Leukemia

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Introduction to Leukemia

- Definition
- Historic Perspective
- Etiology and Risk Factors
- Incidence
- Classification
- Comparison of Acute and Chronic Leukemia

Leukemia

Definition

Leukemia is a malignant disease of hematopoietic tissue characterized by the accumulation abnormal white cells (neoplastic or leukemic) in the bone marrow leading to bone marrow failure, a raised circulating white cell count (leukocytosis) and infiltrate organs (e.g liver, spleen, lymph nodes, brain)

Leukemia

Historic Perspective

- 1945
- The initial description of leukemia as a clinical entity was made by Bennett in Scotland and in Germany.

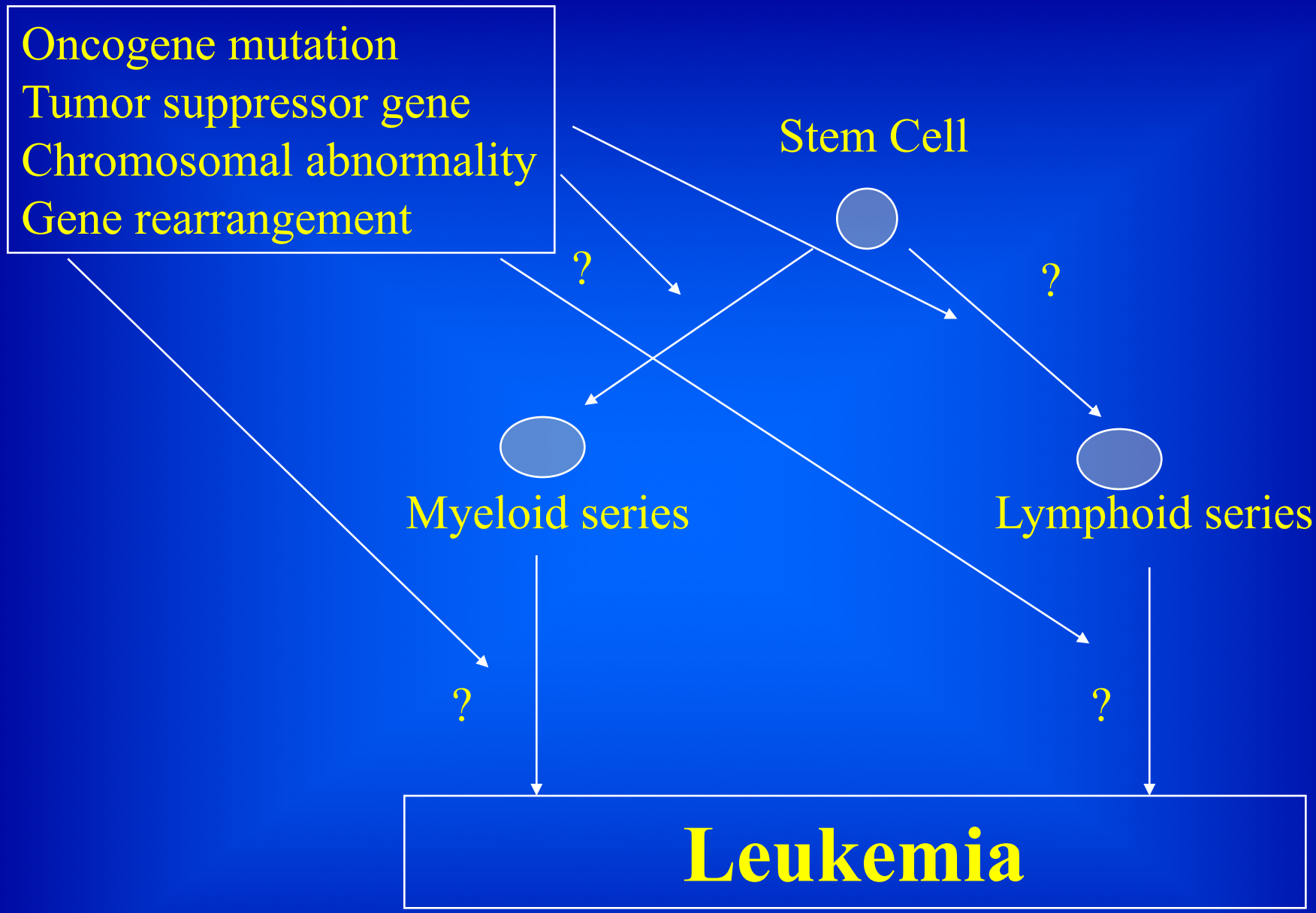
Leukemia

Etiology and Risk Factors

The etiology of leukemia is unknown.

