Chronic Leukemias

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Chronic Myeloid Leukemia (Chronic Granulocytic Leukemia)

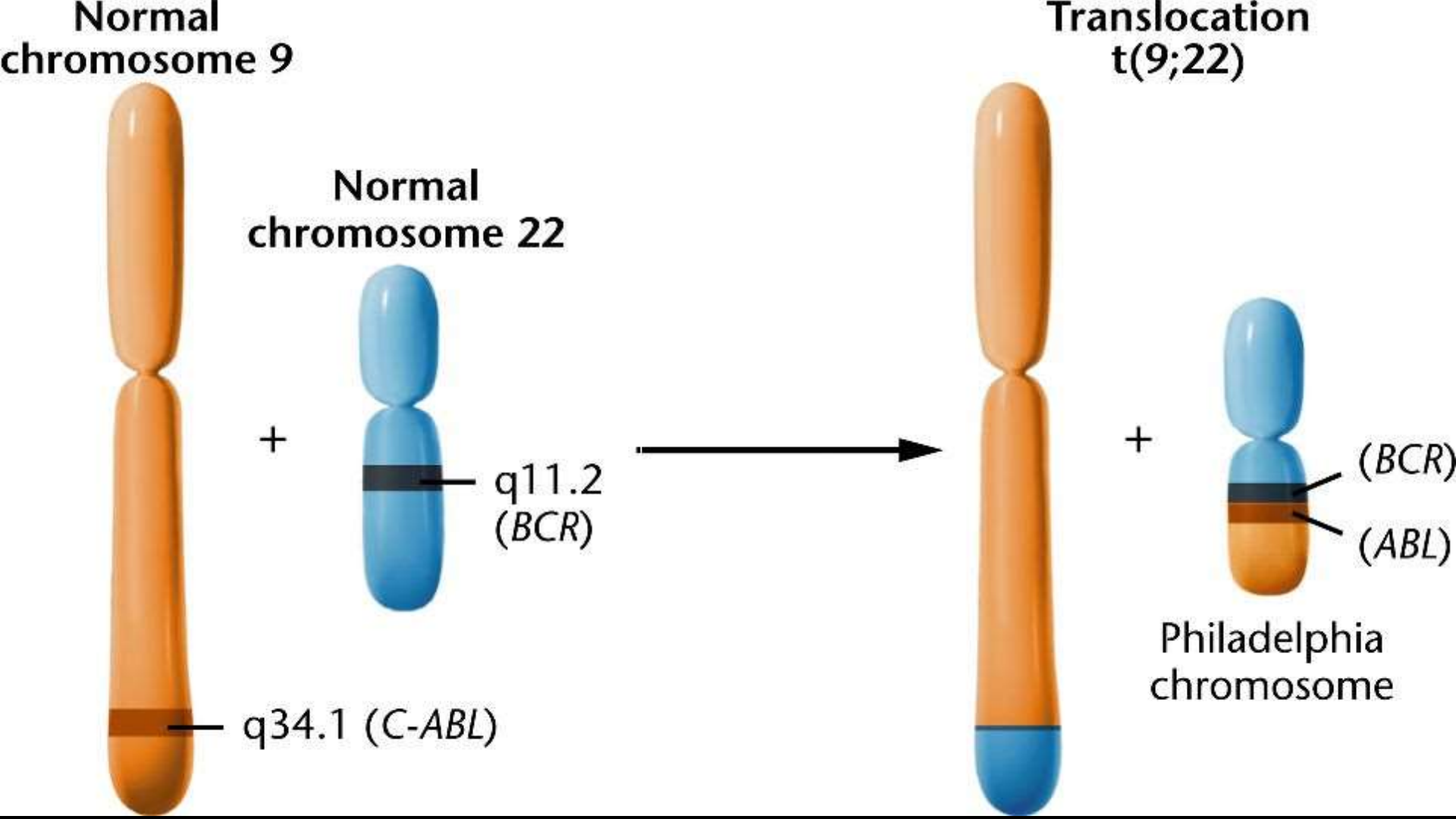
CML or CGL is a clonal disease that results from an acquired genetic change in a pluripotential hemopoeitic stem cell. This altered stem cell will proliferate and generate a population of differentiated cells that gradually replaces normal hemopoeisis and leads to a greatly expanded total myeloid mass.

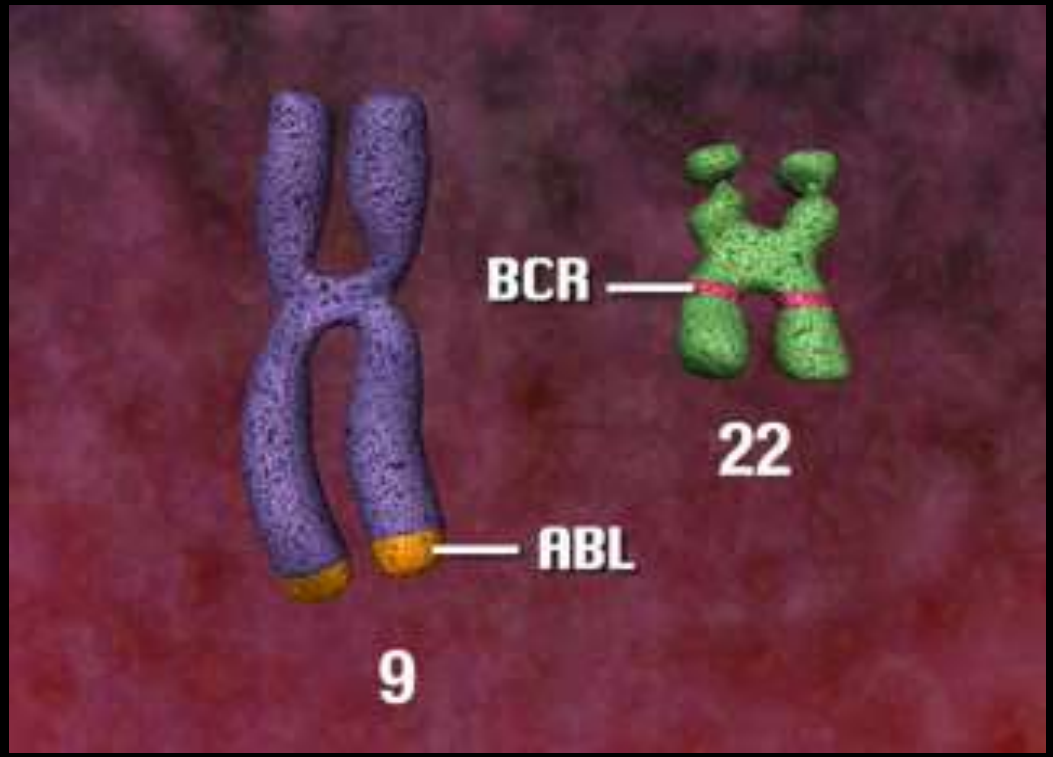
Incidence:

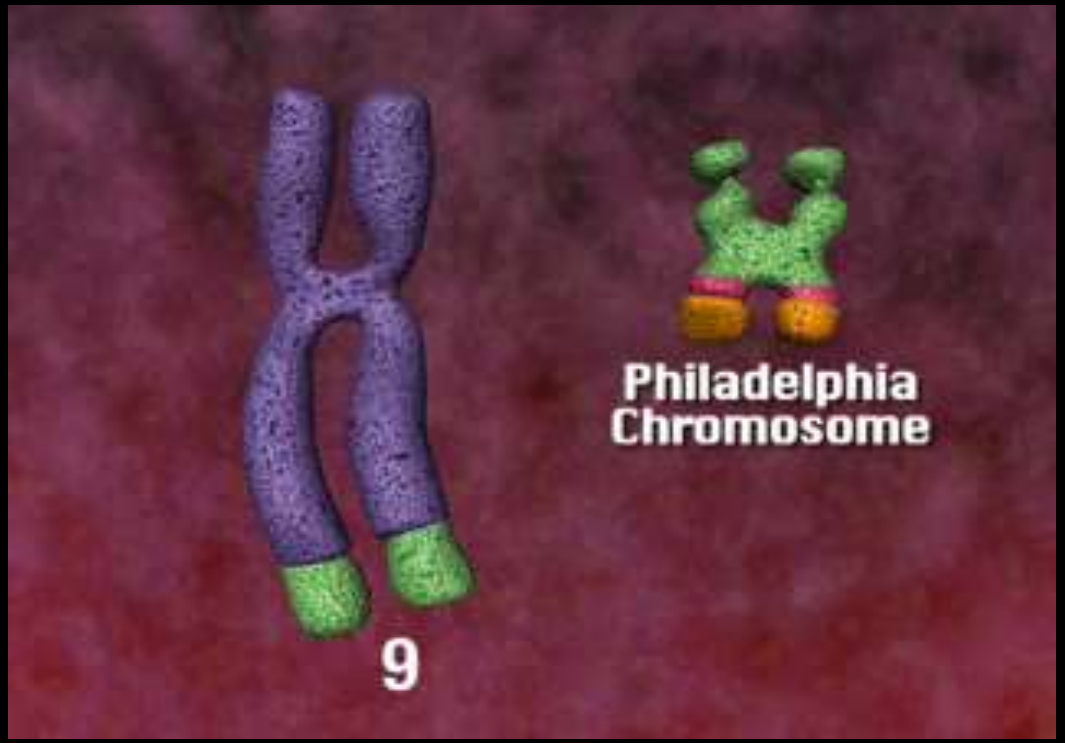
The incidence of CML is about 1.0-1.5/100000/year. It is rare below the age of 20 years, but occurs in all decades, with a median age of onset of 40-50 years. The incidence is slightly higher in males than in females.

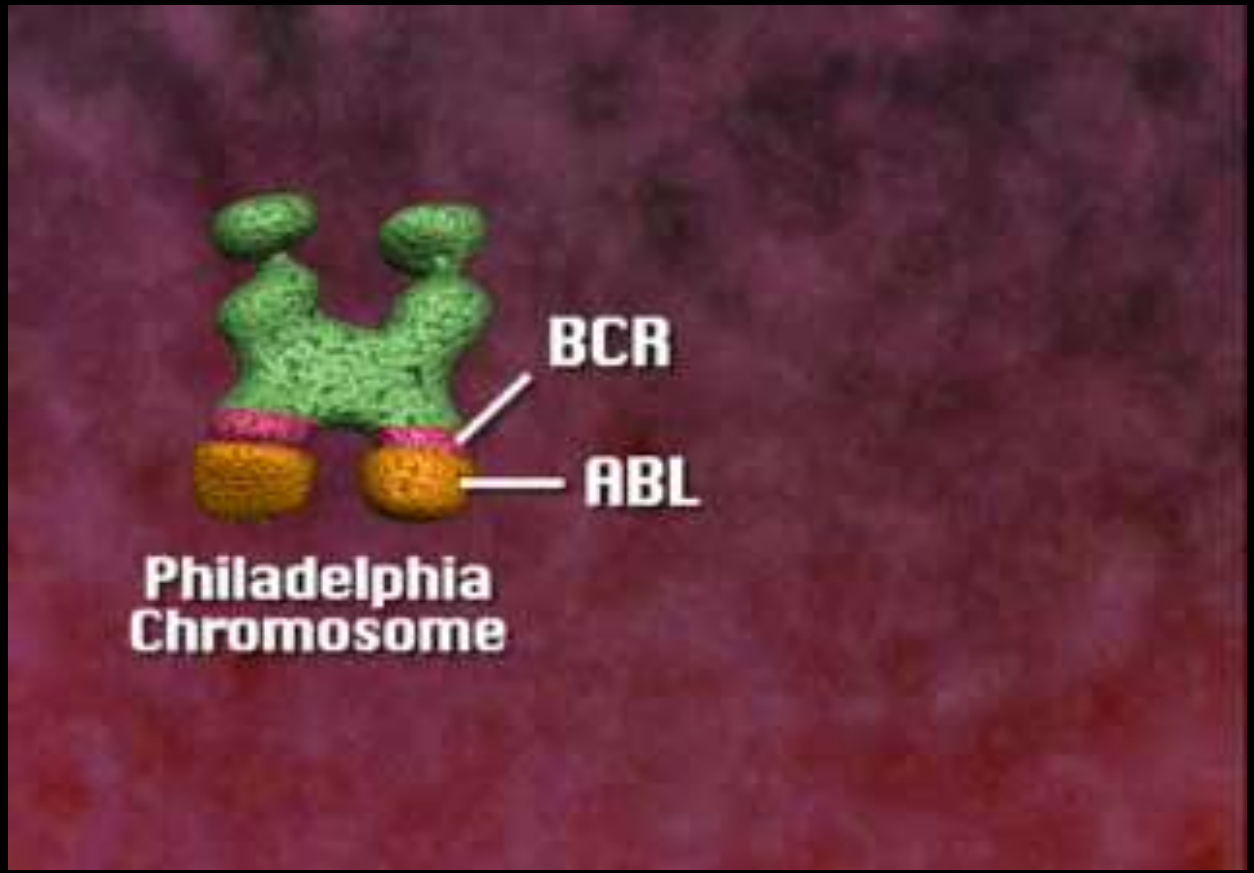
Cytogenetics:

The typical t (9; 22) giving rises to the Philadelphia chromosome (Ph chromosome) is found in about 95% of cases of CGL (Ph + CML). The Ph chromosome is the chromosome 22. The t (9; 22) results in fusion of some of the sequences of the BCR (Break Point Cluster) gene at 22q11 with some of the sequences of the ABL oncogene which have been translocated from 9q34.

