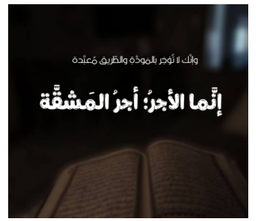
Myeloid Neoplasms

- Neoplasms originating from **hematopoietic progenitors**
- Primarily involve the bone marrow, replacing normal marrow elements
- Secondary involvement of:
- Lymph nodes (LN)
- Spleen
- Liver

Classification (based on cell of origin & differentiation)

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

جمّد قلبك ، سمي وقول يارب



Lecture 2,3,4

Three Broad Categories

1. Acute Myeloid Leukemia (AML)

- Block at early stage of development
- Accumulation of immature myeloid cells (blasts) in BM and PB

Acute Myeloid Leukemia (AML)

General Features
- Affects all age groups (peak > 60 years)
- Symptoms result from replacement of normal marrow elements:
- Anemia
- Thrombocytopenia
- Neutropenia
- Acute disease → develops within weeks
- Splenomegaly & lymphadenopathy are less prominent than ALL

Risk Factors
- Increasing age
- Male sex ♂
- Previous cancer treatment
- Radiation exposure
- Chemical exposure (e.g., benzene)
- Smoking (linked due to benzene)
- Other blood disorders (MDS, MPN)
- Genetic disorders (e.g., Down syndrome)

Pathogenesis
- Mutations in genes encoding transcription factors → block myeloid differentiation
- Leads to accumulation of blasts in bone marrow

Example: t(15;17) in APL acute promyelocytic Leukemia
- Fusion of:
- RARA gene (chr 17)
- PML gene (chr 15)
- **Forms PML/RARA fusion protein**
- Blocks differentiation at **promyelocyte stage**

Treatment Insight
- **ATRA (all-trans retinoic acid):**
- Overcomes differentiation block
- Converts promyelocytes → neutrophils
- Highly specific effect
- AML with t(15;17):
- Best prognosis
- 90% curable

2. Myeloproliferative Neoplasms (MPN)

- Cells continue to terminal differentiation
- Increased or dysregulated growth

📌 Definition
- A group of disorders characterized by:
- Presence of mutated, constitutively activated tyrosine kinases or related signaling molecules
- → Leads to growth factor independence
- Important:
- Tyrosine kinase mutations do NOT impair differentiation
- → Result: increased production of mature blood elements

- Neoplastic progenitors:
- Seed secondary hematopoietic organs:
- Spleen
- Liver
- Lymph nodes
- → Causes hepatosplenomegaly
- → Due to extramedullary hematopoiesis
- MPNs may transform into:
- AML

🧬 Chronic Myeloid Leukemia (CML)

📌 Pathogenesis
- Characterized by:
- BCR-ABL fusion gene
- From:
- BCR (chromosome 22)
- ABL (chromosome 9)
- Occurs in 95% of cases via:
- t(9;22) translocation (Philadelphia chromosome)
- Also seen in some cases of:
- B-ALL

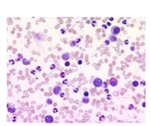
📌 Mechanism
- BCR-ABL:
- Produces continuous signals
- → Mimics growth factor activation
- → ↓ dependence on growth factors
- Does NOT block differentiation

→ Leads to:
- Overproduction of relatively normal cells
- Especially:
- Granulocytes
- Platelets

📌 Morphology

🩸 Peripheral Blood (PB)
- Leukocyte count ↑ ↑ (often >100,000/μL)
- Cells include:
- Neutrophils
- Metamyelocytes
- Myelocytes
- Also increased:
- Basophils
- Eosinophils
- Platelets

Left shift



🧬 Polycythemia Vera (PCV)

📌 Definition
- Excess proliferation of:
- Erythroid
- Granulocytic
- Megakaryocytic cells

→ Panmyelosis
- Main issue:
- ↑ Red cell mass

📌 Differential Diagnosis

Must distinguish from:
1. Relative polycythemia
   - Due to hemoconcentration
2. Reactive absolute polycythemia
   - Has ↑ erythropoietin

👉 PCV:
- Has LOW erythropoietin

growth factor–independent proliferation يسبب•

📌 Pathogenesis
- 97% cases:
- JAK2 mutation ⊙
- JAK2 function:
- Acts in erythropoietin signaling pathway
- Mutation effect:
- ↓ dependence on growth factors

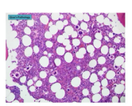
🧬Essential Thrombocythemia

📌 Definition
- Characterized by:
- Megakaryocyte proliferation
- → Overproduction of platelets
- Platelet count:
- > 600 × 10⁹/L
- Distinguished from:
- PCV → no polycythemia
- Primary Myelofibrosis → no marrow fibrosis

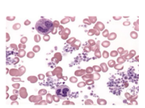
📌 Pathogenesis
- Associated with:
- JAK2 mutation (~50%)
- JAK2:
- Normally activated by thrombopoietin
- Mutation effect:
- → Makes progenitors thrombopoietin-independent
- → Causes hyperproliferation
- Important:
- Same JAK2 mutation as in PCV
- Why PCV vs ET occurs → not fully understood

📌 Morphology

🦴 Bone Marrow
- Cellularity:
- Usually mildly increased
- Megakaryocytes:
- Markedly increased
- Abnormally large forms



🩸 Peripheral Blood
- Large abnormal platelets
- Often:
- Mild leukocytosis



🧬 Primary Myelofibrosis (PM)

📌 Definition
- Hallmark:
- Obliterative marrow fibrosis

→ Leads to:
1. Cytopenias
2. Extensive extramedullary hematopoiesis

- Histology:
- Same as spent phase of MPNs

📌 Pathogenesis
- JAK2 mutation (50–60%)
- Others:
- Mutations → ↑ JAK signaling
- Not fully understood:
- Why JAK2 → PCV vs PM

