LEUKEMIA

no disclosures

ABNORMALITIES OF CELLULAR PROLIFERATION IN AL

	Normal	Leukemic
Stem Cells	Normal	Abnormal
Maturation	Synchronous with proliferation; terminates division	Asynchronous Does not terminate division
Feedback	Controls production	Absent or ineffective
Steady State	Yes	No
Release	Orderly	Random
End Product	Mature cells-cannot resume division	Immature cells-can resume division

LEUKEMIA CLASSIFICATION

ACUTE :	LYMPHOCYTIC	NONLYMPHOCYTIC
CHRONIC :	LYMPHOCYTIC	MYELOGENOUS

ACUTE LEUKEMIA

A DIVERSE GROUP OF NEOPLASMS ARISING FROM TRANSFORMATION OF UNCOMMITTED OR PARTIALLY COMMITTED HEMATOPOIETIC STEM CELLS

ACUTE LEUKEMIA PATHOGENESIS

- Leukemic cell abnormalities: cytogenetic abnormality leading to clonal proliferation of leukemic cell; maturation arrest of leukemic cells

- Leukemic cells inhibit normal cell lines from proliferating leading to : anemia, bleeding, infection; electrolyte imbalance; leukostasis

- Invasive & infiltrative effects

ACUTE LEUKEMIA: PRESENTATION

- Symptoms of only a few weeks duration
- Symptoms reflect bone marrow failure +/- involvement of extramedullary sites
- Fever, documented infections in up to half
- Symptomatic anemia
- May have bleeding, but hemorrhage rare
- Bone pain, fatigue

ACUTE LYMPHOCYTIC LEUKEMIA

- Mainly occurs in children- peak ages: 2-8, >60
- Worse prognosis with: increasing age
- Philadelphia chromosome
- WBC >30K
- Sex: equal
- Rare in blacks

ALL-PREDISPOSING FACTORS

- Irradiation early in life
- Ataxia telangiectasia
- Mongolism
- Leukemia in family
- Identical twin

ALL FAB CLASSIFICATION

FAB Class	Cell Size	Nucleus	Cytoplasm
L1	Small hoogeneous	Round, occasional cleft or fold; homogeneous, finely dispersed chromatin; nucleoli small or not visible	Usually scanty slight to moderate basophilia
L2	Large heterogeneous	Fine to coarse chromatin; clefts 1 or more nucleoli	Abundant, variable basophilia
L3	Large homogeneous	Oval to round, dense finely stippled chromatin; 1 or more prominent nucleoli	Moderately abundant, intensely basophilic , prominent vacuoles

ACUTE LYMPHOCYTIC LEUKEMIA: PRESENTATION

- Half have hepatomegaly, splenomegaly &/or lymphadenopathy
- Mediastinal masses primarily in T cell lineage ALL
- <10% with CNS involvement
- Other sites of extramedullary involvement: testis, retina, skin, any organ infiltrated

ALL: ADDITIONAL CLINICAL FEATURES

- C ALL: most common in children; lymphadenopathy common; gum, skin, mediastinal infiltration uncommon; muramidase staining-low or normal

- T cell ALL: most common in 2nd & 3rd decades; blasts more common in blood; frequent extra medullary disease-CNS, mediastinum

- B cell ALL: no distinct findings; responds poorly to conventional therapy

- Ph-positive ALL: shorter remissions than C ALL

ALL: GOOD PROGNOSTIC FEATURES

- Age less than 35 (best 3-9)
- WBC < 30,000
- Blasts < 80%
- Early complete remission after start of chemotherapy
- Absence of translocations
- Presence of hyperdiploid state
- CALLA+ phenotype
- Female

DIAGNOSIS

- Lymphoblasts seen on blood smear and bone marrow

  May be difficult to distinguish from myeloblasts

  Flow cytometry helpful in differentiating ALL from AML

- Evaluate CSF for CNS involvement

ALL: TREATMENT

- Daunorubicin, Vincristine and Corticosteroids are key drugs in induction
- Maintenance therapy at least 2 years
- CNS Prophylaxis
- Imatinib in Ph+ with chemotherapy
- Radiation in bulky mediastinal disease
- SCT if poor prognostic features or progressive disease

ACUTE NONLYMPHOCYTIC LEUKEMIA

- Group of marrow based malignancies, clinically similar, BUT DISTINCT morphologically, immunophenotypically, and cytogenetically
- Must distinguish from ALL
- More common in adults

