenomegaly (*ALL>AML*)
- CNS manifestations (*ALL>AML*)
  - *Headache, vomiting, nerve palsies*

### Acute Leukemias (AML/ALL)

- Laboratory
  - Leukocytosis (>100,000 or <10,000) with “blasts” in circulation and BM
  - Lymphoblasts: with + PAS aggregates
  - Myeloblasts: + myeloperoxidase
- Immunophenotyping
  - Tdt (DNA polymerase): + in 95% of ALL
  - Lineage specific markers: *CD19* (B cell), *CD2* (T cell)
- Karyotyping (predictive of prognosis)
  - Usually nonrandom abnormalities
  - Pre - B: Hyperdiploidy with *t(12,21)* - good  
Ph chromosome - poor

### Plasma Cell Dyscrasias

- B-cell neoplasms
- Expansion of a single clone of Ig-secreting cell:
  - ↑ in single serum level of a homogeneous Ig or its fragments (*M component*)
  - called “*monoclonal gammopathies*”
- MGUS: M component + in normal elderly people
- Types:
  - Multiple Myeloma
  - Plasmacytoma, Lymphoplasmacytic lymphoma, Heavy chain disease, Primary amyloidosis, MGUS

## Multiple Myeloma

- Most common malignant plasma cell dyscrasia
  1. Clonal plasma cell "myeloma cell" proliferation in BM by *IL-6* (produced by fibroblasts and macrophages)
  2. Lytic bone lesions
- Translocation involving IgG on Chromosome 14
- M component:
  - IgG (60%), IgA (25%), K or  $\lambda$  (20%), rare IgM, IgD, IgE
- Light chains excreted in urine as *Bence Jones Protein*
  - *Light chain disease* - light chains only (no M component)
  - 80% of patients will synthesize complete Ig molecules and excess light chains

## Multiple Myeloma

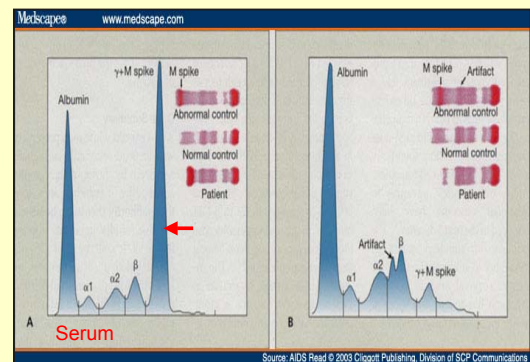
- Lytic bone lesions throughout skeletal system
  - "punched out lesions" on X-ray
  - Vertebral column > ribs > skull > pelvis > femur
  - Medullary cavity  $\rightarrow$  erode cancellous bone  $\rightarrow$  cortical bone
  - Resorption by cytokines produced by myeloma cells
    - (IL-6, TNF, IL-1 $\beta$ )
  - D/D lymphoplasmacytic lymphoma - no lytic lesions
- Diagnosis:
  - Bone Marrow: plasma cells (with abnormal features)
  - Characteristic "punched out lesions",
  - Serum and urine electrophoresis
- Plasma cell infiltration in other tissue (spleen, liver, etc.)
  - Myeloma Nephrosis + calcification

## Multiple Myeloma

Bone marrow aspirate of a patient with multiple myeloma

Left femoral radiogr... of patient with m...

Image Preview



## Multiple Myeloma

- Clinical Features:
  - Bone pain – pathologic fractures, hypercalcemia
  - CNS Sx (from hypercalcemia)
  - Anemia – BM effacement by plasma cells
  - Infections – suppression of normal Ig secretion
  - Hyperviscosity syndrome – excessive secretion and aggregation of myeloma proteins
  - Renal failure
  - Amyloidosis (5-10%)
- Nonsecretory myelomas (1%) - Ig present in the plasma cell masses only not in serum or urine
- **Course:** progressive, 2-4 years median survival

