Chronic Leukemia

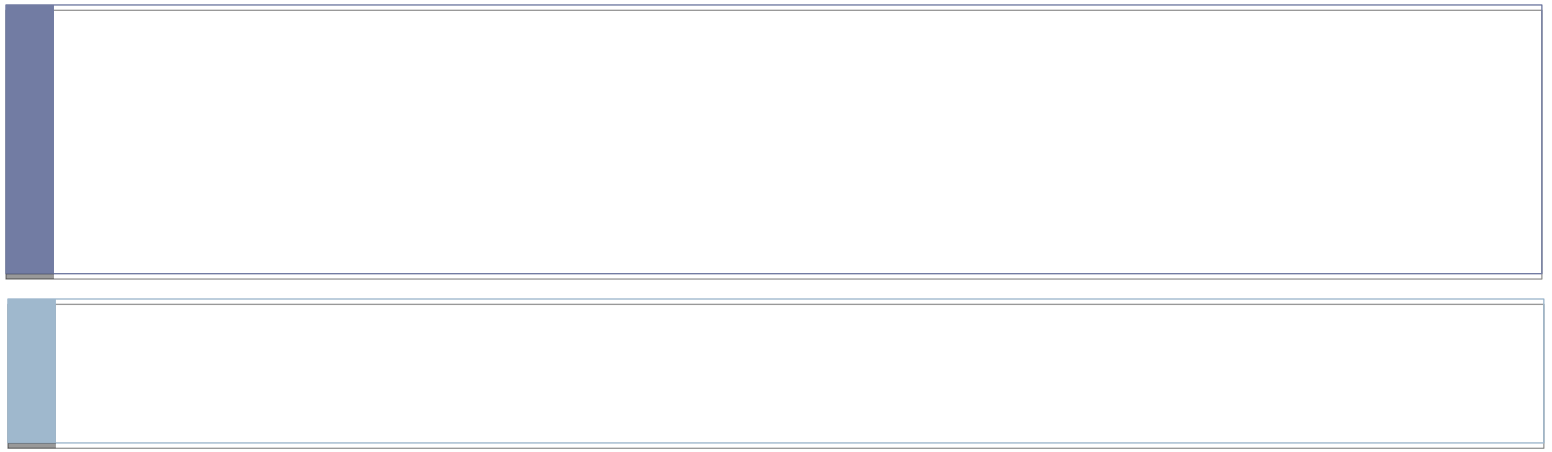
Dr Khalid khan

Learning Objectives

- By the end of this lecture students will be able to:

- Discuss the pathophysiology of chronic leukemia
- Describe the morphologic features of Chronic leukemias
- Able to diagnose a case of chronic leukemia

Chronic Lymphocytic Leukemia(CLL)
Small Lymphocytic Lymphoma(SLL)



- CLL is a Clonal neoplastic disease
- Characterized by proliferation and accumulation of morphologically mature but immunologically dysfunctional lymphocytes
- Increase in anti-apoptotic protein bcl-2
- Progressive accumulation of long lived mature lymphocytes

- Chronic lymphocytic leukemia and small lymphocytic lymphoma are the same disease
- In CLL blood and bone marrow are involved
- In SLL cancer cells are restricted to the lymph nodes
- Small lymphocytic lymphoma is a type of non-Hodgkin lymphoma.

- Peripheral absolute lymphocyte count of 5000 per mm^3 is required for CLL
- Fairly common disorder
- Median age at diagnosis is 60 years
- 2 : 1 male predominance

Etiology

- 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

Pathogenesis

- Chromosomal translocations rare
- Most Common cytogenetic abnormilities are
- Deletions of 13q,14, 11q, and 17p
- Trisomy 12q
- DNA sequencing revealed somatically hypermutated Ig genes in CLL

