6/11

Acute Leukemia

432 ***Hematology*** *Team*

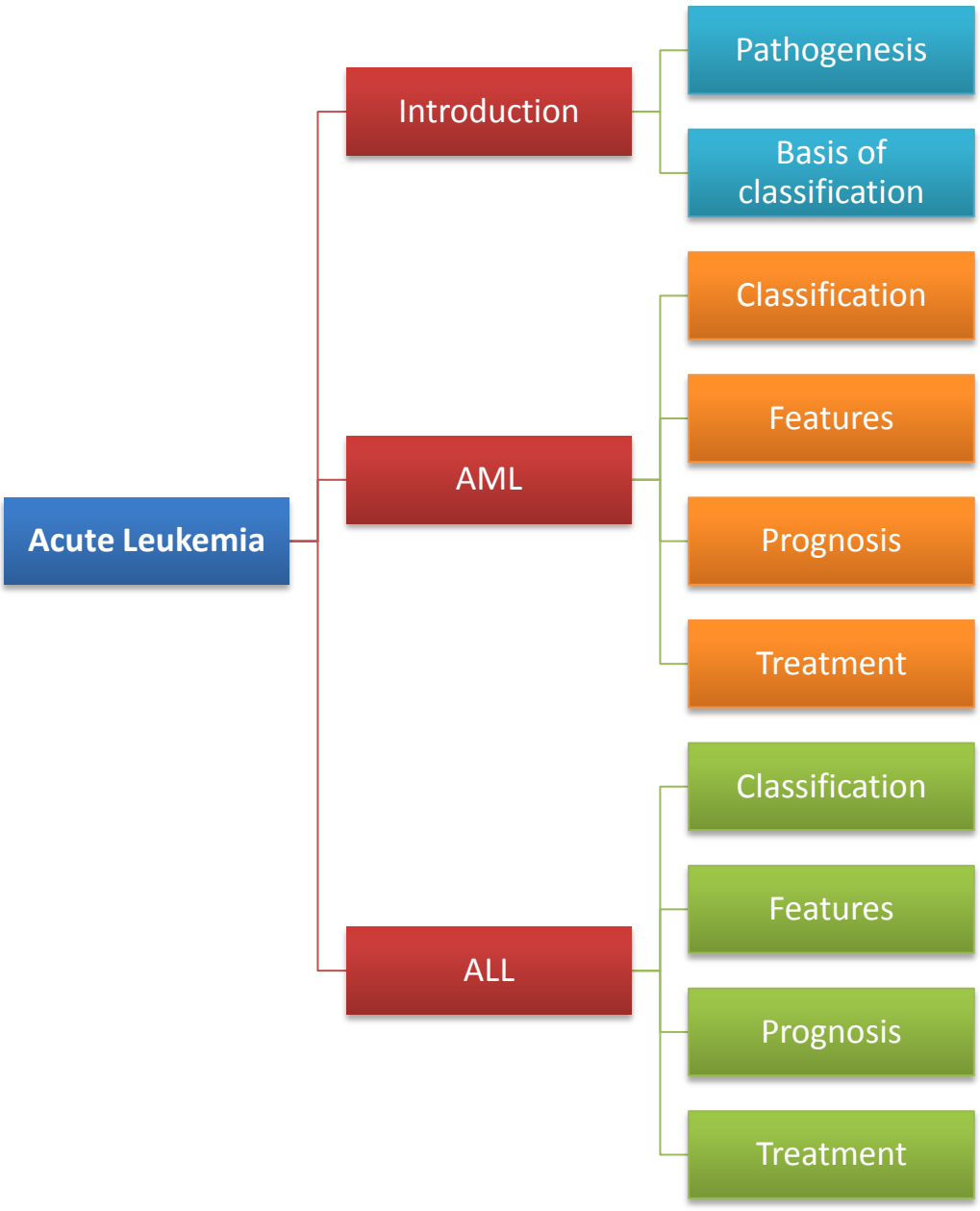
Done By: Fahad *Al-Dhahri*

Reviewed By: Ghadah *Al-Harbi*

Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

Acute Leukemia

Mind Map:



Acute Leukemia

Introduction:

Acute Leukemia which means “white blood” in Greek, is an aggressive malignant hematopoietic disorder, and it’s defined as **accumulation of abnormal (blasts/stem cells/ Immature precursors) of WBC in bone marrow and blood** leading to:

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

- Pathologist named Virchow in 1845 named it.
- Classified by FAB classification systems in 1976.
- Reclassified by World Health Organization in 2001 & 2008.

NOTE: **The main difference between Chronic and Acute leukemia is the presence of blasts in the peripheral blood, which happens, only in Acute Leukemia**

Pathogenesis:

It's called **SECONDARY** AL, usually in patients who had previous treatment. **CHEMOTHERAPY**

Previous therapy

Infection

Other hematological disorders

Most important factor, **BUT** can't trigger the disease on its own.

