

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 & 2017

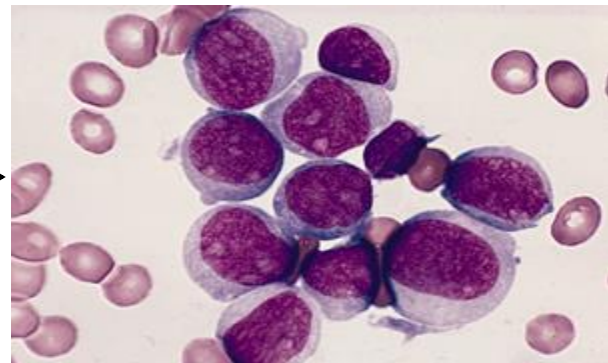
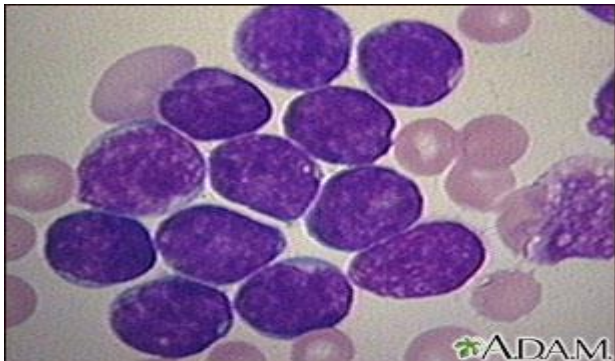
PATHOGENESIS



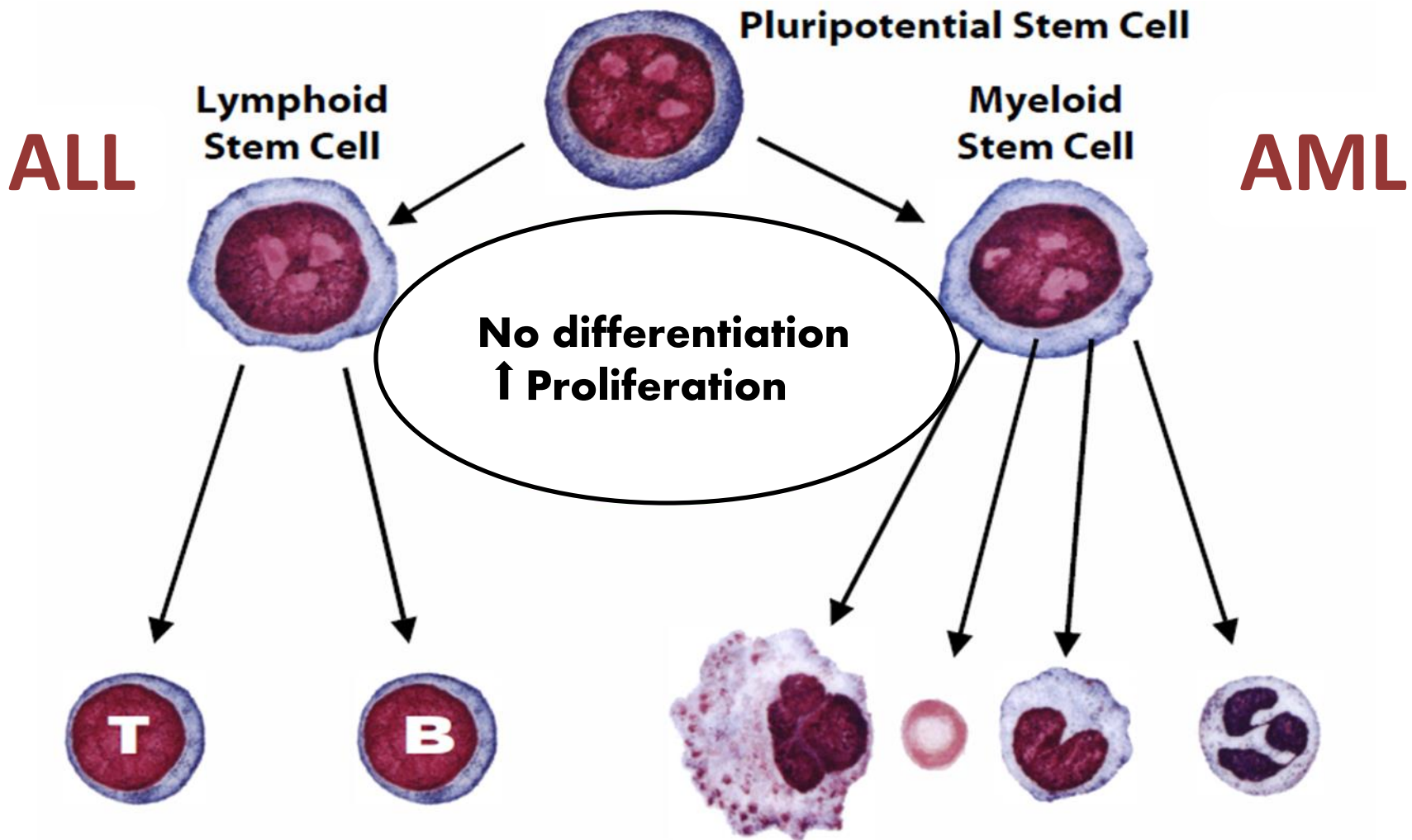
Unknown Mechanism

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

Acute leukemia

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graph TD; A[Acute leukemia] --> B[Acute Myeloid Leukemia]; A --> C[Acute Lymphoid Leukemia]; A --> D[Acute Leukemia of Ambiguous Lineage];
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**Acute Myeloid
Leukemia**