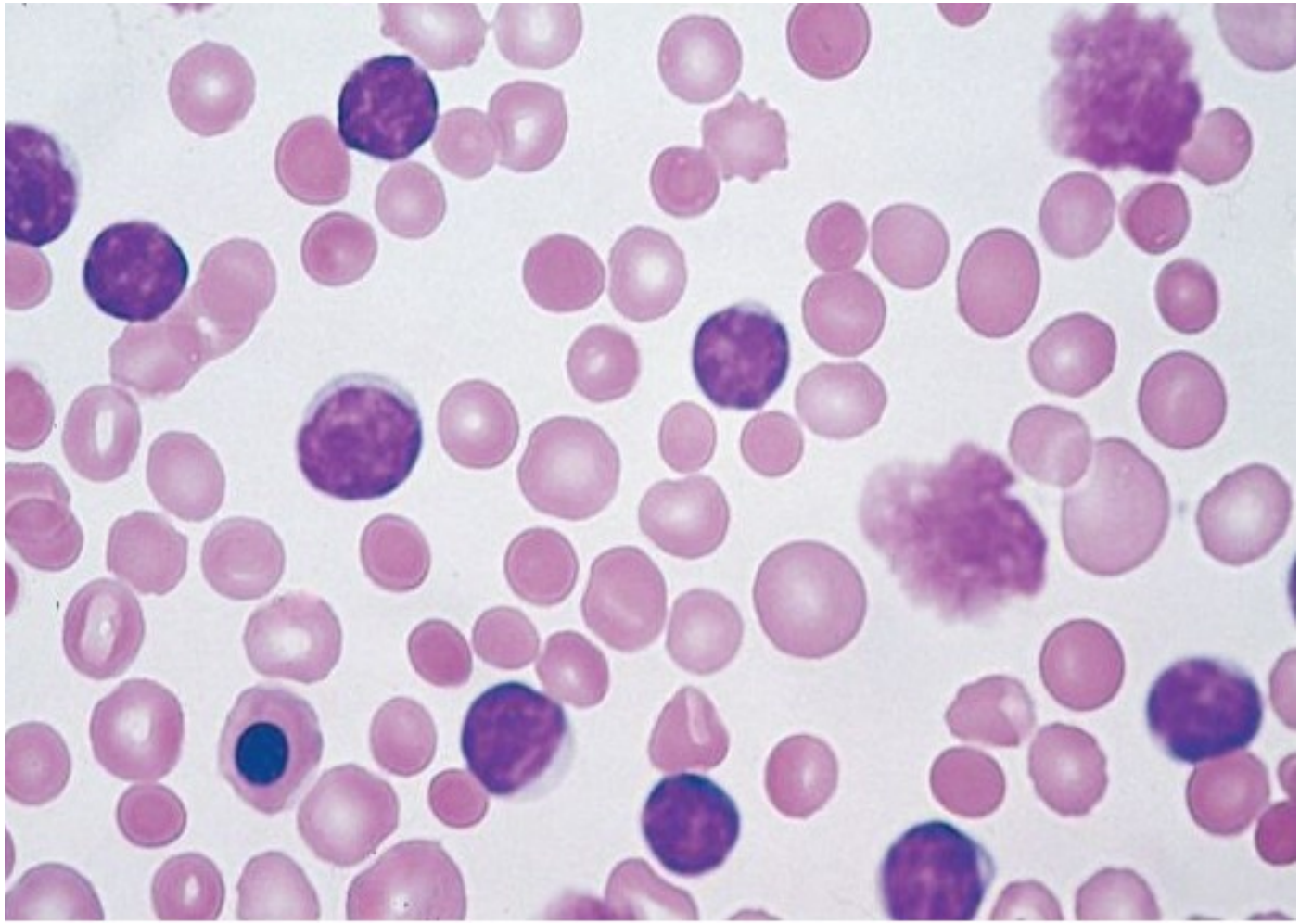
- Tumors with unmutated Ig segments are more aggressive
- In proliferation centers Stromal cells express variety of factors to stimulate activity of the transcription factor NF-κB resulting in longer cell survival
- Most cases of CLL have overexpressed proto-oncogene c-fgr member of the src gene family of tyrosine kinases

Lab Diagnosis

- Smear
- Bone marrow examination
- Trephine biopsy
- Immunohistochemistry
- Lymph node biopsy
- Immunohistochemistry on lymph nodes

