Acute & Chroinc 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.

Etiology and Risk Factors

- The etiology of leukemia is unknown.
- Oncogenes mutation and tumor suppressor gene alteration.
- Host factors. Environmental factors

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

- 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.

Bone marrow syndrom

- Patients with BMD 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.

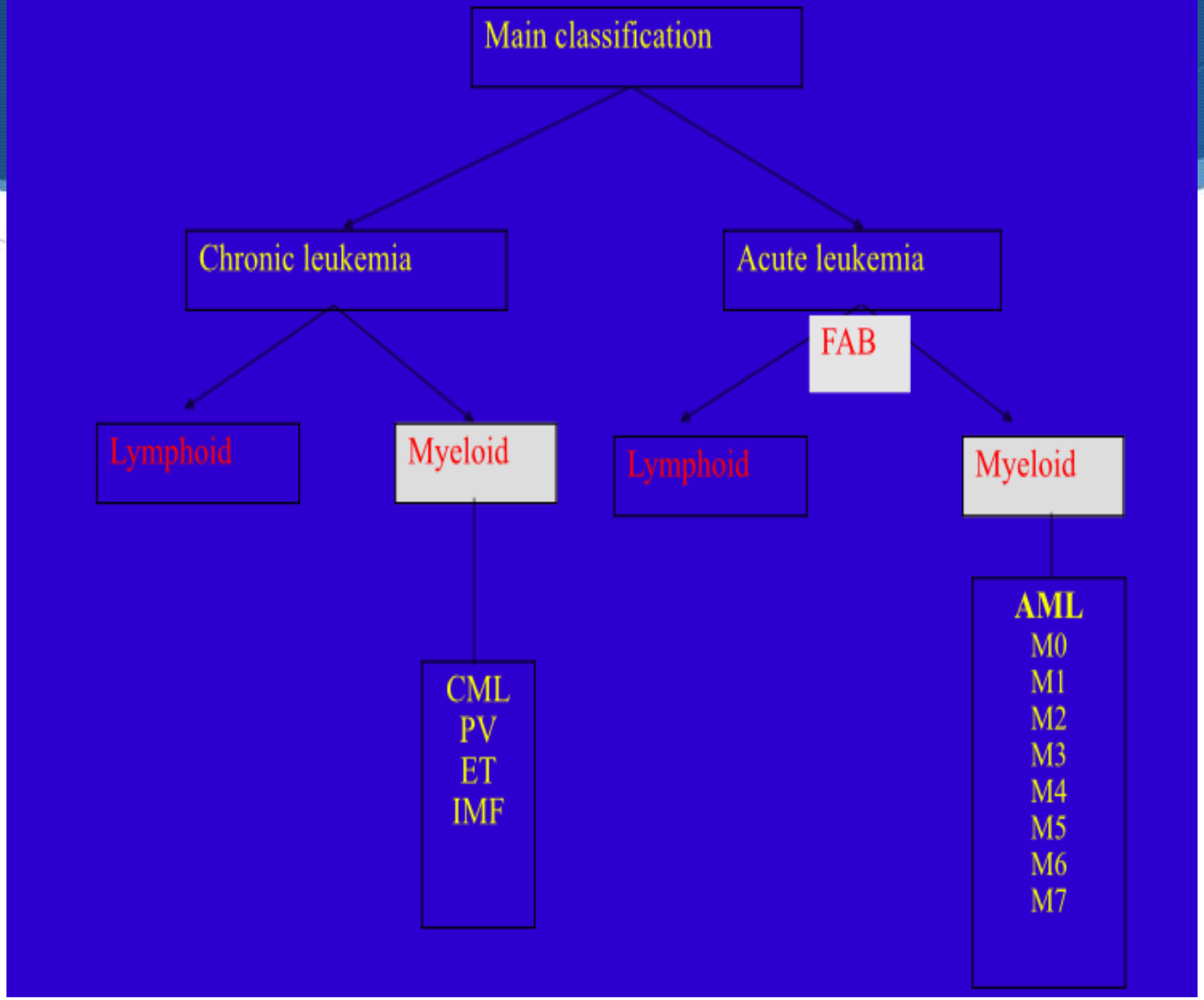
Viruses

• 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

Etiology of AML

- 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

- • 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

- 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

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

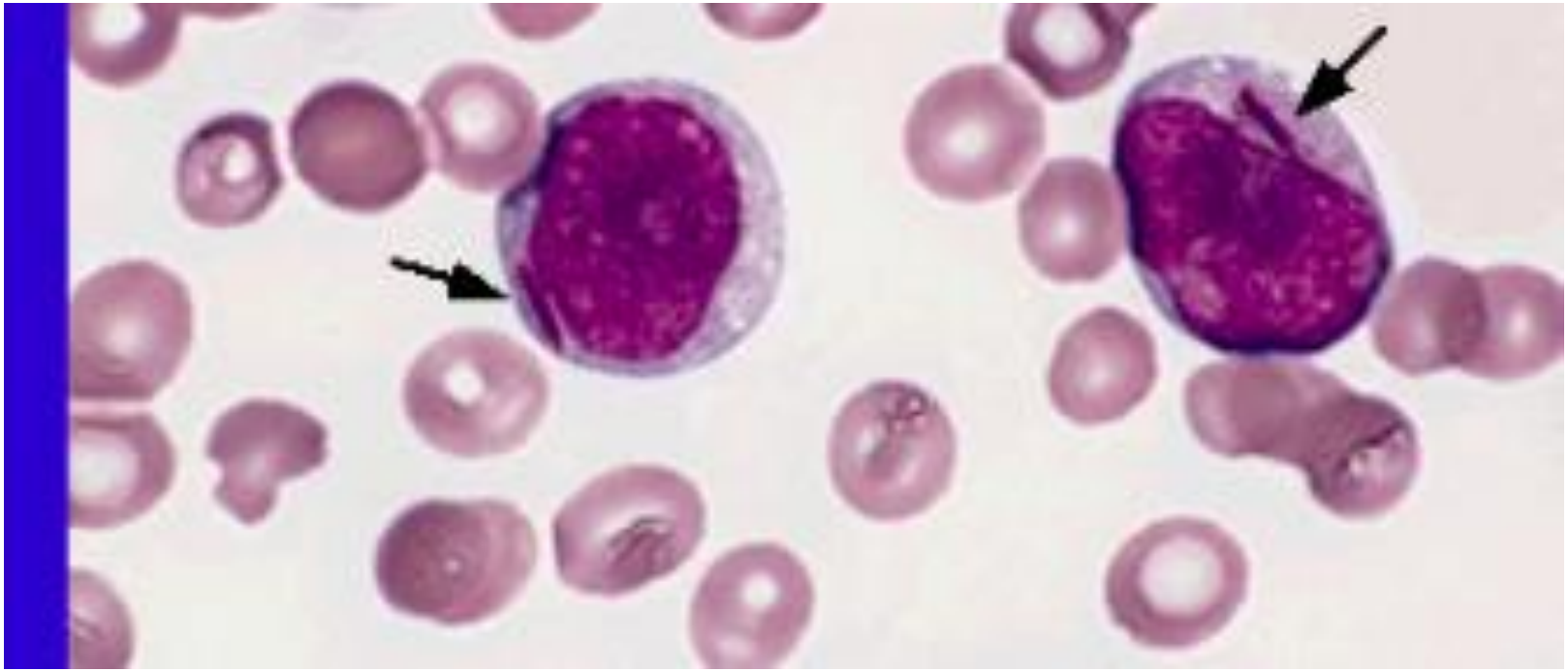
- Fever
- – almost always due to infection, small minority have fever related solely to underlying leukemia
- • Skin
- – pallor, petechiae, ecchymoses, infiltrative lesions (leukemia cutis or granulocytic sarcoma)
- • Eyes
  – retinal hemorrhages and/or exudates, pale conjuctivae
- • Oropharynx
  – gingival 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)
- Bone marrow is important

Diagnosis of AML

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



- 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%, 79 with relapse rates of 33%, 50%, and 78% respectively1

1Wheatley et al. *Br J Haematol* 1999 **107**:69

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

Induction Therapy

- • 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
- Most common regimen (“7+3”)
- cytarabine IV continuous infusion 100-200 mg/m2 x 7 days, and
- daunorubicin 45-60 mg/m2 x 3 days (Day 1-3) (use 30 mg/m2 in elderly patients)

