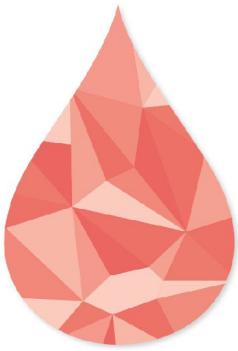


= Haematology 435 =

إن أحسنا فمن الله عزوجل, وإن أخطأنا فمن أنفسنا والشيطان.
نظراً لشمولية العمل لمحاضرات الطلاب والطالبات بإمكانكم اعتماده كمصدر للمذاكرة.

➢ **Color Codes:**

- Pink: Girls' notes. Blue: Boys' notes. Red: Important Notes. Gray: Extra notes.
- Purple: Lecture notes & Pathoma notes.

➢ **Done by:** **Abdulaziz Alshalan** , Ibrahim Alnafisah , Ziyad Alsalem , Naif Alhadi , Khalid Alzhrani , Sami Aljuhani

➢ **Revised by:** **Raghda Alqassim , Samar Alotaibi**

➢ **References:**

- Girls&Boys Doctors Slides and Notes.
- Team 434 & 433.

Revised by
هشام الغفيلي & خولة العماري

➢ **Correction file:** (HERE)

➢ **Check Your Understanding!** (HERE)

❖ Acute leukemia

- Leukemia is named by pathologist Virchow in 1845 which means white cells **Why ? because PCV shows high white cells and low Red cells which is abnormal .**
- Aggressive malignant hematopoietic disorders.
- Accumulation of abnormal blasts (Immature precursors of WBCs) in bone marrow and blood leading to:

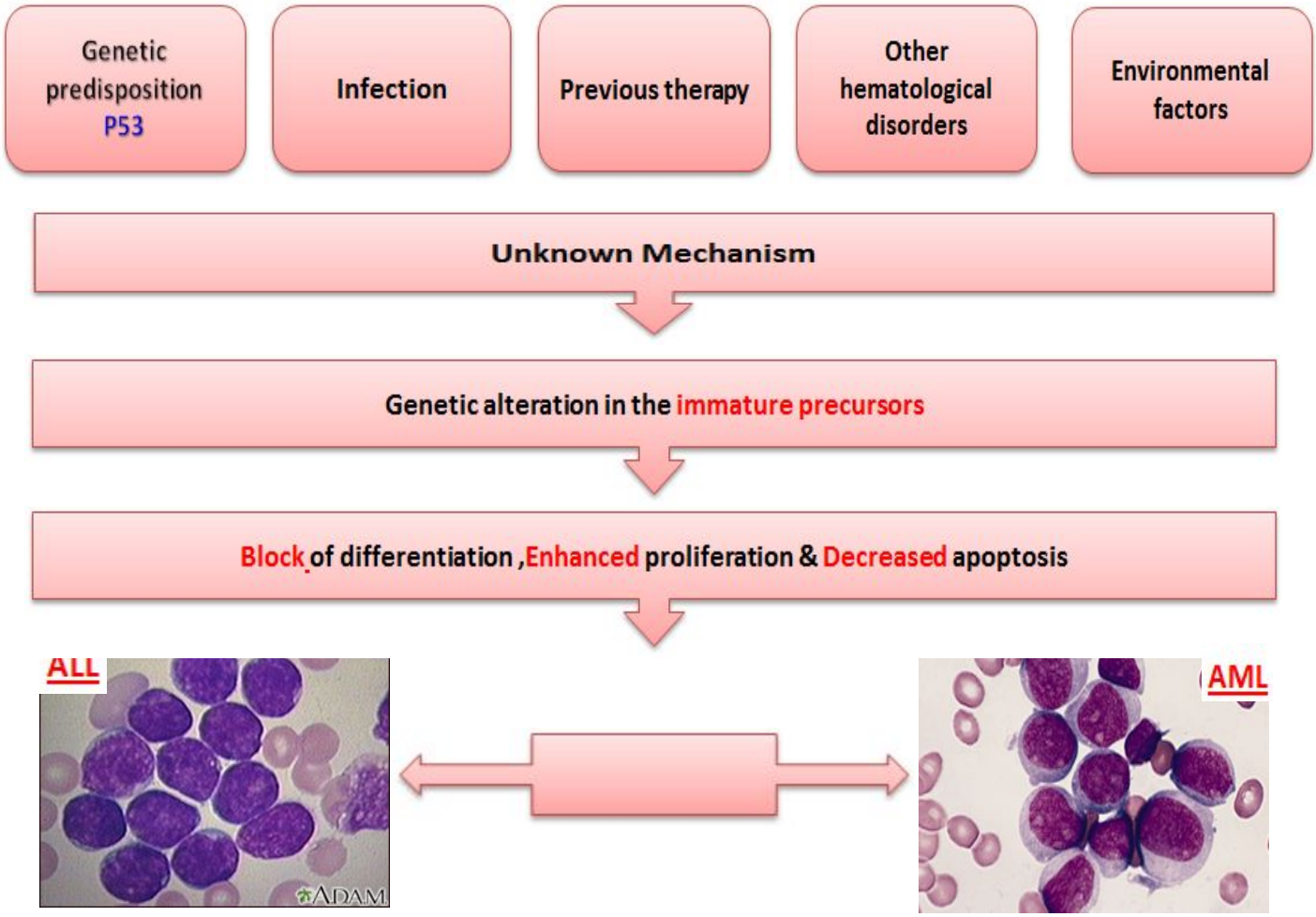
  1- Bone marrow failure (anemia>fatique , neutropenia>infection & thrombocytopenia>bleeding)

