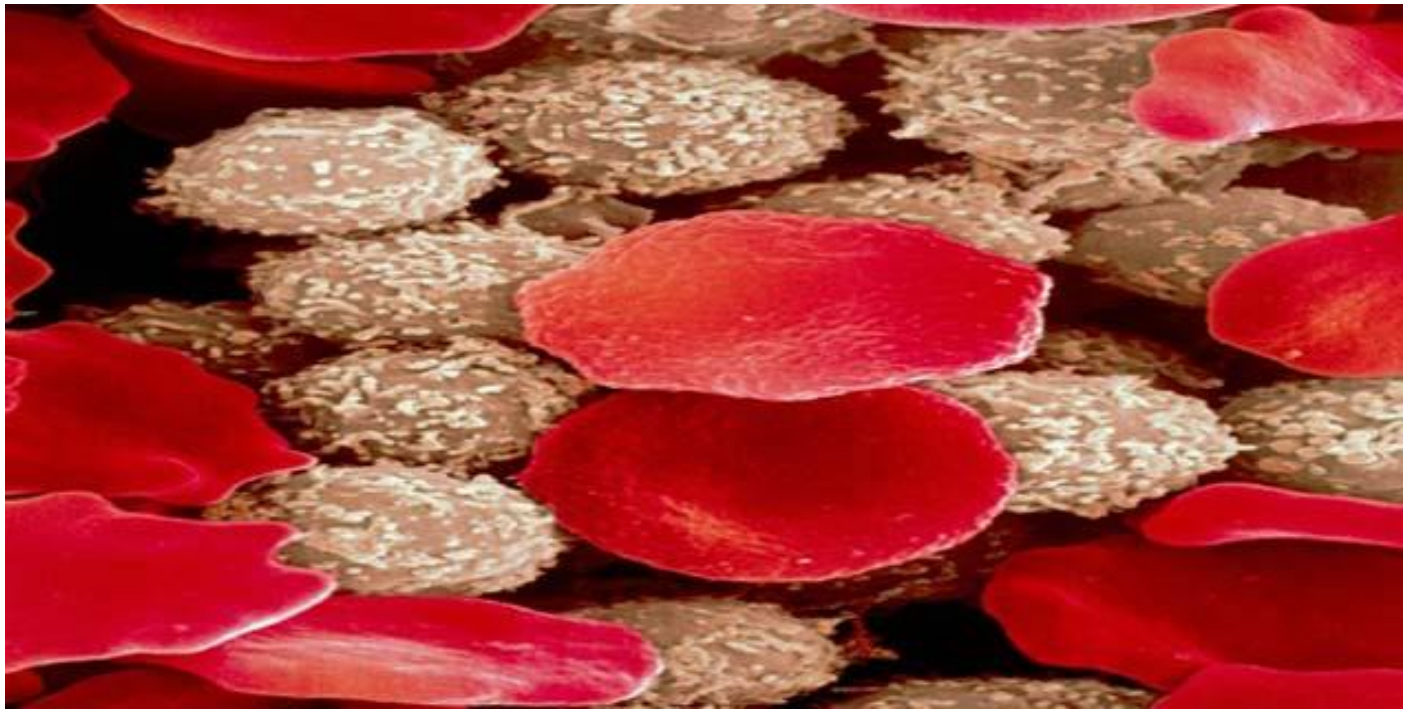
Chronic Leukaemia



Dr Durga Moratuwagama

Objectives

- Define & classify chronic leukaemias
- Describe the clinical features
- Describe laboratory investigations and interpretation of tests
- List the complications of chronic leukaemias
- Management of chronic leukaemias

What are the Chronic Leukemias?

- Neoplasms of either the myeloid or lymphoid lineage which are capable of differentiation to mature cells.

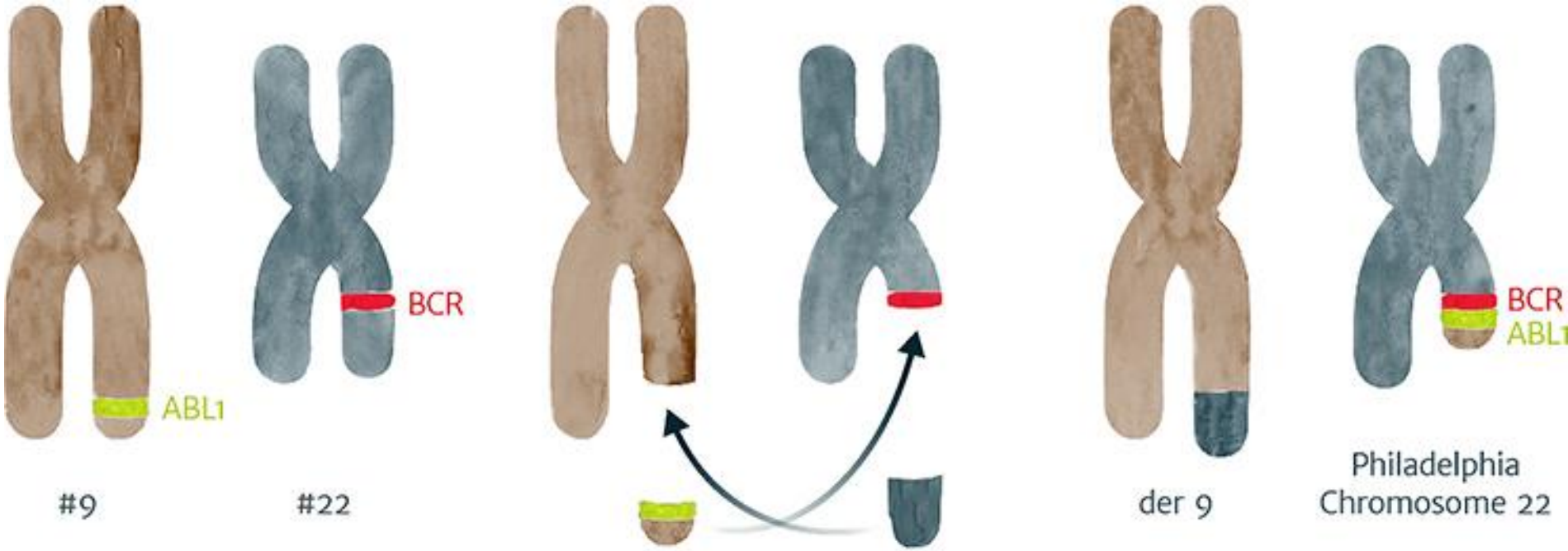
Types of Leukemia

	Acute – no maturation beyond blast	Chronic – maturation beyond blast
Lymphocytic - T or B lineage	ALL	CLL
Myeloid – (granulocytes, monocytes, erythrocytes, platelets)	AML	CML

CML

- Clonal disorder of pluripotent stem cells
- Characterized by **Philadelphia chromosome**

