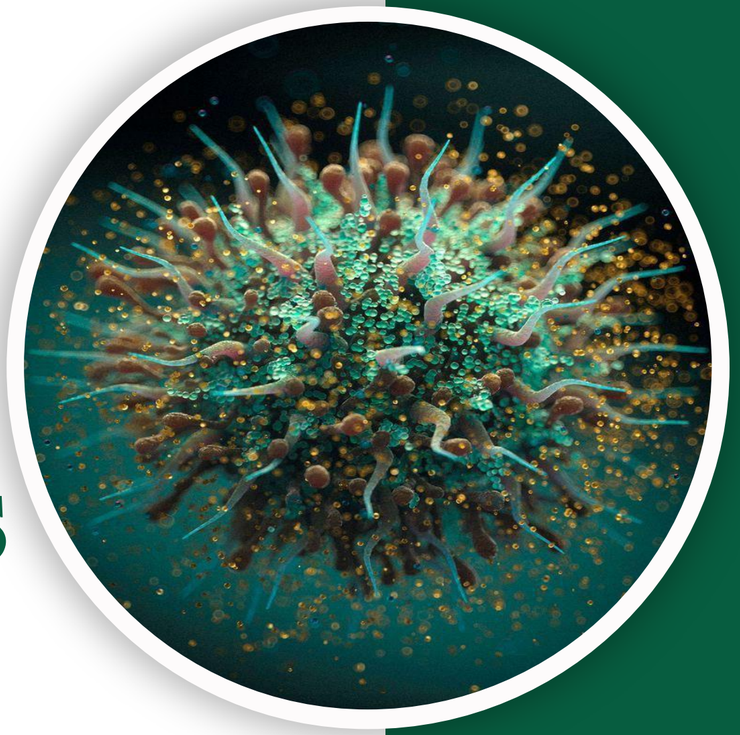
بسم الله الرحمـٰن الرحيم

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MSS Pathology | FINAL 6

Acute Leukemia & Histocytic Neoplasms



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Pathology of hematolymphoid system
Acute Leukemia
Histiocytic tumors

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إن سُئلتم فيم تُلهمون لا تظنّون إلّا لإلهام

- In contrast to erythroid cell disorders, Most WBC disorders are neoplastic.
- Acute leukemia (with its 2 types: myeloid & lymphoblastic) is the most aggressive WBC disorder.

ACUTE MYELOID LEUKEMIA (AML)

- Occur at all age groups, but more common in elderly

  In contrast to acute lymphoblastic leukemia (ALL), which occurs at all age groups, but more common in children.

- Heterogonous (with many subtypes), diagnosis is made by morphologic, immunophenotypic (the antigens they express) and karyotype (chromosomes) studies (searching for mutations)
- Prognosis depends most importantly on type of mutations (molecular and cytogenetic studies
- Symptoms are accelerated, become significant within few weeks
- Bone marrow becomes rich in “blasts” instead of normal mature cells, as a result,

Symptoms are related to cytopenia: anemia, thrombocytopenia and neutropenia

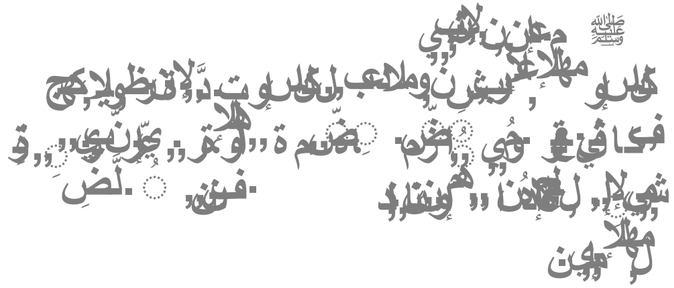
- Myoblasts mostly remain confined to the BM and peripheral blood (in contrast to ALL), so

Involvement of LN, spleen and solid organs is rare. When occurs, it is called myeloid sarcoma (acute monoblastic leukemia)

PATHOGENESIS

- Mutations in genes of transcription factors required for maturation and differentiation of myeloblasts (they don't mature)
- Additional mutations in tyrosine kinase pathways (RAS) (most common)
- Epigenetic mutation is common (20%); mutation in isocitrate dehydrogenase (IDH) produces an oncometabolite that blocks enzyme of epigenome and interferes with myeloblast differentiation

