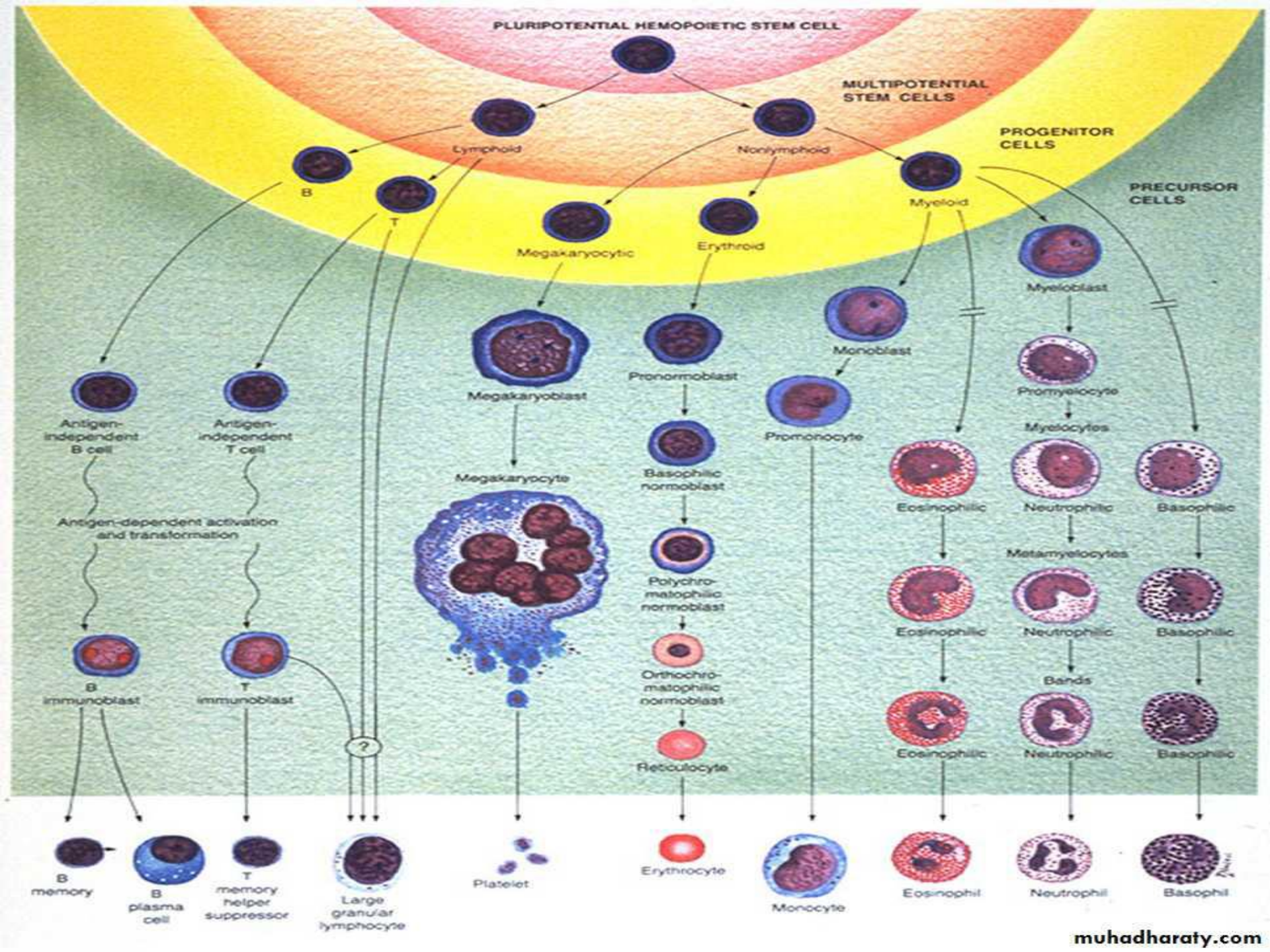
Diyala University – collage of medicine

Hematology -5th stage

Lec 8

ACUTE LEUKEMIA

DR.ZAHRAA NAJAH



Acute Leukemia

- **Define** : The leukemia's are a group of disorders characterized by the immature, neoplastic leukemic ‘blast’ cells proliferate and accumulate, but fail to mature. The blasts diffusely replace the normal bone marrow and a variable number of these accumulate in the peripheral blood.
- Acute leukemia should be diagnosed when the blast cells constitute more than 20% of the nucleated cells in the marrow (normally blast cells are less than 5%).

- there is evidence to suggest that the **initiating event** is acquisition of a **balanced chromosomal abnormality** (i.e. translocation, inversion) in an early bone marrow haemopoietic stem/progenitor cell generating chimeric oncoproteins, which induce leukemic transformation with the accumulation of additional cooperating mutations.

Leukemia

- **Incidence** of leukemia of all types; 10/100 000 annual
- **Classification :**

1. **Acute** (M : F 3:2)
   - Acute myeloid leukemia
   - Acute lymphoblastic leukemia (T-ALL & B-ALL)
2. **Chronic**
   - Chronic myeloid leukemia (M:F 1.3: 1)
   - Chronic lymphocytic leukemia (M : F 2:1)

Risk factors for leukemia

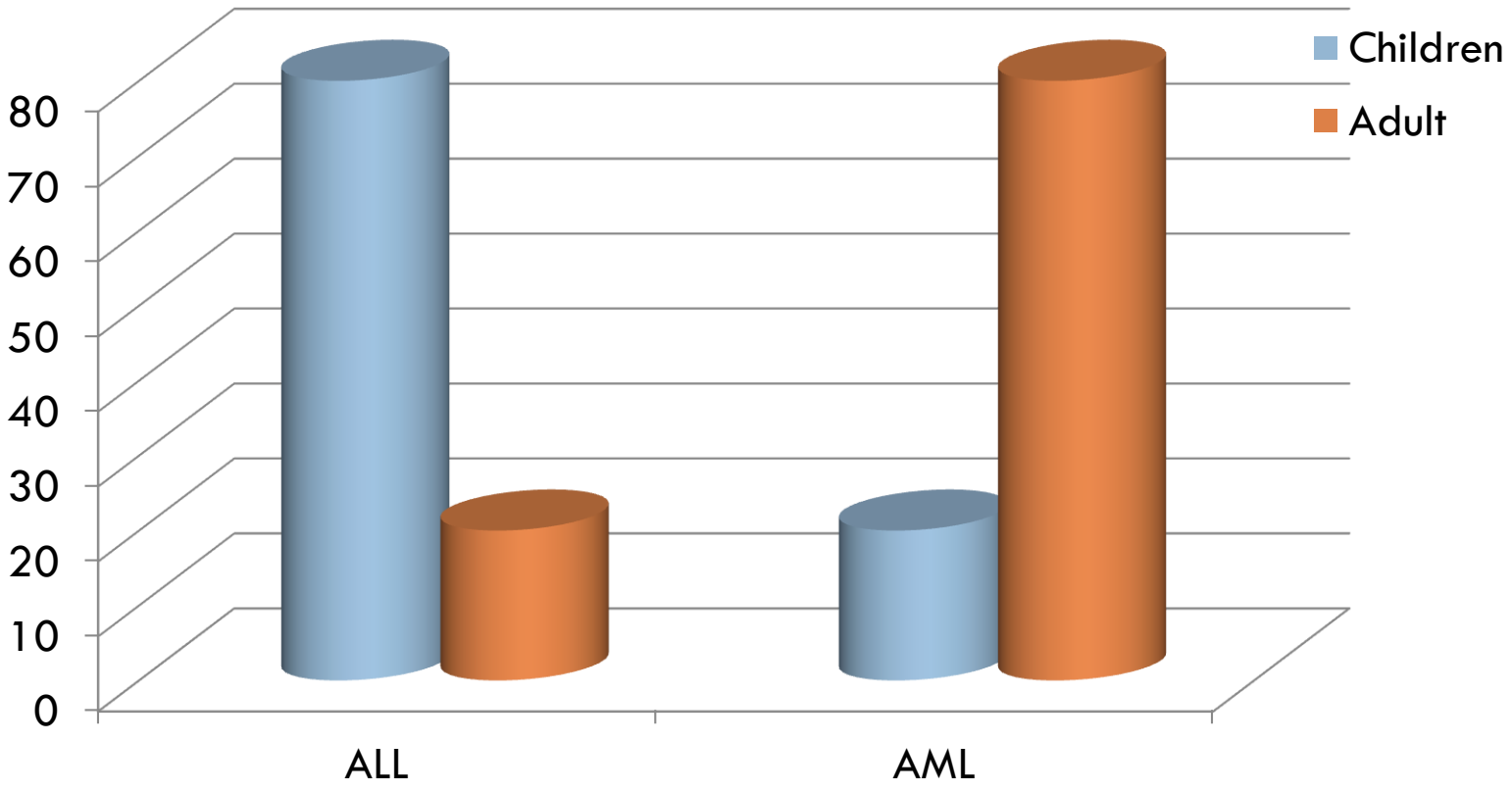
1. **Ionizing radiation**
   - Radiotherapy for ankylosing spondylitis
   - Diagnostic X - rays of the fetus in pregnancy
2. **Cytotoxic drugs:** Especially alkylating agents (myeloid leukemia , usually after a latent period of several years) Industrial exposure to benzene
3. **Retroviruses :**some cases of T - cell leukemia /lymphoma show association with Retroviruses infection
4. **Genetic** as in Identical twin of patients with leukemia and Down's syndrome and certain other genetic disorders
5. **Immunological** as in Immune deficiency states (e.g.hypogammaglobulinaemia)

Pathogenesis of acute leukemia

- **Genetic damage** is believed to involve several key biochemical steps resulting in: (i) **an increased rate of proliferation; (ii) reduced apoptosis and (iii) a block in cellular differentiation.**
- Together these **events cause accumulation** of the early bone marrow hemopoietic cells which are known as blast cells
- The **dominant clinical feature** of these diseases is usually **bone marrow failure** caused by accumulation of blast cells although **organ infiltration** also occurs. If untreated these diseases are usually rapidly fatal but, paradoxically, they are also easier to cure than chronic leukemias.

Clinical Features

- AL could occur at any age, and could be classified accordingly into:
  1. Childhood AL (age < 15 years), which is usually lymphoblastic (ALL)
  2. Adult AL (age ≥ 15 years), which is usually myeloblastic (AML).



Clinical Features

- **Clinically**; AML and ALL are indistinguishable, apart from few exceptions, e.g. gum hypertrophy commonly seen in AML, while lymphadenopathy is more common in ALL.
- The **onset** may be sudden, especially in children, or insidious.
- The **common symptoms & signs** at presentation are mainly attributed, directly or indirectly, to the proliferation of leukemic cells and their infiltration into normal tissue.