Philadelphia chromosome

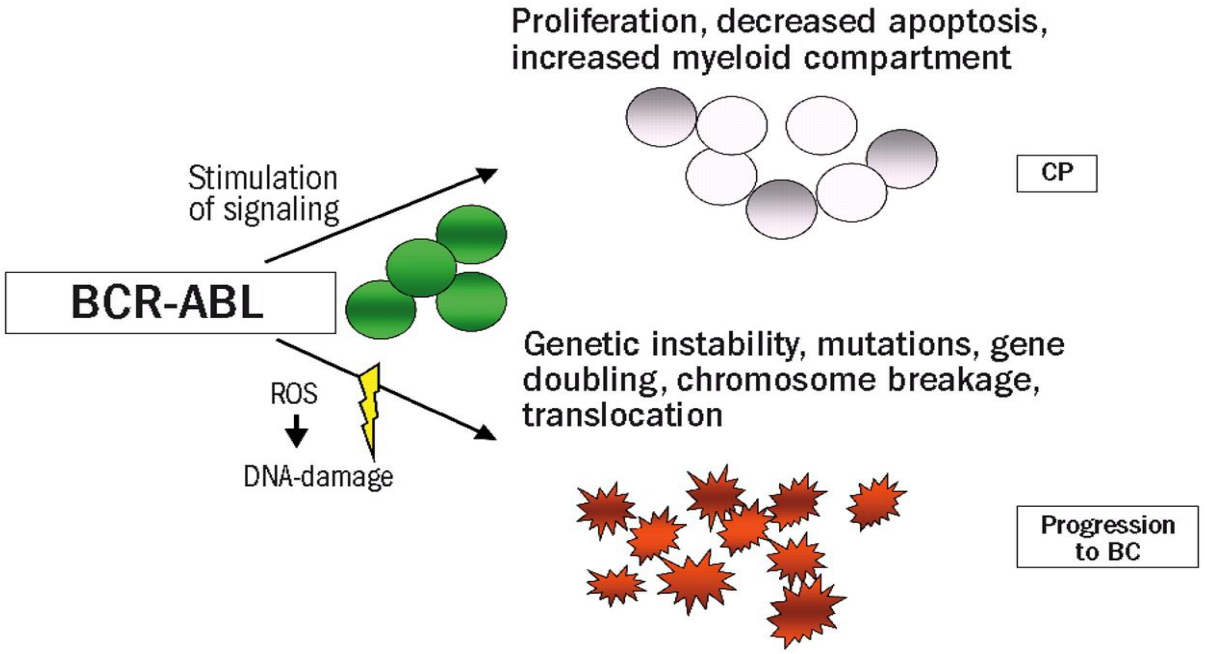


The bcr/abl fusion protein

- Uncontrolled kinase activity
- Deregulated cellular proliferation
- Decreased adherence of leukemia cells to the bone marrow stroma
- Leukemic cells are protected from normal programmed cell death (apoptosis)

Natural history

- 3 Phases
- Chronic
- Accelerated
- Blastic



Clinical features

- Male : Female=1.4:1
- 40-60y
- Symptoms related to hypermetabolism
- Massive splenomegaly
- Features of anaemia
- Bleeding manifestations
- Hyperuricaemis-Gout/Renal impairment
- Rare-visual disturbances/priapism
- **Incidental finding-50%**

Laboratory findings

1.FBC+BP

Leucocytosis

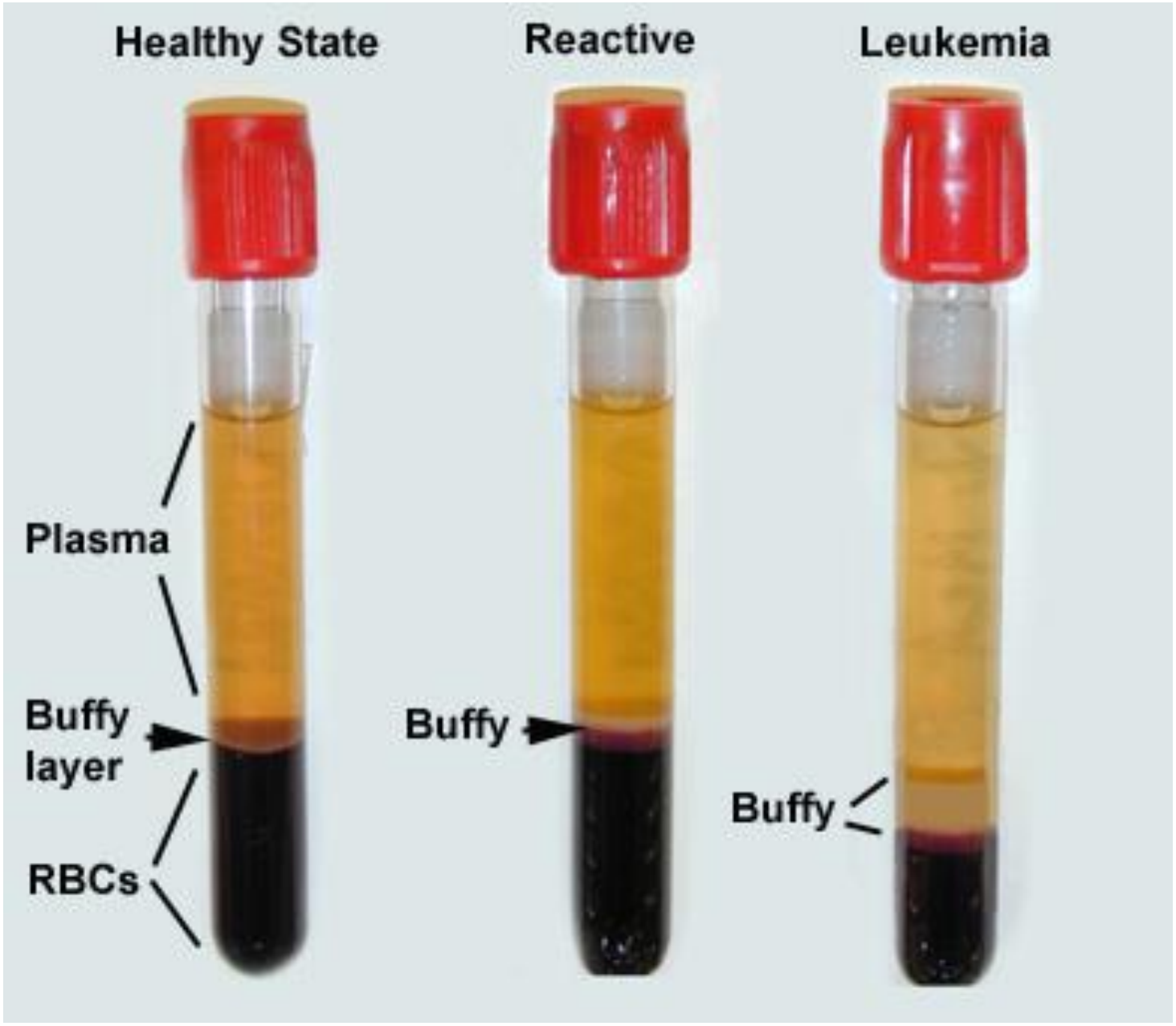
Complete spectrum of myeloid cells in the peripheral blood(left shift)