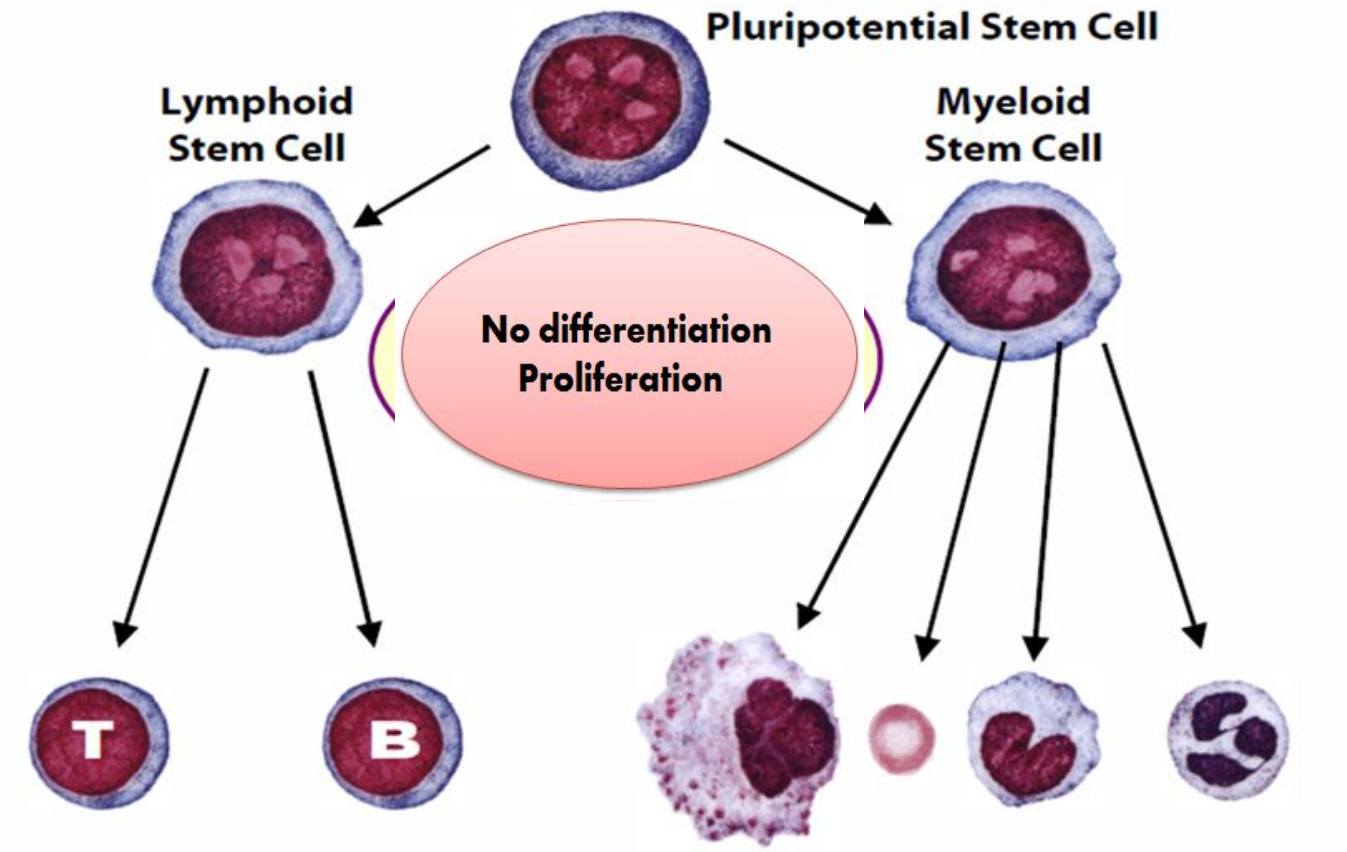
  2- Organ infiltration (hepatosplenomegy , lymphadenopathy)

