Leukaemias

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Leukaemias

- Leukaemias are a group of disorders characterized by the accumulation of malignant white cells in the bone marrow and blood.

- abnormal cells cause symptoms because of:

(i) bone marrow failure (i.e. anaemia, neutropenia, thrombocytopenia) and

(ii) infiltration of organs (e.g. liver, spleen, lymph nodes, meninges, brain, skin or testes).

Classification of leukaemia

Table 12.1 Classification of leukaemias.

Acute (see Table 12.2)
Acute myeloid leukaemia: M_0–M_7
Acute lymphoblastic leukaemia: L_1–L_3
Chronic (see Tables 13.1 and 15.1)
Chronic myeloid leukaemias
Chronic lymphoid leukaemias

Acute leukaemias

- Acute leukaemias are usually aggressive diseases in which malignant transformation occurs in the haemopoietic stem cell or early progenitors.

- Genetic abnormalties results in:

1- an increased rate of proliferation

2- reduced apoptosis and

3- a block in cellular differentiation.

- Acute leukaemia is associated with accumulation of the early bone marrow haemopoietic cells which are known as ***blast cells.***

Acute leukaemias

- Acute leukaemia is defined as the presence of over 20% of blast cells in the blood or bone marrow at clinical presentation

- Accumulation of blasts results in:

1- Bone marrow failure.

2- organ infiltration

- Acute leukaemias are fatal if not treated.
- However, acute leukaemias are easier to treat than chronic leukemias.
- Acute leukaemias are classified into myeloidand lymphoid according to the thype of blast cells.

Morphological classification of acute leukaemias

AML	Cytogenetic abnormality
M_0 undifferentiated	
M_1 without maturation	
M_2 with granulocytic maturation	t(8; 21)
M_3 acute promyelocytic	t(15; 17)
M_4 granulocytic and monocytic maturation	inv (16)
M_5 monoblastic (M_{5a}) or monocytic (M_{5b})	
M_6 erythroleukaemia	
M_7 megakaryoblastic	
ALL	
L_1 blast cells small, uniform high nuclear to cytoplasmic ratio	
L_2 blast cells larger, heterogeneous, lower nuclear to cytoplasmic ratio	
L_3 vacuolated blasts, basophilic cytoplasm (usually B-ALL)*	

Classification of acute myeloid (AML) and acute lymphoblastic (ALL) leukaemia according to the French-American-British (FAB) groups

ALL versus AML

Acute lymphoblastic leukaemia (ALL) can be distinguished from Acute myeloid leukaemia (AML) by: morphology, cytochemistry, immunological markers (flow cytometry), and chromosome analysis (cytogenetics).

	ALL	AML
Cytochemistry		
Myeloperoxidase	–	+(including Auer rods)
Sudan black	–	+(including Auer rods)
Non-specific esterase	–	+in M_4, M_5
Periodic acid–Schiff	+(coarse block positivity in ALL)	+(fine blocks in M_6)
Acid phosphatase	+in T-ALL (Golgi staining)	+in M_6 (diffuse)

Immunological markers in AML Vs ALL

Marker	AML	ALL	
		Precursor B*	T
Myeloid			
CD13	+	–	–
CD33	+	–	–
CD117	+	–	–
Glycophorin	+ (M_6)	–	–
Platelet antigens (e.g. CD41)	+ (M_7)	–	–
Myeloperoxidase	+ (M_0)		
B lineage			
CD19	–	+	–
cCD22	–	+	–
cCD79a	–	+	–
CD10	–	+ or –	–
cIg	–	+ (pre-B)	–
SIg	–	– (early pre-B)	–
TdT	–	+	+
T lineage			
CD7	–	–	+
cCD3	–	–	+
CD2	–	–	+
TdT	–	+	+

ALL

- ALL is the most common form of leukaemia in children.
- Can be either B-cell ALL or T-cell ALL.
- B-cell ALL or T-cell ALL can be further classified into subtypes according to the moderate splenomegaly, hepatomegaly and meningeal syndrome
- immunological markers (Immunophenotype).
- **Clinical features:**

1- **bone marrow failure** leads to: Anaemia (pallor, lethargy and dyspnoea); neutropenia (fever, malaise, features of mouth, throat, skin, respiratory infections and throbombocytopenia (spontaneous bruises, pupura, bleeding gums.

