"NEOPLASTIC PROLIFERATION OF WHITE BLOOD CELLS" 🩸

Definition

- Neoplastic (malignant) clonal proliferation of WBCs
- Arise from hematopoietic stem cells or committed progenitors
- Characterized by uncontrolled growth, maturation arrest, and tissue infiltration

---

BROAD CLASSIFICATION 🧠

Based on Cell Lineage

1. Lymphoid neoplasms
2. Myeloid neoplasms
3. Histiocytic neoplasms

LYMPHOID NEOPLASMS 🧬

Types

- Leukemia → Predominantly bone marrow & blood
- Lymphoma → Solid masses in lymphoid tissues
- Plasma cell neoplasms → Terminally differentiated B cells

IMPORTANT PRINCIPLES (ROBINS FAVOURITES ⭐)

- B- and T-cell tumors are arrested at specific stages of normal differentiation
- Germinal center B cells are at high risk due to:
  - Class switching
  - Somatic hypermutation
- All lymphoid neoplasms are clonal
- Cause immune dysfunction
- Non-Hodgkin lymphomas (NHL) are usually widely disseminated at diagnosis

📌 Buzzword: monoclonality

WHO CLASSIFICATION OF LYMPHOID NEOPLASMS 🧠📊

Basis of WHO Classification

- Morphology
- Immunophenotype
- Genotype
- Normal cell counterpart
- Clinical features

WHO – LYMPHOID NEOPLASMS (SIMPLIFIED) ⭐⭐⭐

1️⃣ Precursor B-cell Neoplasms

- B-ALL / B-lymphoblastic lymphoma

2️⃣ Peripheral (Mature) B-cell Neoplasms

- CLL / SLL
- B-cell prolymphocytic leukemia

- Follicular lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Burkitt lymphoma
- Plasma cell neoplasms (Plasmacytoma, Multiple myeloma)

3️⃣ Precursor T-cell Neoplasms

- T-ALL / T-lymphoblastic lymphoma

4️⃣ Peripheral T / NK-cell Neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Anaplastic large cell lymphoma
- Enteropathy-associated T-cell lymphoma

5️⃣ Hodgkin Lymphoma

- Nodular sclerosis
- Mixed cellularity
- Lymphocyte-rich
- Lymphocyte-depleted
- Nodular lymphocyte-predominant

ORIGIN OF LYMPHOID NEOPLASMS 🧠🔁

Concept

> Each lymphoma corresponds to a specific stage of normal B- or T-cell differentiation

Flowchart (Conceptual) 🔁

Common lymphoid precursor (CLP)
→ B-cell lineage (bone marrow)
→ Pre-B → Naive B → Germinal center B → Memory / Plasma cell

OR

→ T-cell lineage (thymus)
→ Double negative → Double positive → CD4 / CD8 T cells

📌 Exam pearl:
All lymphomas are monoclonal and reflect stage-specific arrest

LEUKEMIA 🩸

WHO Definition

> Leukemia is a cancer of blood and bone marrow caused by rapid production of abnormal WBCs.

BASIC FEATURES OF LEUKEMIA 🧠

- Malignant clonal stem cell disorder
- Proliferation of poorly differentiated blast cells
- Normal hematopoiesis suppressed
- Bone marrow infiltration
- Extra-medullary infiltration (liver, spleen, lymph nodes)
- Spillover of malignant cells into peripheral blood

CLASSIFICATION OF LEUKEMIAS 📊

Acute	Chronic
ALL	CLL
AML	CML

ACUTE vs CHRONIC LEUKEMIA (VERY HIGH-YIELD)

⭐⭐⭐

Feature	Acute	Chronic
Progression	Rapid	Slow
Treatment	Immediate	Can be delayed
Age group	Children / young	Older adults
Symptoms	Severe	Often asymptomatic
Cells	Blasts	Mature cells

ACUTE LEUKEMIA 🧬🔥

Definition

Malignant clonal disorder of hematopoietic stem cells characterized by:

- Blast proliferation
- Maturation arrest
- Rapidly fatal if untreated

EPIDEMIOLOGY 🧠

- ALL → Children (≈80%)
- AML → Adults (≈80%)

PREDISPOSING FACTORS ⚠️

- Genetic / hereditary
- Radiation & toxins
- Viruses
- Chemicals
- Gene mutations
- Idiopathic

PATHOGENESIS 🧬

ALL - Pathogenesis

- Chromosomal abnormalities → transcription factor dysfunction
- T-ALL:
  - ~70% have NOTCH1 gain-of-function
- B-ALL:
  - Loss of function mutations in PAX5
- Result:
  - Maturation arrest
  - Increased self-renewal (hallmark of cancer)
- Additional mutations:
  - Tyrosine kinase
  - RAS pathway

