Acute leukemia I & II

GNT Block

COLOR INDEX:

- Main text
- Dr. Notes
- Male's text
- Femal's text
- Important
- Extra

Editing file:

Objectives

*No objectives were found in both male and female slides

Our YouTube's playlist for this lecture!

This lecture was given by: Dr. Mansour Aljabry and Prof. Fatma Al Qahtani

EXTRA

Leukaemias Overview

Definition

The leukaemias are a group of disorders characterized by the **accumulation of malignant white cells in the bone marrow and blood**
These abnormal cells cause symptoms because of

- **bone marrow failure** (e.g. anaemia, neutropenia,thrombocytopenia)
- **infiltration of organs** (e.g. liver, spleen, lymph nodes, meninges, brain, skin or testes). (less commonly)

Leukemia

Classification based on

Disease state

Chronic

distinguished from acute leukaemias by their slower progression

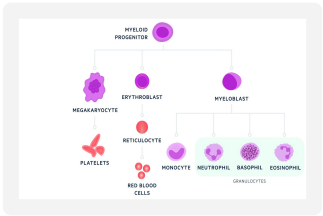
Acute

usually aggressive diseases

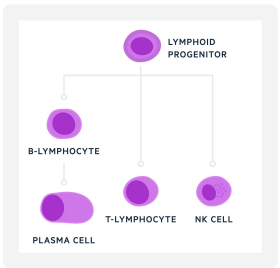
accumulation in the bone marrow of early hematopoietic cells known as **blast cells**

Cell lineage

Myeloid



Lymphoid



The major types of leukemia are:

