Hematopoietic and Lymph Node Pathology

Red Blood Cell Maturation
&
Anemias

Normal Development

Differentiation of Hematopoietic Cells
Bone Marrow

Bone Marrow

Bone Marrow, RBC Precursors

RBC Expelling the Nucleus

Myeloid Maturation
Anemias

- Not a disease in itself
- Just a symptom, like a fever
- Must Understand why.
- Fix underlying cause
- Unpredicted outcomes

Anemia

- Acute
  - Trauma
    - Blood loss, either internal or external
    - Reticulocytes 10-15% in a week
- Chronic
  - Time to adapt
  - GI bleeds, colon ca
  - Increased demands of pregnancy

Anemia Workup

- History, History & More History
  - Age, sex, medications, duration...
- Physical
  - Nailbeds, mucus membranes....
- Lab
  - CBC
    - RBC size, shape, Hgb, RDW, MCV, MCHC
  - Reticulocyte count
  - Chemistries
    -Liver B & Tz, Parats
    -Bone Marrow
  - Fancy stuff

Erythrocytes

- Size
  - Anisocytosis (an/i-so/cytosis)
- Shape
  - Poikilocytosis (poikilo/cytosis)
    - Fragmented cells
- Hemoglobin content of cells and whole blood
  - HBG and HCT
  - MCH & MCHC
- Mean volume of the RBCs (MCV)
  - Uniformity (RDW)
- Cytoplasmic inclusions
  - Congenital problems
    - Sickle cell among others
Anemias by Etiology

- Blood loss
  - Acute, no time to accommodate
  - Trauma
  - Massively bleeding ulcer or esophageal varices
  - Chronically, slow with some adaptation
  - GYN loss
  - Ulcer
  - Colon cancer
- RBCs are ‘normocytic’
- Retic count better go up
- History and Physical

Anemias by Etiology

- Congenital
  - Hemoglobin
  - Sickle cell
  - Enzyme
    - G6PD
  - Membrane
    - Spherocytosis

Sickle Cell Disease

- Hemoglobin vs. hemoglobinopathy
- Genetic variants
- RNA editing
- Hemoglobinization inducers
- Other factors
- Relative mean survival for SC

Hemolytic Anemias

- Premature destruction or removal of RBCs
- Genetic
  - S5
  - Spherocytosis
- Acquired
  - Antibody mediated
- Intravascular
  - Antibody mediated
  - Free hemoglobin
- Extravascular

Problems of RBC Production

- Genetic related
- Nutritional deficits
  - Iron
  - B12
    - Dietary or problems of absorption?
  - Chronic gastritis
  - Folic acid
  - Chronic renal failure (no erythropoietin)
  - Aplasia of RBC line in bone marrow
Nutrient Deficit
- Inadequate dietary source?
- Absorption?
- Utilization?

Thalassemia
- Genetic
- Collection of problems of production of one of the hemoglobin chains
- Beta and Alpha chains

Thalassemia
- Microcytic
- Small RBCs
- Target cells
- Mismatched production of β and α chains
- Hemoglobin globs in RBC
- Reduced RBC survival

B12 Deficiency
- Dietary
- Pernicious Anemia
  - Absorption
  - Binding factor missing
  - Chronic gastritis
- Macrocytic anemia
  - Large cells
  - Delayed nuclear maturation
- Neurological signs
  - Myelin production

Macrocytes and Megaloblasts
- Macrocyte
- Large RBC
- Megaloblast
- Large BM precursor
- Folic acid can have similar look
- CNS with B12 only
  - Be careful correcting B12 deficiency with folic acid
  - Anemia corrects, but neurological problems progress
Folic Acid and B12

- DNA
- N^5-, N^10-Methylene FdR
- dTMP
- dUMP
- Thymidylate Synthetase

Iron Deficiency
- Dietary?
  - Rarely in US
  - How much anyway?
- Blood loss
  - Chronic
  - GYN
  - Colon cancer
- RBCs are
  - Microcytic
  - Hypochromic
  - Lack iron for hemoglobin production

Microcytic Anemia
- Small RBCs
- Iron deficiency
- Thalassemia

Iron Deficiency
- Problem is of excessive drive to store iron.
- Chronic inflammation
  - Arthritis
  - TB
  - Even cancer
- Most of incoming iron is sent to storage
  - Part of the normal response to inflammation
- In time anemia develops because of
  - Reduced iron for utilization
  - Not dietary lack or
  - Failed absorption

Anemia of Chronic Disease
- Over Production of RBCs
  - Believe it or not, it's not a good thing.
  - Response to increased need
  - High altitude living
  - Lung disease
  - Emphysema
  - Over production of erythropoietin
    - Renal disease
    - Tumors
    - Uncontrolled production at bone marrow level