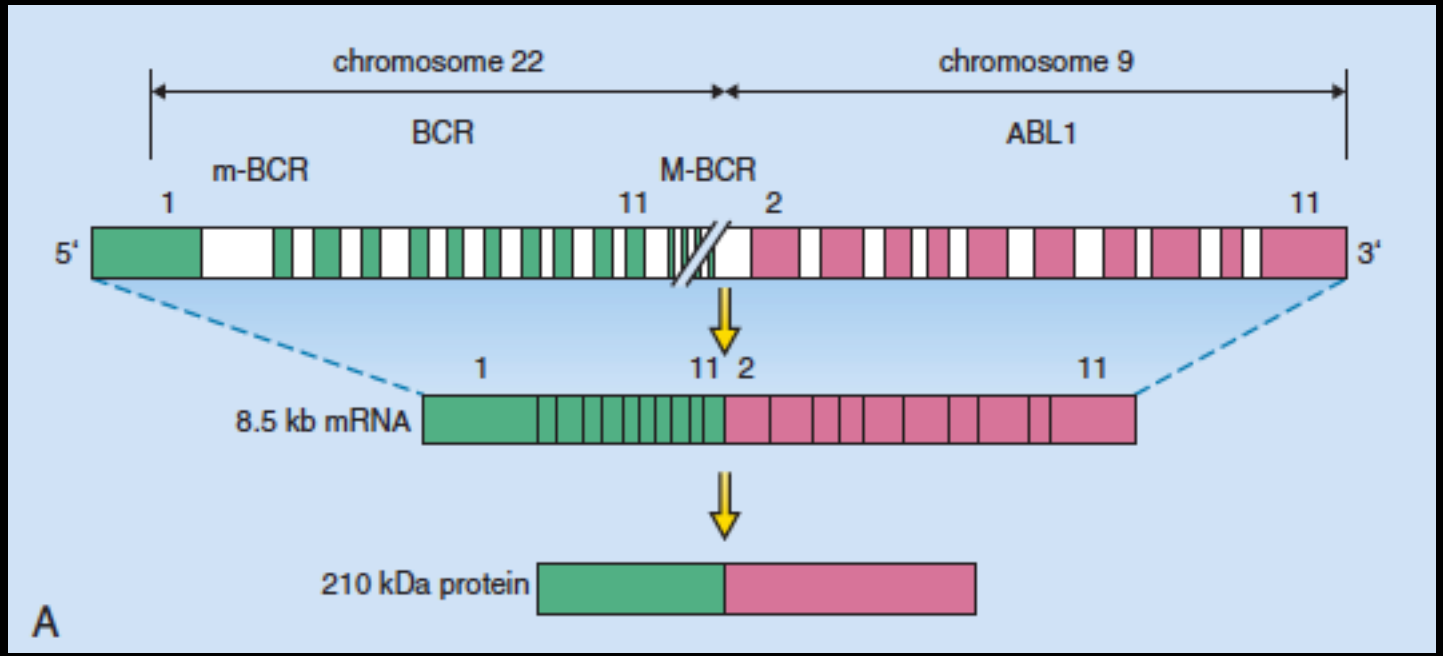

Normal
chromosome 9
Normal
chromosome 22
+
q11.2
(BCR)
q34.1 (C-ABL)
Translocation
t(9;22)
+
(BCR)
(ABL)
Philadelphia
chromosome

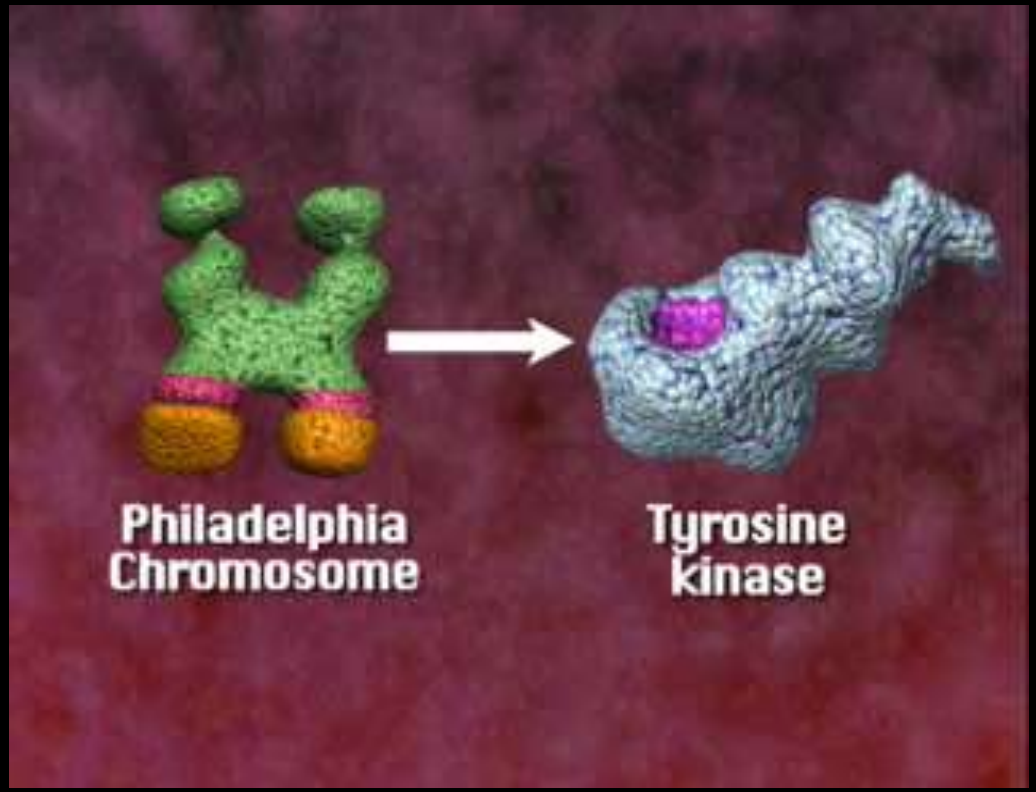

BCR
22
ABL
9

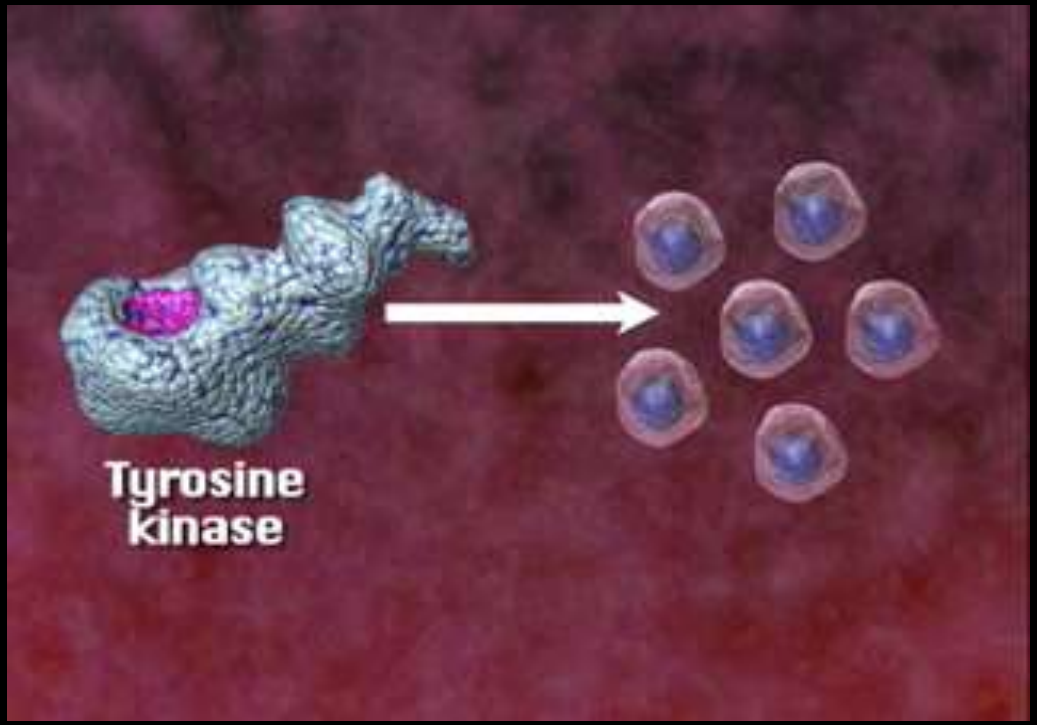

Philadelphia
Chromosome
9


BCR
ABL
Philadelphia
Chromosome

A hybrid gene BCR-ABL is formed on chromosome 22. BCR-ABL codes for a protein called p210 (210 KDa molecular weight). This protein has tyrosine kinase activity and induces myeloid proliferation. There is also an ABL-BCR fusion gene on chromosome 9 but it is of uncertain significance.


chromosome 22
chromosome 9
BCR
ABL1
m-BCR
M-BCR
1
11
2
11
5'
3'
1
11
2
11
8.5 kb mRNA
210 kDa protein
A

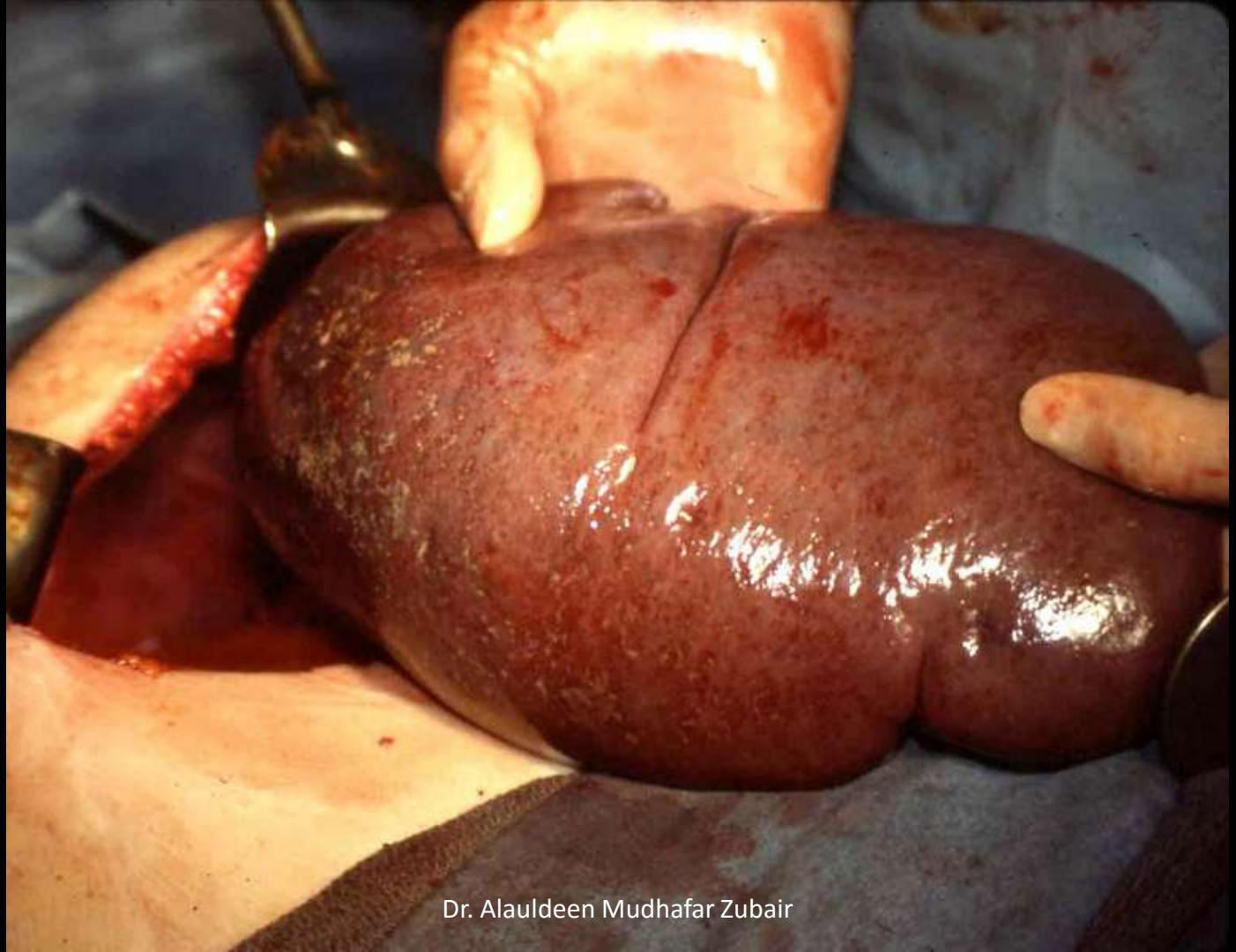

Philadelphia
Chromosome
Tyrosine
kinase

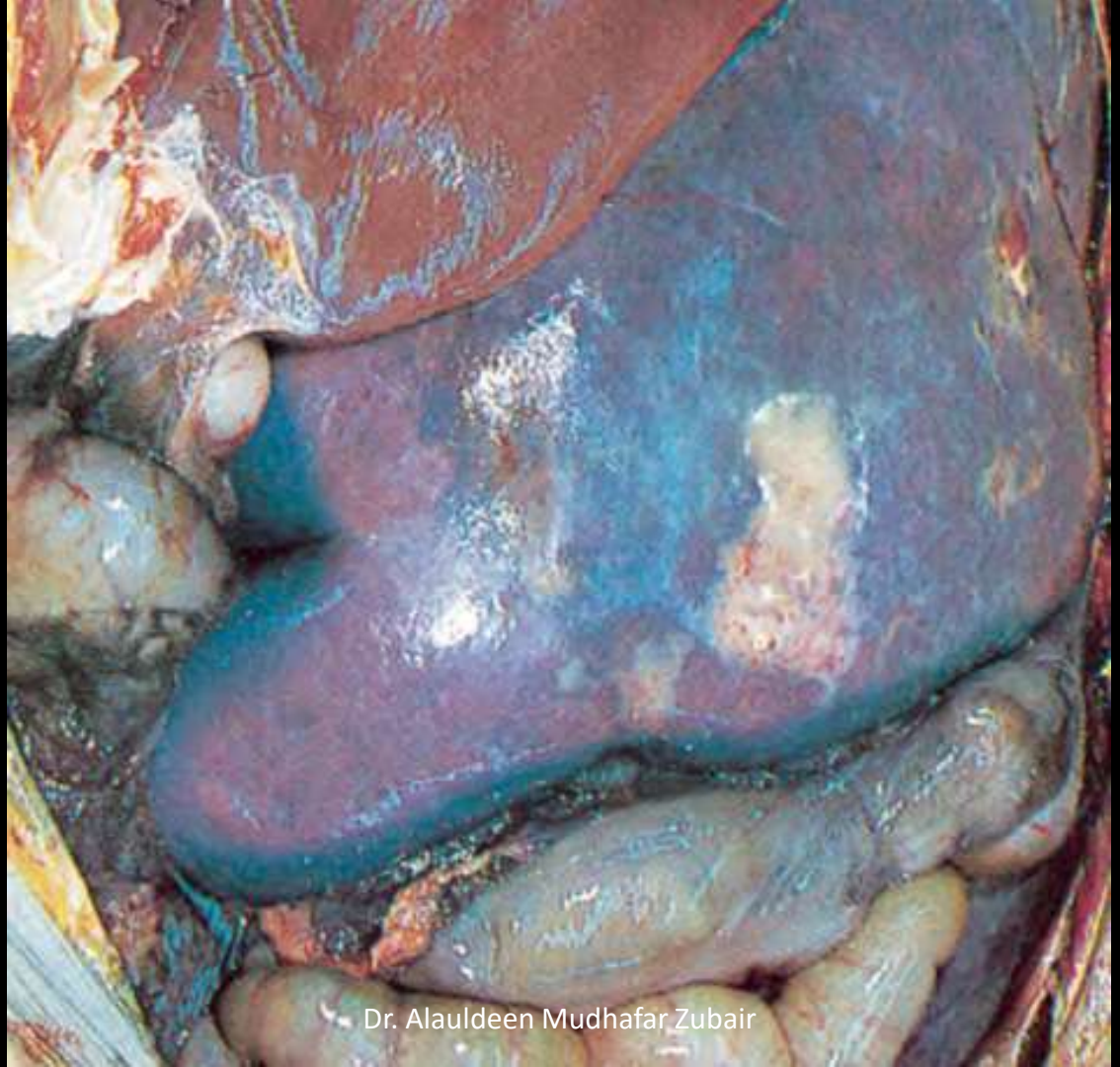

Tyrosine
kinase

Clinical Features:

- In developed countries, about 50% of the patients are discovered during a routine check up. The most common clinical features are:

1) Symptoms related to hypermetabolism e.g.: weight loss, lassitude, anorexia or night sweats.
2) Splenomegaly is nearly always present and is frequently massive. In some patients splenic enlargement is associated with considerable discomfort, pain or indigestion.





3. Features of anemia may include pallor, dyspnea, and tachycardia.
4. Bruising, epistaxis, menorrhagia or hemorrhage from other sites due to abnormal platelet function.
5. Gout or renal impairment due to hyperuricemia from excessive purine breakdown.
6. Rare symptoms include visual disturbance and priapism (hyperviscosity).

Laboratory Findings:

I. Leukocytosis usually > 50 × 10^9/ l and sometimes > 500 × 10^9/ l.

A complete spectrum of myeloid cells is seen in the peripheral blood (normally present only in bone marrow) with predominance of neutrophils and myelocytes.


