Acute Leukemia 1

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Objectives

1) To understand the definition of acute leukemia and recognize the general features of leukemia
2) To understand the general concepts of leukemia pathogenesis
3) To recognize the importance of early diagnosis of acute leukemia
4) To understand the general themes of classification and the basic tool of diagnosis
5) To recognize the most common presenting features of AML and their significance in management
6) To know the most important indicators implicated in prognosis of AML

Acute leukemia

- Aggressive malignant hematopoietic disorders
- Accumulation of abnormal blasts (Immature precursors of WBC)

  in bone marrow and blood leading to:

  1- Bone marrow failure (anemia ,neutropenia & thrombocytopenia)

  2- Organ infiltration (hepatosplenomegy ,lymphadenopathy)

HISTORY

- Means “white blood” in Greek.
- Named by pathologist Virchow in 1845.
- Classified by FAB classification systems in 1976.
- Reclassified by World Health Organization in 2001 & 2008.

PATHOGENESIS

Genetic predisposition

Environmental factors

Infection

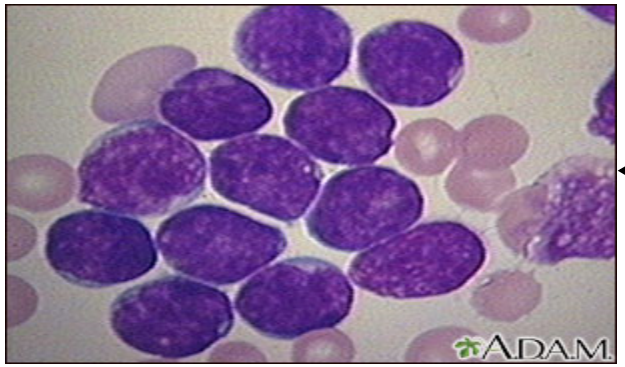
Previous therapy

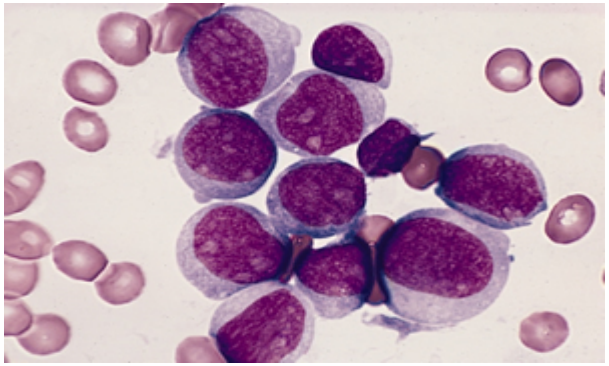
Other hematological disorders

Unknown Mechanism

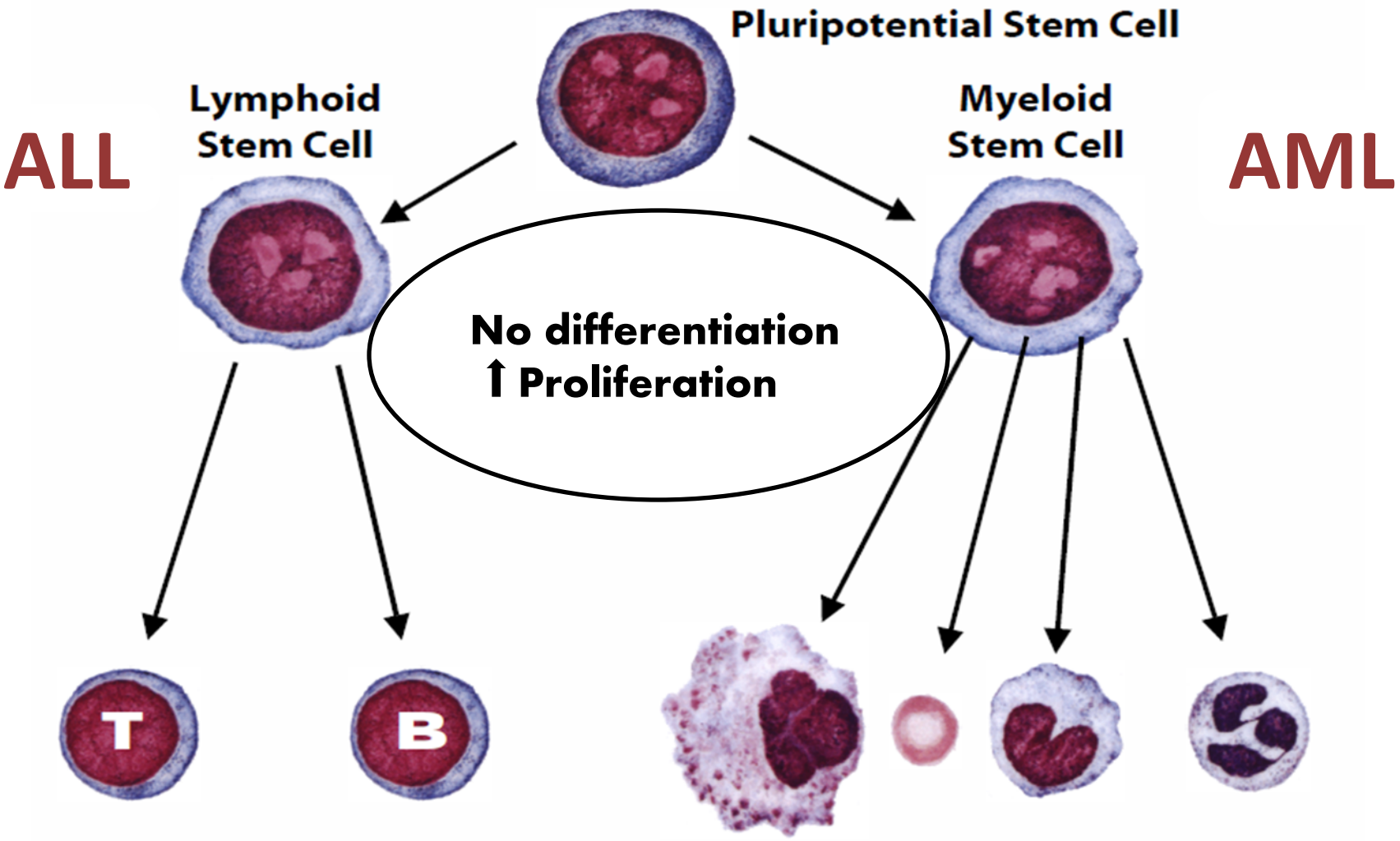
Genetic alteration in the immature precursors