Neutrophil and myelocyte peaks

Increased basophils/eosinophils

NC/NC anaemia

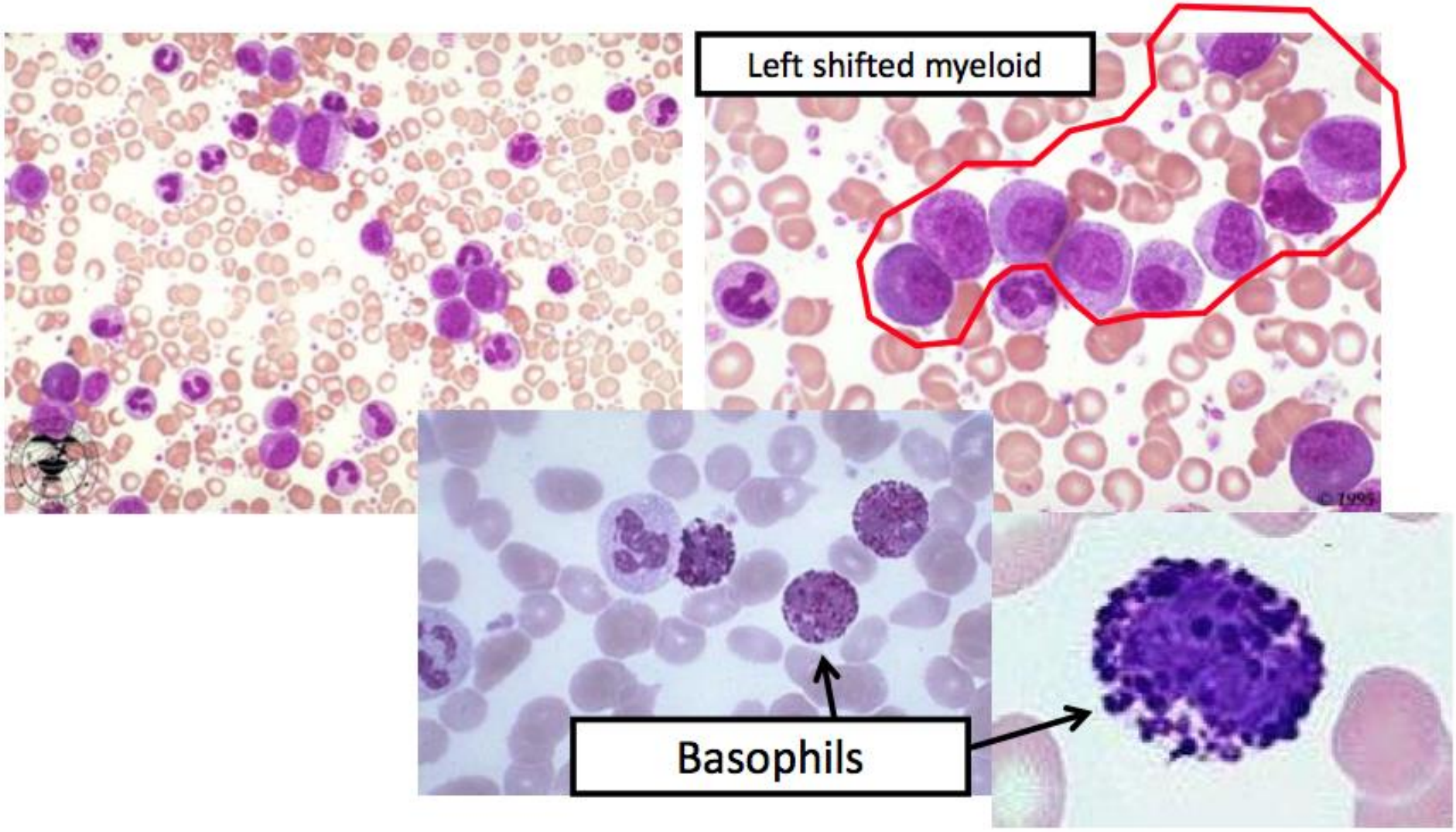
Platelets-increased/NL/decreased


Healthy State
Reactive
Leukemia
Plasma
Buffy layer
RBCs
Buffy
Buffy

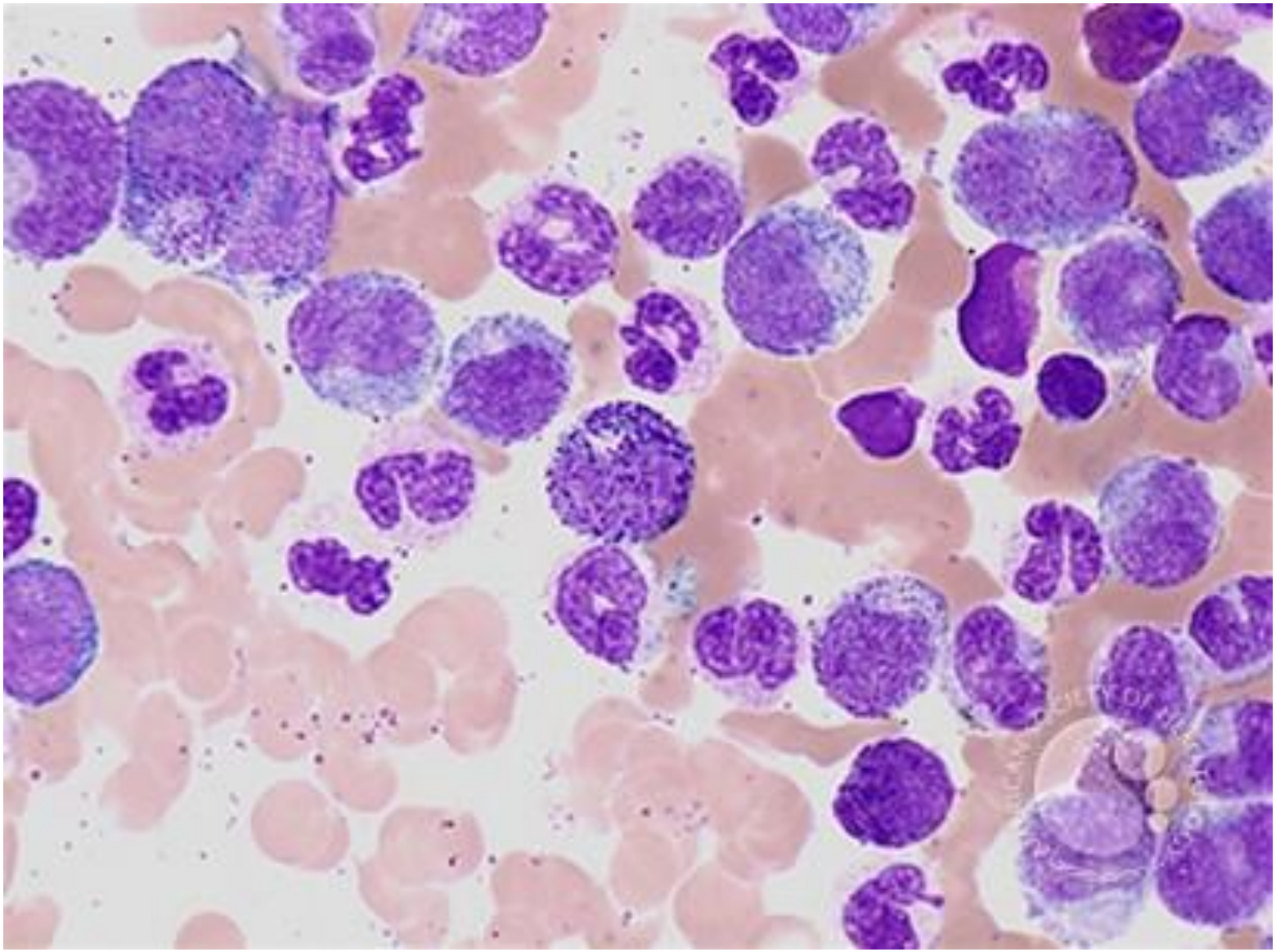
CML - blood count

WBC x 10^9/L	122	[4-11]
Hb g/dL	9.85	[12.0-16.0]
MCV fl	87	[79-98]
Platelets x 10^9/L	843	[150-450]
Neuts x 10^9/L	**80**	[2-7.5]
Lymphs x 10^9/L	2.0	[1.5-4]
Monos x 10^9/L	2.0	[0.2-0.8]
Eos x 10^9/L	**1.0**	[0-0.7]
Basos x 10^9/L	**5.0**	[0-0.1]
Metamyelocytes x 10^9/L	4.0	[0]
Myelocytes x 10^9/L	**20.0**	[0]
Promyelocytes x 10^9/L	4.0	[0]
Blasts x 10^9/L	2.0	[0]
Nucleated red cells x 10^9/L	2.0	[0]