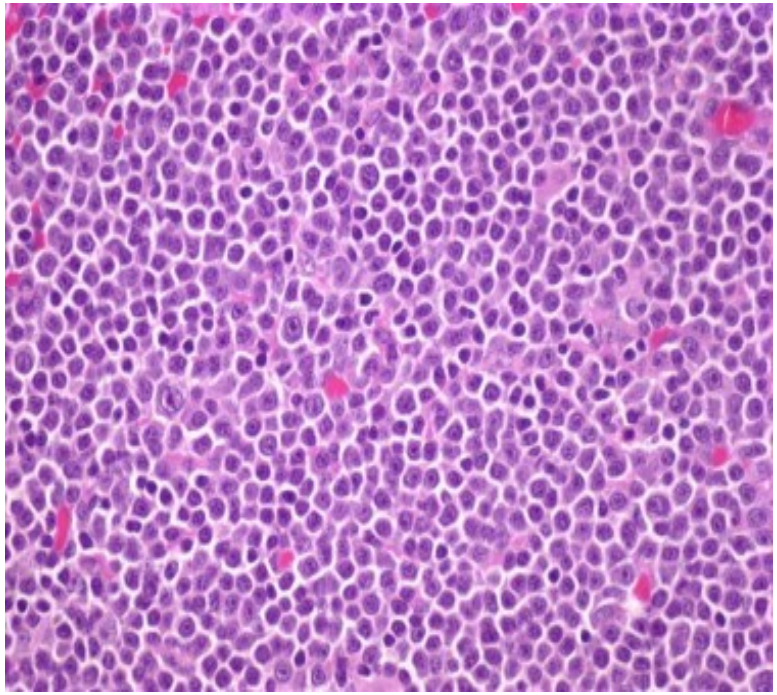
Morphology

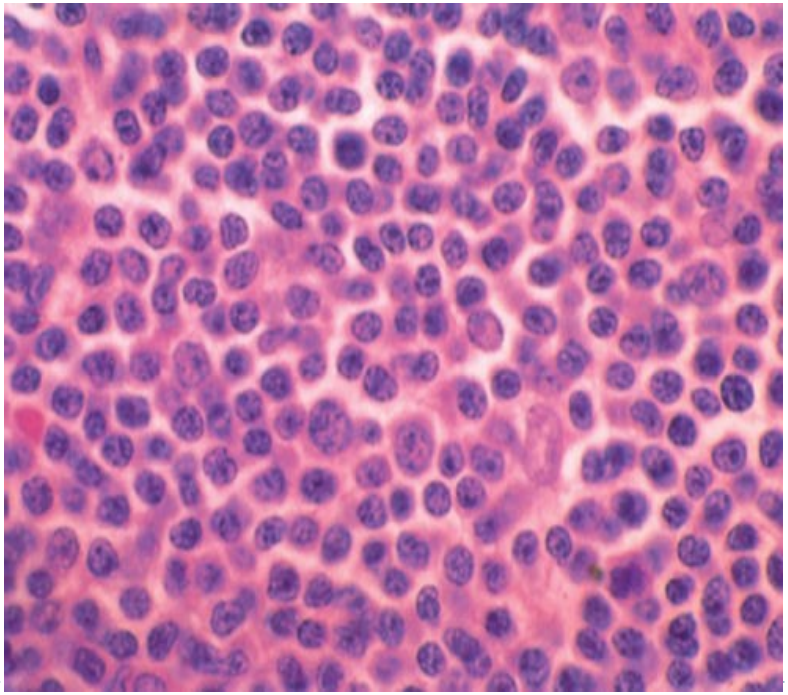
- Absolute lymphocyte count above 5000/cmm
- Mostly normal small mature Lymphocytes
- Blood smears show ruptured lymphocytes (“smudge” cells)
- Scanty cytoplasm with condensed chromatin
- No nucleoli



Bone Marrow

- Hypercellular
- Diffuse infiltration carry poor prognosis
- Other cell lines depressed





Immunoistocemistry

- The tumor cells express
- Pan-B cell markers CD19 and CD20
- CD23
- CD5
- Dim Surface immunoglobin
- Negative for
- FMC 7
- CD 79b

- Hypogammaglobulinemia or agamma-globulinemia are often observed
- 10 - 25% of patients with CLL develop autoimmune hemolytic anemia
- Direct Coombs' test Positive
- Anemia of chronic disorder is another finding
- Hemolytic anemia and thrombocytopenia are due to autoantibodies made by non-neoplastic B cells

Clinical Features

- Mostly Asymptomatic
- Common symptoms are easy fatigability, weight loss, and anorexia
- Generalized lymphadenopathy and hepatosplenomegaly are present in 50% to 60% of symptomatic patients
- CLL/SLL disrupts normal immune function
- Hypogammaglobulinemia with increased susceptibility to infections

The Rai Staging System

Stage 0 Lymphocytosis only (> 15,000/mm^3)