📌 Mechanism of Fibrosis
- Caused by:
- Fibrogenic factors from megakaryocytes

Important factors:
1. PDGF (Platelet-derived growth factor)
2. TGF-β
   - Collagen deposition
   - Angiogenesis

3. Myelodysplastic Syndromes (MDS)

- Differentiation occurs but is disordered and ineffective
- Dysplastic BM precursors + peripheral blood cytopenias

📌 Definition
- Group of:
- Clonal stem cell disorders

Characterized by:
- Maturation defects
- Ineffective hematopoiesis
- Cytopenias
- High risk of → AML

📌 Key Concept
- Bone marrow:
- Contains abnormal stem cells
- Can differentiate into:
- RBCs
- Granulocytes
- Platelets
- BUT:
- In ineffective & disordered way

👉 Cells stay in BM → not released properly

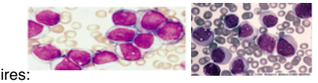
📌 Bone Marrow vs Peripheral Blood
- BM:
- Hypercellular / normocellular
- PB:
- Cytopenias

📌 Progression
- Cells are:
- Genetically unstable

→ Acquire mutations

→ Transform to AML

Morphology



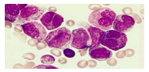
- Diagnosis requires:
- **≥20% myeloid blasts or promyelocytes in bone marrow**

Myeloblasts

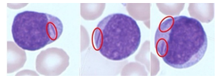
- Delicate nuclear chromatin
- 2–4 nucleoli
- Larger cytoplasm than lymphoblasts
- Fine azurophilic granules

Auer Rods

- Red-staining, needle-like granules
- Common in AML
- Numerous in APL



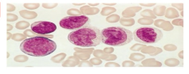
Other Findings



- Different subtypes may show:
- Monoblasts
- Erythroblasts
- Megakaryoblasts
- Blasts may be absent in PB → **aleukemic leukemia**
- Bone marrow exam is essential in pancytopenia

Monoblasts

- Folded or lobulated nuclei
- No Auer rods



Immunophenotype

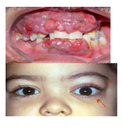
- Common markers:
- CD13, CD33, CD14, CD15, CD117 (KIT)
- CD34 → stem cell marker
- ***Myeloperoxidase (MPO)* → *most specific***
- Helps:
- Distinguish AML from ALL
- Identify poorly differentiated AML

Clinical Features

- Rapid onset (weeks to months)
- Symptoms:
- Fatigue (anemia)
- Fever (neutropenia)
- Bleeding (thrombocytopenia)
- CNS involvement: less common than ALL

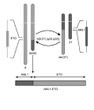
Special Features

- t(15;17) AML:
- High risk of **DIC** (due to procoagulants)
- Monocytic AML:
- Skin infiltration (leukemia cutis)
- Gingival involvement
- Can present as:
- **Myeloblastoma / granulocytic sarcoma**



Prognosis

- Generally poor disease
- Good-risk cytogenetics:
- t(8;21)
- inv(16)

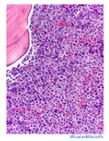


→ ~50% long-term survival

- Overall survival:
- **15–30%** with conventional chemotherapy

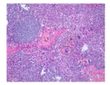
Bone Marrow (BM)

- Hypercellular
- Increased:
- Granulocytic precursors
- Megakaryocytic precursors



Spleen

- Resembles bone marrow
- Shows:
- Extensive extramedullary hematopoiesis



Clinical Features

- Peak: 4th–5th decade
- Symptoms:
- Fatigue
- Weakness
- Weight loss
- Splenomegaly:
- Causes dragging abdominal sensation
- Important:
- Must distinguish from leukemoid reaction
  (infection, stress, chronic inflammation..)

Disease Course

- Slowly progressive
- Median survival (untreated): ~3 years

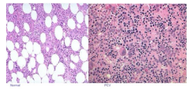
Progression:

1. Accelerated phase (additional genetic mutations).
   - Anemia
   - Thrombocytopenia
2. Blast phase
   - 70% → AML
   - 30% → ALL
3. Rare:
   - Spent phase (fibrosis)

Treatment

- Tyrosine kinase inhibitors (TKIs)
- Example: Imatinib
- Effects:
- Induce remission
- Prevent progression
- Suppress mutation acquisition

Morphology



Blood Changes

- ↑ Blood volume & viscosity
- Hb:
- 16.5 g/dL (males) ♂
- 16 g/dL (females) ♀

Organs

- Congestion of tissues
- Hepatomegaly
- Spleen:
- Slight enlargement

Complications

- Thrombosis & infarction
- Due to ↑ viscosity
- Platelets:
- Dysfunctional
- → Thrombosis + bleeding
- Hemorrhage sites:
- GIT
- Oropharynx
- Brain
- Peripheral blood:
- Often shows basophilia

Bone Marrow

- Hypercellular
- Increased:
- RBC precursors
- Myeloid cells
- Megakaryocytes

Progression

- May progress to:
- Spent phase — the marrow is largely replaced by fibroblasts & collagen
- Fibrosis
- ↑ extramedullary hematopoiesis

Prognosis

- Without treatment:
- Death within months
- With treatment:
- Survival ~10 years

Treatment:

- Repeated phlebotomy
- ↓ RBC count

Clinical Features

- Indolent disease
- Long asymptomatic periods
- Occasional:
- Thrombosis
- Hemorrhage
- Diagnosis requires:
- Excluding reactive thrombocytosis
- (inflammation, iron deficiency)

Additional Features

- Platelets:
- ↑ number + functional abnormalities
- Thrombosis:
- Similar to PCV
- Characteristic symptom:

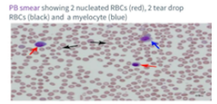
- Erythromelalgia
- Burning + throbbing in hands/feet
- Due to platelet occlusion of small vessels
- Also seen in PCV

Prognosis

- Median survival:
- 12–15 years
- Transformation:
- Myelofibrosis → uncommon
- AML → rare

Morphology

PM - Morphology



Peripheral Blood

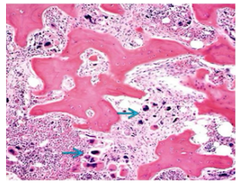
- Markedly abnormal:
- Leukoerythroblastosis

Includes:

1. Abnormal RBC shapes:
   - Poikilocytes
   - Teardrop cells
2. Nucleated RBCs
3. Immature WBCs:
   - Myelocytes
   - Metamyelocytes
4. Large abnormal platelets

Bone Marrow

- Advanced:
- Hypocellular + diffuse fibrosis
- Thickened trabeculae
- Early:
- Hypercellular
- Focal fibrosis
- Megakaryocytes:
- Large + clustered



Clinical Features

- Age:
- 60 years

- Symptoms:
- Anemia
- Splenomegaly
- Fatigue
- Weakness
- Night sweats

- Labs:
- Normocytic normochromic anemia
- Leukoerythroblastosis
- Diagnosis:
- Bone marrow exam essential

Prognosis

- Median survival:
- 4–5 years
- AML transformation:
- 5–20%
- Harder to treat than:
- PCV, CML
- Treatment:
- JAK2 inhibitors
- HSCT

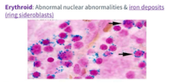
Pathogenesis

- Most cases:
- Idiopathic
- Secondary causes:
- Carcinogens
- Chemotherapy (alkylating agents)
- Radiation
- ~10%:
- TP53 mutation
- Chromosomal instability
- Poor prognosis

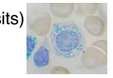
Morphology

Bone Marrow

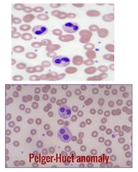
- Hypercellular
- Dysplasia in:



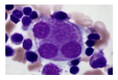
1. Erythroid
   - Abnormal nuclei
   - Ring sideroblasts (iron deposits)



2. Myeloid
   - Abnormal segmentation
   - Abnormal granulation
   - Pseudo–Pelger-Huët cells
   - (bilobed neutrophils)



3. Megakaryocytes
   - Single nuclear lobes
   - Multiple separate nuclei
   - “Pawn ball” appearance



Clinical Features

- Mostly:
- Elderly (70s)
- Often:
- Incidental finding
- Symptoms (due to pancytopenia):
- Weakness
- Infections
- Hemorrhage

Treatment & Outcome

- Poor response to:
- Conventional chemotherapy
- Transformation to AML:
- 10–40%
- Faster in therapy-related MDS

Prognosis

- Variable
- Median survival:
- 9–29 months

📌 Clinical Features

- Insidious onset (late middle age)
- Patients:
- Plethoric
- Cyanotic
- Symptoms:
- Pruritus (histamine release)
- Headache
- Dizziness
- Complications:
- Thrombosis
- Hemorrhage
- Hypertension
- GIT bleeding (hematemesis, melena)

📌 Long-term Outcome

- May progress to:
- Spent phase (~10 years)
- Bone marrow fibrosis
- Hematopoiesis shifts to spleen
- Marked splenomegaly

1. Overview

Reactive Lymphadenitis

- Non-neoplastic (reactive) enlargement of lymph nodes.

Neoplastic Proliferations of White Cells (Lymphoid Neoplasms)

Forms of Presentation

Lymphoid neoplasms can manifest as:

1. Leukemias
- Involve bone marrow (BM) and peripheral blood (PB)
- Usually (but not always)
2. Lymphomas
- Form masses in lymph nodes or other tissues
3. Other
- Plasma cell neoplasms

➡️ All types can spread to:

- Lymph nodes
- Liver
- Spleen
- Bone marrow
- Peripheral blood

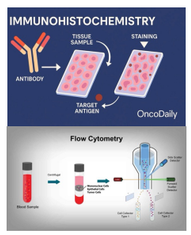
2. Classification & Diagnosis

Cell Origin

- Tumors arise from B-cells or T-cells
- Cells are arrested at a specific stage of differentiation

Diagnostic Methods

- Immunohistochemistry
- Flow cytometry



➡️ Detect:

- Cell lineage (B, T, NK)
- Maturity markers

Cluster of Differentiation (CD markers)

Definition

- Surface markers used to identify cell types

Examples

- B-cell markers: CD19, CD79, CD20
- T-cell markers: CD3, CD4, CD8

Special Marker

- TdT
- Marker of early lymphoid cells (lymphoblasts)

3. Pathogenesis

B-cell Activation

- Occurs in germinal centers
- Leads to:
- Class switching
- Somatic hypermutation

➡️ Purpose: Antibody diversification

⚠️ Problem:

- Error-prone process → genetic mutations

→ responsible for most B-cell lymphomas

4. Clinical Impact

Lymphoid neoplasms can cause:

1. Immunodeficiency
- ↑ susceptibility to infections
2. Autoimmunity
3. Association with immune deficiency
- Especially EBV-related lymphomas

5. Major Categories

- B-cell neoplasms
- T-cell neoplasms

Two Main Lymphoma Groups

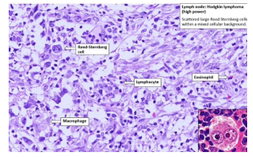
1. Hodgkin Lymphoma (HL)
2. Non-Hodgkin Lymphoma (NHL)

➡️ WHO classification based on:

- Morphology
- Phenotype
- Genotype
- Clinical features

For reading

- HL → فيه Reed–Sternberg + انتشار منظم
- NHL → ما فيه Reed–Sternberg + انتشار غير منتظم



Classification (based on cell of origin & differentiation)

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

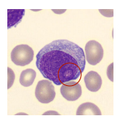
Acute Lymphoblastic Leukemia/Lymphoma (ALL)

Definition

- Neoplasm of immature lymphoid cells (lymphoblasts)

Types

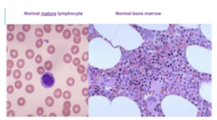
- Pre-B ALL (85%)
- Most common childhood cancer
- Peak: 3 years
- Usually presents as leukemia
- Pre-T ALL (15%)
- Often presents as thymic lymphoma
- Peak: adolescence



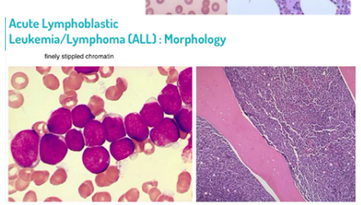
Genetics

Pre-B ALL

- Hyperdiploidy (>50 chromosomes)
- t(12;21)
- t(9;22) → BCR-ABL



Acute Lymphoblastic Leukemia/Lymphoma (ALL) : Morphology



Pre-T ALL

- NOTCH1 mutations
- CDKN2A mutations

Morphology

- Bone marrow: hypercellular, packed with lymphoblasts
- Lymphoma form: mediastinal mass

Blast characteristics:

- Scant basophilic cytoplasm
- Fine chromatin
- Small nucleoli

⚠️ Pre-B and Pre-T look identical → need immunophenotyping

Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL)

Definition

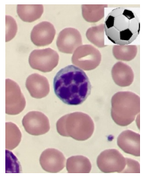
- Indolent tumor of mature B-cells

➡️ CLL and SLL are the same disease

- CLL: PB lymphocytes >5000/μL
- Most common leukemia in Western adults

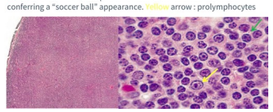
Morphology

- Small lymphocytes:
- Dark nuclei
- Clumped chromatin (“soccer ball”)
- Scant cytoplasm
- Prolymphocytes:
- Larger cells
- Prominent nucleoli



Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) : Morphology

Green arrow: cells w Clumped chromatin & white areas in between conferring a “soccer ball” appearance. Yellow arrow : prolymphocytes



Immunophenotype

- CD20 (B-cell marker)
- CD5 (important diagnostic clue)

CD5 (diagnostic clue, only SLL & MCL express it)

Clinical Features

- Elderly patients
- Often asymptomatic

Symptoms:

- Fatigue
- Weight loss
- Lymphadenopathy
- Hepatosplenomegaly

Other:

- Lymphocytosis (>5000)
- Autoimmune hemolytic anemia (10–15%)

➡️ Indolent but curable only with stem cell transplant (HSCT)

Follicular Lymphoma

Epidemiology

- ~40% of adult NHL Non-Hodgkin Lymphoma (NHL)
- Age >50

Pathogenesis

- t(14;18) → BCL2 overexpression (an inhibitor of apoptosis)

→ inhibits apoptosis → ↑ survival

Morphology

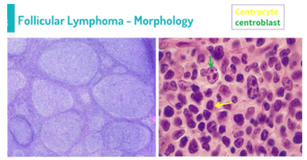
- Nodular (follicular) pattern

Cells:

1. Centrocytes
   - Cleaved nuclei
2. Centroblasts
   - Large, vesicular chromatin

Follicular Lymphoma - Morphology

Centrocyte centroblast



Immunophenotype

- B-cell markers
- CD10 (germinal center marker)

CD10 → GC marker (expressed in Burkitt lymphoma, B- ALL & some DLBCL)

Diffuse Large B-Cell Lymphoma

Clinical Features

- Painless generalized lymphadenopathy
- Bone marrow involvement (80%)

➡️ Indolent, not curable

➡️ 40% transform → DLBCL (poor prognosis)

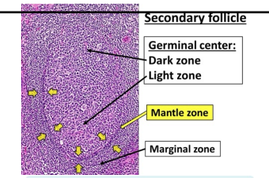
Diffuse Large B-Cell Lymphoma aggressive !!!

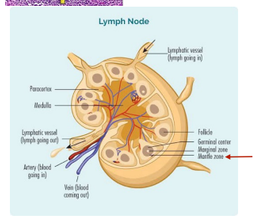
dismal prognosis

Mantle Cell Lymphoma

Origin

- Naive B-cells from mantle zone





Epidemiology

- Men >50 years

Pathogenesis

- t(11;14) → Cyclin D1 overexpression

→ promotes cell cycle (G1 → S)

Immunophenotype

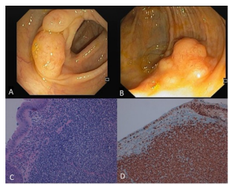
- B-cell markers
- CD5 CD5 (as CLL/SLL)
- Cyclin D1 (key differentiator from CLL)

Morphology

- Diffuse lymph node involvement
- Slightly larger cells
- Irregular nuclei

➡️ Bone marrow involvement common

➡️ May affect GIT → lymphomatoid polyposis



Clinical Features

- Fatigue
- Generalized lymphadenopathy

Disseminated disease:

- Bone marrow
- Spleen
- Liver
- GIT

➡️ Moderately aggressive

➡️ Not curable

➡️ Median survival: 4–6 years

Clinical Features

Presentation

1. Bone marrow failure:
- Anemia
- Neutropenia
- Bleeding
2. Tissue infiltration:
- Bone pain
3. CNS involvement:
- Headache
- Vomiting
- Nerve palsies