- 2- ***Organ infiltration*** Tender bones, lymphadenopathy, splenomegaly and hepatomegaly.

Lab investigations in ALL

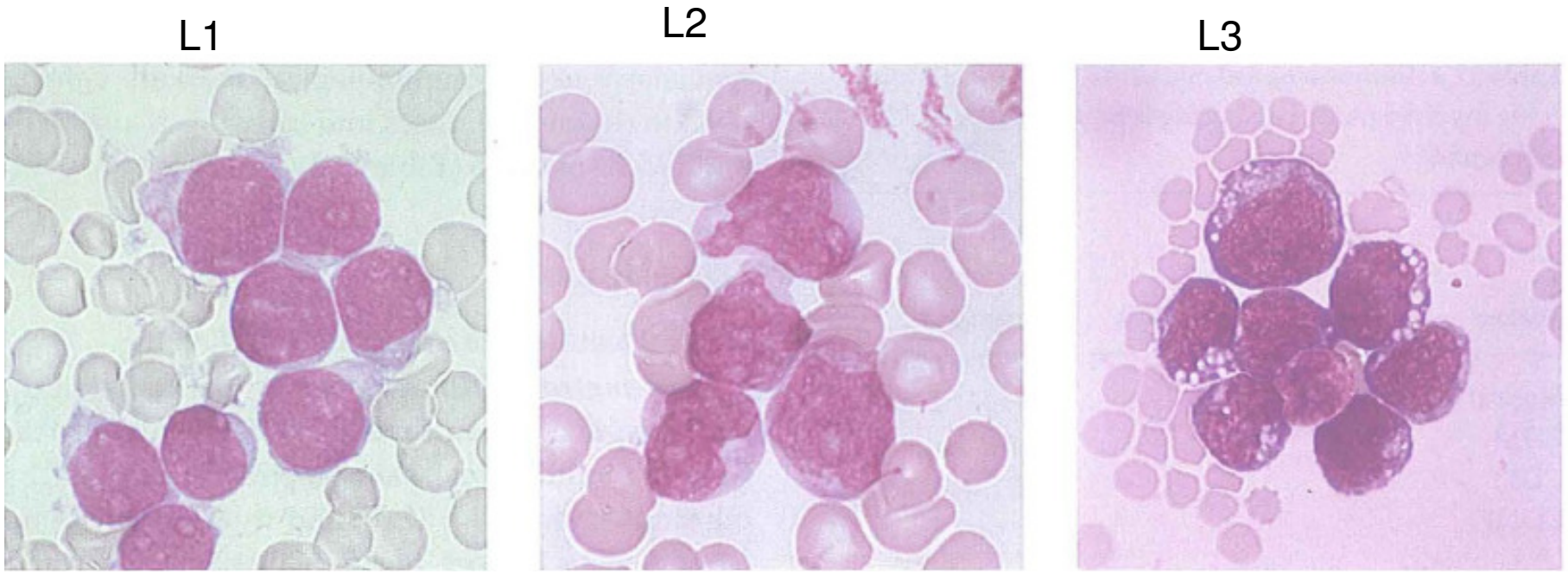
1- Normochromic normocytic anaemia.

2- presence of > 20% blasts in the BM.

3- blast cells are characterized by morphology, immuological tests and cytogenetic analysis.

4-

Morphological classification of ALL



(a) L1 subtype-blasts show scanty cytoplasm without granules.
(b) L2 subtype-blasts are larger and heterogeneous with more abundant cytoplasm.
(c) L3 subtype-blasts are deeply basophilic with cytoplasmic vacuolation.