**Acute Lymphoid
Leukemia**

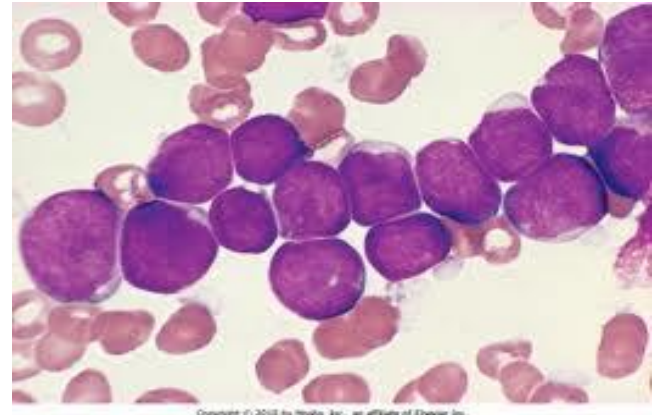
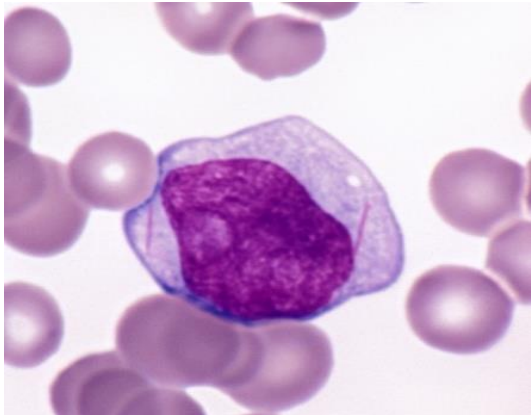
**Acute Leukemia
of Ambiguous
Lineage**

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:

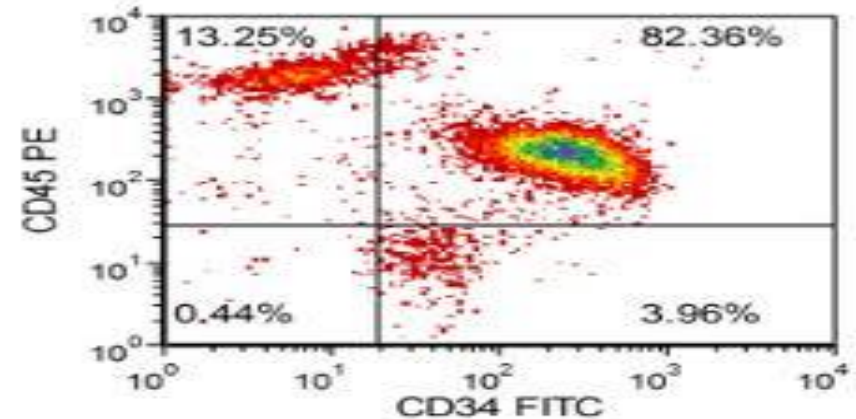
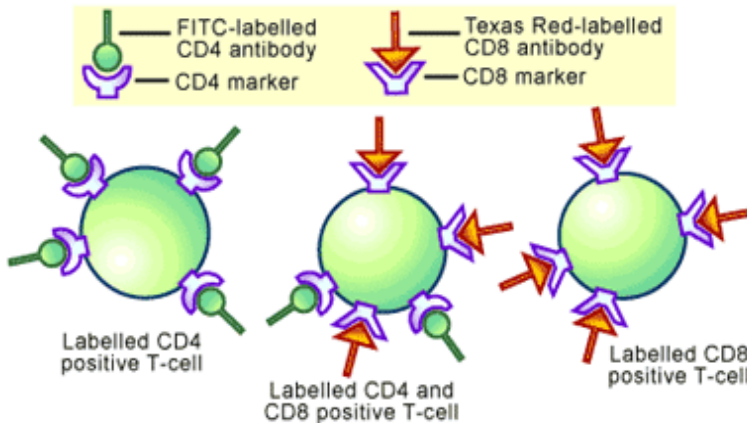
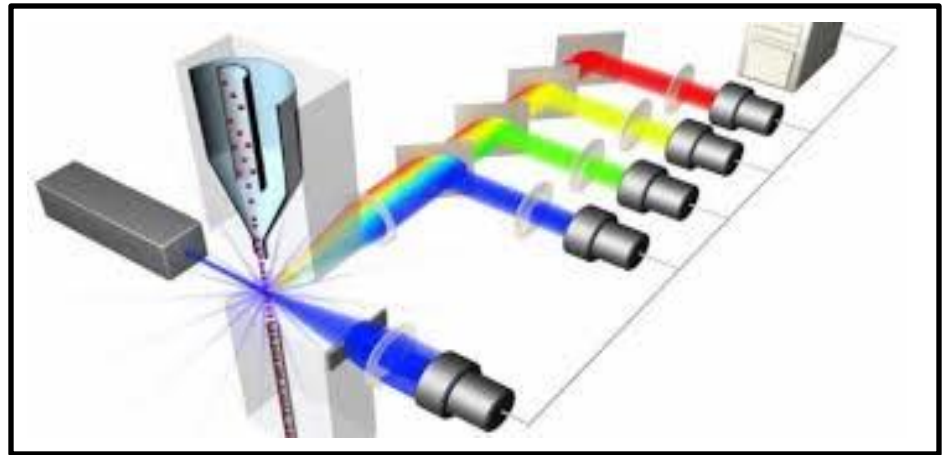
- Size**: medium-Large
 - Nucleous**: round, oval or irregular
 - Nucleolus**: prominent
 - Cytoplasm**: abundant, granular
- Auer rods is characteristic**