A. **Acute lymphoid leukemia (ALL)**

B. **Acute myeloid leukemia (AML)**

C. **Chronic lymphoid leukemia (CLL)**

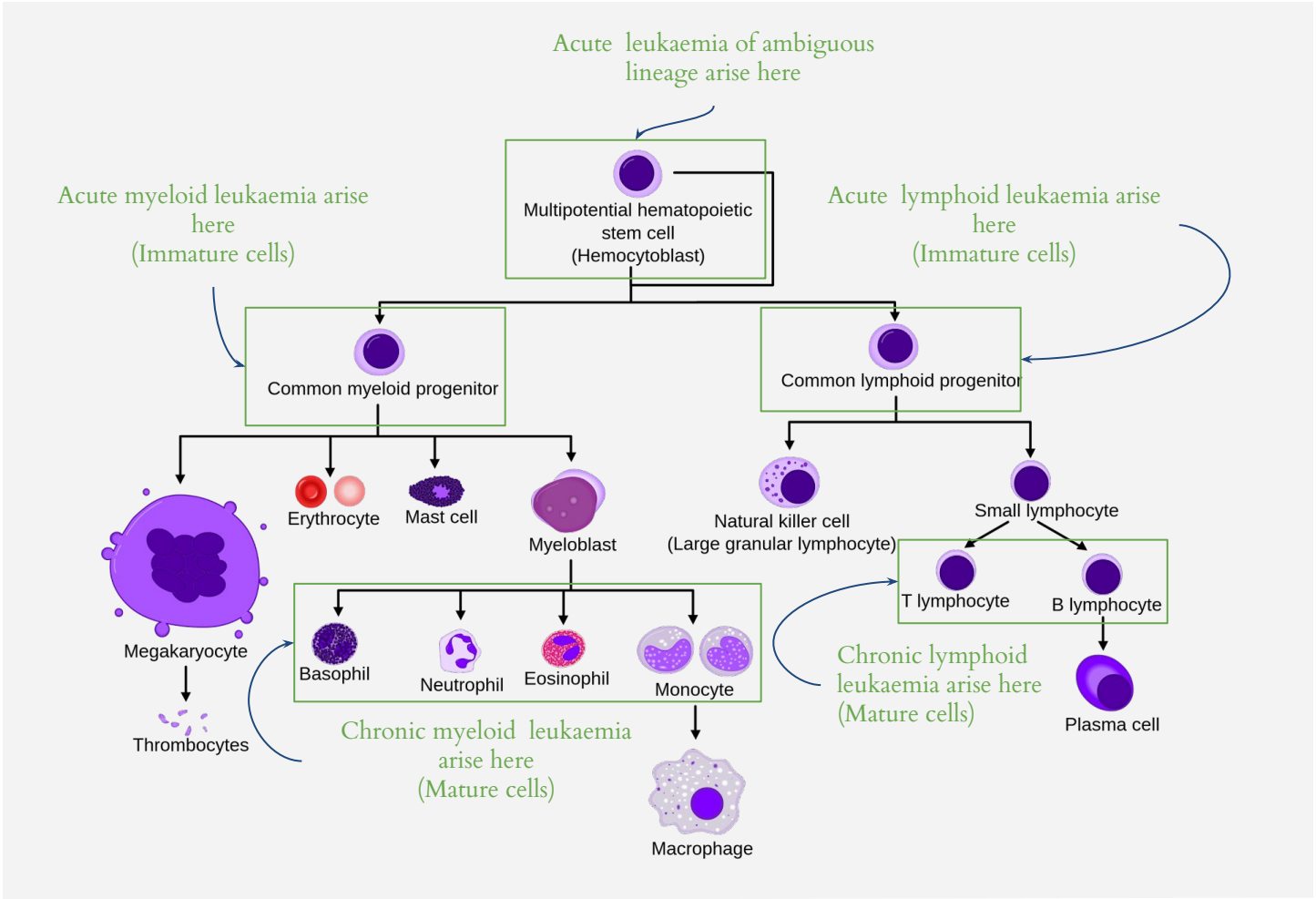
D. **Chronic myeloid leukemia (CML)**

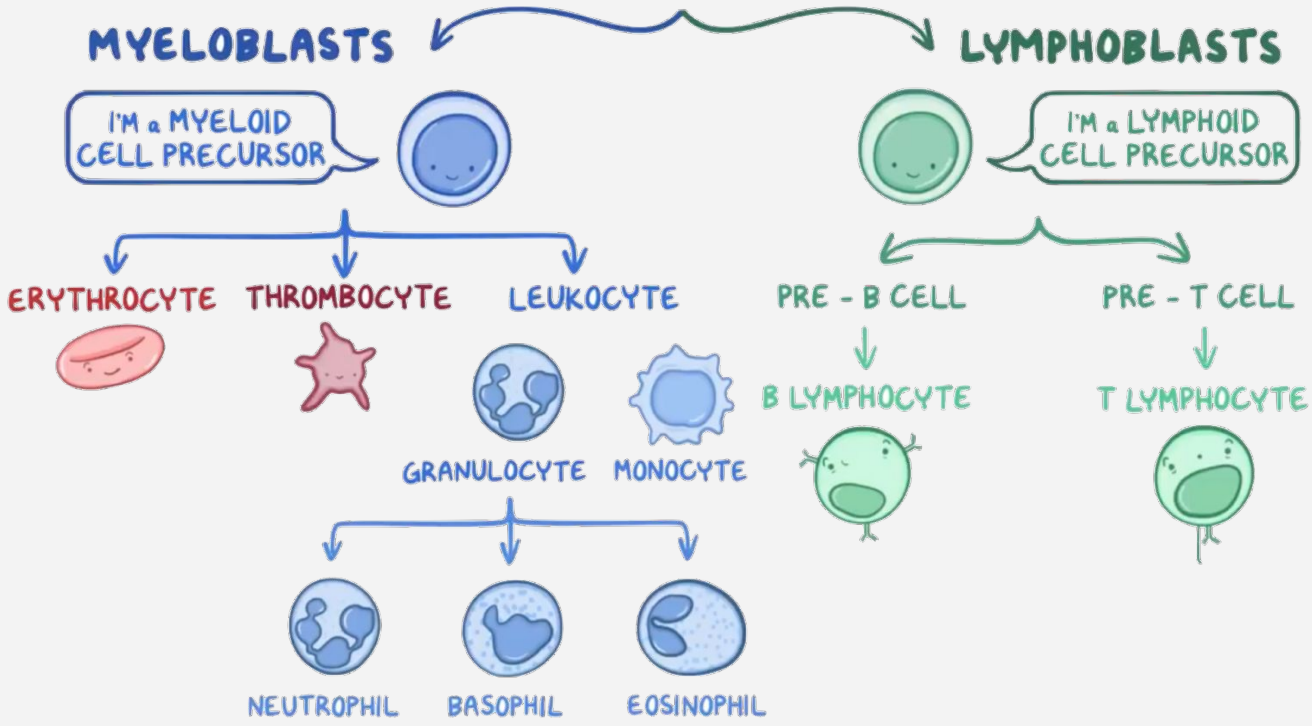
E. **Others:**

- Myelodysplastic syndromes (**MDS**) “Chronic”
- Acute Leukemia of **Ambiguous Lineage** “Acute””

Difference between chronic and acute leukaemia

EXTRA





Acute Leukemia

Acute leukemia

- Aggressive malignant hematopoietic disorders
- Accumulation of abnormal (not functioning) blasts (Immature precursors of WBC)
- in bone marrow and blood leading to:

1. **Bone marrow failure** (anemia,neutropenia & thrombocytopenia)
2. **Organ infiltration** (hepatosplenomegaly, lymphadenopathy)

History

- Leuko- means “white blood” in Greek.
- Named by pathologist Virchow in 1845.
- Classified by FAB (French, American & British) classification systems in 1976
- Reclassified by World Health Organization (WHO) in 2001 & 2008.

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

Acute Leukemia

Pathogenesis

- Genetic predisposition Ex:P53 mutation
- Infection
- Environmental factors
- Previous therapy
- Other hematological disorders

Unknown mechanism

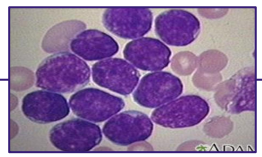
Genetic alteration in the immature precursors

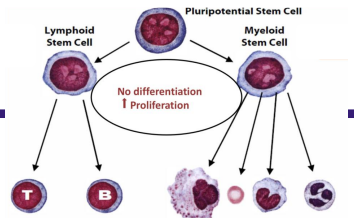
