OVERVIEW

* Leukemia → Cancer of blood.
* Lymphoma → Solid organs (mass).

Haematopoietic stem cells.

HSC

Tri lineage

Common myeloid progenitor cell.
- Erythroid p. → RBC.
- Megakaryocytes → platelets
- myeloblast → N, B, E, Monocyte.

Common Lymphoid progenitor.
- lymphoblast. → T, B Lymphocytes.

AML, ALL → MB & LB in blood

CML, CLL → Pm, M, MM, B etc too in blood + blasts

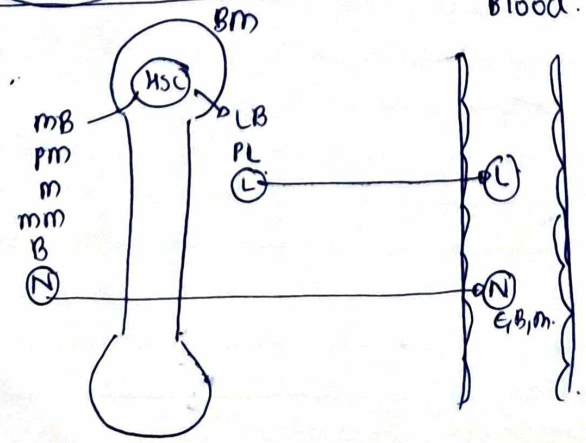
myeloblast.
1. promyelocyte
2. myelocyte.
3. Metamyelocyte.
4. Band form.
5. Neutrophil.

lymphoblast.
1. prolymphocyte → Natural killer cells.
   - Small lymphocyte → B lymphocyte, T lymphocyte.

In blood → Leukemia → can go to other organs → lymphoma.

In bone marrow → Immature cells ✓

In blood → only mature cells
- never immature cells



If Blasts Come in Blood.
myeloblast, lymphoblast.

Leukemia.

Why? → blast cells → mutation → uncontrolled division → spilled over to blood.

Q) Define acute Leukemia.

- Classify acute myeloid Leukemia.
- Importance of cytogenetics in acute myeloid Leukemia.
- Draw blood picture in acute promyelocytic Leukemia.

ACUTE LEUKEMIA

- Acute Leukemia is a malignant disease of the bone marrow stem cell and it's characteristic features are —
  - Blast cells > 20% of nucleated cells in Bone marrow
  - Abnormal numbers and forms of immature white blood cells.

Myeloblast	Lymphoblast
• larger	• Smaller.
• cytoplasm.	• scanty.
Auer body ✓	• Absent ✗
Nucleoli: - prominent 1-4.	Indistinct.

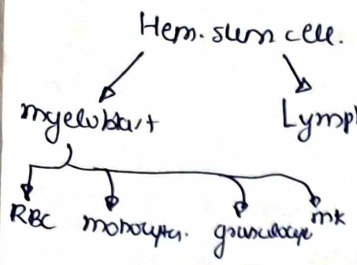
Auer rod – red rod ✓

WHO Classification

Acute Myeloid Leukemia

1. AML with recurrent genetic abnormalities.
2. AML with MDS-related changes.
3. therapy related myeloid neoplasms.
4. AML not otherwise specified.
5. Myeloid Sarcoma.
6. myeloid proliferation related to down syndrome.

Acute Leukemia



- In acute Leukemia, there is loss of ability for blast cells to mature.
  ↓
  So blast cell ↑.

- Acute Leukemia is a neoplastic proliferation of blasts.