Block of differentiation ,Enhanced proliferation & Decreased apoptosis





PATHOGENESIS



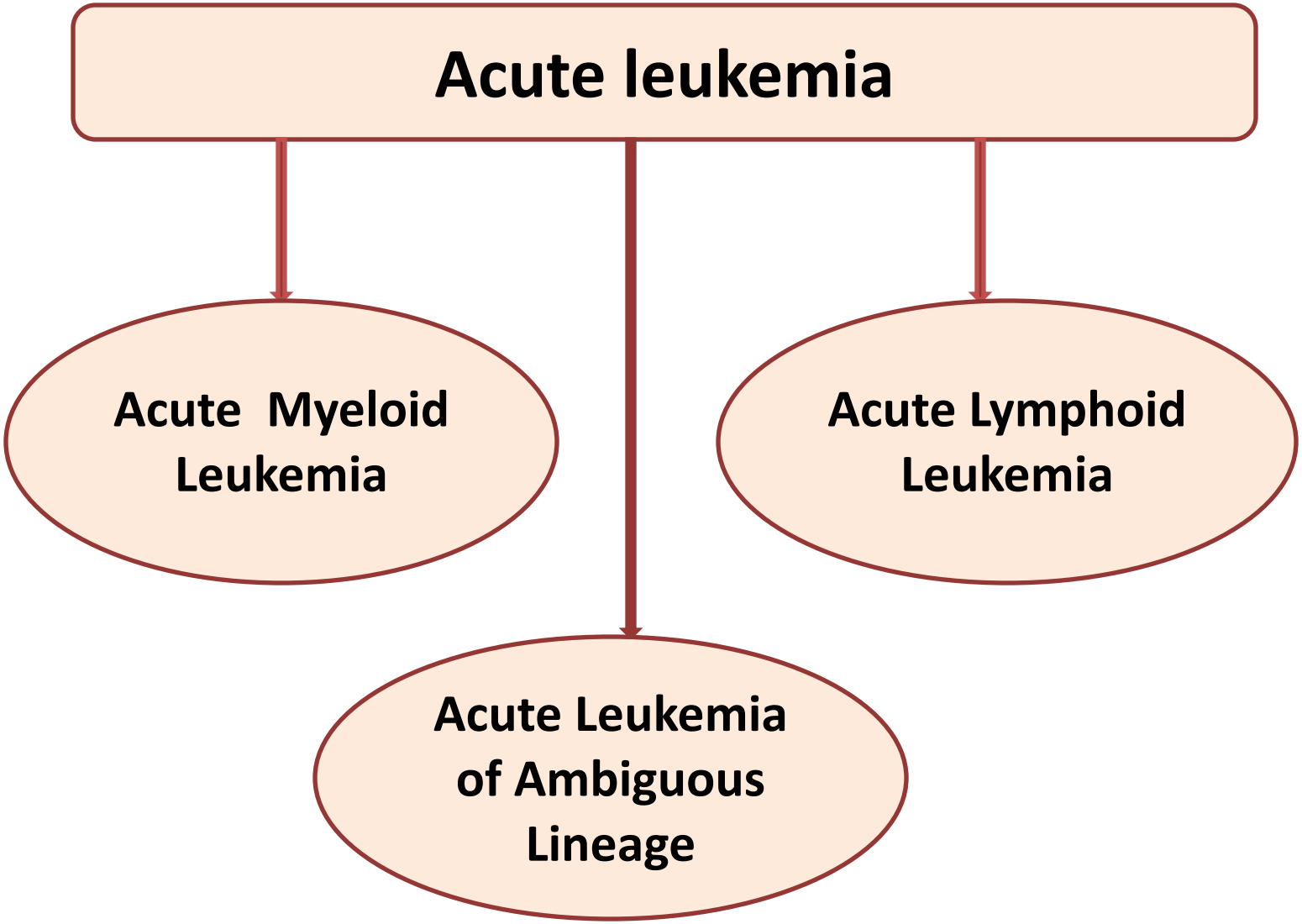
Epidemiology

- AL represent about 8% of neoplastic disease & cause about 4% of malignancy related deaths !

- AML has an incidence of 2 – 3 per 100 000 per year in children, rising to 15 per 100 000 in adults.

- ALL has an incidence of 30 per million & represent about 76% of childhood leukemia .

General Classification

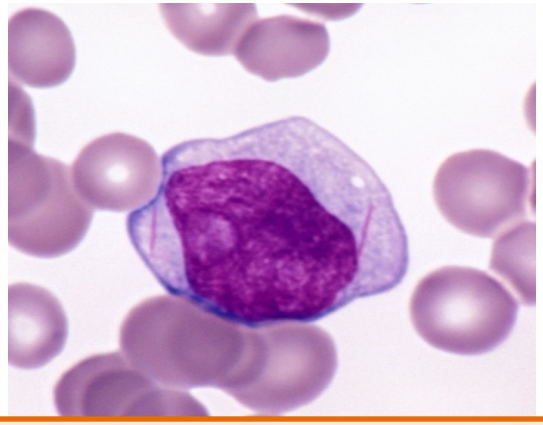


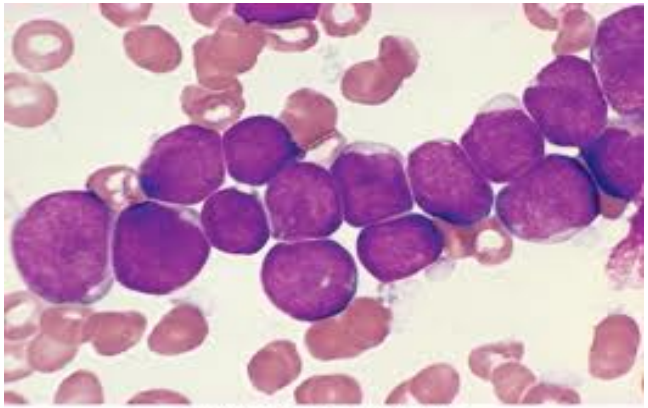
Basis of Classification

1. Clinical history (Previous therapy)
2. Morphology
3. Flow cytometry
4. Chromosomal Karyotyping
5. Molecular study

1- Light microscopy (blood smear, bone marrow aspirate & biopsy)

- Blast count : it should be >20% out of the total cells
- Blast morphology :





Myeloblast:

-Size: medium-Large
-Nucleous: round, oval or irregular
-Nucleolus: prominent
-Cytoplasm: abundant, granular

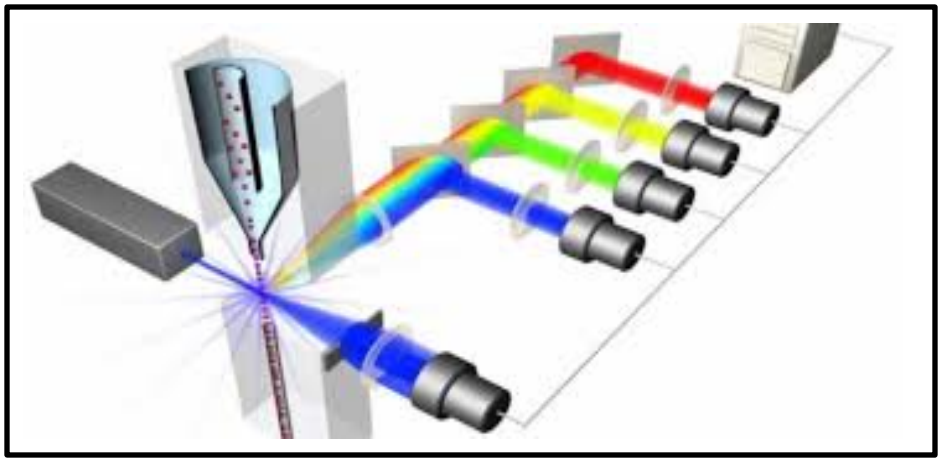
Auer rods is characteristic

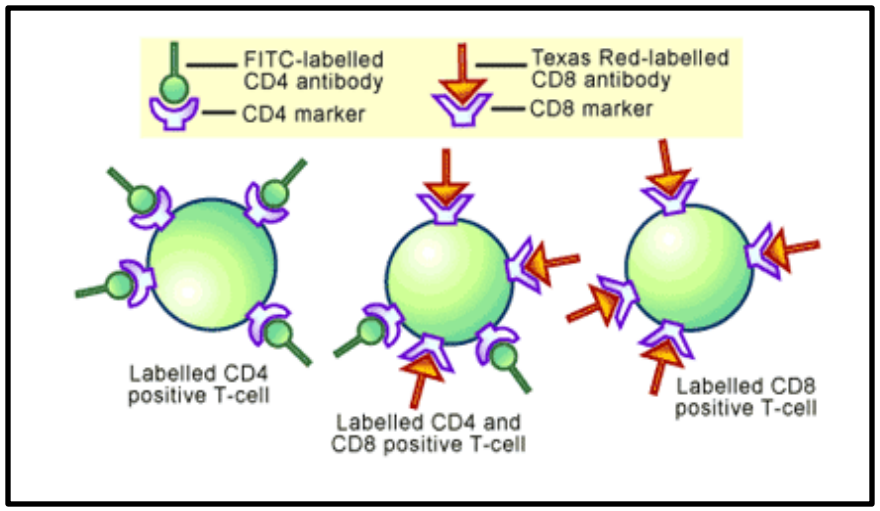
Lymphoblast:

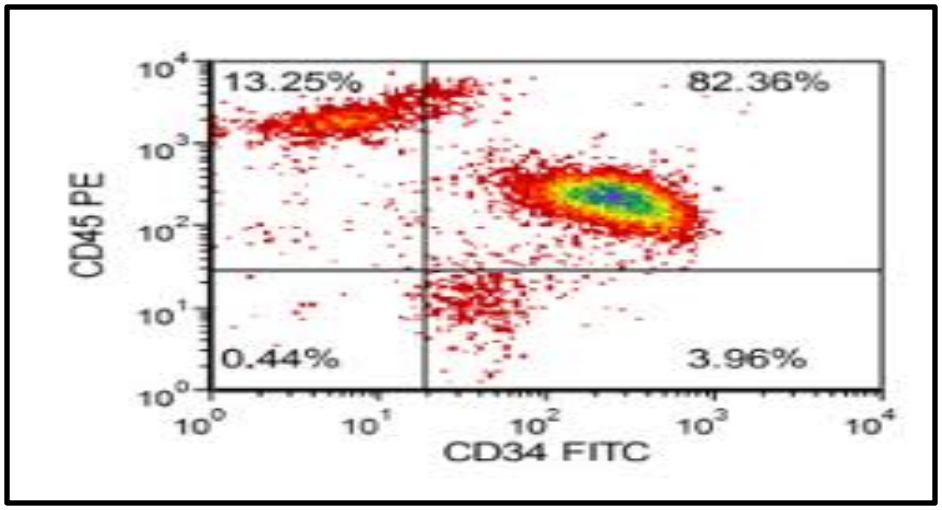
- Size: small- medium
- Nucleous: round
- Nucleolus: not prominent
- Cytoplasm: scanty ,agranular
  may be vacuolated

2-Flow cytometry:

Laser based technology allows for cells counting & detection of their surface &cytoplasmic markers by suspending them in a stream of fluid followed by analysis through electronic system.