1. Block of differentiation that will lead to accumulation
2. enhanced proliferation
3. decreased apoptosis of abnormal cells

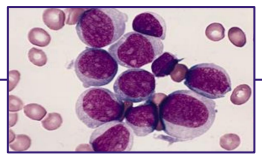
General Classification :

General classification of Acute leukemia

- Acute Lymphoid leukemia
- Acute leukemia of ambiguous lineage
- Acute Myeloid leukemia





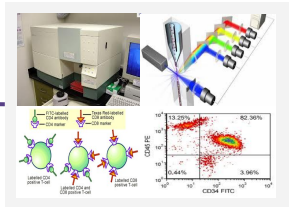


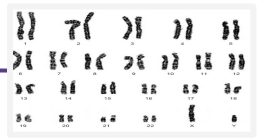
Acute leukemia of ambiguous lineage, also known as mixed-phenotype acute leukemia (MPAL), is a rare type of leukemia where the leukemic cells display characteristics of both lymphoid and myeloid lineages. In other words, the cancerous cells have features of both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).
This condition poses diagnostic and therapeutic challenges because it does not fit neatly into either the ALL or AML category. Classification is typically based on the expression of specific markers on the surface of the leukemic cells.
patient has to have CD34, MPO AND CD3 Positive.

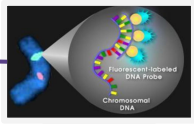
Acute Leukemia

Basis of classification

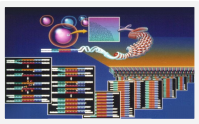
- Clinical history (Previous therapy)
- Morphology
- Flow cytometry
- Chromosomal Karyotyping
- Molecular study







FISH



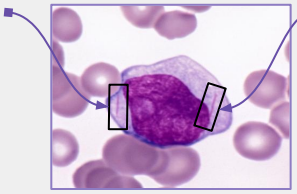
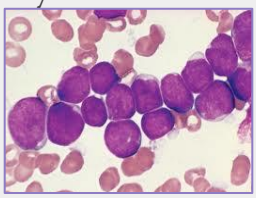
PCR

