HEMATOPOIETIC & LYMPHATIC SYSTEM

SUBJECT : Pathology

LEC NO. : 6

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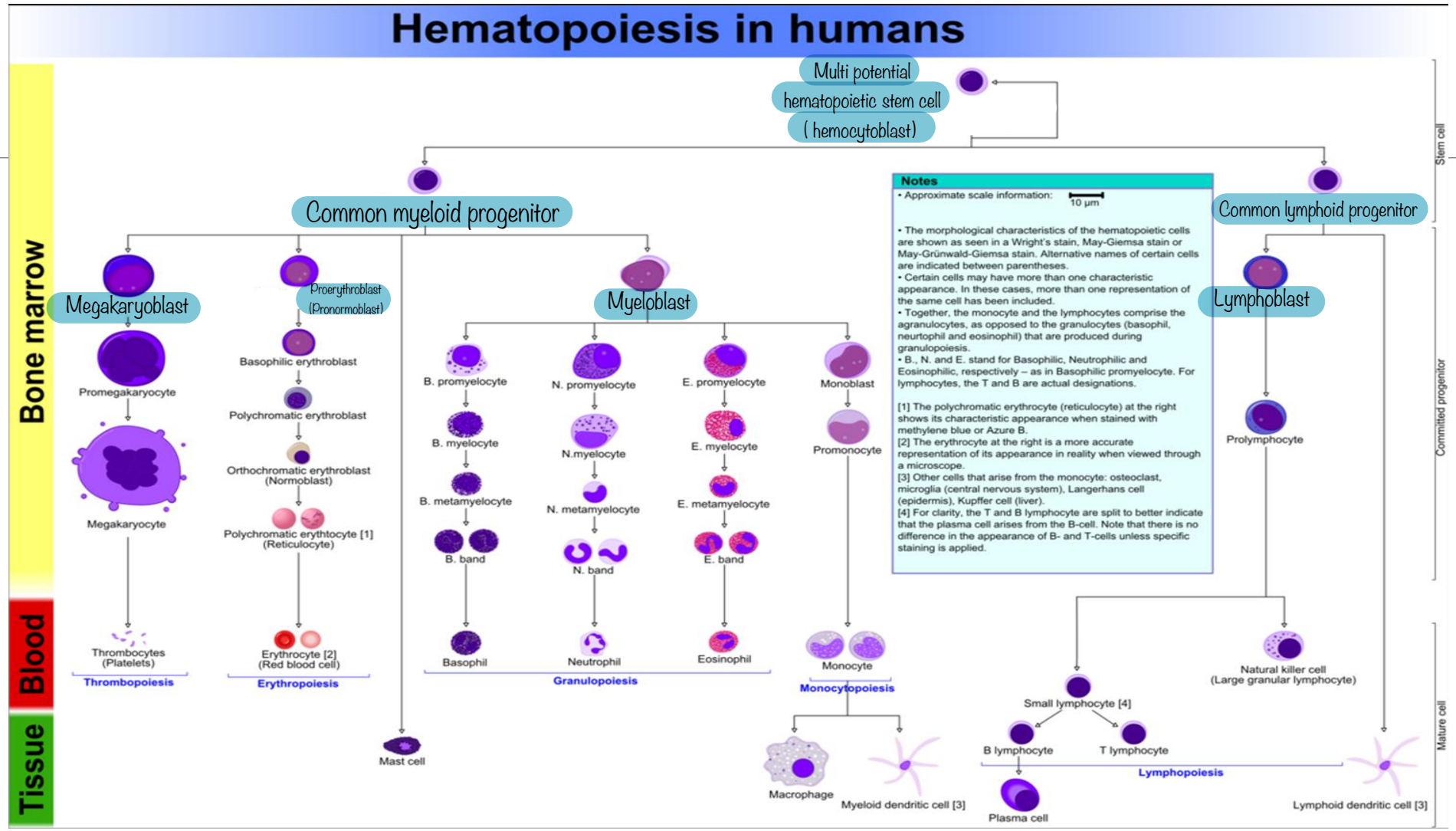
وَقُل رَّبِّ زِدْنِي عِلْمًا

“Hematopoietic And Lymphoid System (HLS)”

Dr. Ola Abu Al Karsaneh

هون بدنا نتذكر الcell في مرحلة الblast لانه بدنا نحكي عن tumours لها علاقة في هاي ال blast



Nonneoplastic Disorders Of White Blood Cells

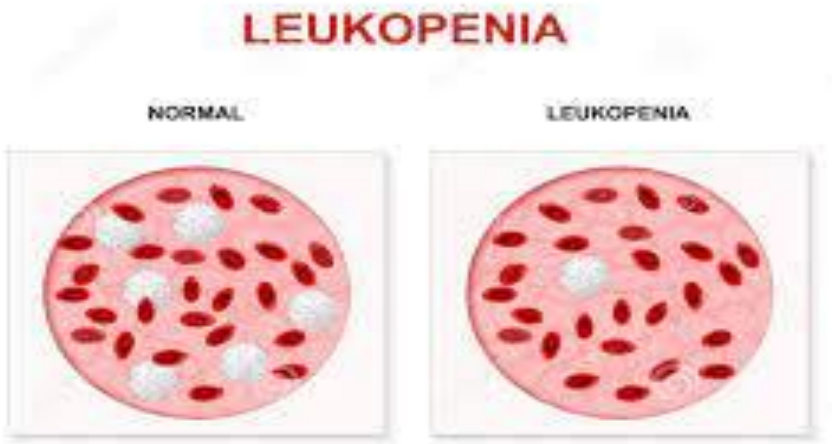
Penia = decrease

❑ Leukopenia

- Is a **decrease** in the leukocyte count in the blood.
- Mostly, from a decrease in granulocytes, **lymphopenia is much less common**.

❑ Lymphopenia :

- Immunodeficiency disease (HIV) infection.
- Therapy with corticosteroids. (anti-inflammatory medicine)
- Certain viral infections.



Neutropenia/Agranulocytosis:

Neutropenia: a reduction in the number of neutrophils in the blood.

Agranulocytosis: a clinically significant reduction in neutrophils. very severe reduction of granulocyt

Pathogenesis:

منطقياً سبب النقص اما انه ما عم يتصنع او الاستهلاك زيادة

1. **Decreased granulocyte production**: mostly by marrow hypoplasia, e.g. by chemotherapy, drugs, or infiltrative tumor.

2. **Increased granulocyte destruction**: in immune-mediated injury by drugs or in overwhelming infections, resulting from increased peripheral use or due to splenomegaly.

⇩

the spleen, which plays a role in filtering and destroying old or abnormal blood cells, is enlarged. An enlarged spleen can lead to increased destruction of granulocytes as they pass through it, contributing to their decreased levels in the bloodstream.