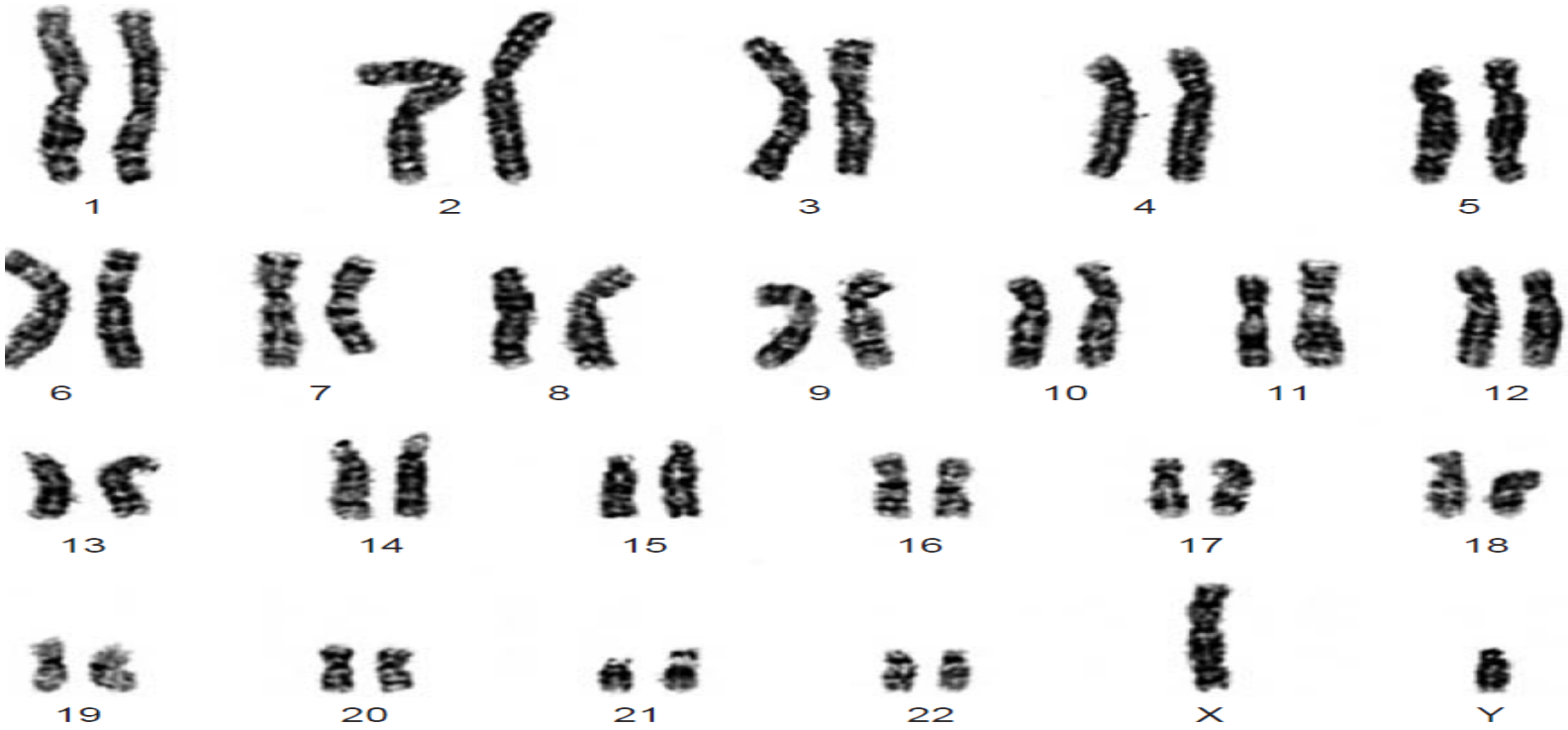
Basis of Classification

Stem Cell Markers: (CD34& TDT)

Myeloid	B-Lymphoid	T-Lymphoid
MPO CD13 CD33 CD14 CD64 CD41 CD235a	CD10 CD19 CD22 CD79a	**CD3** CD4 CD5 CD7 CD8

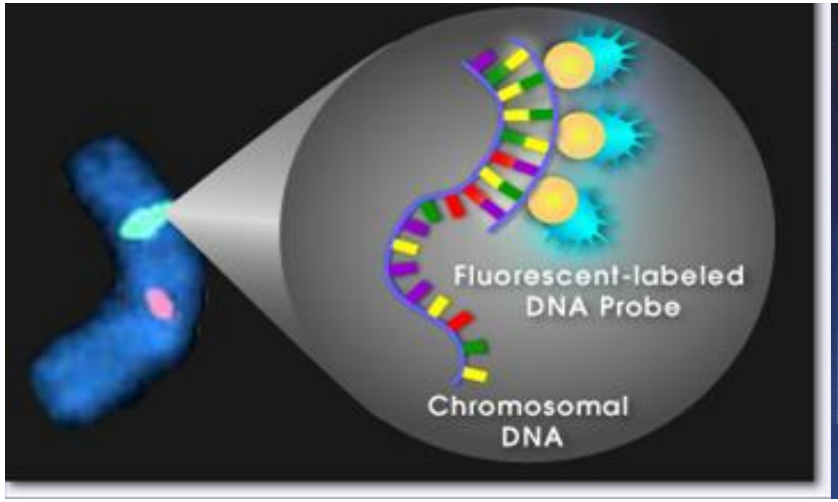
3-Chromosomal Karyotype

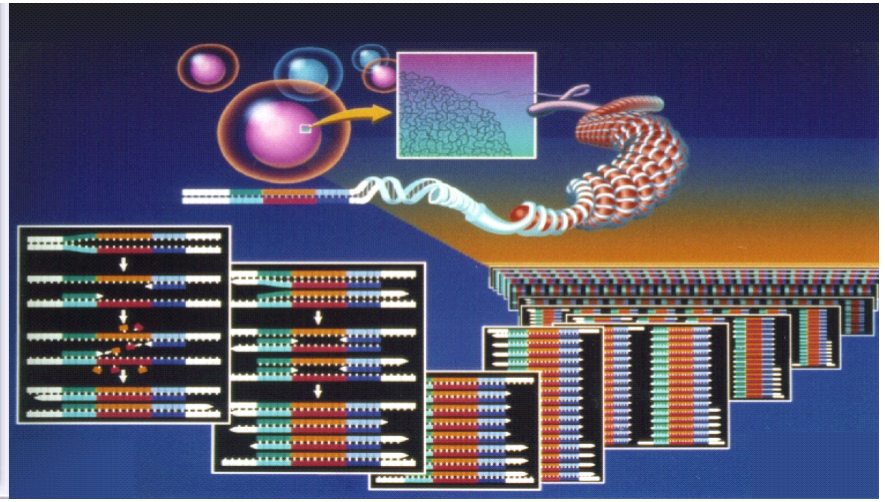
Set of the chromosomes from one cell during metaphase to study the numerical(deletion &trisomy) and structural (translation &inversion) abnormality



4- Molecular studies:

Several techniques used to detect and localize the presence or absence of specific DNA sequences on chromosomes





Fluorescent In-Situ Hybridization (FISH)

Polymerase Chain Reaction (PCR)

Recurrent genetic abnormalities

AML

Karyotype	Molecular
t (8;21)	AML1-ETO
t (16;16) or inv(16)	CBFB-MYH11
t (15;17)	PML-RARA
t (9;11)	MLLT1-MLL