- Oncogenes mutation and tumor suppressor gene alteration.

- Host factors.
- Environmental factors


Oncogene mutation
Tumor suppressor gene
Chromosomal abnormality
Gene rearrangement
Stem Cell
?
?
Myeloid series
Lymphoid series
?
?
Leukemia

Host Factors

- Congenital chromosomal abnormalities

- Increased frequency in patients with congenital disorders that have tendency for chromosomal abnormality.
- Such as : Bloom's syndrome, Fanconi anemia, Down's and Klinefelter's syndromes.
- 18-20 fold increase incidence of AL is seen in children win DS.

- Immunodeficiency

- An unusually high incidence of lymphoid leukemia and lymphoma has been described in patients with hereditary immunodeficiency states (ataxia-telangiectasia and sex-linked agamaglobulinemia).
- Usually related to T and B-lymphocyte gene rearrangement.

Chronic bone marrow dysfunction

- Patients with CBMD syndromes have an increased risk of acute leukemic transformation.
- Examples include the myelodypalstic syndromes, myeloproliferative disorders, aplastic anemia and PNH

Environmental factors

Ionizing radiation

- Leukemia is associated with exposure to ionizing radiation such as nuclear weapons in Hiroshima and Nagasaki.
- Both acute and chronic forms of leukemia including AML, ALL and CML were associated.

Chemical drugs

- A variety of chemicals and drugs have been associated with the development of leukemic transformation
- Examples: Benzene, Chloramphenecol, Phenylbutazone and Cytotoxic alkylating chemotherapeutic agents.