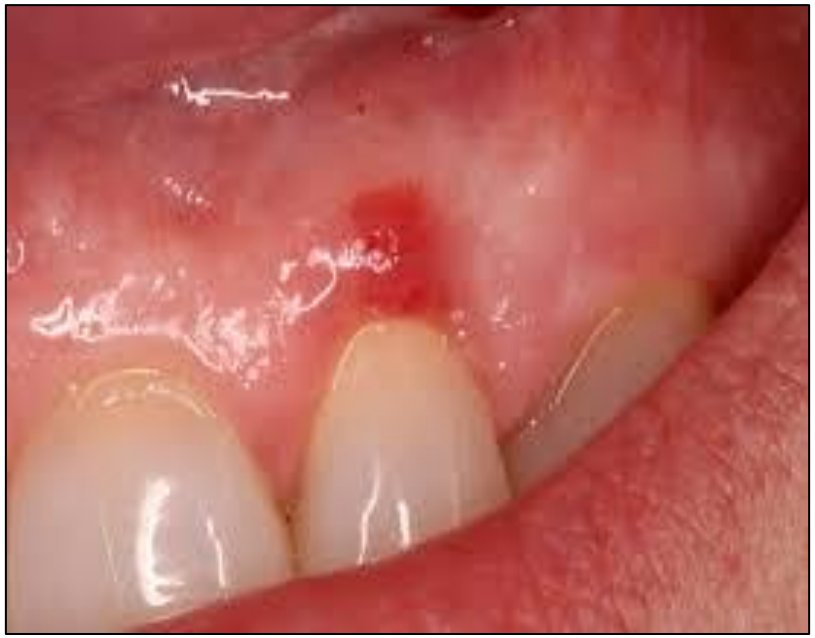
Clinical Features:

- Increased risk for severe bacterial and fungal **infections.**

- Systemic symptoms as malaise, chills, and fever.

- Commonly as necrotizing lesions of the gingiva, floor of the mouth, buccal mucosa or pharynx.

بما ان ال granulocytosis وظيفتهم مناعية المريض رح يزيد عنده ال infection و بالعادة بتصيب بالأغلب ال oral cavity



Morphology:

- The alterations in the bone marrow depend on the cause.

في زيادة في الاستهلاك فال bone marrow عم بزيد التصنيع

- Compensatory marrow hypercellularity when there is excessive neutrophil destruction.

ال chemotherapy بأثر على ال bone marrow
نفسه فرح يتأثر تصنيع جميع الخلايا

- Chemotherapy drugs reduce the number of elements from all lineages.
- Drugs that selectively suppress granulocytopoiesis are associated with decreased numbers of granulocytic precursors and preservation of erythroid elements and megakaryocytes

❑ Reactive Leukocytosis

Cytosis = increase in the number of cells

- An **increase** in the number of white cells in the blood.

- Classified according to the white cell series that is affected.

*** مش مطلوب بس ذكرت المحدد ***

❑ Causes of Leukocytosis:

Neutrophilic Leukocytosis

Acute bacterial infections (especially those caused by pyogenic organisms); sterile inflammation caused by, e.g., tissue necrosis (myocardial infarction, burns)

Eosinophilic Leukocytosis (Eosinophilia)

Allergic disorders such as asthma, hay fever, allergic skin diseases (e.g., pemphigus, dermatitis herpetiformis); parasitic infestations; drug reactions; certain malignancies (e.g., Hodgkin lymphoma and some non-Hodgkin lymphomas); collagen-vascular disorders and some vasculitides; atheroembolic disease (transient)

Basophilic Leukocytosis (Basophilia)

Rare, often indicative of a myeloproliferative neoplasm (e.g., chronic myeloid leukemia)

Monocytosis

Chronic infections (e.g., tuberculosis), bacterial endocarditis, rickettsiosis, and malaria; collagen vascular diseases (e.g., systemic lupus erythematosus); and inflammatory bowel diseases (e.g., ulcerative colitis)

Lymphocytosis

Accompanies monocytosis in many disorders associated with chronic immunologic stimulation (e.g., tuberculosis, brucellosis); viral infections (e.g., hepatitis A, cytomegalovirus, Epstein-Barr virus); *Bordetella pertussis* infection

Infectious Mononucleosis:

it typically resolves on its own without specific medical treatment

- An acute, self-limited disease of adolescents and young adults caused by **EBV.**

- It is associated with **lymphocytosis.**

❑ Clinical features:

- Classically, fever, sore throat, and lymphadenitis.
- Or atypical presentations as little or no fever and only lymphadenopathy. enlargement in lymph nodes

Pathogenesis:

B cells

- The virus initially infects oropharyngeal epithelial cells and then spreads to underlying lymphoid tissue.

- Mature B cells that are infected become "activated," by several **viral proteins,** proliferate and disseminate in the circulation, and secrete antibodies with unusual specificities → The host T cell response controls the proliferation of EBV-infected B cells and the spread of the virus, in addition early in the course of the infection, IgM antibodies are formed against viral antigens. Later the serologic response shifts to IgG antibodies, which persist for life.

- Virus-specific cytotoxic CD8+ T cells appear in the circulation as atypical lymphocytes.

بس ترتيب للفقرة السابقة

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- Later, the serologic response shifts to IgG antibodies, which persist for life.
- Virus-specific cytotoxic CD8+ T cells appear in the circulation as atypical lymphocytes.

normal lymphocytes are typically smaller and rounder.

❑ Morphology:

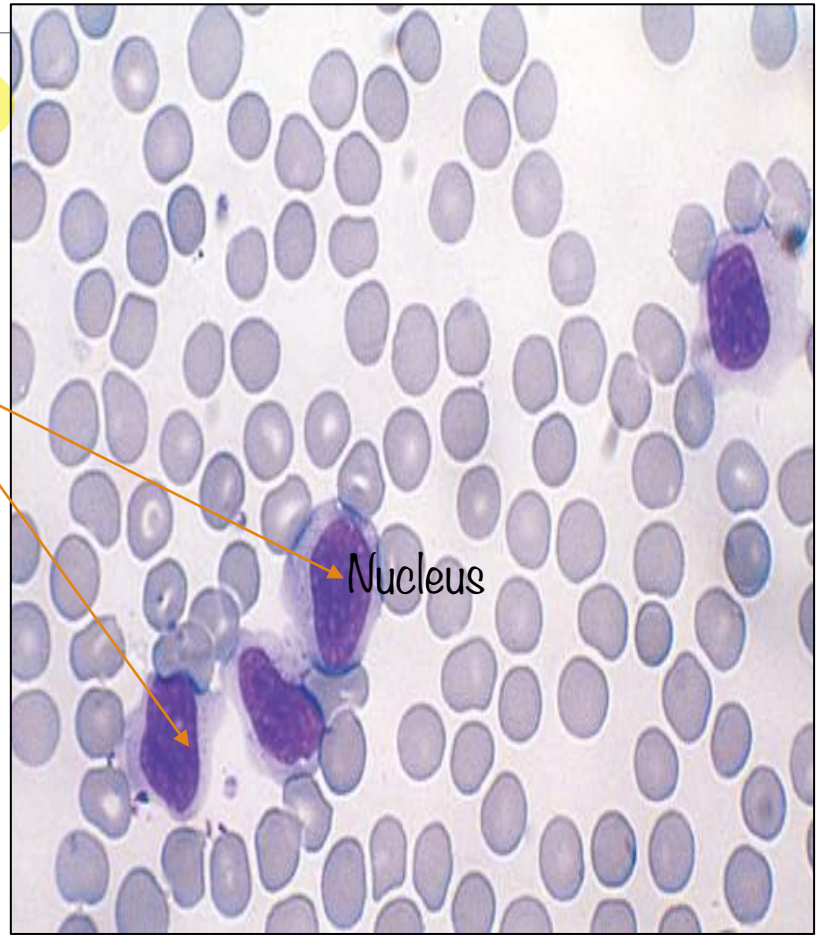
❖ **Peripheral blood: leukocytosis**; more than half of these cells are large **atypical lymphocytes (CD8+ T cell)**.

❖ **Lymph nodes: Lymphadenopathy.**

- Histology: the enlarged nodes are flooded by atypical lymphocytes in the **paracortical (T cell)** areas.