→ defined as accumulation of >20% blasts in bone marrow ★

[Normal 1-2%]

(Strict definition. ↑
>20% blast in BM)

- Blasts "crowd-out" normal hematopoiesis,

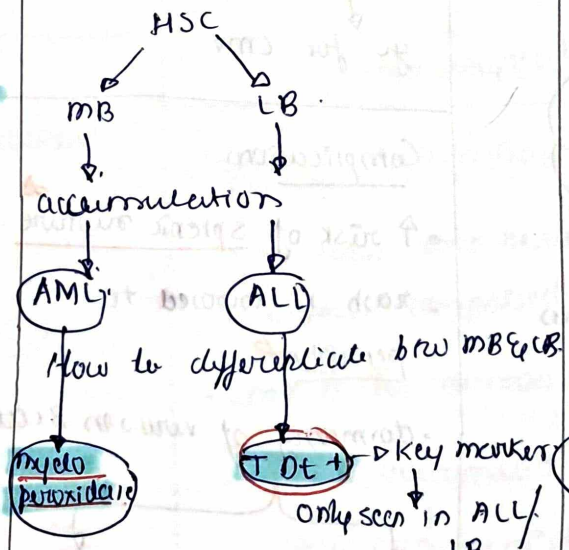
- results in "acute" presentation with anemia, thrombocytopenia, or neutropenia.

[↑ blast cells
↓ mature cells].

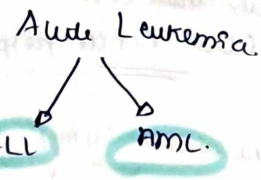
present with anemia, bleeding disorders, ↑ infections
(acute onset)

Blasts usually enter into blood. resulting in high WBC count
↓
Blasts
↓
large, immature cells, punched out nucleoli on blood smear

[larger than RBC.
not much cytoplasm.
punched out - lighter area - nucleoli]



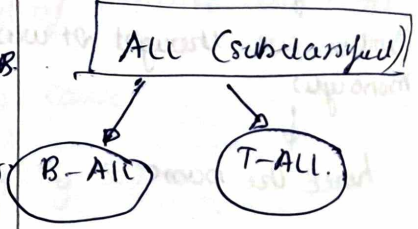
tdt
terminal deoxynucleotidyl transferase



- Based on phenotype of the blasts.

ALL TdT + ★

- neoplastic accumulation of lymphoblast.
- positive nuclear staining for TdT (DNA polymerase)
- TdT (-)
  ↓
  absent in myeloid blast & mature lymphocytes.
- Most commonly arises in children.
- associated with Down Syndrome (Extra triscope of 5)



- Based on surface marker.

- B-ALL is most common type of ALL
- lymphoblasts classically express CD10, CD19 & CD20
- B-ALL has Excellent response to CTX (cyclophosphamide)
- requires prophylaxis to scrotum & CSF.
- Prognosis is good.
- based on cytogenic abnormality.

t(12;21) – good prognosis – more commonly seen in kids.

t(9;22) has a poor prognosis.

more commonly seen in adults.

(ph + ALL).

philadelphia chromosome

t(9;22)

gene: BCR-ABL gene.

T-ALL.

- markers CD2 – CD8
- do not express CD10

→ Presents as a mediastinal Thymic mass in a teenager

- acute lymphoblastic lymphoma.
- Since it's a mass, we call it acute lymphoblastic lymphoma ✓

(not AL leukemia – as they are not floating cells in blood)

- AML is a neoplastic accumulation of myeloblasts.
- myeloblasts are characterized by staining for MPO

Crystal aggregates of MPO may be seen as Auer rods

- AML is commonly seen in older adults.
- average age – 50-60 years

Subclassification

1. cytogenetic abnormality
2. lineage of myeloblast
3. surface markers

- Acute promyelocytic leukemia is characterized by t(15;17)
- RAR (retinoic acid receptor) receptor disrupted; promyelocytes accumulate.
- promyelocytes contain numerous Auer rods; risk for DIC.

ATRA causes blasts to mature

All trans retinoic acid → binds to RAR receptor → maturation

Acute Monocytic Leukemia

- proliferation of monoblasts; lacks MPO
- blasts characteristically infiltrate gums.

Acute megakaryoblastic leukemia

- ↑ megakaryoblasts. lack MPO.
- association with Down syndrome (before age of 5).
- (after age of 5 – ALL)

AML also arise from pre existing dysplasia

eg ↓ due to prior exposure to alkylating agents or radiotherapy

	CML	AML	ALL	CLL
① Introduction	• 4 criteria			
age	>50 years	15-40	Children	
pathogenesis				

CML – Chronic myeloid Leukemia.