Genetics of ALL

- The most common specific abnormality

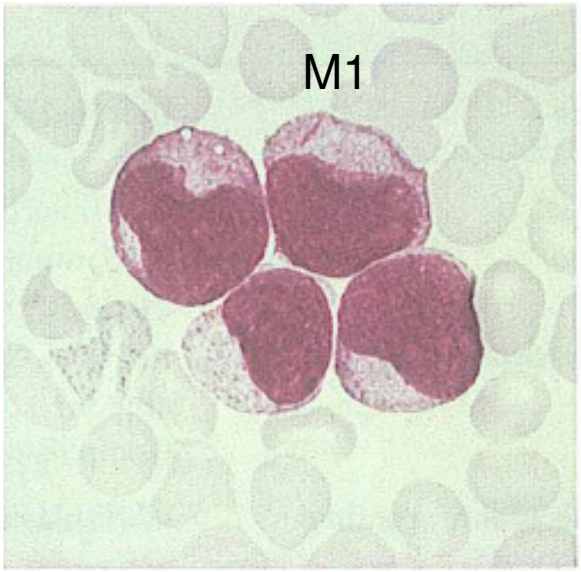
in childhood ALL is the t(12; 21) *TEL-AML1* translocation which results in the formation of TEL-AML1 fusion protein.

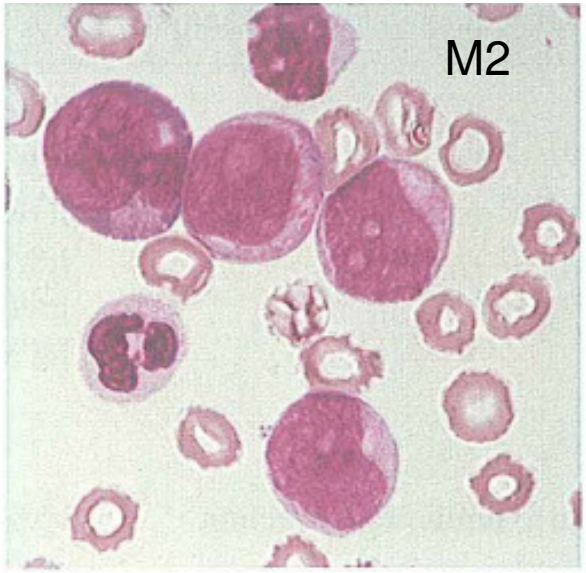
- Philadelphia chromosome translocation t(9; 22) may occur and results in poor prognosis.

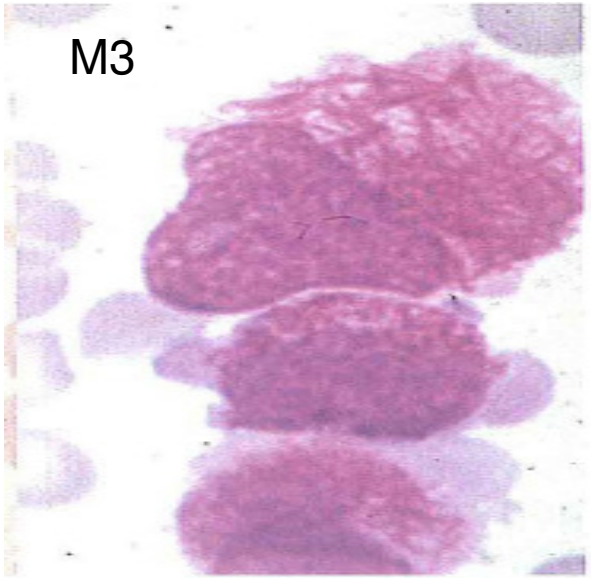
AML

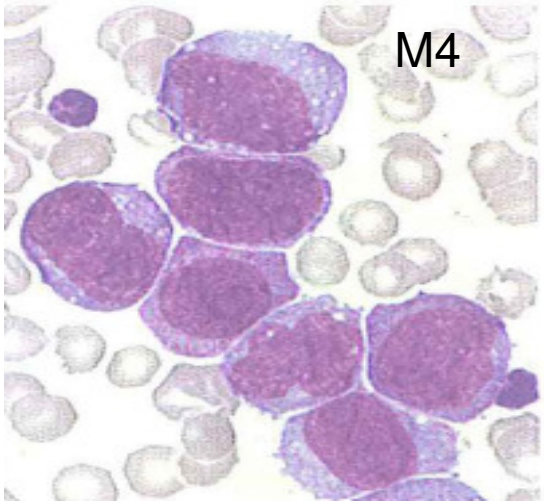
- AML is the most common form of acute leukaemia in adults.
- There is > 20% myeloblasts in the BM or blood.
- AML is classified according to the morphological criteria of the FAB (also include cytochemistry stains, immunological markers, cytogenetics).