Prognosis

Favorable

- Age 2–10 years
- Low WBC
- Hyperdiploidy
- t(12;21)

Poor

- Age <2 or >10
- WBC >100,000
- t(9;22)

⚠️

➡️ Aggressive but 85% curable in children

✅ Summary (High Yield)

- ALL → children, aggressive but curable
- CLL → elderly, indolent, CD5+
- Follicular → BCL2, indolent, transforms
- Mantle → Cyclin D1, aggressive, poor prognosis

B B B T

Extranodal Marginal Zone Lymphoma (MZL / MALT lymphoma)

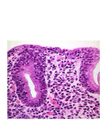
General Features
- An indolent B-cell tumor
- Arises mainly in epithelial tissues:
- GIT
- Salivary glands
- Lungs
- Orbit
- Breast

Etiology / Pathogenesis
- Develops in settings of chronic inflammation:

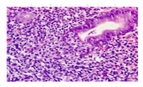
1. Autoimmune diseases:
- Sjögren syndrome (salivary gland)
- Hashimoto thyroiditis (thyroid)

2. Chronic infection:
- Helicobacter pylori gastritis

Morphology
- B-cells infiltrate epithelium forming:



→ Lymphoepithelial lesions



- Tumor cells:
- Have abundant pale cytoplasm
- May show plasma cell differentiation
- Example: gastric MALT lymphoma shows:
- Intraepithelial atypical lymphocytes
- Plasma cells in lamina propria

Immunophenotype
- Positive for B-cell markers

Clinical Features
- Presents as:
- Swelling of salivary gland, thyroid, or orbit
- Or incidental finding in H. pylori gastritis
- If localized:

→ Treated by excision + radiotherapy
→ Often curable

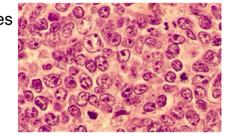
Diffuse Large B-Cell Lymphoma (DLBCL)

General Features
- Most common lymphoma in adults
- Can arise:
- De novo
- From transformation of low-grade lymphoma (e.g., follicular lymphoma) حكيناها فوق

Pathogenesis
- Associated with:
- BCL6 gene mutations/rearrangements

→ Increased BCL6 protein
→ Alters gene expression in germinal center B-cells

Morphology
- Diffuse infiltration by large B-cells:
- 3–4× size of resting lymphocytes
- Variable appearance



Immunophenotype
- B-cell markers
- CD10 positive in some cases

Clinical Features

- Median age: > 60 years (can occur at any age)
- Features:
- Generalized lymphadenopathy
- Extranodal involvement (especially GIT)
- Behavior:
- Aggressive and rapidly fatal if untreated
- ~50% cure with treatment

Burkitt Lymphoma

General Features
- Highly aggressive tumor
- Types:

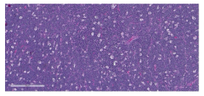
1. Endemic (Africa) → associated with EBV
2. Sporadic

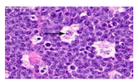
Pathogenesis
- MYC gene translocation (chromosome 8)

→ MYC overexpression
→ Drives:
- Warburg metabolism (aerobic glycolysis) It's faster
- Rapid cell growth
- Known as:

→ Fastest growing human tumor

Morphology
- Medium-sized lymphocytes:
- Variable cytoplasm
- Multiple nucleoli
- Features:
- Very high proliferation and apoptosis
- Numerous mitoses
- Macrophages with ingested debris





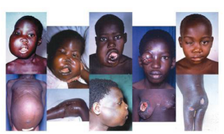
→ Creates "starry sky" appearance

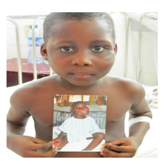
Immunophenotype
- B-cell markers
- CD10 positive

Clinical Features
- Affects:
- Children and young adults

- Extranodal involvement:
- Endemic → jaw (maxillary/mandibular)

- Sporadic → abdomen (bowel, ovaries)
- Treatment:
- Requires intensive chemotherapy
- Potentially curable





Hodgkin Lymphoma (HL)

General Features
- A group of B-cell neoplasms
- Defined by presence of:

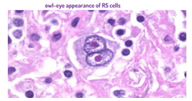
→ Reed-Sternberg (RS) cells
- Spread pattern:
- Starts in a single lymph node/group
- Spreads contiguously

Major Subtypes

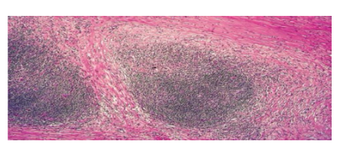
1. Classic HL
- Nodular sclerosis (common)
- Mixed cellularity (common)
- Lymphocyte-rich
- Lymphocyte-depleted

2. Nodular Lymphocyte Predominant HL (NLPHL)

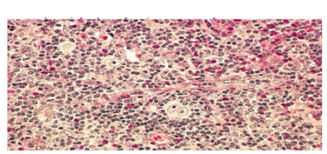
Morphology
- RS cells:
- Very large
- Multilobated nucleus
- Prominent nucleoli
- Abundant cytoplasm
- "Owl-eye appearance"



- Background:
- Mixed inflammatory cells:
- Lymphocytes
- Eosinophils
- Plasma cells
- Macrophages
- Caused by cytokines from RS cells:
- IL-5, TGF-β, IL-13



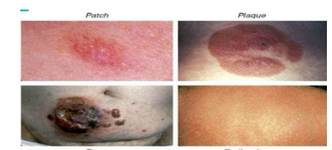
Subtype Morphology
- Nodular sclerosis:
- Collagen bands dividing tumor into nodules
- Mixed cellularity:
- RS cells with mixed inflammatory infiltrate