28250
Blood Transfu

II. Increased circulating basophils and eosinophils in the blood.

III. Platelet count may be increased (most frequently), normal or decreased.

IV. Usually normochromic normocytic anemia.

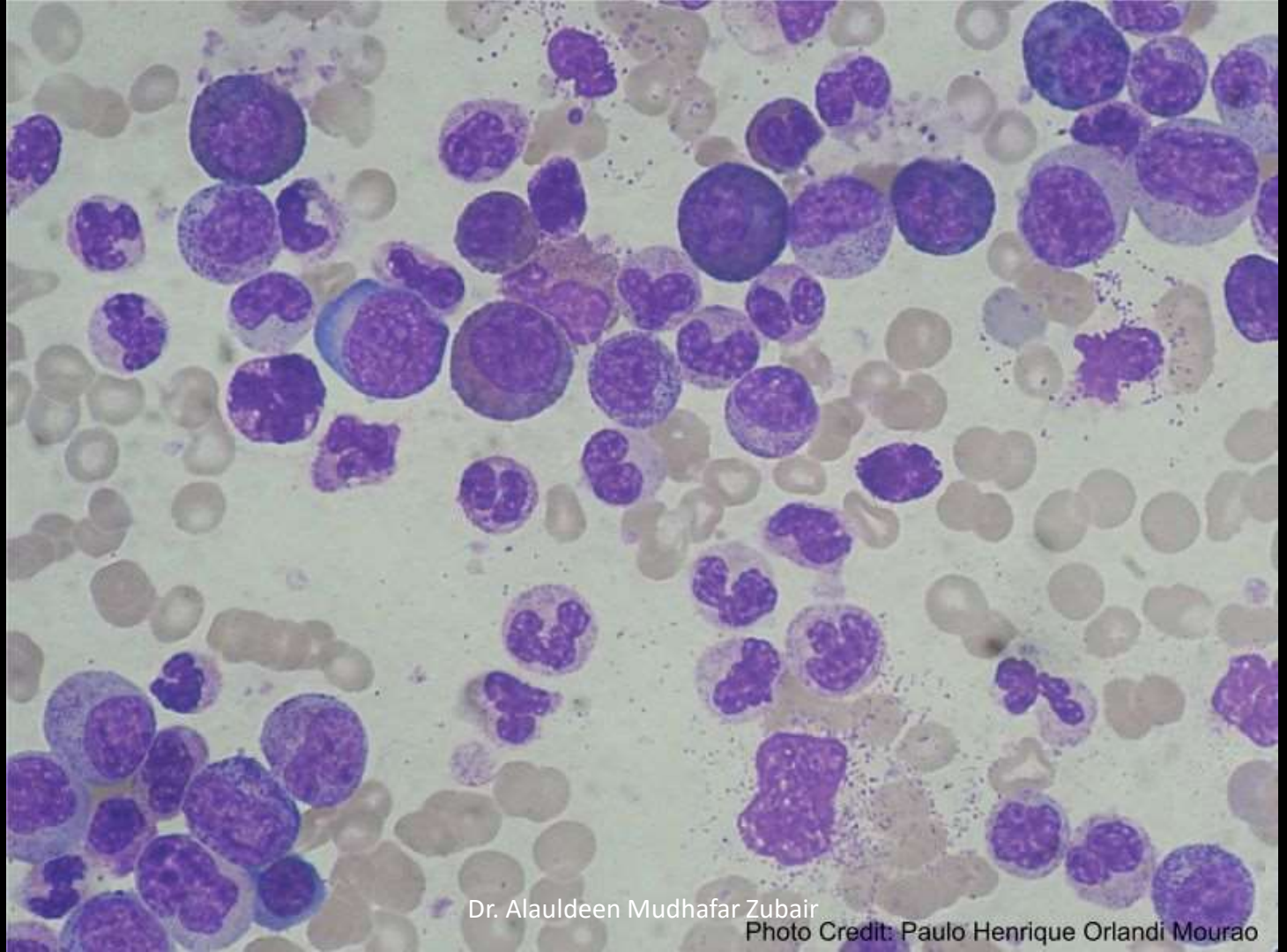
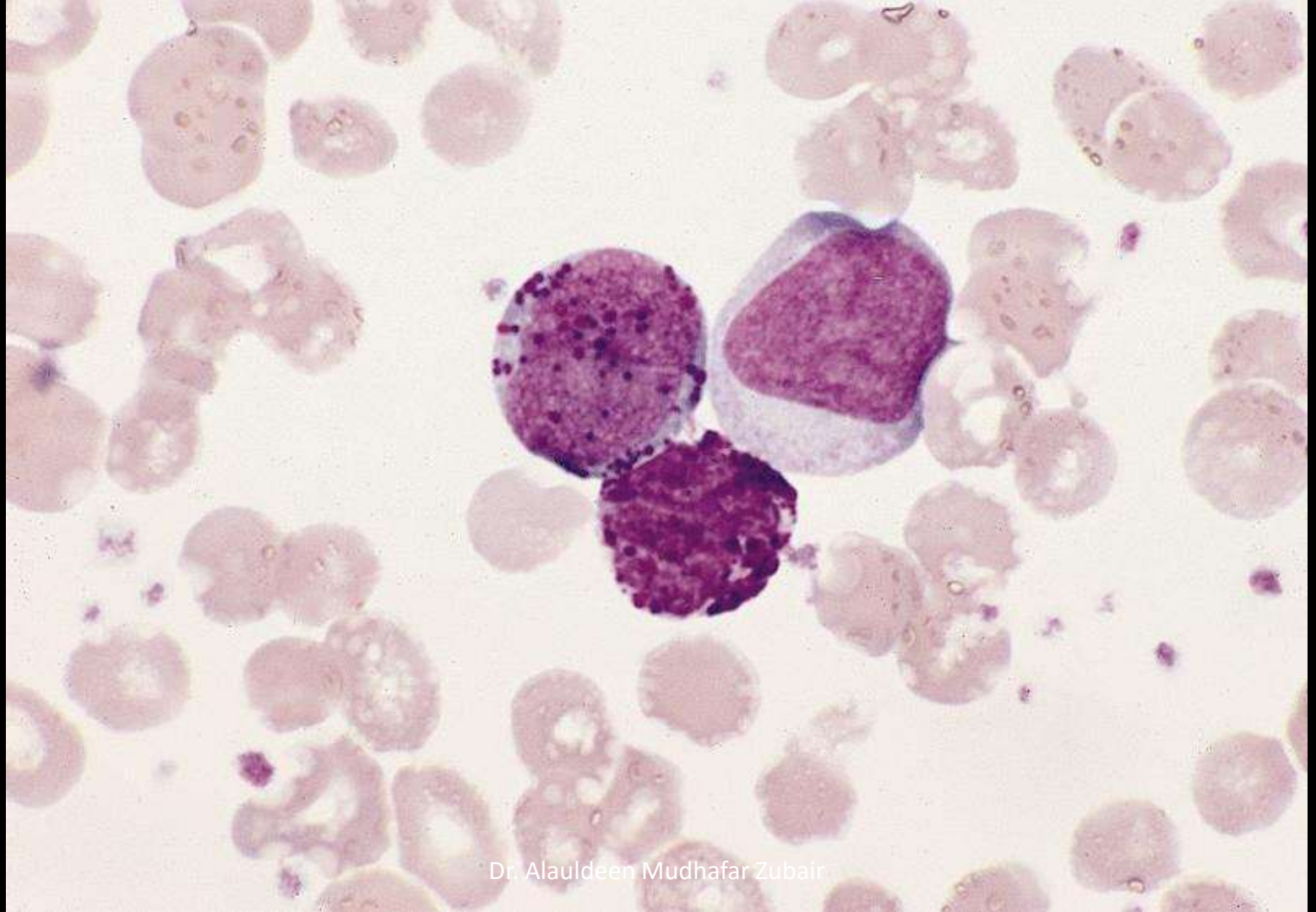
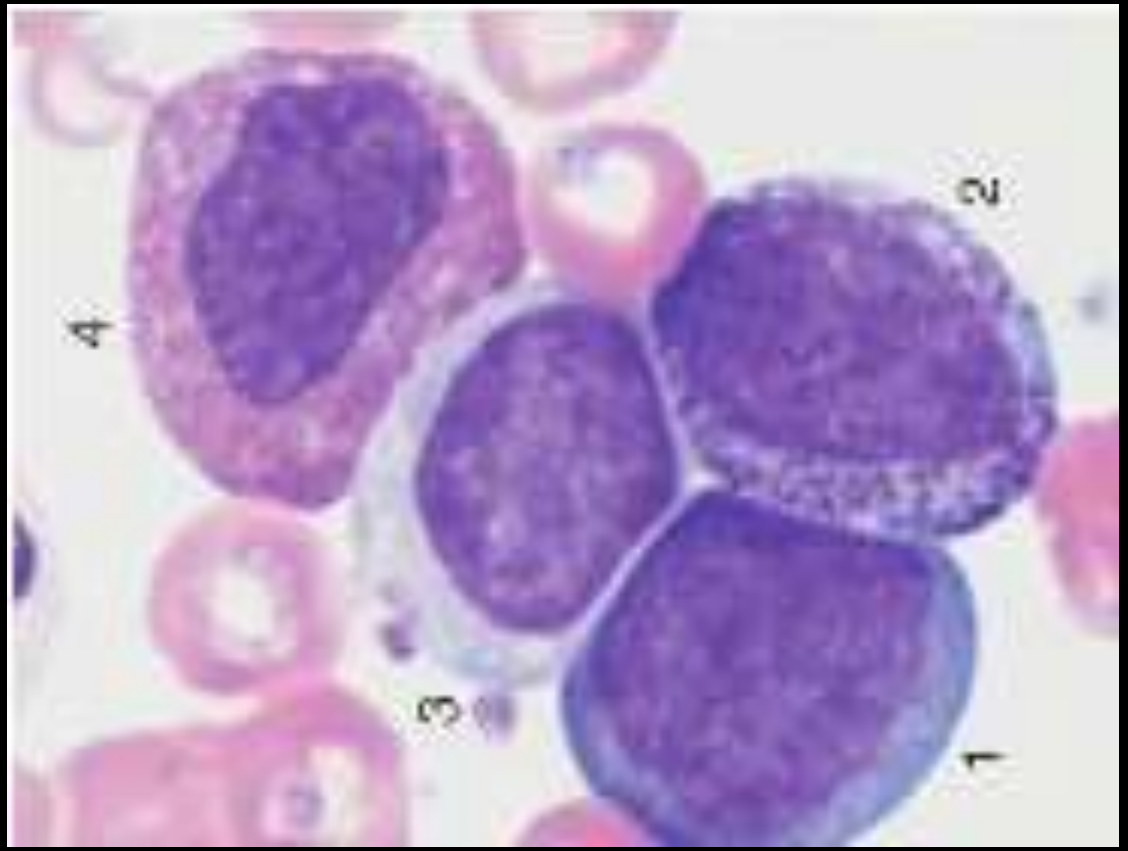


Photo Credit: Paulo Henrique Orlandi Mourao

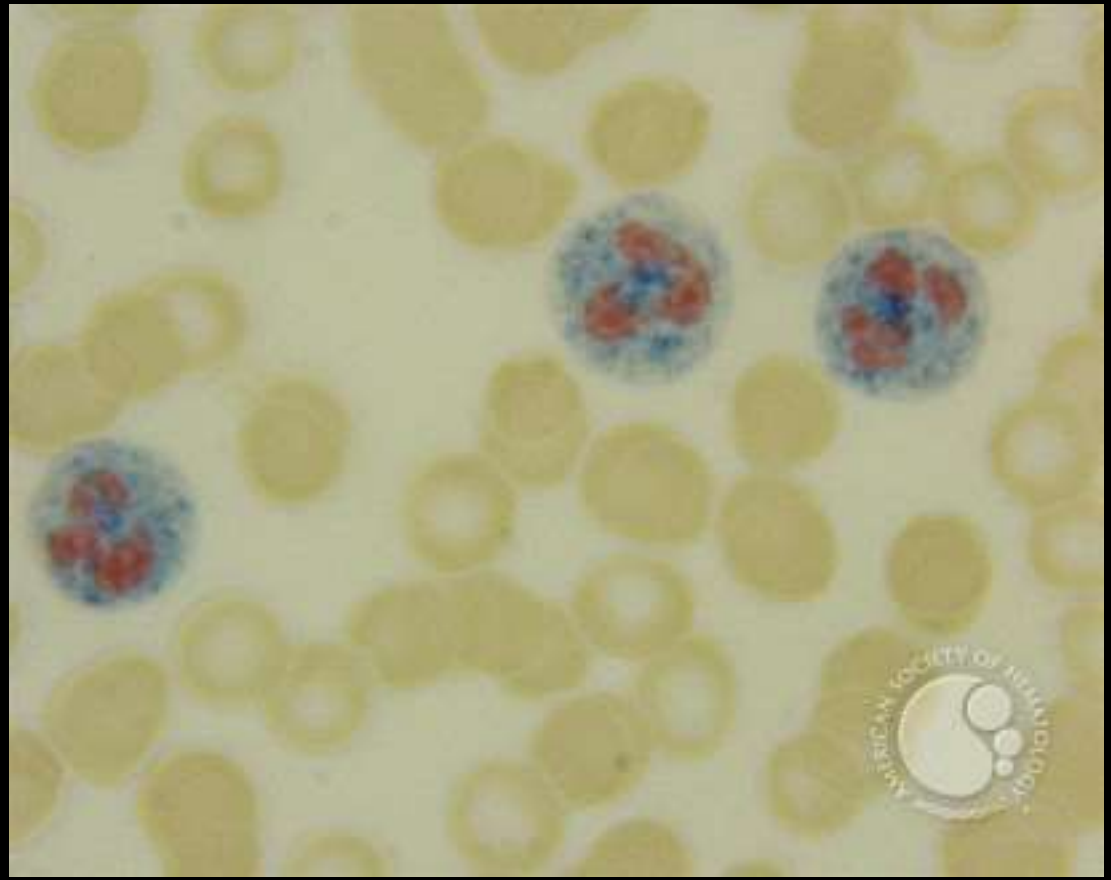



4
3
1

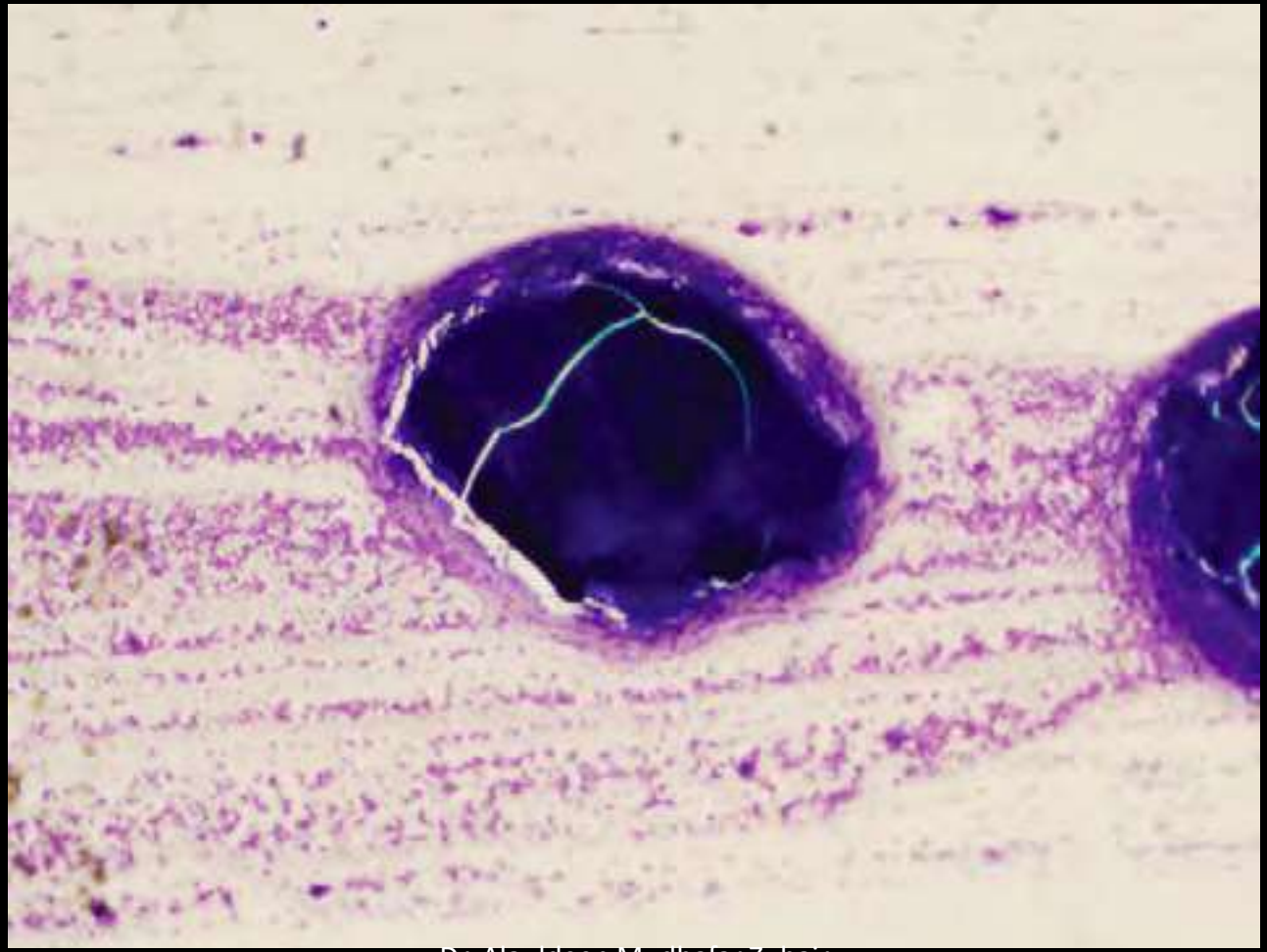
V. Neutrophil alkaline phosphatase score is invariably low.

