Classification of hematopoietic neoplasms

Hematopoietic malignancies can be classified on the basis of:

- State of maturity of the neoplastic cells
  - **Acute** - presence of very immature cells (blasts)
  - **Chronic** - presence of differentiated (mature) cells

- The cell type involved
  - **Lymphoid**
  - **Myeloid**
Leukemias

- The leukemias are malignant neoplasms of the hematopoietic cells characterized by diffuse replacement of the bone marrow by neoplastic cells

- Leukemic cells usually spill over into the peripheral blood

Leukemia versus Lymphoma

- "Leukemia" is used for hematopoietic neoplasms that present with widespread involvement of the bone marrow and blood

- "Lymphoma" is used to describe proliferations arising as discrete tissue masses

- There may not always be a discrete boundary between the two (diseases are then referred to as "leukemia/lymphoma")

Acute Leukemias

- ALL and AML typically present with similar clinical features. It is very important to distinguish these disorders since the treatment is different.
  - In both, there is an accumulation of neoplastic blast cells
    - suppress normal hematopoiesis leading to anemia, neutropenia, thrombocytopenia
  - major clinical features of ALL and AML are usually secondary to these consequences
Acute Leukemias - Clinical features

- Abrupt stormy onset
- Symptoms related to depression of normal marrow function
  - fatigue, often caused by anemia
  - fever, reflecting infection caused by neutropenia
  - bleeding, secondary to thrombocytopenia
- Generalized lymphadenopathy, splenomegaly, hepatomegaly due to neoplastic infiltration (ALL > AML)
- Central nervous system involvement (ALL > AML)

Acute lymphoblastic leukemia (ALL)

- 80% of acute leukemias in children are ALLs
- Most cases occur in individuals younger than 15 years old, with a peak incidence of about 4 years of age
- ALL also occurs in adults of all ages, but is less common than AML

Acute Lymphoblastic Leukemia (ALL)

- Neoplastic cells are lymphoblasts: precursor B (pre-B) or T (pre-T) lymphocytes
- Approximately 85% of ALLs are pre-B cell neoplasms that typically manifest as childhood leukemias (with extensive bone marrow and variable peripheral blood involvement)
T-ALL – Special Clinical Features

- Tends to present in adolescent males often with thymic involvement manifesting as a mass in the mediastinum

- Although the initial presentation is that of a “lymphoma”, this is followed by involvement of the blood and bone marrow (leukemic phase)

ALL - Diagnosis

Microscopic evaluation: Lymphoblasts usually show scant basophilic cytoplasm and fine nuclear chromatin (not clumpy), often nuclear convolutions

Morphology alone does not differentiate ALL from AML and additional analysis is necessary

ALL

[Image of ALL cells]
ALL - Diagnosis

Markers used for diagnosis of ALL:

- T (CD1, 2, 3, 4, 5, 7, 8) or B (CD19, 20, 22) cell markers
- (TdT) Terminal deoxynucleotidyl transferase
  - positive in >95% of cases

ALL - Diagnosis

- Up to 90% of ALL patients have numerical or structural changes in the chromosomes of the leukemic cells, correlating with immunophenotype and sometimes prognosis
  - hyperdiploidy (>50 chromosomes) is common
  - t(12;21) [TEL1-AML1 (ETV6-RUNX1)]
  - t(9;22) [BCR-ABL; Philadelphia chromosome]
ALL - Prognosis

• Advances in the treatment of ALL have led to complete remission rates of 95% in children and cure in about 80%

• Favorable prognostic indicators include:
  – Age 2 to 10 years
  – hyperdiploidy
  – t(12;21) [TEL-AML1 (ETV6-RUNX1)]

ALL - Prognosis

• Unfavorable prognostic indicators include:
  – age under 2
  – adolescent or adult presentation
  – presence of t(9;22) [seen in 3% of childhood ALL, but up to 25% of adult cases]

Ph Chromosome (BCR-ABL), t(9;22)
Acute Myeloid Leukemia

- Primarily a disease of adults, median age of 50 years; only 20% of childhood leukemias
- Heterogeneous disease, reflecting complexities of myeloid cell differentiation
- 21,000 new cases per year