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

MPO

CD13

CD33

CD14

CD64

CD41

CD235a

B-Lymphoid

CD10

CD19

CD22

CD79a

T-Lymphoid

CD3

CD4

CD5

CD7

CD8

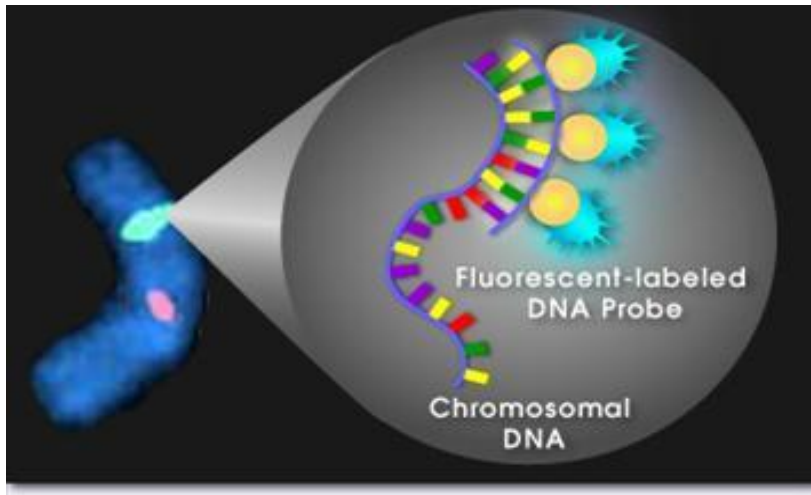
3-Chromosomal Karyotype

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

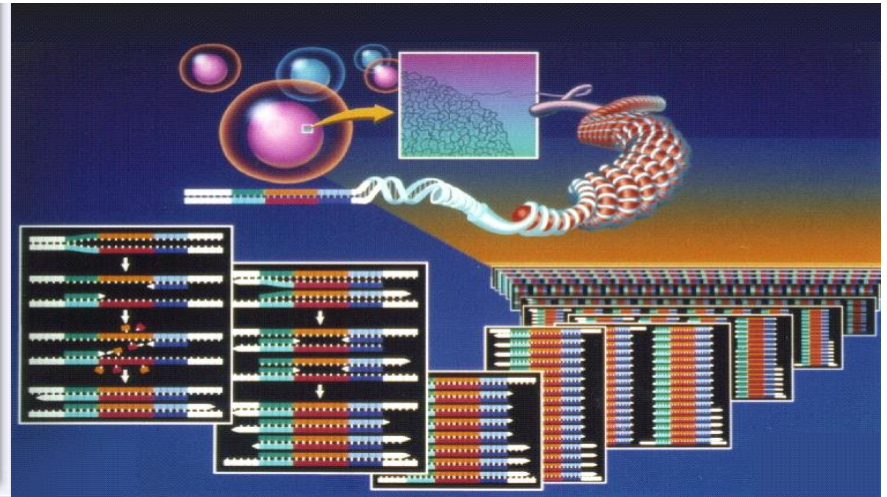


4- Molecular studies:

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

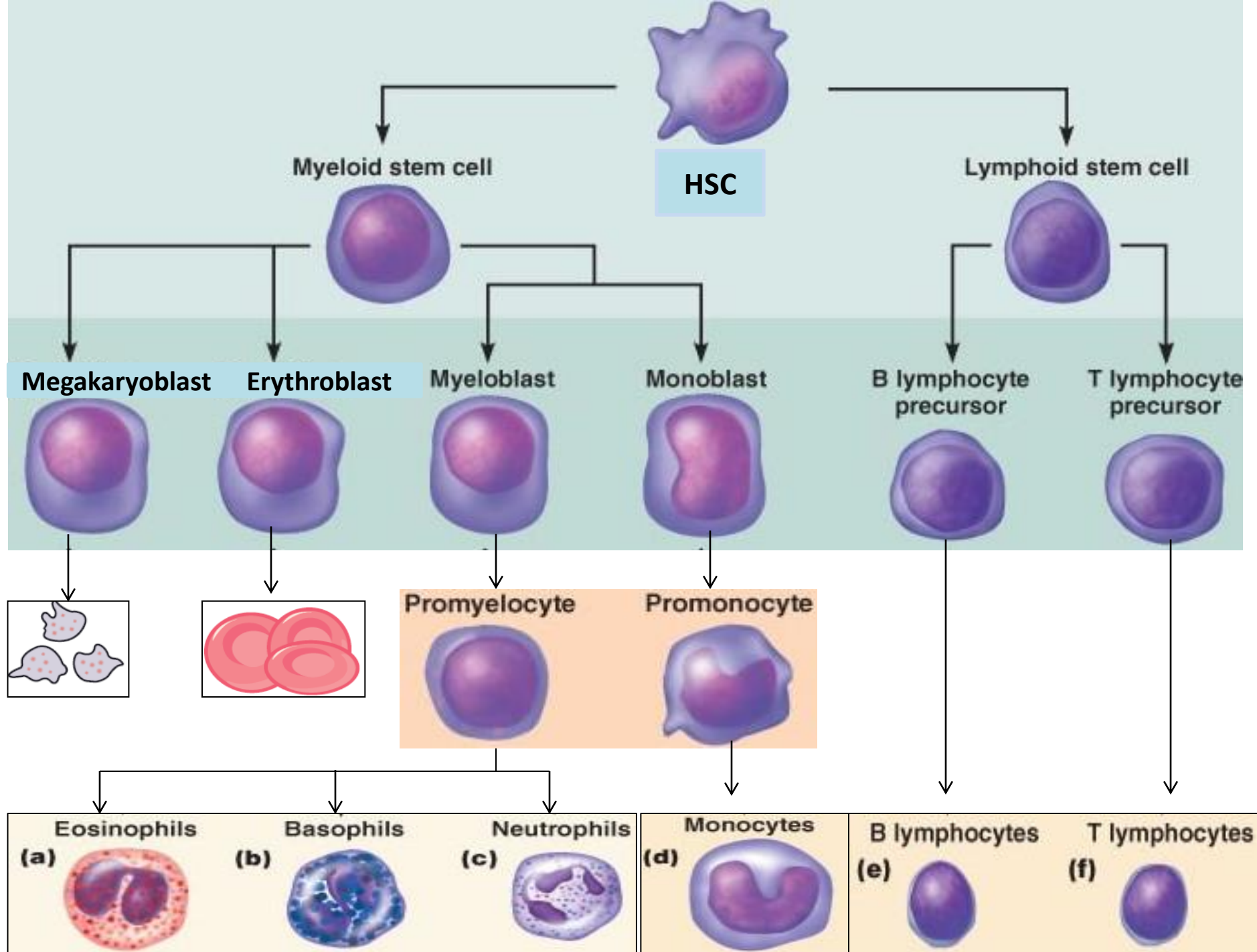
ALL

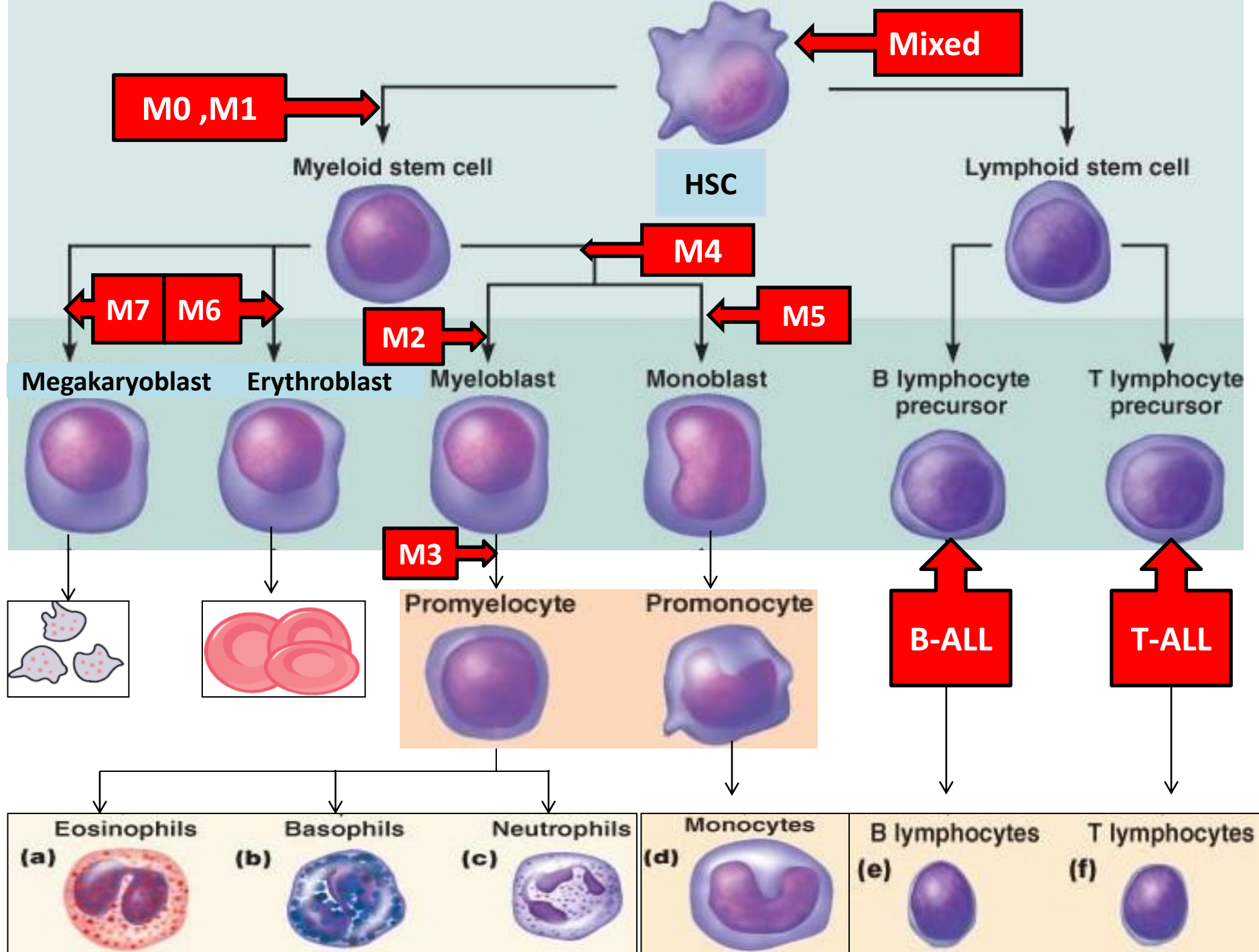
Karyotype	Molecular
t (9;22)	BCR-ABL1
t (4;11)	AF4-MLL
t (12;21)	ETV6-RUNX1
t (5;14)	IL3-IGH

ACUTE MYELOID LEUKEMIA

Acute Myeloid Leukemia

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





FAB Classification

- Based on morphology & flow cytometry

Subtype	Features	Genetics in WHO	Notes
M0	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 \geq 20%
- Significant dysplasia