Genetic predisposition

2 or more will combine in an **uncertain mechanism**

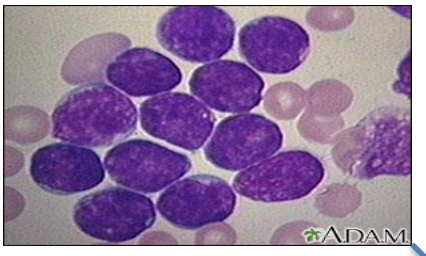
Environmental factors

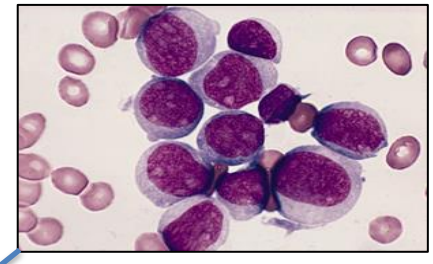
- Radiation
- Chemical/nuclear weapons.

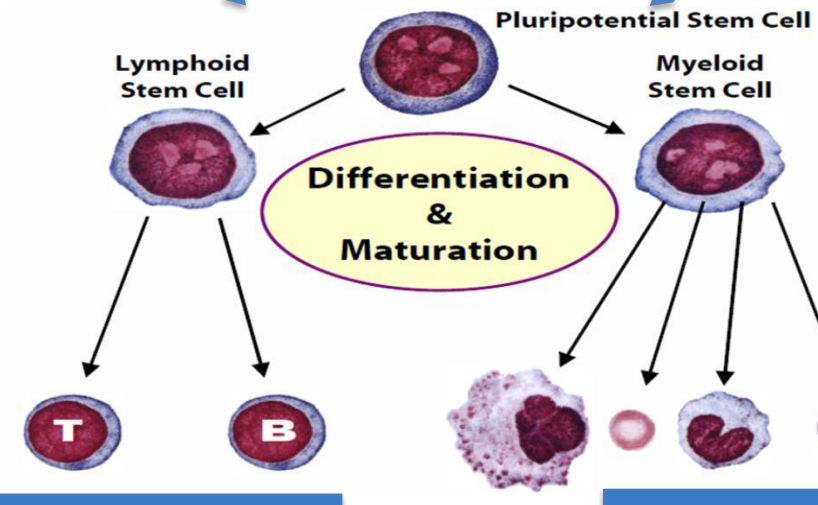
Genetic alteration in the immature precursors

In other words, mutation will stop the normal function of blasts (maturation into leucko/lymphocyte) and trigger unwanted functions.

Mutations Block differentiation + Enhance proliferation + Decrease apoptosis







Acute Lymphoid Leukemia (ALL)

Acute MEYLOID Leukemia (AML)

Malignant blasts will invade: Bone marrow, Blood and Tissue

NOTE: There is a third type/lineage of AL called **AMBIGUOUS lineage**, which is of an **indefinite** cause.

Basis of Classification & Diagnosis:

Classification (and diagnosis) of AL depend on the following aspects:

1. Clinical history of **previous chemotherapy** (i.e. from adenocarcinoma)
2. **Morphology → Light microscopy**

   Generally, a blood or bone marrow sample should show the following:

   A. Blasts should count **20% or more** of total cells.

   B. Blasts show special morphology:

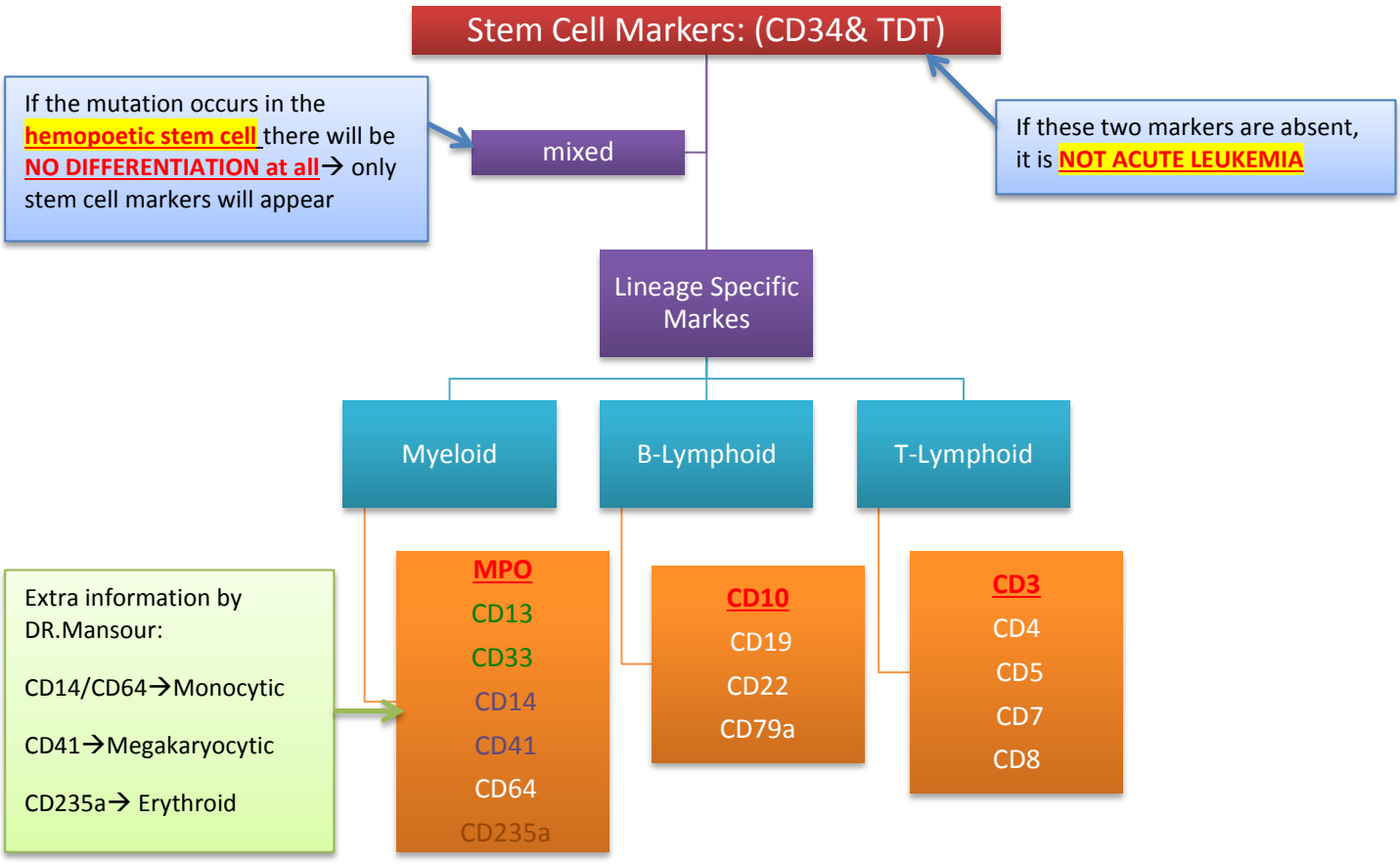
      a. Myeloblasts:

         i. Size: medium-Large
         ii. Nucleolus: round, oval or irregular
         iii. Nucleolus: prominent
         iv. Cytoplasm: abundant, **granular**
         v. **Auer rods are characteristic**

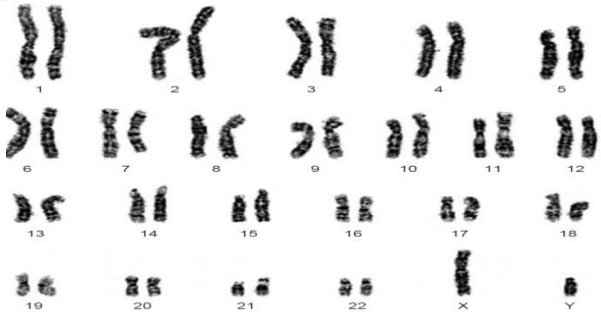
      b. Lymphoblasts:

         i. Size: small- medium
         ii. Nucleous: round
         iii. Nucleolus: not prominent
         iv. Cytoplasm: scanty, a granular
         v. May be vacuolated

3. Flow cytometry (immunophenotypic analysis) → A laser based technology that detect amounts of malignant cells, and **surface and cytoplasmic markers** which are important for both diagnosis and therapy:



4. Chromosomal Karyotyping →Helps detecting type of mutation (numerical or structural) and expecting prognosis [i.e. t(9,21), t(16,16)]



5. Molecular study → a very specific method (FISH or PCR) for detect and localize the presence or absence of DNA sequences and their mutations.
   - Following is an example of AML and ALL Molecular vs. Karyotype studies (not for memorizing):

AML

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

ALL

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

Note: (additional)
1. Fluorescence in situ hybridization (FISH): This is a sensitive technique that can detect extra copies of genetic material.

2. Polymerase chain reaction (PCR): Can be performed on both blood or bone marrow for a specific translocations such as t(9;22) and t(15;17).

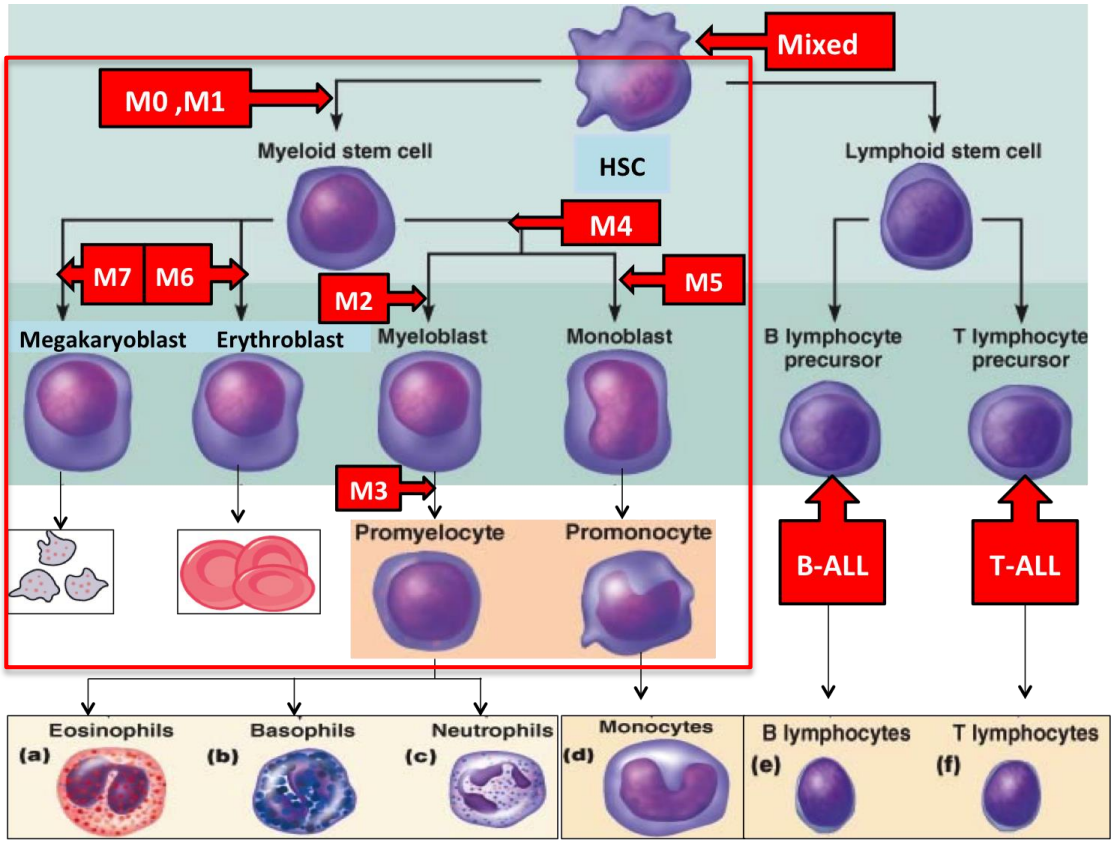
3. Malignant transformation occurs as a result of the accumulation of genetic mutations in cellular genes.