Remember
Epigenetic factors: factors that control DNA transcription



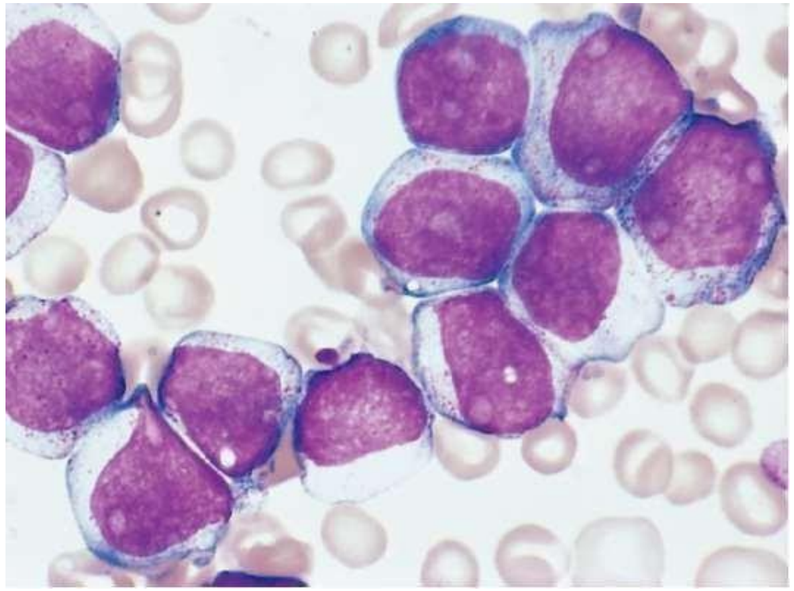
WHO-CLASSIFICATION

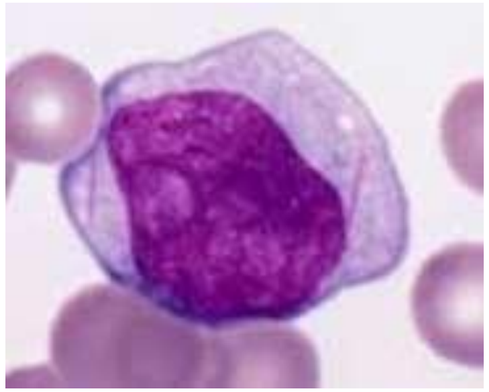
- Therapy related AML –very poor prognosis- : occurs after treatment with chemo or radiotherapy they are harmful to BM stem cells.
- AML with common recurrent cytogenetic mutation, if present, its called by its name.
- AML with myelodysplasia: occurs de novo (Rapidly) or complicates MDS (slow)

MDS: The earliest phase of AML, it's neoplastic but does **not** release huge amounts of cells, can be distinguished by morphology.

- If any of the previous cases does not exist: AML-Not otherwise specified
- Diagnosis of AML: 20% blasts in peripheral blood or bone marrow (of nucleated cells)

If less than 20% but still elevated (e.g. 19%), we call this: MDS .





- Morphology: large cells, high N/C ration, fine granules in cytoplasm mostly containing myeloperoxidase, fine chromatin ***(pale immature nuclei),*** prominent nucleoli (normal mature cells don't contain nucleoli).
- Auer rods: small pink rods (needles) present in cytoplasm, represent peroxidase enzyme
- Myeloblasts express CD34, myeloperoxidase (MPO), CD13, CD33
- CD34 is only expressed in immature "blast" cells.
- Sometimes: monoblast, erythroblast, megakaryoblast, myeloblast is the most common.

OUTCOME

Standard therapy

- Generally poor, <30% responds to chemotherapy (aggressive disease)
- Worse than ALL
- P53 mutation: more worse outcome
- IDH inhibitors are new promising drugs

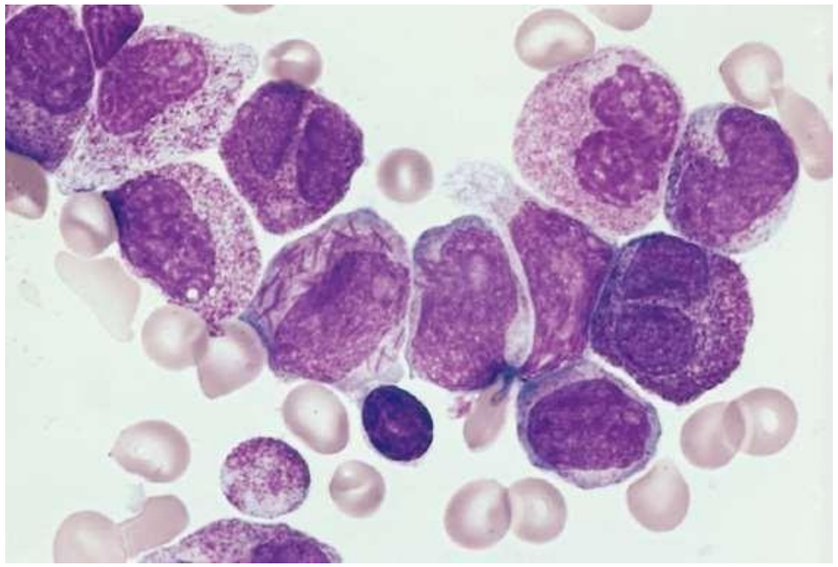
IDH: isocitrate dehydrogenase

- Promyelocyte is the next cell after the myeloblast.
- Promyelocytes are heavily granulated (much more granules than myeloblasts). They are CD34 negative.
- Vitamin A is important for myeloid cell maturation.