Prognosis:
poor

Therapy related AML

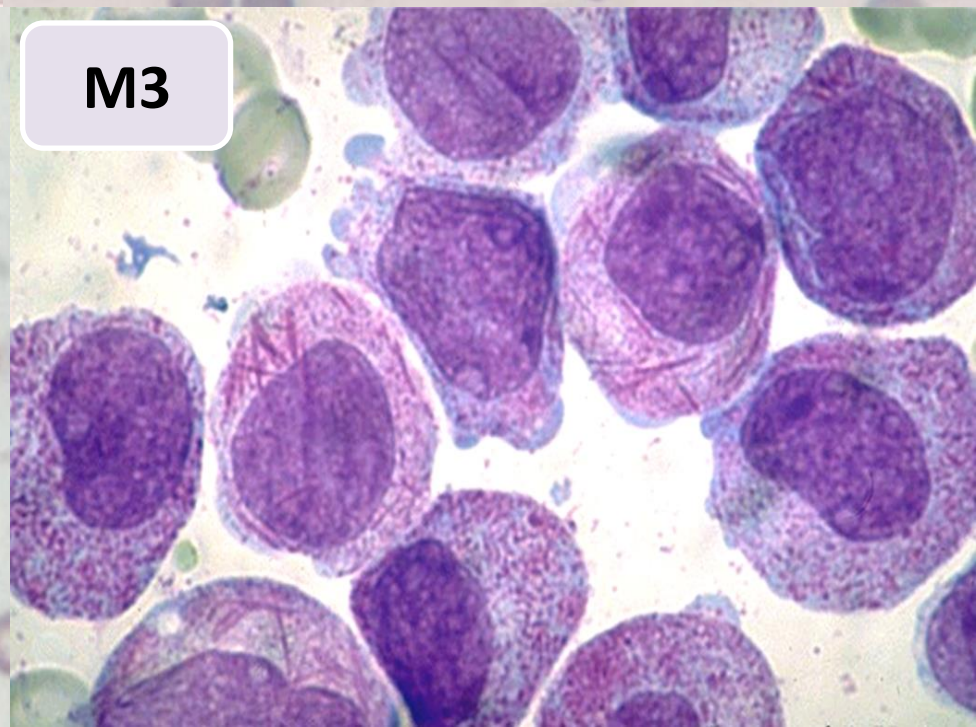
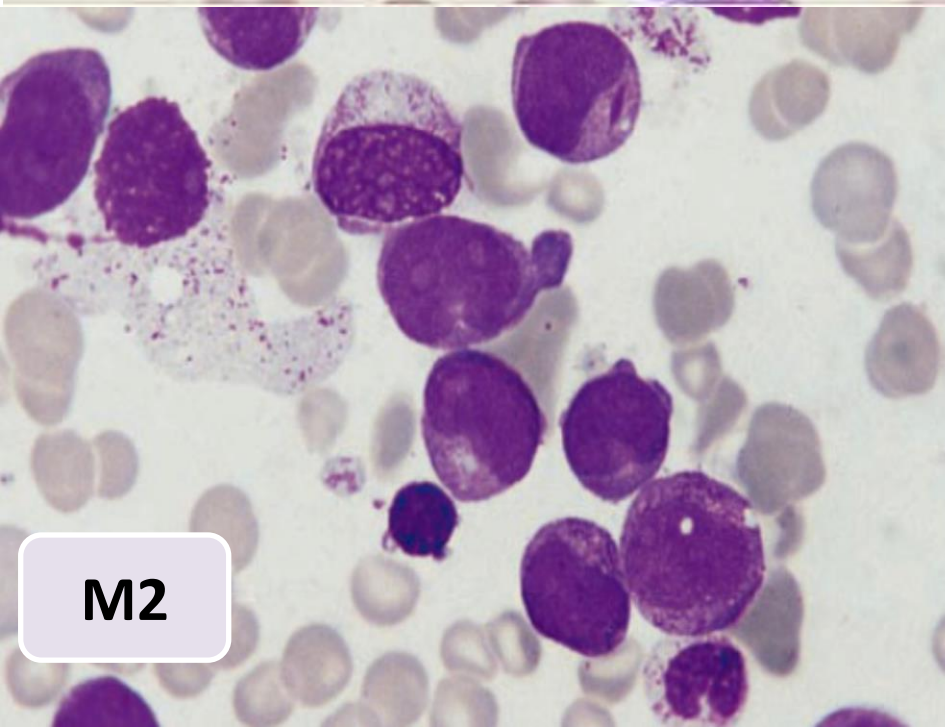
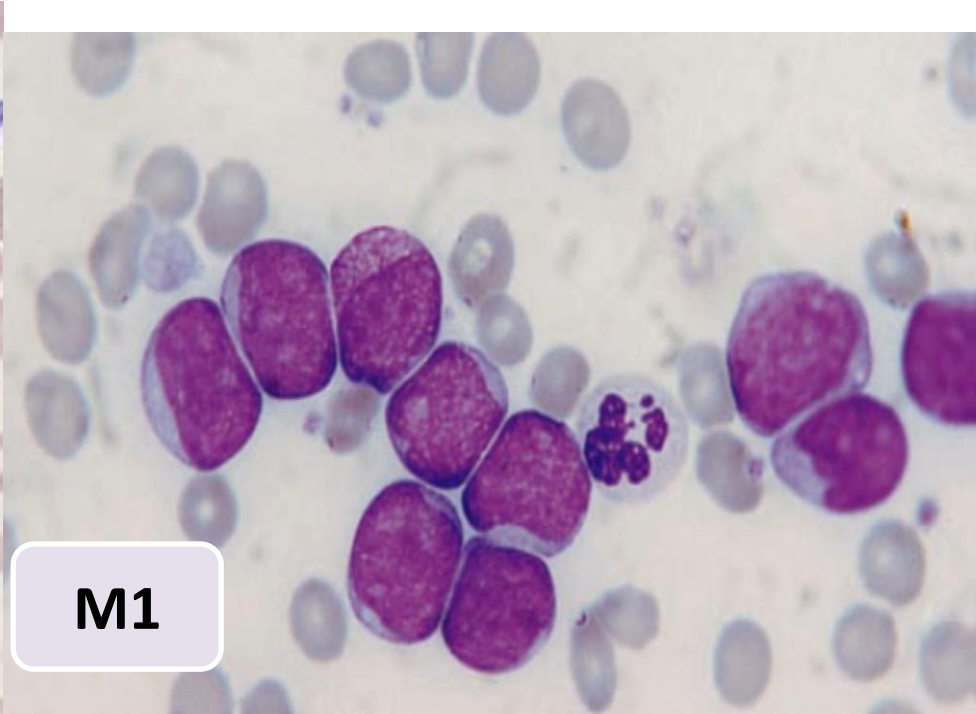
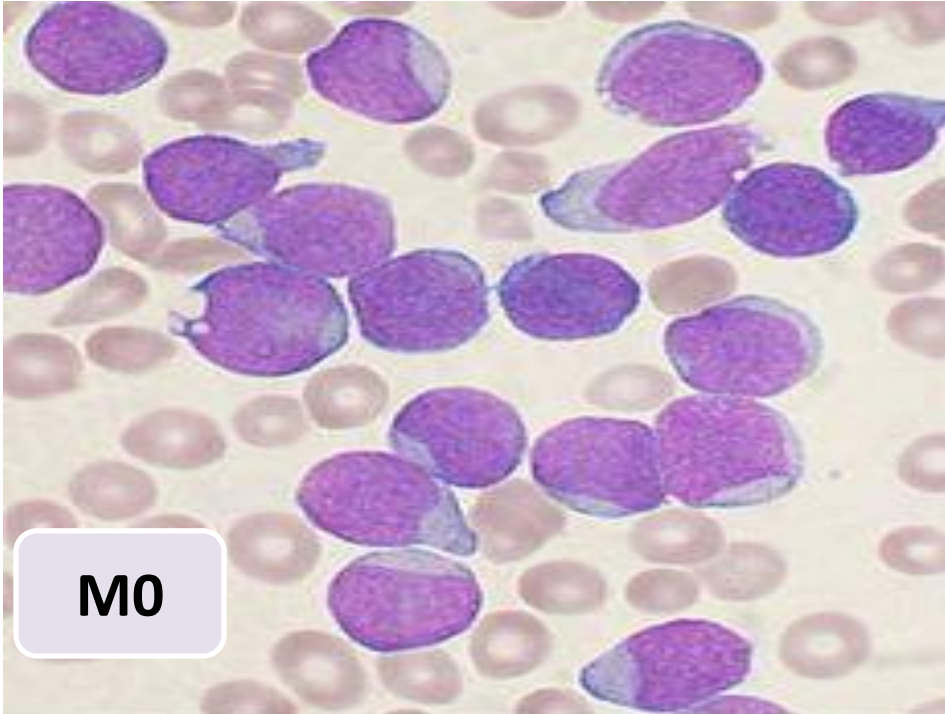
- Blasts \geq 20%
- Previous chemotherapy