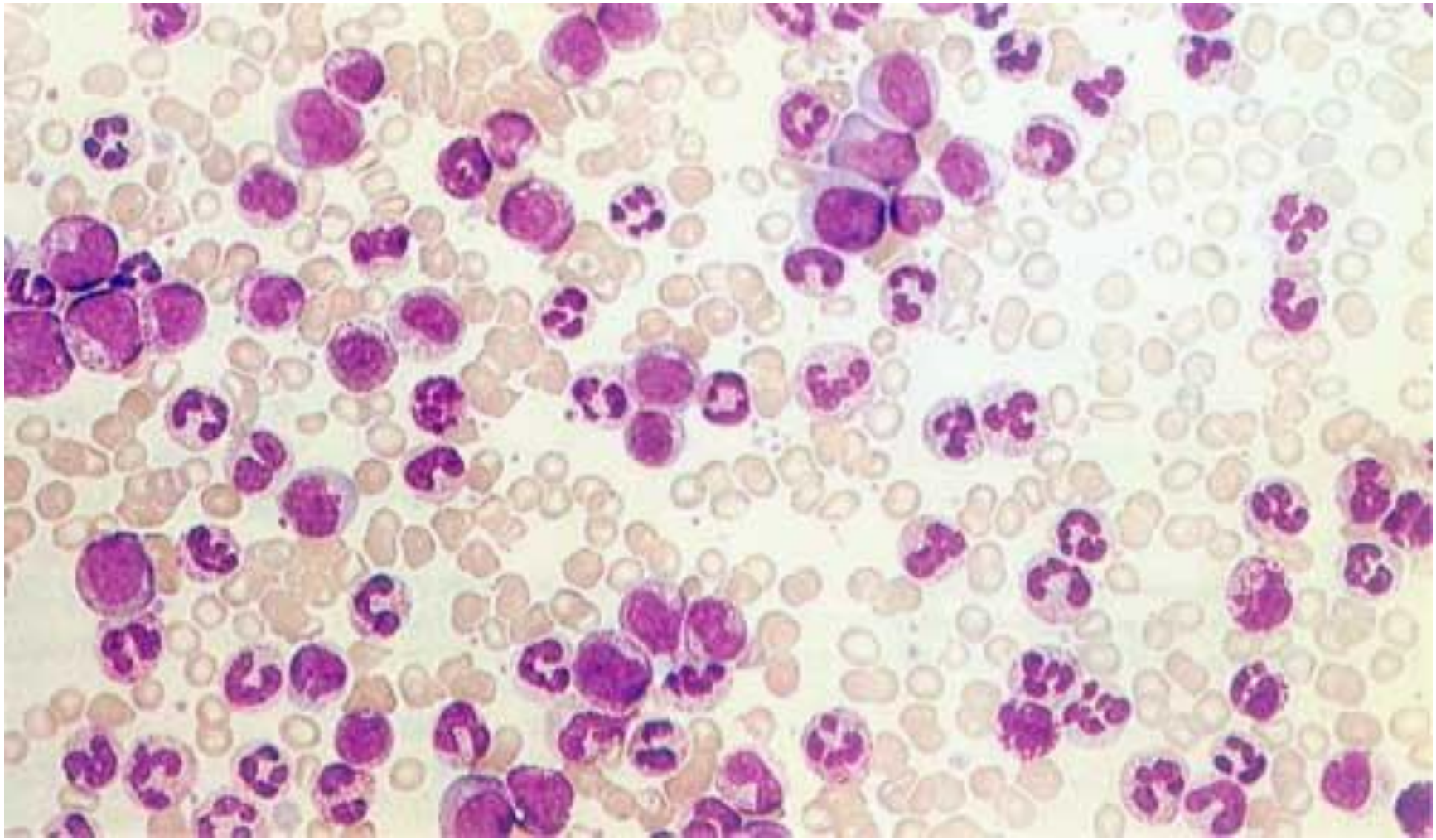
CML -BP



CML -BP



CML -BP

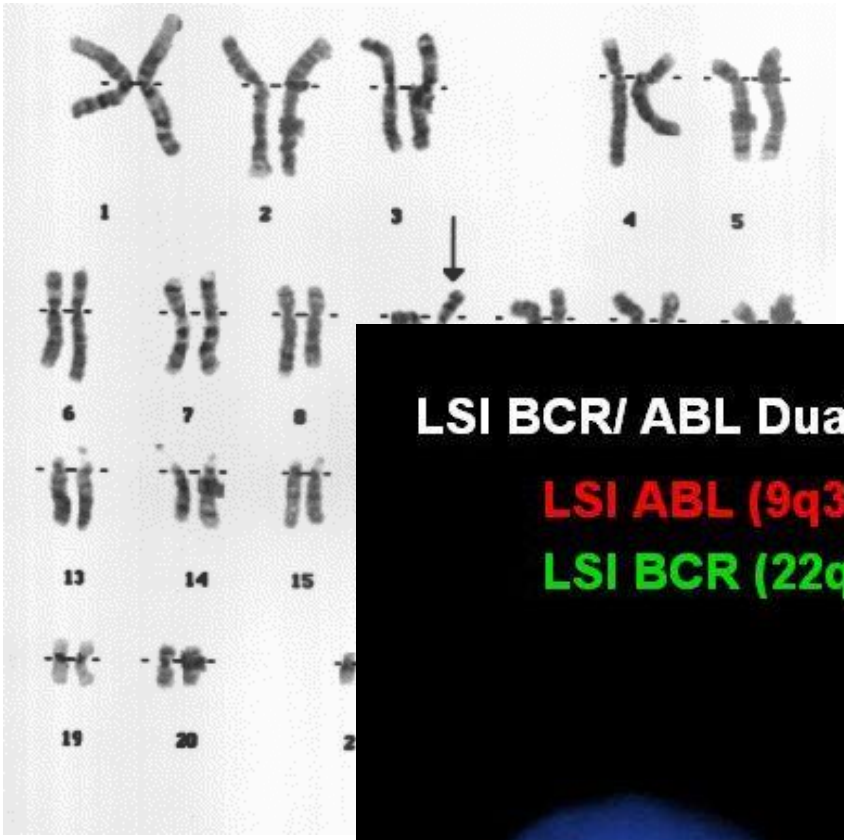


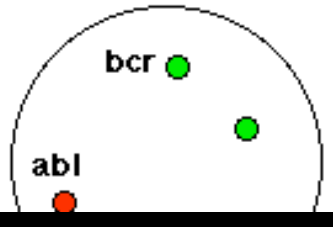
2. Demonstration of underlying genetic abnormality