## Lymphoplasmacytic Lymphoma

- Older adults (6<sup>th</sup>-7<sup>th</sup> decade)
- IgM globulins ---pentameric large molecules *increases blood viscosity* → *Waldenstrom's macroglobulinemia*:
  - *Visual impairment*
  - *CNS: headaches, dizziness, deafness*
  - *Bleeding: CF complex with macroglobulins*
  - *Cryoglobulinemia: pptn of macroglobulins at low T*
    - *Raynaud phenomenon*
    - *Cold urticaria*
- Longer survival than MM

## Myeloid Neoplasms

- Acute myeloblastic leukemias (AML)
  - Block in differentiation → "myeloblasts"
- Myelodysplastic syndromes (MDS)
  - Disordered terminal differentiation
  - Dysplastic BM precursors
  - "cytopenias"
- Chronic myeloproliferative disorders (CMPD)
  - No block in terminal differentiation, but with dysregulated growth
  - CML, PV, MMMF, ET

*"Blurred divisions" MDS and CMPD transform to AML*

## Acute Myeloblastic Leukemia

- Usually adults, incidence ↑ with age
- Diverse:
  - Predominant line of differentiation
  - Cell maturity
- S/Sx: like lymphoblastic leukemia, due to BM failure: fatigue, pallor, bleeding, infections, & "granulocytic sarcoma"
- Diagnosis:
  - Morphology
    - Myeloblasts
    - Auer rods
  - Histochemistry
  - Immunophenotype
  - Karyotype

### FAB Classification of AML

Class	Morphology	Comments
M0	Blasts lack cytologic markers	2-3%
M1	Very immature myeloblasts	20% (Ph chromosome worsens prognosis)
M2	Myeloblasts & promyelocytes	30%, t(8;21) good prognosis
M3	Hypergranular promyelocytes "many auer rods"	5-10% <b>DIC, t(15,17) Responds to ATRA</b>
M4	Myelocytic & monocytic diff.	20-30%, inv16/del16q better prognosis
M5	Monoblasts & promonocytes	10%, pediatric age-young adults, 11q23 abnormalities
M6	Erythroblasts > myeloblasts	5%, older adults
M7	Megakaryocytic blasts	Myelofibrosis

### Acute Myeloblastic Leukemia

- Morphology: blasts with delicate nuclear chromatin, azurophilic granules and "auer rods"
- Classification: good, intermediate, bad risk
  - based on karyotyping (ie, good risk aberrations t[8,21], inv [16] )
  - M3 t(15,17) results in abnormal *PML/RARA fusion protein that blocks differentiation at promyelocytic stage which is overcome by retinoic acid (ATRA)*
- Histochemistry: MPO positive
- Immunophenotype
  - Myeloid asso. antigens: CD13, CD14, CD15, CD64, CD33
  - Platelet asso. antigens: GPIIb/IIIa, CD42b, CD61, CD41
- Course:
  - Conventional therapy -15 -30% disease free survival
  - Stem cell transplant

### Acute Myeloblastic Leukemia

- Prognosis depends on cytogenetic risk categories
  - 5 Yr Survival
    - 70 - 90% - AML with t(15;17) with ATRA + CT
    - 10 - 30% - AML with multiple cytogenetic aberrations
- Indication for stem cell transplant or bone marrow transplant: very high risk in first remission or after relapse
- Results of BMT in AML:
  - 30 - 50 % cure rate at 5 yrs
  - 15 - 35% transplant related mortality within 100 d

### Myelodysplastic Syndromes

- Clonal stem disorder: maturation defect, ineffective hemopoiesis, ↑↑ AML transformation
- Etiology: idiopathic, post CT or RT
- BM: hypercellular PS: pancytopenia
- Unstable stem cell clone prone to mutations → AML
- Cytogenetics: 5 and 7 (loss or long arm deletions)
- Clinical: adults with hemorrhages, anemia, infection
- Treatment:
  - Poor response to CT (underlying stem cell failure)
  - May respond to T cell immunosuppressants

## Chronic Myeloproliferative Disorders

- Chronic myelogenous leukemia (CML)
- Polycythemia vera (PV)
- Myeloid metaplasia with myelofibrosis (MMF)
- Essential thrombocythemia

