

## HEMATOLOGIC NEOPLASIA LECTURE II

### V. ACUTE MYELOCYTIC LEUKEMIA (AML) = acute myelogenous leukemia

- A. Incidence: > 10-20% of all adult leukemias  
**median age >40 y/o** , sporadic early cases
- B. Presentation: anemia, bleeding problems, unexpected infections
- C. Hematology:
  1. BM: crowded out by "blasts"
  2. PB: total WBC variable sometimes < 5000 cells/mm<sup>3</sup> because blasts remain in BM.  
AML is subclassified as M1-M5–  
M3 is predominantly promyelocytic  
***Auer rods found in M2, M3 can aid in diagnosis***  
***thrombocytopenia causes capillary bleeding and purpura***
  3. Serum: lysozyme = muramidase = bactericidal enzyme released from immature granulocytes
- D. Organ Pathology: massive splenomegaly ( > 5 kg), hepatomegaly due to leukemic cell infiltration, rare masses of immature granulocytes invade soft tissue = chloroma
- E. Molecular Genetics and Pathogenesis:
  1. partial gene deletions: 7q<sup>-</sup>, 5q<sup>-</sup> after chemotherapy, radiation or severe chemical exposures. The region in 5q encompasses genes for several hematopoietic growth factors: IL3 (multiple colony growth), IL5 (eosinophil differentiation), CD14 (myelomonocytic differentiation)
  2. translocation t(15;17) in promyelocytic subtype (M3): juxtaposes PML from chromosome 15 and RAR- $\alpha$  on chromosome 17. This codes for an aberrant retinoic acid receptor that interferes with normal receptor function. A potent all-trans-retinoic acid can induce differentiation of the malignant promyelocytes and prolong survival
- F. Prognosis: untreated M1, M2 patients usually die within 1 yr due to rapid BM failure with infections & hemorrhage. Chemotherapy prolongs life, but toxicity can cause cardiac or pulmonary damage. In M3, DIC may result from release of immature granules. BM transplant currently offers the best chance for long term survival

### VI. ACUTE MYELOMONOCYTIC LEUKEMIA = AMMoL (M4)

- A. Neoplastic cells are phenotypic hybrids of granulocytes and monocytes
- B. most often seen in adolescents/young adults (15-35 y/o)
- C. cells infiltrate the gums or skin more often than cells of M1-M3 leukemias

## NEOPLASIA OF LYMPHOCYTIC LINEAGE

Ig = immunoglobulin H chain =  $\mu$ ,  $\gamma$ , etc L chain =  $\kappa$  or  $\lambda$   
EBV = Epstein-Barr virus (herpesvirus family) HIV = lentivirus causing AIDS

### I. INTRODUCTION TO THE LYMPHOCYTIC NEOPLASIA

A. Monoclonality: lymphocytic neoplasms are almost always monoclonal

B. Cells of origin: B cell most common

1. B cell malignancies - in several examples, the neoplastic clone evolves from a multipotent BM progenitor. These include ALL, Hodgkin's disease and multiple myeloma. In other lymphomas, neoplastic B cell clones resemble more mature B cell precursors found in LN germinal centers.
2. T cell malignancies are less common. T lymphoblastic leukemia / lymphoma probably arises from thymic precursors. Other T cell lymphomas probably arise from more mature T cell precursors in the LN paracortex.

C. Genetic instability and phenotypic variability: Rearrangements of B cell immunoglobulin or T cell receptor genes, create an immense potential for neoplastic variations. The predominant clone that emerges is merely a caricature of its normal counterpart. **Lineage infidelity means that neoplastic clones can express maturation "markers" of more than one normal phenotype** ( e.g. neoplastic B cells can express myeloid or T cell CD antigens).

D. Complex Terminologies: Experts have begun to employ a "Revised European-American Lymphoma Classification" ("REAL").

### II. THE BROAD CATEGORIES OF LYMPHOCYTIC MALIGNANCIES

A. Lymphocytic leukemia (may be chronic or acute) -- the predominant manifestation is lymphocytosis with >15,000 neoplastic cells /  $\mu$ L

B. Malignant lymphoma (non-Hodgkin) -- solid masses of malignant lymphocytes -- may localize in LN or extranodal sites: GI tract, skin, brain, gonads, soft tissue

C. Hodgkin's disease -- a LN disease in which malignant Reed-Sternberg B or T cells are surrounded by reactive lymphocytes, macrophages (histiocytes), and inflammatory cells.