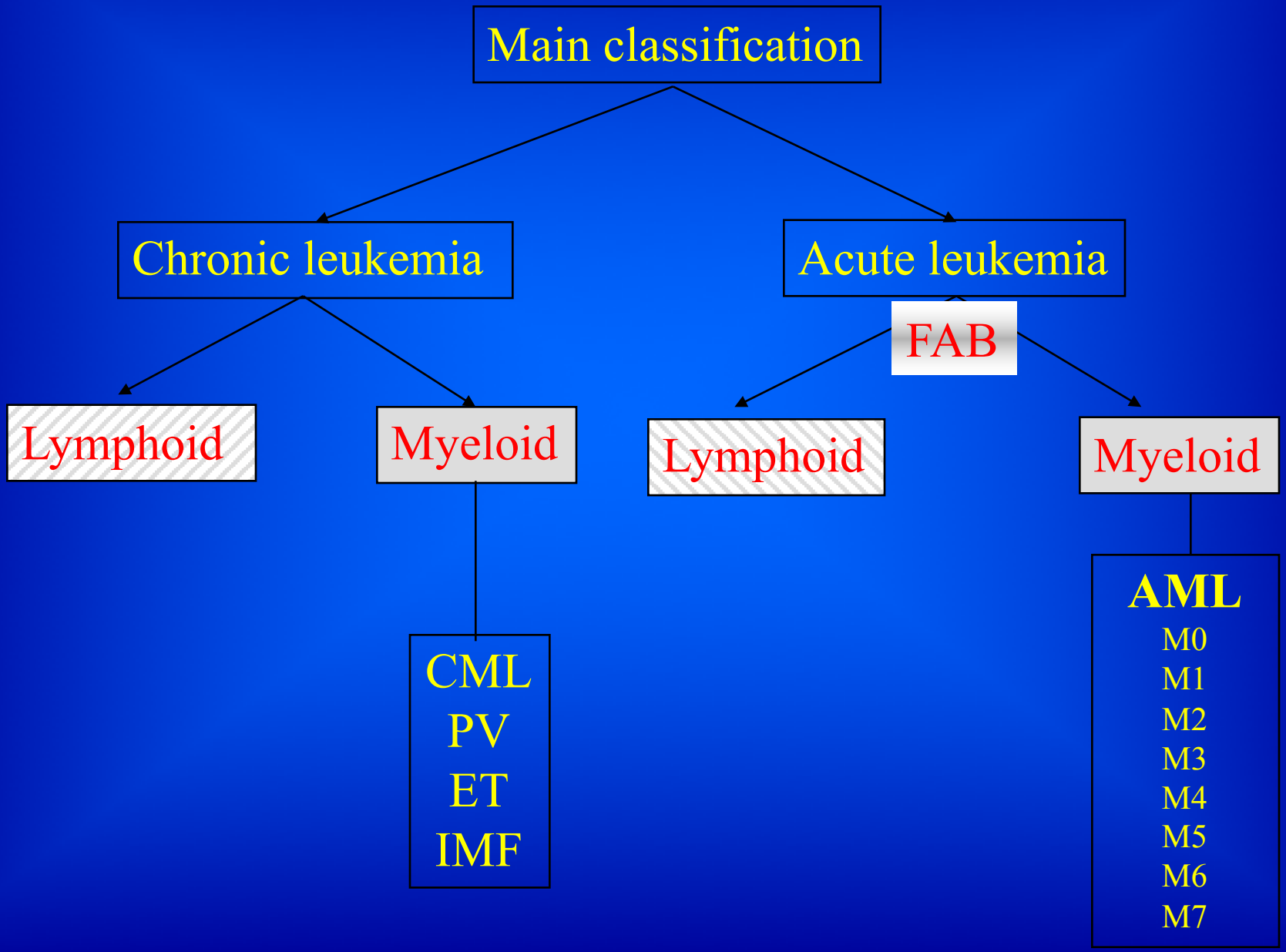
Viruses

- The human T-cell leukemia-lymphoma virus-I (HTLV-I) has been implicated as a causative agent of adult T-Cell leukemia-lymphoma.
- Another related virus HTLV-II has been isolated from patients with atypical hairy cell leukemia (CLL)
- The Epstein's Barr virus has been linked to Burkitt's lymphoma.

Incidence

- In the USA 8-10 new cases per 100,000 individuals annually.
- Approximately 28,600 new cases were reported about 50% acute and 50% chronic
- Leukemia strike more in adult than children (10:1) and has slightly increase incidence in males than females (1-2:1)

Classification of leukemia



Classification of leukemias

Two major types (4 subtypes) of leukemias

Acute leukemias

- Acute lymphoblastic leukemia (ALL)
- Acute myelogenous leukemia (AML)
  (also "myeloid" or "nonlymphocytic")

Chronic leukemias

- Chronic lymphocytic leukemia (CLL)
- Chronic myeloid leukemia (CML)

(Within these main categories, there are typically several subcategories)

Comparison of acute and chronic leukemia

	Acute	Chronic
Age	All ages	Adults
Clinical onset	Sudden	Insidious
Leukemic cells	Immature	Mature
Anemia	Mild to severe	Mild
Thrombocytopenia	Mild to severe	Mild
WBC	Variable	Increased
Organomegaly	Mild	prominent