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 study1 in 596 patients using four courses of cytarabine at low (100 mg/m2 per day) or intermediate doses (400 mg/m2 per day) as continuous infusion x 5 days, or at high doses (3 g/m2 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)

Allogeneic Transplantation

- Long-term disease free survival in adult patients with AML who receive allo-HCT while in first CR is ~45-65%
- • 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)

Acute Lymphoblastic Leukemia

Children

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 (NSAID), mosquitocidal agent (Baygon)

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

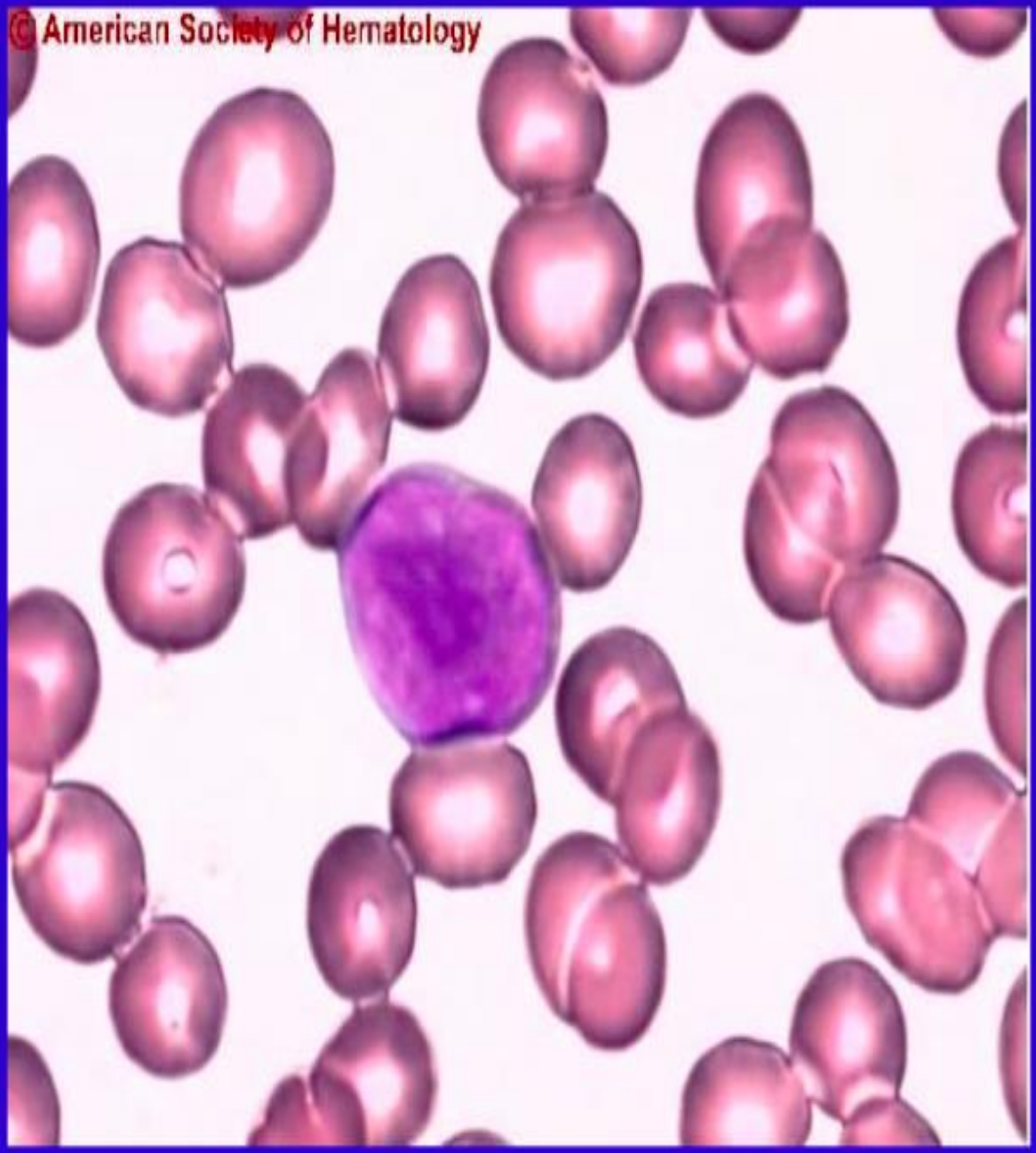
- Hyperuricemia
- • Elevated LDH
- • Tumour lysis
- – Hyperkalemia, hyperphosphatemia, hypocalcemia
- • Hypercalcemia
- – Bony infiltration, PTH-like substance