Basis of classification (Detailed)

1- Clinical history (previous therapy)

2- Morphology

Light microscopy: (blood smear, bone marrow aspirate & biopsy)
Blast count: it should be >20% out of the total cells
Blast morphology:

	Myeloblast	Lymphoblast
Size	medium-Large	small- medium
Nucleus	round, oval or irregular	round
Nucleolus	prominent	not prominent
Cytoplasm	abundant, granular	scanty ,agranular
biopsy	Auer rods is characteristic 	May be vacuolated 

Acute Leukemia

Basis of classification (Detailed)

3- 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

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

- CD = cluster of differentiation = is a protocol used for the identification and investigation of cell surface molecules
- if you see CD34,TDT on a cell that means it is immature blast (knowing it is leukemia)

1. For example if a patient have CD34, MPO positive that means he has myeloid type of leukemia
2. if a patient have CD34, CD10,CD19 positive that means he has B-lymphoid type of leukemia
3. if a parinte was CD34,CD3 positive that means he has T-lymphoid type of leukemia
4. if a patient was CD34,MPO,CD3 positive then he has what?? he has acute leukemia of ambiguous lineage

- so if a patient was CD34,MPO positive, you don't rush and diagnosis him with myeloid type, he needs to test negative for the rest of the CD so we can make sure he doesn't have leukemia of ambiguous lineage

4- Chromosomal Karyotype:

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

5- Molecular studies:

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

1. **Fluorescent In-Situ Hybridization (FISH)**
2. **Polymerase Chain Reaction (PCR)**

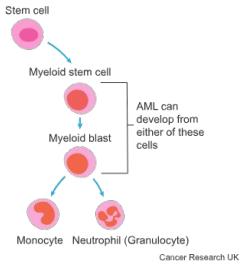
Recurrent Genetic Abnormalities

AML	Karyotype	t (8;21) Common	t (16;16) or inv (16)	t(15;17) Very aggressive	t (9;11)
	Molecular	AML1-ETO	CBFB-MYH11	PML-RARA	MLLT1-MLL
ALL	Karyotype	t (9;22)	t (4;11)	t(12;21)	t (5;14)
	Molecular	BCR-ABL1	AF4-MLL	ETV6-RUNX1	IL3-IGH

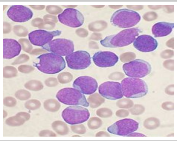
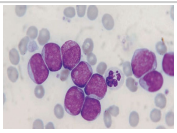
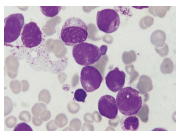
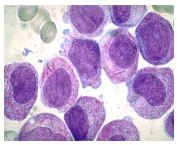
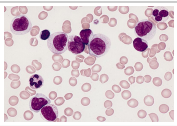
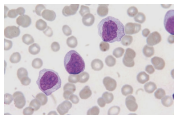
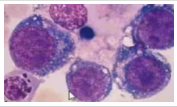
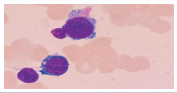
Acute Myeloid Leukemia (AML)

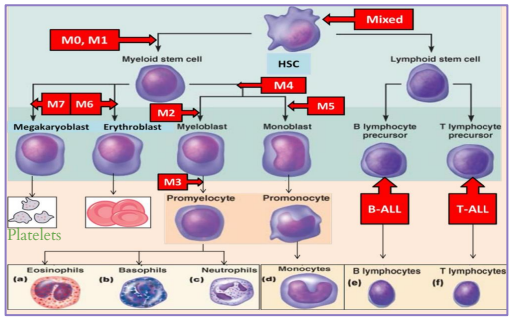
Introduction

- 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** (Acute Lymphoid Leukemia)