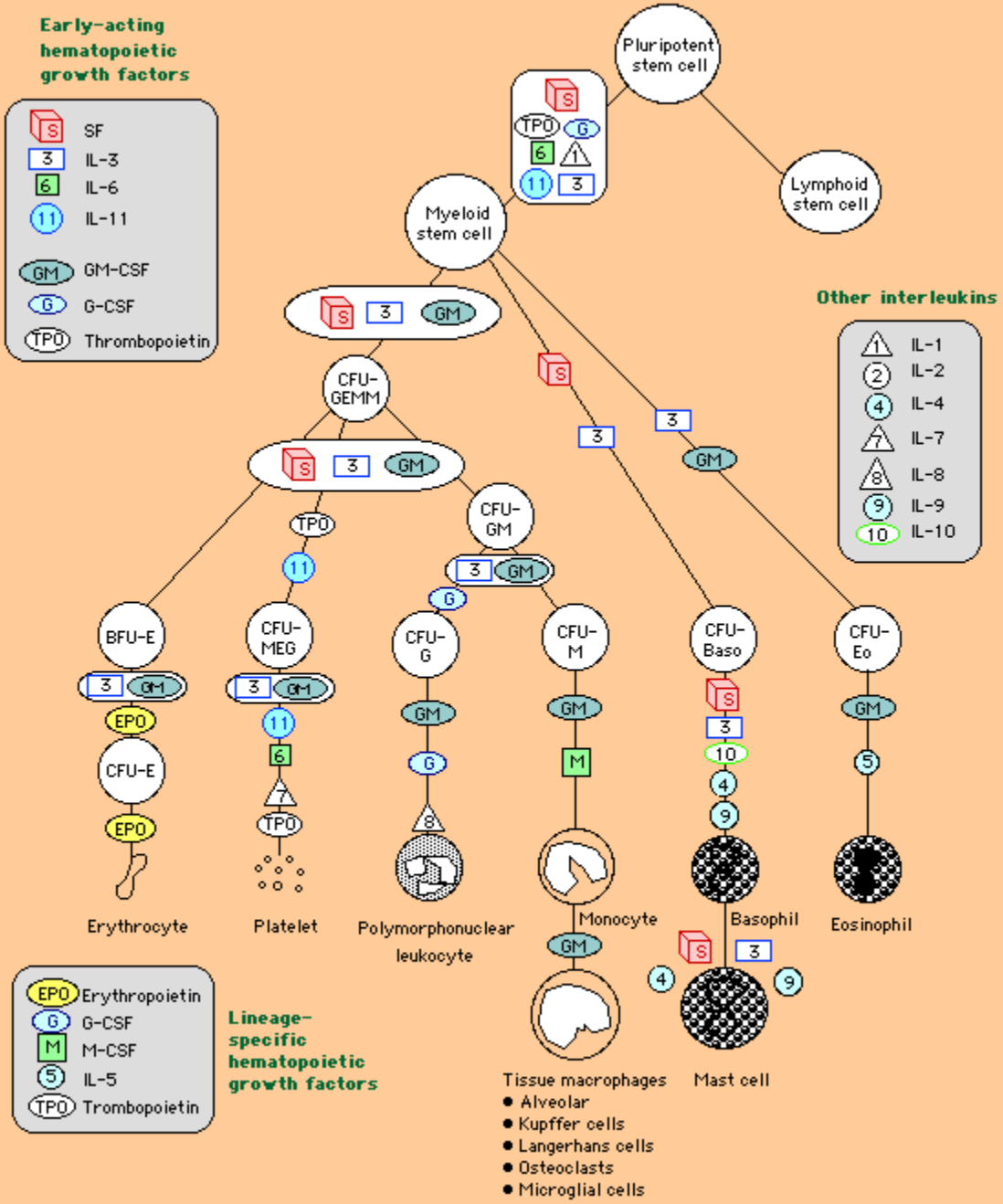
AML

Epidemiology of AML

- Accounts for 35% of all new cases of acute leukemia
- Predominant form of leukemia in neonatal period, but only a small proportion (15-20%) of childhood & adolescent cases
- Majority of adult leukemia (~80%)
- Slightly more common in males

Pathogenesis

- Characterized by clonal proliferation of myeloid precursors with reduced capacity to differentiate into more mature elements
- Accumulation of leukemic forms in bone marrow, peripheral blood, and other tissues, with a marked reduction in red cells, platelets, and neutrophils



Regulation of myelopoiesis

Hierarchical relationship of pluripotent hematopoietic stem cells (PHSC), progenitors, and mature cells of the myelopoietic, erythrocyte, and platelet lineages together with major cytokine sources and actions. Cells of the bone marrow microenvironment such as macrophages, endothelial cells, and reticular fibroblastoid cells produce M-CSF, GM-CSF, G-CSF, IL-6, and probably Steel factor (SF) after induction with endotoxin or IL-1/TNF. T-cells produce IL-3, GM-CSF, and IL-5 in response to antigenic and IL-1 stimulation. These cytokines have overlapping actions during hematopoietic differentiation, as indicated, and, for most lineages, optimal development requires a combination of early- and late-acting factors. MSC = myeloid stem cell; CFU-MEG = megakaryocyte colony-forming unit; other abreviations are explained in the text.

Therapy-related AML (t-AML)

- Alkylating agent-induced DNA damage (e.g. cyclophosphamide)
  - ~5-7 years following therapy of primary CA
  - usually associated with an antecedent MDS
  - complete loss or interstitial deletion of the long arm of chromosomes 7 and/or 5, rearrangements of the MLL gene in chromosome band 11q23, and polymorphisms in genes that encode glutathione S-transferases (wildtype detoxifies potentially mutagenic chemotherapeutic agents)
- DNA topoisomerase II inhibitors (e.g. etoposide)
  - shorter latency period (30-34 months) presenting with over leukemia and rarely with MDS
  - most often involve MLL gene at 11q23, but has also been associated with t(15:17) of APL, as well as t(4;11) of ALL
- Bimolane for psoriasis
- Immunosuppressive and G-CSF for aplastic anemia

Etiology of Mutational Events

- Ionizing radiation
  - damages DNA by inducing double strand breaks that my cause mutations, deletions, or translocations
    - increased incidence of AML in atomic bomb survivors as well as radiologists & technicians chronically exposed to high levels of radiation before 1950
- Chemical exposure
  - organic solvents (benzene, petroleum products) have been associated with a higher risk of disease (less than twofold)
  - the presence of RAS mutations in patients with AML has been associated with specific occupational exposure to chemicals