- Classified by **French–American–British** (FAB) is morphological classification systems in 1976.
- Reclassified by World Health Organization (WHO) is genetics classification in 2001 & 2008.

➢ PATHOGENESIS : (IMPORTANT)

Remember : cancer does not depend on single factor to develop .





➢ Epidemiology :

- AL represent about 8% of neoplastic disease & cause about 4% of malignancy related deaths ! (cure rate is very high)
- Acute myeloid leukemia is more common in adults > 15 per 100.000/year.
- Acute lymphoid leukemia is usually affecting children 76% of childhood leukemia.
-

➢ Acute Leukemia Classification:

1. Acute Myeloid Leukemia.
2. Acute Lymphoid Leukemia.
3. Acute Leukemia of Ambiguous Lineage.

➢ **Basis of Classification:** you should do all of them, one isn't enough.

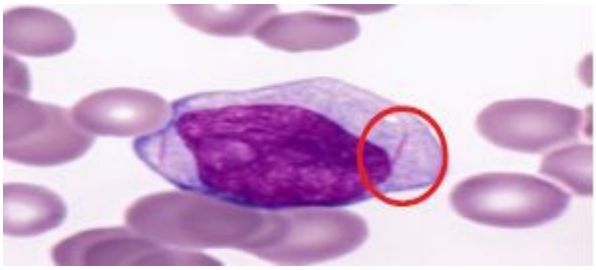
- Clinical history (Previous therapy)
- Morphology
- Flow cytometry
- Chromosomal Karyotyping
- Molecular study

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

- Blast count : it should be **>20%** (more than or equal 20) out of the total cells
- Blast morphology :

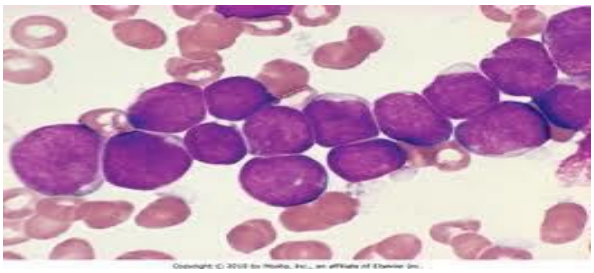
- Myeloblast:

❑ Size: medium-Large
❑ Nucleous: round, oval or irregular
❑ Nucleolus: prominent
❑ Cytoplasm: abundant, **granular**
Auer rods is characteristic (red granules that looks like rods)



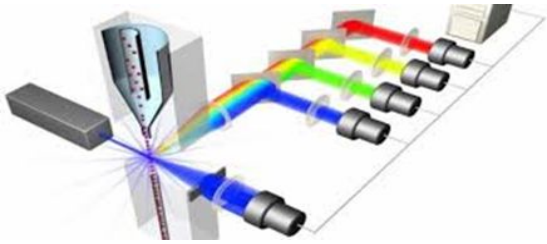
- **Lymphoblast:**

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



2-Flow cytometry: (video)

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.