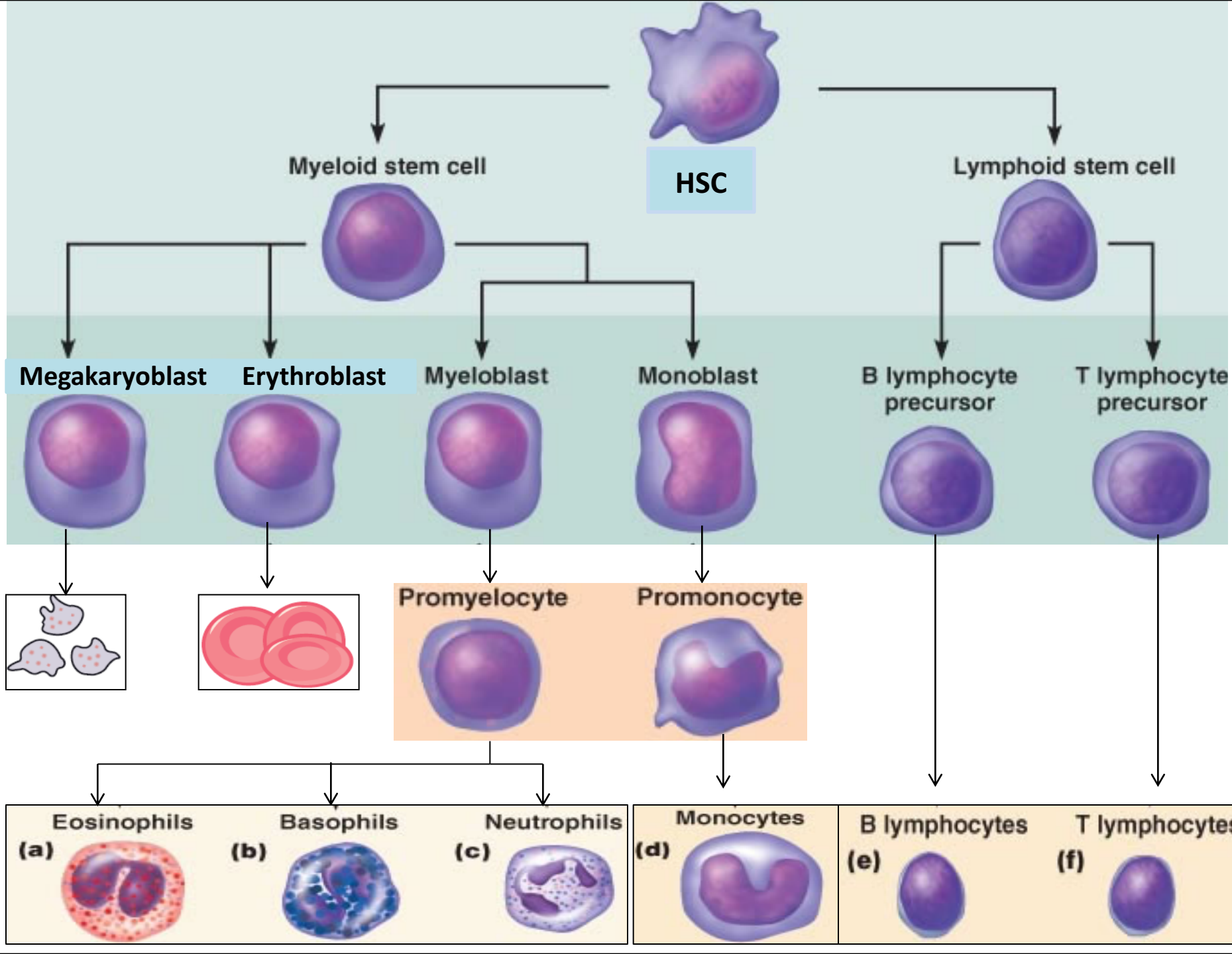
ALL

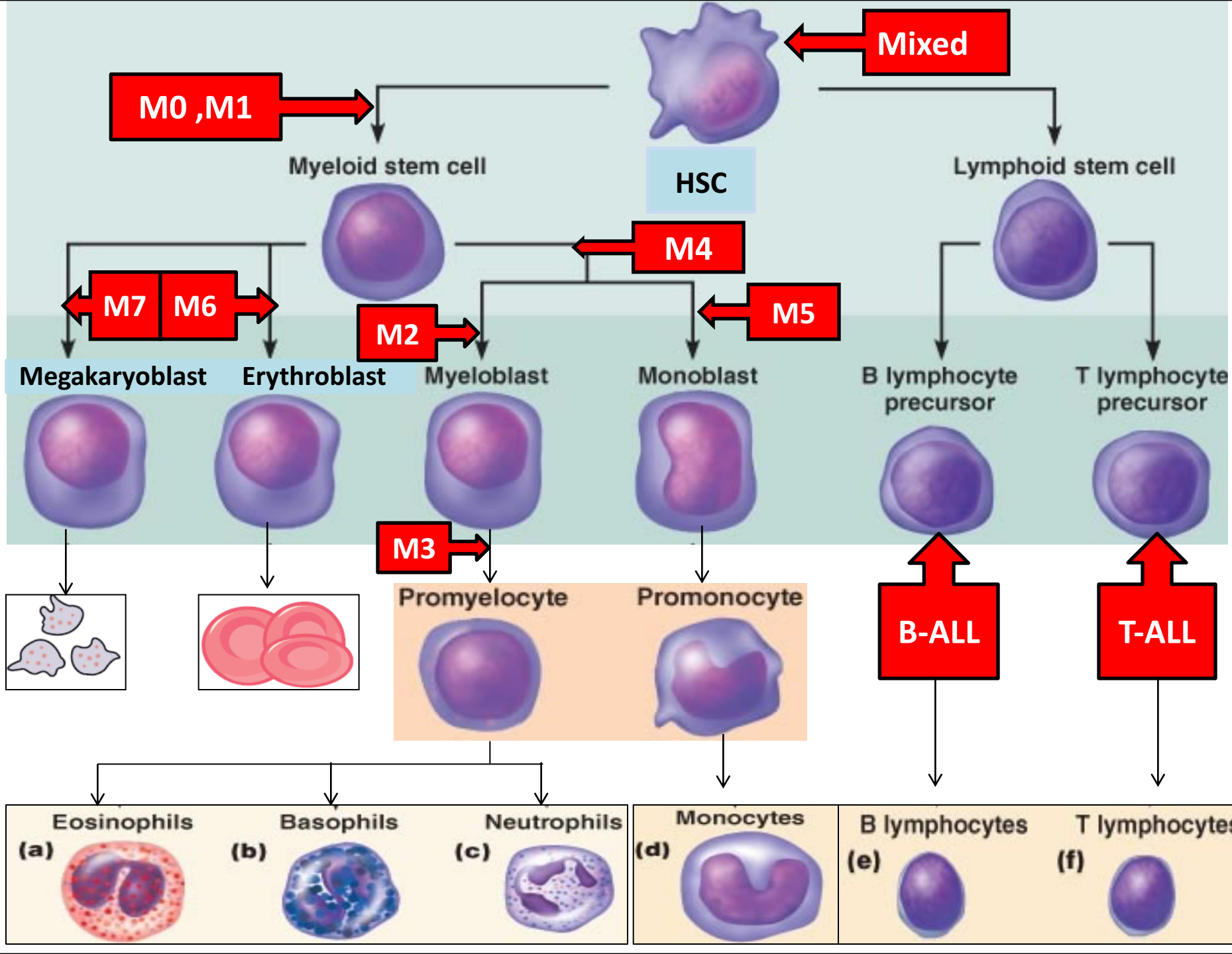
Karyotype	Molecular
t (9;22)	BCR-ABL1
t (4;11)	AF4-MLL
t (12;21)	ETV6-RUNX1
t (5;14)	IL3-IGH

ACUTE MYELOID LEUKEMIA

Acute Myeloid Leukemia

- Group of hematopoietic neoplasms caused by proliferation of malignant myeloid blasts in bone marrow and blood.
- The blast ≥20% or t(8;21) t (16;16) or t(15;17).
- More in Adults (do occur in infants!)
- Worse than ALL