❖ **Spleen:** Enlarged with heavy infiltration of atypical lymphocytes

❖ **Liver:** Atypical lymphocytes usually also infiltrate the portal areas and sinusoids



***Atypical lymphocytes are often larger and have irregular shapes

***Atypical lymphocytes may have irregular or convoluted nuclear contours, prominent nucleoli, and increased cytoplasmic basophilia,

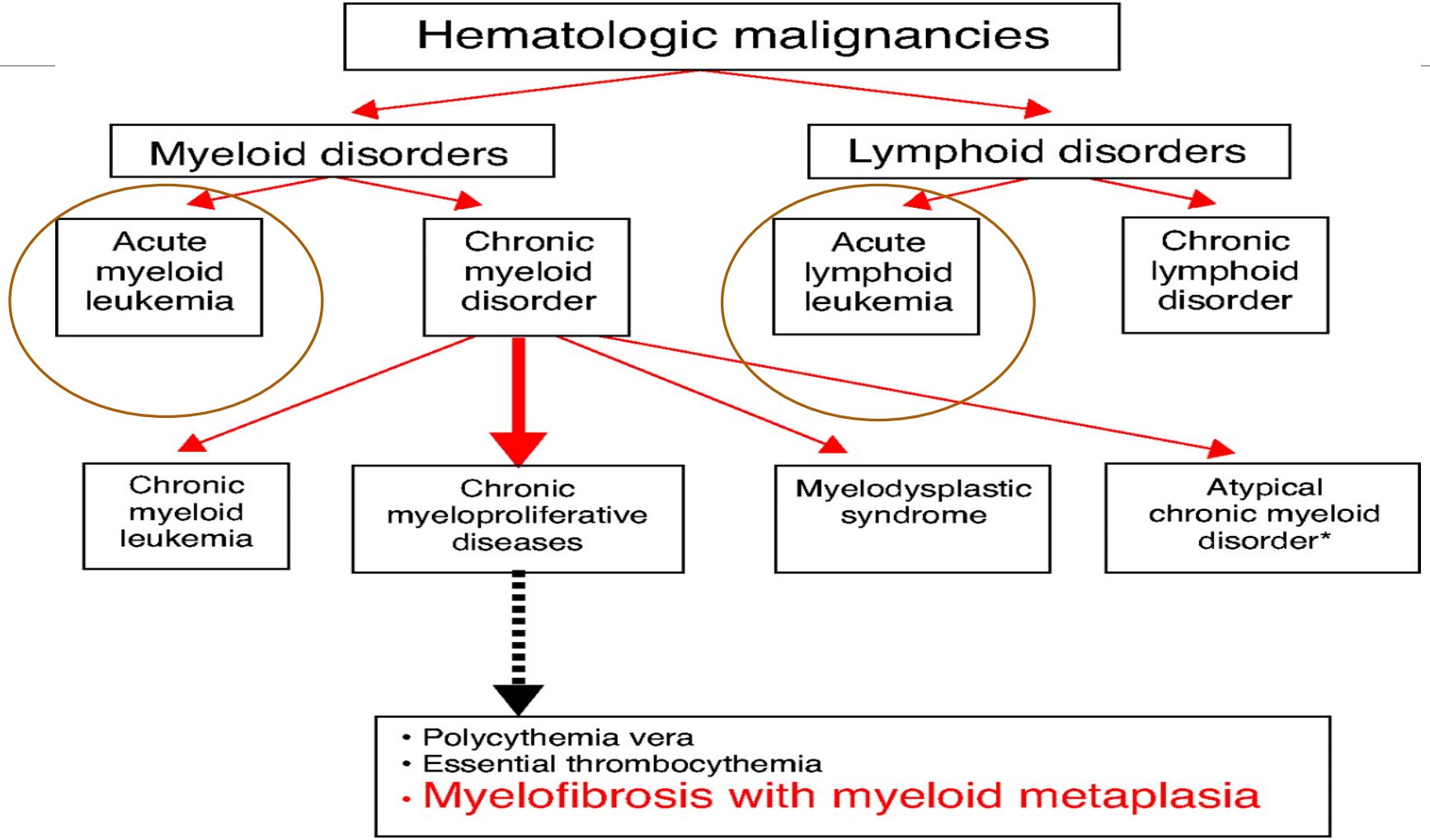
❑ Diagnosis

(1) The presence of atypical lymphocytes in the peripheral Blood

(2) A positive heterophil reaction (Monospot test)

(3) A rising titer of antibodies specific for EBV antigens

Neoplastic Proliferations Of White Cells



Acute Leukemia

-**Leukemia**: Tumors that involve the **bone marrow and peripheral blood predominantly**.

هاد ال tumour مكون من ال blast

- Malignant clonal expansion of hematopoietic or lymphoid cells associated with **early stages of differentiation** and characterized by:

- Poor response to normal regulatory mechanisms
- Decreased capacity for normal differentiation

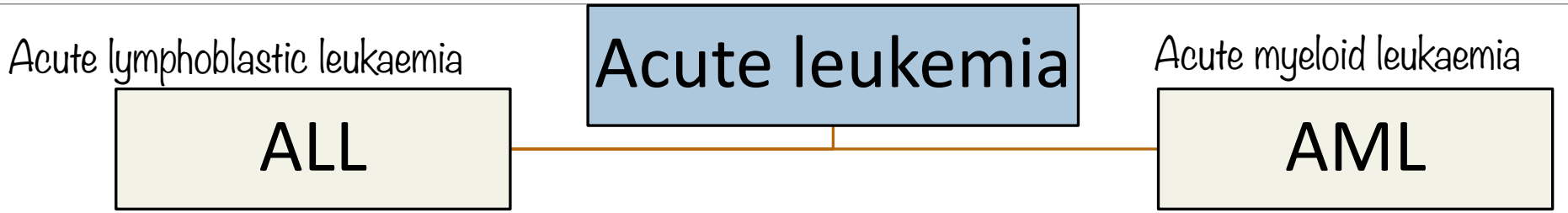
early stages of differentiation لهيك رح يضلوا

- A growth advantage over normal hematopoietic cells

→ the abnormal leukemia cells have a greater capacity for proliferation and survival compared to the normal cells in the bone marrow.

the leukemia cells rapidly accumulate, leading to overcrowding of the bone marrow and suppression of normal blood cell production

Epidemiology



- 70% are AML
- 1/3 of all cancers in children

  - 80% are ALL & 20% are AML

- **ALL** is a childhood disease

Most common

- **AML** is an adulthood disease.

Precursor B- & T-cell Acute Lymphoblastic Leukemia/Lymphoma (ALL)

- Definition:

Malignant clonal expansion of **immature** pre-B or T lymphoid cells **(lymphoblasts)** involving bone marrow, blood, and occasionally involving nodal and extranodal sites (lymphoblastic lymphoma).

- **Leukemia if more than 20% lymphoblasts in BM or blood**
- **Lymphoma if mass lesion present, and less than 20% lymphoblasts in BM or blood** اكثر lymph nodes موجودين بال

Epidemiology:

- Aggressive tumors occur predominantly in **children & young adults**.
- About 85% are B-ALLS, typically present as acute "leukemias" (peak at age of 3).
- The less common T-ALLS present in adolescent males as thymic "Lymphomas" as a mediastinal mass.

Major

Less common

area between the lungs.

- ALL is the **most common cancer in children**.
- More in whites and boys.

Etiologic associations

Chronic exposure to chemicals

Ionizing radiation

Immunodeficiency states

Pathogenesis:

-Stems from chromosomal aberrations that dysregulate the function of transcription factors that are required for the normal differentiation of B and T cell progenitors.

