HAEMATOLOGY 436

MEDICINE
KING SAUD UNIVERSITY

تمت المراجعة
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Acute leukemia I&II

Objectives:

- To understand the definition of acute leukemia and recognize the general features of leukemia
- To understand the general concepts of leukemia pathogenesis.
- To understand the clinical presentation and recognize the importance of early diagnosis of acute leukemia
- To understand the general themes of classification and the basic tool of diagnosis
- To recognize the most common presenting features of acute myeloid leukemia and their significance in therapeutic approaches
- To know the most important indicators implicated in prognosis of acute myeloid leukemia.
- To emphasize on the general aspects of leukemia including definition, common feature and general classification and the basic diagnostic tool for acute leukemia
- To understand the clinical features of acute lymphoblastic leukemia
- To understand the difference between T-ALL and B-ALL in term of clinical and pathological features
- To recognize the most important prognostic factor for ALL.

References:

436 girls & boys' slides
435 teamwork slides

Important. Extra. Doctor's Notes

Editing file

Do you have any suggestions? Please contact us!

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or simply use this form

Acute leukemia

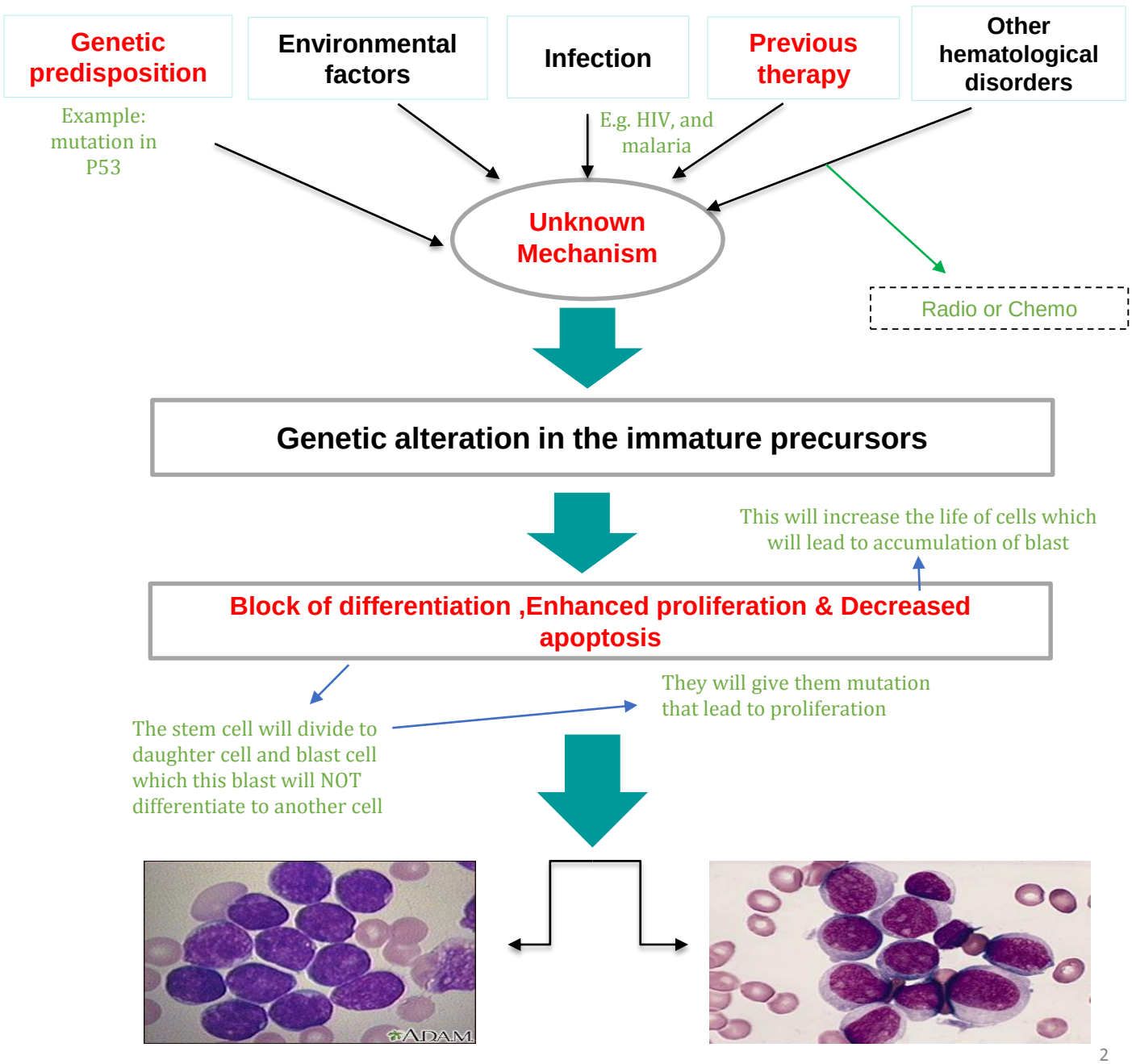
we recommend you to watch the video first 10:18