AML FAB CLASSIFICATION

FAB Class	Predominant cell type
M1: undifferentiated myelocytic	Myeloblasts
M2: myelocytic	Myeloblasts, promyelocytes, myelocytes, blasts
M3: promyelocytic	Promyelocytes, blasts
M4: myelomonocytic	Promyelocytes, myelocytes, proonocytes, monocytes, blasts
M5: monocytic	Monoblasts, myeloblasts
M6: erythroleukemia	Erythroblasts, myeloblasts
M7: megakaryocytic leukemia	Abnormal appearing megakaryocytes myeloblasts

ANLL RISK FACTORS

- Exposure to ionizing radiation
- Exposure to chemicals: benzene, chloramphenicol, phenylbutazone
- Exposure to drugs: alkylating agents and topoisomerase II inhibitors
- Genetic factors: Mongolism, Bloom’s syndrome, Fanconi’s anemia
- MDS, Myelofibrosis, Polycythemia, CGL

ANLL PROGNOSTIC FACTORS

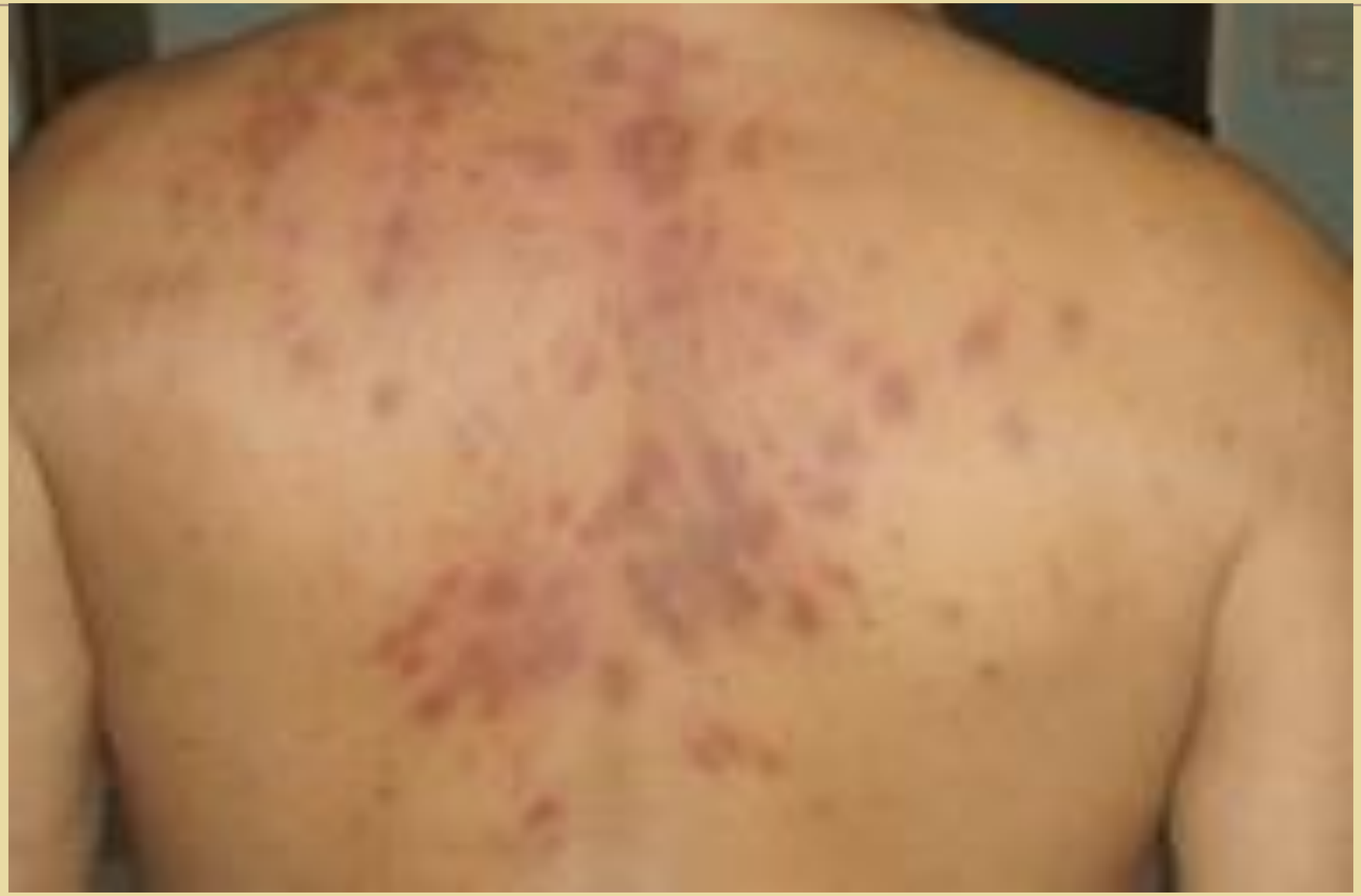
Worse if

- Age>60
- Poor performance status
- AML secondary to prior chemotherapy or bone marrow dysfunction
- WBC > 20K

CLINICAL FEATURES

- S & S secondary to anemia, thrombocytopenia, leukopenia or leukocytosis
- Hyperleukocytosis (>100K blasts): most common in hyper granular APL causing obstruction, vascular injury and hypoxia (due to pulmonary congestion) & ischemia increasing risk of stroke
- Coagulation abnormalities: abnormal platelet function; consumption (DIC)-M3>M4 or M5
- Typhilitis-mimics appendicitis
- Metabolic abnormalities: tumor lysis syndrome; renal tubular dysfunction
- Extramedullary : granulocytic sarcoma-M5, soft tissue involvement-skin, gingiva, lungs, lymph nodes(splenomegaly uncommon), CNS: headache, mental status change, nerve palsy