-Also, mutations that increase tyrosine kinase activity and cell proliferation in a growth factor–independent fashion

general idea ال

في عنا tumour مكون من immature cells لي ؟؟

اكيد صار عند المريض mutations /chromosomal aberrations

اثرت على transcription factors المهمة لل differentiation

عشان هيك الخلايا توقفت في مرحلة immature

بس هيك ما بكفي حتى يصير عندي tumour لازم يصير كمان proliferation

لهيك بدي كمان mutations تأثر على cellular proliferation

ALL Genetics (mutations)

B- ALL:

- Hyperdiploidy : ≥ 50 chromosomes/ cell
- t (12;21)
- 25% of adult pre-B cell tumors harbor t (9;22) involving the ABL and BCR genes.

T –ALL: diverse chromosomal aberrations.

اغلب هاي الأعراض سببهم هاي النقطة

❖A growth advantage over normal hematopoietic cells

•Clinical Features:

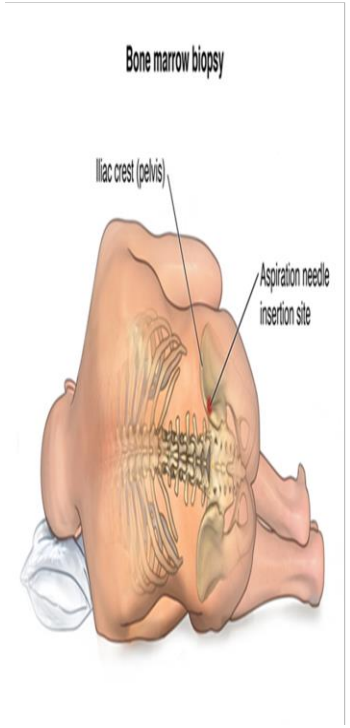
Are primarily due to replacement of normal hematopoietic elements by blasts leading to **paucity** of:
Red cells
Platelets
Normal white cells

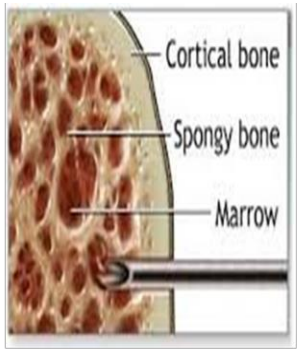
- Anemia and pallor ↓RBCs
- Weakness and fatigue
- Fever ↓WBCs → infection
- Thrombocytopenia and bleeding ↓ Platelets
- Bone pain
- Hepatosplenomegaly and generalized lymphadenopathy (caused by the dissemination of the leukemic cells)
- CNS involvement from the meningeal spread. (headache, vomiting)
- Testicular involvement is common in ALL

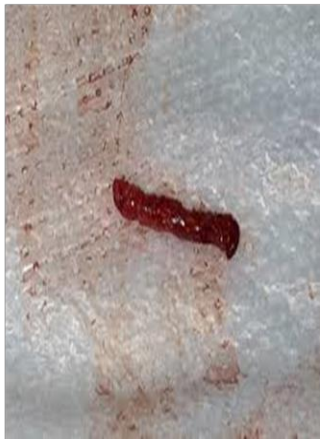
- **Diagnosis:**

  - **CBC**

    - Anemia. A decreased level of red blood cells (RBCs) or hemoglobin, which can lead to symptoms like fatigue, weakness, and pallor.
    - Thrombocytopenia. A decreased level of platelets
    - WBC count variable :
      - Leukocytosis with blasts (>25%)
      - Normal or decreased WBC (50%)
      - **Neutropenia** is a common finding
  - **Peripheral blood smear**
  - **Bone marrow aspiration and biopsy.**







- Morphology:

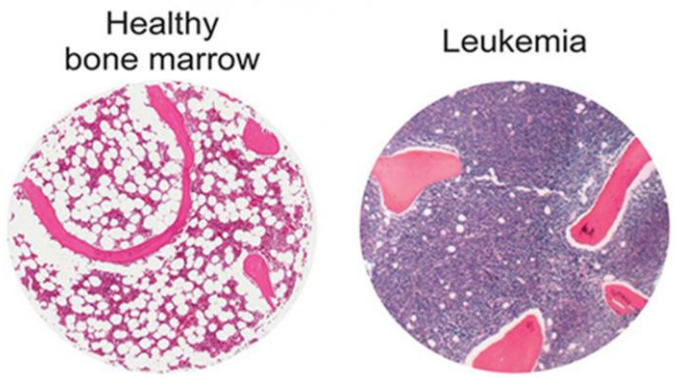
- **BP**: Identifications of blasts.

- **Bone marrow:** is hypercellular and packed with **lymphoblasts**

كمية قليلة جدا

❖ Scant **A**granular basophilic cytoplasm and nuclei with delicate, finely stippled chromatin and small nucleoli.

❖The cytoplasm has glycogen stains positive with PAS stain.



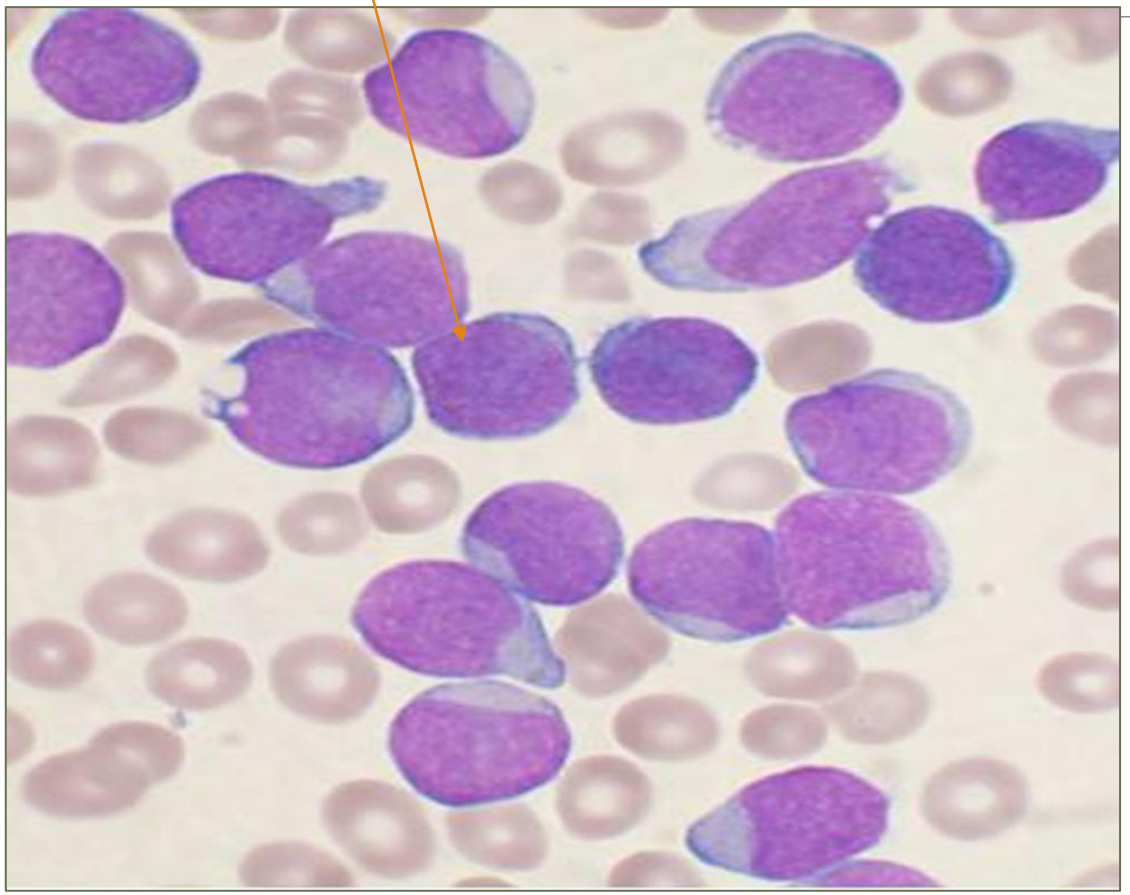
- **Mediastinal masses** occur in T-ALLS.