- Leukemia is named by pathologist Virchow in 1845 which means white cells 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:

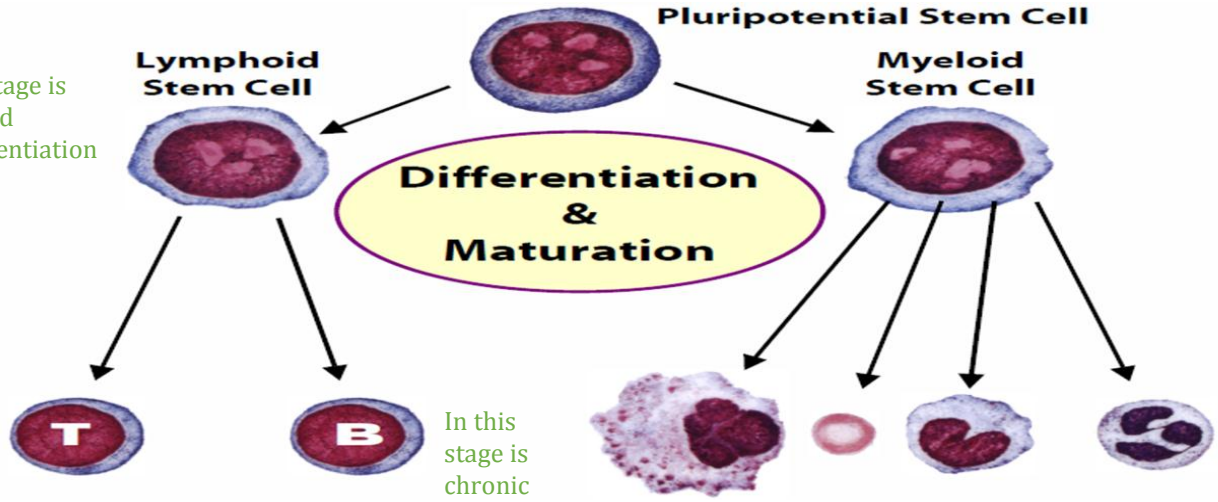
1- Bone marrow failure (anemia , neutropenia , thrombocytopenia)

2- Organ infiltration (hepatosplenomegy , lymphadenopathy)

Pathogenesis : Note: one single factor can NOT lead to cancer



In this stage is acute and undifferentiation



In this stage is chronic

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 (AML). In Adults

2- Acute Lymphoid Leukemia (ALL). In children

3- Acute Leukemia of Ambiguous Lineage.

Basis of Classification

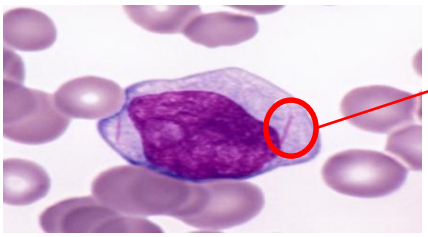
1- Clinical history. (previous therapy) 2- Morphology.

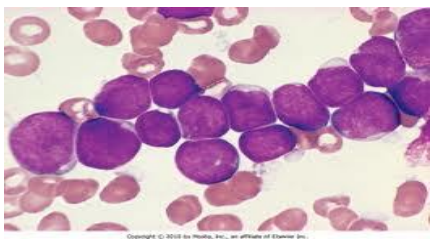
3- Flow cytometry. (BM or Periphery) 4- Chromosomal typing. 5-Molecular study.