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



Lymphoblast in the peripheral blood

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 M4E0, 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

Chronic Myelogenous Leukemia (CML)

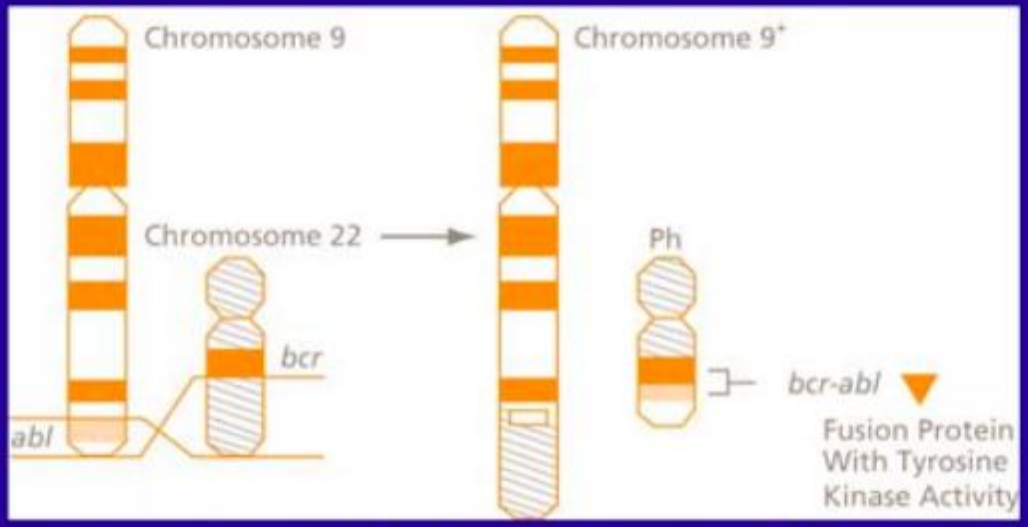
- Excessive development of mature neoplastic granulocytes in the bone marrow
- – Move into the peripheral blood in massive numbers
- – Ultimately infiltrate the liver and spleen

CML: Epidemiology

- Leukaemia accounts for ~3% of all cancers in humans[1-3]
  - Incidence: 5-10 cases per 100,000 population
- CML accounts for 15%-20% of all adult leukaemias[4,5]
  - Incidence: 1-2 cases per 100,000 population[4,6]
  - Occurs slightly more frequently in men than women (1.4-2.2:1)[7]
- Median patient age at diagnosis: 55-60 years[7]
- CML is rare in persons aged ≤19 years (~1-2 cases per million population)[6]
- CML was the first cancer to be shown to be caused by an underlying genetic abnormality[8]

1. Ferlay J et al. GLOBOCAN 2002. Available at: http://www-dep.iarc.fr. 2. Cancer Research UK. Available at: http://www.cancerresearchuk.org/aboutcancer/statistics/incidence. 3. Ferlay J et al. EUCAN. Available at: http://www-dep.iarc.fr/eucan/eucan.htm. 4. Druker BJ. *Cancer Cell*. 2002;1:31-36. 5. Greenlee RT et al. *CA Cancer J Clin*. 2001;51:15-36. 6. Ries LA et al. SEER Cancer Statistics Review, 1975-2001. Available at: http://seer.cancer.gov/csr/1975_2001/. 7. Cortes J. *Hematol Oncol Clin North Am*. 2004;18:569-584. 8. Nowell PC et al. *J Natl Cancer Inst*. 1961;27:1013-1035.