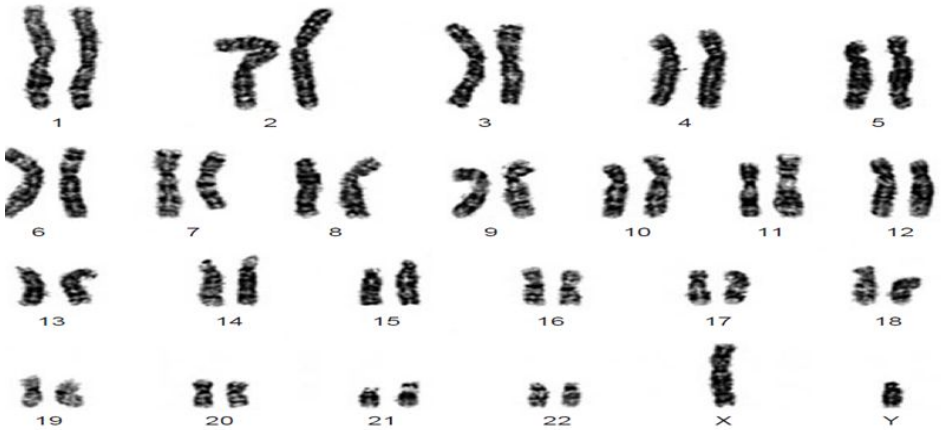


Stem Cell Markers: (**CD34 & TDT**) (tdt is absent in myeloid blasts and mature lymphocytes)		
Myeloid	B-Lymphoid	T-Lymphoid
MPO (myeloperoxidase) CD13 CD33 CD14 CD64 CD41 CD235a	**CD10** **CD19*** CD22 CD79a	**CD3** CD4 CD5 CD7 CD8

*If CD34 & TDT +ve you see the MPO +ve for myeloid OR CD3 +ve for T-lymphoid are enough for diagnosis.
But CD19 +ve is not enough you should see the CD10 , CD22 & CD79a to diagnose it as B-Lymphoid.

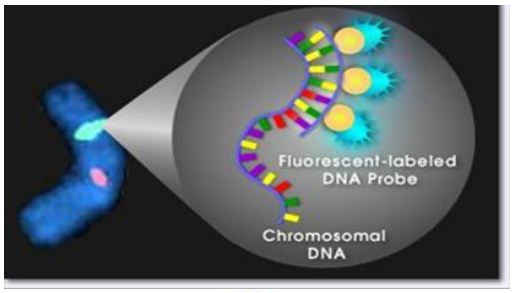
3-Chromosomal Karyotype:

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

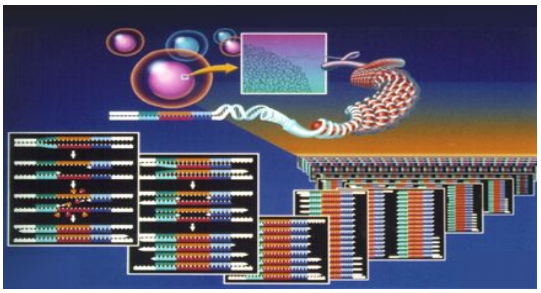


4-Molecular studies: (more advanced technique and expensive)

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 leukaemia:

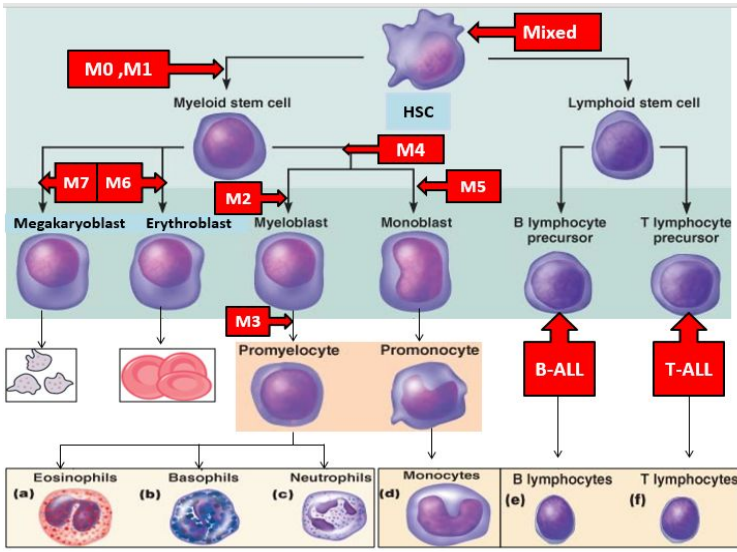
- Group of hematopoietic neoplasms caused by proliferation of **malignant myeloid blasts** (immature cells) in bone marrow and blood.
- To diagnose: Either the blasts must be >20% or t (8;21) t (16;16) or t (15;17)

(يعني ما نقدر نقول انه اكيوت ليوكيميا الا اذا كانت البلاستس اكثر من 20% أو وجدت هذه الطفرات)

- Common in **adult** (but do occur in infants)
- worse than ALL.

➢ FAB classification

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		
M7	Megakaryocytic		
M8	Basophilic		



M3 is the most important and you should know the ones with gum hypertrophy

M6 is very rare .

➢ WHO Classification:

1- AML with **recurrent genetic abnormalities**: (genetic predisposition is the main pathogenesis here): t(8;21) 2- t(16;16) 3- t(15;17), Prognosis is good.