Clinical Features

- Increased cell proliferation has metabolic consequences and infiltrating cells also disturbs tissue function.

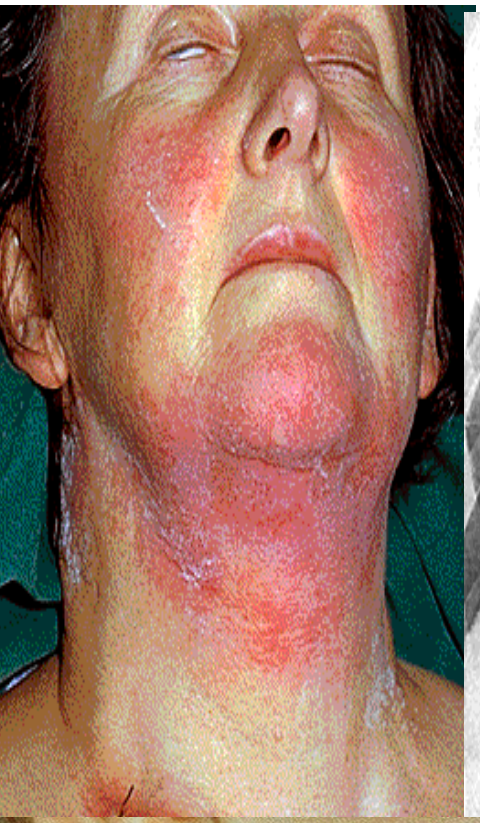
1. Bone marrow failure:

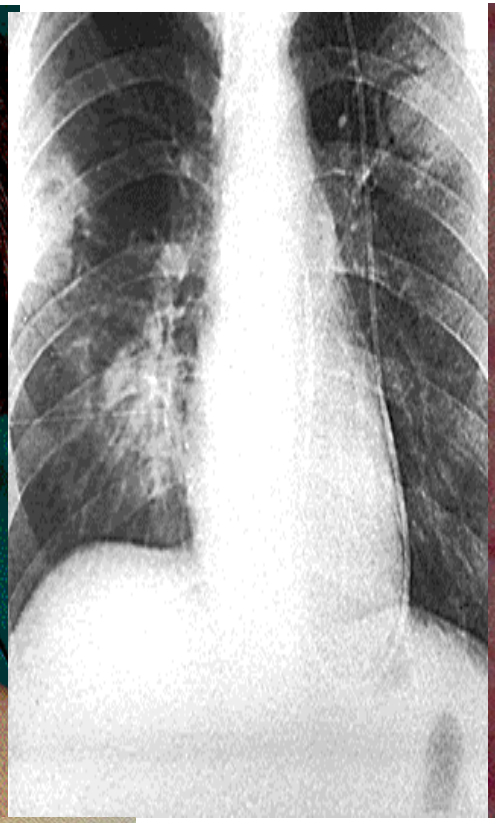
- **Anemia;** pallor, weakness, fatigue, lethargy, dyspnea on exertion, angina, and palpitation**.**
- **Neutropenia;** Infections due to reduced immunity, especially
- **Thrombocytopenia;** Bleeding manifestations into the skin;

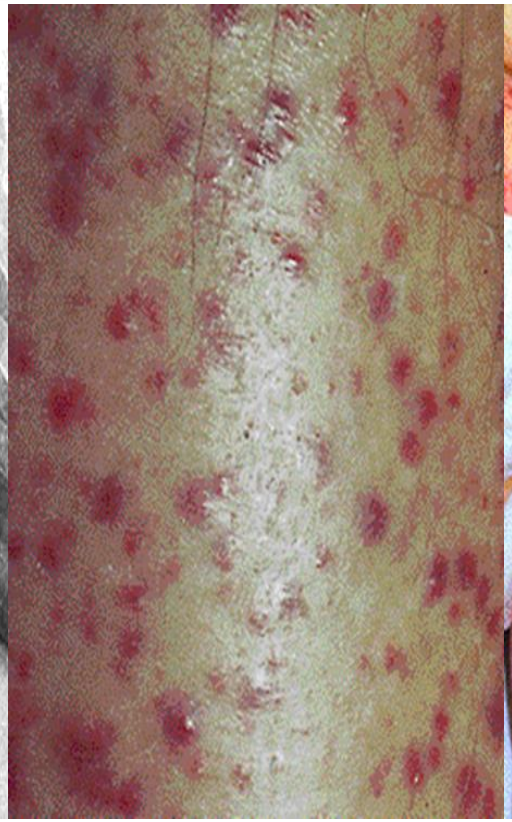
2. Organ and Tissue Infiltration by the leukemic cells:

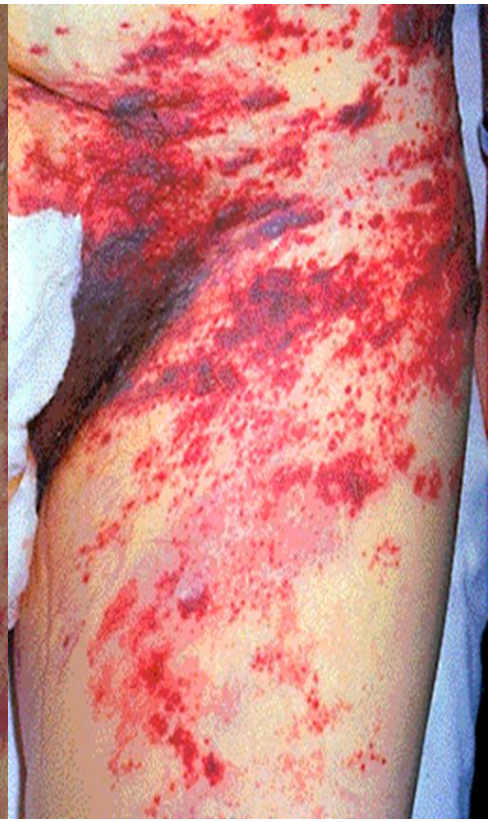
- Splenomegaly.
- Hepatomegaly.
- Bone pain.
- Arthralgia.

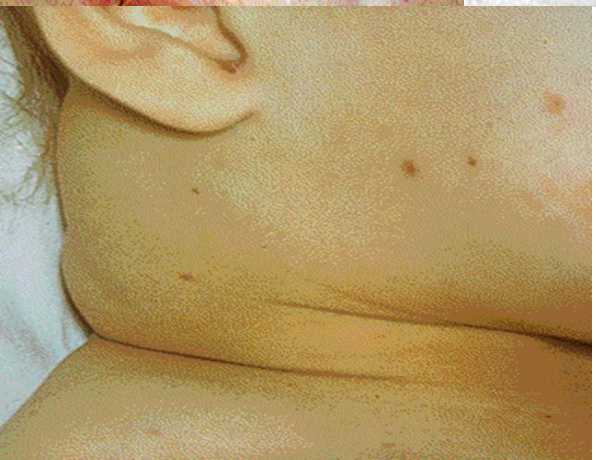
Skin infection Respiratory infection (Purpura) (Ecchymosis)