GRANULOCYTIC SARCOMA

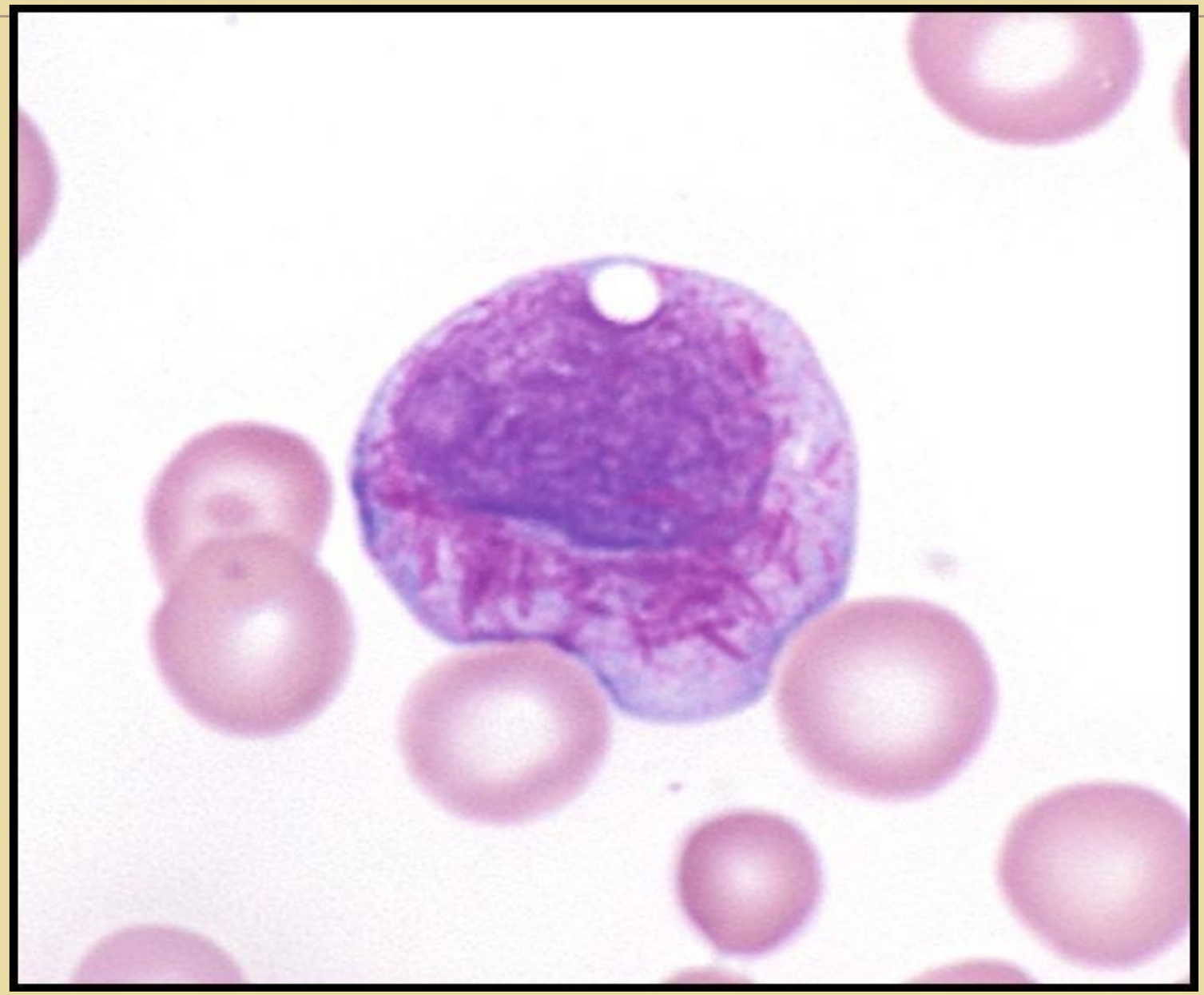


1.jpg

ANLL: LABORATORY FEATURES

- Anemia universally present; reticulocyte count low
- Thrombocytopenia nearly always present (decreased production & survival)
- Leukopenia in 20% with absolute neutropenia
- Leukocytosis >50%; myeloblasts almost always present in blood
- Auer rods <10%

AUER RODS



ANLL: BONE MARROW FINDINGS

- Blasts
- Decrease in normal blood cell progenitors
- Cytogenetics performed to identify any genetic abnormality diagnostic of a particular FAB class
- Immunophenotyping

ANLL: IMMUNOPHENOTYPE

- May help establish diagnosis, more precise than morphology alone
- Distinguishes ALL from ANLL, identifies subtypes, recognizes biphenotypic
- Characteristic ANNL: CD 13 & 33+
- Often CD 11& 14+
- CD34 unfavorable
- Lymphoid markers may be expressed

ANLL: TREATMENT

- Address concurrent medical problems

- Supportive care:

-Blood product transfusion

-Broad spectrum antibiotics for fever and neutropenia

-Antifungal & antiviral therapy

-Nutrition

ANLL: THERAPY

- Remission induction: 7+3 regimen: ARA-C + daunorubicin= 60-80% CR

- Postremission therapy:

  -Consolidation with Ara-C

  -Allogeneic SCT

- APL: ATRA + chemotherapy

CHRONIC LEUKEMIA

no disclosures

CHRONIC LYMPHOCYTIC

Most common leukemia in Western world

Median age at diagnosis: 65

Median survival: 9 years