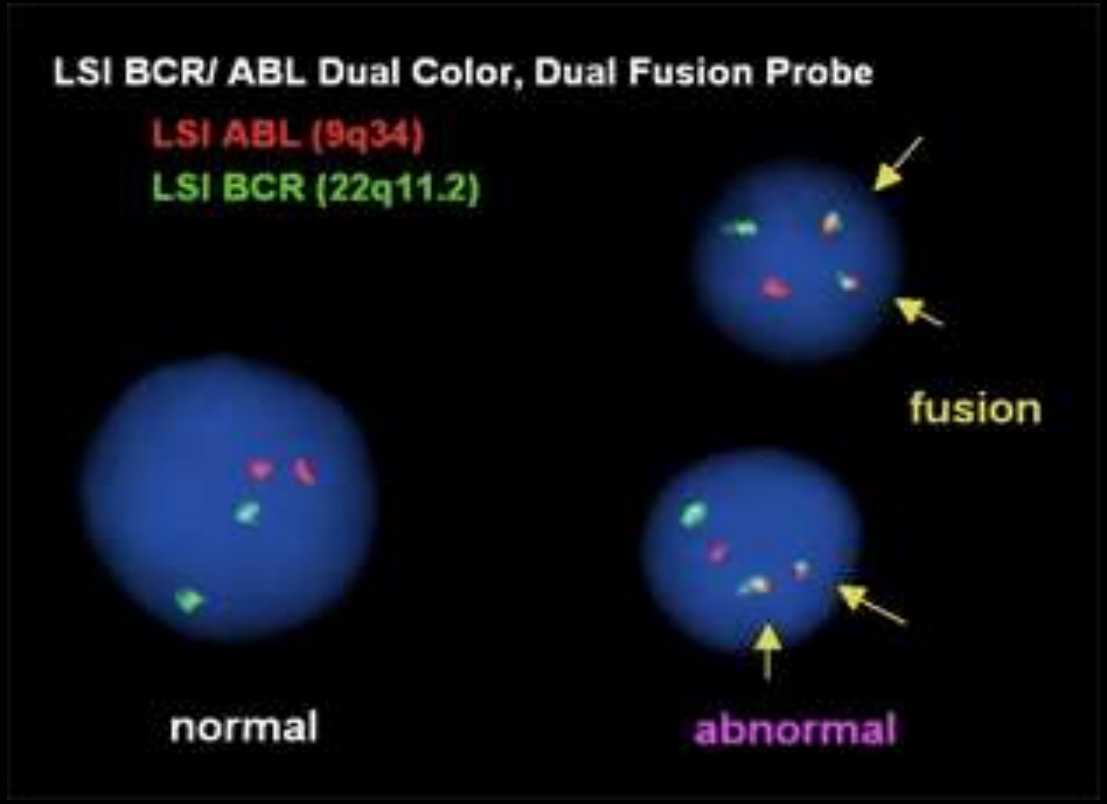
VI. Ph chromosome present on cytogenetic analysis of blood or bone marrow. (or BCR-ABL fusion gene by FISH or PCR).

VII. Bone marrow aspirate: hypercellular with myeloid hyperplasia and greatly increased M:E ratio >10:1.



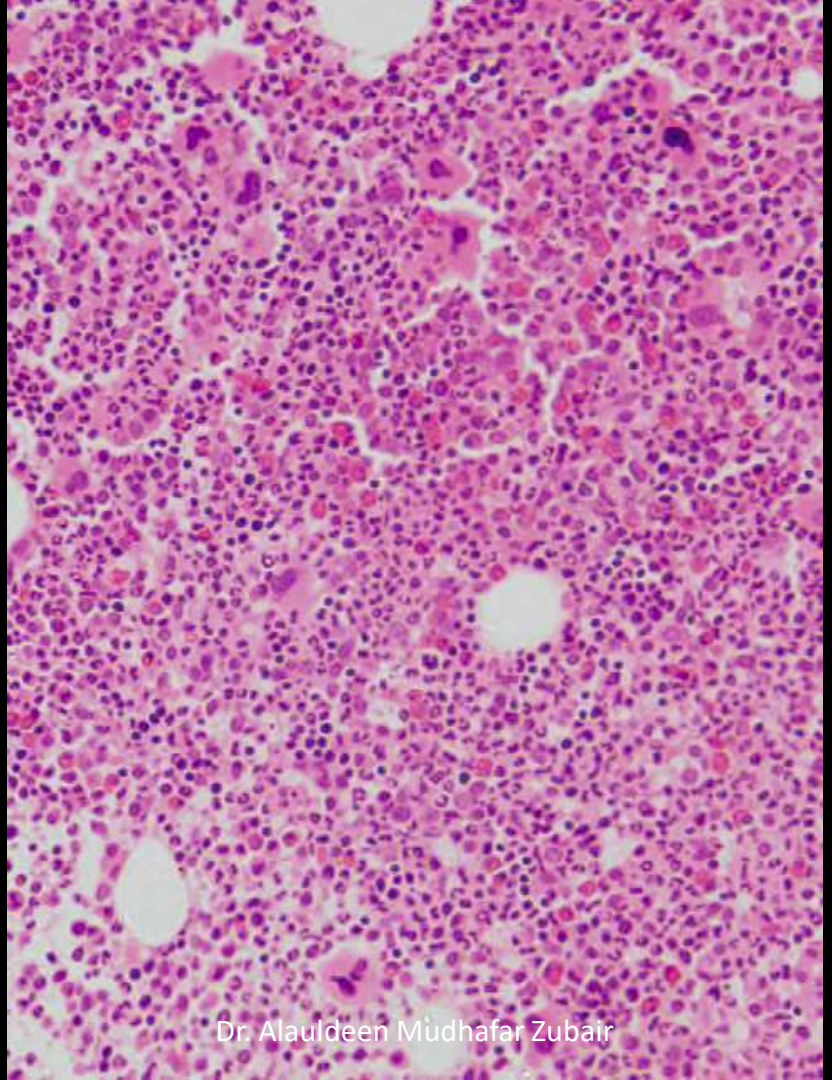
Neutrophil alkaline phosphatase



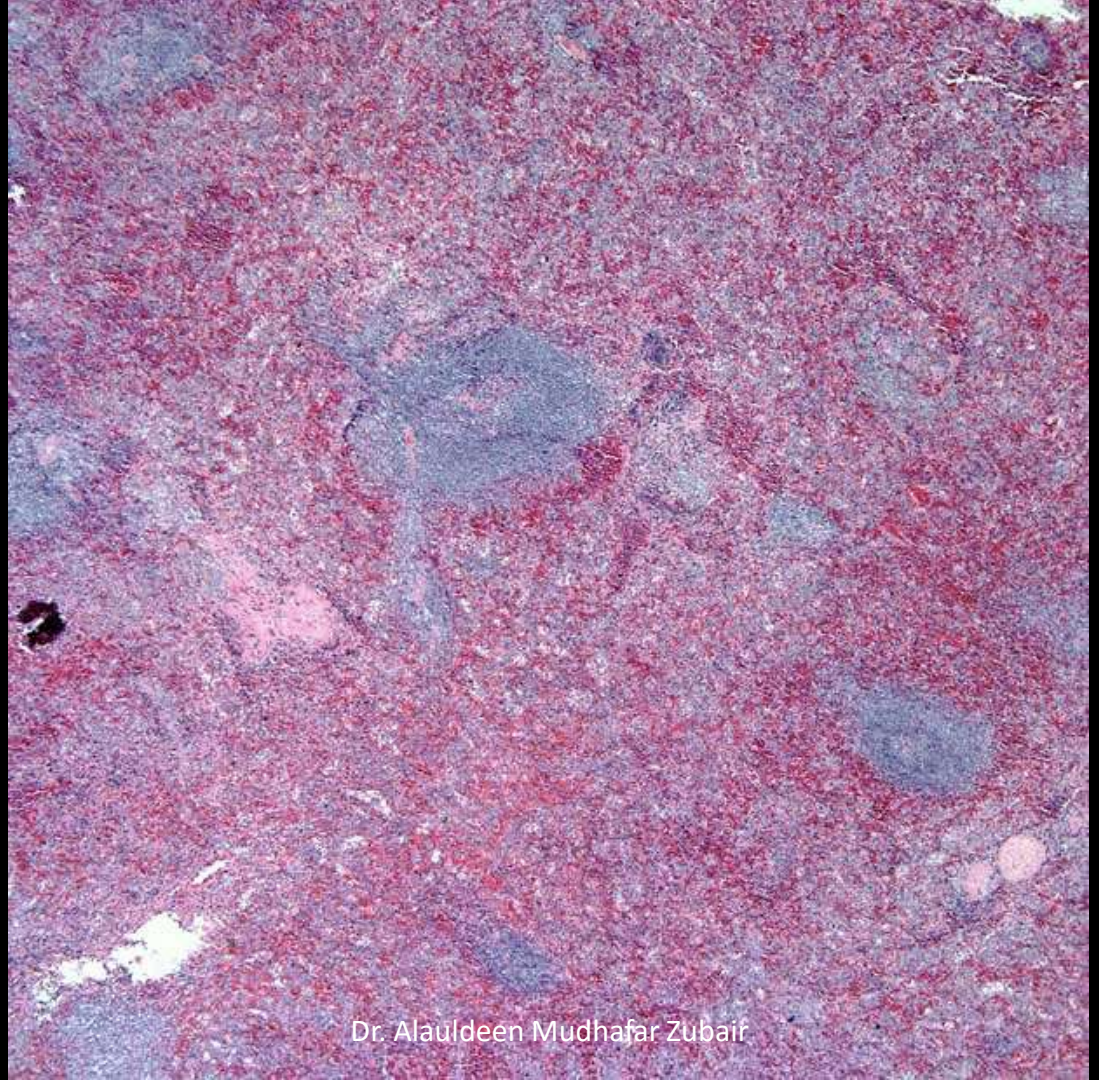

LSI BCR/ ABL Dual Color, Dual Fusion Probe
LSI ABL (9q34)
LSI BCR (22q11.2)
fusion
normal
abnormal

VIII. Bone marrow biopsy: not needed routinely but to exclude acceleration and marrow fibrosis.

- It shows hyperplasia and diminished fat spaces. The number of megakaryocytes is increased with tendency to form clusters.



Splenomegaly is common. The red pulp is diffusely expanded with infiltration of the cords and sinuses filled with mature and immature myeloid cells. The malpighian corpuscles (white pulp) are reduced in size and number or are completely absent

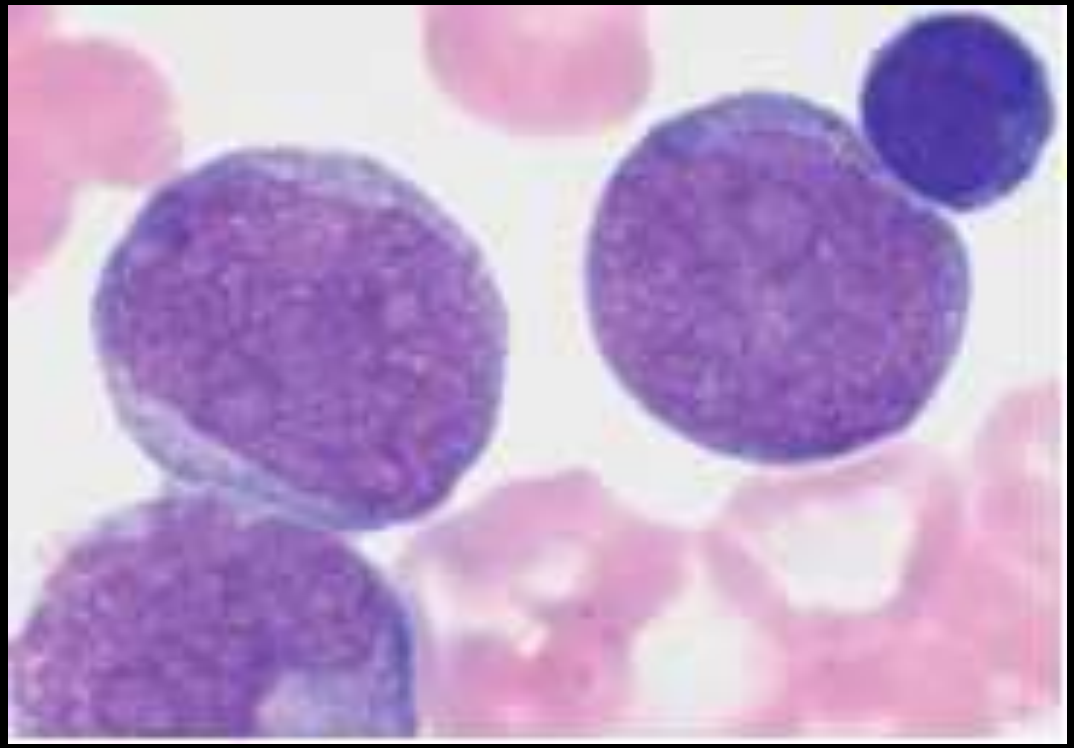


Natural History of CML:

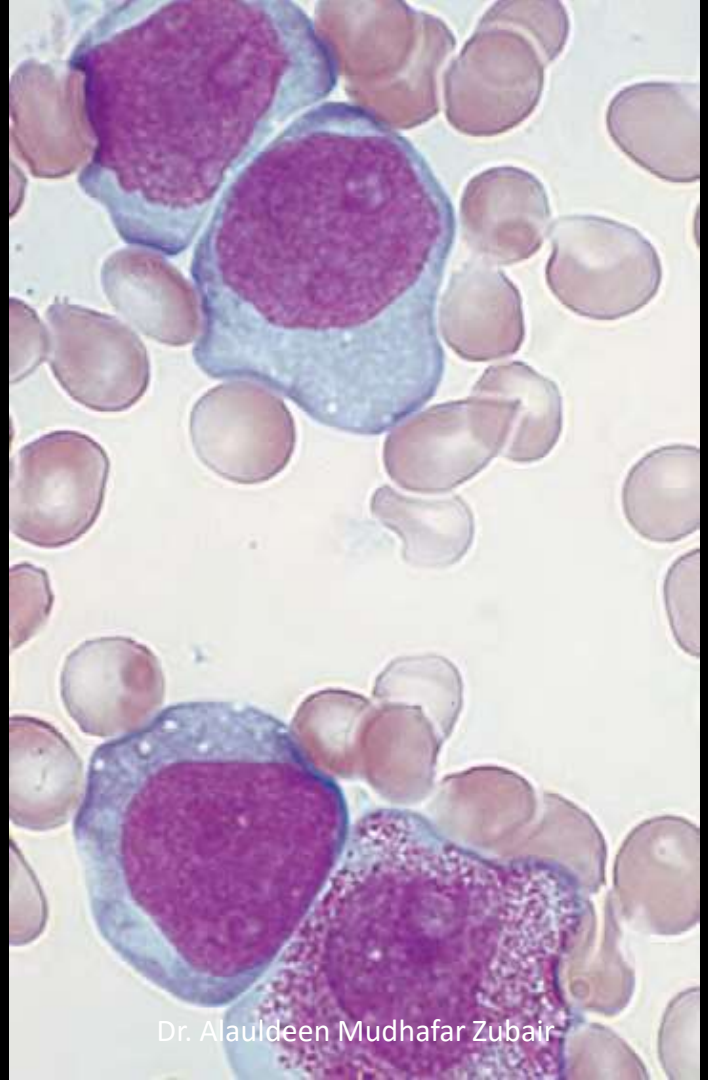
The chronic phase lasts typically or 2-7 years, but it may last more. In about 50% of patients the chronic phase transforms abruptly to a more aggressive phase called **blast crisis** or **blast transformation** (Acute Leukemia).