- High mitotic rate.

- The appearance of the blasts is identical in pre-B and pre-T ALLs

- For this reason, definitive diagnosis relies on stains specific for B AND T cell antigens.

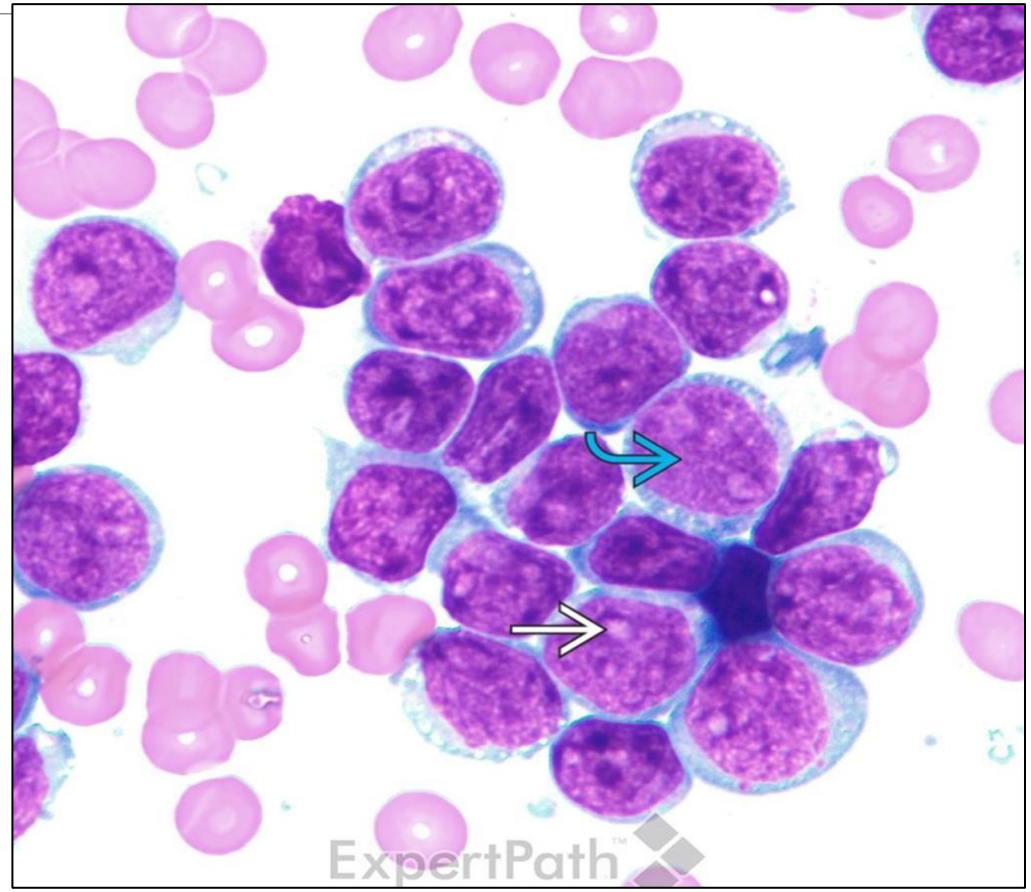
ALL (lymphoblasts): with high N/C ratio, fine chromatin (curved arrow), small nucleoli (white solid arrow), and basophilic cytoplasm.



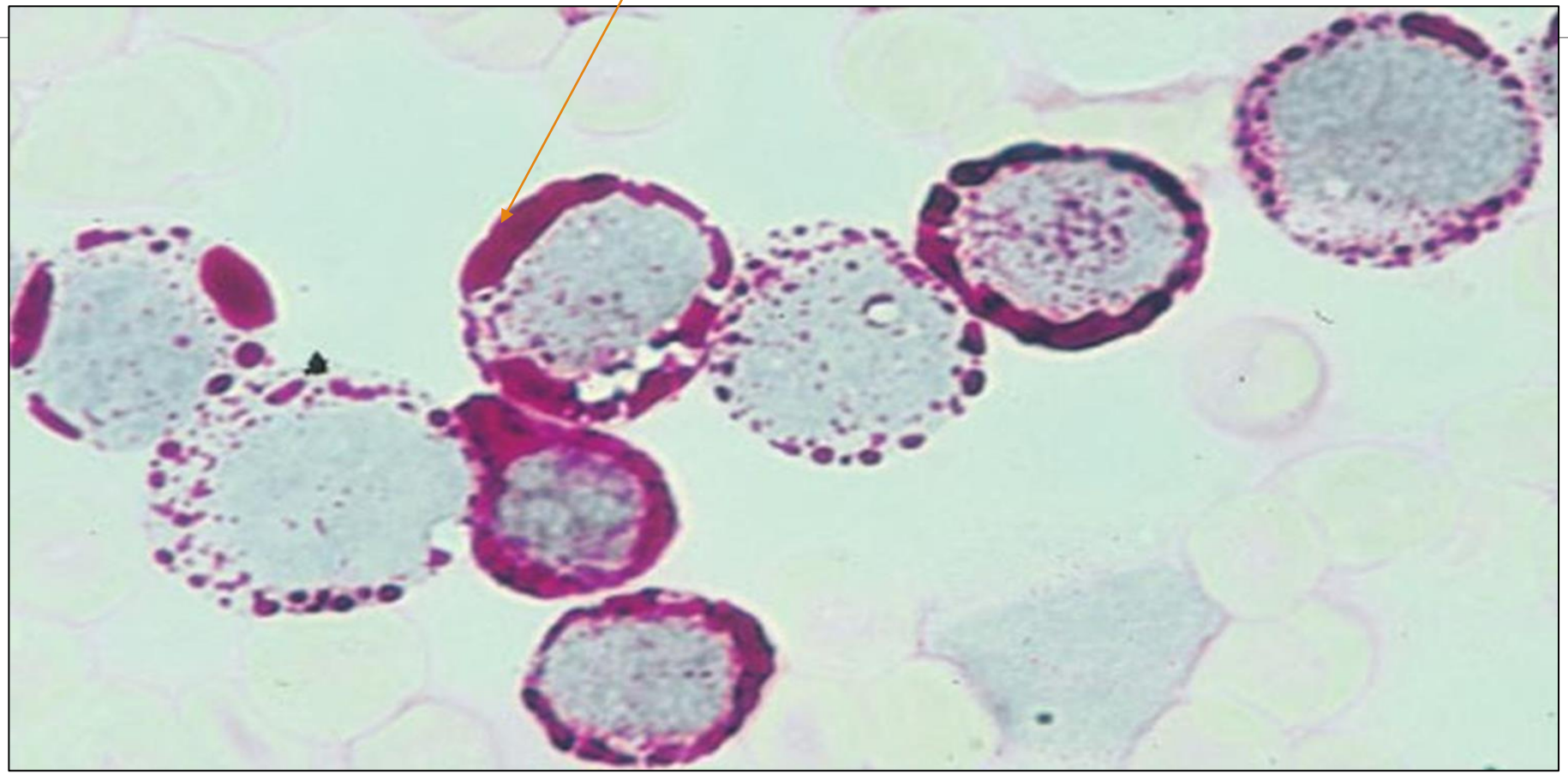
Blue cytoplasm

Agranule

small nucleoli



Lymphoblasts: Positive PAS cytoplasmic stain.



