Hematology

438 teamwork

Acute leukemia

Color index:
Red: Important
Gray: notes
Blue: extra

Editing file

Acute leukemia

Aggressive malignant hematopoietic disorders Accumulation of > 20% blasts in the bone marrow.

- Accumulation of abnormal blasts (**Immature** precursors of WBC) in bone marrow and blood leading to:
  -  Bone marrow failure (anemia ,neutropenia & thrombocytopenia "low blood platelet count")
  -  Organ infiltration (hepatosplenomegaly ,lymphadenopathy)

- **Leukemia** = Means "white blood" in greek.
- Classified by FAB "French–American–British" classification systems in 1976
- Named by pathologist Virchow in 1845
- Reclassified by World Health Organization 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 .

→ Pathoma

Anemia (fatigue); thrombocytopenia (bleeding); neutropenia (infection)

Pathogenesis

Genetic prediction

Environmental factors

Infection

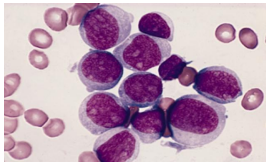
Previous therapy

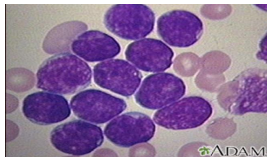
Other haematological disorders

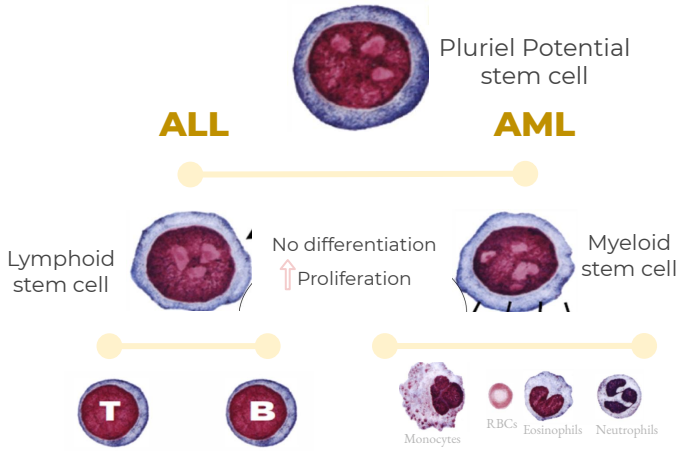
Unknown mechanism

Genetic alteration in the immature precursors

Block of differentiation, Enhanced proliferation & Decreased apoptosis







Stem cells shouldn't be found in blood normally and if present they should be in scanty amount otherwise there is an abnormality
Every cell has type of leukemia, if it :
Mature → chronic leukemia
Immature → acute leukemia

Classification of Acute leukemia

Based on the phenotype of the blasts.

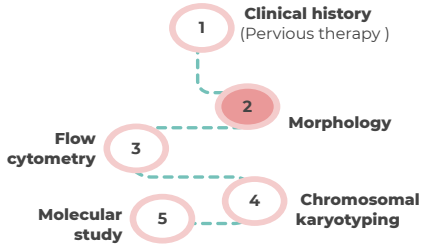
- Acute myeloid leukemia
- Acute lymphoid leukemia
- Acute myeloid of Ambiguous lineage

basis of classification

All of those test should done to the patient

1. **Clinical history** (Pervious therapy)
2. **Morphology**
3. **Flow cytometry**
4. **Chromosomal karyotyping**
5. **Molecular study**

Light microscopy



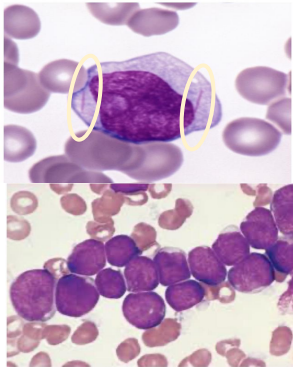
→ **Blast count :** it should be *>20%* out of the total cells in bone marrow.