Advanced disease has increased morbidity and mortality from infection: T cell dysfunction, lack of ability to make Ig, results of treatment

CLL: DIAGNOSIS

- Lymphocytosis (ALC> 5000) small, mature lymphocytes
- Bone marrow involvement >30% lymphs
- < 55% atypical/immature lymphoid cells in peripheral blood
- Clonal expansion of abnormal B lymphs
  -B-cell surface ags (CD 5, 19, 20, 23)

CLL: CLINICAL COURSE

- Incidental finding of lymphocytosis
- Asymptomatic at time of diagnosis and for a prolonged period of time

CLL CLINICAL COURSE

- Progressive bone marrow impairment
- Progressive neutropenia and hypogammaglobulinemia increasing risk of infection
- Autoimmune phenomena
- Richter's transformation

CLL: AUTOIMMUNE COMPLICATIONS

- Coombs' + hemolytic anemia in 15%
- ITP
- Pure red cell aplasia
- Granulocytopenia

CLL: RAI STAGING

Stage	Risk	Features	Surv yr
0	Low	Lymphocytosis	> 12
I	Intermediate	Adenopathy	8
II	Intermediate	Splenomegaly +/- Hepatomegaly	6
III	High	Anemia	1.6
IV	High	Thrombocytopenia	1.6

CLL: POOR PROGNOSIS

- Advanced stage at diagnosis
- Short lymphocyte doubling time (6 mos)
- Diffuse pattern of marrow infiltration
- Advanced age/male
- 17p or 11q deletion
- High serum levels of B2 microglobulin and CD23
- CLL-PLL
- Richter's syndrome

CLL TREATMENT

- Incurable
- Observation is appropriate for early stage or asymptomatic CLL
- No proven advantage to early chemotherapy if asymptomatic