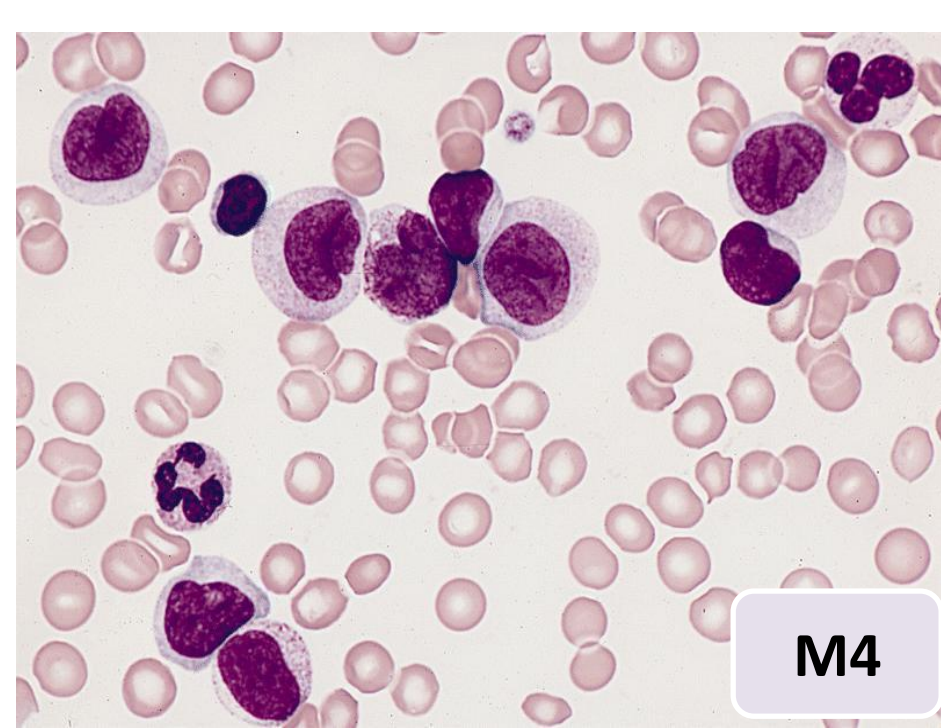
Prognosis:
poor

AML, not otherwise specified (FAB)

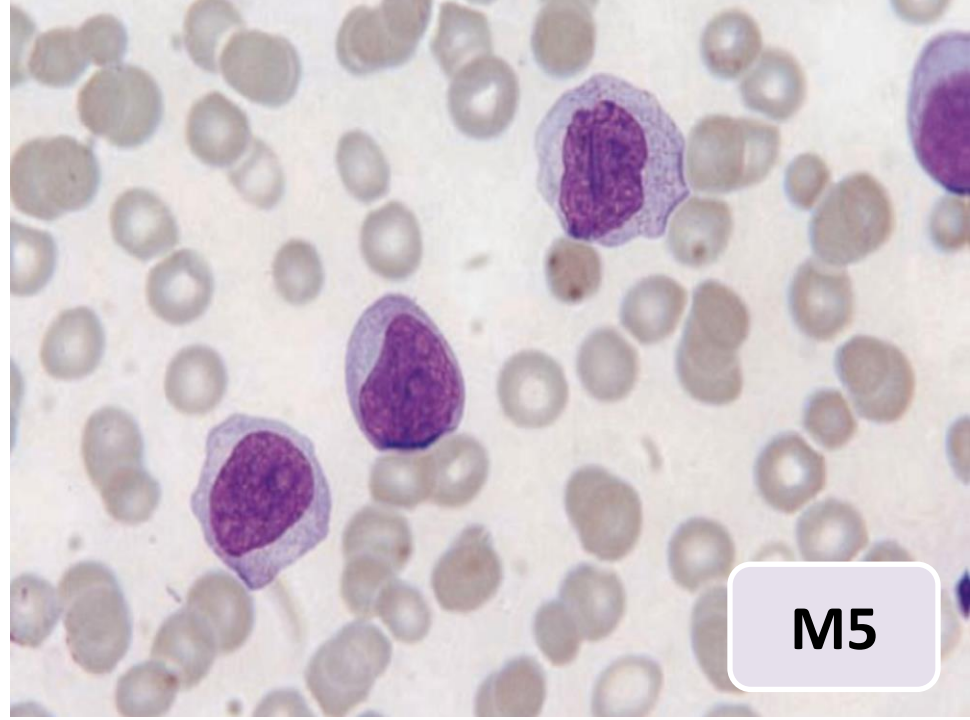
- Blasts \geq 20%
- Genetic: N
- No dysplasia