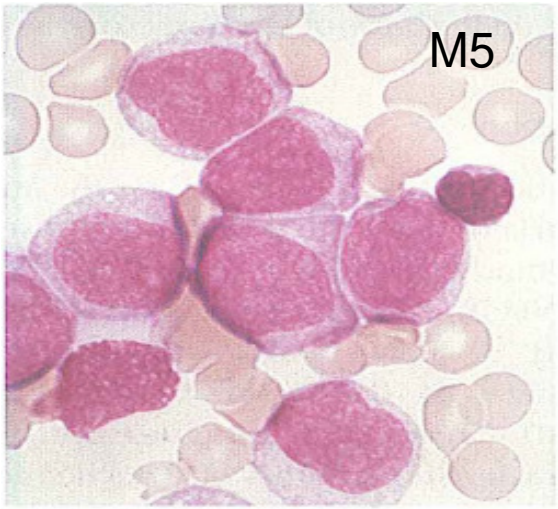
Subtypes of AML

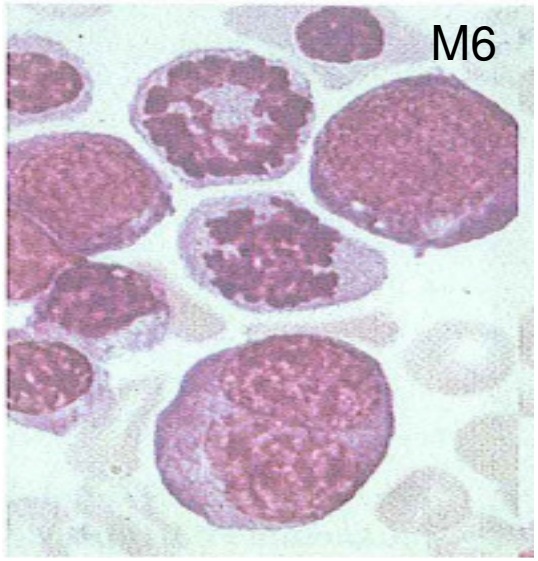












Clinical features of AML

- Anaemia and throbmbocytopenia are often profound.
- bleeding tendency caused by thrombocytopenia.
- disseminated intravascular coagulation (DIC) in M3 variant of AML.
- Organ infiltration
- skin involvement and CNS disease in M4 &M5.