Acute MYELOID Leukemia:

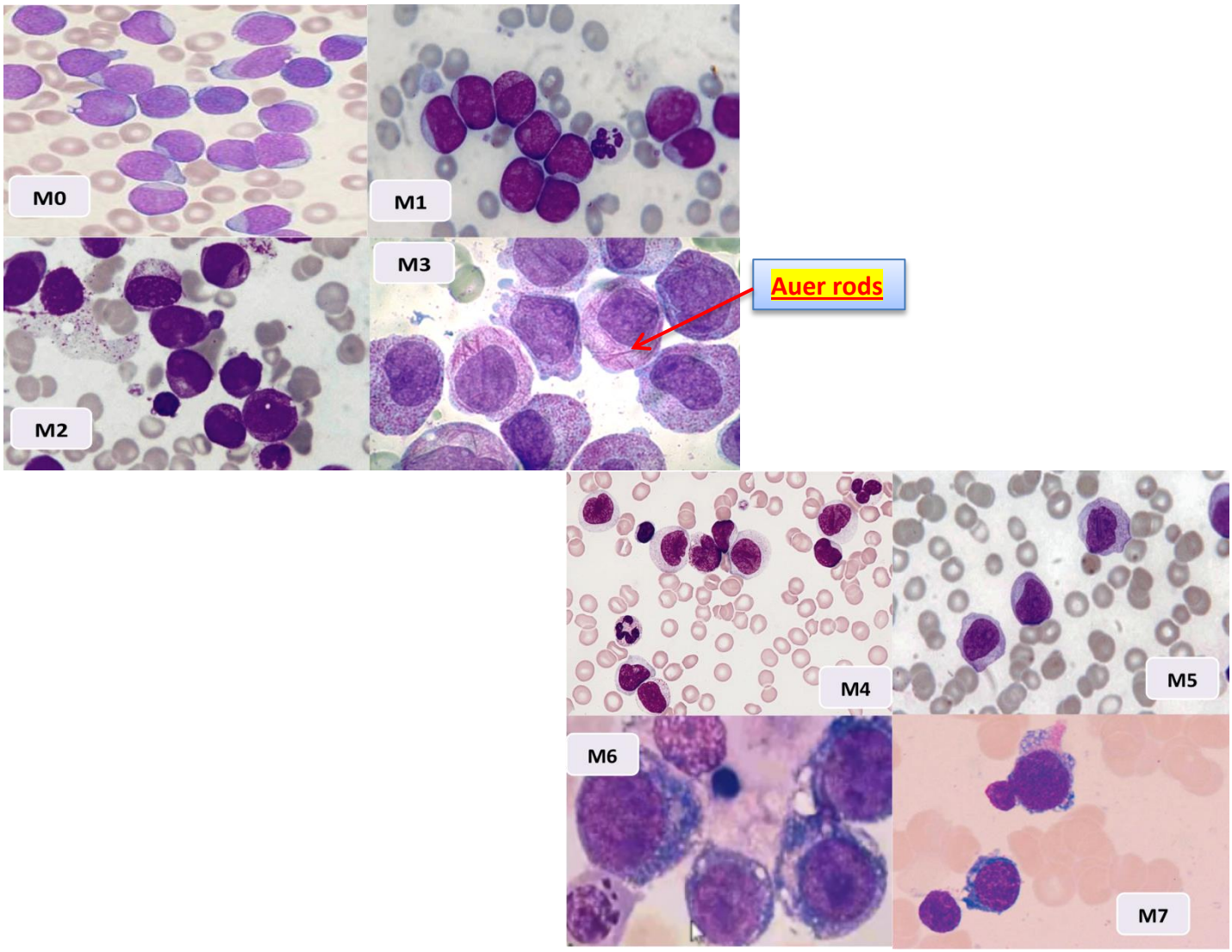
- Group of hematopoietic neoplasms caused by proliferation of **malignant myeloid blasts** in bone marrow and blood.
- The disease is determined by either:
  1) Number of blasts ≥20%
  2) Translocation t (8; 21), t (16; 16) or t (15; 17) "No matter what percentage the blasts occupy".
- More in Adults (do occur in infants!)
- Worse than ALL (because it's usually an adult disease → adults' tolerance is weaker than children).