CML Pathogenesis: Philadelphia (Ph) Chromosome



- CML first cancer demonstrated to have underlying genetic abnormality[1,2]
  - Associated with Ph chromosome
- Result of translocation between chromosomes 9 and 22[3]
- Detected in ~95% of patients with CML[4]

CML karyotype image courtesy of John Kimball, 2004.

1. Nowell PC. *Science.* 1960;132:1497. 2. Nowell PC et al. *J Natl Cancer Inst.* 1961;27:1013-1035. 3. Rowley JD. *Nature.* 1973;243:290-293. 4. Sawyers CL. *N Engl J Med.* 1999;340:1330-1340.

Parameter	Phase of Ph+ CML		
	Chronic	Accelerated	Blast
Median duration prior to availability of imatinib therapy	5-6 years	6-9 months	3-6 months
WBC count	≥20 × 10^9/L	–	–
Blasts	0%	≥10%	≥30%
Basophils	↑	≥20%	–
Platelets	↑ or normal	↑ or ↓	↓
Bone marrow	Myeloid hyperplasia →		
Cytogenetics	Ph+ →		
BCR-ABL	+	+	+

Clinical Presentation of Ph+ CML[1-3]

Parameter	Phase of Ph+ CML		
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Bone marrow	Myeloid hyperplasia →		
Cytogenetics	Ph+ →		
BCR-ABL	+	+	+

Ph+, Philadelphia chromosome positive.

1. Faderl S et al. *Oncology*. 1999;13:169. 2. Kantarjian HM et al. *Biol Ther Chronic Myelogenous Leukemia*. 1998;12:31-80. 3. Spiers AS. *Semin Oncol*. 1995;22:380.

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
- Jack II
- Bone marrow
- Treatment

Initial Treatment

Tyrosine kinase inhibitors are for first-line therapy in chronic phase CML

- Imatinib (Gleevec)
- Dasatinib (Sprycel)
- Nilotinib (Tasigna)

1. *All 3 agents are considered to be (category 1) based on the NCCN guidelines and recommendations.*
2. *Second-generation TKIs (dasatinib or nilotinib) produce faster and deeper response than imatinib*

CLL - Definition

- CLL is a neoplastic disease characterized by proliferation and accumulation (blood, marrow and lymphoid organs**)** of morphologically mature but immunologically dysfunctional lymphocytes

CLL - Definition

- Clonal B cell malignancy.
- Progressive accumulation of long lived mature lymphocytes.
- Increase in anti-apoptotic protein bcl-2.
- In most cases, the cells are monoclonal B lymphocytes that are CD5+
- Intermediate stage between pre-B and mature B-cell.
- T cell CLL can occur rarely

CLL - Epidemiology

- Most common leukemia of Western world.
- Less frequent in Asia and Latin America.
- Male to female ratio is 2:1.
- Median age at diagnosis is 65-70 years.
- Uncommon (10%) in patients under 50 years
- In US population incidence is similar in different races.

CLL - Etiology (1)

- The cause of CLL is unknown
- There is increased incidence in farmers, rubber manufacturing workers, asbestos workers, and tire repair workers
- Genetic factors have been postulated to play a role in high incidence of CLL in some families

CLL – Initial symptoms

- Approximately 40% are asymptomatic at diagnosis – discovered by a CBC
- In symptomatic cases the most common complaint is fatigue
- Well's syndrome – increase sensitivity to insects bites
- B symptoms – fever, sweats, weight loss
- Less often the initial complaint are enlarged nodes or the development of an infection (bacterial)

CLL - Clinical findings

- Most symptomatic patients have enlarged lymph nodes (more commonly cervical and supraclavicular) and splenomegaly
- The lymph nodes are usually discrete, freely movable, and nontender
- Hepatomegaly may occure
- Less common manifestation are infiltration of tonsils, mesenteric or retroperitoneal lymphadenopathy, and skin infiltration
- Patients rarely present with features of anemia, and bruising or bleeding