D. Plasma cell neoplasms = solid masses of B cell monoclonal secreting Ig or Ig fragments - may localize in BM = multiple myeloma or in LN = Waldenstrom's disease

## LYMPHOCYTIC LEUKEMIAS

### I. ACUTE LYMPHOCYTIC LEUKEMIA = ALL = LYMPHOBLASTIC LEUKEMIA

- A. Incidence: in **children 3-9 y/o** : the most common malignant disorder ~ 2,500 new cases each year  
in adolescence or adults: 15-20% of acute leukemia cases
- B. Clinical presentation: flu-like, loss of appetite, petechiae or purpura, weight loss, bone pain
- C. Physical findings: signs of hemorrhage, hepatosplenomegaly, diffuse lymphadenopathy, bone tenderness (sign of subperiosteal growth)  
neurologic signs are associated with meningeal infiltration.
- D. Hematologic findings:
  1. BM: replaced by lymphoblasts (60-100% of cells)
  2. PB: WBC up to 200,000/ $\mu$ L, mostly "blasts" with scant cytoplasm (see Robbins Fig. 14-17B)
- E. Immunodiagnosis / molecular genetics
  1. early pre-B cell phenotype in 60-70% of childhood cases: TdT +, H-chain gene rearranged, CD19+, but usually lack surface Ig
  2. usually express common ALL-antigen = CALLA (CD10) and CD20
  3. T cell origin in about 15% of cases: typically adolescent / young adult with mediastinal tumor = lymphoblastic lymphoma (details below)
  4. The Ph<sup>1</sup> karyotype or myeloid antigens are found in ~ 25% of adult ALL cases, some childhood cases. It suggests a multipotent stem cell origin.  
the BCR-cABL chimeric protein is often p190 vs. p210 in CML
  5. interferon gene deletions occur in up to 30% of children
- F. Etiology / Pathogenesis Gene deletions suggest defective cytokine regulation of cell proliferation
- G. Complications: blast crisis = > 150,000 blasts / $\mu$ L in PB,  
>90% blasts in BM  
meningeal leukemia with cerebral hemorrhages
- H. Prognosis:
  1. Childhood early pre-B cell: 90% complete remission after intensive combination chemotherapy combined with prophylaxis for meningeal leukemia, about 2 /3 "cured."
  2. Myeloid markers, the Ph<sup>1</sup> karyotype or T cell phenotype convey a poor prognosis: In general, prognosis is less favorable adults than children. BM transplant is a hope.

### II. CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

- A. Incidence: at least 25% of all leukemias in Caucasians 2/3 > 60 y/o
- B. Clinical Presentation: insidious with fatigue, lymphadenopathy
- C. Physical findings: hepatosplenomegaly, multiple lymphadenopathy, enlarged pharyngeal tonsils, skin lesions in 50%, tender sternum
- D. Hematologic findings:
  1. BM: gradual infiltration, dangerous when > 50% of BM is replaced.

2. PB: lymphocyte counts in range of 10,000-150,000 /  $\mu$ L  
monotonous small lymphocytes with mature nuclei, inconspicuous cytoplasm (see Robbins Fig. 15.9)

cells with fragile nuclei = "smudge cells"

3. Cytogenetics: many abnormal karyotypes in metaphase cells  
deletion of long arm of chromosome 13 most common

trisomy 12 can be detected in 5-20% by Fluorescent In-Situ Hybridization (example of FISH in Fig. 15-31)

E. Immunodiagnosis / molecular genetics:

1. mature B cell phenotype (CD19+,CD20+), also CD5+
2. genes for H and L chain genes are rearranged  
each B cell clone produces a slg with a unique idotype  
a pure T cell phenotype is very rare
3. cells express a high level of antiapoptotic bcl-2

F. Pathophysiology:

1. daily production of lymphocytes is 15 x normal
2. lymphocytes accumulate in G<sub>0</sub> phase and do not undergo apoptosis

G. Etiology/Pathogenesis:

1. 50% with abnormal karyotypes, expression of bcl-2
2. evidence of familial predisposition: 2-7 X risk in 1<sup>st</sup> degree relatives  
identical twin concordance, rare in Asia

H. Complications

1. 20-25 % of patients develop hemolytic anemia  
often begins during chemotherapy  
due to autoimmune, type II hypersensitivity (?? anti-CD5)
2. increasingly severe anemia, thrombocytopenia  
infections due to granulocytopenia.
3. up to 5% of patients develop skin, colon or prostate cancers  
**data supports the immune surveillance theory of cancer.**

**Richter syndrome = transformation to a diffuse large B cell lymphoma (see below)**

I. Prognosis:

1. up to 15 yr with normal karyotype
2. < 8 yr with abnormal karyotypes
3. worst prognosis in patients with trisomy 12 or with Richter transformation.  
BM allo-transplantation is being utilized in some cases.

III. HAIRY CELL LEUKEMIA (= leukemic reticuloendotheliosis)

A. Incidence: rare, 45-55 y/o, predominance (younger than usual CLL)

B. Clinical presentation: vague symptoms, splenomegaly

C. Hematologic findings

BM: lymphocyte infiltration and fibrosis

PB: lymphocytes display multiple hairlike projections

**react for tartrate-resistant acid phosphatase**

- D. Neoplastic lymphocytes: B cells - H & L chain genes rearranged, monocyte-associated antigens
- E. Etiology/Pathogenesis: ?? retrovirus
- F. Complications: opportunistic mycobacterial infection
- G. Prognosis: often good response to therapy.