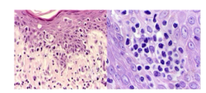
Mycosis Fungoides & Sézary Syndrome

General Features
- Cutaneous T-cell lymphoma
- Neoplastic CD4+ T-cells that home to skin

Clinical Stages (MF)
1. Patch stage → nonspecific rash (erythroderma)
2. Plaque stage
3. Tumor stage



Morphology
- Infiltration of:
- Epidermis
- Upper dermis
- Tumor cells:
- Cerebriform nuclei (folded nuclear membrane)



Immunophenotype
- CD4+
- CD8-

Sézary Syndrome
- Variant of MF with:

1. Generalized exfoliative erythroderma
2. Circulating tumor cells (Sézary cells) in blood

Clinical Features
- Early MF:
- Long survival (many years)
- Advanced disease / Sézary syndrome:
- Poor prognosis
- Survival: 1–3 years

Immunophenotype

- Classic HL:
- CD15+, CD30+
- Negative for B- and T-cell markers
- NLPHL:
- CD20+ (B-cell marker)
- CD15-, CD30-
- Immune evasion:
- RS cells express PD ligands

→ Suppress T-cell response

Clinical Features

- Common in:
- Young individuals (but any age possible)
- Presentation:
- Painless lymphadenopathy
- Common sites:
- Cervical
- Mediastinal

بمشي عالترتيب

- Rare extranodal involvement
- Advanced disease (Stage III–IV):
- B symptoms:
- Fever
- Weight loss
- Night sweats
- Pruritus
- Anemia

Course & Treatment

- Spreads contiguously
- Treatment:
- Chemotherapy ± radiotherapy
- Prognosis:
- Excellent
- >90% 5-year survival in early stages

Classification (based on cell of origin & differentiation)

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

Hodgkin Lymphoma	Non-Hodgkin Lymphoma
More often localized to a single axial group of nodes (cervical, mediastinal, paraaortic)	More frequent involvement of multiple peripheral nodes
Orderly spread by contiguity	Noncontiguous spread
Mesenteric nodes and Waldeyer ring rarely involved	Mesenteric nodes and Waldeyer ring commonly involved
Extranodal involvement uncommon	Extranodal involvement common

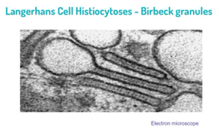
Langerhans Cell Histiocytoses (LCH)

General Concept
- Histiocytosis is an umbrella term for proliferative disorders of:
- Dendritic cells
- Macrophages
- Spectrum:
- Highly malignant → rare histiocytic sarcomas
- Benign/reactive → most histiocytic proliferations in lymph nodes
- Intermediate group → Langerhans cell histiocytoses

Langerhans Cells
- Specialized immature dendritic cells
- Located mainly in the epidermis (also present in other organs)
- Function:

→ Capture antigens and present them to T cells

Immunophenotype & Markers
- Express:
- MHC class II
- CD1a
- Langerin
- Langerin:
- Transmembrane protein
- Found in Birbeck granules



Birbeck Granules
- Cytoplasmic rod-like tubular structures
- Characteristic “tennis racket” appearance on electron microscopy

Pathogenesis
- Frequently associated with:
- BRAF kinase mutation → increased activity
- Same mutation seen in:
- Benign nevi
- Malignant melanoma
- Papillary thyroid carcinoma
- Some colon cancers

Morphology
- Under light microscopy:
- Do NOT resemble normal dendritic cells
- Features:
- Abundant, often vacuolated cytoplasm
- Vesicular nuclei
- Appearance resembles:

→ Tissue macrophages (histiocytes)

Classification of LCH

A. Multisystem LCH (Letterer–Siwe Disease)

Epidemiology
- Affects children < 2 years

Clinical Features
- Multifocal cutaneous lesions (seborrheic-like rash)
- Systemic involvement:
- Hepatosplenomegaly
- Lymphadenopathy
- Pulmonary lesions
- Later: osteolytic bone lesions

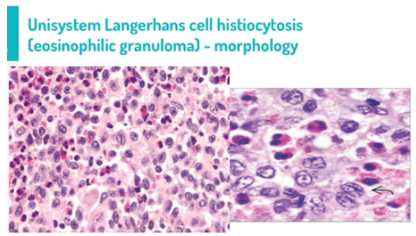
Complications
- Extensive bone marrow infiltration

→ Leads to pancytopenia

Prognosis
- Rapidly fatal if untreated
- With intensive chemotherapy:

→ ~50% 5-year survival

B. Unisystem LCH (Eosinophilic Granuloma)



General Features
- Can be:
- Unifocal
- Multifocal
- Characterized by:
- Proliferation of Langerhans cells in:
- Bone (most common; medullary cavity)
- Skin
- Lungs
- Stomach

Cellular Composition
- Mixed inflammatory infiltrate:
- Lymphocytes
- Plasma cells
- Neutrophils
- Prominent eosinophils

Common Bones Affected
- Calvaria Skull bones 💀
- Ribs
- Femur

1. Unifocal Disease
- Involves single bone
- Symptoms:
- May be asymptomatic
- Pain, tenderness
- Pathologic fracture
- Behavior:
- Indolent
- May:
- Heal spontaneously
- Be cured by excision or irradiation

2. Multifocal Disease
- Usually affects children
- Features:
- Multiple erosive bone lesions
- May extend to soft tissues
- Special complication:
- Posterior pituitary involvement (~50%)

→ Causes diabetes insipidus

Outcome
- Some cases:

→ Spontaneous regression
- Others:

→ Respond well to chemotherapy

Disorders of the Spleen

Classification by Size

1. Massive Splenomegaly (>1000 g)

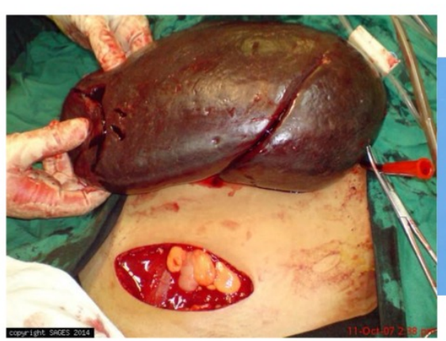
- Causes:
  - Myeloproliferative neoplasms:
  - CML
  - Primary myelofibrosis
  - Indolent leukemias:
  - CLL
  - Hairy cell leukemia
  - Lymphomas
  - Infections (e.g., malaria)
  - Gaucher disease

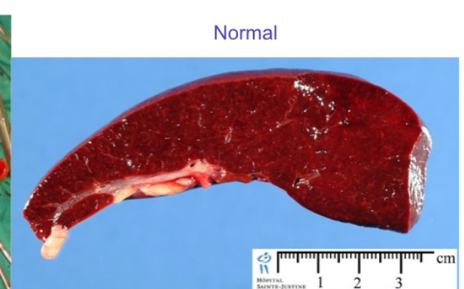
2. Moderate Splenomegaly (500–1000 g)

- Causes:
  - Chronic congestion:
  - Portal hypertension
  - Splenic vein obstruction
  - Acute leukemias
  - Extravascular hemolysis:
  - Hereditary spherocytosis
  - Thalassemia major
  - Autoimmune hemolytic anemia
  - Infections:
  - Infective endocarditis
  - Tuberculosis
  - Typhoid
  - Metastatic disease

3. Mild Splenomegaly (<500 g)

- Causes:
  - Acute splenitis
  - Acute congestion
  - Infectious mononucleosis
  - Septicemia
  - Intra-abdominal infections





Splenomegaly

General Features
- Spleen is involved in many systemic diseases
- Response:

→ Enlargement (splenomegaly)

Symptoms
- Dragging sensation in left upper quadrant
- Discomfort after eating

Hypersplenism
- Enlarged spleen removes excess blood cells:
- RBCs → anemia
- WBCs → leukopenia
- Platelets → thrombocytopenia
- Platelets:
- Most affected due to sequestration in red pulp

→ Thrombocytopenia is most common and severe

General Function
- Thymus plays a crucial role in T-cell maturation
- Can be involved in:
- Lymphomas (especially T-cell lineage)

Thymus Disorders

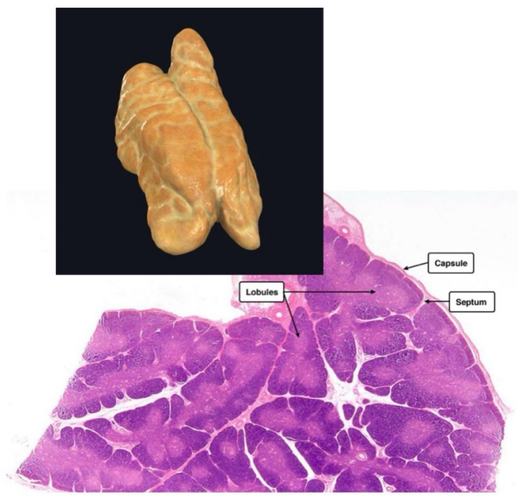
A. Thymic Hyperplasia

Features
- Enlargement with:
- Lymphoid follicles (germinal centers) in medulla
- Germinal centers contain:
- Reactive B cells (normally few in thymus)

Associated Diseases
- Most commonly:
- Myasthenia gravis (MG)
- Also seen in:
- Systemic lupus erythematosus (SLE)
- Rheumatoid arthritis

Management
- Early removal of thymus:

→ Often beneficial



Definition
- Tumors of thymic epithelial cells

B. Thymomas

1. Benign (Encapsulated Thymoma)
- Cytologically and biologically benign

Epidemiology
- Rare tumors
- Usually affect middle-aged adults

2. Malignant Thymoma

- **Type I:**
  - Cytologically benign
  - Locally invasive/aggressive
- **Type II (Thymic carcinoma):**
  - Cytologically and biologically malignant

Clinical Features
- 30%:
- Asymptomatic
- 30–40%:
- Local symptoms:
- Cough
- Dyspnea
- Superior vena cava syndrome
- Remaining cases:
- Associated with systemic diseases

Associations
- Most common:
- Myasthenia gravis
- Present in 15–20% of MG patients
- Tumor removal → clinical improvement
- Other paraneoplastic syndromes:
- Pure red cell aplasia
- Hypogammaglobulinemia
- Multiorgan autoimmunity

Neoplastic Proliferations of White Cells – Plasma Cell Neoplasms & Related Entities

1. Plasma Cells (Normal Features)

- Represent the final stage of B-cell maturation
- Immunophenotype:
- CD138 positive
- Lose CD19
- Functional characteristics:
- Cannot switch antibody classes
- Produce one specific type of antibody (single class of immunoglobulin)

Morphology

- Eccentric nucleus
- Perinuclear halo (due to Golgi apparatus)

2. Plasma Cell Neoplasms – General Features

- Neoplasms of B-cell origin containing plasma cells
- Always produce:

→ Monoclonal immunoglobulin (or fragments)

Significance

- Serve as:
- Tumor markers
- Cause pathologic effects
- Most important and deadly form:

→ Multiple Myeloma

3. Monoclonal Proteins

M Protein

- Monoclonal immunoglobulin found in blood
- Characteristics:
- High molecular weight
- Confined to plasma and extracellular fluid
- Not excreted in urine

M protein (Monoclonal protein) is:
→ An abnormal immunoglobulin produced by a single clone of plasma cells

What is it made of?