1- Light microscopy: (Microscopy in malignancies is important)

(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 :





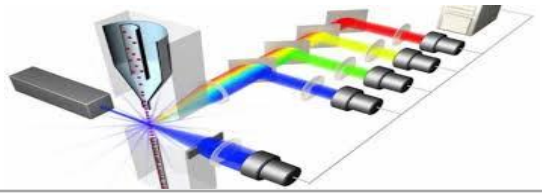
- Myeloblast:
  - ❑ Size: medium-Large
  - ❑ Nucleous: round, oval or irregular
  - ❑ Nucleolus: prominent
  - ❑ Cytoplasm: abundant, granular

Auer rods is an important characteristic!

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

•2-Flow cytometry: a very important technique

• 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. (CD; cluster of differentiation)



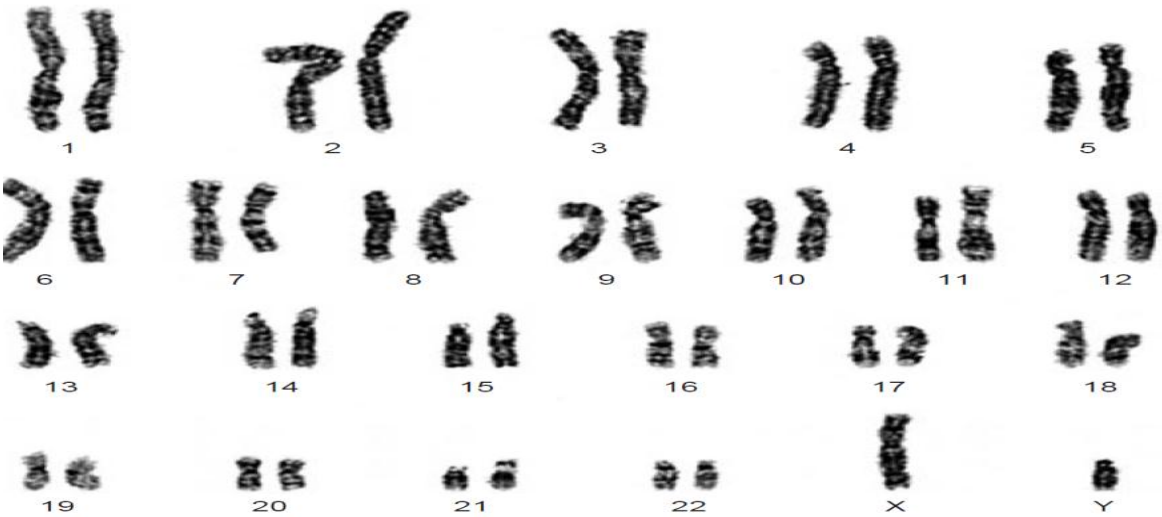
Stem Cell Markers: (CD34& TDT)

When CD34 or/and TDT positive means acute leukemia

Myeloid	B-Lymphoid	T-Lymphoid
enough to diagnose AML ← **MPO** CD13 CD33 CD14 CD64 CD41 CD235a	CD10 CD19 CD22 CD79a To diagnose B-ALL We need at least to markers, usually one is CD19 and the other could be anyone from the list.	enough to diagnose T-ALL ← **CD3** CD4 CD5 CD7 CD8

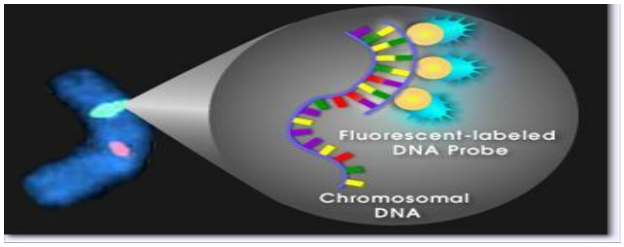
•3-Chromosomal Karyotype

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

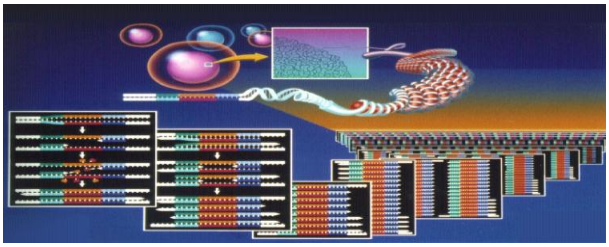


4- Molecular studies:

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 (AML):

- **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.