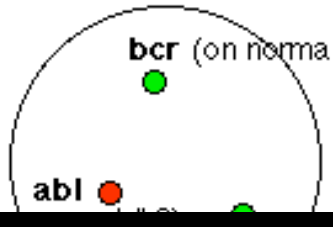
Philadelphia chromosome- Karyotyping

BCR-ABL fusion gene-FISH

PCR

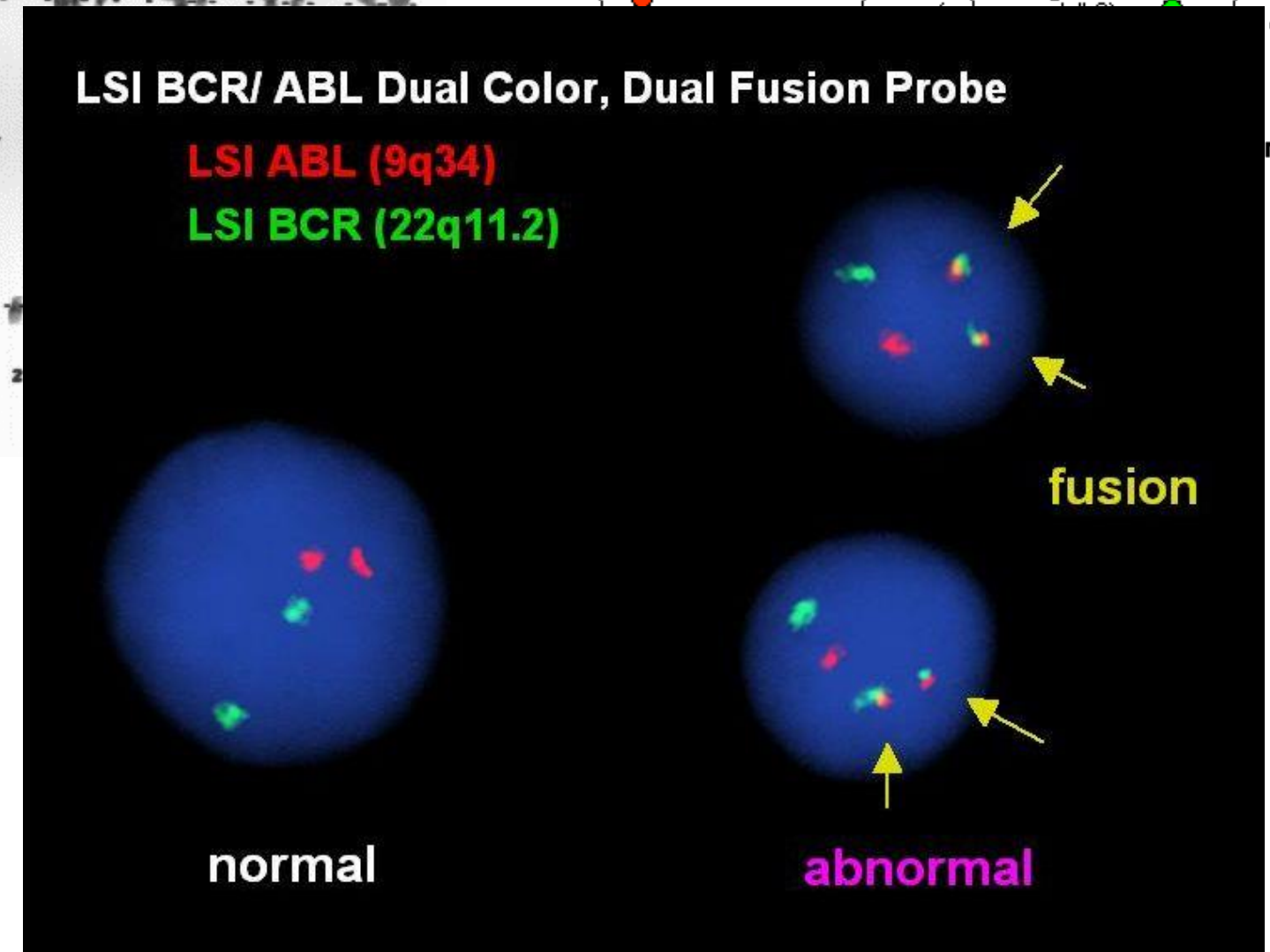



bcr
abl


bcr (on normal # 22)
abl

gene

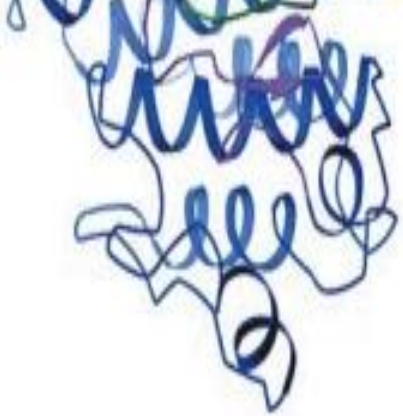
ng


LSI BCR/ ABL Dual Color, Dual Fusion Probe
LSI ABL (9q34)
LSI BCR (22q11.2)
fusion
normal
abnormal

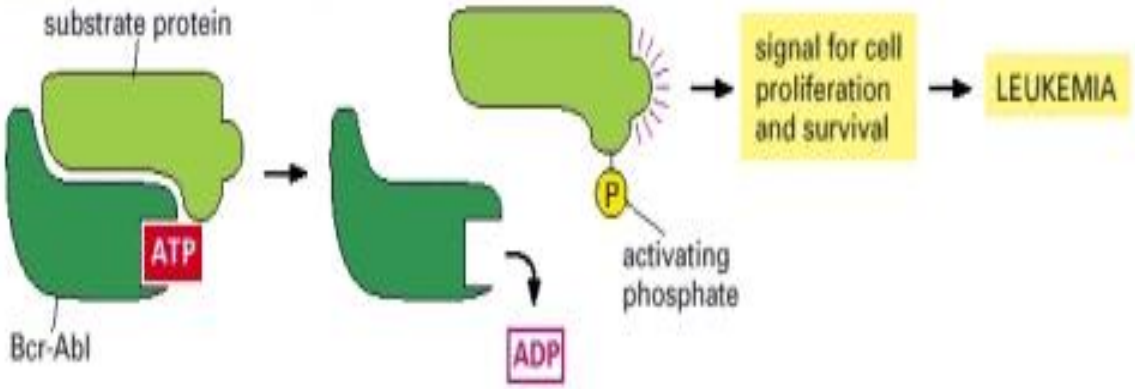
- BM Biopsy-Hypercellular,granulocytic hyperplasia
- USS-abdomen-Splenomegaly
- Serum-Uric acid raised