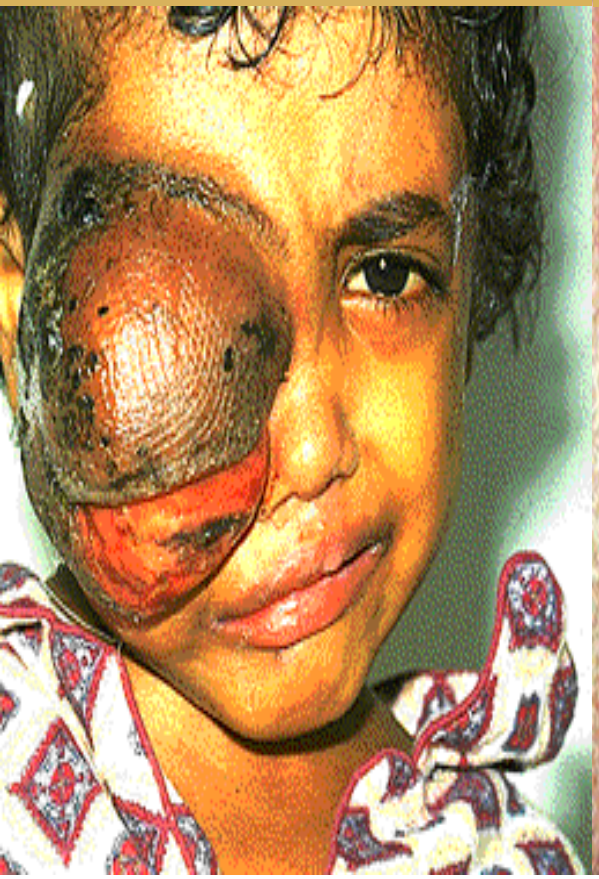




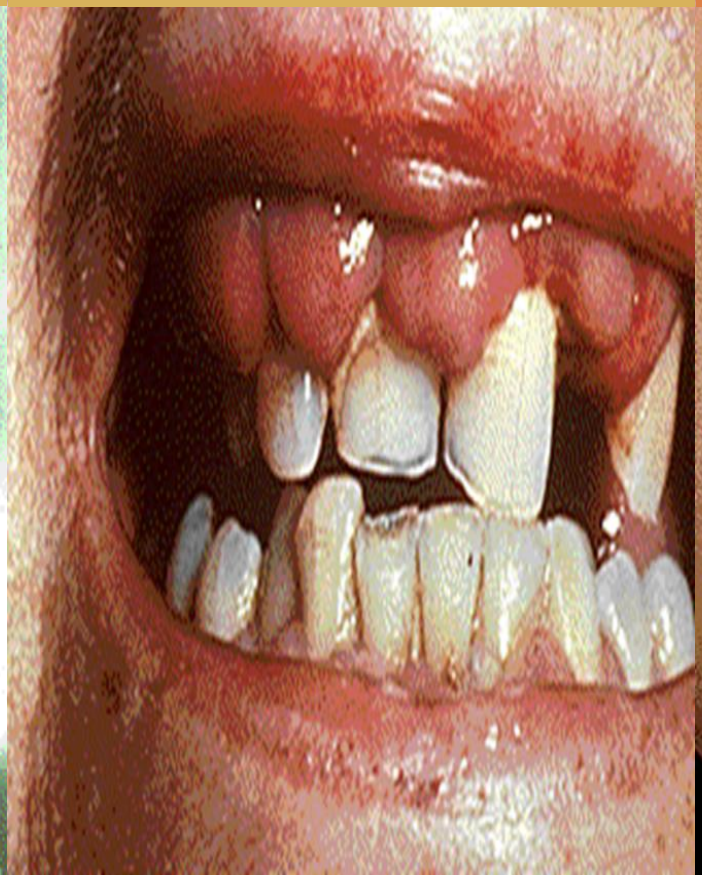


Lymphadenopathy

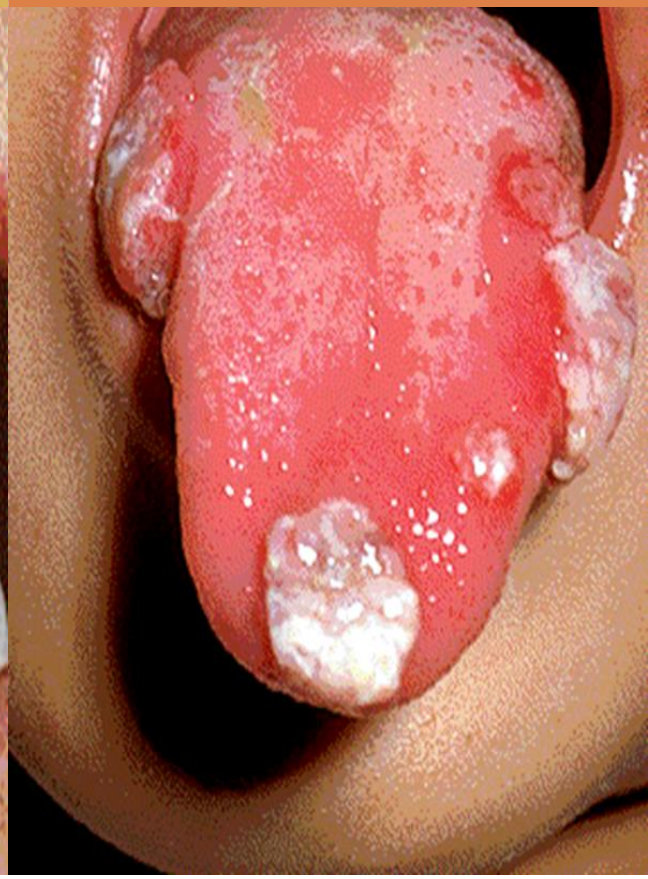
- Ocular infiltration



- Gum infiltration



Tongue infiltration

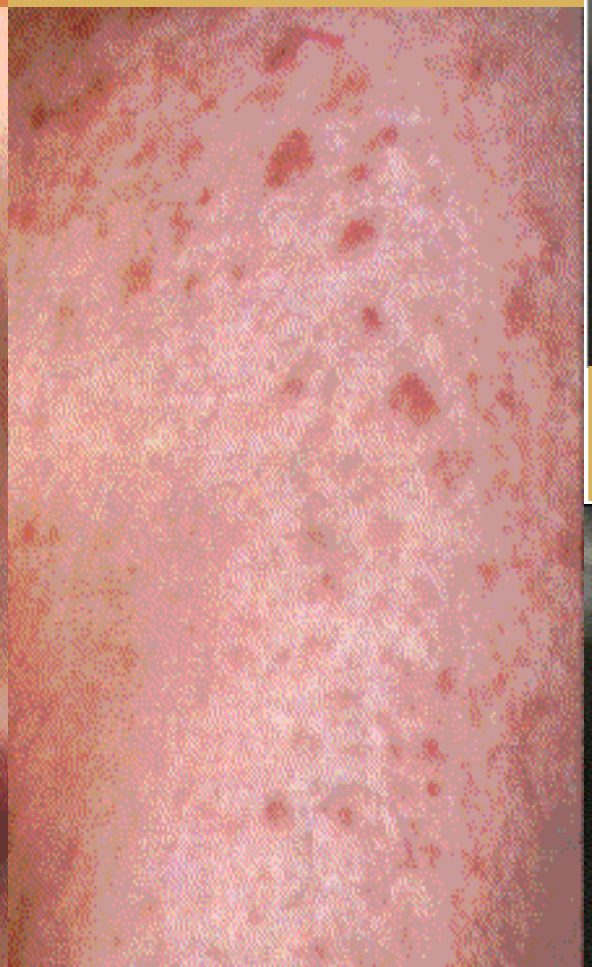


- **Skin infiltration**

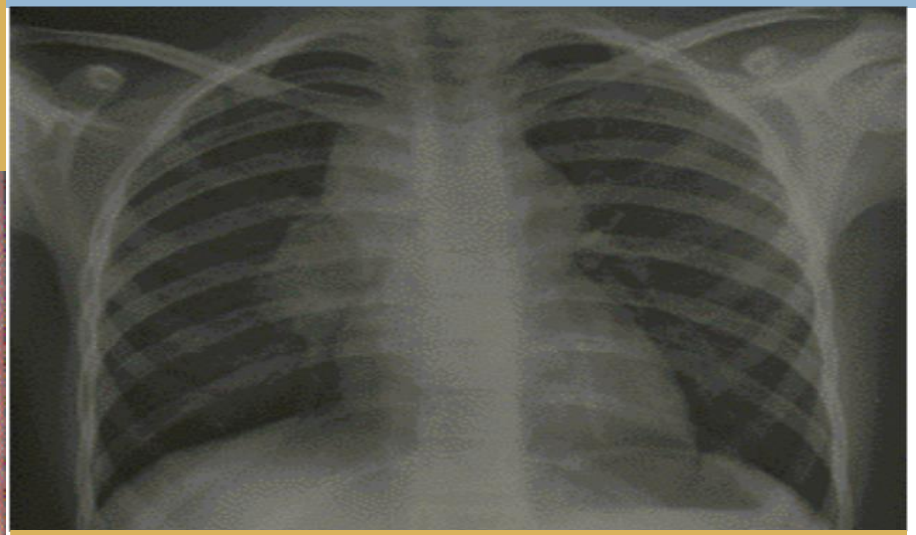
- **Mediastinal LN enlargement due to leukemic infiltration**

Nodular lesion

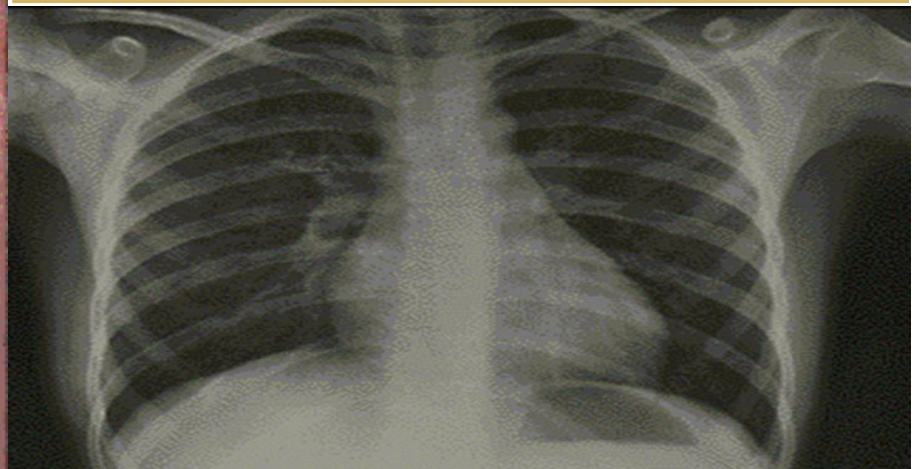
Raised erythematous lesion



Mediastinal widening



After radiotherapy (normal)



Diagnosis:

- It is based on the **presence of ≥ 20 % blasts** in the bone marrow and/or peripheral blood.

- However; it can be **diagnosed with even < 20 % blasts if ; specific** leukemia-associated cytogenetic or molecular genetic abnormalities are present such as t(8; 21) , t(15; 17) ,inv (16).

- **Diagnosis depend** on:
  - ✓ Blood film
  - ✓ Bone marrow aspirate
  - ✓ Bone marrow trephine biopsy

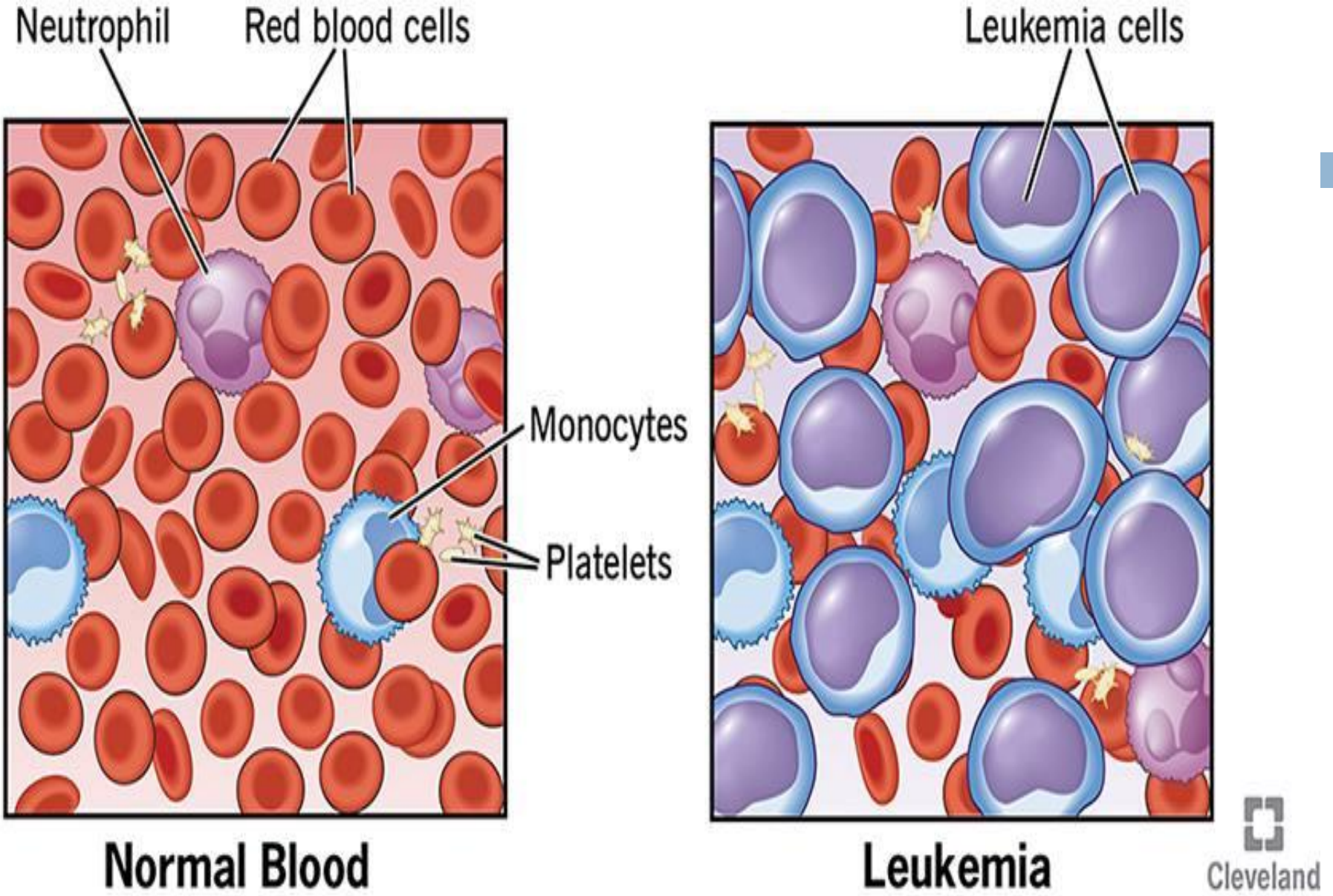
DIAGNOSIS

Blood film:

A. **RBCs**: anemia is almost always present and is usually normochromic normocytic.

B. **WBCs**: the total WBC count is variable: leukocytosis where blasts are self-evident, or leukopenia blasts may be present or absent, or may be *normal count* , Neutropenia is also a common finding in the PB.