- According to the recommendation of WHO, the diagnosis of CML in blast crisis (CML-BC) is made when:

1. Blasts are 20% of bone marrow nucleated cells or peripheral blood differential count.
2. Large foci or clusters of blasts are present in the bone marrow biopsy sections.
3. There is evidence of extramedullary tissue infiltration by blast cells.



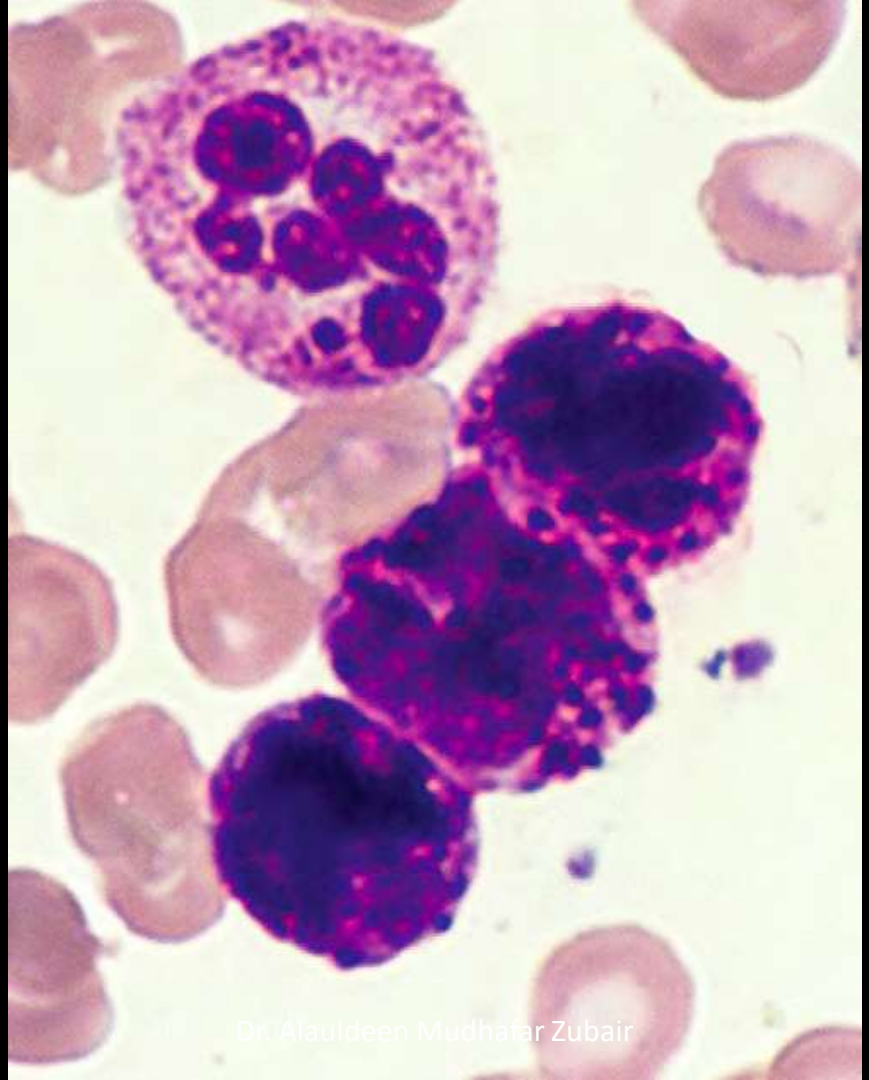
Blast crisis of CML



- In the other 50%, the disease evolves more gradually through an intermediate phase called **acceleration** which may last months or occasionally years before frank blast transformation.

- **Accelerated phase** of CML is often associated with a decline in the patient's clinical condition along with certain laboratory findings.
- The diagnosis of CML in accelerated phase (CML-AP), according to the WHO recommendation, is based on the presence of one or more of the following:

1. The presence of 10–19% blasts in blood or bone marrow samples.
2. Basophilia of 20%.
3. Persistent thrombocytopenia of 100,000/µL or thrombocytosis of 1,000,000/µL.
4. Progressive splenomegaly and/or increasing leukocyte count.
5. Cytogenetic or molecular evidence of clonal evolution.



Chronic Lymphocytic Leukemia (CLL)

CLL is a chronic B-lymphoproliferative disorder. It accounts for about 25% of all leukemias. In adults over the age of 50 years, it is the most common form, particularly in the west. Its incidence is 3/100000/year.

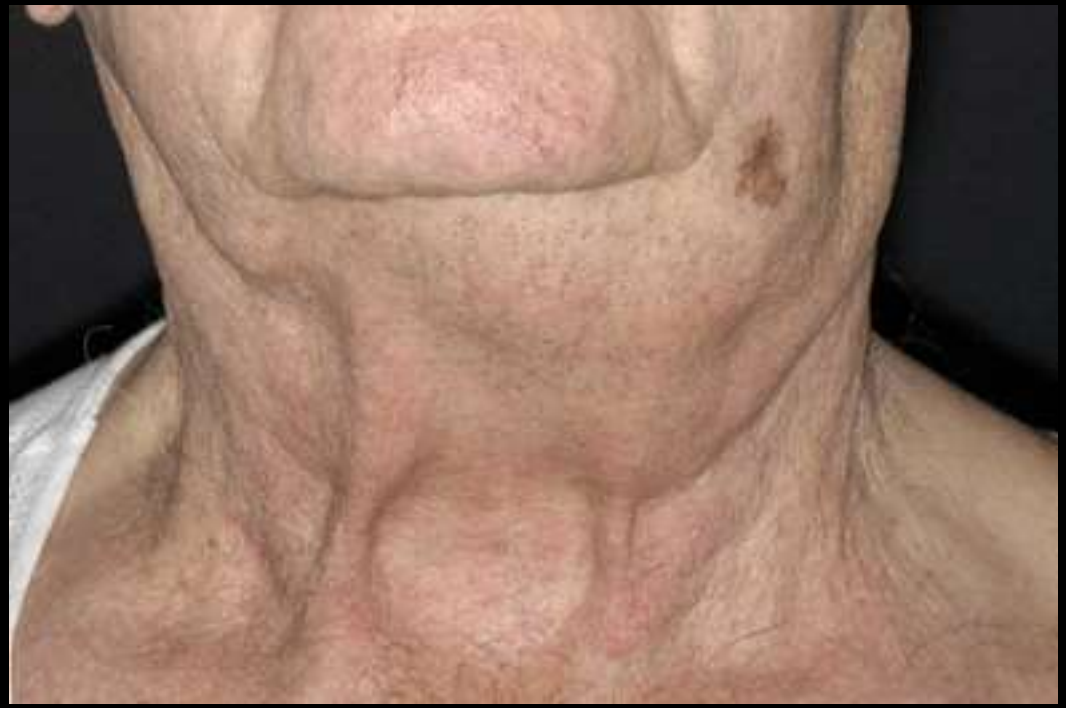
- It is the most common of the lymphoproliferative disorders accounting for 80% of cases.
- CLL affects in 2:1 male: female ratio, with a peak incidence between 60 & 80 years. It is rarely diagnosed below the age of 40 years.

Of all the leukemias, CLL has the highest familial incidence, which can be documented in 2% of patients.

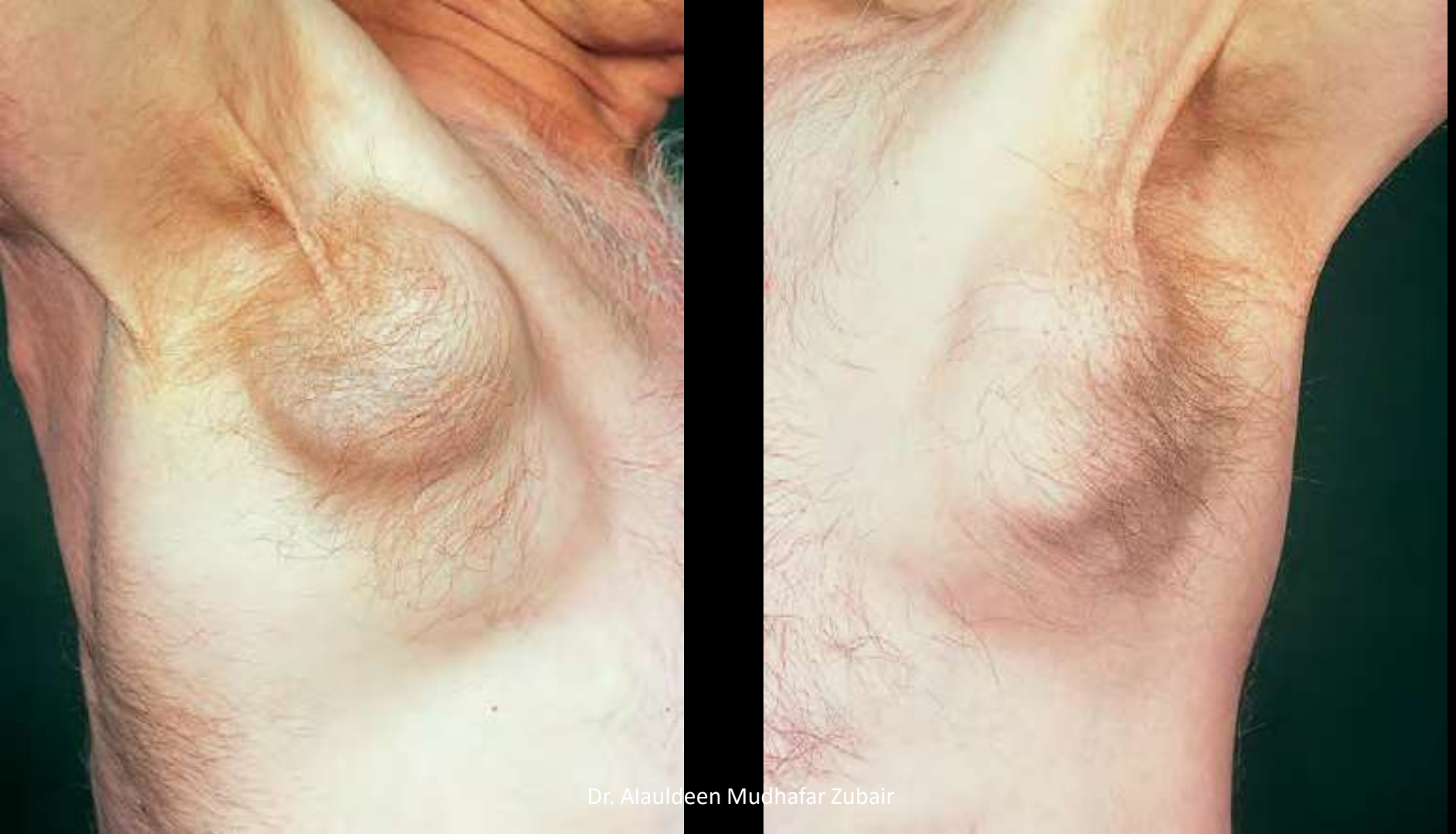
Pioneering work independently developed by Dameshek and Galton in the 1960s introduced the concept of CLL as a progressive accumulation of immunologically incompetent lymphocytes, starting in lymph nodes and/or the bone marrow and gradually expanding to most haemopoietic organs.

Clinical Features:

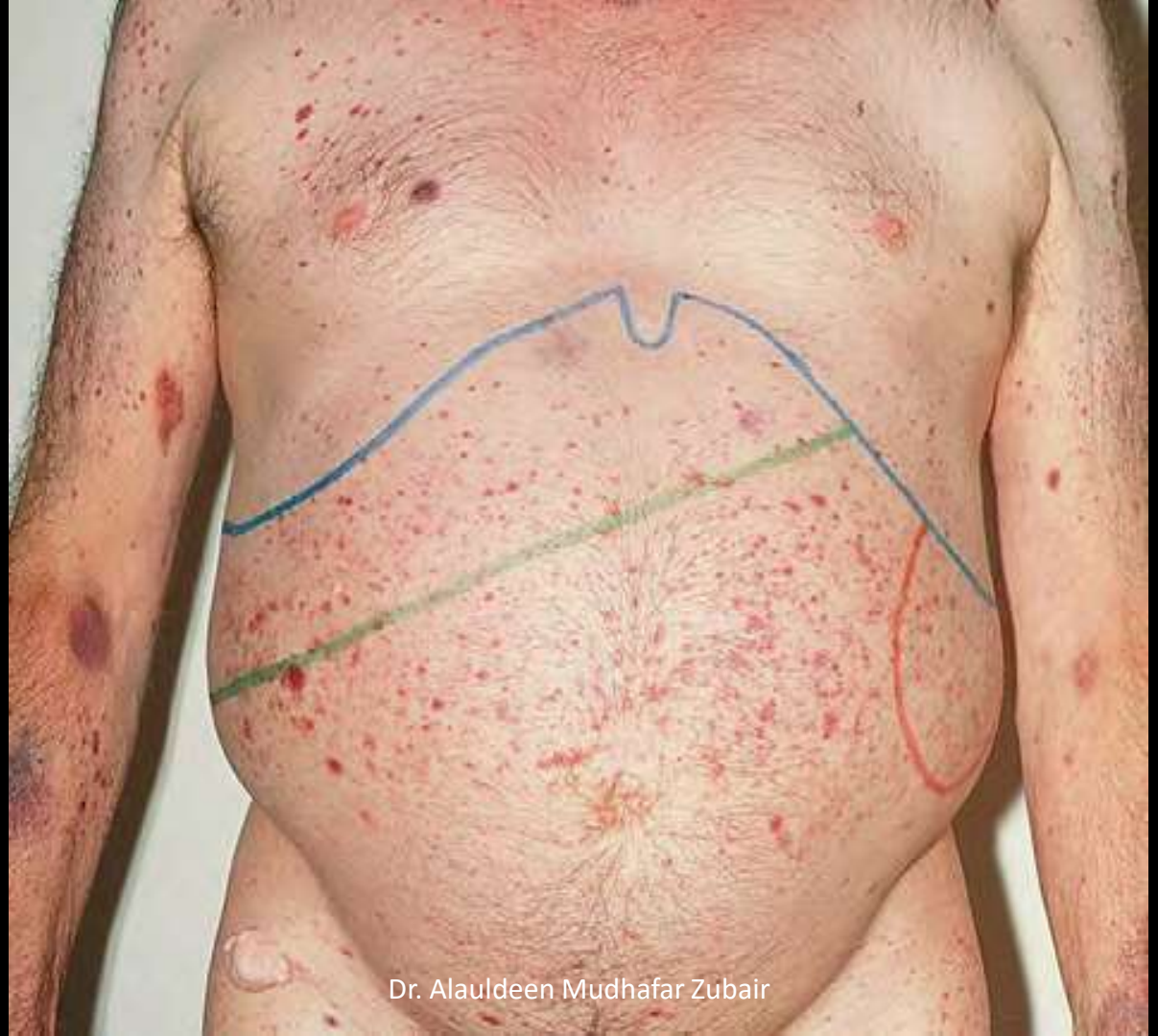
1. The disease is diagnosed by chance in 30% of patients.
2. Lymphadenopathy: Symmetrical enlargement of superficial lymph nodes is found in many patients. The nodes are usually discrete and non-tender.