FBA Classification:-

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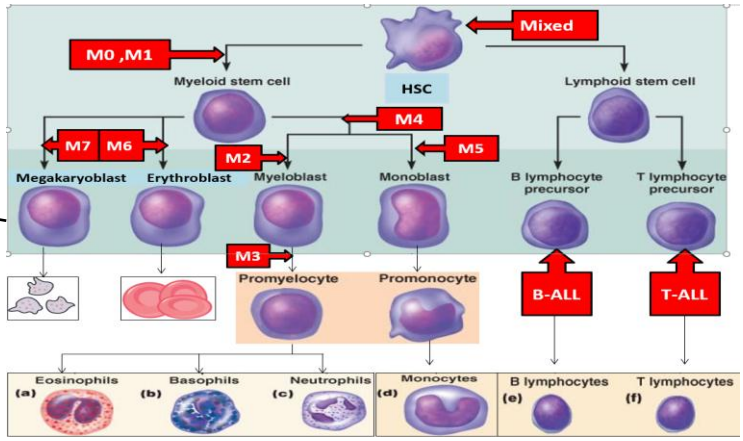
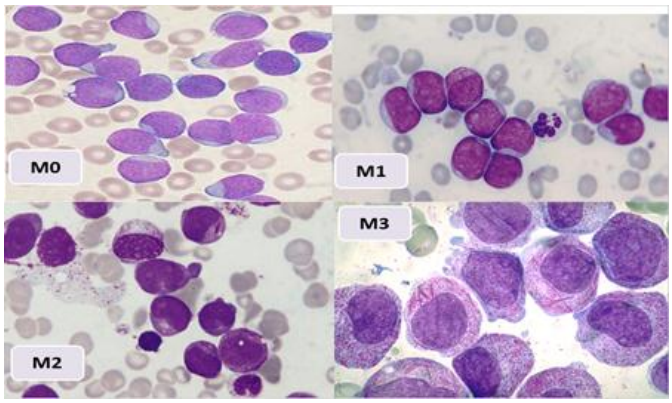


Type	Block differentiation of (lead to accumulation of)	Genes	Notes
M2 (Acute myeloblastic leukemia with maturation)	Myeloblast	t(8;21)	-
M3 (Acute promyelocytic leukemia)	promyelocyte	t(15;17)	Assosiated with DIC
M4 (Acute myelomonocytic leukemia)	Both Myeloblast & Monoblasts	t or inv(16;16)	Assosiated with Gum Hypertrophy
M5 (Acute monocytic leukemia)	Monocytes	t(9;11)	

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		



*This classification is based on morphology and flow cytometry.
*Important to know the notes about M3, M4 and M5 .
- M6 is very rare .

- WHO Classification:

AML with **recurrent genetic abnormalities**:	• 1-t(8;21) • 2- t(16;16) • 3- t(15;17), • **Prognosis:** good
Myelodisplasia 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

Clinical features of AML:

1. Pancytopenia : (deficiency in the mature cells of al blood components) **acute onset:**

• ↓WBC→ infection (fever ,septic shock)

• ↓Hb (because the BM is shut down, BM does not produce mature cells)→ anemia (fatigue ,headache , pallor ,SOB….)

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

2. Organ infiltration:

• Hepatosplenomegaly Why ? because these two are extramedulary hemaptosis (neonatal life)

• Lymphadenopathy (rare)

• Myeloid sarcoma (solid tumor composed of immature RBCs)