- Immunophenotyping:

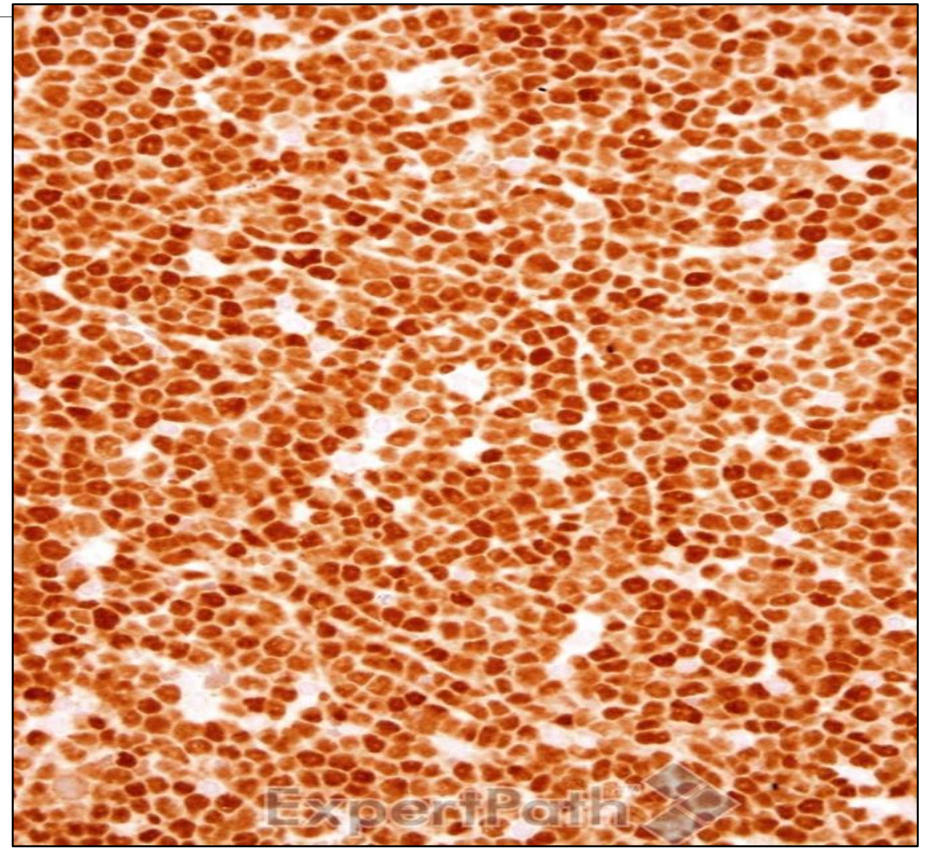
مهم جداً
+ مطلوب حفظ
الملون

- Performed by IHC on tissues:
- B-ALL (85%)
  - **TdT+** ,CD10+, **CD19+**, **CD20+**, CD22+, **CD79+**, PAX5+
- T-ALL (15%)
  - **TdT+**, CD2+, **CD3+**, **CD5+**, CD7+

مش مهم نميز بين B/ t
المهم نعرف نميز بين ال
lymphoid و ال Myeloid
من خلال TdT+

Terminal deoxynucleotidyl transferase (TdT), an enzyme specifically expressed in pre-B and pre-T cells.

+ve TDT



- ## Prognosis:

  - Generally, has an **excellent prognosis** with aggressive chemotherapy, but rapidly fatal if untreated.

  - In children with chemotherapy, 95% remission rate and 75-85% cure rate (if **favorable prognostic features**).

  - Only 35% to 40% of affected adults are cured.

بروح المرض بس ممكن يرجع

بروح المرض و ما برجع

احفظوا ال favorable بس والunfavorable العكس

Factor	Favorable	Unfavorable
Age	2-10	<2, >10
WBC count	<50,000	>50,000
# chromosomes	Hyperdiploidy (>50)	Hypodiploidy (<44)
Cytogenetics	T(12,21)	T(4,11), t(9.22), t(1,19)
CNS disease	Absent	Present
CD10	Positive	negative

** شرح خارجي لهاد العامل بس للفهم

# chromosomes	Hyperdiploidy (>50)	Hypodiploidy (<44)

In acute lymphoblastic leukemia (ALL), the number of chromosomes, known as the karyotype, can vary. Hyperdiploidy refers to having more than the usual number of chromosomes, typically greater than 50. Conversely, hypodiploidy refers to having fewer than the usual number of chromosomes, typically less than 44.

1. Hyperdiploidy (>50 chromosomes):

- In hyperdiploid ALL, the cancer cells have additional copies of chromosomes, which may confer a survival advantage.
- The extra copies of chromosomes can result in a more differentiated and less aggressive phenotype of leukemia cells.
- Hyperdiploidy is associated with a better response to chemotherapy and overall prognosis in ALL.
- It is more commonly found in children and is associated with a younger age of onset.

2.Hypodiploidy (<44 chromosomes):

- Hypodiploid ALL is characterized by a reduced number of chromosomes, which can lead to genomic instability and increased aggressiveness of the cancer.
- The loss of genetic material may disrupt normal cellular functions and lead to uncontrolled cell growth and resistance to treatment.
- Hypodiploidy is associated with a poorer response to chemotherapy and worse overall outcomes in ALL.
- It is more commonly found in adolescents and adults with ALL and is considered a high-risk feature.

Acute Myeloid Leukemia (AML)

- Malignant clonal expansion of cells blocked at an early stage of myeloid cell development (**immature myeloid cells (myeloblasts))** that accumulate in the marrow and frequently circulate in the peripheral blood.

Myeloid blasts or promyelocytes make up more than 20% of the bone marrow cellular component.

- Older adults (50 yrs). عكس ال ALL

❖ Pathogenesis:

- Most harbor **mutations** in **genes** encoding **transcription factors** required **for normal myeloid cell differentiation, which** interferes with the differentiation of early myeloid cells, leading to the accumulation of myeloid precursors (blasts) in the marrow.

e.g t(15,17) ⟹ results in the fusion of ***(RARA)*** gene and the ***PML*** gene. The chimeric gene produces a PML/RARA fusion protein that blocks myeloid differentiation **at the promyelocytic stage.**

Treatment

- ❑ All-*trans* retinoic acid **(ATRA)** overcomes this block and induces the neoplastic promyelocytes to differentiate into neutrophils.

- Mutations that lead **to activation of growth factor signaling pathways,** which increase cell proliferation.

❖ Clinical Features ما بختلفوا عن ALL

- Usually related to the replacement of normal marrow elements by leukemic blasts.

- Fatigue

- Pallor

- Infections (fever)

- Abnormal bleeding (Cutaneous petechiae, ecchymoses, serosal hemorrhages into the linings of the body cavities and viscera)

- Splenomegaly and lymphadenopathy generally are less prominent than in ALL

- Rarely, AML mimics a lymphoma by manifesting as a discrete tissue mass (a so-called “granulocytic sarcoma”).