CLL – Lab findings

a) Blood test — lymphocytosis ≥ 5G/l (4 weeks)

b) Morphology — monoconal population of small mature lymphocyte

c) B-cell CLL phenotype — clonal CD5+/CD19+ population of lymphocyte

d) Markers of clonality — κ/λ light chain restriction; cytogenetical abnormalities

e) Bone marrow infiltrate — > 30% of nuceated cells on aspirate

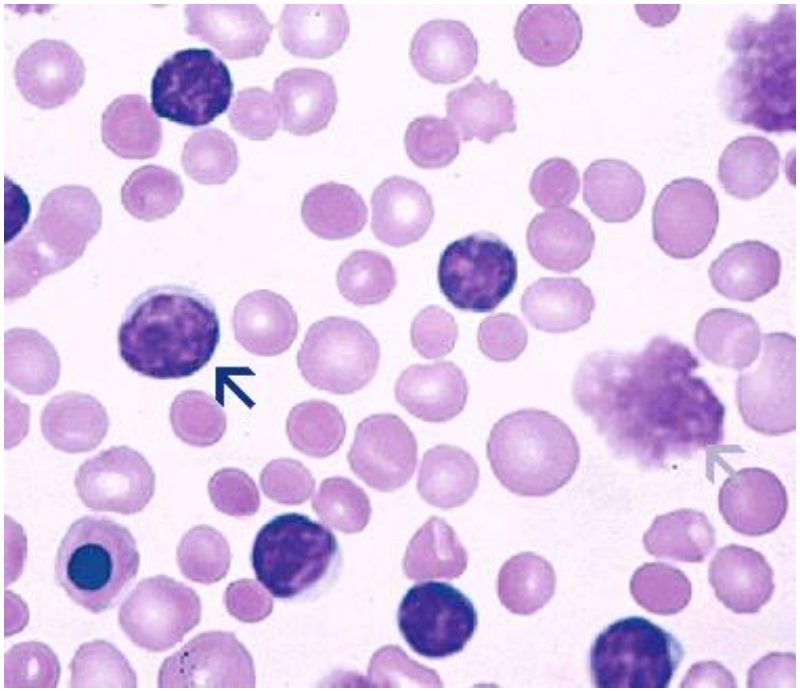
f) Lymph node — diffuse infiltrate of small lymphocye

CLL - Laboratory findings (1)

- The blood lymphocyte count above 5.000/mmc
- Leukemic cells have the morphologic appearance of normal small lymphocytes
- In the blood smears are commonly seen ruptured lymphocytes (“basket” or “smudge” cells)
- Careful examination of the blood smear can usually differentiate CLL, and the diagnosis can be confirmed by immunophenotyping

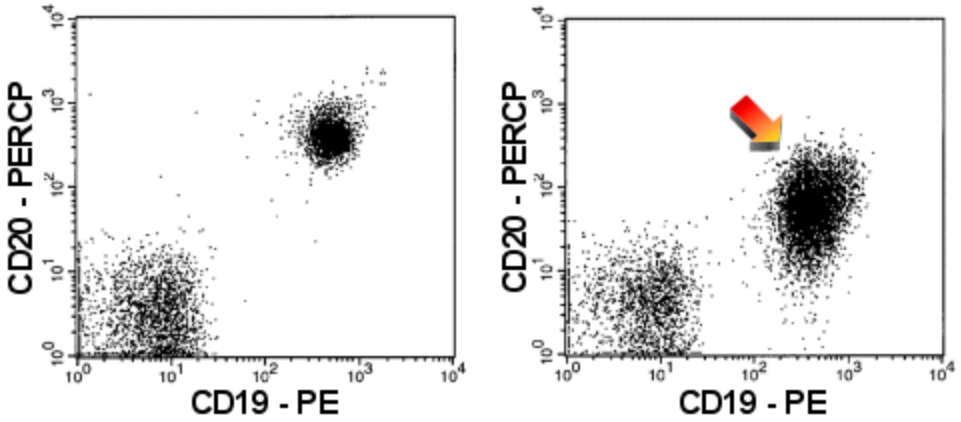
CLL - Peripheral Blood

- Absolute lymphocytosis
- Lymphs = B cells
  - Thin cytoplasm
  - Dense nucleus
  - Partially aggregated chromatin
  - No recognizable nucleoli
- Smudge cells