Treatment

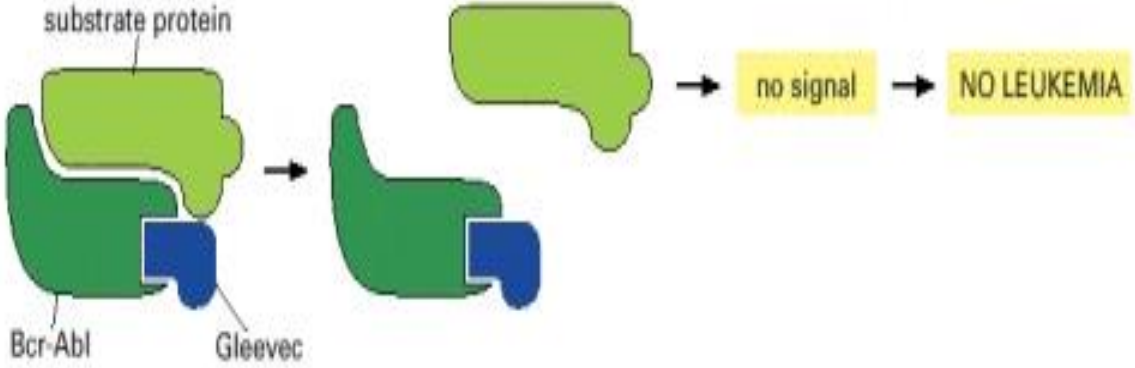
- Chronic phase
- Thyrosine kinase inhibitors-Imatinib(Glivec)



BCR-ABL ACTIVE



BCR-ABL BLOCKED WITH GLEEVEC



Other options

- Chemotherapy-Hydroxyurea
- Alpha interferon
- Allogenic stem cell transplantation

Progression of the disease

- Accelerated-10-19% blasts, anaemia, thrombocytopenia,increasing basophils, enlarging spleen

- Blastic phase->20% blasts,

  myeloid or lymphoid

Chronic Lymphocytic Leukaemia(CLL)

- Disease of old age-60-80y
- Indolent course
- Common in European countries
- Persistent lymphocytosis>$5x10^9/l$

CLL - Pathology

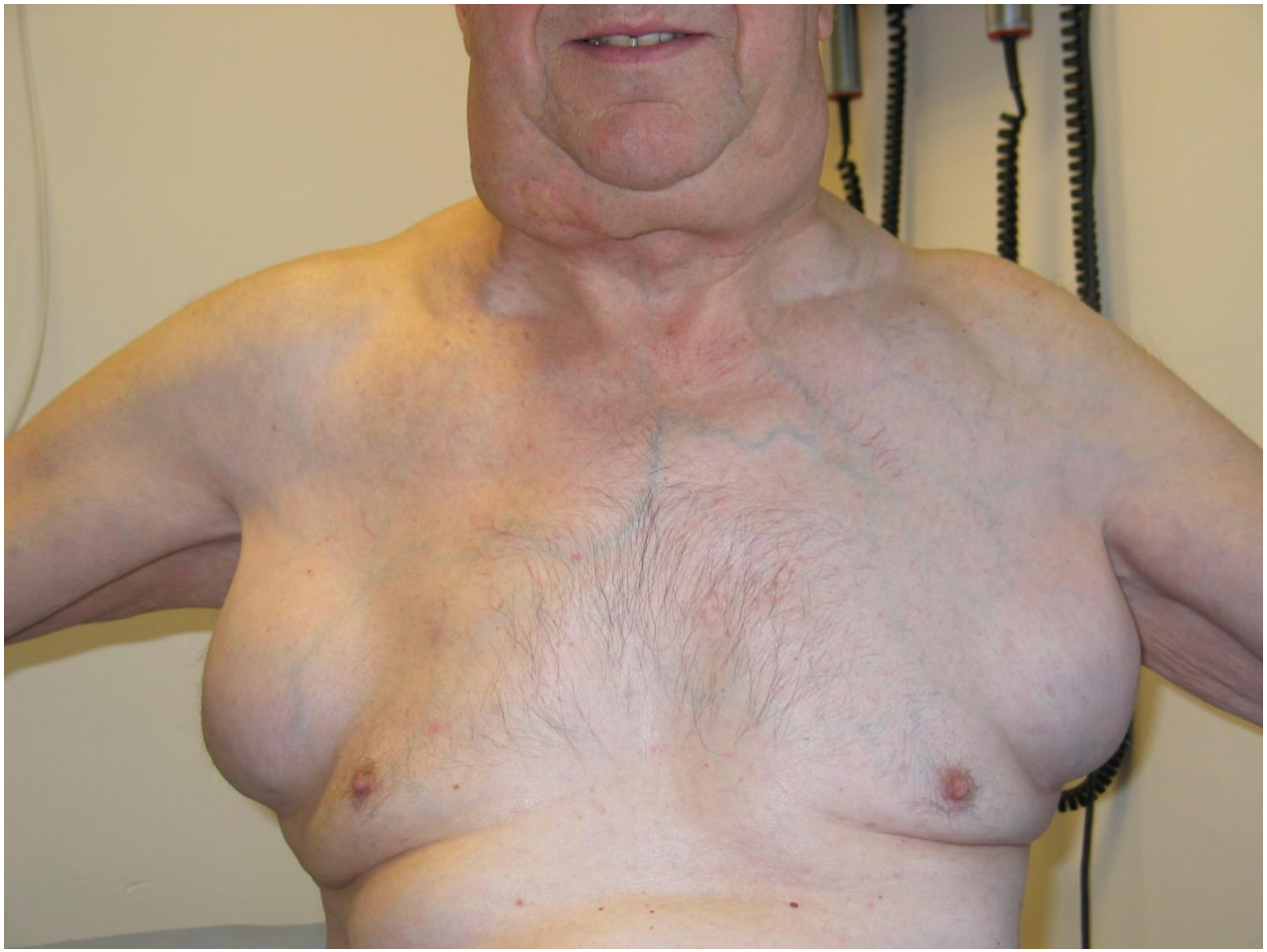
- Genetic change in B-cell clone
- Slow proliferation exceeds apoptosis
- Gradual accumulation of neoplastic B-lymphocytes – marrow, blood,nodes, spleen

CLL –clinical features

- Asymptomatic lymphocytosis
- Lymphadenopathy
- Marrow failure
- Hepatosplenomegaly
- ‘B-symptoms’
- Immunodeficiency

B-CLL clinical symptoms

Cervical and axillary Lymphadenopathy in 60-years old patient with B-CLL



CLL - Diagnosis

- Increase in blood lymphocyte count
- Demonstrate presence of a B-lymphocyte clone of appropriate immunophenotype
  - *Surface marker analysis – 'flow cytometry' (CD5/23 +,fmc7/79b -)*

Laboratory findings

- FBC+BP+ Retic count
- Flow cytometry/IHC
- Coombs test
- BMA+Trephine biopsy
- Serum protein electrophoresis/Ig levels
- Scans-for staging
- Genetic tests-For prognosis ex:P 53 mutation
- Liver/renal function tests-for treatment