Etiology of Mutational Events

- Familial leukemia
  - Risk of AML in a non-identical sibling is 2-3x that of general population
  - Trisomy 8 syndrome: characteristic facial & skeletal muscle dysmorphism, development of hematologic disorders (aplastic anemia, MDS, AML, CML)
  - Trisomy 21 (Down syndrome): 10-18 fold increased risk for leukemia; in age <3, most frequently AML of FAB-M7 subtype; ALL more common age>3
- Familial disorders leading to AML
  - inherited (AR or AD) disorders with defective DNA repair
    - Bloom's syndrome, Fanconi's anemia, neurofibromatosis, Li-Fraumeni syndrome, Wiskott-Aldrich syndrome, Kostmann's syndrome, Diamond Blackfan anemia
- Retroviruses
  - no clear association of a retrovirus with leukemogenesis in humans

Clinical Presentation—History

- Symptoms related to pancytopenia
  - weakness, easy fatigue, SOB
  - infections
  - gingival bleeding, ecchymoses, epistaxis, menorrhagia
- Infrequent bone pain (sternum, long bones)
- Onset weeks to months

Past Medical History

- Prior hematologic disorder
  - Myelodysplastic syndrome
  - Myeloproliferative disorder
  - Fanconi's anemia
- Prior chemotherapy and/or radiation therapy
- CHF and cardiac disease
- Prior transfusion or pregnancies
- Drug allergies
- History of HSV infection

Physical Exam

- Fever
  - almost always due to infection, small minority have fever related solely to underlying leukemia
- Skin
  - pallor, petechiae, ecchymoses, infiltrative lesions (leukemia cutis or granulocytic sarcoma)
- Eyes
  - retinal hemorrhages and/or exudates, pale conjuctivae
- Oropharynx
  - gingival hypertrophy (leukemic infiltration), candidiasis, herpetic lesions
- Organomegaly
  - palpable adenopathy rare, HSM uncommon
- Joints
  - polyarthritis, arthralgias, bone pain & tenderness

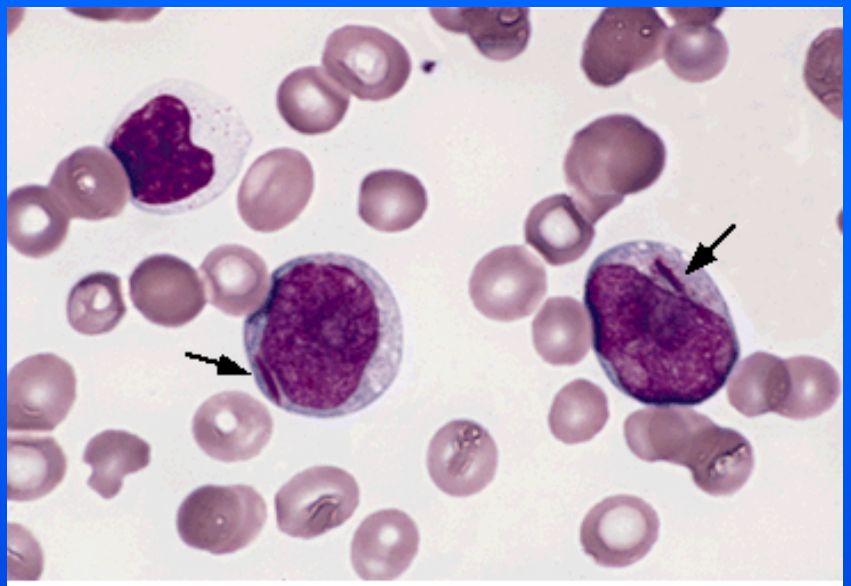
Laboratory Testing

- Routine blood work
  - CBC, differential, and smear
    - presumptive diagnosis of AML can be made via PBS if circulating leukemic blasts
  - electrolytes, renal and liver function tests, uric acid, LDH, calcium, phosphate
  - INR, aPTT, fibrinogen, D-dimer
- Bone marrow aspirate & biopsy
- Flow cytometry
- Cytogenetics
- Other: CXR, EKG, LVEF, LP, HLA typing, viral serology (CMV & HSV)

Diagnosis of AML

- Requires all four of:
  - Bone marrow infiltration
  - Myeloid origin of leukemic cells
  - FAB/WHO classification
  - Karyotypic analysis

Auer Rods



Myeloblasts with Auer rod Peripheral smear from a patient with acute myeloid leukemia. There are two myeloblasts, which are large cells with high nuclear-to-cytoplasmic ratio and nucleoli. Each myeloblast has a pink/red rod-like structure (Auer rod) in the cytoplasm (arrows). (From Brunning, RD, McKenna, RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.)