Chronic Myeloid Leukaemia

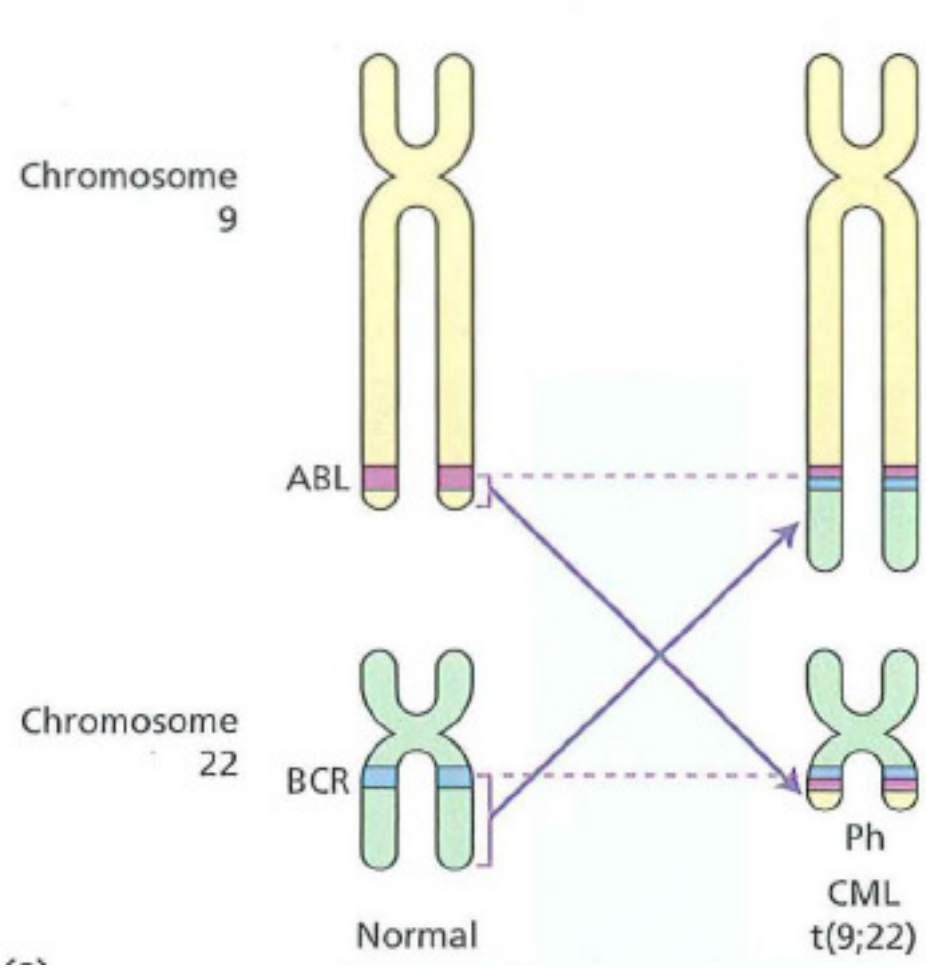
- Chronic myeloid leukaemia (CML) is a clonal disorder of a stem cell.
- accounts for around 15% of leukaemias and may occur at any age.
- The main feature is the presence of Philadelphia chromosome (Ph) which occurs due to t(9,22) translocation.
- t(9,22) results in the formation of a new *BCR-ABL* fusion gene which encode the BCR-ABL fusion protein.
- BCR-ABL has higher tyronase activity and give the leukaemic cells the following features:

1- High proliferation rate.

2- Survival and protection from apoptosis.

3- Adhesion defects (cells migrate from BM to peripheral blood).

Ph chromosome



Clinical course of CML

1- **Chronic phase:** may last between 3-5 years. Respond to treatment if diagnosed early.

2- **Blastic phase:** disease transform to aggressive acute leukaemia (AML or ALL) and acquire more genetic abnormalities. Very difficult to treat and only stem cell transplantation may cure the disease.

Clinical features

- CML most frequently affect people between the ages of 40 and 60 years. However, it may occur in children. Symptoms include:

1- Symptoms related to hyper-metabolism (e.g.weight loss, anorexia-poor appetite- or night sweats).

2- Splenomegaly.

3- Features of anaemia may include pallor, dyspnoea and tachycardia.

4- Bruising, nose bleeding, menorrhagia or haemorrhage from other sites because of abnormal platelet function.

5- Gout or renal impairment caused by elevated levels of uric acid may be a problem.

6 Rare symptoms include visual disturbances.

7- In up to 50% of cases the diagnosis is made incidentally from a routine blood count.

Lab findings in CML

1- Leucocytosis is usually >50 x 109/L and sometimes >500 x 109/L (Fig. 13.2).

-The levels of neutrophils and myelocytes exceed those of blast cells and promyelocytes (Fig. 13.3).

2- Increased circulating basophils.