Note: (additional)
1. Children may have predisposition to ALL from their germline constitution.
2. Children with high level of social activity, notably those attending early nursery daycare, have a reduced incidence of ALL.

Types & Classifications



FAB	Features	GENETICS/MARKERS	IMPORTANT NOTES
M0/M1	M0(Minimal differentiation) M1 (without maturation)	**Only MPO is detected**	0% differentiation
M2	With maturation	t(8,21)	Few maturation is present
M3	Promyelocytic	t(15,17)	**It's a dangerous stage!!** Causes Disseminated Intravascular Coagulopathy → patient should be treated within less than 24h.
M4	Granulocytic & monocytic	Translocation or inversion (16,16)	Tissue involvement→ mainly skin lesions and **Gum hypertrophy**
M5	Monoblastic (M5a) Monocytic (M5b)	t(9,11)	
M6	Erythroid	**CD235a**	No RBC maturation → severe anemia.
M7	Megakaryocytic	**CD41**	Severe thrombocytopenia.
M8	Basophilic		



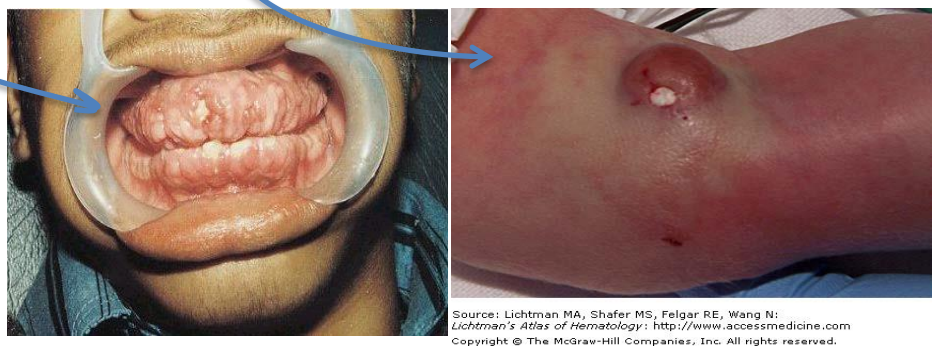
AML Classification (WHO)

AML with recurrent genetic abnormalities	Myelodysplasia related AML (2 malignancies at once: Myeodisplasia + AML)	Therapy related AML (Secondary)	AML, not otherwise specified (FAB)
1- t(8;21) 2- t(16;16) 3- t(15;17) **Prognosis:** Good	•Blasts≥ 20% •Significant dysplasia **Prognosis:** poor	•Blasts≥ 20% •Previous chemotherapy **Prognosis:** poor	•Blasts≥ 20% •Genetic: N •No dysplasia **Prognosis:** Standard

Clinical Features:

1) Pancytopenia:
   a. ↓WBC→infection (fever ,septic shock)
   b. ↓Hb→anemia (fatigue, headache, pallor, SOB….)
   c. ↓Platelets →bleeding (bruises, epistaxis, menorrhagia…)
2) Organ infiltration:
   a. **Hepatosplenomegally**.
   a. Lymphadenopathy (rare)
   b. Myeloid sarcoma
   c. Gum hypertrophy
   d. CNS disease

More with Acute Monoblastic Leukemia



3) Leuckostasis → Increased blood viscosity
4) Disseminated Intravascular Coagulation DIC:

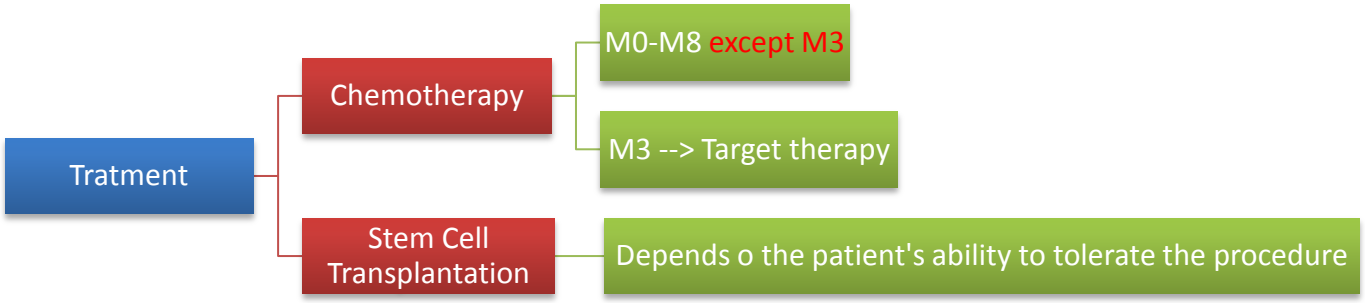
More with Acute **Promyelocytic leukemia** (M3)

Widespread activation of coagulation system

Leading to intravascular fibrin deposition &consumption of platelet and coagulation factors that can be manifested as bleeding (85%) or thrombosis (15%).