Prognosis:
Standard



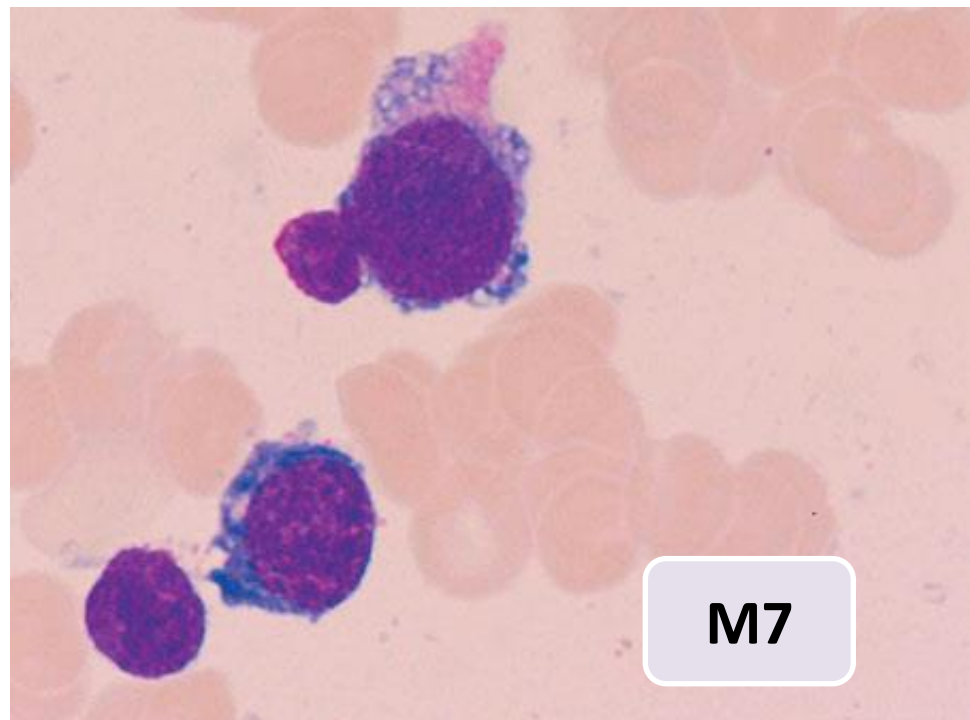
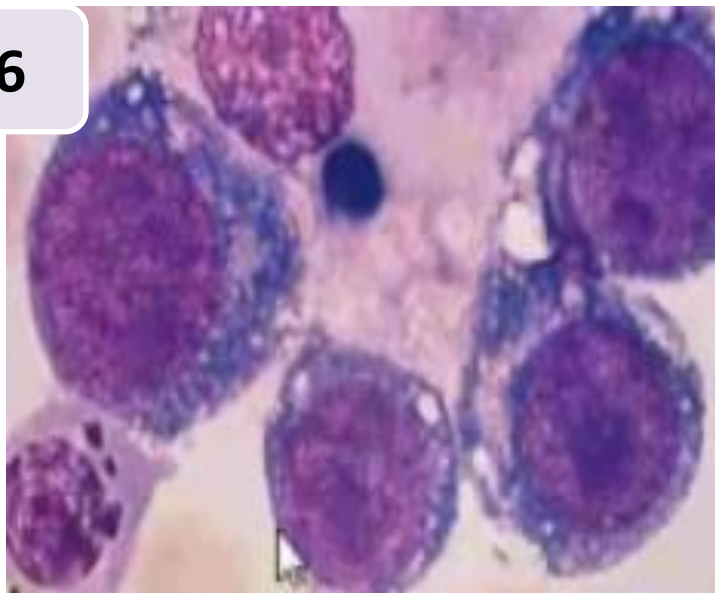


M4



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):

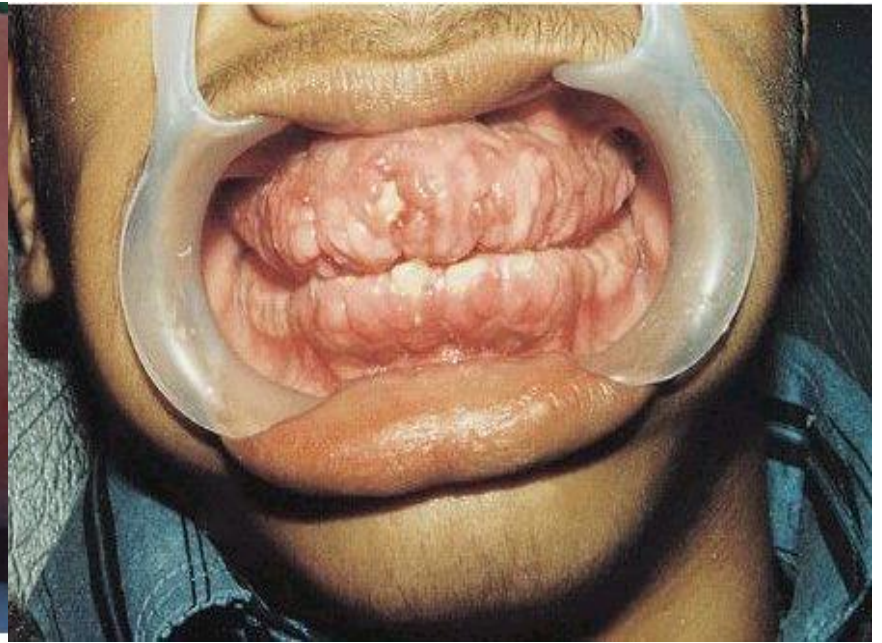
Widespread activation of coagulation system leading to intravascular fibrin deposition & consumption of platelet and coagulation factors which can be manifested as bleeding (85%) or thrombosis (15%)

More with Acute Promyelocytic leukemia (M3)