Aplastic Anemia
- Something kills precursor in BM.
  - Virus
  - Radiation
  - Chemotherapy

Over Production of RBCs
Hemolytic Disease of Newborn

- Pregnant mother is Rh−, fetus is Rh+
- If mom should have antibodies to the Rh factor, they will cross the placenta.
- Destruction of baby’s RBCs
- Previous maternal exposure
  - Miscarriage
  - Previous delivery
  - Wrong transfusion
- Treatment: Mom gets Rhogam

WBC Disorders

- Quantity
  - Do we have enough WBCs
- Quality
  - If the number looks right, are the cells working?
  - Higher than expected number (leukocytosis)
    - Cell type
      - Reactive or
      - Neoplastic
        - Benign
        - Malignant
    - Leukopenia

Leukopenia

- Low WBC count
  - Under 3,000 per mm³
- Causes
  - Production problem
    - Sick BM
  - Replacement of BM space
  - Peripheral destruction
    - Autoimmune destruction
  - Sequestration of cells
    - Large spleen
    - Rheumatoid arthritis

Leukocytosis

- High WBC count in peripheral blood
  - >12,000 per mm³
- Cell type?
- Healthy Cells?
- Reaction to need
  - Pneumonia
  - Incr granulocytes; bacterial infection, necrosis
  - Incr monocytes; TB, brucella, rickettsia
  - Incr lymphocytes; virus, tumor response
  - Incr eosinophil; allergic, parasite
Distinguish Malignant Proliferation

- History and physical
- Maturity of cells
  - Visual inspection of blood smear
  - Flow cytometry
  - Nuclear maturity
  - Nucleoli
  - Cellular inclusions
- Chromosomal studies
- Bone marrow

Leukemia

- Malignant proliferation of WBCs and/or precursors.
- Classification
  - Cell line: Granulocytes or Lymphocytes
  - Cell population:
    - Chronic, mature, slower developing
    - Acute, immature cells, rapidly developing
- The big three features: All three cell lines affected
  - RBC
  - WBC
  - Platelets
- Causes
  - Chromosomal breaks, but why?
  - Viruses, chemical exposure, radiation...

Leukemia

- Organs involved
  - BM
  - Blood
  - Nodes
  - Liver and Spleen
  - Brain
- Common presenting symptoms
  - Recurrent serious infections
    - Pneumonia
  - Bleeding tendency
  - Anemia
  - Fever with no obvious cause
  - Bone pain

Lymphocyte Maturation

Lymphoid Malignancies

- ‘Solid’ vs. ‘Liquid’
  - Leukemia
    - Bone marrow predominately
  - Lymphoma
    - Lymph nodes
- Cell type and level of maturation
  - Cell size
  - CD typing
  - Where did it come from in the follicle?

Acute Lymphoblastic Leukemia

- Children
  - Less common, but does occur in adults
- Precursor B leukemia
  - CD19, TdT +
  - Ig locus t(12:21)
  - Marked BM replacement
- Precursor T leukemia
  - CD1 and TdT +
  - Chromosomal breaks
  - Adolescent males
  - Mediastinal mass
  - +/- spleen and liver
Acute Myelogenous Leukemia

- Myeloid line
  - Many subtypes
  - Level of maturation determines what malignant cells look like.
- Adults
  - Aure rods ->
- Adults
  - Rarely pure monocytic
- Symptoms
  - Infections
  - Mouth ulcers
  - Gingival hypertrophy (mono)

Chronic Lymphocytic Leukemia

- Mature lymphocytes
- High WBC count
- B-Cells
- Adult and older
- Indolent course
- Tissues
  - BM
  - Nodes
  - Liver and Spleen
- May accelerate
  - Blast crisis
  - Richter’s syndrome

Chronic Myelocytic Leukemia

- Middle age and older
- High WBC count
- Stem cell is malignant
- All phases present
- Low LAP (cells don’t work)
- Ph’ Chromosome + t(9;22)
- Organs
  - BM
  - Spleen
  - Blast crises
  - Soft tissue met
  - Chloroma

Ph’ Chromosome
Splenomegally in Chronic Granulocytic Leukemia

Myelofibrosis Etc
- Myelofibrosis
  - Scarring process
  - Reticulum fibers
  - Loss of marrow space
  - Extramedullary hematopoiesis
  - Metastatic cancer

Preleukemia
- RBC abnormalities easiest to spot.
- All cell lines have abnormal maturation.
- Chromosomal abnormalities
- Some end in leukemia
- Most end with myelofibrosis