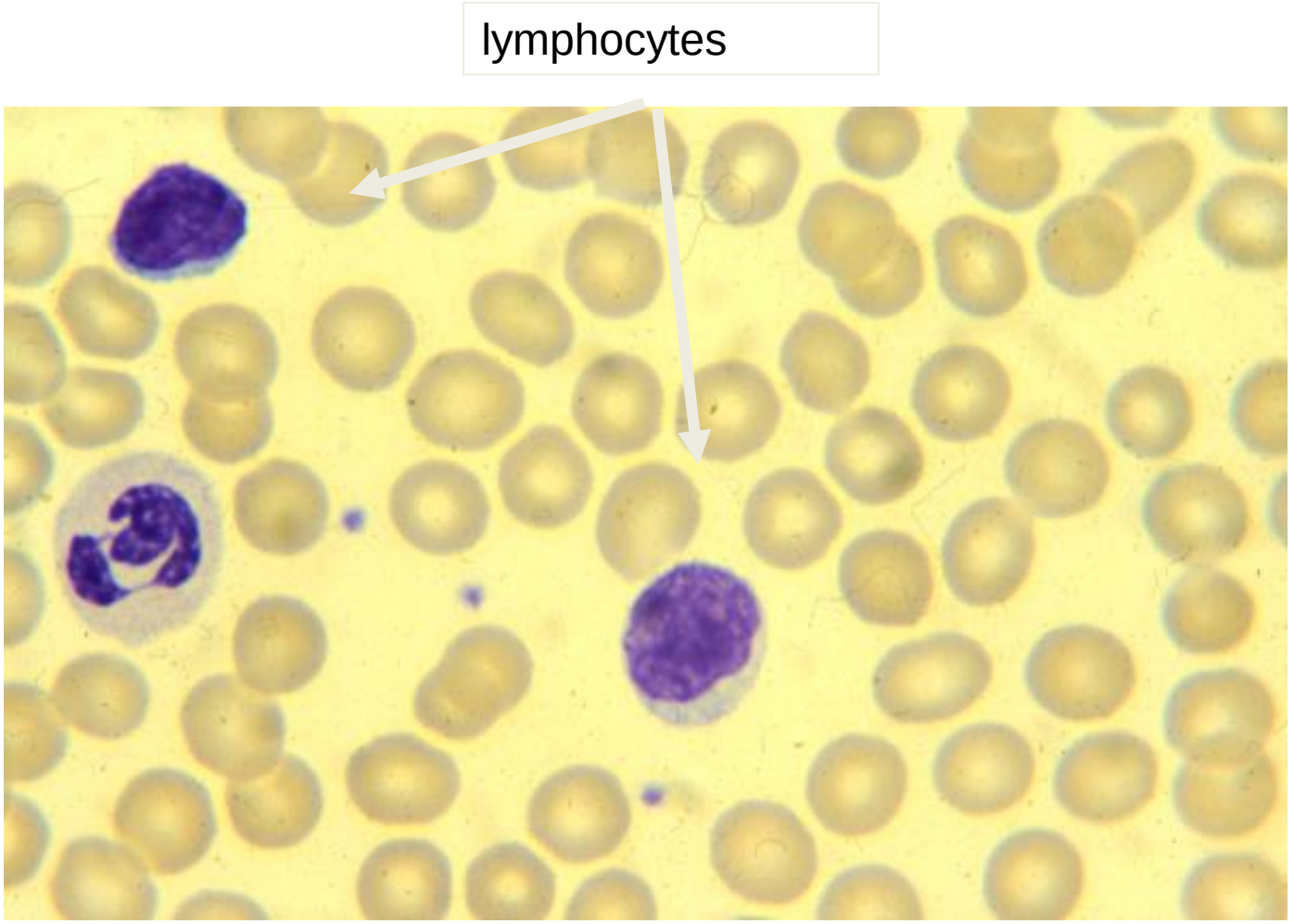
CLL - blood count

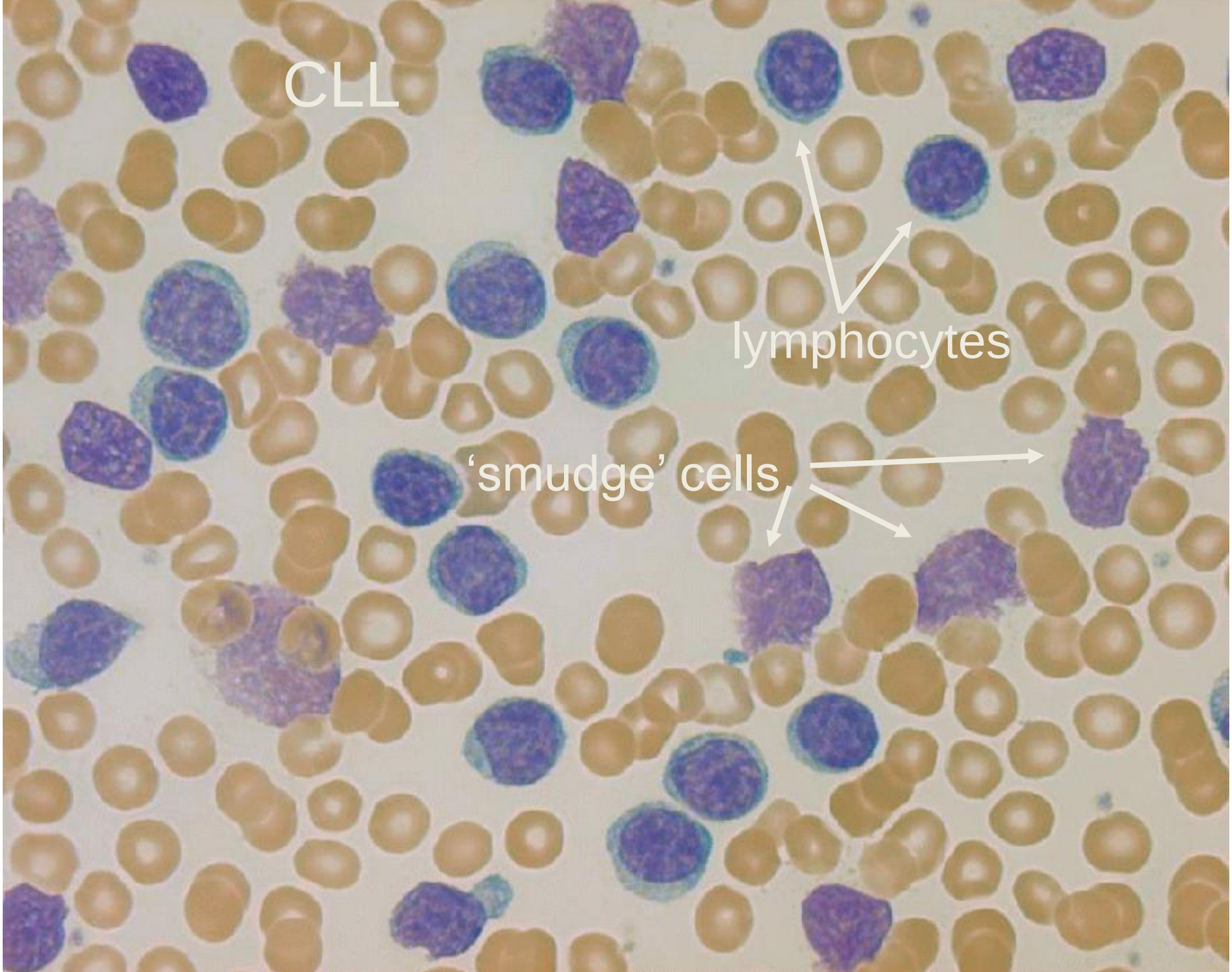
WBC x 10^9/L	150	[4-11]
Hb g/L	98	[120-160]
MCV fl	87	[79-98]
Platelets x 10^9/L	48	[150-450]
Neuts x 10^9/L	1.5	[2-7.5]
Lymphs x 10^9/L	130	[1.5-4]
Monos x 10^9/L	0.5	[0.2-0.8]
Eos x 10^9/L	-	[0-0.7]
Basos x 10^9/L	-	[0-0.1]