- Characterized by → 4 criteria
  1. Leukocytosis with granulocytic immaturities
     2 lakh
  2. Basophilia
  3. Splenomegaly
  4. Distinct chromosomal abnormality – philadelphia chromosome.

* "garden party" appearance in peripheral Blood smear.

210 KD fusion protein

phases of CML.

Chronic phase	Accelerated phase	Blast crisis
<10%	10-20%	>20%

Age – old age (>50 years)

Clinical feature.

(A) Due to Bone marrow failure

(a) anemia → pallor, lethargy, dyspnoea. (RBC ↓)

(b) Bleeding. (platelet ↓)

(c) Infections. (WBC ↑↑ {immature forms})

(B) Hypermetabolism → weight loss, lassitude, anorexia, night sweats.

(C) splenomegaly → massive.

CML

Imatinib

Imatinib

Lab diagnosis.

- Blood.
  - Hb ↓
  - platelet ↓
  - WBC ↑.
    - Marked leukocytosis >2 lakh.
    - Immature – pm, m, mm, B.
    - Basophilia, Eosinophilia
    - garden party appearance
- Bone marrow
  - Cellularity
    - hypercellularity (pauci myeloid cell).
  - erythro, megakaryopoiesis ↓.
- cytogenetics
  - t(9;22)
- special stain cytochemistry
  - Neutrophil alkaline phosphatase
    - NAP score less ↓
    - Leukemoid reaction ↑.
    - NAP score
- others.
  - S. uric acid ↑

Differential diagnosis.

- Leukemoid reaction – 50,000 – 1 lakh.
- not cancer.
- occurs in response to infection, but no mutation
- occurs due to infection, drugs etc...

- Chronic myelogenous Leukemia.

It is one of the myeloproliferative neoplasms of pluripotent hematopoietic stem cell characterized by overproduction of cells of myeloid series which results in marked splenomegaly and leukocytosis.

Acute myeloid leukemia.

- usually 40-50 years (not old age)

Pathophysiology

- mutation only occurs in myeloblast
- not in pm, m, mm, Band.

brain location / mutation occurring in myeloblast

① t (8; 21)
② t (15; 17)
③ inversion (16)

Clinical features.

① Anaemia
② Bleeding.
③ Infection.

→ myeloid solid organs
↓
lymphoma.

AML ✓ CML never occurs ✗

↓
differentiating features!

due to organ infiltration, there can be →

- Bones.
- lymphadenopathy.
- splenomegaly.
- hepatomegaly
- leukemia
- Gum hypertrophy - M4, M5
- Chloroma - M2

Fab

M0 — minimally diff. AML.
M1 — without maturation. X.
M2 — with maturation. — t (8; 21), chloroma-max chance. Most Common.
M3 — acute promyelocytic leukemia. → DIC, t (15; 17), max Auer rod,
M4 — acute myelomonocytic leukemia. — inversion 16.
M5 — acute monocytic leukemia. t (9; 11)
M6 — acute erythroleukemia.
M7 — acute megakaryocytic leukemia. — least Common type.
worst prognosis
Down syndrome.

MPO (-). rest all are MPO (+).

Lab diagnosis.

- Auer rods - faggot cells
- M_3
- myeloblast

Lab.

- Blood
  - Hb ↓
  - WB ↑↑
  - platelet ↓
- Bone marrow
  - hypercellular
  - leukemic cells
    - myeloblast > 20%
    - Auer rods ✓
  - erythropoiesis ↓
  - megakaryopoiesis ↓
- cytogenetics
  - M_2 - t (8;21)
  - M_3 - t (15;17)
  - M_4 - inv 16.
- cytochemistry
- Immunophenotyping

Cytochem / stain

CML	AML	ALL
NAP/LAP ↓	(Auer rod ✓)	(Auer rod ✗)
	MPO (+)	MPO (-)
	Sudan black (+)	Sudan black (-)
	NSE (+)	NSE (-)
	PAS (-)	PAS (+)
	acid phosphatase (-)	(+)

NSE (+) → M_3, M_4, M_5

Treatment

- Bone marrow transplantation
- chemotherapy → cytosine arabinoside, anthracyclines, 6-thioguanine.
- No targeted therapy.
- M_3 → ~~Tretinoin~~ Tretinoin therapy due to DIC ✗ no chemotherapy.