→ Blast morphology:

	Myeloblast	Lymphoblast
Size	Medium/ large	Small/ medium
Nucleus	Round, oval or irregular	Round
Nucleolus	Prominent	Not prominent
Cytoplasm	Abundant , granular **Aur rods is charestristic**	Scanty, agranular maybe **vacuolated**

→ Pathoma

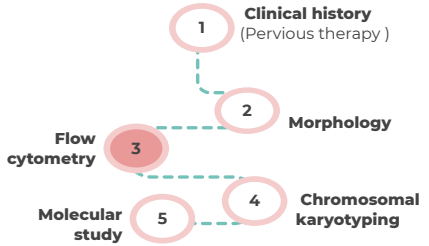
Crystal aggregates of MPO may be seen as Auer rods



Myeloblast
very malignant cells
Auer rods

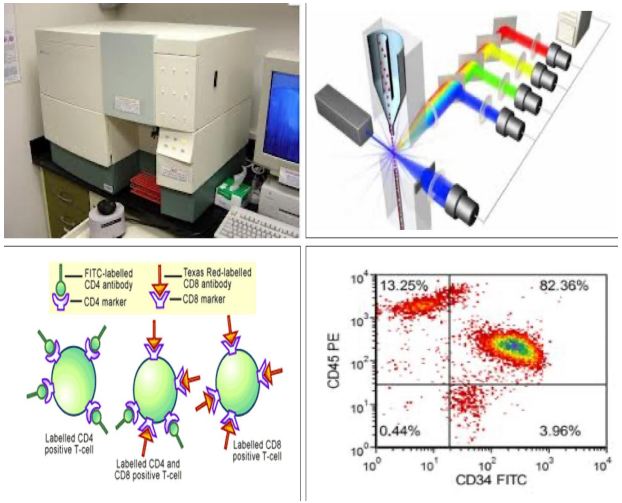
Lymphoblast
There's **NO** cytoplasm

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

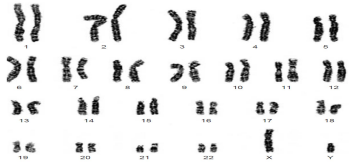
Myeloid
- MPO "Myeloperoxidase"
- CD33
- CD14
- CD64
- CD13
- CD41
- CD235a

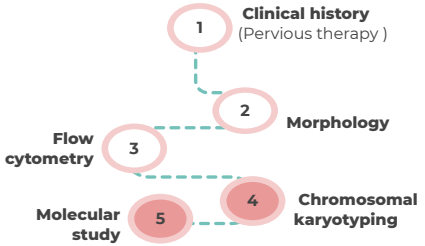
B-Lymphoid
- CD10
- CD19
- CD22
- CD79a

T-Lymphoid
- CD3
- CD4
- CD5
- CD7
- CD8

Chromosomal karyotyping

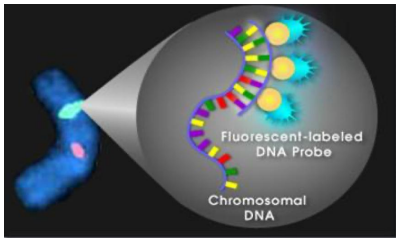
→ Set of the chromosomes from one cell during metaphase to study the **numerical** (deletion & trisomy) and **structural** (translation & inversion) abnormality



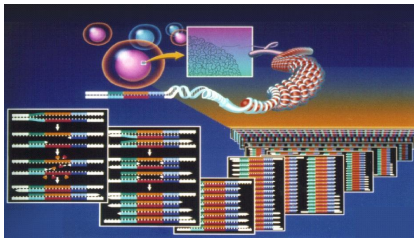


molecular studies

→ 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

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)

* Most serious type of leukemia (M3: Promyelocytic)