HSC
Myeloid stem cell
Lymphoid stem cell
Megakaryoblast
Erythroblast
Myeloblast
Monoblast
B lymphocyte precursor
T lymphocyte precursor
Promyelocyte
Promonocyte
Eosinophils
(a)
Basophils
(b)
Neutrophils
(c)
Monocytes
(d)
B lymphocytes
(e)
T lymphocytes
(f)


Mixed
M0 ,M1
Myeloid stem cell
HSC
Lymphoid stem cell
M4
M7
M6
M2
M5
Megakaryoblast
Erythroblast
Myeloblast
Monoblast
B lymphocyte precursor
T lymphocyte precursor
M3
Promyelocyte
Promonocyte
B-ALL
T-ALL
Eosinophils
(a)
Basophils
(b)
Neutrophils
(c)
Monocytes
(d)
B lymphocytes
(e)
T lymphocytes
(f)

FAB Classification

- Based on morphology& flow cytometry

Subtype	Features	Genetics in WHO	Notes
Mo	Minimal differentiation		
M1	Without maturation		
M2	With maturation	t(8;21)	
M3	Promyelocytic	t(15;17)	DIC
M4	Granulocytic and monocytic	t or inv(16;16)	Gum hypertrophy
M5	Monoblastic (M5a) Monocytic (M5b)	t(9;11)	
M6	Erythroid		CD235a
M7	Megakaryocytic		CD41
M8	Basophilic		

AML Classification (WHO)

AML with recurrent genetic abnormalities

1- t(8;21)
2- t(16;16)
3- t(15;17)
Prognosis:
Good

Myelodysplasia related AML

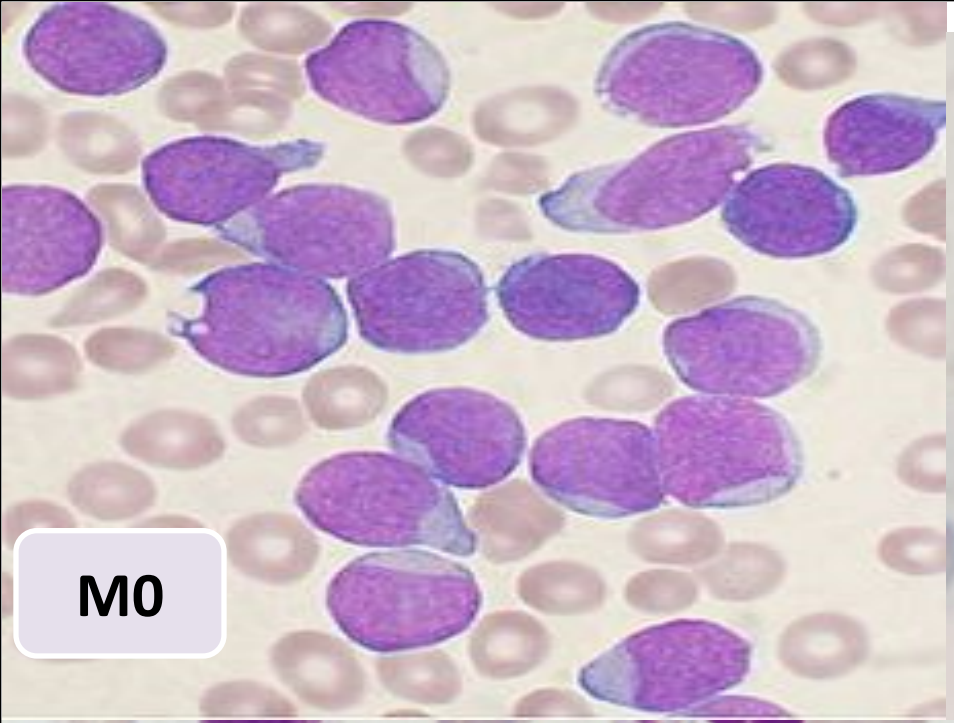
•Blasts≥ 20%
•Significant dysplasia
Prognosis:
poor

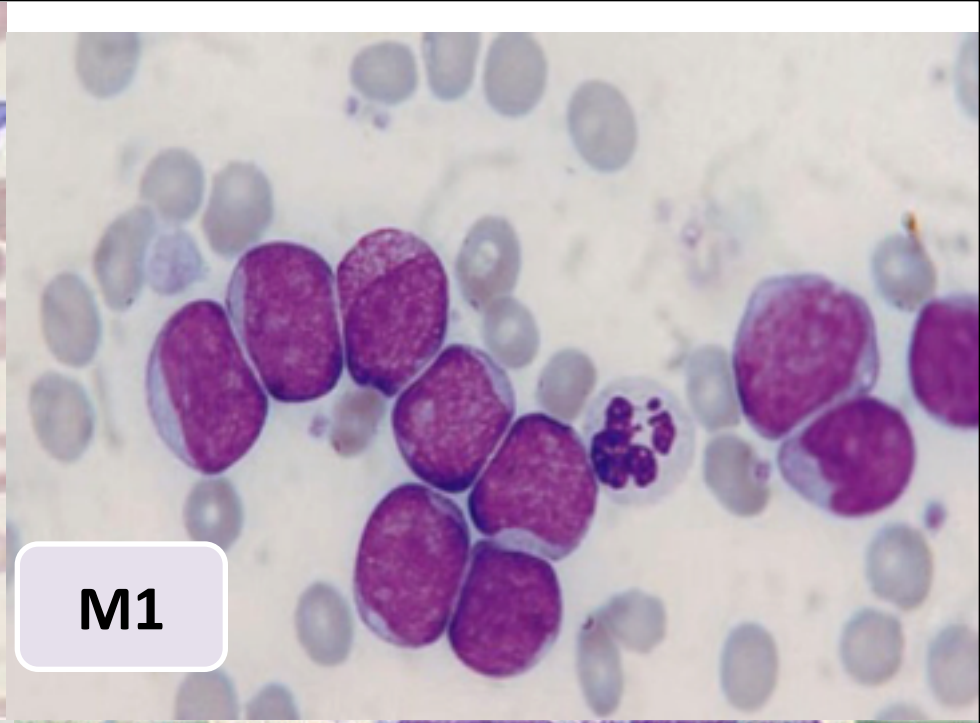
Therapy related AML

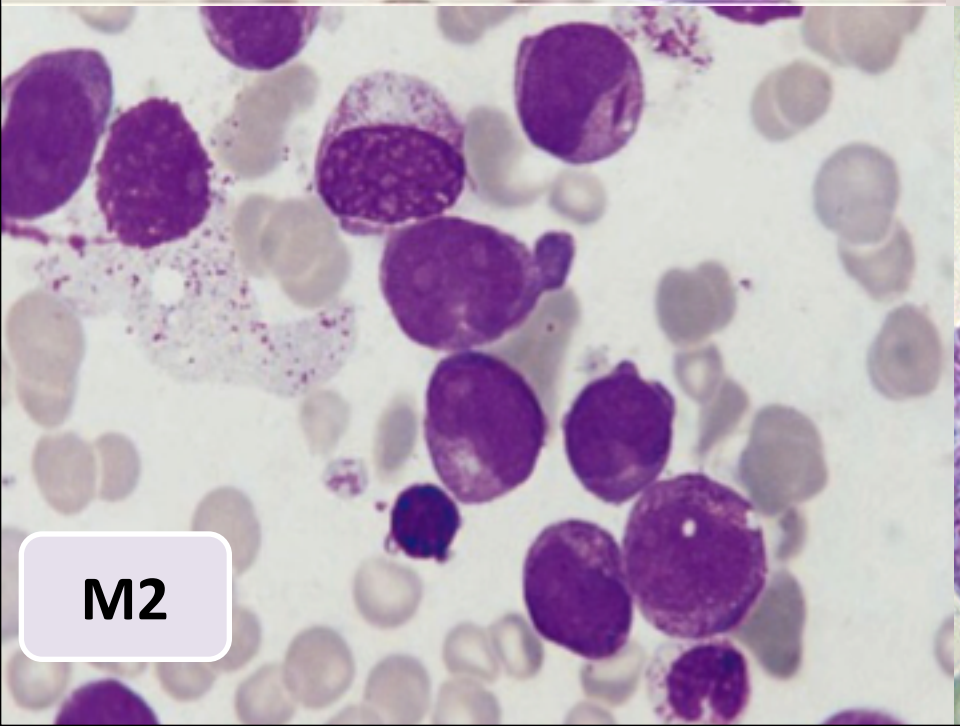
•Blasts≥ 20%
•Previous chemotherapy
Prognosis:
poor