Prognostic factors

Good	Bad
• age < 40	age < 2, > 55
• m_2 m_3 m_4	m_0, m_6, m_7
• with Auer rod	Complex.
• TLC < 25×10^9	TLC > 100×10^9.
★ t (15;17) t(8;4) inv 16.	★ deletion 5q, 7q

Acute Lymphoblastic Leukemia / Lymphoma

- only LB are seen in peripheral Blood.
- age group – typically Children.

① pre B -cell ALL → 3-5 y

② pre T -cell ALL → Adolescent male

→ school uniform without Auer rod.

Pathogenesis

- pre -B cell ALL.
  - hyperdiploidy. → major
  - hypodiploidy.
  - loss of function mutations → PAX5, E2A or EBF gene.
  - t(9;22) translocation (BCR & ABL). 190 KD fusion gene size.
- Pre T cell ALL.
  - Gain of function mutations → NOTCH 1 gene

FAB classification

ALL

L_1 – Commonest, best prog.

L_2 –

L_3 – rare, worst prog.

Clinical feature.

- Anaemia
- Bleeding
- infection.

★ Organ infiltration → Bone, Lymph node.

Unique in ALL: ★ mediastinal Lymph node, ★ meningeal, ★ testicular } involvement

AML → orbit m_2, Gum m_4 m_5.

ALL → mediastinal, meningeal, testicular.

CML → no X

Lab diagnosis

Blood picture.

- all are lymphoblast.
- school uniform
- no Auer rods.

Bone marrow.

- hypercellular.
- Lymphoblast
- erythro, megakaryo } ↓

Cytogenetics

- hyperploidy
- Hypdiploidy.
- t(9;22).
- NOTCH.

Cytochemistry

MPO (−)
Sudan black. (−)
NSE (−)
PAS. (+)
Acid phosphatase. (+)

Treatment

no targetted therapy.
- BM transplant
- chemo
- Vincristine.
- prednisolone.
- Anthracyclines.
- L-asparaginase.

Prognostic.

good	bad
2–10.	<2, >10.
Female	M.
white	Black.
CNS pract test (−)	(+).
< 1 lakhs	>1 lakhs.
hyperdiploidy.	hypodiploidy.
trisomy 4 710.	t(9;22).
t(4;12)	
t(12;21)	

Chronic Lymphoid Leukemia (CLL)

- No blastoX ★.
- mature Lymphocytes ★ in Blood.
  that are matured.
- No blast cells → CLL.

Age ≈ 80 years

Pathogenesis.

- 99% lymphocytes in blood.
- mutation.
- deletion of 13q most common } monosomy.
  - 11q
  - 17p.
- trisomy 12q.

- Clinical feature - Same
  - Enlarged Superficial Lymph nodes.
  - splenomegaly & hepatomegaly.

Lab diagnosis

Blood – normal
mature lymphocytes

- Smudge cells. in CLL.
  Vimentin abnormality

B – CD19, 20, 23
CD5.

Leukopenia & Leukocytosis

Hematopoietic $CD34^+$ stemcell

- myeloid stem cell.
  - erythroblast → RBC
  - myeloblast → N, B, Eosinophil.
  - monoblast → monocytes
  - Megakaryoblast → Megakaryocytes.
- Lymphoid stem cell.
  - B lymphoblast → Naive B cells → plasma cells
  - T lymphoblast → Naive T cells → $CD8^+$ T cells, $CD4^+$ T cells

Normal is 5-10K.