M protein can be:
- Full immunoglobulin (e.g., IgG, IgA, IgM)
- Or parts of it:
- Light chains (κ or λ) → appear in urine as:

→ Bence Jones proteins

Bence Jones Proteins

- Free light chains (κ or λ)
- Characteristics:
- Small size
- Excreted in urine

Detection

- By:

→ Serum Protein Electrophoresis (SPEP)

Plasma Cell Neoplasm Spectrum

A. Multiple Myeloma (MM)

- Most important plasma cell neoplasm

General Features
- One of the most common lymphoid malignancies

- Median age: ~70 years
- More common in males
- Primarily involves:
- Bone marrow
- Causes lytic bone lesions

Immunoglobulin Production
- Most common:
- IgG (60%)
- Followed by IgA
- Produces:
- κ or λ light chains

Pathogenesis
- Chromosomal translocations:
- IgH gene (chromosome 14) fused with oncogenes:
- Cyclin D1
- Cyclin D3
- Affects:
- Skeleton →
- Immune system
- Kidneys

A. Bone Effects
- Major feature: Bone destruction

Mechanism:
- Tumor cells:
- ↑ RANKL expression → activates osteoclasts
- Inhibit osteoblasts

Result:
- ↑ Bone resorption →
- Hypercalcemia
- Bone pain
- Pathologic fractures

B. Immune Effects
- Suppression of normal B-cell function

→ ↓ functional antibodies
→ ↑ risk of bacterial infections

C. Renal Effects

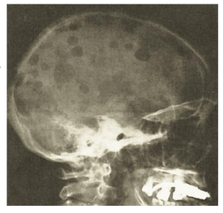
Causes of kidney damage:
1. Bence Jones protein casts (tubular obstruction)
2. Light chain deposition:
   - Amyloid or linear deposits
3. Hypercalcemia:
   - Dehydration
   - Renal stones
4. Bacterial pyelonephritis

B. Variants

- **Solitary plasmacytoma**
  - Single mass in bone or soft tissue
  - **Smoldering myeloma**
  - High M protein
  - No symptoms

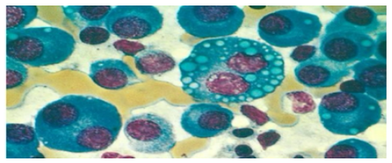
Morphology

Gross

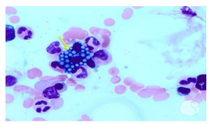


- Multiple lytic lesions:
- Vertebrae
- Ribs
- Skull
- Pelvis
- Femur
- “Punched-out defects”
- Leads to fractures (often first presentation)

Microscopic



- Bone marrow:
- >30% plasma cells
- Special cells:
- Mott cells:
- Plasma cells with immunoglobulin inclusions
- Called Russell bodies



Clinical Features
- Bone pain & fractures
- Hypercalcemia:
- Confusion
- Lethargy
- Weakness
- Recurrent bacterial infections:

→ Most common cause of death

- Renal dysfunction:

→ Second most common cause of death
- Median survival:

→ 4–7 years
- Prognosis:
- Variable
- No cure

Laboratory Findings
- ↑ Immunoglobulins in blood
- ± Bence Jones proteins in urine

Distribution:
- 70%: both present
- 20%: only light chains
- 1%: nonsecretory

Other findings:
- Anemia
- Thrombocytopenia
- Leukopenia
- ↑ Creatinine / urea

C. MGUS (Monoclonal Gammopathy of Undetermined Significance)

- No symptoms
  - Small to moderate M protein levels
  - Very common in elderly
  - Has low but constant risk of progression to MM

Lymphoplasmacytic Lymphoma

General Features

- B-cell neoplasm
- Occurs in older adults

Immunoglobulin Production
- Produces IgM
- Leads to:

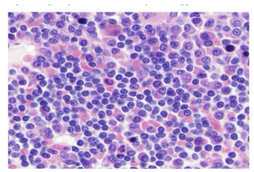
→ Waldenström macroglobulinemia

Key Characteristics
- Hyperviscosity syndrome
- Rare:
- Renal failure from light chains
- No bone destruction

Pathogenesis
- Associated with:

→ MYD88 mutation (all cases)

Morphology
- Bone marrow infiltration by:
- Lymphocytes
- Plasma cells
- Plasmacytoid lymphocytes



D. Waldenström Macroglobulinemia

- High levels of IgM
  - Causes:

→ Hyperviscosity syndrome
  - Associated with:

→ Lymphoplasmacytic lymphoma

*Waldenström Macroglobulinemia

Pathophysiology
- Due to high IgM levels
- IgM properties:
- Large size

→ Causes increased blood viscosity

Clinical Features

1. Visual Problems
- Venous congestion
- Retinal hemorrhages

2. Neurologic Symptoms
- Headache
- Dizziness
- Deafness

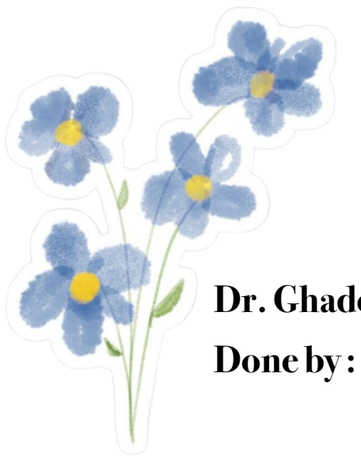
→ Due to sluggish blood flow

3. Bleeding
- Caused by:
- IgM interfering with clotting factors
- Platelet dysfunction

4. Cryoglobulinemia
- IgM precipitates in cold

→ Causes:

- Raynaud phenomenon



Dr. Ghadeer Hayel

Done by : Raghad Mrayat

إنّا بشر و قد نخطئ، نعتذر عن وجود اي خطأ