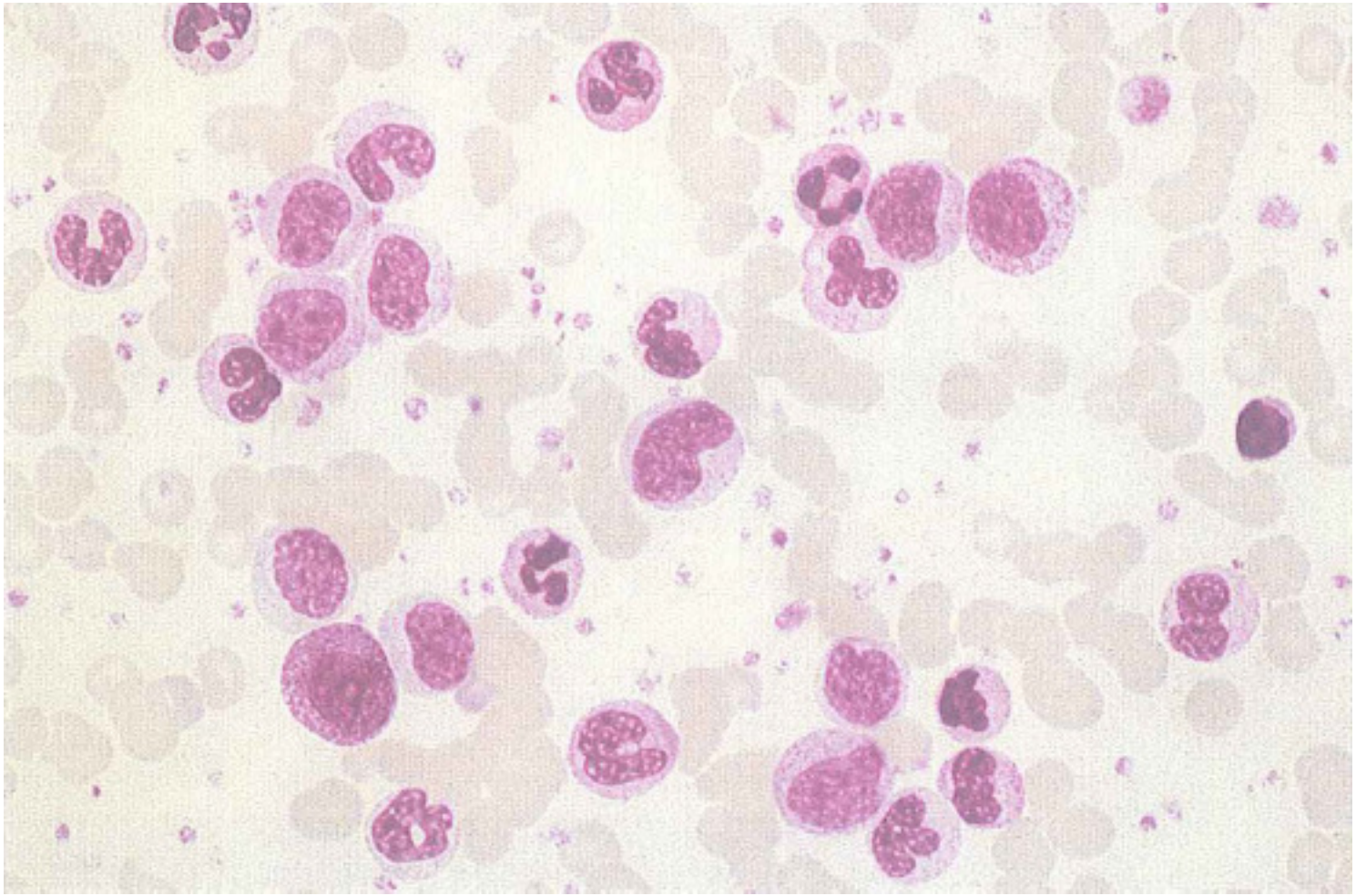
3- Normochromic, normocytic anaemia is usual.

4 Platelet count may be increased (most frequently)..

5- Bone marrow is hypercellular with predominance of granulocytes.

6- Ph chromosome on cytogenetic analysis (conventional or FISH) of blood or bone marrow.

7- Serum uric acid is usually high.



CML: peripheral blood film showing various stages of granulopoiesis.

Treatment of CML

- The first-line drug in the management of chronic phase disease is Glivec (IMATINIB).
- Imatinib is highly effective in reducing the number of tumour cells in the bone marrow.
- *Stem cell transplrmtntion:*

Allogeneic stem cell transplantation (SCT) is the only established curative treatment for CML.

Chronic Lymphoid Leukaemias (CLL)

- Characterized by accumulation in the blood of **mature** lymphocytes of either B- or T-cell type.
- chronic persistent of lymphocytosis.
- Subtypes of CLL are distinguished by morphology, immunophenotype and cytogenetics.