Bleeding Disorders
- Takes three things working for hemostasis
  - Platelets
  - Clotting proteins
  - Vessels
- The question is always
  - Quantity
  - Quality

Platelet Related Bleeding
- Platelet problems
  - Petechiae
  - Bruises (purpura)
- Quantity
  - 120,000-400,000
  - Production
  - Destruction
- Quality
  - Aspirin
  - Renal failure
**Clotting Factor Related Bleeding**
- Hematoma
- Deep muscle
- Joint bleeds
- Bleeding gums
- Poor wound healing
- Quantity
- Can you make it
- Genetics
- Liver disease
- Quality

**Hemophilia A & B**
- Hemophilia A
  - X-linked recessive
  - Boys express
  - Factor VIII enzymatic deficiency
- Hemophilia B
  - Christmas Disease
  - Factor IX
  - Also X-linked recessive
  - Not as severe as VIII

**Von Willebrand’s**
- Factor VIII, ‘structural’
- Platelet binding
  - Collagen of damaged vessel
  - Platelet – platelet binding
- Clinically, bleeding looks more like platelet abnormality.
- Autosomal dominant
- Multiple types
  - Type I
    - Most common
    - Reduced quantity of vWF
  - Type II
    - Problem with multimeric form of vWF

**Generic Platelet Problems**
- Quantity (thrombocytopenia)
  - Lack of bone marrow production
  - Autoimmune destruction (ITP)
  - Heparin induced thrombocytopenia
  - Lack of stabilizing factor (TTP)
- Quality
  - Aspirin induced platelet dysfunction

**Disseminated Intravascular Coagulation**
- Runaway train
- Oil disaster
- Sepsis and endothelial cell injury
- Massive muscle injury
Diseases of Lymph Nodes

Lymph Node Disorders
- Reactive vs. Neoplastic
- History & Physical Exam
- Histological pattern
  - Nodal architecture recognizable?
  - Effaced?
  - Diagnostic inflammatory changes

Reactive Conditions
- Non-neoplastic reaction to
  - Infections, necrosis, tumors
- Histological pattern
  - Follicular
  - Sinusoidal
  - Specific patterns
    - Abscess
    - Granuloma

Neoplastic Diseases
- Classification is very important
- Treatment options
- Predicting outcome
- Histological pattern
  - Hodgkin lymphoma vs. Non-Hodgkin Lymphoma
  - Cell type (where did it come from in the node?)
  - Degree of differentiation (grade)
  - Diffuse or Follicular
- Stage (extent of spread)
  - Know the difference between stage and grade
- Systemic symptoms (so-called B-symptoms)
  - Fever
  - Night sweats
  - Weight loss
Non-Hodgkin Lymphoma, SLL
- Small cell lymphocytic lymphoma
- Tissue phase of CLL
- Diffuse replacement of nodal architecture
- Long-lived B-cells (CD19, CD20)
- Surface immunoglobulins

Non-Hodgkin Lymphoma, Follicular Pattern
- Nodal architecture is effaced
- Nodular or follicular pattern
- ‘Centrocytic’ cells (from germinal centers)
- B-cell markers
- Surface immunoglobulins

Burkitt’s Lymphoma
- Two types
  - American
    - Retroperitoneal
  - African
    - Jaw
    - EB virus association?
- ‘Starry sky’ appearance
- B-cell

African Burkitt’s

Hodgkin’s Disease
- Distinguished from NHL by
  - Reed-Sternberg cell -->
    - In its proper background
    - This is the malignant cell
    - The others are reactive
  - Bimodal age distribution
  - Distinctive patterns
    - Nodular sclerosis
      - Lacunar cells -->
    - Mixed-cellularity
    - Lymphocyte predominate
Hodgkin’s Staging

- **Stage I**
  - Single node or single extranodal site (I-e)

- **Stage II**
  - Two or more nodal regions on the same side of the diaphragm

- **Stage III**
  - Both sides of the diaphragm
  - +/- Splenic involvement (III-s)
  - +/- Extranodal (III-e)

- **Stage IV**
  - Multiple disseminated foci

Multiple Myeloma

- Plasma cell malignancy
- Term refers to holes in the bone because of nest of plasma cells
- The replace marrow space
- The cells make an intact, or fragment, of immunoglobulin
- Real problems with infections
  - No inflammatory cells
  - Bleeding
    - Protein coats platelets
  - Renal failure
    - Protein clogs tubules

Multiple Myeloma

- Protein electrophoresis
- Large amount of abnormal protein in blood
- Immunoglobulin
- Patient sample
  - Huge gamma band
  - All of it is kappa light chain