Acute myeloid leukemia

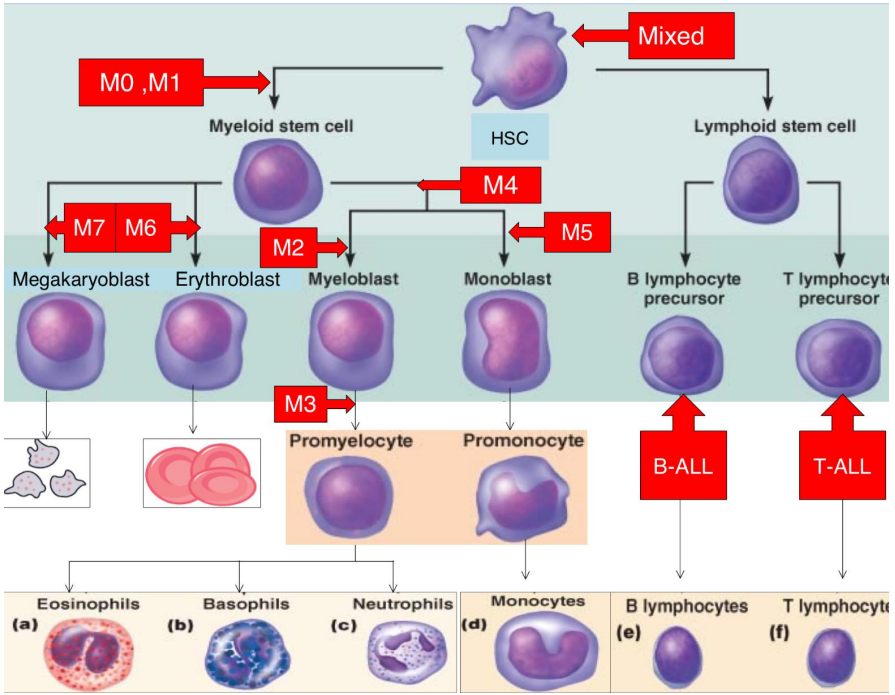
→ Group of hematopoietic neoplasms caused by proliferation of malignant ***myeloid blasts*** in bone marrow and blood.

→ The blast ≥**20%** or **t(8;21) t (16;16) or t(15;17).**

→ More in **Adults** (do occur in infants)

→ **Worse** than ALL

Dr notes: reading

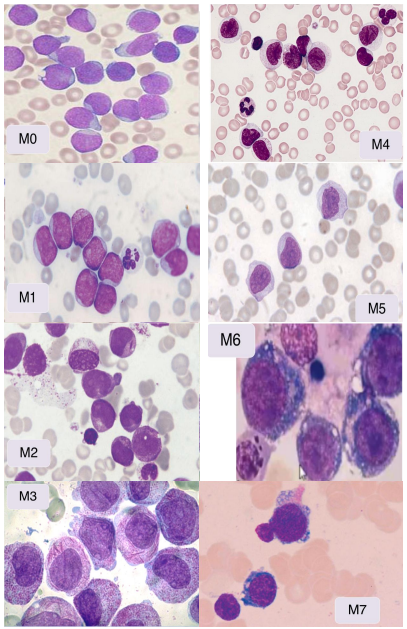


AML classification

FAB classification

WHO classification

Subtype	Feature	Genetic 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	Mono Plastic (M5a) Monocytic (M5b)	**t(9;11)**	
M6	Erythroid		CD235a
M7	Megakaryocyte		CD41
M8	Basophilic		



- FAB classification is based on microscopic features (morphology)
- In M6 myeloid leukemia (Erythroid leukemia) there will be excessive production of immature RBCs which will die quickly and the patient will present with severe anemia

AML classification

FAB classification

WHO classification

01

AML with recurrent genetic abnormalities

1- t(8;21)

2- t(16;16)

3- t(15;17)

- Prognosis: Good

02

Myelodysplasia related AML

- Blasts ≥ 20%
- Significant **dysplasia**
- Prognosis: poor

03

Therapy related AML

- Blasts ≥ 20%
- **Previous chemotherapy** "Around 5-7 years"
- Prognosis: poor

04

AML, not otherwise specified (FAB)