C. **Platelets**: thrombocytopenia is present in most cases (i.e. the platelet count is decreased $<150 \times 10^9$/L).


Neutrophil
Red blood cells
Monocytes
Platelets
Normal Blood
Leukemia cells
Leukemia
Cleveland Clinic
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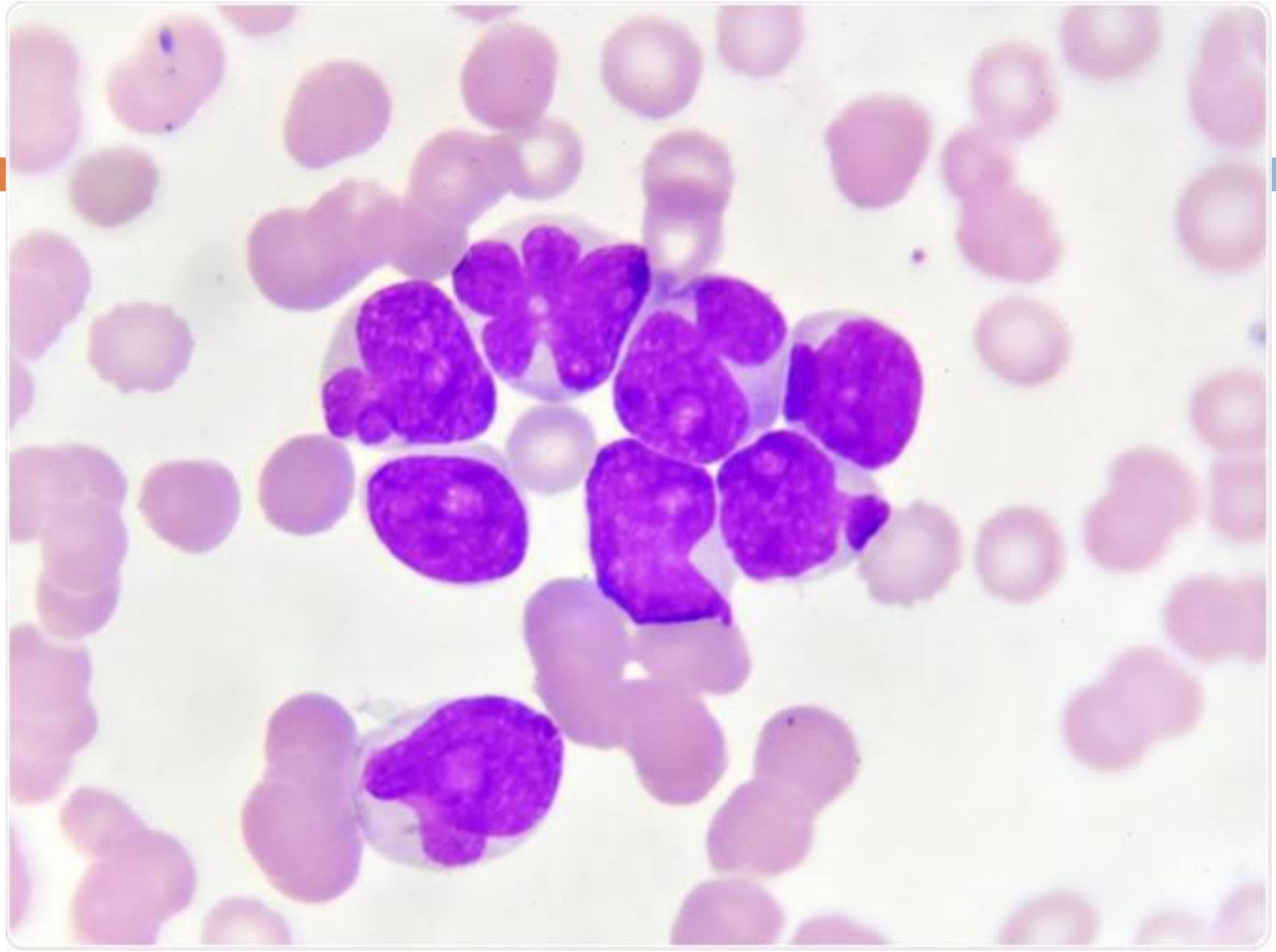
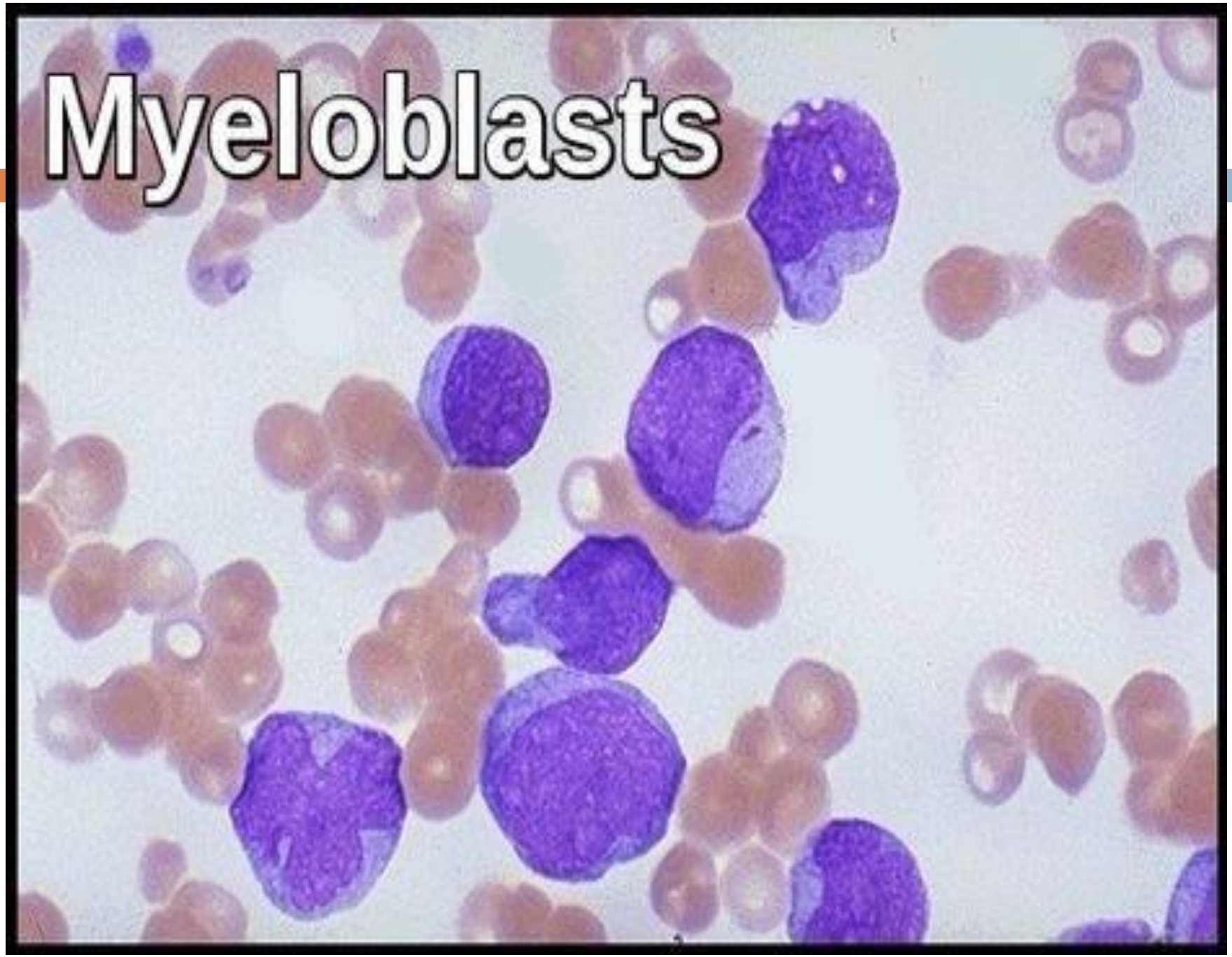
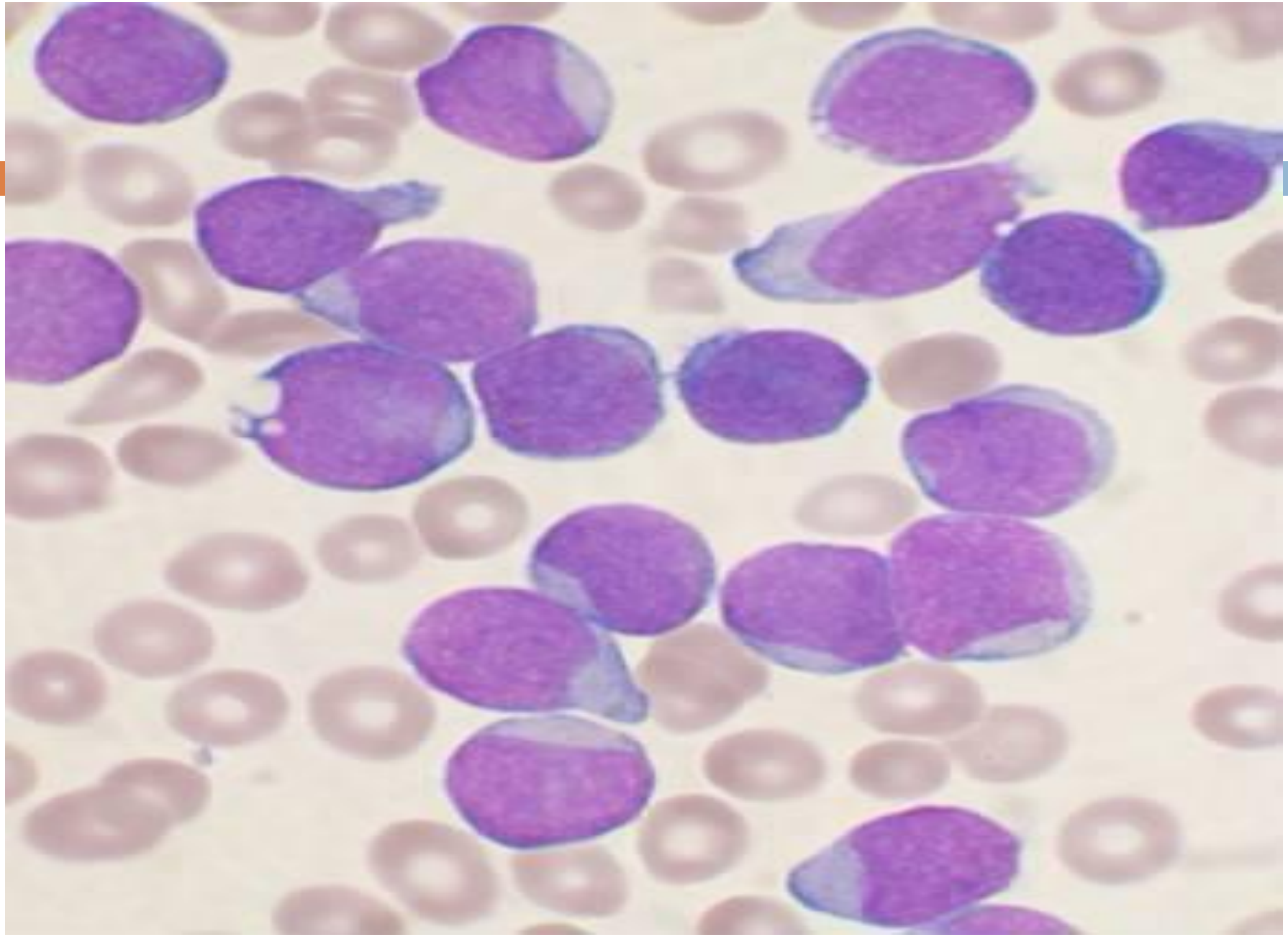
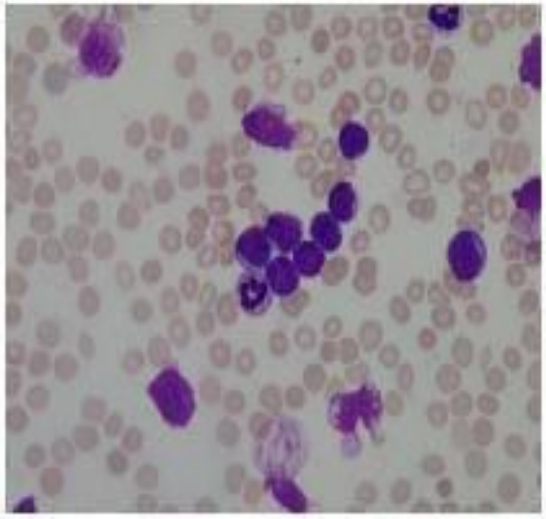
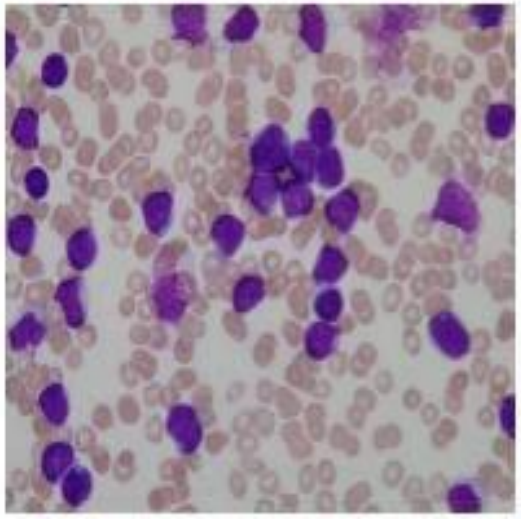
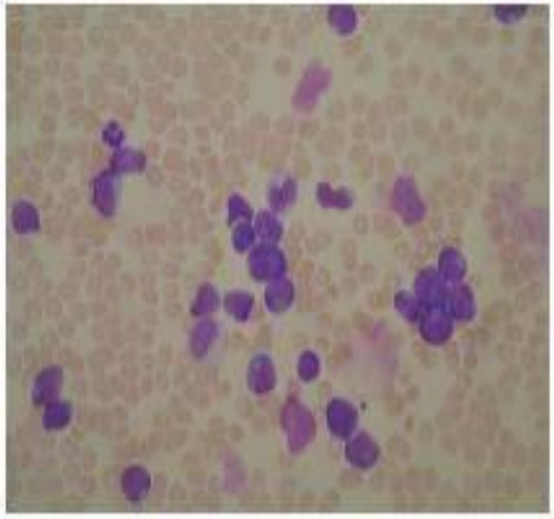