ACUTE PROMYELOCYTIC LEUKEMIA

- Also called AML-M3
- Maturation is arrested at promyelocyte stage
- Leukemic cells appear similar to promyelocytes instead of myeloblasts (heavy cytoplasmic granules, numerous Auer rods, negative for CD34)
- Carry recurrent mutation: t(15;17) fusion between PML gene (chrom 15) with alpha retinoic acid receptor (RARA) on chrom 17. Chimeric fusion gene produces a protein that blocks promyelocyte maturation by inhibiting the action of retinoic acid.
- All trans-retinoic acid (ATRA), a high dose vitamin A analogue, overcomes this block and force the cell to mature. Effect is synergistic with arsenic trioxide (toxic) (degrades oncoprotein). If they're given together they may cause synergistic effects.
- Malignant promyelocyte secrete tissue factor, causing DIC (special for this leukemia)

(Disseminated intravascular coagulation: widespread thrombosis and severe bleeding till death)



- APL: malignant promyelocytes show numerous cytoplasmic granules and Auer rods. The nuclei are commonly cleaved.

- We can observe 2 nuclei because of the malignancy.
- CD34 Negative.

PRECURSOR B AND T CELL NEOPLASMS

2 types

- Lymphoblastic lymphoma when occurs in solid tissue (T>B) T is more common.
- It can arise in the bone marrow or in the tissue. When it arises in tissues then we call this case: lymphoblastic lymphoma.
- Acute lymphoblastic leukemia when circulates peripheral blood and involve bone marrow (B>T) B is more common.
- B-ALL is the most common **childhood** malignancy.
- Neoplastic cells are lymphoblasts, the most immature lymphoid cell. Aggressive neoplasms, express CD34 and TDT Terminal deoxynucleotidyl transferase
- ***T***-ALL is less common, presents in **adolescents**, involving ***T***hymus (the most common site), more common in boys
- ***B***-ALL tends to disseminate to solid organs (brain, testis, spleen)

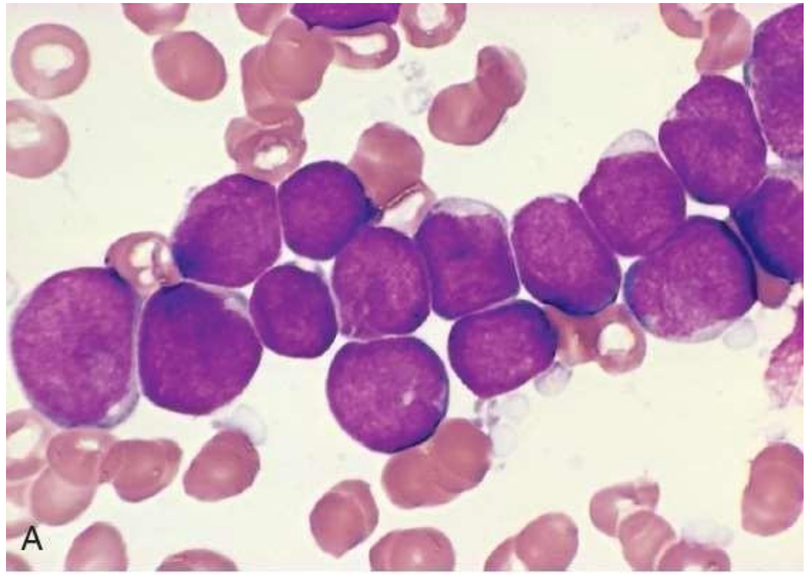
- **AML** can affect all age groups, but more common in **elderly**.
- **ALL** can affect all age groups, but more common in **children** and teenagers.

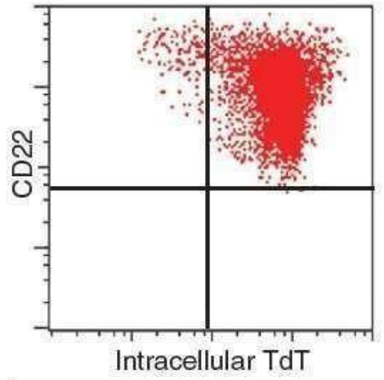
PATHOGENESIS

- Mutations in transcription factors for genes responsible for maturation of blasts
- In ***B***-LL, mutation in ***P***AX5 gene
- Mutations in RAS signaling and tyrosine kinase proteins promoting cell survival (in both AML &ALL)
- Most childhood B-ALL have hyperdiploidy (>50 chromosomes) (has a good prognosis) and t(12;21), involving ETV6 & TUNX1 genes, creating new transcription factor
- Adult B-ALL exhibits t(9;22) between ABL and BCR Genes in Philadelphia chromosome, similar to chronic myeloid leukemia CML (will be discussed later), creating a new tyrosine kinase (imatinib)
- ***T***-ALL shows mutation in NO***T***CH1 gene (70% of cases), P***T***EN gene (tumor suppressor) and CDKN2A (promotes cell cycle)