Stage 1 Lymphocytosis and lymphadenopathy

Stage 2 Lymphocytosis and splenomegaly with or without lymphadenopathy

Stage 3 Lymphocytosis and anemia (Hb <11 g/dL) with or without lymphadenopathy or hepatosplenomegaly

Stage 4 Lymphocytosis and thrombocytopenia (Plt < 100,000/UL) with or without anemia, lymphadenopathy or hepatosplenomegaly

The Binet Staging System

Stage A	No anemia, no thrombocytopenia, involved nodal areas	<3
Stage B	No anemia, no thrombocytopenia, involved nodal areas	>3
Stage C	Anemia (Hgb < 10 g/dL) and/or thrombocytopenia (Plt < 100,000/uL)	

Course and prognosis

- Variable course
- Depends on the clinical stage
- Overall median survival is 4 to 6 years
- Bad Prognostic factors are
- High tumor burdens at diagnosis
- Presence of deletions of 11q and 17p
- Lack of somatic hypermutation
- Expression of ZAP-70, a protein that augments signals produced by the Ig receptor

- Transformation to more aggressive Large B cell Lymphoma(Richter syndrome)
- Increase in the number of peripheral prolymphocytes
- Lymphocyte doubling time
- Serum Beta 2 Microglobulin
- CD38 expression

Transformation

- Large- cell lymphoma/ Richter's
  - Aggressive presentation
  - Extranodal involment
  - Sharp rise in LDH
  - CHOP is standard treatment.
- Prolymphoctic leukemia.
  - > 55% increase in prolymphocytes
  - Progression of splenomegaly & cytopenias
  - Refractoriness to treatment.

Chronic Myeloid Leukemia

- A myeloproliferative pluripotential stem cell disorder characterized by
- Anemia
- Extreme blood leukocytosis with left shift
- Basophilia
- Thrombocytosis
- Splenomegaly

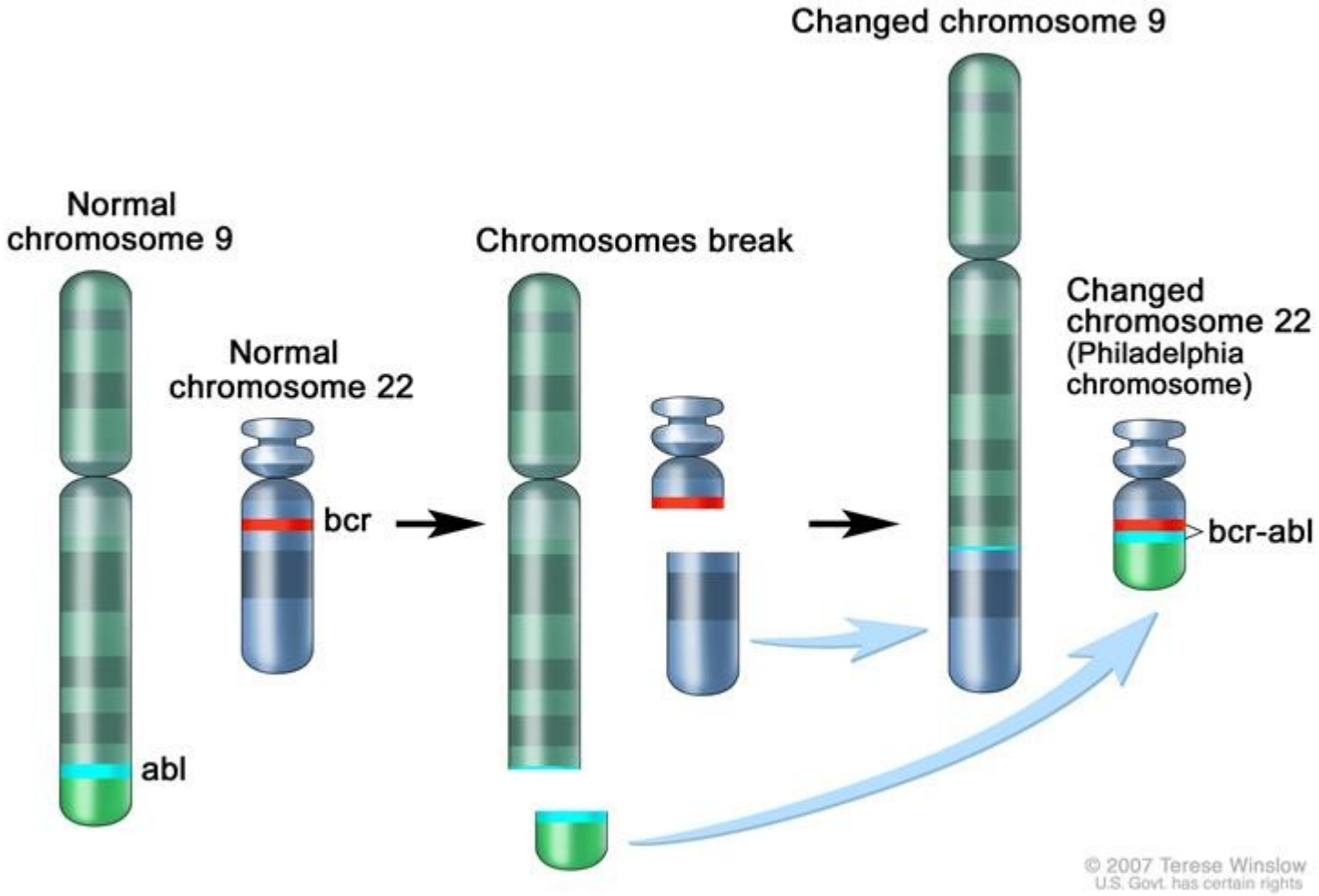
- Consistently associated with the BCR-ABL1 fusion gene located in the Philadelphia (Ph) chromosome
- Comprises about 14% of all adult leukemias
- Males slightly higher than females