AML - Pathogenesis

- Mutations in transcription factors regulating myeloid differentiation
- t(15;17) in Acute Promyelocytic Leukemia (APL)
    - Produces PML-RARA fusion protein
    - Blocks differentiation at promyelocyte stage
- Treated with ATRA (All-trans retinoic acid) 🧪
- Also:
    - Epigenetic alterations
    - TK & RAS mutations

📌 Exam pearl: APL = DIC risk + ATRA treatment

CLINICAL FEATURES OF ACUTE LEUKEMIA 🩺

Due to Bone Marrow Failure 🩸

- Neutropenia
  → Infections (fever, throat, skin, lungs)
- Anemia
  → Pallor, fatigue, dyspnea

- Thrombocytopenia
  → Bruises, purpura, epistaxis, gum bleeding, menorrhagia

Due to Tissue Infiltration 🧠

- Lymphadenopathy
- Hepatosplenomegaly
- CNS involvement (5–10% ALL)
- Bone pain & tenderness (ALL)
- Mediastinal mass (T-ALL)
- Testicular enlargement (ALL)
- Gum hypertrophy (AML)
- Skin & CNS infiltration (AML)
- DIC (especially AML-M3)
- Hyperleukocytosis

CASE-BASED QUESTION 🎯

A 6-year-old child presents with fever and bone pains. Physical examination shows generalized lymphadenopathy. Complete Blood Count WBC 98,000. Hemoglobin 9.0g/dl. Platelets 102000. Differential Count Neutrophil 5%. Lymphocytes 10%. Monocytes – Eosinophil 1%. Blast 84%

Case Summary

- 6-year-old child
- Fever, bone pain
- Generalized lymphadenopathy
- WBC: 98,000
- Hb: 9 g/dL
- Platelets: 102,000
- Blasts: 84%

Diagnosis ✅

➡ Acute Lymphoblastic Leukemia (ALL)

📌 Why?

- Child

- High blast count
- Pancytopenia features
- Bone pain

FINAL EXAM PEARLS 💡

- Leukemia = bone marrow + blood
- Lymphoma = solid tissue mass
- Acute leukemia = blasts
- ALL → children, bone pain, CNS & testis
- AML-M3 → DIC + ATRA
- All lymphoid neoplasms are monoclonal

LABORATORY DIAGNOSIS OF ACUTE LEUKEMIA 🧬🩸

OVERVIEW ⭐

A suspected case of acute leukemia is diagnosed using:

☐ Complete Blood Picture (CBC)

2️⃣ Peripheral Blood Smear

3️⃣ Bone Marrow Examination

4️⃣ Cytochemistry

5️⃣ Immunophenotyping (Flow cytometry)

6️⃣ Cytogenetics / Molecular studies

📌 Exam tip: Always write in this order.

1️⃣ COMPLETE BLOOD PICTURE (CBC) 🧪

Typical Findings

- TLC:
  - Low / Normal / High
  - May be markedly increased (up to $200 \times 10^9/L$)
- Hemoglobin: Decreased → anemia
- Platelets: Decreased → thrombocytopenia

📌 Key concept:

Pancytopenia occurs due to marrow replacement by blasts

2️⃣ PERIPHERAL BLOOD SMEAR 🔬

Findings

- Variable number of blast cells
- Normocytic normochromic anemia
- Thrombocytopenia

Smear Appearance

- Normal smear → mature WBCs, RBCs, platelets
- Leukemia smear → blasts dominate, ↓ platelets

📌 MCQ pearl:
Presence of blasts in peripheral blood is abnormal and suspicious for acute leukemia

---

3️⃣ BONE MARROW EXAMINATION (CONFIRMATORY) ⭐⭐⭐

Diagnostic Criteria

- Hypercellular marrow (most cases)
  (Rarely hypocellular)
- Blast cells ≥ 30% of nucleated cells *(classic teaching)*

📌 Modern WHO uses ≥20% blasts, but many exams still quote 30%

Blast Identification

- Based on:
  - Morphology
  - Immunophenotyping

MORPHOLOGICAL DIFFERENCES: AML vs ALL 🔬📊

Feature	AML (Myeloblast)	ALL (Lymphoblast)
Chromatin	Delicate	Clumped
Cytoplasm	Moderate	Scanty

Granules	Present	Absent
Auer rods	Present	Absent
Nucleoli	Prominent	Indistinct

📌 Auer rods = Myeloid lineage (Pathognomonic)