MORPHOLOGY OF ALL

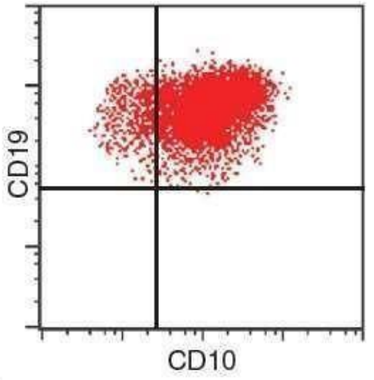
- Blasts are large, high N/C ration higher than in myeloblasts
- Chromatin is open (pale)
- Nucleolus sometimes present (White dots)
- Cytoplasm is not granular





Up + Right= positive for both TdT & CD22

- B-ALL



Up + Right= positive for both CD10 & CD19

- B-ALL

CLINICAL FEATURES

- Anemia, thrombocytopenia –can be fatal–
  - Bone pain
  - Lymphadenopathy and hepatosplenomegaly
  - Testicular enlargement
  - Mediastinal mass (T-ALL) (chest mass, which compresses the lungs)
  - CNS involvement, that's why it's difficult to be treated
- Damage to solid organs secondary to leukemic infiltration leading to death
- Favorable prognostic factors in B-ALL: hyperdiploidy, low WBC count, age between 2-10 years
- Poor prognostic factors in B-ALL: age < 2 years, age in adolescents or adults,WBC count >100k
  - It needs harder therapy than AML.

LANGERHANS CELL HISTIOCYTOSIS

Tumor

- Neoplasm of dendritic cells
- Langerhans cells express CD1a and Langerin
- **Langerin** is a transmembrane protein, attached to Birbeck granules (tennis ricket shape under electron microscope)
- Proliferating Langerhans cells appear large and vacuolated, similar to macrophages (histiocytes)
- Pathogenesis: acquired mutation in serin/threonine kinase BRAF, leads to hyperactivity of this kinase

But actually they're totally different from each other's

MULTISYSTEMIC LCH

- Occurs mostly in children less than 2 years (infants)
- Multiple cutaneous lesion, composed of LCs
- Hepatosplenomegaly and lymphadenopathy
- Pulmonary lesions
- Osteolytic lesions
- Extensive bone marrow infiltration leads to pancytopenia then death
- Treated with chemotherapy

AKA eosinophilic granuloma although it's a misnomer since it is a neoplastic condition not inflammatory

UNISYSTEM LCH

- Under the microscope, the neoplastic dendritic cells attract other normal WBCs leading to mass formation, this mass consists heavily of these neoplastic cells + normal inflammatory cells like eosinophils and neutrophils.

- Affects a single organ, most commonly **bone**, then skin, lung, stomach
- Can be unifocal (usually asymptomatic) or multifocal (symptomatic)
- Unifocal is commonly asymptomatic, can cause pain
- Multifocal unisystem disease presents in children, commonly affects calvaria bone (base of the skull), extends to pituitary gland causing diabetes insipidus, exophthalmous (Hand-Schuller-Christian triad).
- Proliferating LCs are admixed with numerous eosinophils, lymphocytes, plasma cells and neutrophils
- Treatment: unifocal: surgical excision, multifocal: chemotherapy, sometimes spontaneous regression

Pathology Quiz 2



QUIZ

رسالة من الفريق العلمي:

آية كريمة، حديث شريف..
دعاء أو نصيحة..
أي شيء بدك توصله لدارس الملف
لا تتركها فارغة واكسَب الأجر.

كلنا بنسمع إنه **سيستم الهيماتو هو سيستم الباثو**، وعشان هيك مهم يكون عندك مصدر موثوق يساعدك تفهم **مادة الباثولوجي** وتتعامل معها بطريقة صحيحة.

بهذا القروب على التليجرام، زميلتنا **حنين البنا** بتوفّر نصائح وإرشادات لكيفية التعامل مع كل مادة في السيستم، بالإضافة إلى **شرح لمادة الباثو بسعر مميّز مع امكانية تجربة الشرح قبل الإشتراك.**

إذا بدك تفهم المادة بشكل أفضل وتدخل مادة الفاينل وأنت مستعد، هاي فرصتك، هذا رابط القروب ::

HLS Pathology By Haneen

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			