Etiology

- Very high doses of ionizing radiation
- No relation with Chemicals like benzene and alkylating agents
- No hereditary predisposition
- No relation to smoking/diet/lifestyle
- Median age of onset is 53 years

Molecular pathogenesis

- Presence of Chimeric BCR-ABL fusion gene
- Results from a reciprocal (9;22)(q34;q11) translocation
- Also called Philadelphia chromosome [Ph]
- *BCR-ABL* directs the synthesis of a BCR-ABL tyrosine kinase
- In CML it is usually 210 kDa in size
- This BCR-ABL tyrosine kinase leads to the abnormal growth and survival of the cancer cells


Changed chromosome 9
Normal chromosome 9
Chromosomes break
Normal chromosome 22
Changed chromosome 22 (Philadelphia chromosome)
bcr
bcr-abl
abl
© 2007 Terese Winslow
U.S. Govt. has certain rights

- BCR-ABL tyrosine kinase promote proliferation and survival as follows

- Decreased adhesion of the leukemis cells to bone marrow stroma

- Activation of various proliferation pathways including RAS,JAK-STAT,PI3K-AKT etc

- Inhibition of apoptosis by up regulating Bcl-2

Clinical features

- Primarily a disease of adults
- 30 to 50 % are asymptomatic at the time of diagnosis
- Mild-to-moderate anemia
- Fatigability, weakness, weight loss, and anorexia
- Sometimes the first symptom is a dragging sensation in the abdomen caused by splenomegaly