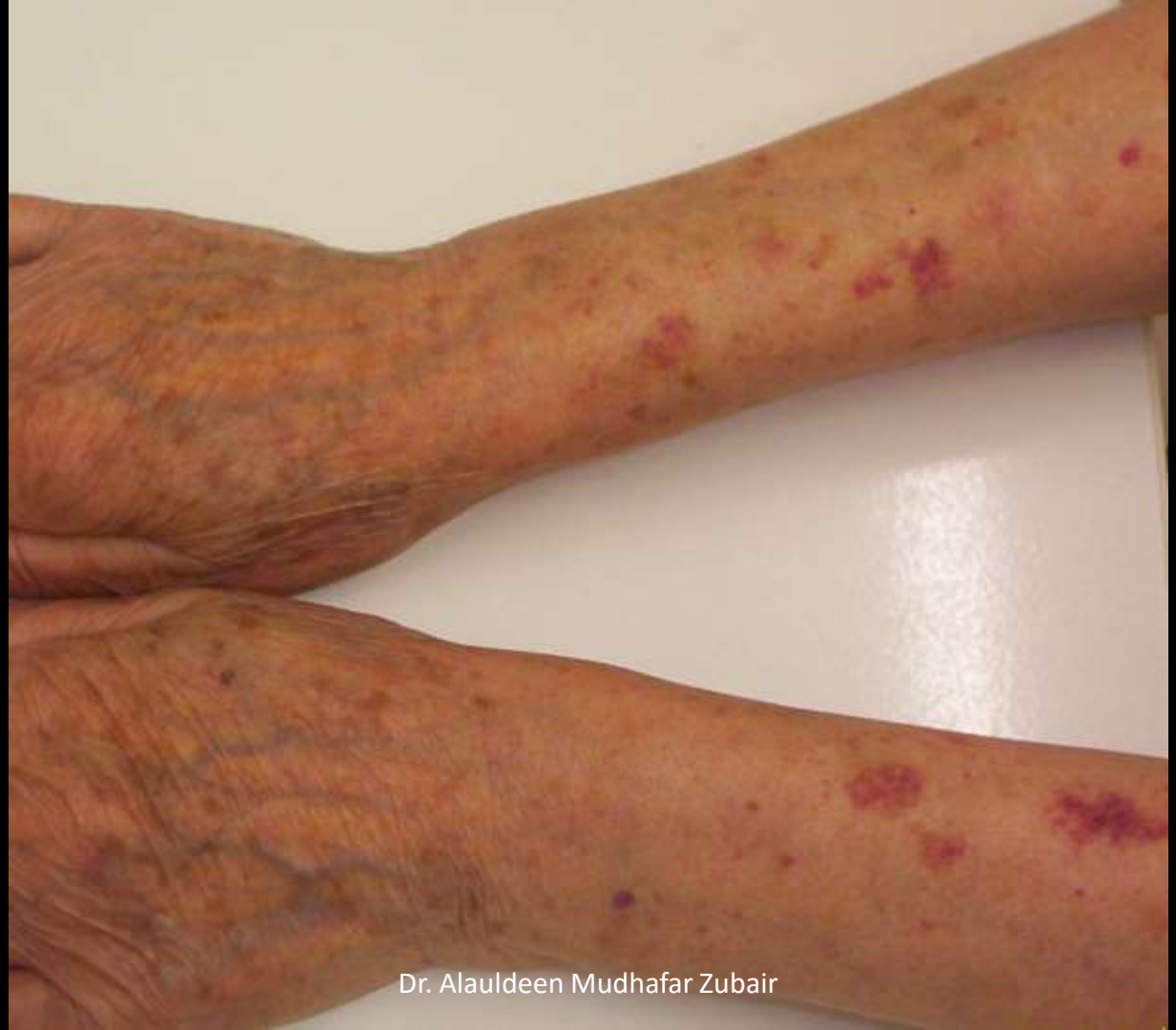


Cervical lymphadenopathy

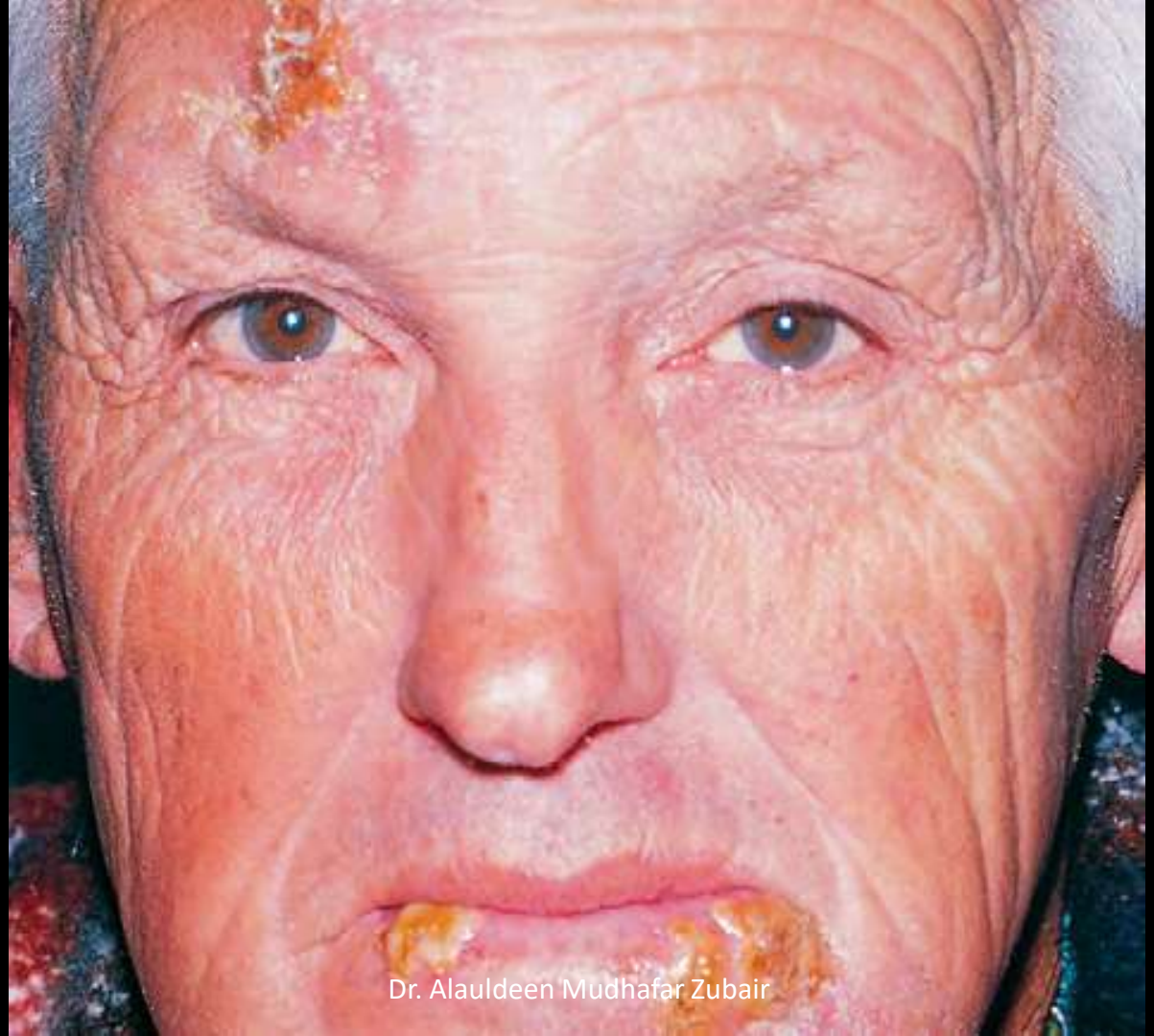


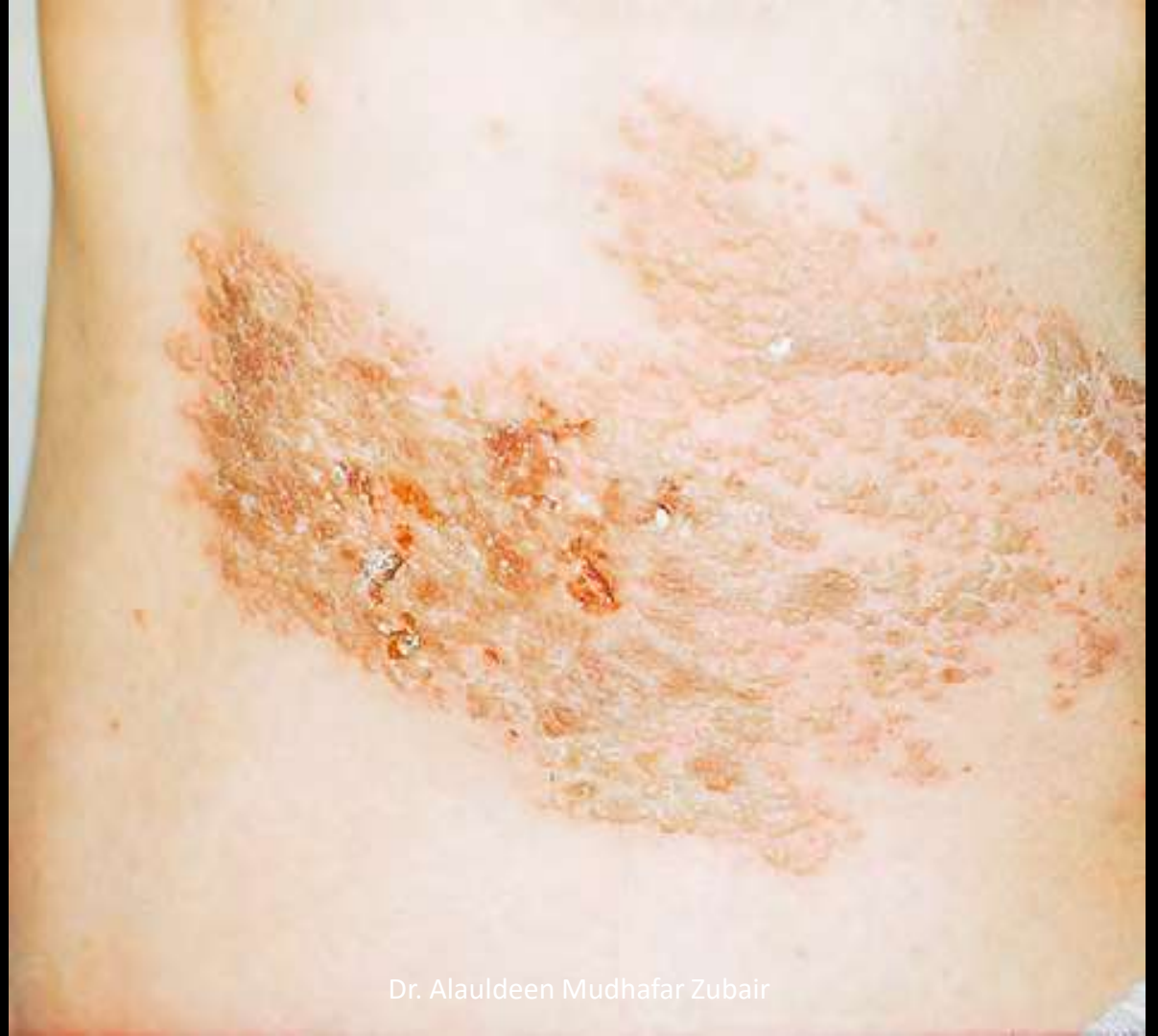
3. Features of anemia may be present e.g.: pallor & dyspnea. Causes: marrow infiltration, autoimmune hemolytic anemia, bleeding.
4. Splenomegaly and hepatomegaly are usual in later stages.
5. Patients with thrombocytopenia may show bruising or purpura.