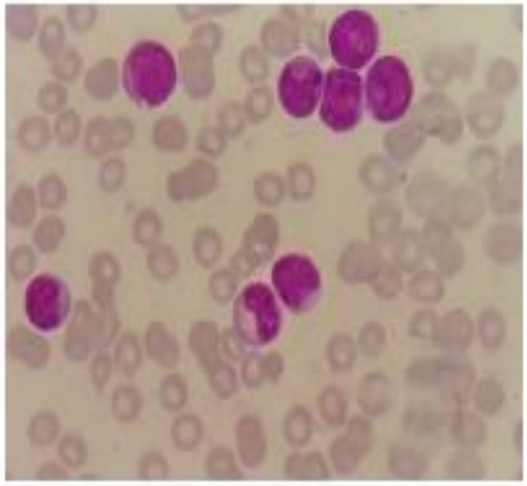
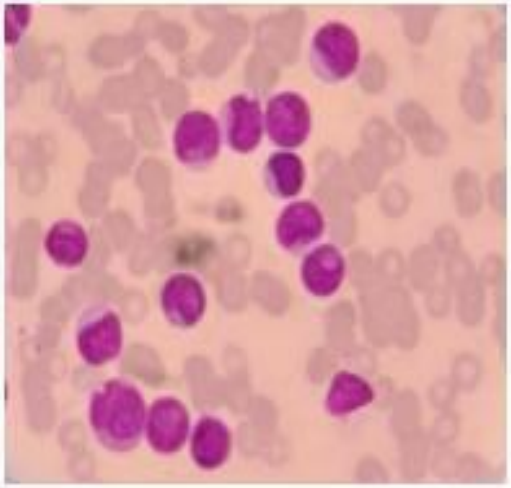
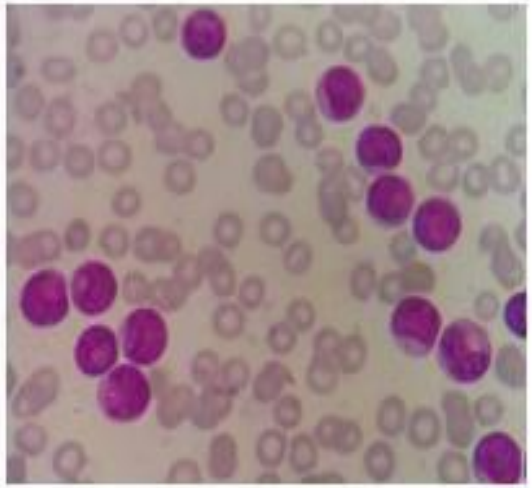

Myeloblasts



Acute Lymphoblastic Leukemia (ALL)

Acute Myeloid Leukemia (AML)