WHO Classification of AML

- AML with recurrent genetic abnormalities
- AML with multilineage dysplasia
- AML and MDS syndromes, therapy-related
- AML, not otherwise categorized

Adverse Prognostic Factors (1)

- Advanced age (>60)
- Performance status (Karnovsky score <60%)
- Karyotype
  - Good risk: favorable karyotype, including t(8;21), t(15;17), inv(16)/t(16;16)/del(16q), or FAB M3
  - Standard (intermediate risk): neither good risk nor poor risk, normal cytogenetics
  - Poor risk: adverse karyotype [monosomy 5 or 7, del(5q), abn (3q26), trisomy 8, complex karyotype] or resistant disease after the first course of chemotherapy (>15% blasts in BM), and no good risk features
  - MRC study (1711 AML patients age ≤55): 5-year survival for good, standard, and poor risk patients was 70%, 48%, and 15% with relapse rates of 33%, 50%, and 78%, respectively[1]

[1] Wheatley et al. *Br J Haematol* 1999;107:69-79

Treatment of non-M3 AML

- Remission induction
- Post-remission therapy
  - consolidation chemotherapy
  - hematopoietic stem cell transplantation
- Relapsed or resistant AML

Considerations Before Treatment

- Goals of therapy
  - intensive therapy (to achieve CR) may not be advisable due to advanced age, significant co-morbidities, prior therapies
- Side effects of treatment
- Effect on patient's employment & other financial issues
- Power of attorney for personal care
- Code status

Remission Induction Therapy (1)

- Goal: rapid restoration of normal BM function
- Complete remission: recovery of normal peripheral blood counts, blasts <5% in BM, and no leukemic phenotype
- Substantial burden of leukemia cells persists undetected (minimal residual disease), leading to relapse within weeks or months in no further therapy given

Remission Induction Therapy (2)

- Most common regimen ("7+3")
  - cytarabine IV continuous infusion 100-200 mg/m^2 x 7 days, and
  - daunorubicin 45-60 mg/m^2 x 3 days (Day 1-3) (use 30 mg/m^2 in elderly patients)
- Initial response rate has not been improved by increasing the dose of cytarabine or daunorubicin, or addition a third or fourth drug (e.g. etoposide, fludarabine, topotecan, thioguanine)
- Idarubicin is a more lipophilic analogue of daunorubicin, and has been associated with higher rates of CR rates (62% vs 53%) and 5-year survival (13% vs. 9%)[1]; usual IV dose 12-13 mg/m^2 x 3 days (Day 1-3)
- Our centre uses IDAC (idarubicin & cytarabine)
- Side effects: myelosuppression, mucositis, diarrhea

1. *Br J Haematol* 1998 **103**(1):10

Consolidation Chemotherapy

- The same chemotherapy regimen used for remission induction can be repeated for one or more cycles as consolidation treatment, or potentially non-cross-resistant drugs can be used for consolidation
- High dose cytarabine (HDAC) in young patients is preferred
  - CALGB RCT study[1] in 596 patients using four courses of cytarabine at low (100 mg/m^2 per day) or intermediate doses (400 mg/m^2 per day) as continuous infusion x 5 days, or at high doses (3 g/m^2 every 12 hrs on days 1, 3, and 5)
  - In patients age<60, 4-year DFS 44% in HDAC arm vs. 29% and 24% in intermediate and low dose groups; 5% TRM in HDAC group
  - Older patients had poor outcome (4-year DFS <16% in all groups) and higher toxicity (esp. cerebellar ataxia in HDAC group)
- In older patients (age>60), best results from consolidation therapy achieved after two cycles of daunorubicin (30-45 mg/m^2 x 2 days) and cytarabine (100 mg/m^2/day x 5 days)[2]

[1] Mayer et al. *NEJM* 1994 331(14):896-903
[2] Stone et al. *Hematol Oncol Clin North Am* 1993 7(1):65-79