## Chronic Myelogenous Leukemia (CML)

- Adults, usually 40-50
- Philadelphia chromosome
- Clinical: slow onset, nonspecific s/sx, marked splenomegaly
- Lab: leukocytosis (>100,000)
  - PMNs, myelocytes, eosinophils, basophils, <5% "blasts"
- BM: hypercellular (granulocytic/megakaryocytic)
- D/D: leukemoid reaction (↑LAP)
- **Course:** 50% accelerated phase
  - ↑ anemia, ↓ PLTs, abn cytogenetics, blastic crisis

## Chronic Myelogenous Leukemia (CML)

### Course:

- 50% abrupt blast crisis:
  - 30%: Tdt + blasts that express B lineage (+CD19/20)
  - 70%: "myeloblasts"
  - Clonal gene rearrangements
- 50% accelerated phase
  - ↑ anemia, ↓ PLTs, Cytogenetic abn, with final acute leukemia transformation (blastic crisis)

### Treatment: Gleevec (Imatinib®)

Tyrosine kinase that targets BCR-ABL fusion protein

## Polycythemia vera (PV)

- Adults (40-60)
- Trilineage clonal proliferation (from a single neoplastic stem cell)
  - Absolute ↑ RBC mass with ↓ Epo
  - D/D: Relative polycythemia ↑ Epo
- Clinical: thrombotic/hemorrhagic symptoms
  - plethora/cyanosis, pruritus, headache
  - GI/gum/nose bleeding, gout, stroke, Budd-Chiari S.
- Lab: ↑ RBC (6-10M/uL), ~60% Hct, ↑ WBC/PLTs
- BM: Hypercellular (trilineage) + Fibrosis

## Polycythemia vera (PV)

### Course:

- Natural History: progressive transition to a “spent phase” towards MMMF
- BM Fibrosis → extramedullary hematopoiesis (splenomegaly)
- Leukemia Transformation
  - Less frequent than CML
  - AML (2%) in those treated with phlebotomy
  - AML (15%) in those treated with RT, chlorambucil

## Myeloid Metaplasia w/ Myelofibrosis (MMMMF)

- Early occurrence of “spent phase”
  - may begin with PV or CML features
- Clinical: marked hepatosplenomegaly, anemia and thrombocytopenia
- Etiology: fibroblastic proliferation (polyclonal)
  - by *PDGF* and *TGF-β*
- BM: Hypocellular with diffuse fibrosis
- Lab: PS-Leukoerythrocytosis, No Ph chromosome
- **Course:** 5-15% “blast crisis”

## Histiocytic Neoplasms

### Langerhans Cell Histiocytosis

- *Langerhans cell proliferation* (+*HLA-DR/CD1*)
  - “*HX bodies*” (*Birbeck granules*)
- *3 conditions:*
  - *different expressions of the same disorder*
  - Hand Schuller Christian (HSC) disease
  - Letterer-Siwe Disease: < 2 y/o, skin lesions, hepatosplenomegaly, osteolytic bone lesions
  - Eosinophilic Granuloma: unifocal vs. multifocal
- ✓ “*HSC triad*”
  - *exophthalmos, diabetes insipidus, calvarial bone lesions*

## Disorders of the Thymus and Spleen

- Hyperplasia of the thymus
  - + Lymphoid follicles in the medulla
  - M. gravis, SLE, Rheumatoid arthritis
- Thymoma (neoplastic epithelial cells)
  - Benign thymoma: cytologically/biologically benign
  - Malignant thymoma:
    - Type I: cytologically benign/biologically aggressive
    - Type II: thymic carcinoma (5%)
      - usually squamous cell carcinomas
      - Lymphoepithelioma-resemble NSP carcinomas with EBV genome, anaplastic epithelial cells in a background of benign lymphocytes
- Splenomegaly:
  - Massive, Moderate, Mild

## Splenomegaly

- Massive (>1000 g)
  - Chronic myeloproliferative disorders (CML, MMMF)
  - CLL (less massive)
  - Hairy cell leukemia, Lymphomas, Malaria, Gaucher
- Moderate (500-1000 g)
  - Chronic congestive splenomegaly (portal HTNO)
  - Hereditary spherocytosis
  - AIHA, Amyloidosis, NP disease, TB
- Mild (<500 g)
  - Acute splenitis
  - Infectious mononucleosis
  - Acute splenic congestion