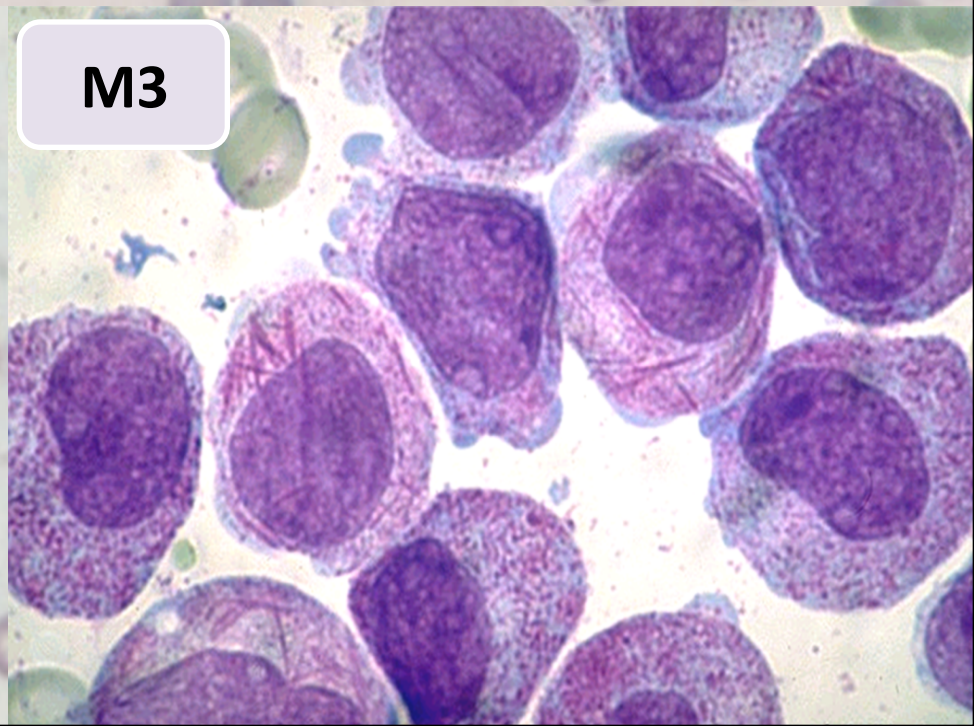
AML, not otherwise specified (FAB)

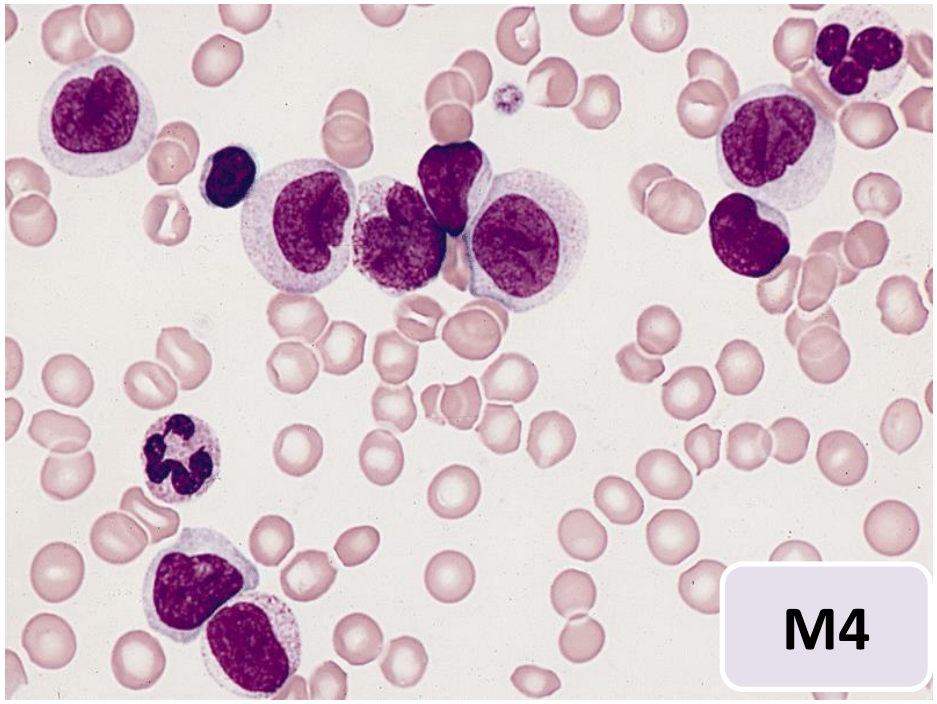
•Blasts≥ 20%
•Genetic: N
•No dysplasia
Prognosis:
Standard