Allogeneic Transplantation

- Long-term disease free survival in adult patients with AML who receive allo-HCT while in first CR is ~45-65%
- 5-year survivals for patients with AML receiving allo-HCT at the following times[1]:
  - untreated first relapse or second CR: 35% if first CR >6 months, 20% if first CR<6 months
  - primary induction failure: 15%
  - refractory first relapse or beyond second CR: 5%
- HLA-matched allo-HCT should be considered in:
  - high-risk patients in first remission (e.g. young patient with normal karyotype or abnormality of chromosome 5 or 7, 11q23 abnormalities, & other high-risk cytogenetics)
  - any patient at first relapse or second remission
- Most centers restrict myeloblative HCT to patients <age 60; also limited by donor availability (only 25-30% have matched HLA siblings, 50% URD match rate for Caucasians, 10% for minorities)

[1] Grigg et al. *Br J Haematol* 1999;107:409-418

Acute Lymphoblastic Leukemia

Epidemiology

- Children
  - Most common leukemia (>80%)
  - Incidence peaks ages 2 to 5 yr
    - 30 cases per million per year in the US
- Adults
  - 20% of adult leukemias
  - Incidence ~ 1/3 in children
  - Second peak around age 50
  - Steady rise in incidence with age

Etiology in children

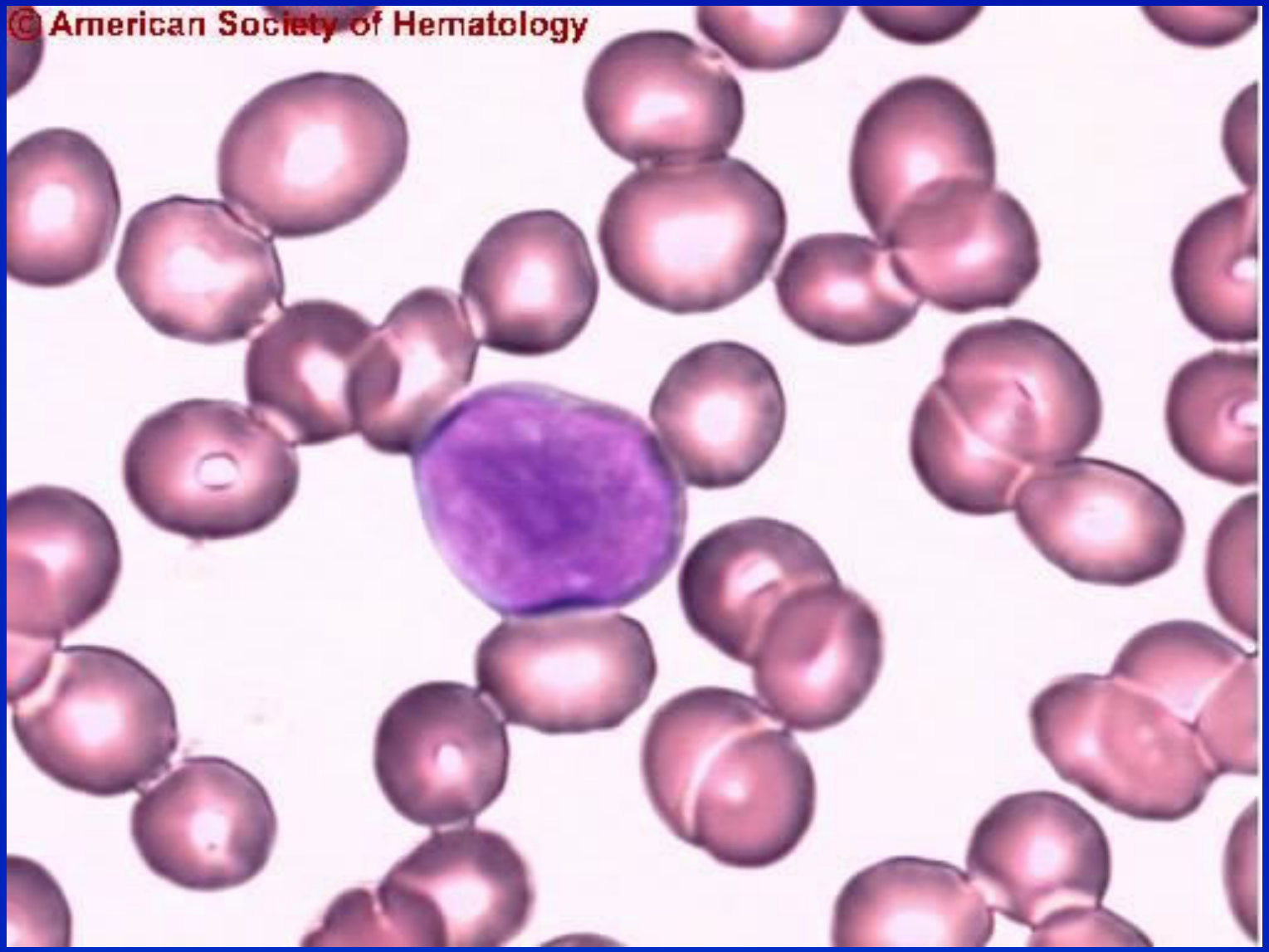
- Genetic syndromes
  - Down syndrome (both ALL and AML)
  - Others: Bloom syndrome, neurofibromatosis, Schwachman syndrome, ataxia telangeictasia, Klinefelter's
- In utero exposure
  - Ionizing radiation
  - Related to MLL = inhibition of topoisomerase II: ?quinolones, flavonoids, catechins, podophyllin, benzene metabolites, estrogens, dipyrone