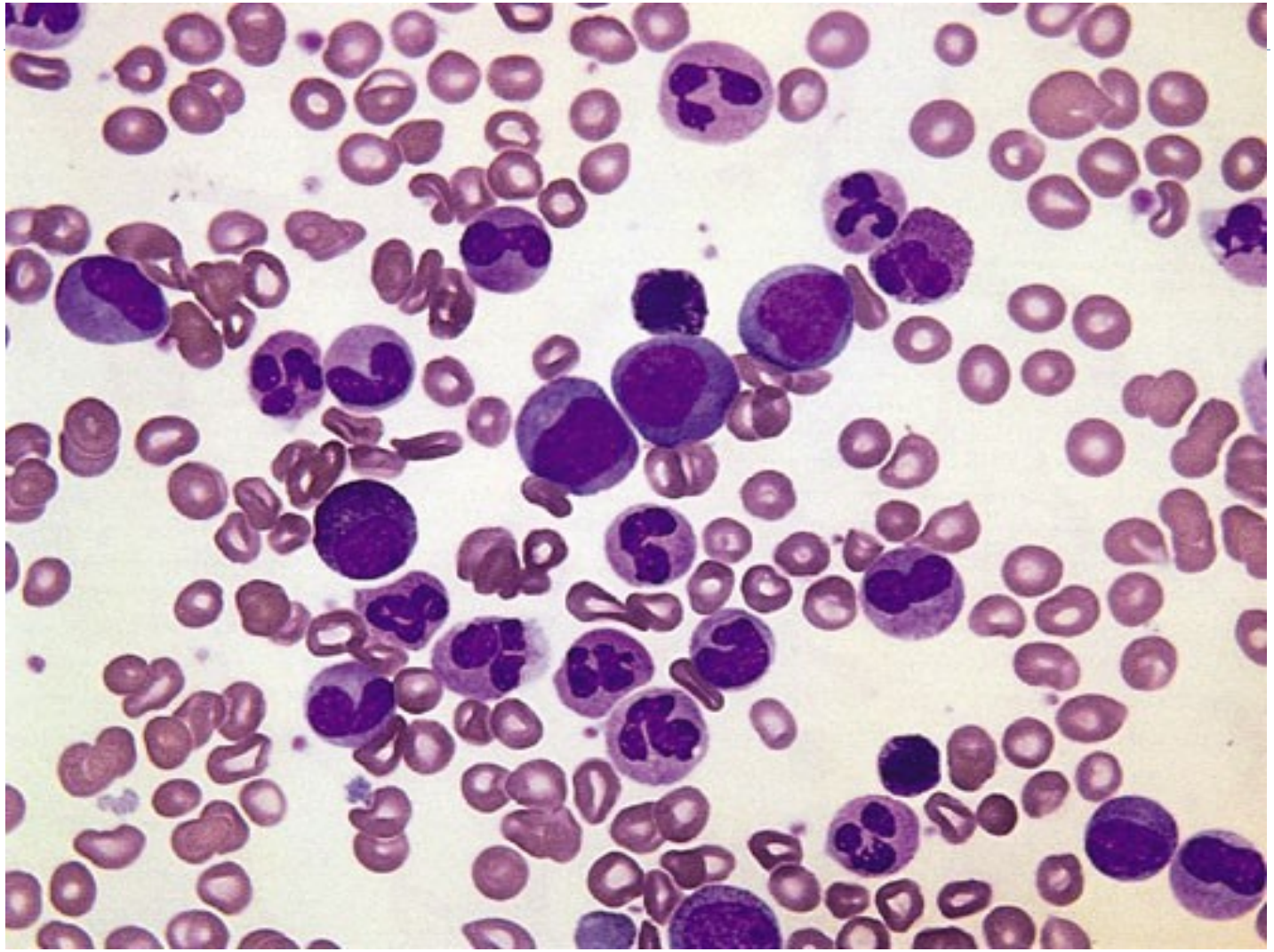
- Pallor
- Splenomegaly
- Sternal tenderness
- Lymhadenopathy
- Hepatomegaly
- Purpura
- Retinal haemorrhage

Phases of CML

Chronic phase	Accelerated phase	Blast crisis
≤10% blast cells in blood and bone marrow	10%–19% blast cells in blood and bone marrow	≥20% blast cells in blood and bone marrow
• WBCs still capable of fighting infection	• High basophil count (≥20% of WBC differential) • Persistent thrombocytopenia unrelated to therapy • Persistent thrombocytosis unresponsive to therapy • Increasing WBC and spleen size unresponsive to therapy • Cytogenic evidence of clonal evolution	• Large clusters of blasts in bone marrow • Extramedullary blast proliferation
Mild symptoms, if any	Fever, poor appetite, weight loss, fatigue	Fever, loss of appetite, weight loss, fatigue, bleeding, infections common, stomach pain, bone pain