FAB Classification

Subtype	Features	Genetics In WHO	Notes	Pic
M0	Minimal Differentiation			
M1	Without Maturation Presence of differentiation			
M2	**With Maturation**	t(8;21)	Good prognosis usually	
M3	**Promyelocytic**	t(15;17)	**DIC** M3 have granules that induce DIC→consumes platelet and coagulation factors →induce bleeding	
M4	Granulocytic and Monocytic	t or inv(16;16)	**Gum Hypertrophy** usually due to the usage of **phenytoin**, Therefore you should rule out the usage of antiepileptic drugs before anything	
M5	Monoblastic (M5a) Monocytic (M5b)	t(9;11)		
M6	Erythroid		**CD235a**	
M7	Megakaryocytic		**CD41**	
M8	Basophilic			



Acute Myeloid Leukemia (AML)

WHO Classification

AML with recurrent genetic abnormalities	**Myelodysplasia** related AML	**Therapy** related AML	AML, not otherwise specified **(FAB)**
Prognosis: Good • t(8:21) • t(16:16) • t(15:17)	**Prognosis: poor** • Blasts ≥ 20% • Significant dysplasia	**Prognosis: poor** • Blasts ≥ 20% • Previous chemotherapy	**Prognosis: Standard** • Blasts ≥ 20% • Genetic: N • No dysplasia

Clinical features:

1

Pancytopenia:

- ↓WBC→ infection (fever, septic shock)
- ↓Hb →anemia (fatigue, headache. Pallor, SOB….)
- ↓platelets →bleeding (bruises, epistaxis, menorrhagia…)

Acute onset

2

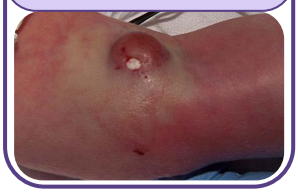
Organ infiltration:

1. **Hepatosplenomegaly.** 2. **Lymphadenopathy (rare)**
3. Myeloid sarcoma 4. Gum hypertrophy
5. CNS disease

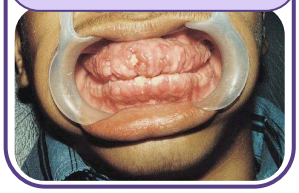
3, 4 and 5 more with Acute Monoblastic Leukemia

Hepatosplenomegaly is very common presentation in AML

Myeloid sarcoma



Gum hypertrophy



3

Leukostasis (increased blood viscosity)

4

Disseminated Intravascular Coagulation (DIC):

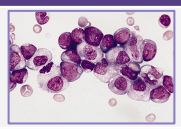
Widespread activation of **coagulation system** leading to **intravascular** fibrin deposition & consumption of platelet and coagulation factors which can be manifested as bleeding (85%) or thrombosis (15%).

More with Acute Promyelocytic leukemia (M3)

Acute Myeloid Leukemia (AML)

Case study

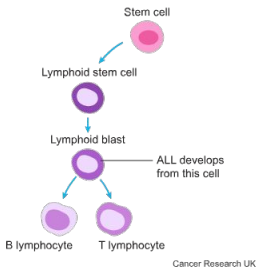
- 65 years old Male presented to ER with Fatigue , Fever and nose bleeding for 2 weeks.
- O/E : moderate hepatosplenomegaly & multiple bruises.
- CBC :
  - WBC :40 x10^9/L
  - HB : 7g/dL (low)
  - PLT : 51 x10^9/L (low)

Details						
Blood smear & bone marrow:	AML with maturation (M2) (FAB) Remember FAB refers to morphological classification					
Flow cytometry Blasts are:	Positive for	CD34	CD13	CD33	CD117	MPO
	Negative for	CD3	CD10	CD19	CD79a	-
Karyotype :	t(8;21)(q22;q22)					
Diagnosis	The final diagnosis: AML with t(8;21) (WHO) Remember WHO refers to genetic classification					
Prognosis :	Better prognosis : ★ Genetics: t(8;21), inv(16;16) or t(15;17) • age: < 60 years • Primary better than secondary					
Treatment:	1- Chemotherapy: ○ AML: M0-M8 but not M3 (same protocol) ○ AML: M3 (ATRA or arsenic)					2- Stem cell transplantation
Extra	If the patient was CD34, MPO AND CD3 Positive, what type of leukemia would he have?					Answer: Acute Ambiguous Leukemia