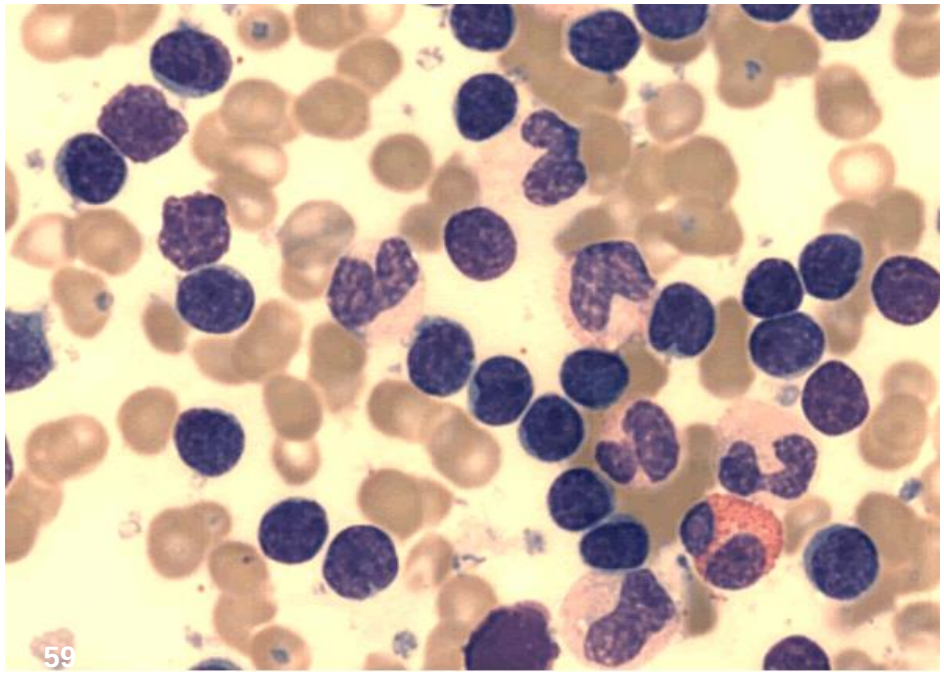
CLL - Immunophenotype

- Detect antigens on surface of cells
  - Specific antibodies
  - Use flow cytometry or immunohistochemistry
- CLL = mature B cells
  - CD5
  - CD19
  - CD20 - low
  - CD22 - low
  - CD23
  - Light chains (κ, λ)



CLL - Bone Marrow

- Infiltrates of small lymphocytes
  - Causes neutropenia, anemia, thrombocytopenia
- Extramedullary expansion
  - Splenomegaly
  - Hepatomegaly
  - Lymphadenopathy



CLL – treatment (1)

- **Watch and wait**
- **Monotherapy**
  - glucocorticoids
  - alkylating agents (Chlorambucil, Cyclophosphamide)
  - purine analogues (Fludarabine, Cladribine, Pentostatin)
- **Combination chemotherapy**
  - Chlorambucil/ Cyclophosphamide + Prednisone
  - Fludarabine + Cyclophosphamide +/- Mitoxantrone
  - CVP, CHOP
- **Monoclonal antibodies (monotherapy and in combination)**
  - Alemtuzumab (anti-CD52)
  - Rituximab (anti-CD20)
- Splenectomy
- Radiotherapy

CLL – treatment (2)

- **Hematopoietic stem cell transplantation**
  - allogeneic with reduced intesity conditioning
  - autologous
- **New and novel agents**
  - **Oblimersen – bcl2-directed antisense oligonucleotide**
  - **Lenalidomide**
  - **Flavopiridol**
  - **Anti-CD23**
  - **Anti-CD40**
- **Vaccine strategies**

Case 1

Case

- • 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???
- Bone marrow ??

- 45 years old man presented to the clinic with abdominal pain, his CBC is showing marked leukocytosis of 15.000, HGB 11gm, Platelets 400.000, his abdominal examination revealed splenomegaly, his peripheral blood is showing marked left shift with features suggestive of chronic myeloid leukemia.
- Test for diagnosis???
- Send leucocyte alkaline phosphatase level.
- Peripheral blood molecular test for BCR/ABL gene test.
- Ask for Jak2 mutation test.

Thanks