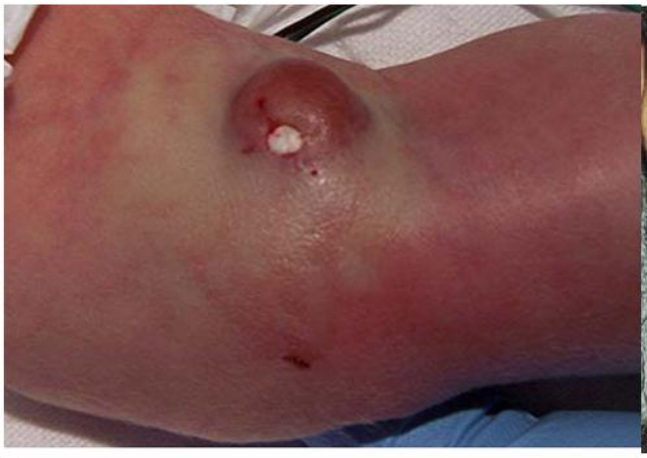
• gum hypertrophy

•CNS disease

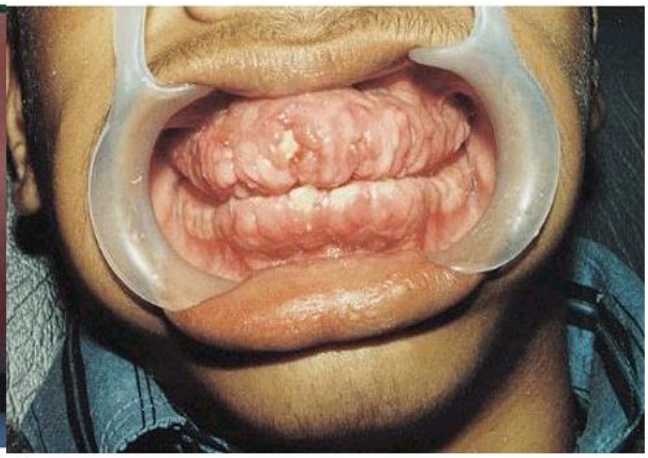
→ More with Acute Monoblastic Leukemia (M4&M5)

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)** (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

Better Prognosis:-

- Genetics: t(8;21) , inv(16;16) or t(15;17) (if you discover and treat them early)
- 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.

Case Study:-

- 65 years old male presented to ER with fatigue ,fever and nose bleeding for 2 weeks.
- **On Examination :** moderate hepatosplenomegaly & multiple bruises.
- **CBC :** WBC :40 x109/L HB: 7g/dL PLT: 51 x109/L

Indicate AML ↓

- **Flow cytometry :**

- The blast are positive for **CD34** (indicate Acute Leukemia),CD13,CD33,CD117 and **MPO**
- They are negative for CD3 (-ve for B-ALL), CD10,CD19&CD79a (-ve for T-ALL).

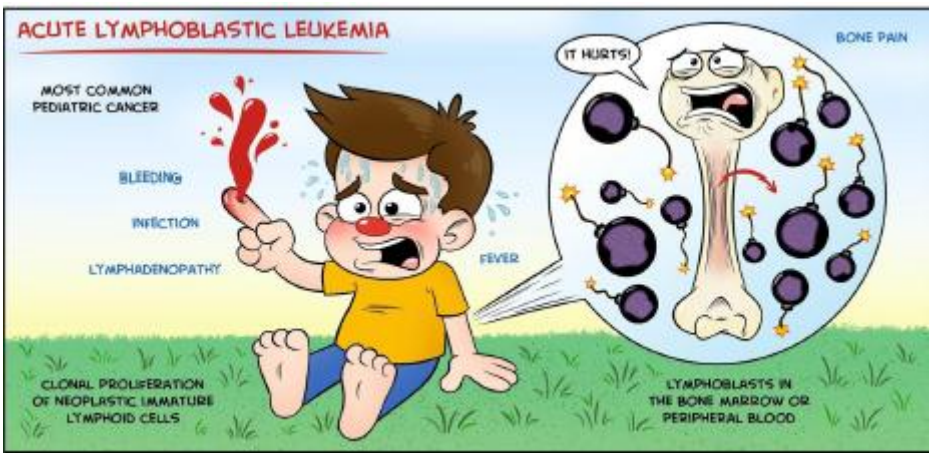
- **Karyotype: t(8;21).**

- **Diagnosis:**

- AML with maturation (M2) (FAB classification)
- AML with t(8;21) (WHO classification)

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:

1. Pancytopenia : (deficiency in the mature cells of al blood components) acute onset:

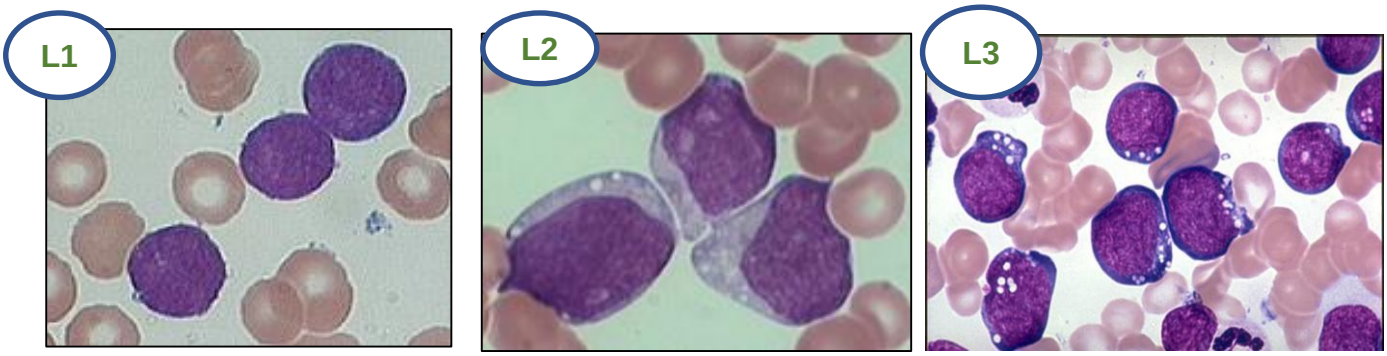
- ↓WBC→ infection (fever ,septic shock)
- ↓Hb (because the BM is shut down, BM is not produce mature cells)→ anemia (fatigue ,headache , pallor ,SOB….)
- ↓platelets →bleeding (bruises , epistaxis ,menorrhagia…)

2. Organ infiltration:

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

Note: there is NO gum hypertrophy

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) c-Myc

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

CD34 and TDT negative

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 yrs**	**<2 - >10 yrs**
Gender	**Female**	**Male**
WBC count	**Low**	**High**
Cell type	**B cell**	**T cell**
B-ALL phenotype	**Common** **They mean positive CD10**	**Others**
B-ALL genetics	**Hyperdiploidy t(12;21)**	**Hypodiploidy t(9;22)**
CNS involvement	**No**	**Yes**

Treatment:

- Chemotherapy (high cure rate)
- Stem cell transplantation

THIS SLIDE IS: IMPORTANT X (10^9)

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.

MCQs:

1-Talal is 25 years old from Hafer Albaten, his blast count were 8% and he has a mutation in t(8;21) So, he doesn't have acute lymphoblastic leukemia:

A-true B-false

2-which one is true about acute lymphoblastic leukemia:

A-Burkitt's is a type of ALL
B-present with gum hypertrophy
C-present with lymphadenopathy

3-A 16 female patient came to the hospital with fever, fatigue and multiple bruises. A blood sample was taken and under the microscope the cells appeared homogeneous with small sizes and not prominent nuclei, then she diagnosed with acute lymphoblastic leukemia, according to the morphological features and (FAB) classification what is the subtype of the disease:

A- L2 B-L3 Burkitt's C-L1

4- which one is NOT clinical feature of acute myeloid leukemia:

A-lymphadenopathy B-myeloid sarcoma
C-CNS disease D-mediastinal mass

5-A patient came to the hospital, he noticed that his testis is enlarge , and he sometimes have epistaxis
also he is short of breath. The doctor diagnosed him with acute lymphoblastic leukemia on further examination the doctor did flow cytometry, the results were:
CD19-negative CD10-negative, CD3-positive, what is the diagnosis?

A- B cell ALL B- T cell ALL
C-acute myeloid leukemia

6-A 65 years old male patient with splenomegaly and Disseminated intravascular
coagulation, genetic test revealed a translocation between chromosome 15 and 17 t(15;17) what is the diagnosis?

A-Acute monoblastic leukemia
B-Acute promyelocytic leukemia
C-Acute myeloid leukemia with maturation
D-Acute myeloid leukemia without maturation

6-B
5-B
4-D
3-C
2-C
1-A

Good Luck!

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