CLL: INDICATIONS FOR TREATMENT

- B Symptoms secondary to CLL: weight loss >10%, night sweats, fever
- Progressive marrow failure
- Massive splenomegaly
- Massive lymphadenopathy

CLL: INDICATIONS FOR TREATMENT

- Progressive lymphocytosis, >50% increase over 2 mos or lymphocyte doubling time <6 mos
- Richter's syndrome-transformation from low to high grade lymphocytic malignancy
- Hemolytic anemia
- ITP

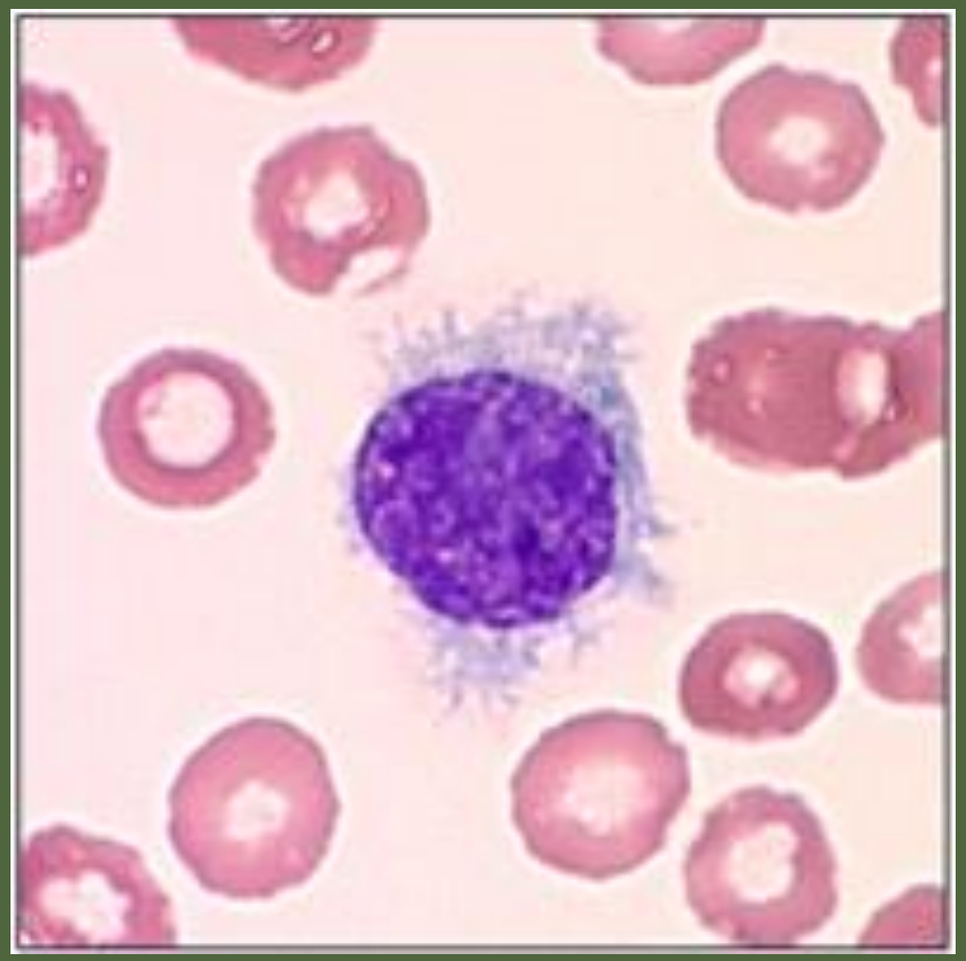
CLL: TREATMENT

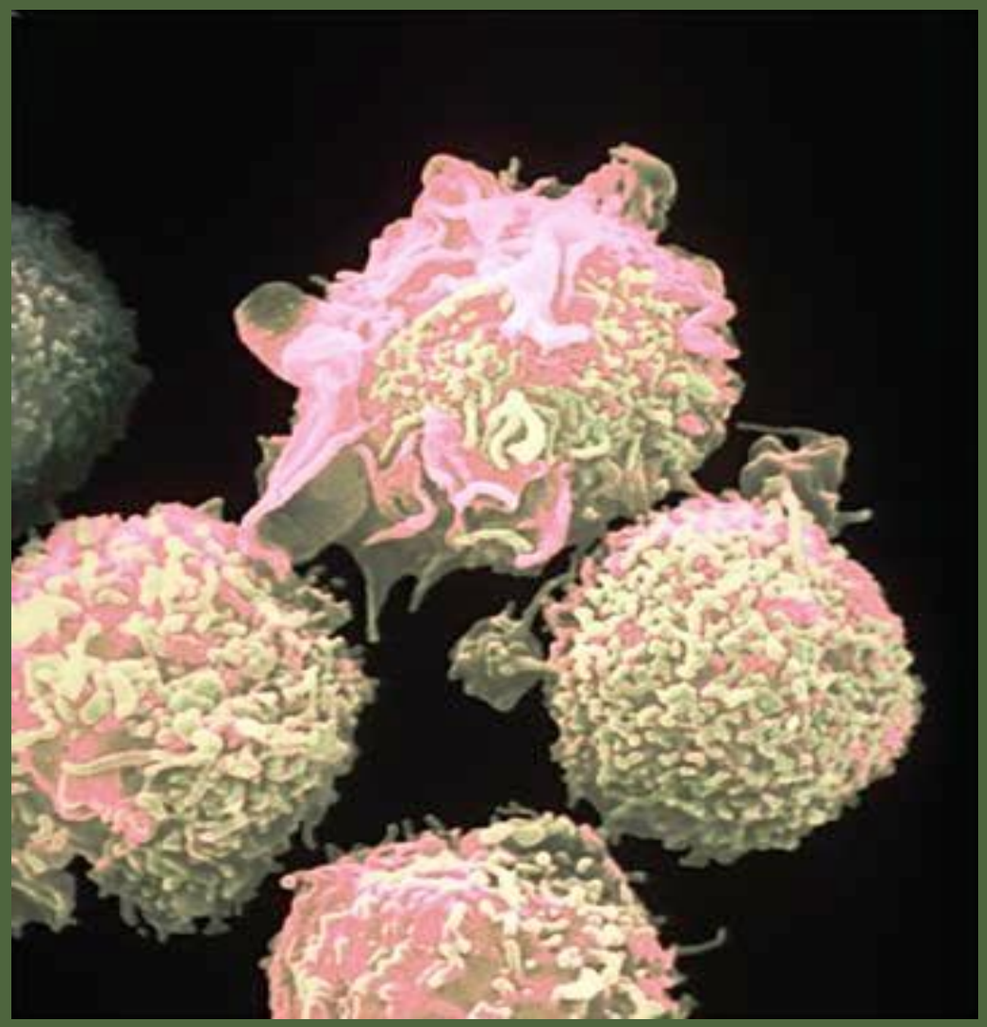
- Alkylating agents: bendamustine, chlorambucil
- cyclophosphamide
- Corticosteroids
- Purine analogs: fludarabine
- cladribine, pentostatin
- Monoclonal abs: Rituximab, Alemtuzumab
-

HAIRY CELL LEUKEMIA

- Rare B-cell leukemia
- Median age of onset: 55
- Strong male predominance
- Presents with pancytopenia and massive splenomegaly
- Characteristic "dry tap" bone marrow due to hypercellularity

HAIRY CELL LEUKEMIA





HAIRY CELL LEUKEMIA

- TRAP +
- Treatment with 2-CDA (cladribine) or Pentostatin induces complete remission in most