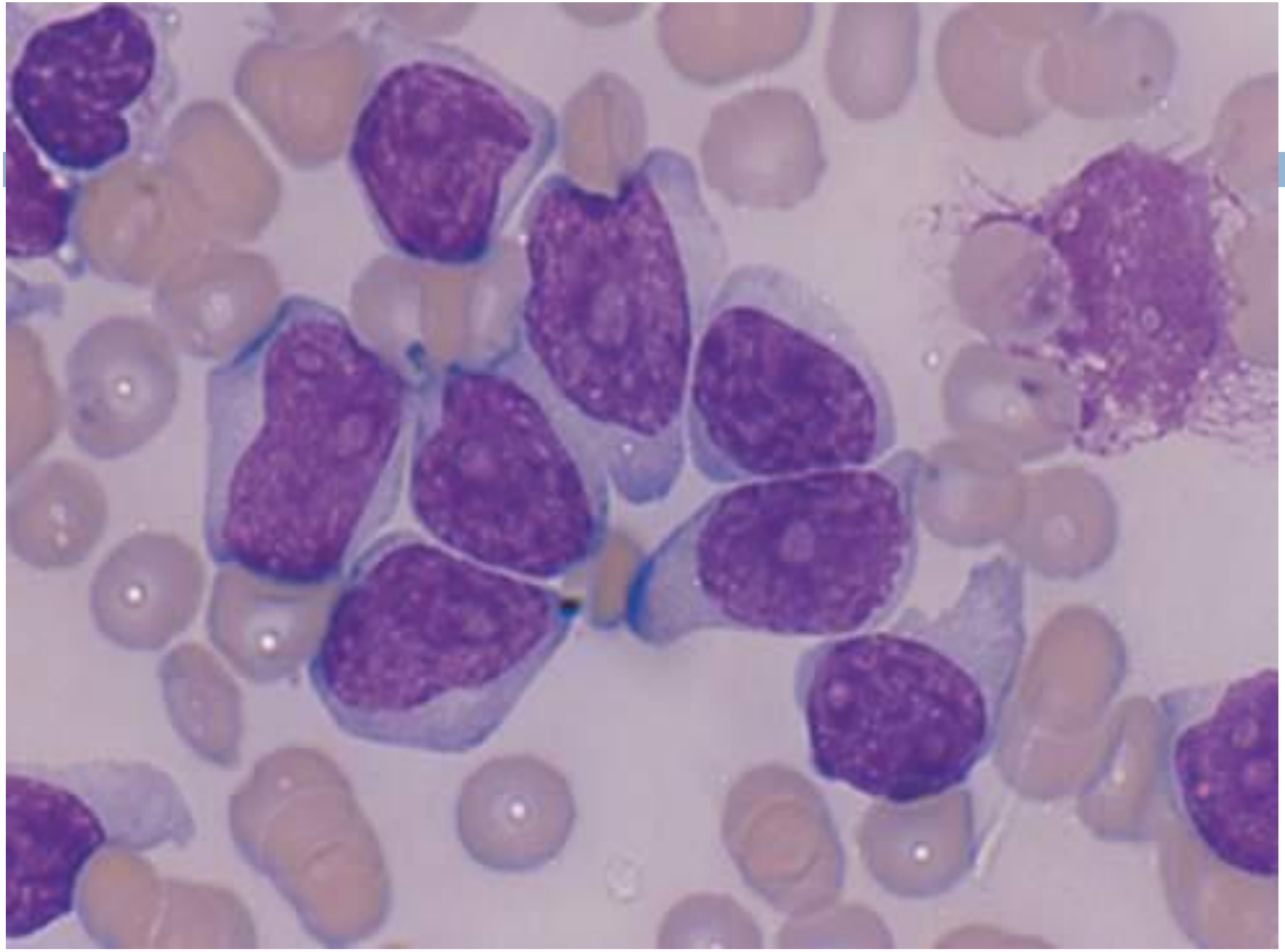




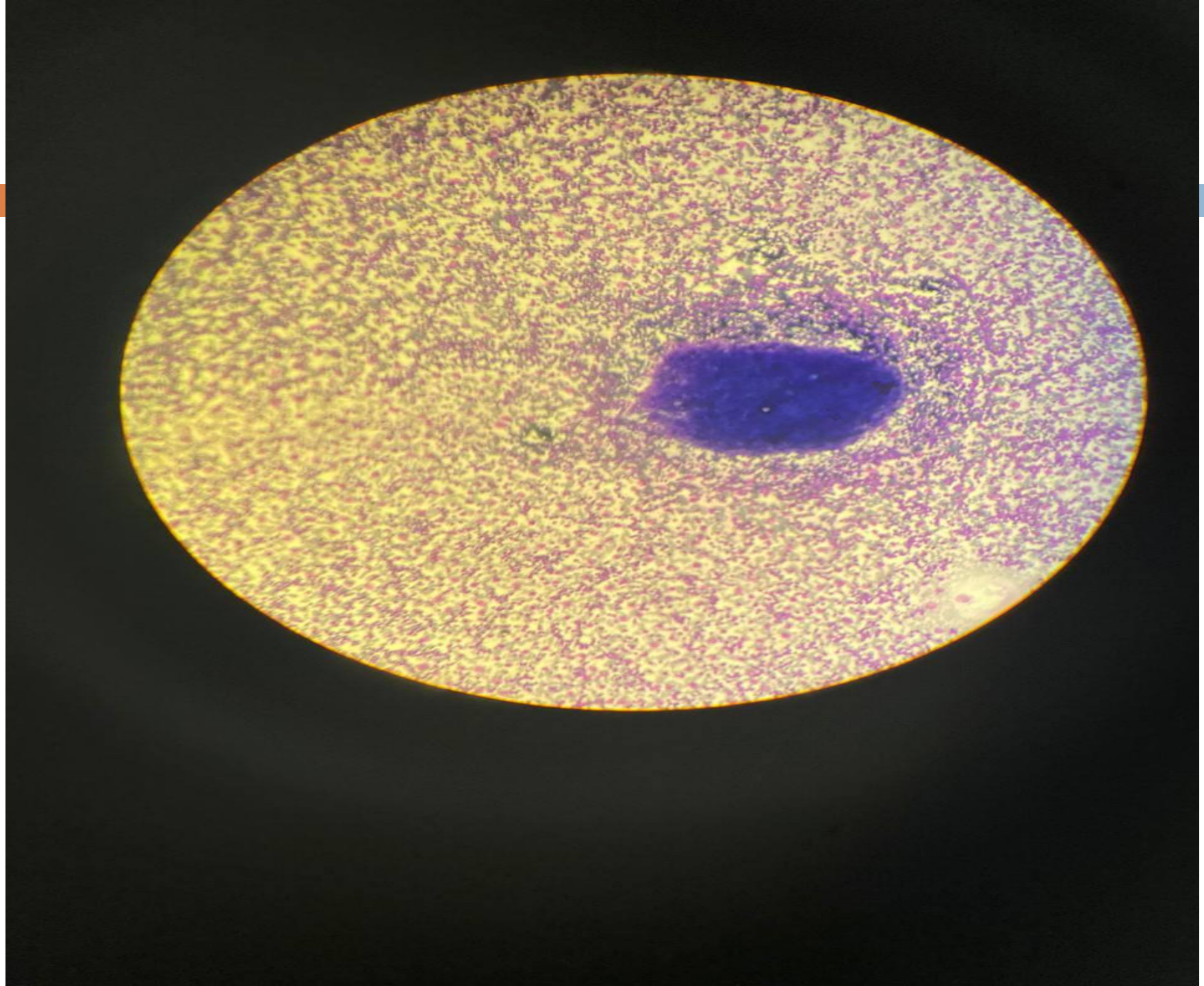
DIAGNOSIS

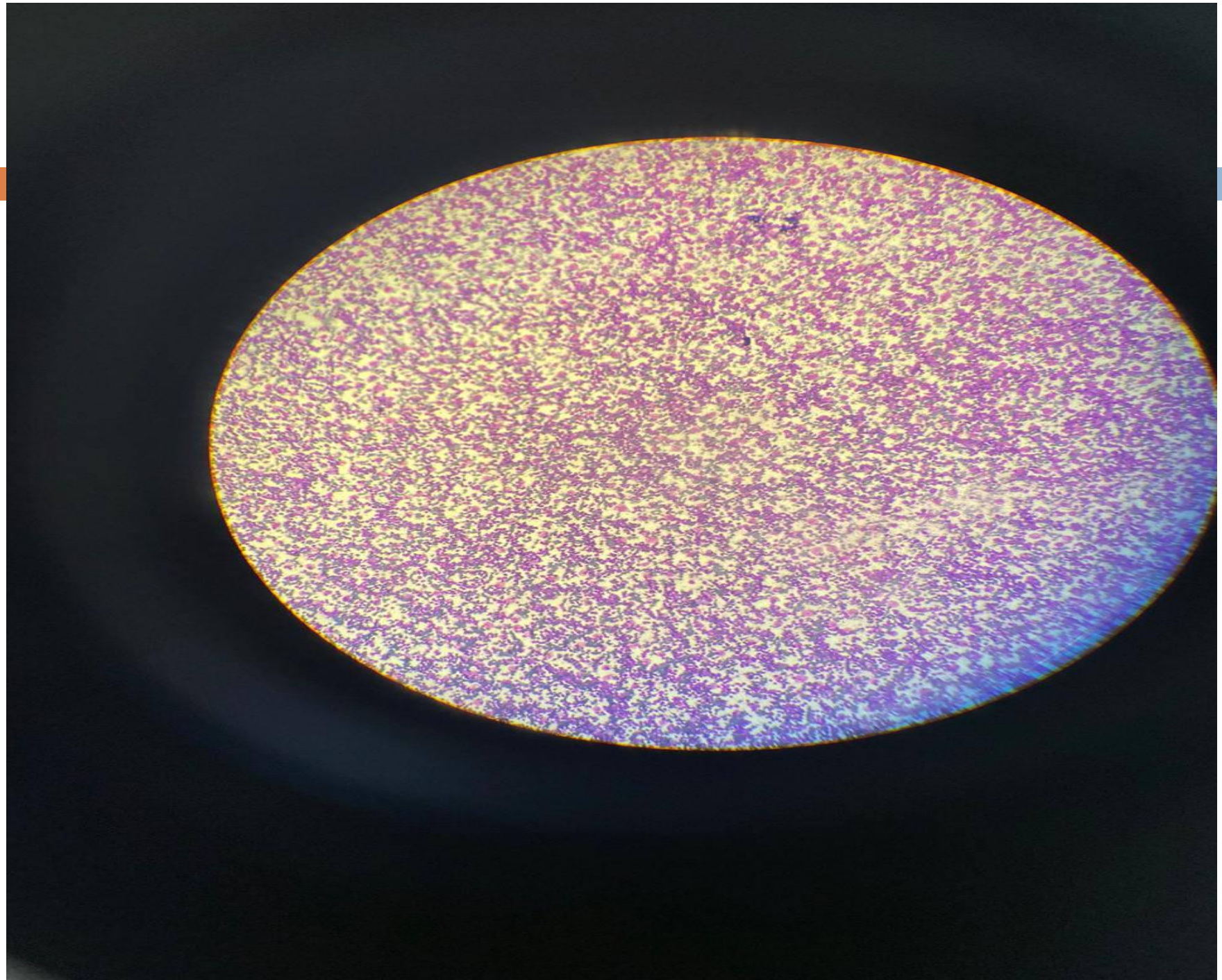
Bone marrow aspirate:

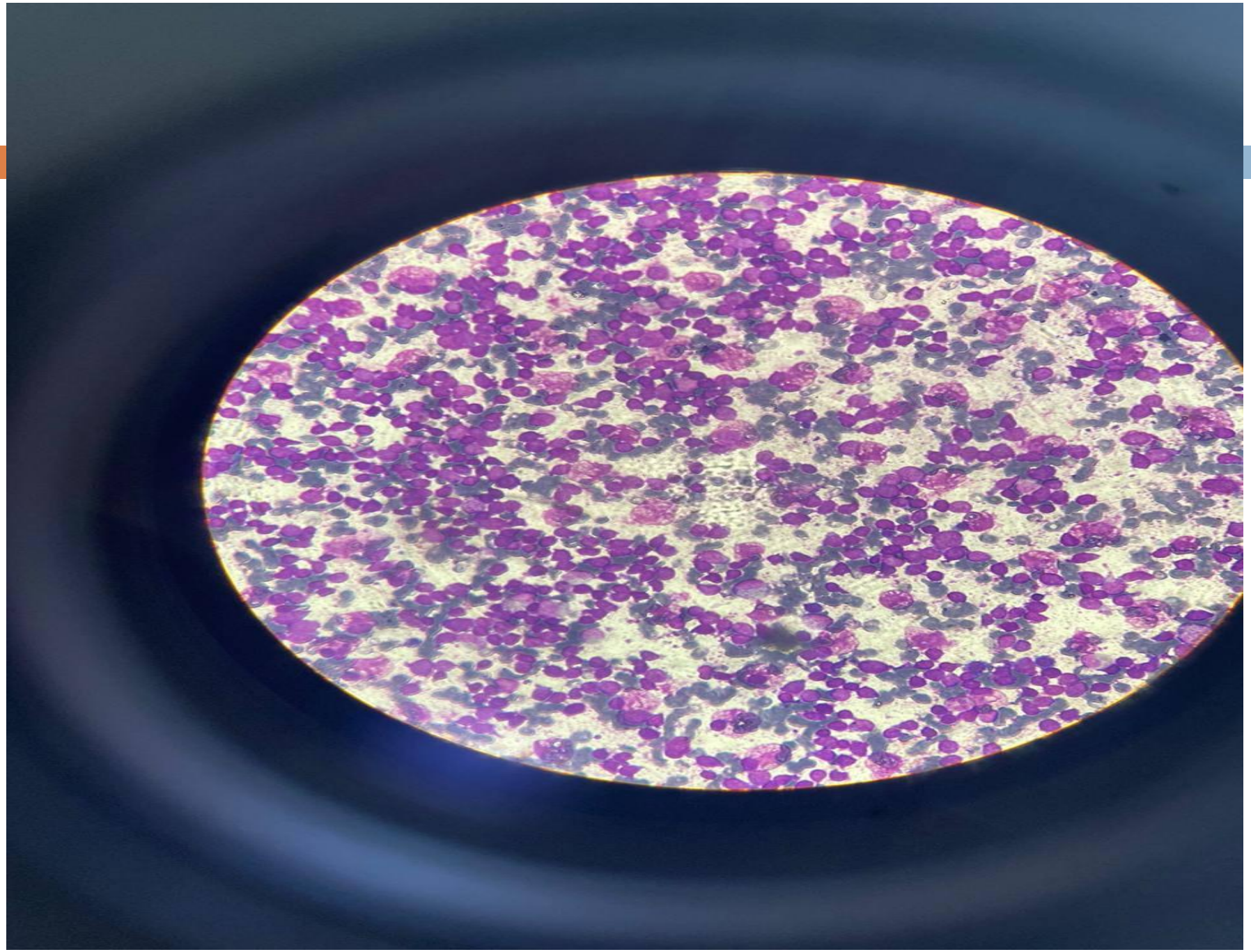
- necessary to confirm the diagnosis (especially when low counts).
- The marrow is usually **markedly hypercellular** with extensive **infiltration by blasts cells**, constituting at least 20% of all nucleated cells (ANC), with suppression of normal hemopoietic elements.
- Based on morphology of the blasts and their pattern of maturation and the use of special stains and sometimes immunological markers, leukemia **could be classified into lymphoid and myeloid and sub-typed within each of these classes.**