Classification of chronic lymphoid leukaemia/ lymphoma

B-cell	T-cell
Chronic lymphoid leukaemias	
Chronic lymphocytic leukaemia (CLL)	Large granular lymphocytic leukaemia
Prolymphocytic leukaemia (PLL)	T-cell prolymphocytic leukaemia (T-PLL)
Hairy cell leukaemia (HCL)	
Plasma cell leukaemia	
Leukaemia/lymphoma syndromes	
Splenic lymphoma with villous lymphocytes	Sézary syndrome
Follicular lymphoma	Adult T-cell leukaemia/ lymphoma
Mantle cell lymphoma	Large cell lymphoma
Lymphoplasmacytic lymphoma	
Large cell lymphoma	

B-cell Chronic lymphocytic leukaemia

- Affects people between 60-80 years of age.
- The tumour cell appears to be a relatively mature B cell with weak surface expression of immunoglobulin (Ig)M.
- The cells accumulate in the blood, bone marrow, liver, spleen and lymph nodes.
- Tumour cells he long survival with impaired apoptosis.

Cliniclal features of B-cell CLL

1- The disease occurs in older subjects (> 50 years old).

2- Most cases are diagnosed when a routine blood test is performed.

3- enlargement of cervical, axillary or inguinal lymph nodes is the most frequent clinical sign.

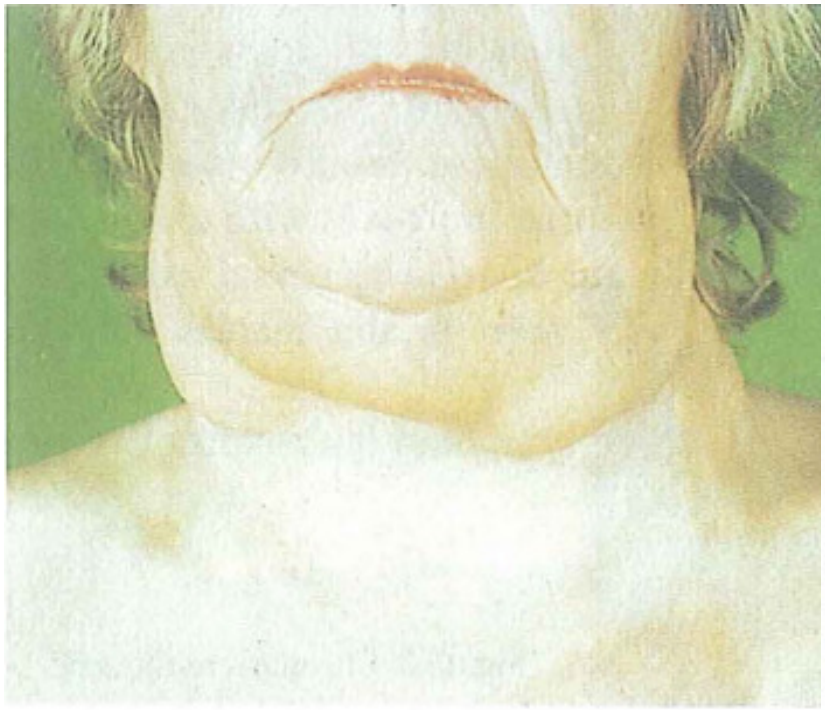
4- Features of anaemia may be present. bruising or purpura may occur due to thrombocytopenia.

5- Splenomegaly and, less commonly, hepatomegaly.

6- Immunosuppression is a significant problem.

bacterial infections followed by viral and fungal infections such as herpes zoster are also seen.