4️⃣ CYTOCHEMISTRY 🧫

Purpose

- Helps differentiate myeloid vs lymphoid blasts

Important Stains (VERY HIGH-YIELD) ⭐⭐

Stain	Myeloblast	Lymphoblast
Sudan Black B	Positive	Negative

Myeloperoxidase (MPO)	Positive	Negative
PAS	Negative	Positive (≈60%)

📌 Mnemonic:

Myeloid = MPO + SBB positive

🅂 IMMUNOPHENOTYPING (FLOW CYTOMETRY) 🧠

Role

- Gold standard for lineage confirmation
- Identifies cell surface antigens (CD markers)

Important CD Markers ⭐

Myeloid Cells

- CD13
- CD33

B-Lymphoid Cells

- CD19
- CD20
- CD22

T-Lymphoid Cells

- CD3
- CD7

📌 Exam pearl:
Immunophenotyping is essential when morphology is ambiguous

6️⃣ CYTOGENETICS / MOLECULAR STUDIES 🧬

Prognostic importance (VERY HIGH-YIELD) ⭐⭐⭐

ALL – Major Cytogenetic Abnormalities

✅ Good Prognosis

- Hyperdiploidy (>50 chromosomes)

- t(12;21) → *ETV6-RUNX1*

❌ Poor Prognosis

- t(9;22) → *BCR-ABL*
- Hypodiploidy
- KMT2A (MLL) rearrangements

AML – Major Cytogenetic Abnormalities

✅ Favorable Prognosis

- t(15;17) → *PML-RARA* (APL)
- t(8;21)
- inv(16) / t(16;16)

❌ Poor Prognosis

- Complex karyotype (≥3 abnormalities)
- -5 / del(5q)
- -7 / del(7q)
- inv(3)
- t(6;9)

📌 APL = DIC risk + ATRA treatment

DIFFERENCE BETWEEN ALL AND AML 🩸📊

Feature	ALL	AML
Age	Children	Adults
Lymphadenopathy	Common	Less common
Hepatosplenomegaly	Common	Less common
Bone/joint pain	Common	Less common
Gum hypertrophy	Rare	Common
Blast type	Lymphoblast	Myeloblast

FAB CLASSIFICATION – ALL 🧠

Feature	L1	L2	L3
Cell population	Homogeneous	Heterogeneous	Homogeneous
Size	Small	Large	Large
Cytoplasm	Scanty	Moderate	Deep basophilic
N/C ratio	High	Lower	Lower
Vacuoles	Absent	Few	Prominent
Nucleoli	Invisible	Prominent	Prominent

Key Associations

- L1 → Childhood ALL

- L3 → Burkitt-type leukemia (mature B cell)

FAB CLASSIFICATION - AML 🧬

- M0 - Minimally differentiated
- M1 - Without maturation
- M2 - With maturation
- M3 - Acute promyelocytic leukemia
- M4 - Myelomonocytic
- M5 - Monocytic
- M6 - Erythroleukemia
- M7 - Megakaryoblastic

📌 M3 = APL = t(15;17)

PROGNOSIS IN ALL 🎯

Parameter	Good	Poor

WBC count	Low	>50 × 10^9/L
Gender	Girls	Boys
Age	2–10 yrs	Infant / Adult
Blast clearance	<1 week	>1 week
Remission	<4 weeks	>4 weeks
CNS disease	Absent	Present
MRD	Negative early	Persistent

CASE-BASED QUESTION 🩺

A 72-year-old man presents with h/o increasing fatigue and repeated bacterial infections. Physical examination reveals multiple enlarged, nontender lymph nodes and

hepatosplenomegaly. His blood complete picture shows leukocytosis with more than 80% lymphocytes. Peripheral smear shows mature looking lymphocytes and smudge cells.

Case Summary

- 72-year-old man
- Fatigue, recurrent infections
- Generalized lymphadenopathy
- Hepatosplenomegaly
- Leukocytosis with >80% lymphocytes
- Peripheral smear: mature lymphocytes + smudge cells

Diagnosis ✅ ➡ Chronic Lymphocytic Leukemia (CLL)

📌 Smudge cells = fragile lymphocytes (CLL hallmark)

FINAL EXAM PEARLS 💡

- ≥30% blasts in marrow → Acute leukemia (exam standard)

- Auer rods = AML
- PAS+ lymphoblasts
- Flow cytometry confirms lineage
- Cytogenetics decide prognosis
- Smudge cells = CLL

-> The End <-