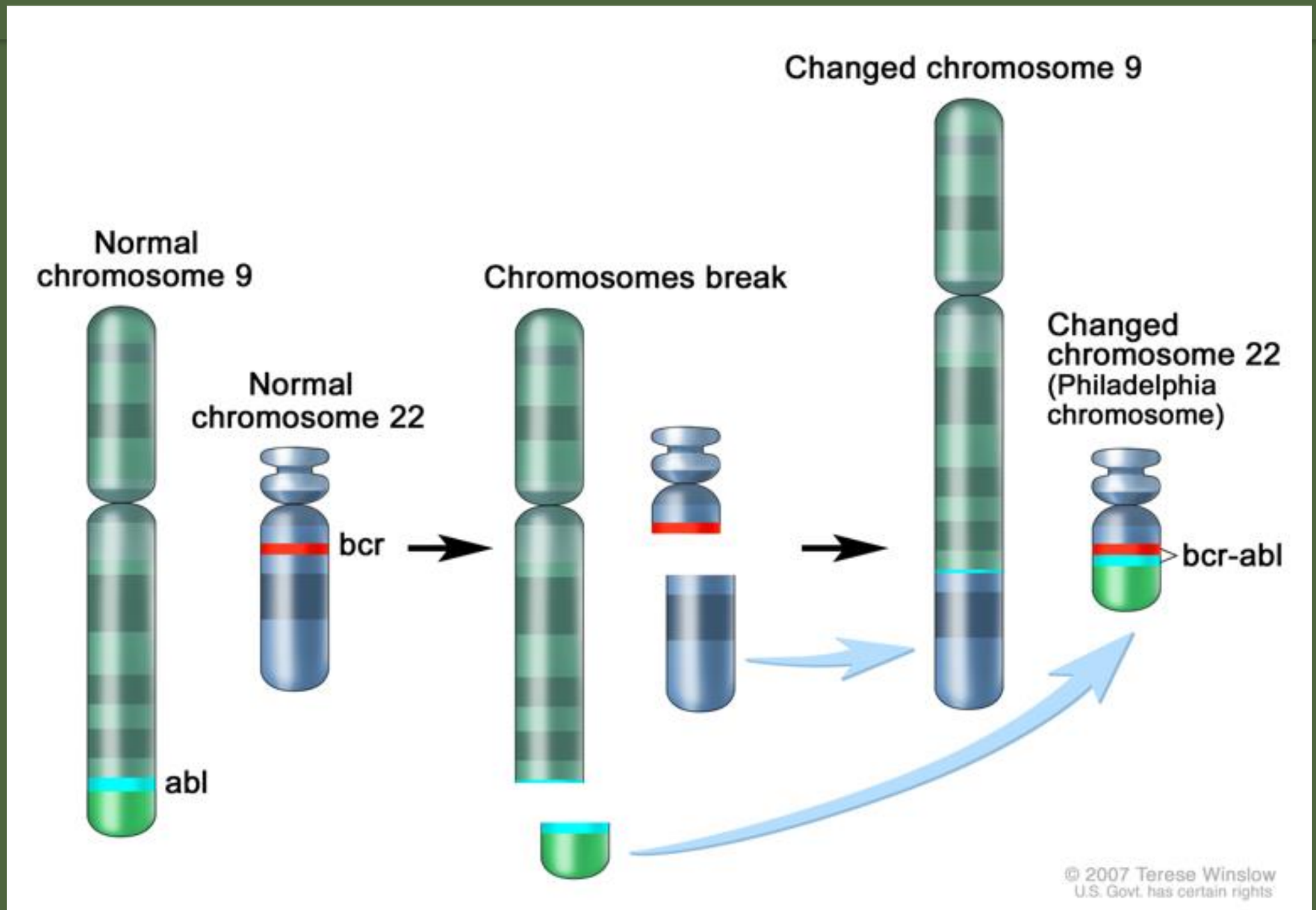
CHRONIC MYELOGENOUS LEUKEMIA

- Clonal myeloproliferative disorder of pluripotent stem cells affecting all cell lines
- Cytogenetic hallmark: Philadelphia chromosome (9;22)
- Molecular hallmark: BCR/ABL
- 7-15% adult leukemias
- Median age: 45-55; 20-30% >60

CML: PRESENTATION

- 85% in chronic phase at diagnosis
- 5% Ph negative
- Symptoms:
- -Most asymptomatic, only leukocytosis
- -LUQ discomfort and early satiety secondary to splenomegaly
- -Unusual infections

PHILADELPHIA CHROMOSONE



PHILADELPHIA CHROMOSONE

Translocation 9;22 = BCR-ABL rearrangement

Leukemia phenotype	Incidence
CML	95%
ALL	25-30% adult
	5% children
AML	1-2%

CML Phases

	Chronic	Accelerated	Blastic
Past	3-5 years	12-18 months	3-9 months
Present	25+ years	4-5 years	6-12 months
	Asympto-matic	Blasts >/= 15% Bl+Pros >29% Basophils>19%	Blasts >29%
		Platelets <100K Clonal evolution	extrmedullary disease with localized immature blasts

CML WORK-UP

Physical exam: performance status, splenomegaly

CBC, diff, chem pro

Bone Marrow

Cytogenetics

CML: CURRENT TREATMENT RECOMMENDATIONS

Frontline:

Imatinib, Nilotinib, Dasatinib

Imatinib failure: nilotinib, dasatinib, bosutinib

Allogeneic SCT

MYELOPROLIFERATIVE DISORDERS

no disclosures

PRIMARY MYELOFIBROSIS

- Progressive generalized reactive fibrosis of bone marrow
- Associated development of hemopoiesis in spleen and liver (myeloid metaplasia)

Primary Myelofibrosis Pathogenesis

- Megakaryocytes release platelet derived growth factor and other cytokines to stimulate fibroblasts
- JAK-2 mutation positive in 50%
- Nonspecific cytogenetic abnormalities in 50%
- Transformation to acute leukemia 10-20%

Primary Myelofibrosis

- Symptoms
  - Weakness
  - Night sweats, weight loss
- Signs
  - Massive hepatosplenomegaly
  - Bone marrow failure
  - Portal hypertension
  - Pulmonary hypertension

Primary Myelofibrosis Lab Findings

- Anemia: tear-drop erythrocytes
- Initial elevation, then decline in WBC & platelet count
- JAK-2 positive in 50%
- Bone marrow fibrosis with increased megakaryocytes

Etiologies of Myelofibrosis

- Infections, ie-TB, osteomyelitis
- Hematological malignancies
- Metastatic cancer, esp breast & prostate
- High exposure to radiation
- Benzene toxicity
- Fluorine toxicity
- Paget’s disease-focal fibrosis
- Osteopetrosis

Primary Myelofibrosis Treatment

- Hydroxyurea
- Transfusion as indicated
- Splenic irradiation or splenectomy
- JAK-2 inhibitors
- Erthropoietin
- Androgen therapy

Polycythemia vera

- Clinical Features
  - Symptoms: headaches, dyspnea, blurred vision, night sweats, pruritus (esp after hot shower)
  - Signs: plethoric facies, retinal venous engorgement, splenomegaly, hypertension, gout, thrombosis (aterial or venous), hemorrhage (GI, uterine, cerebral)

Polycythemia Vera

- Laboratory findings
  - Elevated hemoglobin and hematocrit
  - RBC volume increased
  - Leukocytosis-50%
  - Thrombocytosis-50%
  - Hypercellular bone marrow
  - Low erythropoietin
  - JAK-2 positive-95%

Polycythemia Vera

- Diagnosis
  - JAK-2 positive-no further work-up needed
  - JAK-2 negative
    - No cause of secondary erythrocytosis
    - Splenomegaly
    - Acquired genetic abnormality
    - Thrombocytosis +/- leukocytosis

Etiologies of Secondary Polycythemia

- Tumor related increase in erythropoietin
  - Renal cell cancer
  - Hepatocellular cancer
  - Uterine fibroids
- Hypoxemia
  - COPD
  - Sleep apnea
  - Massive obesity
  - High altitude
- Increased carboxyhemoglobin levels
  - Smoking
  - Chronic carbon monoxide exposure
- Hemoglobinopathy

Differential Diagnosis of Polycythemia

- Step 1
  - H&P, CBC w/diff, ferritin, renal & liver function tests, PFTs, ABG w/carboxyhemoglobin, erythropoietin
  - JAK-2: if negative proceed to step 2
- Step 2
  - Bone marrow biopsy w/cytogenetics
  - Abdominal US
- Step 3
  - O2 dissociation: heart & lung evaluation

Therapy of Polycythemia

- Phlebotomy to Hct < 45%
- Hydrea for platelet count > 400,000
- Aspirin 81 mg daily
- JAK-2 inhibitors

Thrombocytosis

Reactive:

- Hemorrhage
- Trauma
- Postoperative
- Chronic iron deficiency
- Malignancy
- Chronic infections
- Connective tissue diseases
- Postsplenectomy

Endogenous:

Essential thrombocythemia

Can also be seen in:

- Polycythemia vera
- Myelofibrosis
- CML

Essential thrombocythemia

- Clinical findings
  - Asymptomatic
  - Thrombosis (venous or arterial)
  - Hemorrhage (abnormal platelet function)
  - Splenomegaly
  - Erythromelalgia: burning sensation of hands & feet

Essential Thrombocythemia

- Laboratory Findings
  - Platelet count >400,000
  - Abnormal large platelets and megakaryocytic fragments on peripheral smear
  - JAK-2 positive-90%
  - Bone marrow with abnormal megakaryocytes
  - Platelet function studies abnormal
  - Treatment: same as for polycythemia