- low WBC < 5000 - leukopenia.
- high WBC - leukocytosis

- Leukocytosis / penia is predominantly seen due to 1 type of cell.

eg: Neutropenia

① drug toxicity - during chemotherapy
⇒ rapidly dividing cells are affected.
obviously stem cells are rapidly dividing
↓
② Such cases will be treated by GM-CSF / GCSF (granulocyte monocyte colony stimulating factor) pharmacologically.

② Severe infection.
↓
Very severe. (normally ↑ during infection)

Lymphopenia

① Immunodeficiency. → digeorge syndrome.
↓
failure of 3rd & 4th pharyngeal pouch development.
↓
no thymus.

② High Cortisol state - eg: Cushing syndrom
↓

③ Autoimmune destruction - eg: Lupus.

④ whole body radiation.
most sensitive cell in human body to radiation is Lymphocyte.

Neutrophilic leukocytosis.

① Bacterial infection
- tissue necrosis.
- High cortisol state

two driving force of acute inflammation.
↓
↑ Neutrophil production.
↓
Immature cells are released
↓
ie, left shift.
↓
but less Fc receptors.
No proper function.

left shift → immature blast cells
→ marker ↓ CD16 → also ↓ Fc receptors
• They are not properly functioning

• high cortisol.
• cortisol disrupts adhesion of marginated pool of neutrophil.
• there are two types
  → marginated pool
  → circulating pool
• Since adhesion is disrupted.
• marginated pool becomes circulating pool → so count ↑
• when you give steroids
  ↓
  Neutrophilia.

Monocytosis
• Chronic inflammatory conditions.
• Malignancy

Eosinophilia
• allergic reactions
• parasitic infections
• Hodgkin's lymphoma.
  ↓
  due to ↑ IL-5 production

Basophilia
• CML high yield.
  ↓
  Classical.

Lymphocytic Leukocytosis
• Viral infections. (CD8+ T cells)
• Bordetella pertussis
• Bacteria generally causes neutrophilia but this is exception.

How?
• Bacteria bordetella produces a factor called Lymphocytosis promoting factors
  ↓
  blocks lymphocyte leaving blood & entering lymph node.

Bone marrow → Blood → Lymph node.
Lymph node → attempts to produce Ab etc...
Blood → stuck in blood → lymphocytic leukocytosis

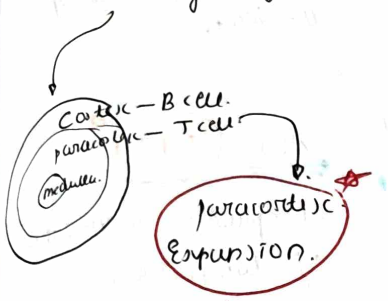
Infectious Mononucleosis.
• EBV virus that results in a lymphocytic leukocytosis comprised of reactive CD8+ T cells.
• CMV is less common cause.
• Virus is transmitted by saliva
  ↓
  called kissing disease

EBV primarily infects
• Oropharynx
• Liver
• B cells.

Plati

there will be -
CD8+ T-cell response.

① generalized lymphadenopathy.
↓
enlarged lymphnode.



↓
EBV infection

② splenomegaly. (periarterial lymphatic sheath) ← Exact area.
↓ due to
white pulp expansion.

③ high white count with atypical lymphocytes.
↓
eg: large nucleus.
large cytoplasm
looks like monocyte.
↓
earlier we thought it was monocytes.
↓
hence the name
Infectious mononucleosis.

CD8+ Lymphocytes ↑.
↓
Infectious mononucleosis

Monospot - Screening test

- It detects IgM heterophile Ab
↓
Ab having affinity to bind to RBC of other species
eg: horse RBC, sheep RBC.

- Usually test turns (+) within 1 week after infection.
- Negative test suggests CMV as the cause.
- definitive diagnosis is made by testing for EBV viral capsid antigen. — confirmatory test.

⇒ patients having classical symptoms of EBV
↓
but (-)
↓
go for CMV

Convenient

Complications

- ↑ risk of splenic rupture.
- rash if exposed to penicillin
- dormancy of virus in B cells.
↓ risk of recurrence.
risk of lymphoma especially in immunodeficient patients.