- Tumors with monocytic differentiation often infiltrate the skin (leukemia cutis) and the gingiva

Bone marrow Biopsy نفس مبدأ ال ALL في البداية رح نوخد

و رح يكون عندي hypercellular حسب شكل و صفات ال Myeloid blasts

رح يكون التميز بين ال ALL & AML

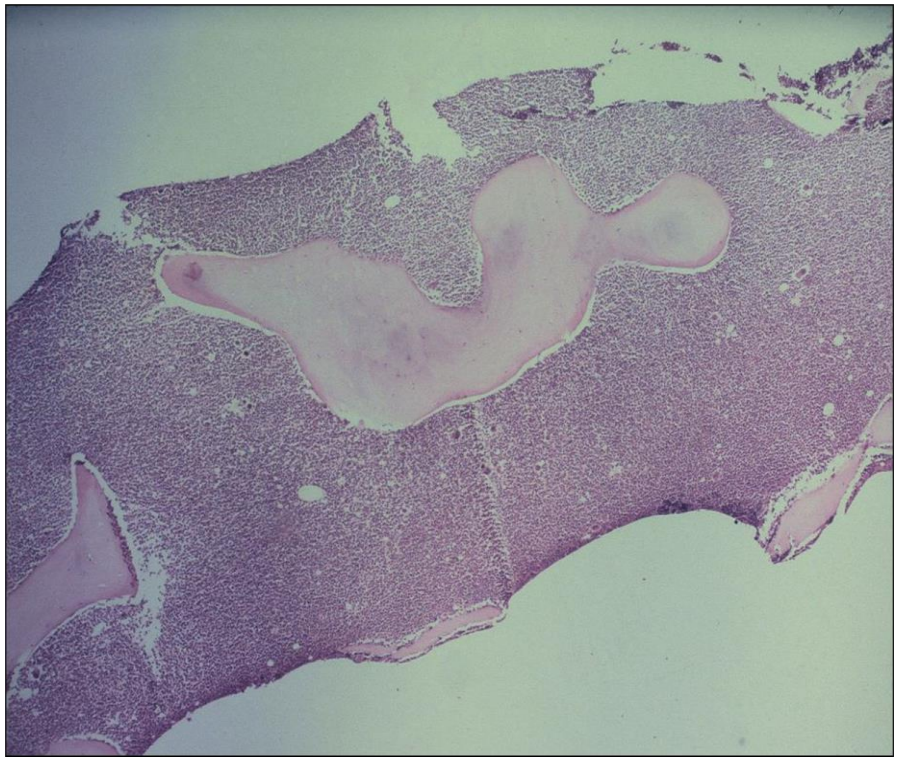
❖ Morphology

- Myeloid blasts make up **more than 20%** of the bone marrow cellularity.

- **Myeloblasts** have delicate nuclear chromatin, three to five nucleoli, and fine azurophilic cytoplasmic granules (peroxidase positive).

- **Auer rods,** distinctive red-staining rodlike structures, may be present in myeloblasts or more differentiated cells; they are particularly **numerous** in **acute promyelocytic leukemia (M3).**

- **Auer rods are specific for neoplastic myeloblasts** and thus are a helpful diagnostic clue when present.

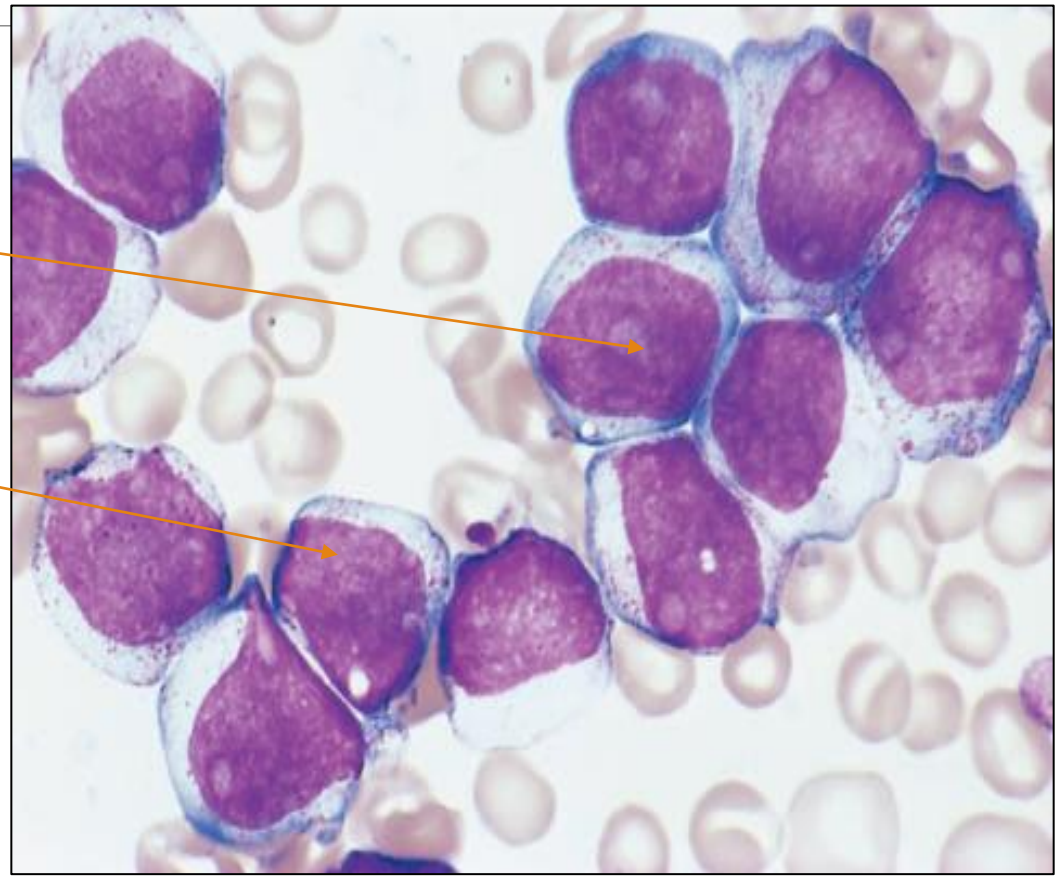


مقارنة عملتها لأهم الاختلافات على مستوى ال morphology

Morphological Feature	Acute Myeloid Leukemia (AML)	Acute Lymphoblastic Leukemia (ALL)
Cell Lineage	Myeloid blasts	Lymphoblasts
Bone Marrow Cellularity	>20% myeloid blasts	Hypercellular, packed with lymphoblasts
Cytoplasm	Azurophilic granules, may contain Auer rods	Scant agranular basophilic cytoplasm, glycogen positivity (PAS stain)
Nucleus	Delicate chromatin, 3-5 nucleoli	Finely stippled chromatin, small nucleoli
Auer Rods	Present, particularly in acute promyelocytic leukemia (M3 subtype)	Absent
Additional Features	-	- Mediastinal masses may occur in T-ALL - High mitotic rate
Diagnosis	Specific stains for myeloid antigens	Specific stains for B and T cell antigens