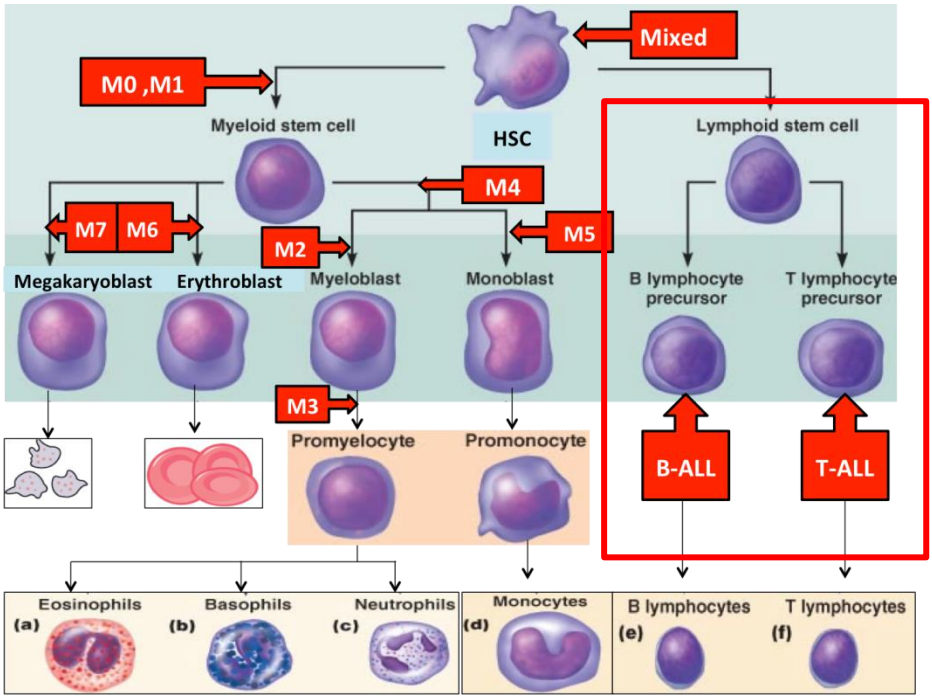
Prognosis: factors that affect the prognosis and life expectancy of ALL, below:

Feature	Bad prognosis	Good Prognosis
Genetic	t(9,11)	t(8;21), inv(16;16) or t(15;17)
Age	More than 60y	Less than 60y
History	Secondary malignancy	Primary malignancy



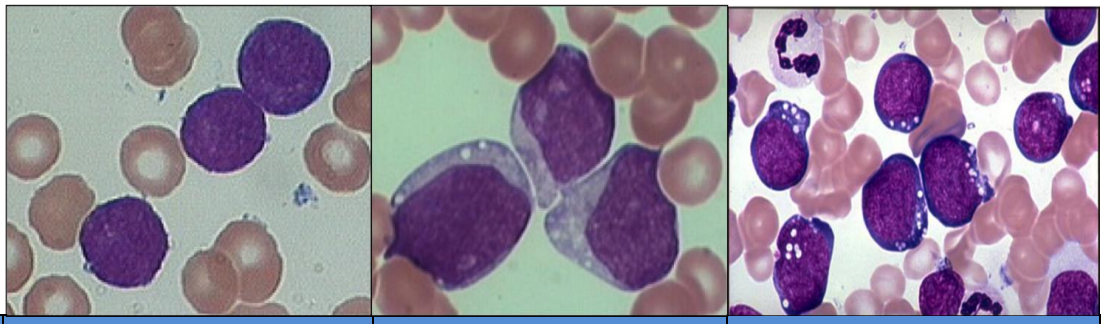
Acute Lymphoid Leukemia:

- Acute leukemia characterized by proliferation of malignant **lymphoid blasts** in bone marrow and blood.
- B and T lineages are affected.
- More common in Children → Better prognosis than AML