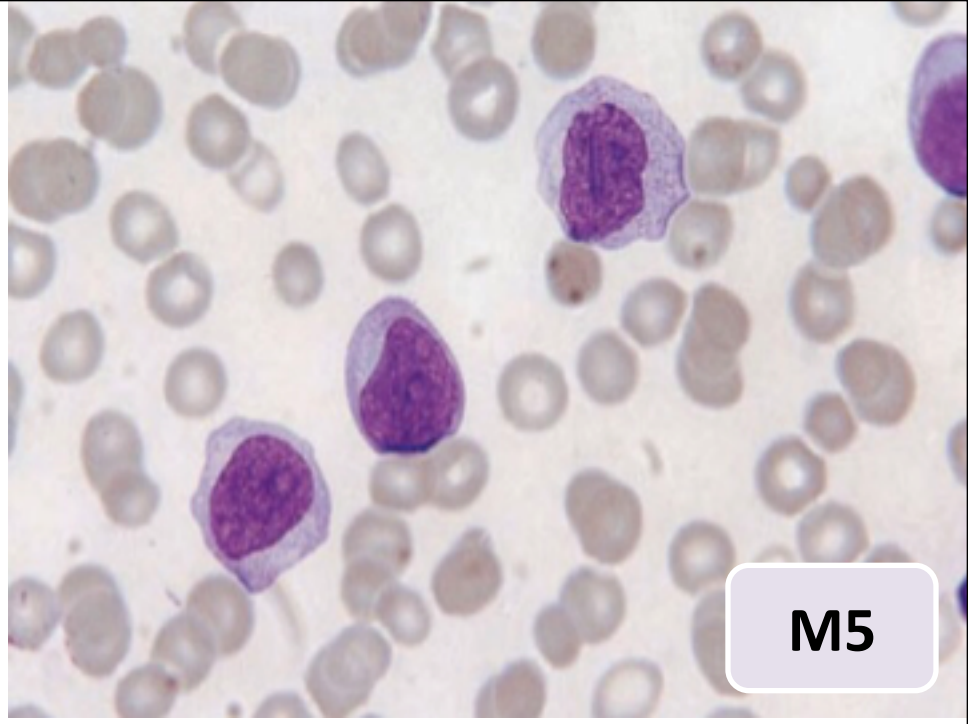

M0

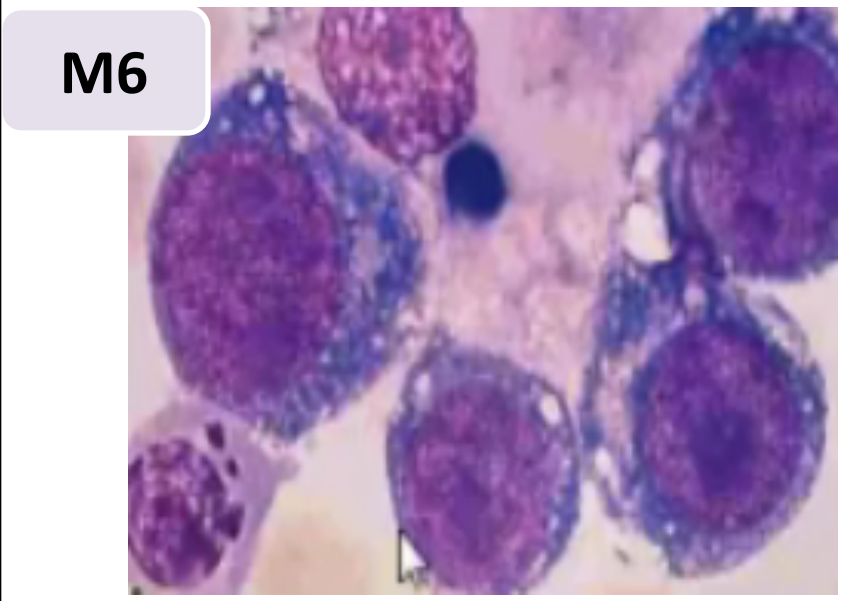

M1

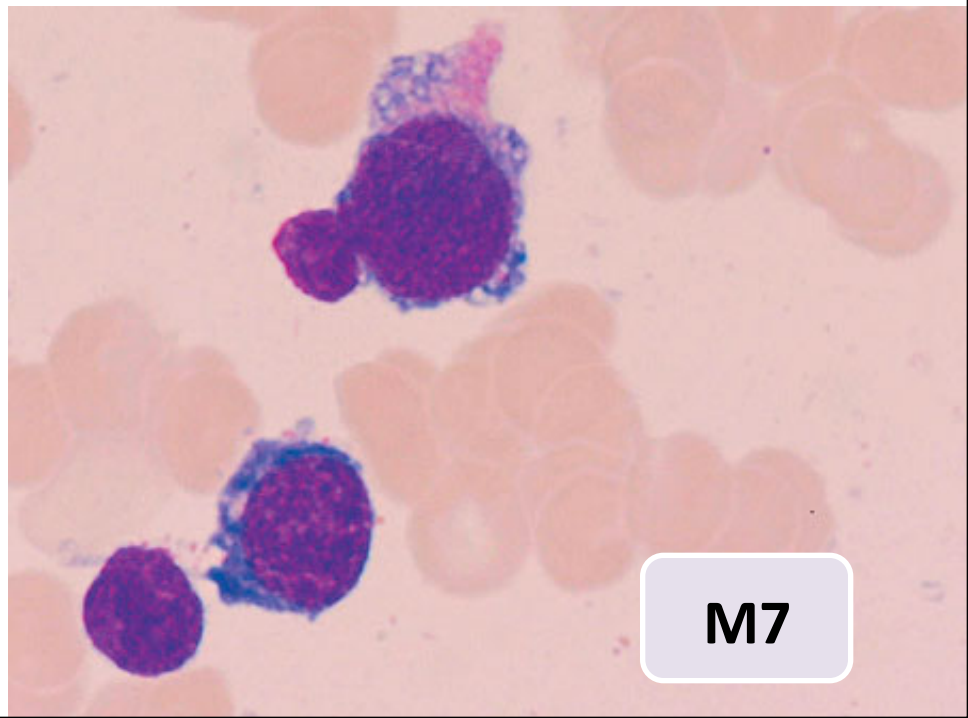

M2


M3


M4


M5


M6


M7

Clinical Features of AML

1-Pancytopenia:

↓WBC→ infection (fever ,septic shock)

↓Hb →anemia (fatigue , headache , pallor ,SOB….)

↓platelets →bleeding (bruises , epistaxis ,menorrhagia…)

Acute onset

2-Organ infiltration:

- Hepatosplenomegally.
- Lymphadenopathy (rare)
- Myeloid sarcoma
- Gum hypertrophy
- CNS disease

More with Acute Monoblastic Leukemia

Clinical Features of AML

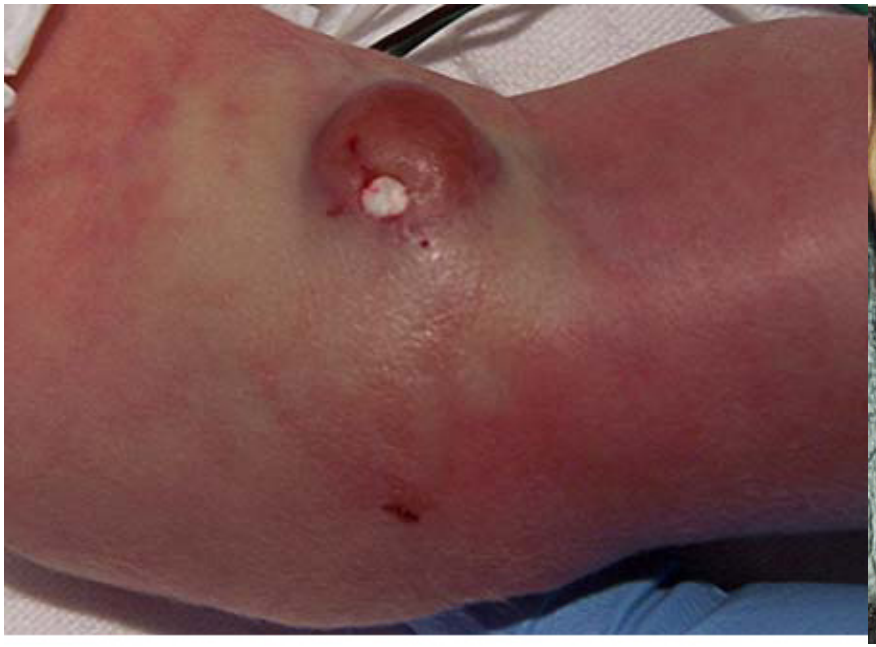
3-Leucostasis (increased blood viscosity)

4-Disseminated Intravascular Coagulation (DIC):

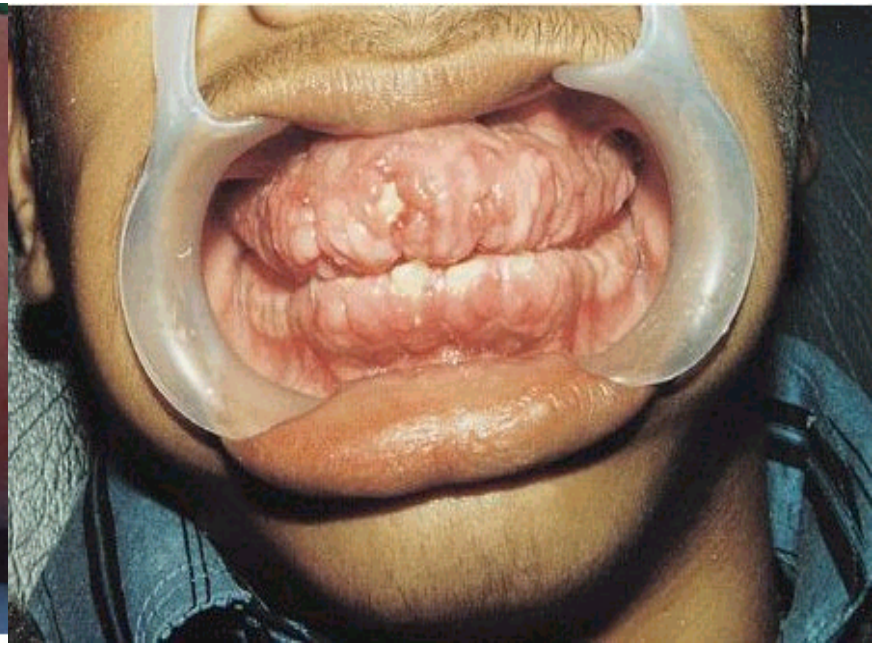
Widespread activation of coagulation system leading to intravascular fibrin deposition &consumption of platelet and coagulation factors which can be manifested as bleeding (85%) or thrombosis (15%)

More with Acute Promyelocytic leukemia (M3)