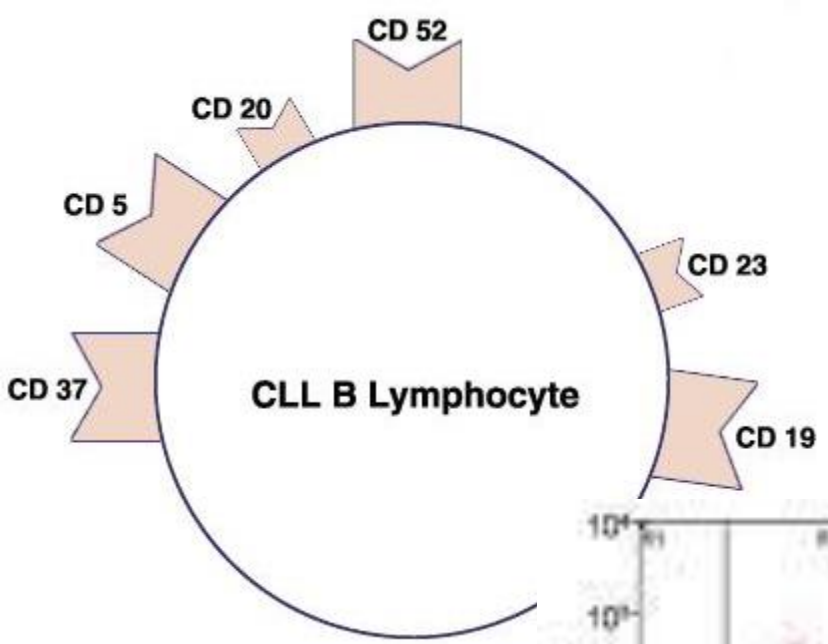
Smudge Cells x 10^9/L 28 [0]

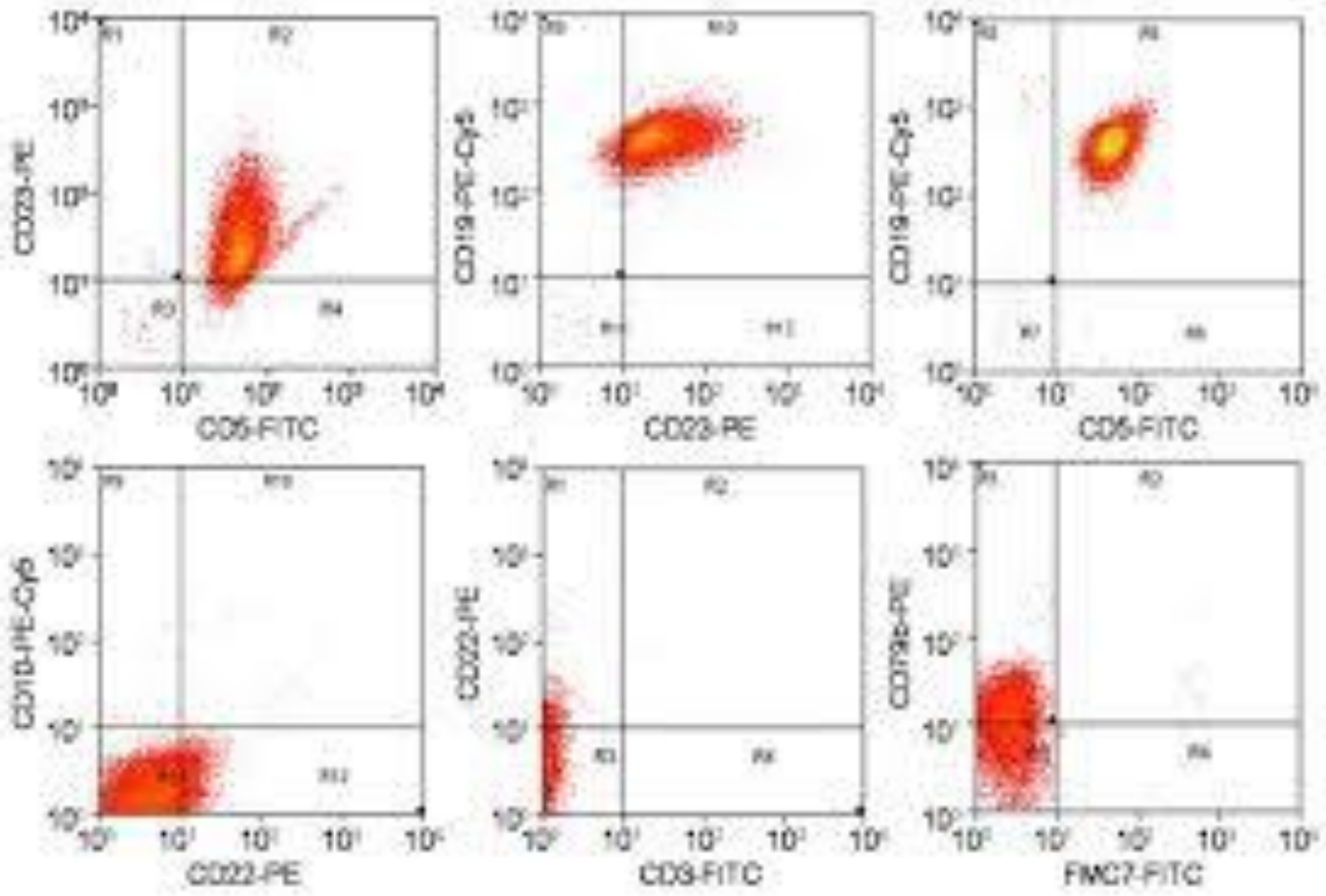
Film Comment: *lymphocytosis with smudge cells: appearances suggest CLL*

Normal




CLL
lymphocytes
‘smudge’ cells


CD 52
CD 20
CD 5
CD 23
CD 37
CLL B Lymphocyte
CD 19


CD23-PE
CD5-FITC
CD19-PE-Cy5
CD23-PE
CD19-PE-Cy5
CD5-FITC
CD10-PE-Cy5
CD22-PE
CD22-PE
CD3-FITC
CD79b-PE
FMC7-FITC

Staging-CLL

- Rai Classification for CLL
  - 0 - lymphocytosis
  - I - lymphocytosis + lymphadenopathy
  - II - lymphocytosis + splenomegaly +/- lymphadenopathy
  - III - lymphocytosis + anemia (Hb <11g%) +/- lymphadenopathy or splenomegaly
  - IV - lymphocytosis + thrombocytophenia+/- anemia +/-lymphadenopathy +/- splenomegaly

- **Binet Classification for CLL**
  - A. < 3 involved areas, Hb > 10g%, Plt > 100G/L
  - B. > 3 involved areas, Hb > 10g%, Plt > 100G/L
  - C. - any number of involved areas, Hb < 10g%, Plt < 100G/L

CLL - complications

- Opportunistic infection (e.g. shingles, pneumonia)
- Autoimmune hemolytic anemia (10%), autoimmune thrombocytopenia, pure red cell aplasia
- Richters transformation

CLL - principles of treatment

- ‘Watch and Wait’
- Chemotherapy

CLL - median survival (years)

- Early - lymphocytosis alone (>10y)
- Late - marrow failure (3-4y)