- Blasts≥ 20%
- Genetic: N
- No dysplasia
- Prognosis: Standard

Clinical Features of AML

01 Pancytopenia

Acute onset

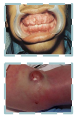
↓ **WBC** → **Infection** (WBC ↓ in mature cells such as neutrophils)
- ➢ Fever
- ➢ Septic shock

↓ **Hemoglobin** → **Anemia**
- ➢ Fatigue
- ➢ Headache
- ➢ Pallor
- ➢ SOB

↓ **Platelets** → **Bleeding**
- ➢ Bruises
- ➢ Epistaxis
- ➢ Menorrhagia

02 Organ infiltration

- Hepatosplenomegally.
- Lymphadenopathy (rare)
- CNS disease.
- Gum hypertrophy
- Myeloid sarcoma



More with Acute Monoblastic Leukemia

Gum hypertrophy is a sign that indicates bad prognosis

03 Leucostasis

- increased blood viscosity

04 Disseminated Intravascular Coagulation (DIC)

Activation of coagulation system (Widespread) → Fibrin deposition (Intravascular) → Consumption of
- ❑ Platelet
- ❑ Coagulation factors

→
- ★ Bleeding (85%)
- ★ Thrombosis (15%)

More with Acute Promyelocytic leukemia (*M3*)

Acute Promyelocytic leukemia (M3) t (15;17) is an emergency condition due to DIC

Prognosis

Better prognosis

- **Primary** — Better than secondary
- **Age** — < 60 years
- **Genetics**
  - ➢ t(8;21)
  - ➢ inv(16;16)
  - ➢ t(15;17)

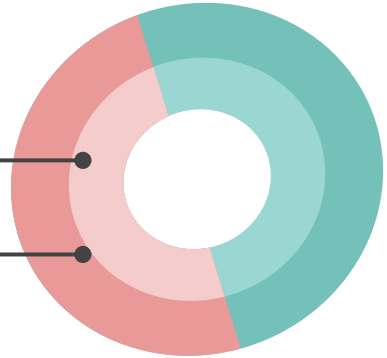
Treatment

Chemotherapy

➔ **AML**

Same protocol
M0-M8 but not M3

ATRA
(all-trans-retinoic acid, a vitamin A derivative)
or arsenic
M3



Stem cell transplantation

Treatment of M3 type myeloid leukemia (promyelocytic leukemia) is by all trans retinoic acid which corrects the t(15;17) translocation

Case study

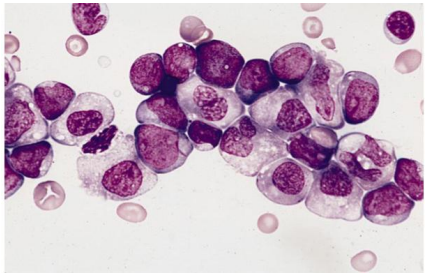
1 - Adult male
2- fatigue → anemia
3- fever → infection → ↓ WBC
4 - nose bleeding and Multiple bruises → low platelet
5 - hepatosplenomegaly → Organ infiltration

65 years old **male** presented to ER with **fatigue** ,**fever** and **nose bleeding** for 2 weeks.

Examination :
Moderate hepatosplenomegaly
Multiple bruises.

CBC : WBC :40 x109/L **Hemoglobin:** 7g/dL **Platelets:** 51 x109/L

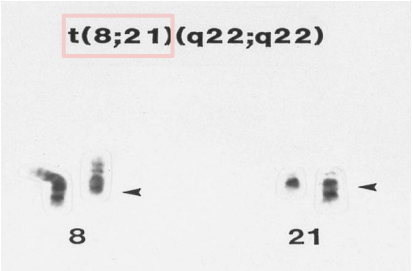
Blood smear & bone marrow:



Flow cytometry :

+ve	CD34	CD13	CD33	CD117	**MPO** (Myeloperoxidase)
-ve	**CD3**	CD10	CD19	CD79a	

Karyotype :



Diagnosis: Acute Myeloid Leukemia with maturation (M2) *FAB with t(8;21) *WHO

Acute Lymphoblastic Leukemia (ALL)

proliferation of malignant lymphoid blasts

in bone marrow & blood.