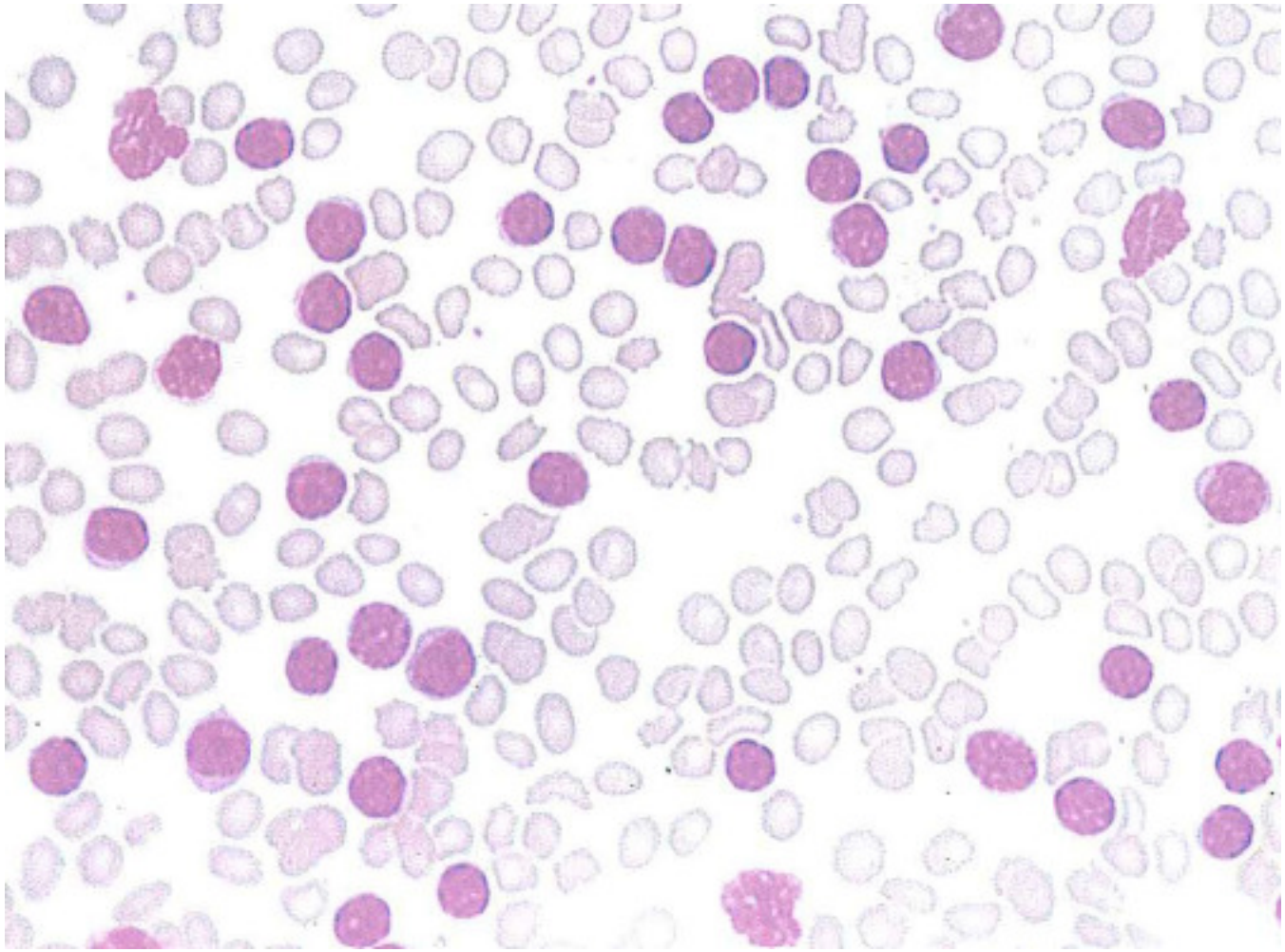
Cliniclal features of B-cell CLL



Cervical lymphadenopathy

herpes zoster infection

Blood film in B-cell CLL



Laboratory findings of B-cell CLL

1- Lymphocytosis.

2- Immunophenotyping: cells express CD19, CD5, CD20, CD23 but lack CD79b. either Kppa or Lambd light chain is expressed.

3- Normocytic normochromic anaemia is present in later stages.

4- Bone marrow aspiration shows lymphocytic replacement of normal marrow elements.

Immunophenotype of chronic B-cell Leukaemia

	CLL	PLL	HCL	FL	MCL
SIg	Weak	++	++	++	+
CD5	+	−	−	−	+
CD22/FMC7	−	+	+	+	+
CD23	+	−	−	−	−
CD79b	−	++	−/+	++	++
CD103*	−	−	+	−	−

CLL, Chronic lymphocytic leukaemia (positive for CD5).
FL, Follicular lymphoma.
HCL, Hairy cell leukaemia (positive for CD103).
MCL, Mantle cell lymphoma.
PLL, Prolymphocytic leukaemia.