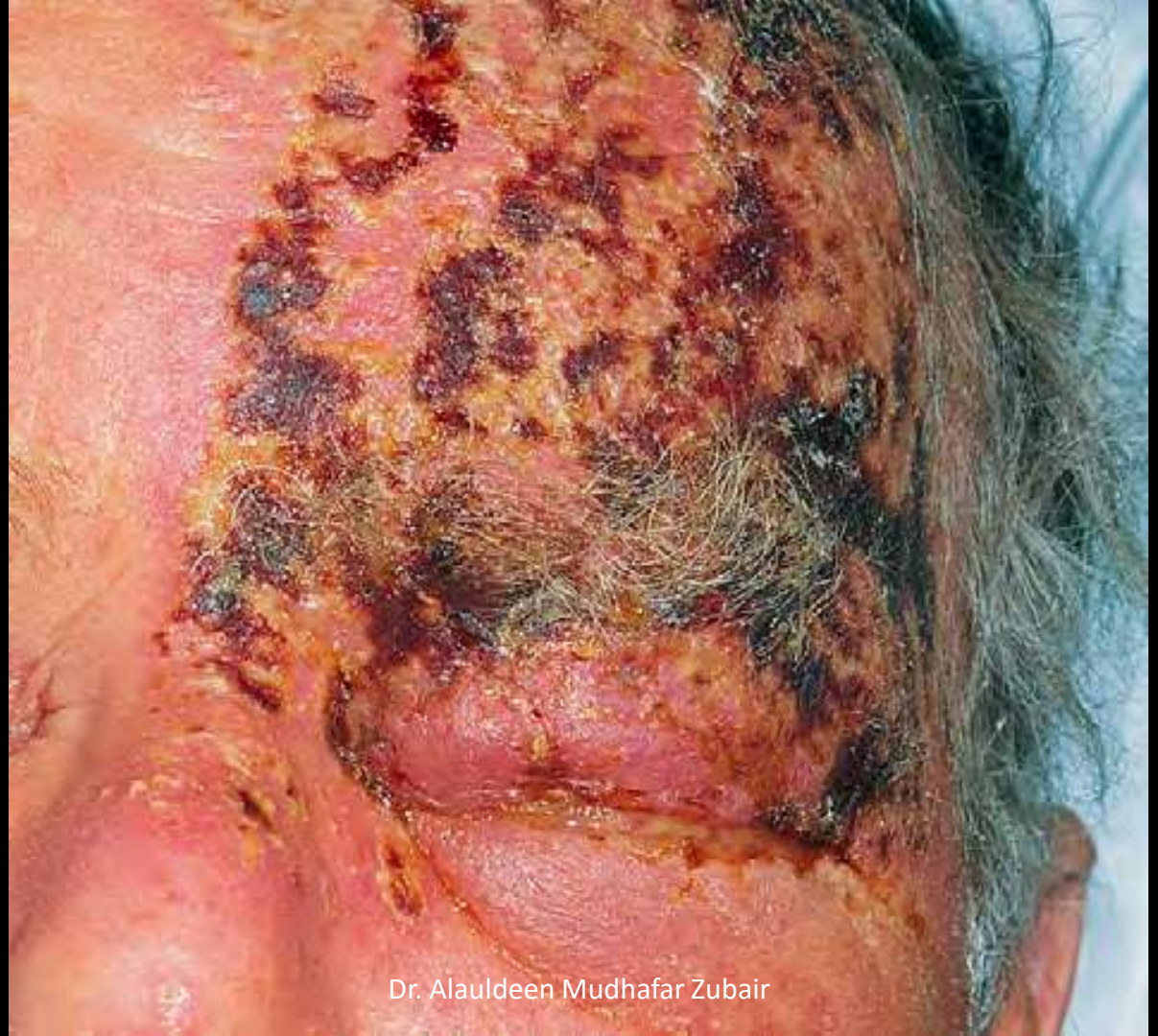


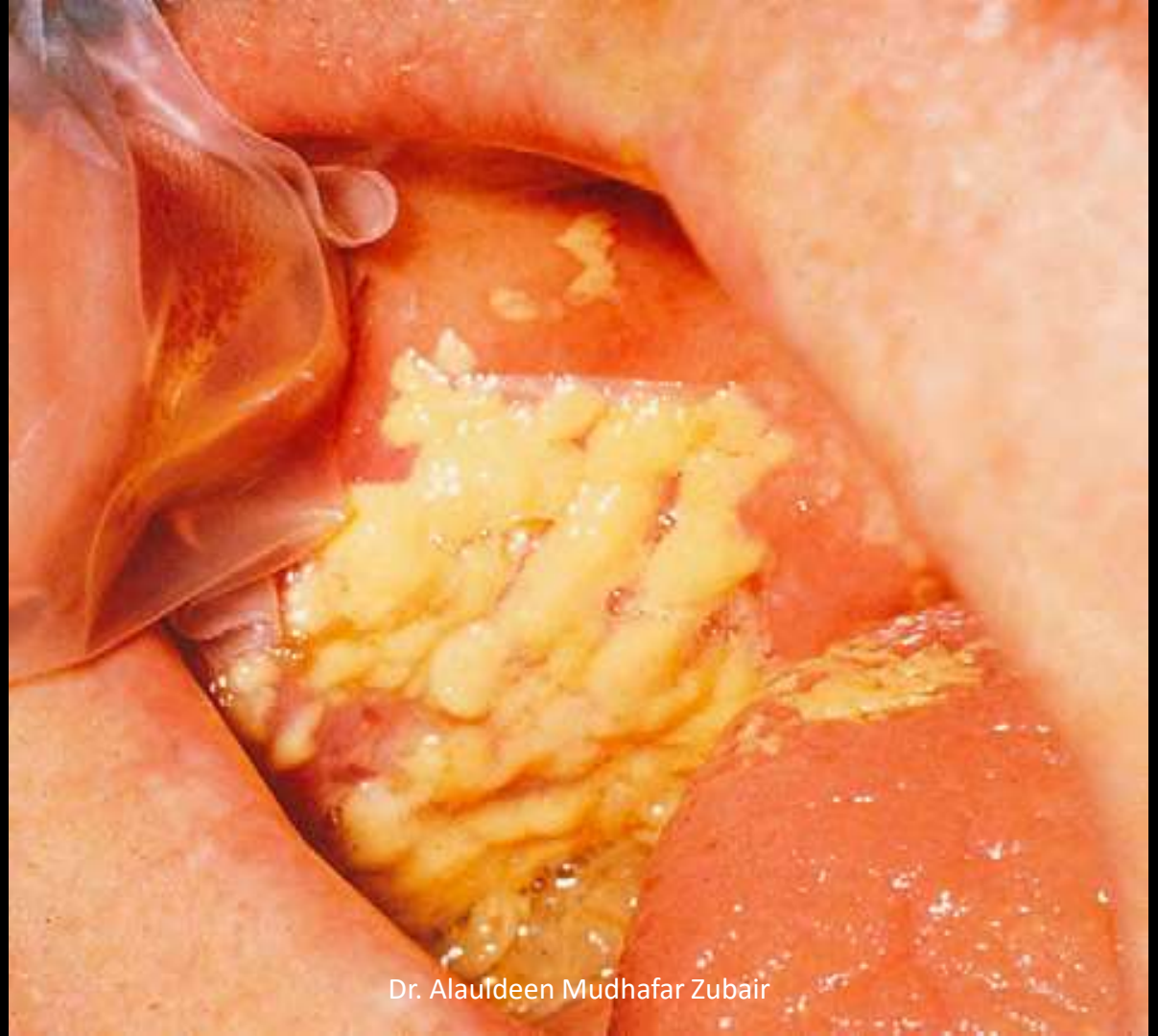


6. Bacterial and fungal infections are common in later stages because of the deficiency of normal immunoglobulins and neutropenia (due to marrow infiltration, chemotherapy or hypersplenism). There is also association with herpes zoster.

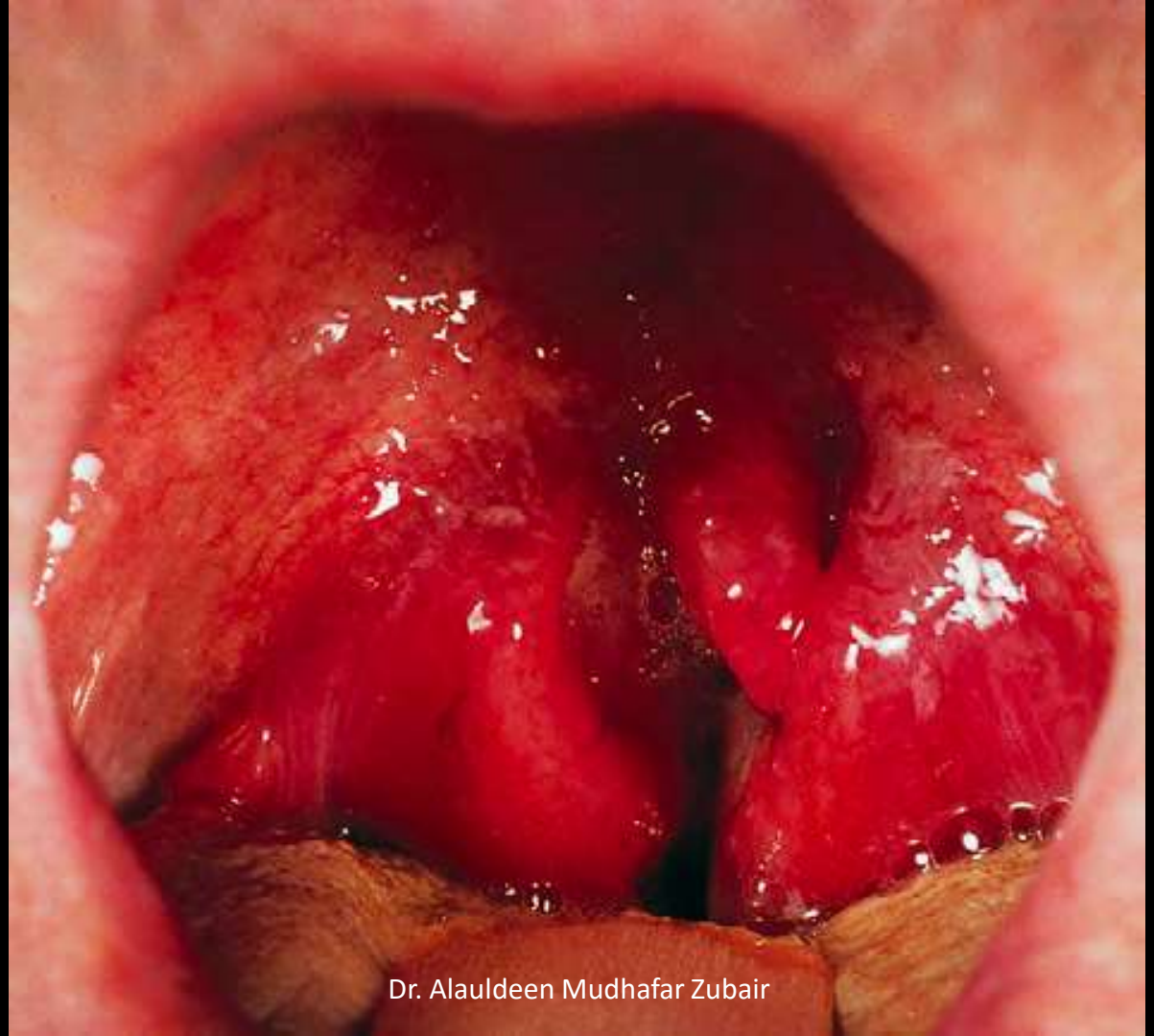








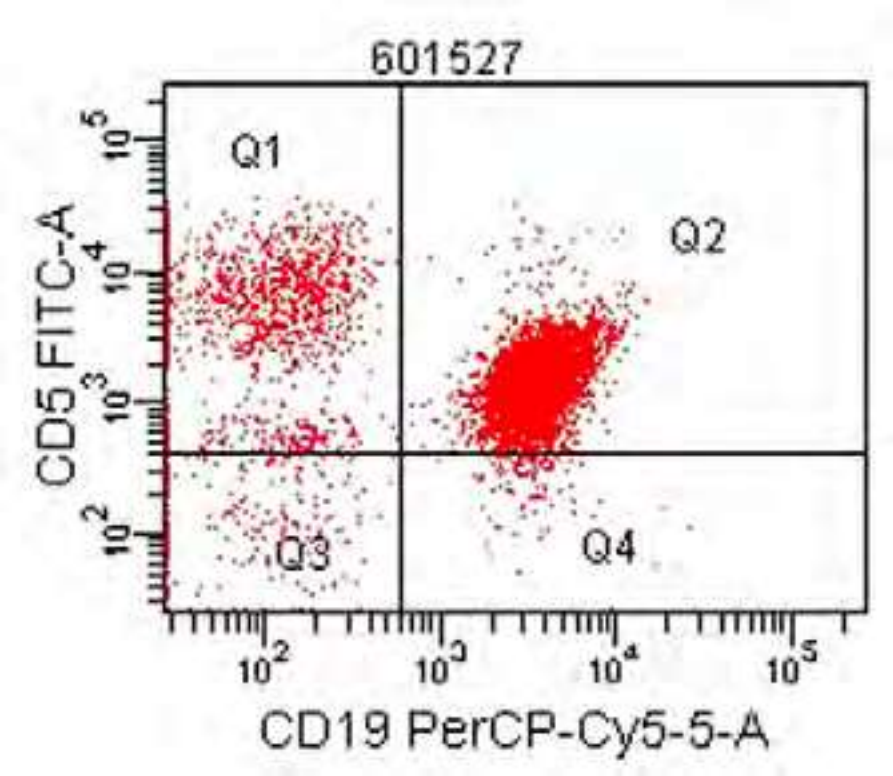
7. Skin infiltration is present in a small number of patients.
8. Tonsillar enlargement may be a feature. Involvement of the salivary and lacrimal glands (Mikulicz's Syndrome) is a rare presentation.



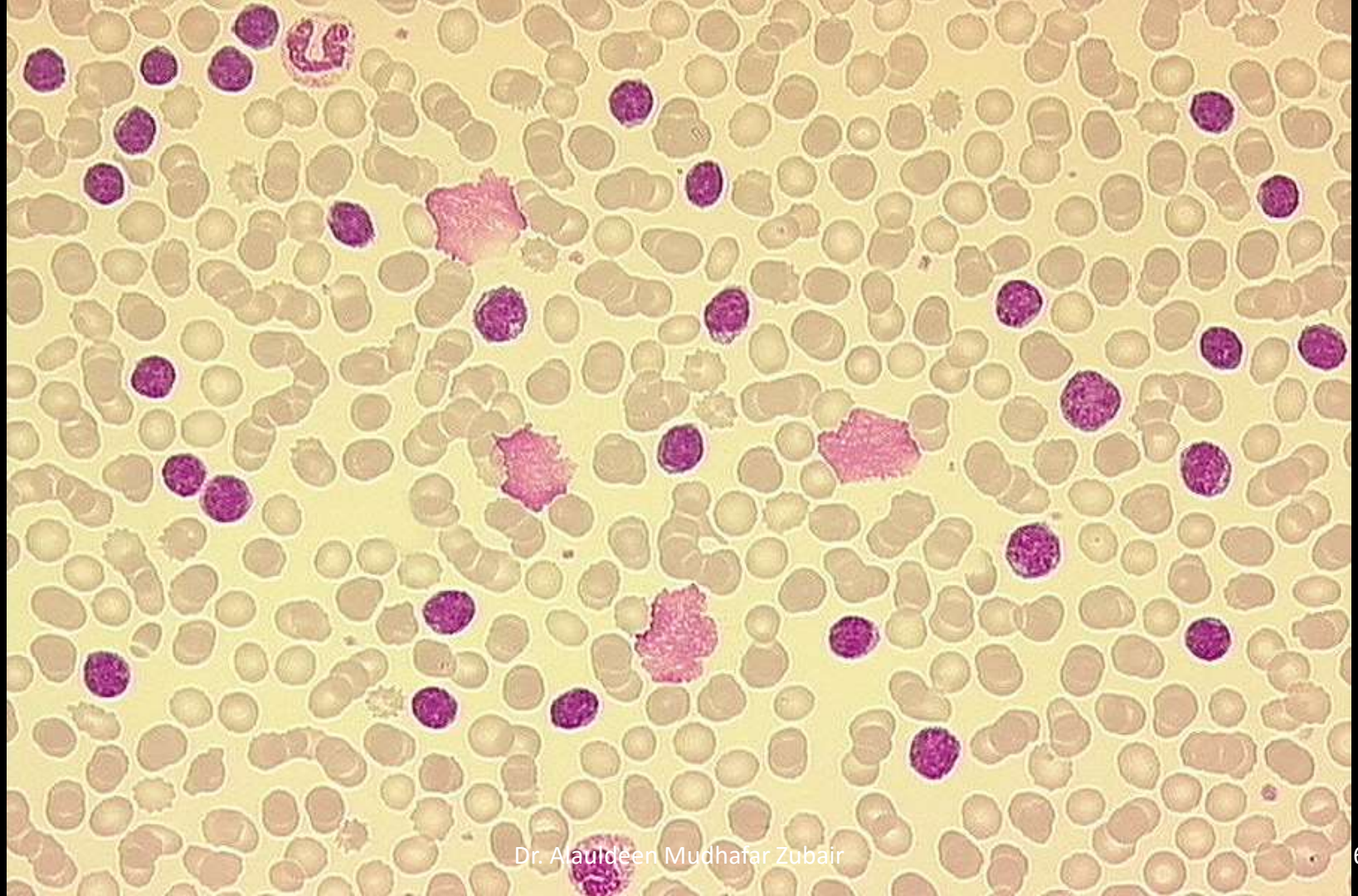
Laboratory findings:

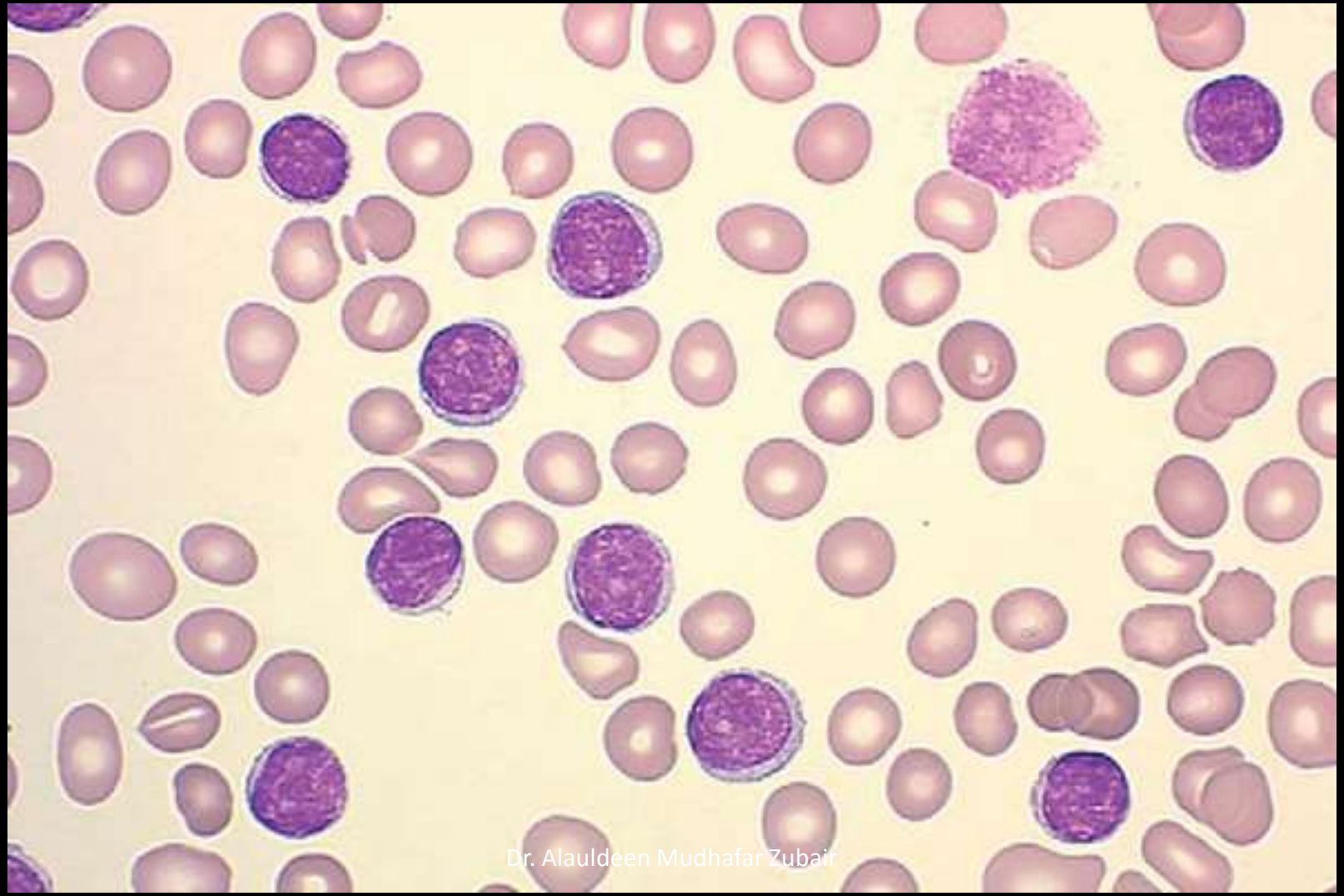
1) **Lymphocytosis:** there is absolute lymphocytosis **>** 5×10^9/liter and may be up to 300×10^9/liter or more. The lymphocytes, in the blood film are small mature looking lymphocytes. There are many smudge (smear) cells in the film but they are not specific for CLL. Immunophenotyping of the lymphocytes shows them to be B-cells.

- Diagnosis is based on the finding of absolute lymphocytosis with appropriate phenotype i.e.: B cells (CD20+, CD19+, CD23+, CD5+ weak sIg). They Express restricted kappa or lambda light chain surface Ig, confirming monoclonality.


601527
Q1
Q2
Q3
Q4
CD5 FITC-A
CD19 PerCP-Cy5-5-A
10^2
10^3
10^4
10^5

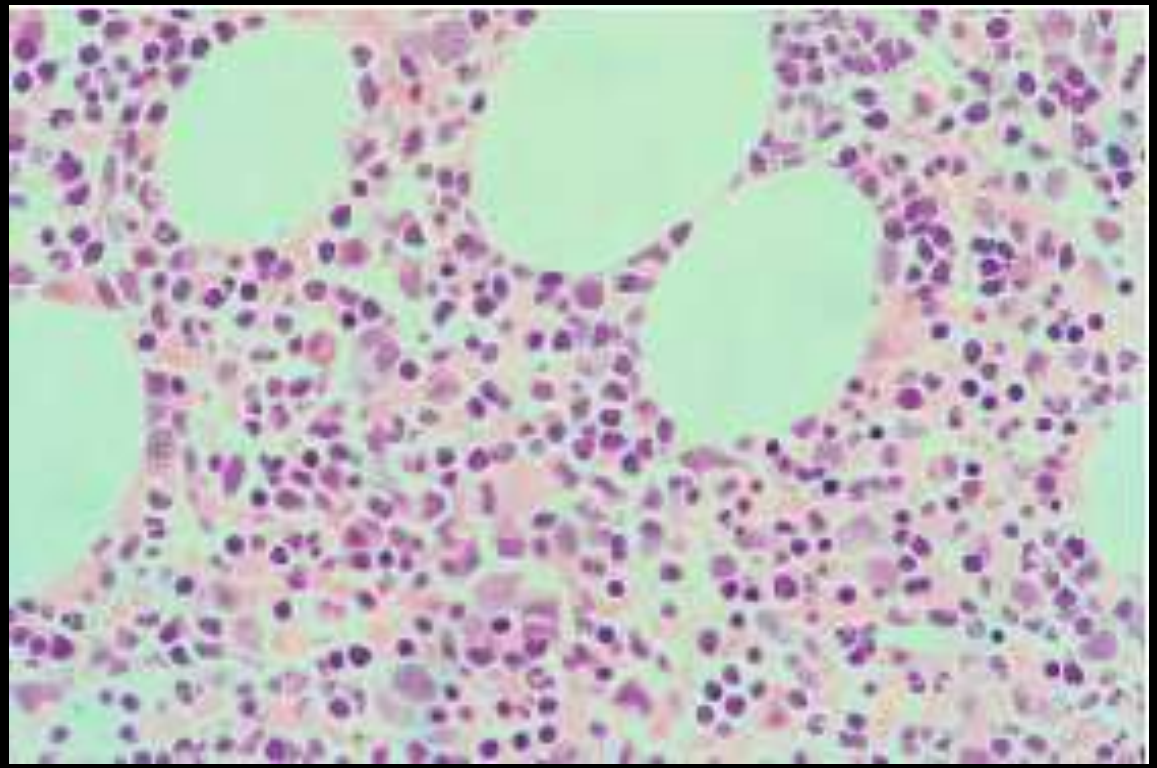
- Marrow study is done only for evaluation of prognosis (pattern of infiltration) or to diagnose the type of anemia (marrow failure, hemolytic, IDA or megaloblastic).



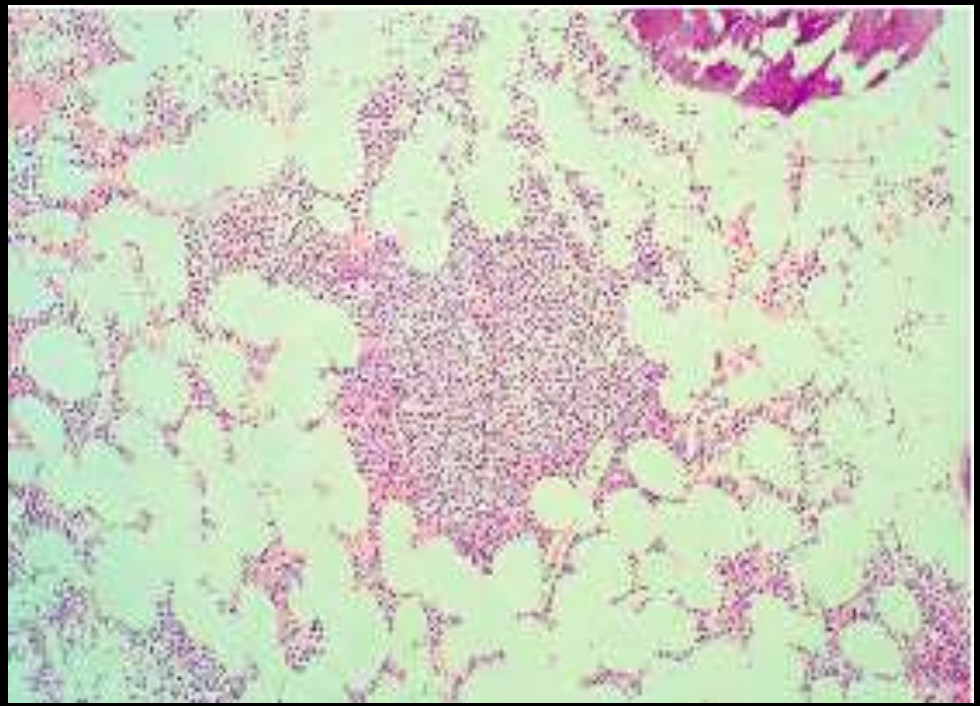


2) Normochromic normocytic anemia is present in later stages due to marrow infiltration or hyperspelism. Autoimmune hemolysis may also occur.
3) Thrombocytopenia occurs in advanced disease.
4) Bone marrow aspirate shows lymphocyte infiltration of the marrow comprising at least 30% or more of the marrow cells.

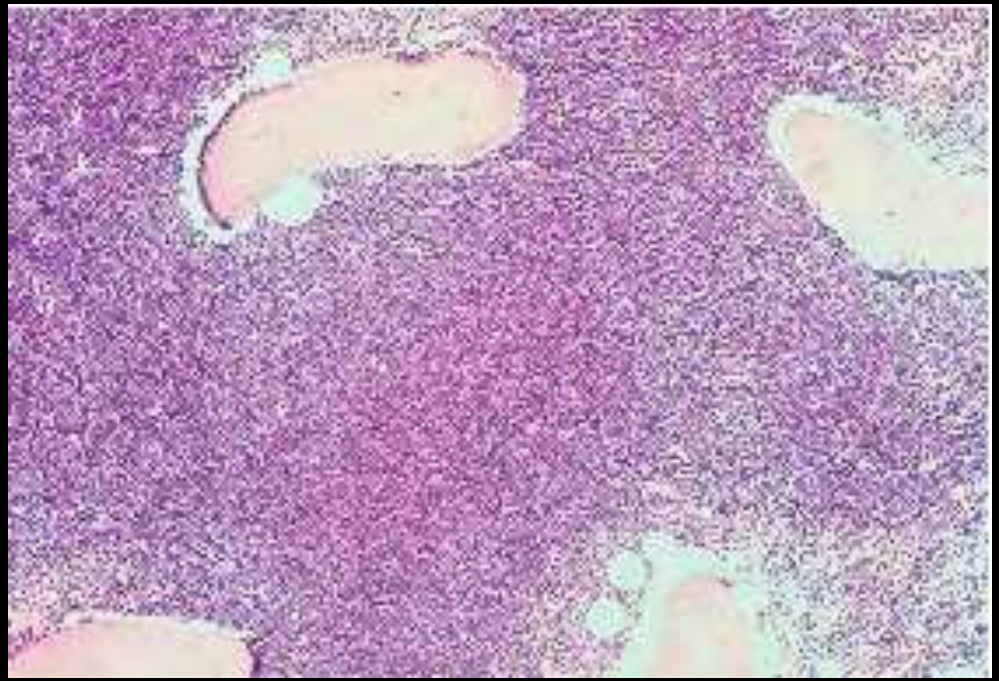
5) Trephine biopsy of the marrow show nodular or interstitial infiltration in the early stages or diffuse pattern in the advance of disease.
6) Reduced concentrations of serum immunoglobulins are found and this becomes more marked with advanced disease. This is called ***hypogammaglobulinemia*** and it is responsible for the high incidence of infections. Rarely a paraprotien is present.



Bone marrow biopsy: CLL interstitial infiltrate



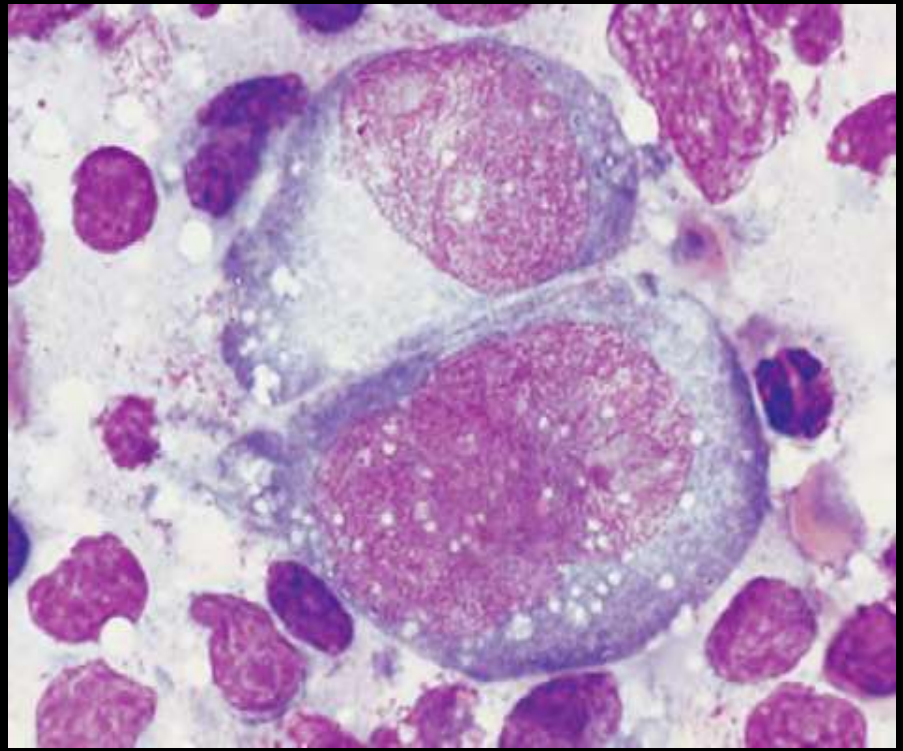
Bone marrow biopsy: nodular CLL



Bone marrow biopsy: diffuse CLL

Richter syndrome

Richter's syndrome (RS) represents the development of an aggressive lymphoma, most commonly a diffuse large B-cell lymphoma (DLBCL) in a patient previously (or simultaneously) diagnosed with CLL. The diagnosis needs to be substantiated by the biopsy of a lymph node



Staging Systems of CLL:

Rai's system

Stage (0)	Absolute lymphocytosis > 15 × 10^9 /liter
Stage (I)	As stage 0 + Lymphoadenopathy
Stage (II)	As stage 0 + Hepatomegaly and/or splenomegaly ± Lymphoadenopathy
Stage (III)	As stage 0 + Anemia Hb < 11.0g/dl
Stage (IV)	As stage 0 + Thrombocytopenia < 100 × 10^9 /liter

Binet's system

Stage (A) Organ enlargement up to 2 areas

Stage (B) Organ enlargement up to 3-5 areas

Stage (C) Anemia Hb < 10.0 gm/ dl or thrombocytopenia (Plt<100×10^9 /liter)

Prognosis of CLL:

- The higher the stage the worse the prognosis.
- Most patients with CLL live for 3-5 years. Younger patients and those with earlier disease do better. Some survive for 10 years or more. Death is usually caused by infection.