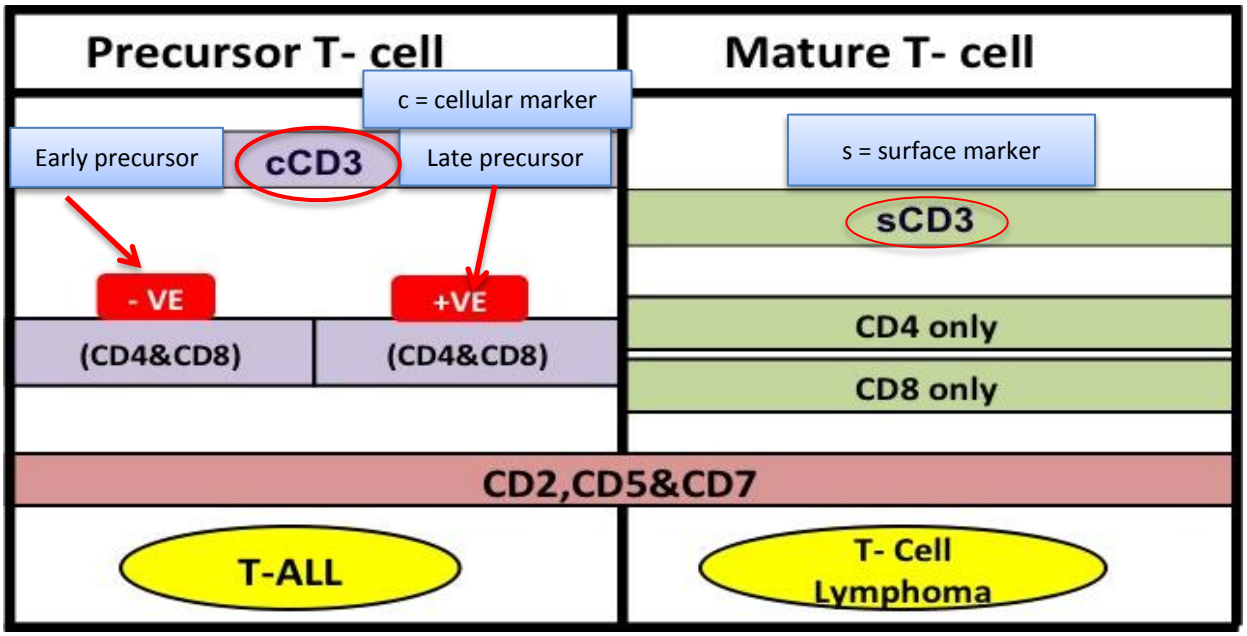
Classification:

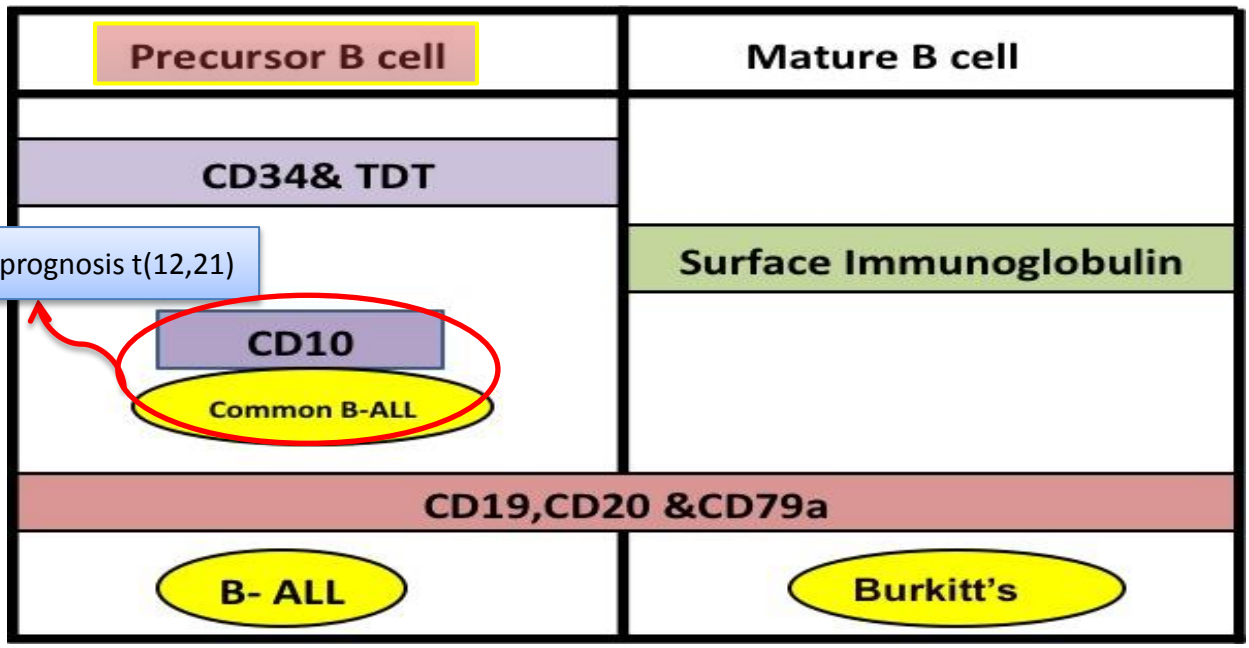
- According to morphology + flow cytometry →by FAB
- According to Immunophenotype (Genetic) →by WHO



FAB	L1	L2	L3 "Burkitt's"
Cell Morphology	Homogenous (same shape & size)	Heterogenous	Homogenous
Size	Small	Variable	Small
Cytoplasm	Little	More	Vacculated
Nucleoli	Not Prominent	Prominent	Prominent
Genetics	Variable	Variable	t(8,14)

WHO	B-ALL	T-ALL
Markers	**CD10**, CD19, CD791	**CD3**
Age	Young	Older
Percentage%	80%	20%
Clinical Characteristics	----------	**Mediastina mass** **CNS involvement**
WBC count	Low compared to T-ALL	High
Genetics	t(9,22), t(4,11), t(12,21)	----------
Prognosis	Better	Worse





NOTE: **L3 (Burkitt's) represents mature lymphoid neoplasm so it is a type of lymphoma not acute lymphoblastic leukemia.**