AML

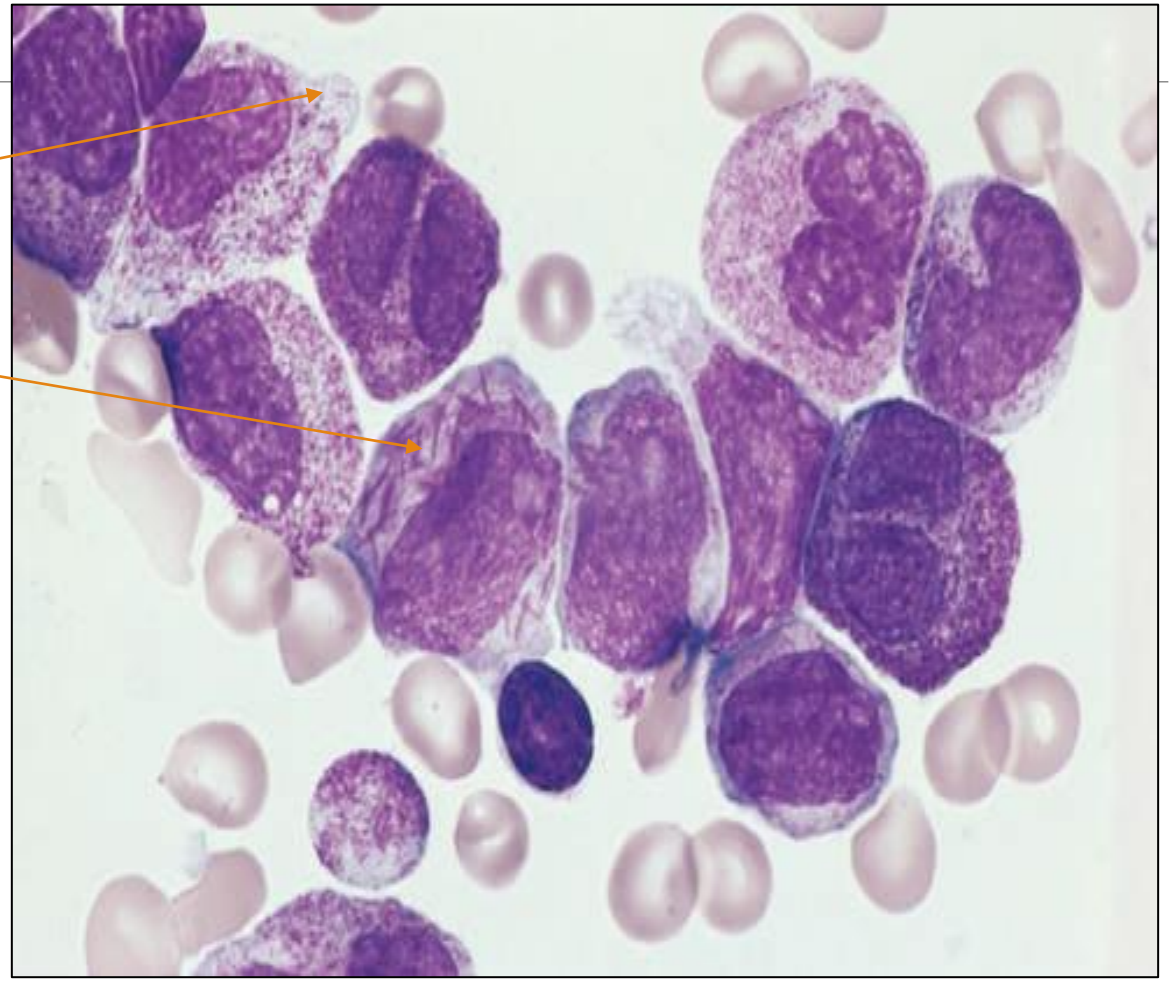
Myeloblasts with delicate nuclear chromatin, prominent nucleoli, and fine azurophilic cytoplasmic granules.

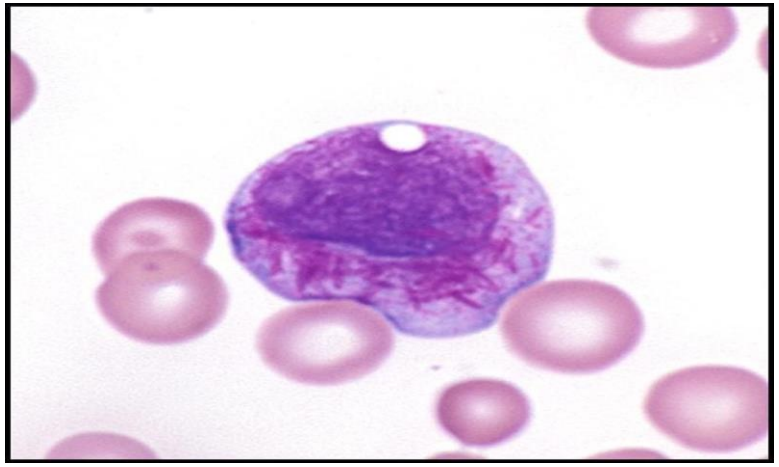


Acute promyelocytic leukemia—bone marrow aspirate

- The neoplastic promyelocytes have abnormally coarse and numerous azurophilic granules.

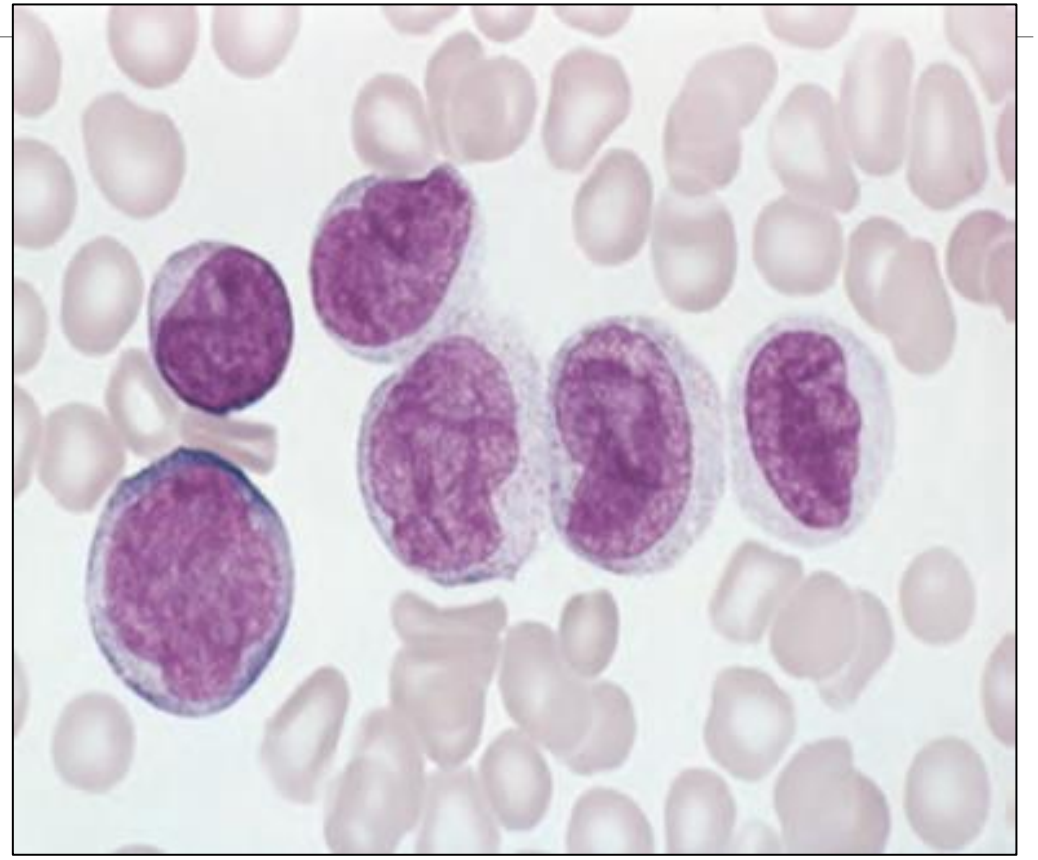
- A cell in the center of the field with multiple needlelike **Auer rods.**





- Monoblasts have **folded** or lobulated nuclei, **lack Auer rods**

موجود بس في المراحل الاولى



❖ Histochemistry

- Cases with granulocytic differentiation are typically positive for the enzyme myeloperoxidase (MPO)

- Monocytic differentiation is demonstrated by staining for lysosomal nonspecific esterase (NSE)

❖ Immunophenotype:

- Positive for myeloid-associated antigens, such as **CD13, CD14**, CD15, CD64, or CD117.

ال ALL نتذكر يلي كان بميزها هو TDT+

NSE highlights blasts of monocytic origin