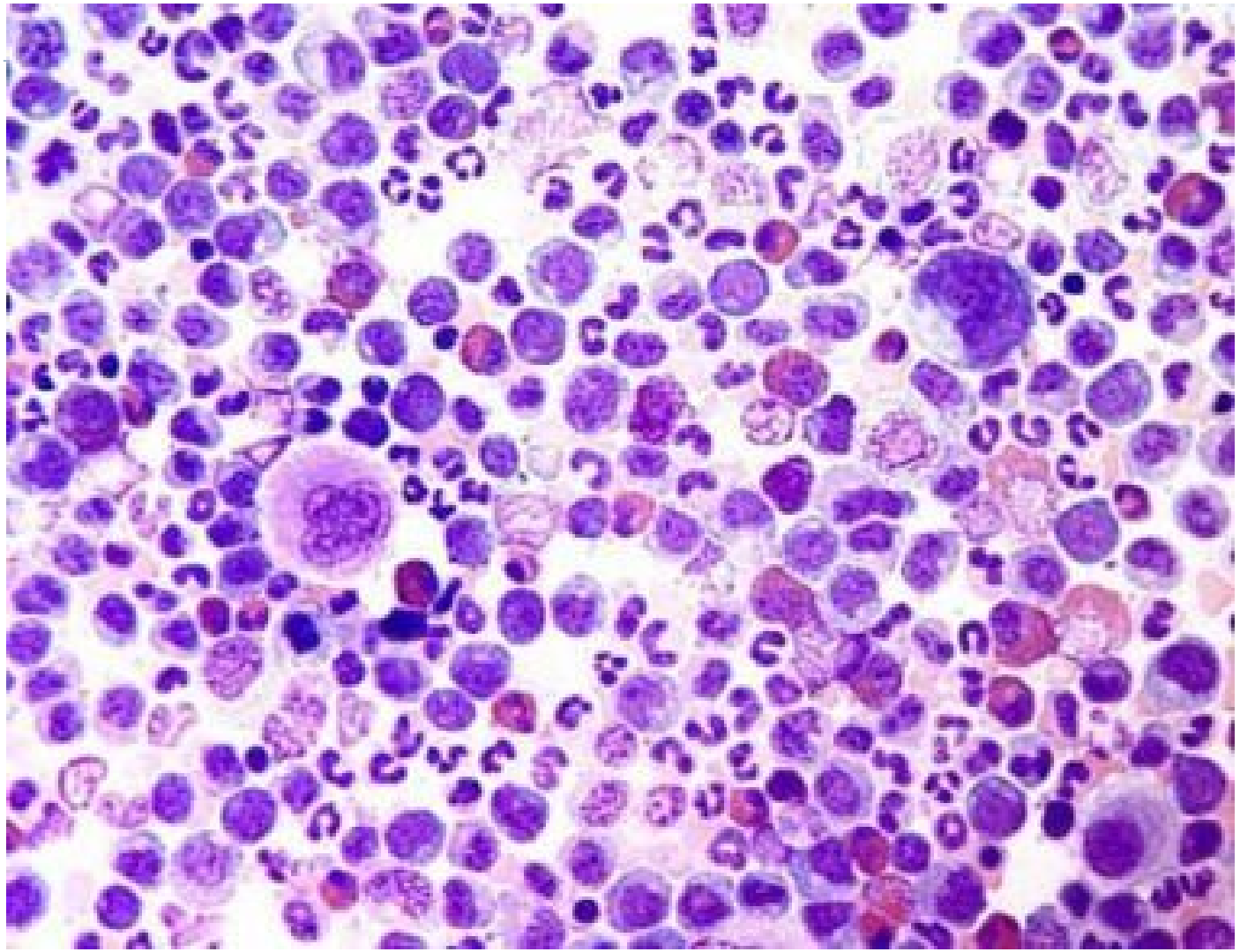
Blood picture

- High Total leukocyte count
- Leucoblasts less than 10%
- Presence of both mature and immature forms of myeloid cells
- Basophilia
- Normal or increased platelet count
- Normal or decreased hemoglobin level
- Eosinopilia



Bone marrow

- Marrow is markedly hypercellular
- Mostly increased numbers of maturing granulocytic cells
- Elevated proportion of eosinophils and basophils
- Erythroid progenitors are present in normal or mildly decreased numbers
- Increased deposition of reticulin is typical, but overt marrow fibrosis is rare early in the course.



Diagnostic approach

1. Smear
2. Bone marrow
3. Reticulin stain
4. PCR or FISH for BCR-ABL
5. U/S abdomen
6. Serum Uric Acid
7. S. LDH

Prognostic factor

Sokal index

- Percentage of circulating blast
- spleen size
- Platelet count
- Age
- Cytogenetic clonal evolution

Was developed based on chemotherapy treated patients

Treatment

- Drugs
- Stem cell transplant.
- Leukaphresis and splenectomy.
- Drugs
- Imatinib mesylate,dasatinib,nilotinib
- Hydroxyurea
- busulphan
- Interferon-alpha
- Anagrelide.
- Cytarabin.

THANK YOU