B and T cells

More common in Children

Better than AML

Clinical Features of ALL

Pancytopenia

Acute onset

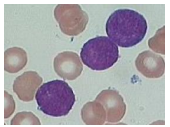
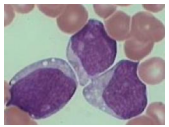
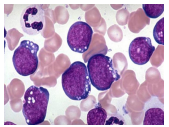
- **WBC** → **Infection**
  - Fever
  - Septic shock
- **Hemoglobin** → **Anemia**
  - Fatigue
  - Headache
  - Pallor
  - SOB
- **Platelets** → **Bleeding**
  - Bruises
  - Epistaxis
  - Menorrhagia

Organ infiltration

- Hepatosplenomegaly.
- **Lymphadenopathy (very common)**
- CNS disease.
- Testicles involvement
- 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) c-myc**
			

Burkitt's lymphoma is the fastest growing tumor

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) :

➢ mature lymphoid neoplasm

➢ a type of lymphoma **not** Acute lymphoblastic leukaemia

Acute Lymphoblastic Leukemia (ALL)

<table>
<tr><th></th><th colspan="3">B-ALL</th><th colspan="4">T-ALL</th></tr>
<tr><td rowspan="2">Precursor cell</td><td>CD34
TDT</td><td rowspan="2">CD19
CD20
CD79a</td><td>B-ALL</td><td><u>c</u>CD3</td><td rowspan="2">CD2
CD5
CD7</td><td>➤ Both CD4 & CD8
➤ None</td><td>T-ALL</td></tr>
<tr><td>Mature cell</td><td>Surface Immunoglobulin</td><td>Burkitt’s</td><td><u>s</u>CD3</td><td>➤ CD4 only
➤ CD8 only</td><td>T- Cell Lymphoma</td></tr>
</table>

➔ Pathoma

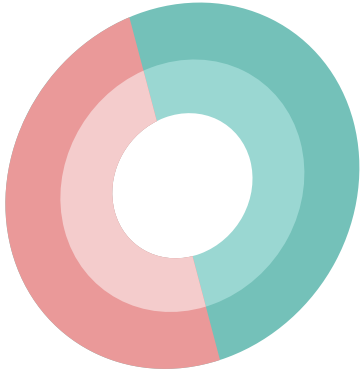
TdT is absent in myeloid blasts and mature lymphocytes.

PROGNOSIS

	Better	Worse
Age	2-10 yrs	Less or more
Gender	Female	Male
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**
- 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

Quiz

Key answers:
1-B 2-C 3-C 4-D 5-C 6-B

1-Gum hypertrophy mostly seen in;

A. Acute lymphoblastic leukemia
B. Acute monoblastic leukemia
C. Chronic leukemia
D. Burkitt's lymphoma

2- 27 years male come to your clinic with fever and bone pain and pale face. On examination CBC shows increased WBCs with 40% blast, microscopic examination show, very malignant cells with granular cytoplasm and Auer rods. What is the translocation in the patient? ***(from dr.notes)***

A. t(9;22)
B. t(5;14)
C. t(5;17)
D. t(8;14)

3- Burkitt's lymphoma cytogenetic abnormality? ***(from dr.notes)***

A. t(8;16)
B. t(5;18)
C. t(8;14)
D. t(8;21)

4- Which one following is associated with worse prognosis in acute leukemia? ***(from dr.notes)***

A. Low WBC count
B. 6 years female
C. B cells type
D. CNS involvements

5- B- ALL genetics in Better prognosis:

A. t(9;22)
B. t(5;14)
C. t(12;21)
D. t(8;14)

6- DIC associated with:

A. M1
B. M3
C. M5
D. M4

THANKS

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