Clinical Features of AML



Myeloid sarcoma

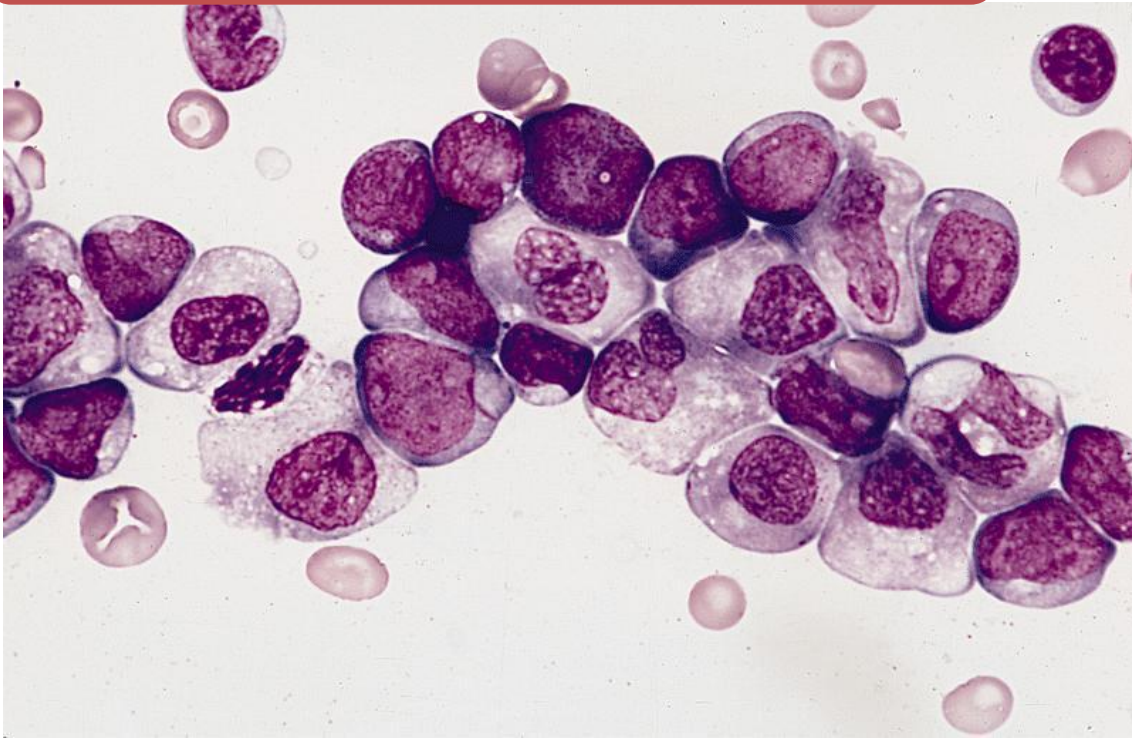


Gum hypertrophy

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 x10⁹/L HB: 7g/dL PLT: 51 x10⁹/L

Blood smear & bone marrow:



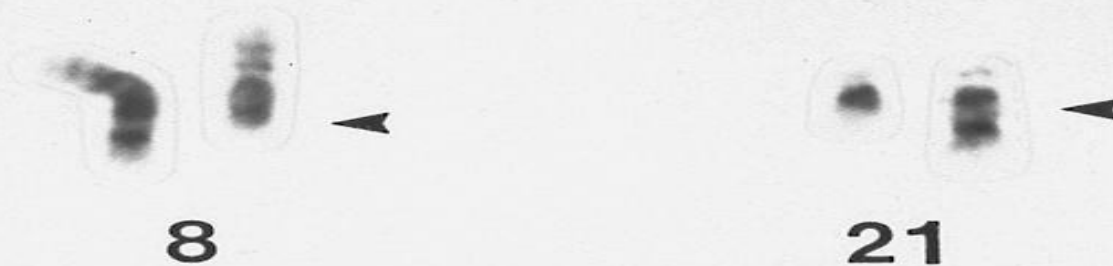
Flow cytometry :

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 :

t(8;21)(q22;q22)



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 LYMPHOBLASTIC LEUKEMIA (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.

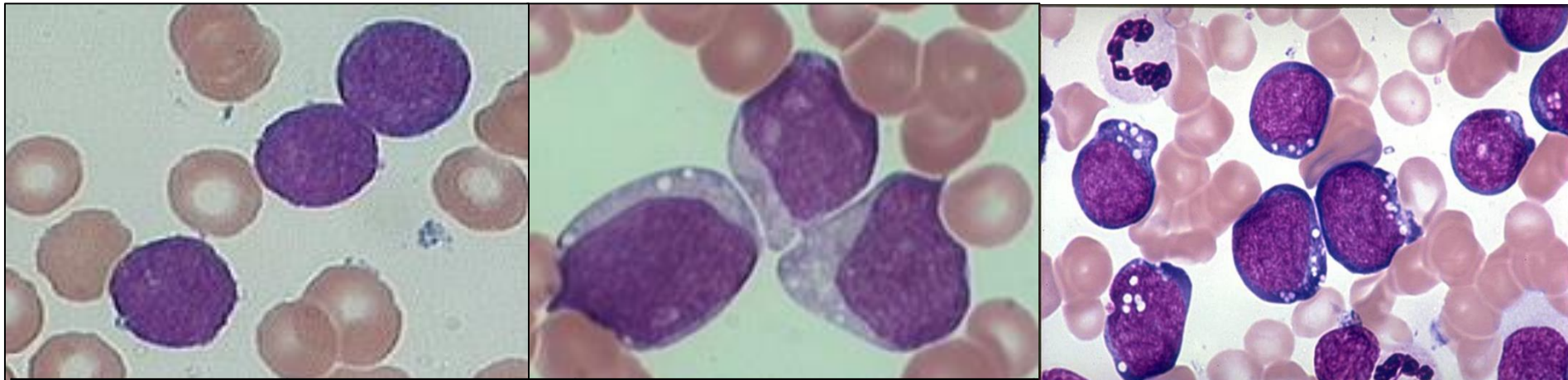
• testicles involvement

•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	Vacuolated
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