2- **Myelodisplasia** (بناخذها بمحاضرة ثانيه) related AML: Blasts **>20** + significant dysplasia, Prognosis is poor.

3- **Therapy** (e.g. chemotherapy, radiation) related AML: previous chemotherapy + blasts >20, prognosis is poor.

4- AML, **not otherwise specified**: blasts >20 without dysplasia or genetic disposition.

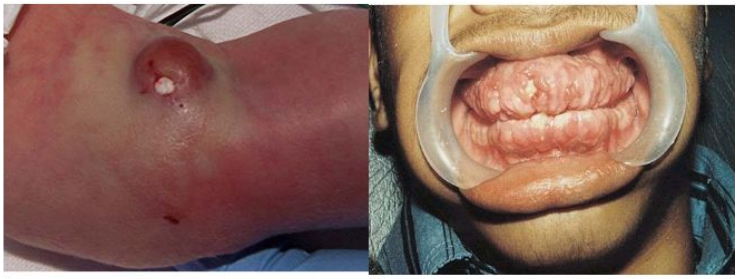
➢ Clinical features:

➢ Pancytopenia[1]: (deficiency in the mature cells)

- ↓WBC→ infection (fever ,septic shock)
- ↓Hb (because the BM is shut down, BM is not produce mature cells)→anemia (fatigue , headache , pallor ,SOB….)
- ↓platelets →bleeding (bruises , epistaxis ,menorrhagia…)

➢ Organ infiltration:

- ➢ Hepatosplenomegaly Why ? because these two are extramedulary hemaptosis (neonatal life)
- ➢ Lymphadenopathy (rare)
- ➢ Myeloid sarcoma (solid tumor composed of immature RBCs) + gum hypertrophy + cns disease → more with acute monoblastic leukemia (M4 and M5)
- ➢ Leucostasis **(increased blood viscosity) (this one and DIC are not supposed to be in organ infilteration)**
- ➢ 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) (Why ? Abnormal promyelocytes contain numerous primary granules that increase the risk for DIC so M3 within 24h either cure (95%) or kill)



Myeloid sarcoma | Gum hypertrophy

➢ Prognosis and treatment:

not otherwise specified : blasts >20 without dysplasia or genetic disposition

Better prognosis: Genetics: **t(8;21)**, inv(16;16) or **t(15;17)**

- Age: < 60 years
- **Primary better than secondary** (as chemotherapy either transplantation or death)

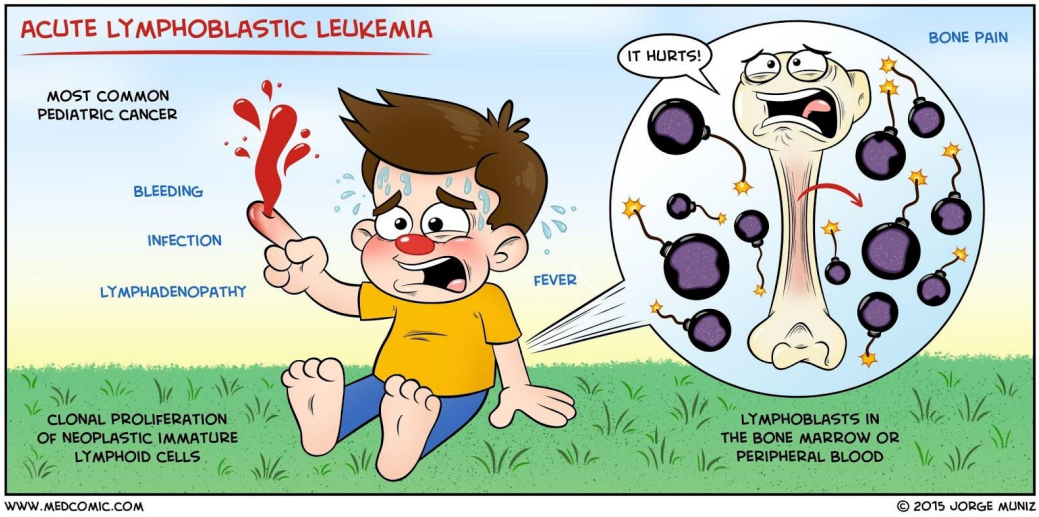
➢ Treatment

- Chemotherapy:
  - ➢ AML: M0-M8 but not M3 (same protocol)
  - ➢ **AML: M3 with target therapy** (ATRA or arsenic) (Treatment is with all-trans-retinoic acid (ATRA, a vitamin A derivative), which binds the altered receptor and causes the blasts to mature)
- Stem cell transplantation.