Clinical Manifestations

- Bone marrow failure
  - Anemia, thrombocytopenia, neutropenia
- Lymphadenopathy, hepatomegaly, splenomegaly
- Bone pain, arthralgias (especially in children)
- Infection, fever
- Extramedullary spread:
  - CNS involvement at diagnosis (5% children, 15% adults)
  - Skin
  - Testes (10-15% boys)
- Mediastinal mass or tissue mass (50% of T cell-ALL)

Laboratory Abnormalities

- Hyperuricemia
- Elevated LDH
- Tumour lysis
  - Hyperkalemia, hyperphosphatemia, hypocalcemia
- Hypercalcemia
  - Bony infiltration, PTH-like substance



Lymphoblast in the peripheral blood

http://www.ashimagebank.org

FAB Classification of ALL

Morphology	L1	L2	L3
Cell size	Small	Large, but heterogeneous	Large, homogeneous
Nuclear chromatin	Homogeneous	Variable	Finely stippled, homogeneous
Nuclear shape	Regular, occasional clefting	Irregular, common clefting	Regular, oval to round
Nucleoli	Not visible, small or inconspicuous	One or more, often large	Prominent, one or more
Cytoplasm	Scanty	Variable, moderately abundant	Moderately abundant
Basophilia	Slight or moderate	Variable, deep	Very deep
Vacuolation	Variable	Variable	Often prominent

Diagnosis

- Cell morphology
- Cytogenetics
- Immunophenotyping

Treatment of ALL - Children

- Induction
- Consolidation/Intensification
- Continuation/Maintenance
- CNS prophylaxis

CNS Leukemia & Ocular Involvement

- CNS Leukemia
  - Less common than patients with ALL
  - LP only done if CNS symptoms (not routine) to confirm involvement
  - Risk higher in patients with $M4E_0$, M5, high circulating blast counts, and relapsed APL (M3)
  - Treatment: IT MTX or cytarabine, ± cranial radiation (cranial nerve involvement)
- Ocular Involvement
  - includes retinopathy (hemorrhage & cotton wool spots) and leukemic infiltration of conjuctiva & lacrimal glands
  - treatment: aggressive chemotherapy, platelet transfusion support, ± radiation (to masses)

Chronic Myelogenous Leukemia (CML)

- Excessive development of mature neoplastic granulocytes in the bone marrow
  - Move into the peripheral blood in massive numbers
  - Ultimately infiltrate the liver and spleen

Chronic Myelogenous Leukemia

- *Philadelphia chromosome*
  - The chromosome abnormality that causes chronic myeloid leukemia (CML) (9 &22)
  - Genetic marker
- Chronic, stable phase followed by acute, aggressive (blastic) phase

Chronic Lymphocytic Leukemia (CLL)

- Production and accumulation of functionally inactive but long-lived, mature-appearing lymphocytes
- B cell involvement
- Lymph node enlargement is noticeable throughout the body
  - ↑ incidence of infection

Unclassified Leukemias

- Subtype cannot be identified
- Malignant leukemic cells may have
  - Lymphoid, myeloid, or mixed characteristics
- Frequently these patients do not respond well to treatment
  - Poor prognosis

Case 1

- 17 ys lady presented to th ER with CBC : WBCs 50,000 , HGB 10 , PLT 15000
- Abnormal circulating blasts 30%

How to proceed with diagnosis and ttt

- CBC
- LDH
- Blood film
- Bone marrow
- Virus study

RECOMMENDED BOOKS

- Essential Hematology (A. V. Hoffbrand, P. A. H. Moss)
- Uptodate
- Oxford Handbook of clinical hematology.