Clinical Features of AML



Myeloid sarcoma

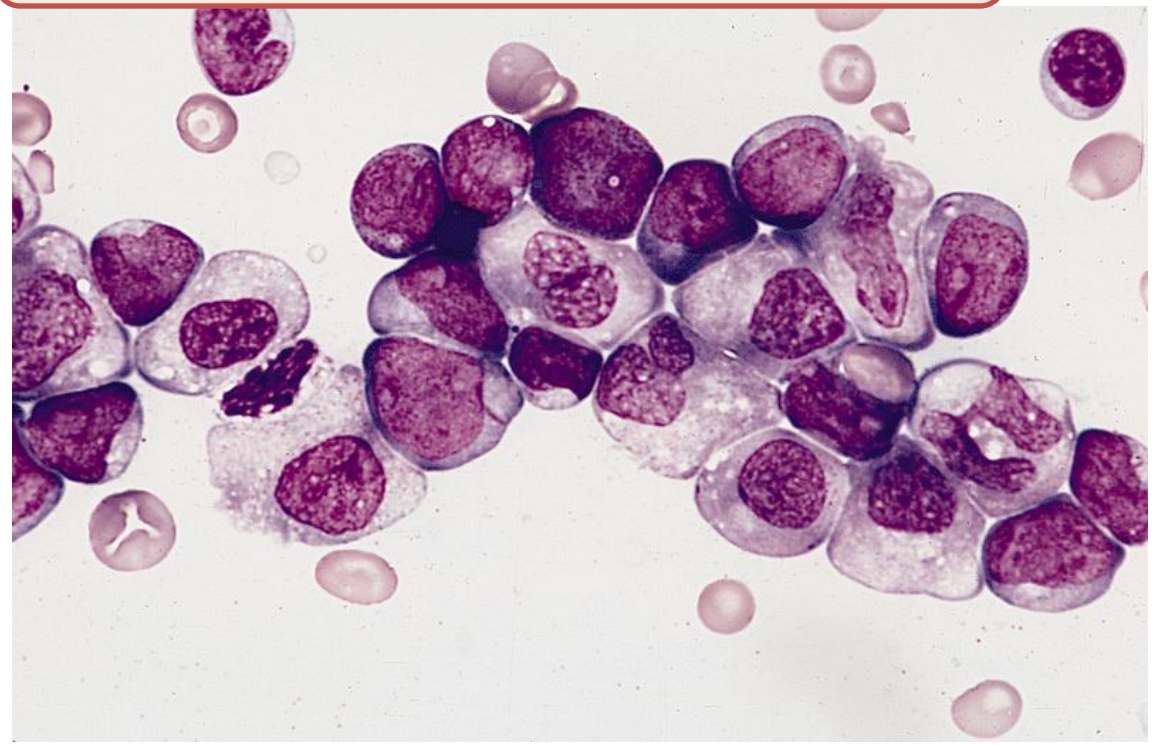


Gum hypertrophy

Case Study

- 65 years old male presented to ER with fatigue ,fever and nose bleeding for 2 weeks.
- O/E : moderate hepatosplenomegaly & multiple bruises.
- CBC : WBC :40 $x10^9/L$ HB: 7g/dL PLT: 51 $x10^9/L$

Blood smear & bone marrow:



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Flow cytometry :

The blast are positive for CD34 ,CD13,CD33,CD117 and MPO

They are negative for CD3,CD10,CD19&CD79a

AML with maturation (M2) (FAB)

Karyotype :

The final diagnosis: AML with t(8;21) (WHO)

Prognosis and treatment

Better prognosis:

- Genetics: t(8;21), inv(16;16) or t(15;17)
- Age: < 60 years
- Primary better than secondary

Treatment

- Chemotherapy:
  - AML: M0-M8 but not M3 (same protocol)
  - AML: M3 (ATRA or arsenic)
- Stem cell transplantation

Acute Leukemia 2

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ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Objectives

1. To emphasize on the general aspects of leukemia including definition , common feature and general classification and the basic diagnostic tool for acute leukemia
2. To understand the clinical features of acute lymphoblastic leukemia
3. To understand the difference between T-ALL and B-ALL in term of clinical and pathological features
4. To recognize the most important prognostic factor for ALL

Acute Lymphoblastic Leukemia (ALL)

- Acute leukemia characterized by proliferation of malignant lymphoid blasts in bone marrow and blood.
- B and T cells
- More common in Children
- Better than AML

Clinical Features of ALL

1-Pancytopenia:

↓WBC→ infection (fever ,septic shock)

↓Hb →anemia (fatigue , headache , pallor ,SOB….)

↓platelets →bleeding (bruises , epistaxis ,menorrhagia…)

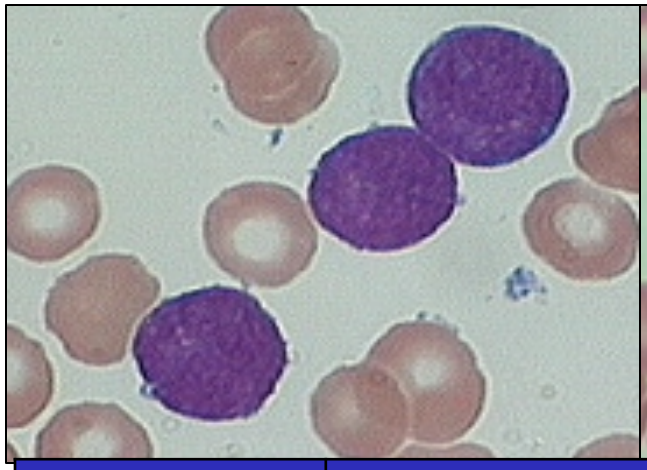
Acute onset

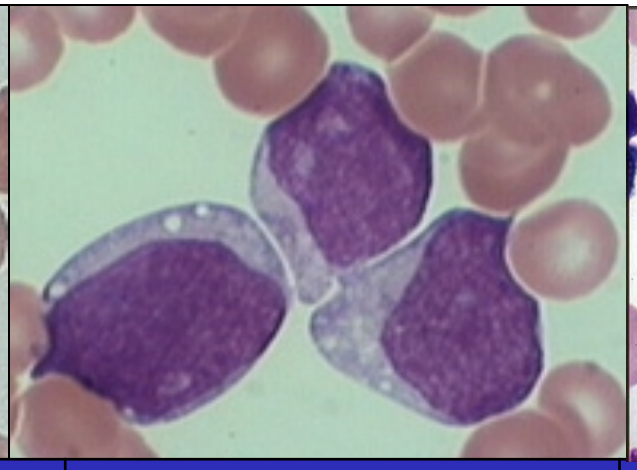
2-Organ infiltration:

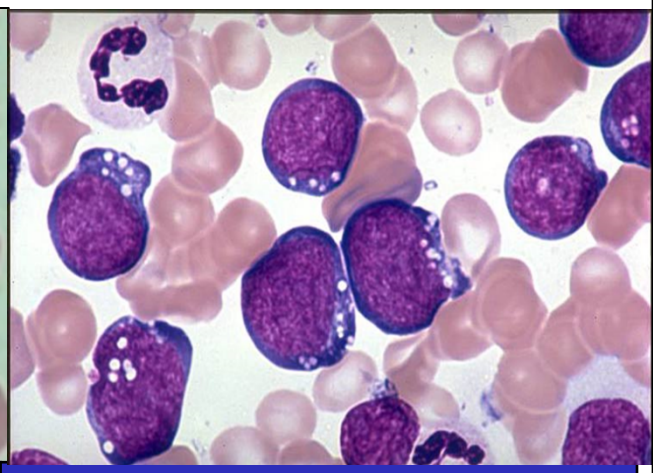
- Lymphadenopathy (very common)
- Hepatosplenomegally.
- testicles involvement
- CNS disease
- Mediastinal mass

Characteristic for T-ALL

Morphological subtypes (FAB)







	L1	L2	L3 Burkitt's
Morphology	Homogenous	Heterogeneous	Homogenous
Size	Small	Variable	Small
Cytoplasm	Little	More	Vaculated
Nucleoli	Not prominent	Prominent	Prominent
Genetics	Variable	Variable	t(8;14) cmyc

Immunophenotypic Subtypes (WHO)

	B cell	T cell
Markers	CD19,CD10,CD79a	CD3
Percentage	80%	20%
Age	Younger	Older
Clinical	-------	Mediastinal mass CNS relapse
WBC count	Less	Higher
Prognosis	Better	Worse
Genetics	t(9;22),t(4;11),t(12;21)	-------

L3 (Burkitt's) represents mature lymphoid neoplasm so it is a type of lymphoma not Acute lymphoblastic leukaemia

Prognosis &treatment

	Better	Worse
Age	2 - 10 yrs	<2 - >10 yrs
Gender	F	M
WBC count	Low	High
Cell type	B cell	T cell
B-ALL phenotype	Common	Others
B-ALL genetics	Hyperdiploidy t(12;21)	Hypodiploidy t(9;22)
CNS involvement	No	Yes

Treatment:

- Chemotherapy (high cure rate)
- Stem cell transplantation

Remember !

- Acute leukaemia is a fatal neoplastic condition
- 20% or more blasts = Acute leukaemia
- Diagnosis requires special investigations
- Auer rods = AML
- AML M3 = DIC &target therapy
- Gum hypertrophy = mostly M4 or M5,
- Mediastinal = T-ALL

Remember !

- Subtypes of AML (M0-M8) + cytogenetic abnormalities
- Subtypes of ALL (T or B cell)
- Main lineages markers are MPO, CD19 and CD3
- Stem cell markers are CD34,TDT
- FAB classification based mainly on morphology
- WHO classification focused more on genetics