[1] Deficiency of all three cellular components of the blood (red cells, white cells, and platelets).

❖ Acute Lymphoblastic Leukemia (ALL):

- Acute leukemia characterized by proliferation of **malignant lymphoid blasts** (immature lymphocytes) in bone marrow , blood and Lymph nodes.
- Subclassified into **B lymphocyte ALL** (most common) and **T lymphocyte ALL.**
- More common in **Children** (80% of childhood leukemia).
- Better than AML.



➢ Clinical Features of ALL:

➢ Pancytopenia:

- ↓ WBC **(neutropenia)** results in ⟶ infection (and causes fever and septic shock).
- ↓ Hemoglobin[2] this results in ⟶ **anemia** it's almost always present (fatigue , headache , pallor ,shortness of breath….).
- ↓ Platelets[3] **(thrombocytopenia)** results in ⟶ bleeding (bruises[4], epistaxis[5], menorrhagia[6]

➢ Organ infiltration:

- Lymphadenopathy[7] (**very common**).Why ? because lymphocyte accumulate within lymph nodes
- Hepatosplenomegaly.
- Testicles involvement. (unilateral painless testicular enlargement) **(characteristic of T-ALL)**
- CNS disease. (headache, vomiting, lethargy and nuchal rigidity) **(characteristic of T-ALL)**
- Mediastinal mass[8] **(characteristic of T-ALL)**

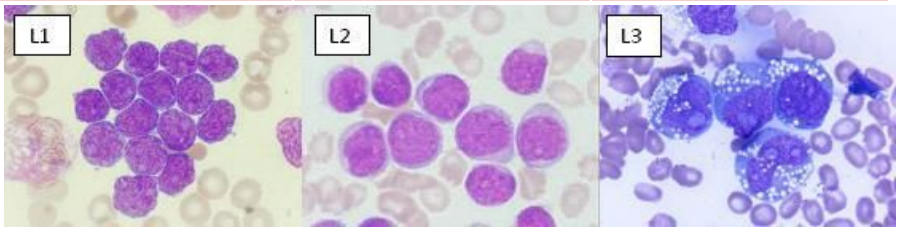
---

[2] Why ? Immature WBCs accumulate in bone marrow and overcrowd or affect the production of other types of cells.
[3] Why ? Same as hemoglobin.
[4] كدمات.
[5] bleeding from the nose.
[6] Heavy menstrual bleeding.
[7] Any disease process affecting a lymph node or lymph nodes.
[8] Any mass, benign or malignant, infectious or reactive, that is found in the mediastinum.

➢ Morphological subtypes (FAB):

The **(FAB) classification systems** refers to a series of classifications of hematologic diseases. It is based on the presence of dysmyelopoiesis قلة تصنيع مكونات الدم and the quantification of myeloblasts and erythroblasts. FAB classification of acute lymphoblastic leukemias: L1–L3 (three subtypes)

	L1	L2	L3 Burkitt's [9]
Morphology	**Homogenous**[10]	**Heterogeneous**[11]	**Homogenous**
Size	**Small**	**Variable**	**Small**
Cytoplasm	**Little**	**More**	**Vaculated**
Nucleoli	**Not prominent**	**Prominent**	**Prominent**
Genetics	**Variable**	**Variable**	**t(8;14) c-Myc** [12]



➢ 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)	-----

➢ Prognosis:

	Better	Worse
Age	2-10 years (Child)	<2y (infante) >10y (Adult)
Gender	F	M
WBC count	Low	High
Cell type	B cell	T cell
B-ALL Phenotype	Common	others
B-ALL genetics	Hyperdiploidy[13] t(12;21) 95% cure	Hypodiploidy t(9;22)
CNS involvement	No	Yes

[9]It represents mature lymphoid neoplasm so it is a type of lymphoma not Acute lymphoblastic leukemia

[10] All are similar with nuclear chromatin, a regular nuclear shape, small or no nucleoli, scanty cytoplasm, and mild to moderate basophilia.

[11]Variety of nuclear chromatin, nuclear shape, nucleoli, amount of cytoplasm and basophilia.

[12]Translocation t(8;14) has moved the **proto-oncogene c-*myc*** from its normal position on chromosome **8** to chromosome **14**.

[13] Because Hyperdiploidy adds extra function, it's better than losing functions

➢ 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**
- **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**