AML- WHO Classification

1) AML with recurrent genetic abnormalities
   - t(8;21) AML1-ETO good
   - t(15;17) PML/RARA good
   - Inv(16) CBFB/MYH11 good
   - t(11q23;v) MLL poor

2) AML arising from myelodysplastic syndrome (MDS) poor

3) Therapy related poor

4) Not otherwise specified intermediate

Myelodysplastic Syndromes (Preleukemia)

- Clonal stem cell disorders showing defective and ineffective hematopoiesis with increased risk for transformation to AML

- Types of MDS:
  1. Primary or Idiopathic
  2. Therapy Related: Following chemo/radiation therapy.
Myelodysplastic Syndromes
Pathophysiology

1. Hypercellular marrow with peripheral cytopenia (ineffective hematopoiesis)

2. Clonal cytogenetic abnormalities (5q-, monosomy 7)

3. MDS arises on a background of stem cell damage

4. Morphologic abnormalities seen in all lineages: nuclear irregularity, nuclear budding, multinucleation, separated nuclear lobes

Myelodysplastic Syndromes
Morphologic findings

Robbins Pathologic Basis of Disease (8th Edition)
Myelodysplastic Syndromes

- Median survival: Primary MDS: 9-29 months. Secondary MDS: 4 to 8 months
- MDS subtypes with higher blasts in blood or marrow are associated with poorer prognosis. Severe peripheral cytopenias and multiple clonal cytogenetic abnormalities are other independent risk factors
- Death may be due to complications of cytopenias or transformation to acute myeloid leukemia

AML - Clinical features

- Clinical findings are similar to ALL
- Signs and symptoms related to infiltration of tissues are usually less striking in AML than in ALL, although mild lymphadenopathy and organomegaly may be appreciated

AML - Clinical features

- CNS spread is less common than in ALL, but may still occur
- The bleeding diathesis may be particularly striking
- In acute promyelocytic leukemia [t(15;17)], particularly, procoagulants released by leukemic cells may produce DIC
Acute promyelocytic leukemia

- Characteristic of acute promyelocytic leukemia
- Important because of its pathogenesis and its effect on therapy
- Fusion gene encodes an abnormal retinoic acid receptor that blocks myeloid cell differentiation
- All-trans-retinoic acid overcomes the differentiation block

AML - Diagnosis

- Myeloblasts (>20%)
- Cytochemical stains: myeloperoxidase or alpha naphthyl butyrate esterase
- Flow cytometry: CD13, CD33, CD34, CD117 (myeloid)
- Auer Rods
- Cytogenetic analysis
MPO (myeloperoxidase) stain

Alpha-naphtyl butyrate esterase

AML - Diagnosis
- Myeloblasts (>20% in the blood or bone marrow)
- Cytochemical stains: myeloperoxidase or butyrate esterase
- Flow cytometry: CD13, CD33, CD34, CD117 (myeloid)
- Auer Rods
- Cytogenetic analysis
Flow cytometry

AML - Diagnosis

- Myeloblasts (>20%)
- Cytochemical stains: myeloperoxidase or butyrate esterase
- Flow cytometry: CD13, CD33, CD34, CD117 (myeloid)
- If an Auer Rod is seen, this is considered to be strong support for the diagnosis of AML
- Cytogenetic analysis
AML - Cytogenetics

- Prognosis is influenced by particular cytogenetic (chromosomal) abnormalities
- t(15;17), t(8;21) or inversion of chromosome 16 are associated with relatively good prognoses
- Translocations involving chromosome 11q23 (MLL) have a poor outcome
- Increasing evidence for genetic mutations: FLT3 (bad), NPM (good)

AML - Prognosis and Treatment

- AMLs arising out of MDS or after chemotherapy have particularly poor prognoses
- Treatment of AML is difficult; while approximately 60% of patients achieve remission with chemotherapy, only 15 to 30% remain disease-free at 5 years
- Bone marrow transplantation is becoming increasingly important in this disorder
- The promise of targeted and differentiation therapy
Thank you!

akini@lumc.edu

@AmeetRKini