Acute lymphoblastic leukemia (ALL)

ALL

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



Clinical features

Pancytopenia

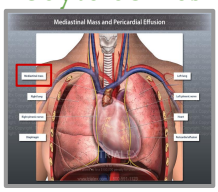
- ↓WBC→ infection (fever ,septic shock)
- ↓Hb →anemia (fatigue , headache , pallor ,SOB….)
- ↓platelets →bleeding (bruises , epistaxis ,menorrhagia…)

[acute onset]

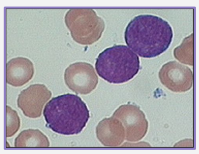
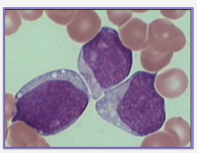
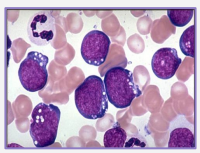
Organ infiltration

- **Lymphadenopathy** (very common)
- Hepatosplenomegaly.
- **testicles involvement**
- CNS disease
- **Mediastinal mass —–> characteristic for T-All**

(a mass in the place of the thymus gland. remember that T-lymphocyte comes from it)



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) C-MYC**
Peripheral blood film			

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

Acute lymphoblastic leukemia (ALL)

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)	—

Types of ALL

Female Slides

	B-ALL			T-ALL	
Cell stage	precursor (immature)		mature	precursor (immature)	mature
Markers	Stem cell markers (CD34 + TDT)	Stem cell markers (CD34 + TDT) & CD10	Surface immunoglobulin	Completely Positive or negative **both** CD4 & CD8 *(+VE): CD4 & CD8 *(-VE): CD4 & CD8	CD4+CD8 One positive and other negative *CD4 Only *CD8 Only
	CD19 CD20 CD79a			**+cCD3** c: cytoplasm	**+sCD3** s: surface
				CD2 CD5 CD7	
Disease	B-ALL	Common B-ALL	Burkitt's lymphoma	T- ALL Acute lymphoid leukemia	T-cell lymphoma

Acute lymphoblastic leukemia (ALL)

Prognosis of Acute lymphoblastic leukemia (ALL)

	Better	Worse
age	2 - 10 yrs	<2 - >10 yrs
Gender	**F**	**M** because testicular involvement
WBC count	low	high
Cell type	**B cell**	T cell
B-ALL phenotype	common	others
B-ALL genetics	**Hyperdiploidy** (more than 46 chromosomes) **t(12;21)**	**Hypodiploidy** (less than 44 chromosomes) **t(9;22)**
CNS involvement	No	Yes
Treatment	1- Chemotherapy (high cure rate) 2- Stem cell transplantation	

Genetics Mutations

EXTRA Summary

AML	t(8;21)	**M2 AML**,Prognosis: **Good**
	t(15;17)	**M3 Promyelocytic AML** ,Prognosis: **Good**,**DIC**
	t or inv(16;16)	**M4 AML**,Prognosis: **Good**,**Gum hypertrophy**
	t(9;11)	**M5 AML** (Monoblastic (M5a) Monocytic (M5b)) **Gum hypertrophy**
Lymphoma	t(8;14)	**L3 Burkitt's** Lymphoma
ALL	T(9;22)	**B-cell ALL**,**Worse prognosis** (Hypodiploidy)
	T(4;11)	**B-cell ALL**
	T(12;21)	**B-cell ALL**,**Better prognosis** (Hyperdiploidy)

Remember !

- Acute leukaemia is a **fatal** neoplastic condition
- **20% or more blasts** = Acute leukaemia, Less than 20% is chronic
- 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**
- **CD3, CD34, MPO Positive = Ambiguous leukemia.**

- Acute when blasts are more than 20%
- Chronic when the blasts are less than 20%
- AML common in Adults
- ALL common in Children
- AML common presentation is Hepatosplenomegaly while Lymphadenopathies are rare
- ALL common presentation is Lymphadenopathy while Hepatosplenomegaly are 2nd common (not rare)

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