Clinical Features

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

Thrombocytopenia is a sign of **ADVANCED** ALL

2. Organ Infiltration:
   - Lymphadenopathy (very common)
   - Hepatosplenomegally.
   - Testicles involvement
   - CNS disease
   - Mediastinal mass (thymus enlargement)

It's common because **lymphnodes are the site of lymphocytic maturation**

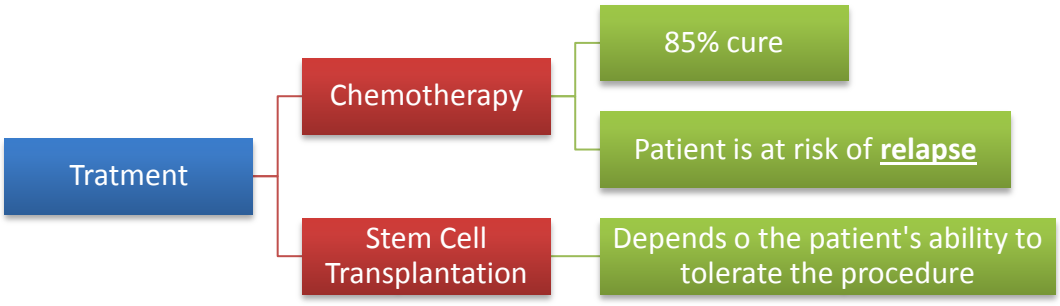
Remember: **One single** leukemic blast could cause a tissue mass

T-ALL characteristic

Prognosis

There are some factors that affect the prognosis and life expectancy of ALL, these are listed below:

Factor	Good Prognosis	Bad Prognosis
Age	2y to 10y	Less than2 or more than10
Gender	Female	Male
WBC count	Low	High
ALL subtype	B-ALL [CD10, t (12; 21)]	T-ALL and Other types of B-ALL especially t (9; 22)
Genetics	Hyperdiploidy	Hypodiploidy
CNS involvement	Absent	Present



NOTE: **1. The incidence of leukemia is greatly increased in some genetic diseases, particularly Down's syndrome.**

2. Benzene is an unusual cause of myelodysplasia or AML.

3. Radiation increases the incidence of all types of leukemia except CLL.

4. The retrovirus human T-lymphotropic virus type 1 is the cause of adult T-cell leukemia/lymphoma.

5. Epstein-Barr virus (EBV) is associated with almost all cases of endemic (African) Burkitt lymphoma.

6. HIV infection is associated with an increased incidence of B-cell origin lymphomas of unusual sites like CNS.

7. In many cases the disease develops new characteristics during its clinical course and this may be accompanied by new genetic changes.

(THESE INFORMATION ARE FOR YOUR OWN KNOWLEDGE)

Summary

From Essential Hematology Book:

- Acute leukemias are aggressive diseases in which transformation of a haemopoietic stem cell leads to accumulation of > 20% blast cells in the bone morrow.
- The clinical features of acute leukemia result from bone marrow failure and include anemia, infection and bleeding.
- AML is rare in childhood but becomes increasingly common with age with a median onset of 65 years.
- The diagnosis is made by analysis of blood and bone marrow using microscopic examination (morphology) as well as immunophenotypic, cytogenetic and molecular studies.
- Cytogenetic and molecular abnormalities are used to classify and indicate prognosis in the majority of cases of AML.
- In young patients treatment is primarily with the use of intensive chemotherapy.
- The prognosis of patients with AML has been improving steadily, particularly for those less than 60 years of age, and approximately one-third of this group can expect to achieve long-term cure. The outcome for elderly people remains disappointing.

Questions

1/ A 40-year-old woman complains of fatigue and nausea of 3 months in duration. Physical examination reveals numerous pustules on the face, as well as splenomegaly and hepatomegaly. Laboratory studies show hemoglobin of 6.3 g/dL and platelets of 50,000/mL. A peripheral smear shows malignant cells with Auer rods. The patient develops diffuse purpura, bleeding from the gums, and laboratory features of disseminated intravascular coagulation (DIC). Which of the following is the appropriate diagnosis?

(A) Acute lymphoblastic leukemia
(B) Acute megakaryocytic leukemia
(C) Acute promyelocytic leukemia
(D) Chronic myelogenous leukemia

2/ Cytogenetic studies in malignant cells from the patient described in Question 1 demonstrate a chromosomal translocation. Which of the following is the mutation?

(A) t (9:11)
(B) t (15:17)
(C) t (8:24)
(D) t (9:22)

3/ A 6-year-old boy presents with fatigue, fever, and night sweats. Physical examination reveals marked pallor. Palpation of his sternum demonstrates diffuse tenderness. Laboratory studies disclose anemia, thrombocytopenia, and leukocytosis. The WBC differential count shows that 90% lymphoid blasts. Which of the following is the appropriate diagnosis?

(A) Acute lymphoblastic leukemia
(B) Acute myelogenous leukemia
(C) Acute promyelocytic leukemia
(D) Chronic lymphocytic leukemia

Answers:

- 1- C
- 2- B
- 3- A

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com

432 Haematology Team Leaders:
Roqaih Al-Dueb & Ibrahim Abunohaiah

*Good Luck ^_^*