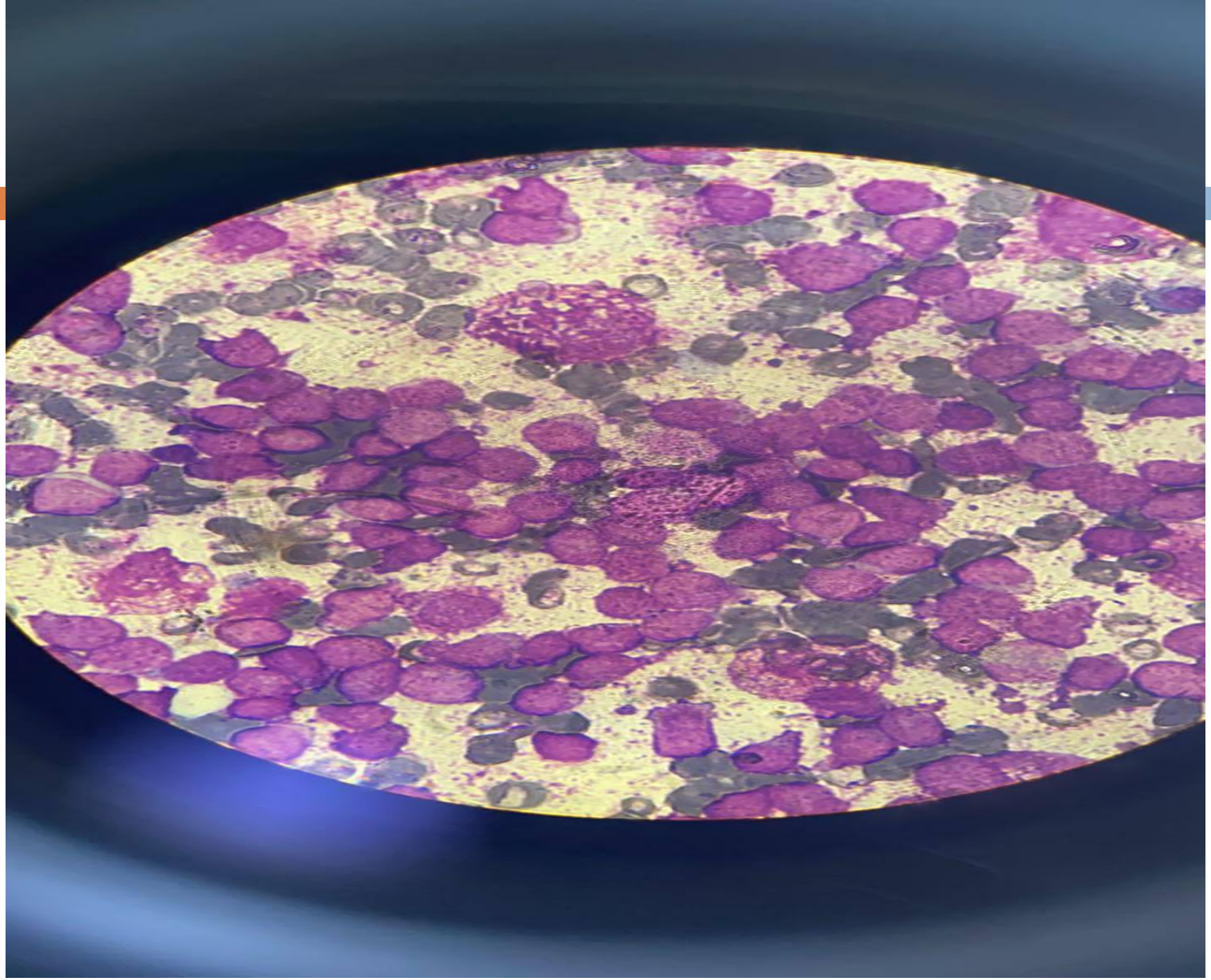

Normal BM Aspirate

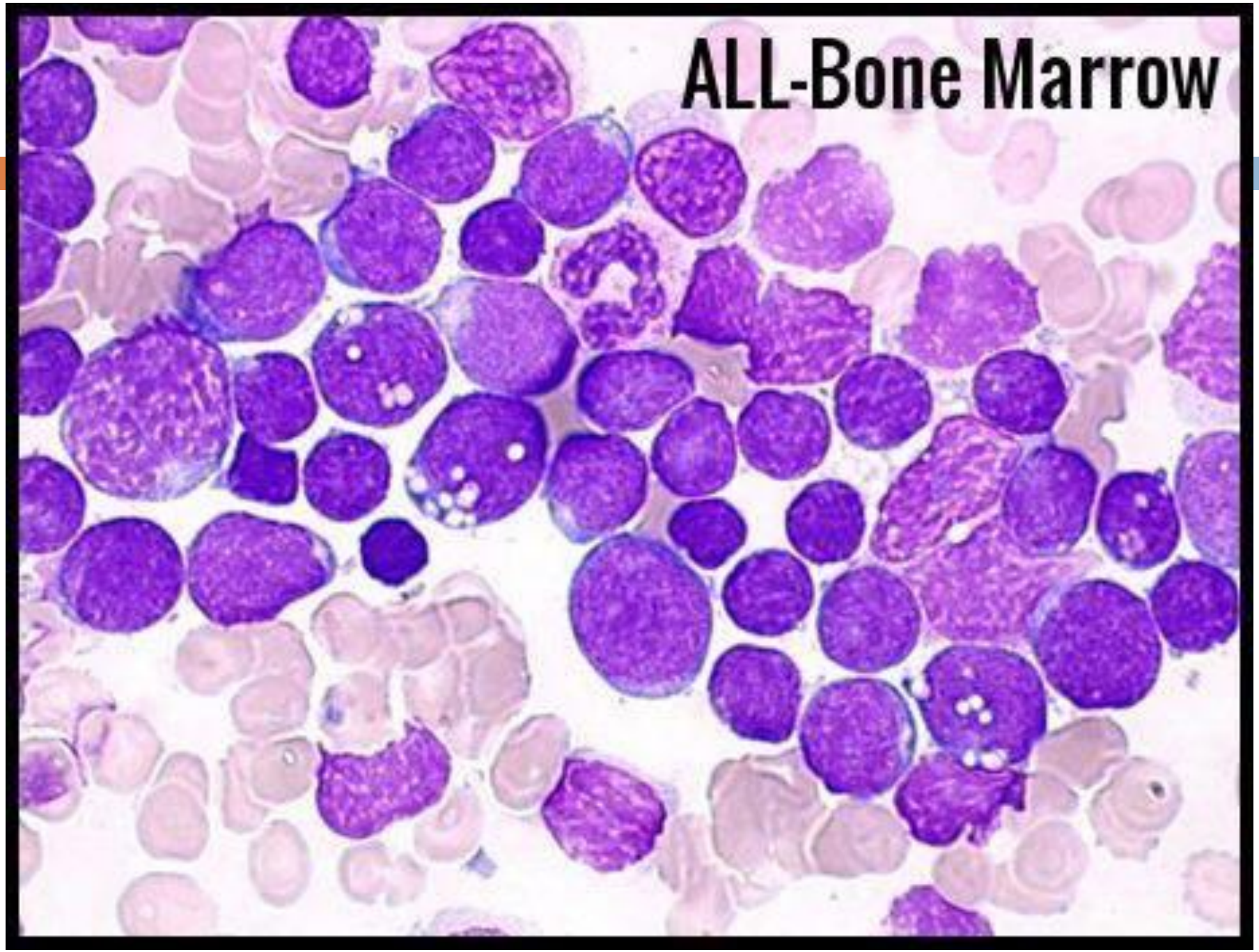










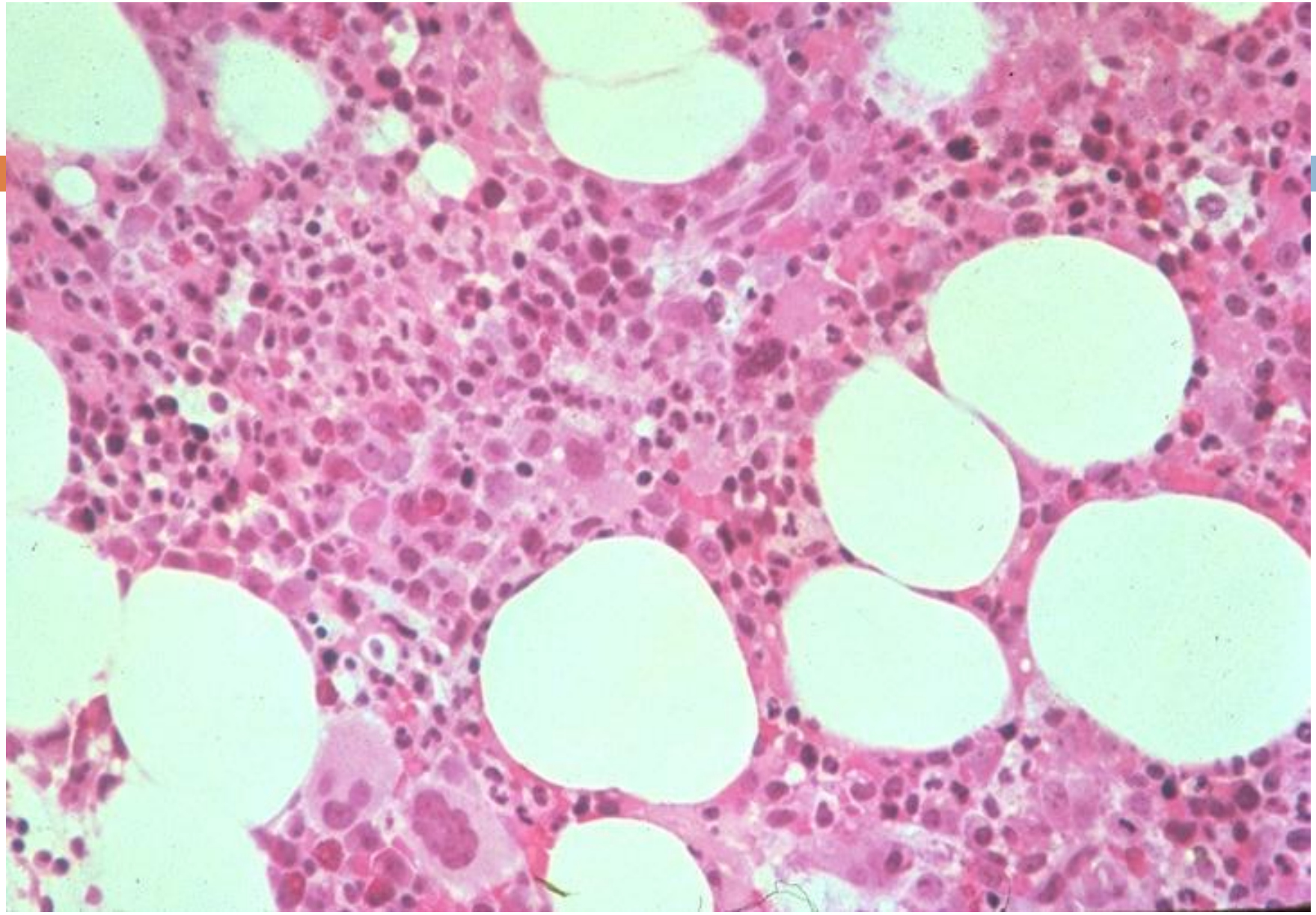

ALL-Bone Marrow

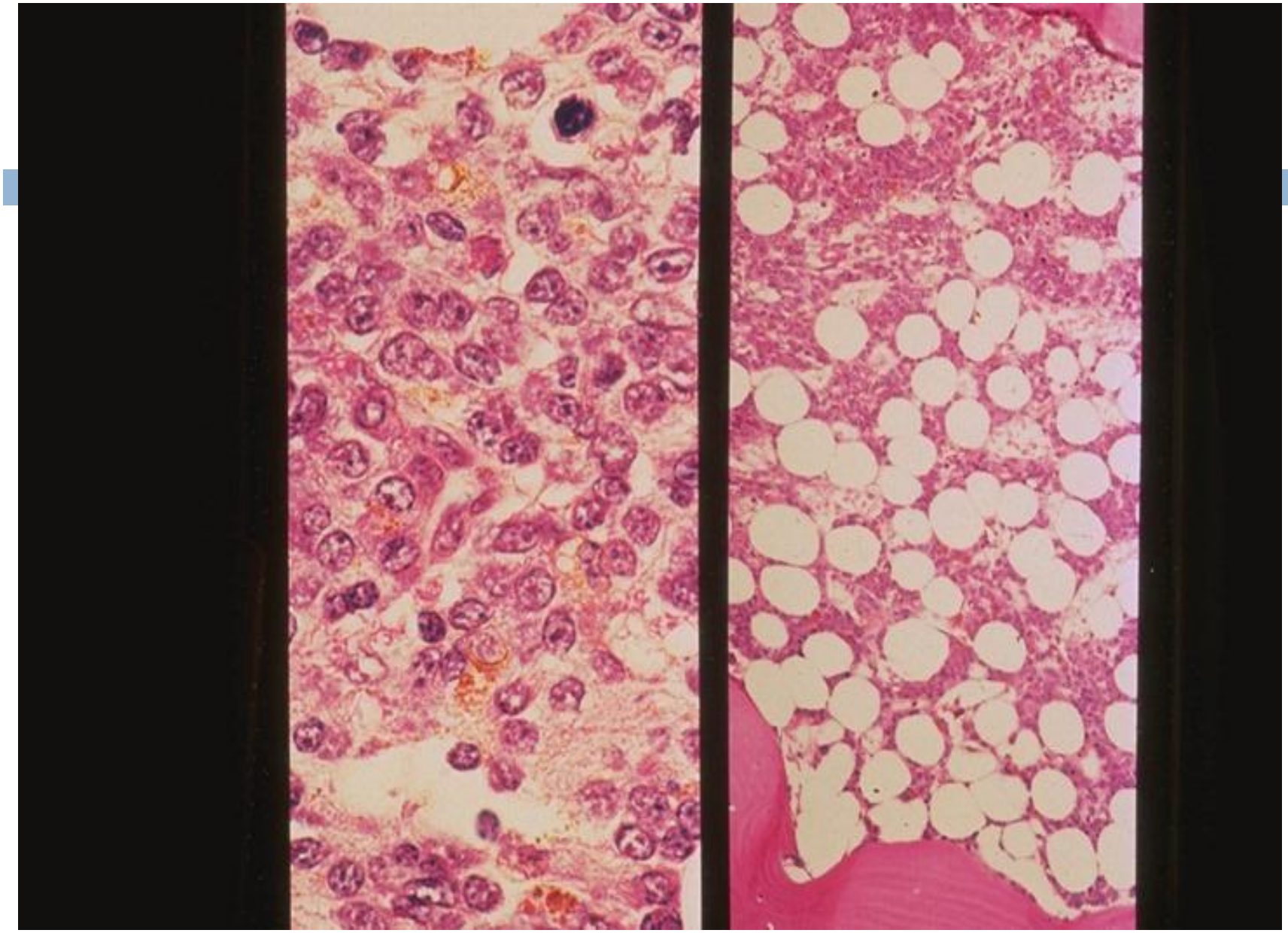
DIAGNOSIS

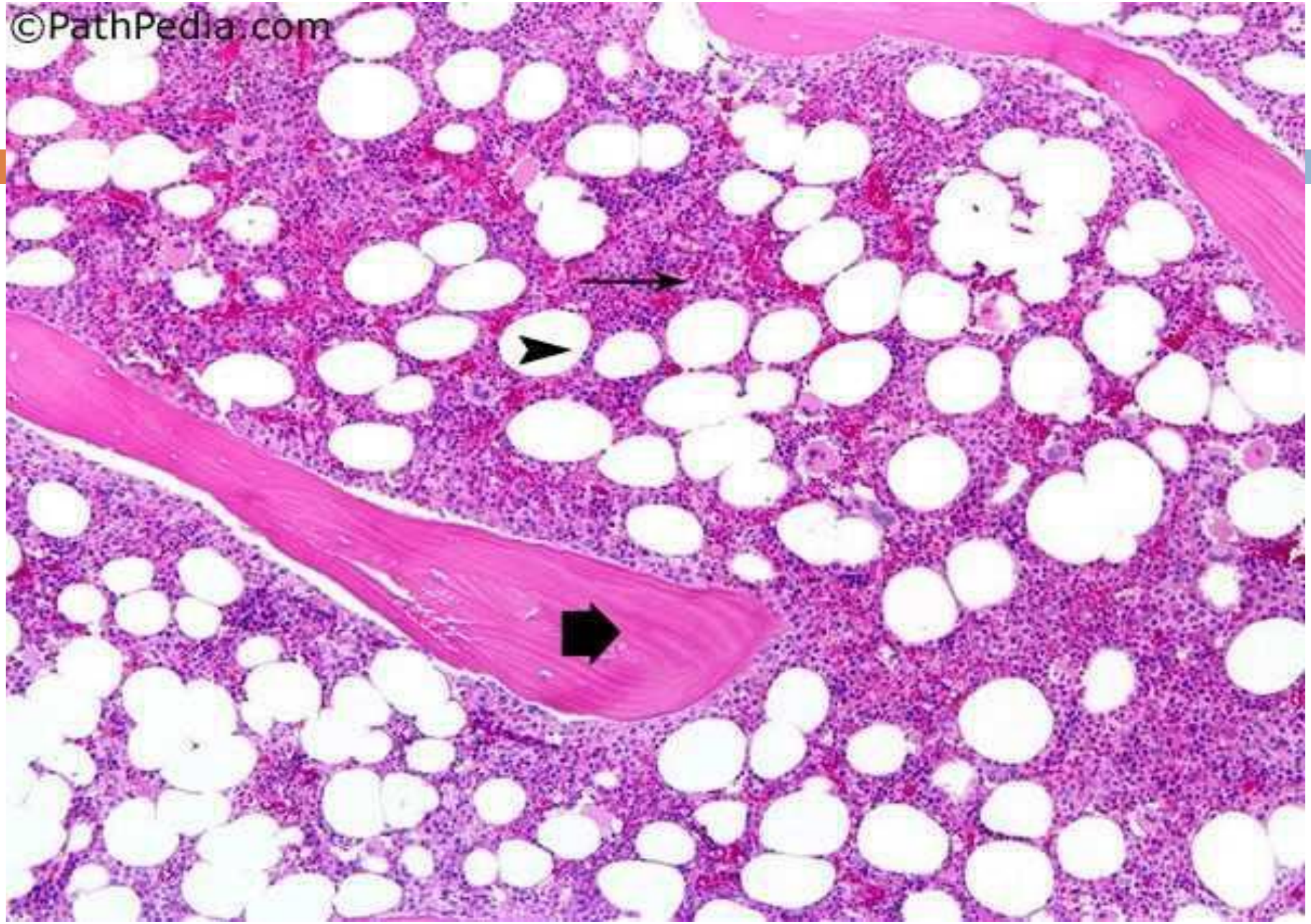
- ***Bone marrow trephine biopsy:***

BMB is of secondary importance **indicated** when :

1. BMA is inadequate;
2. To distinguish a poor aspirate due to hypocellularity from one with persistent leukemia.
3. To follow the effect of treatment, particularly in AML**.**



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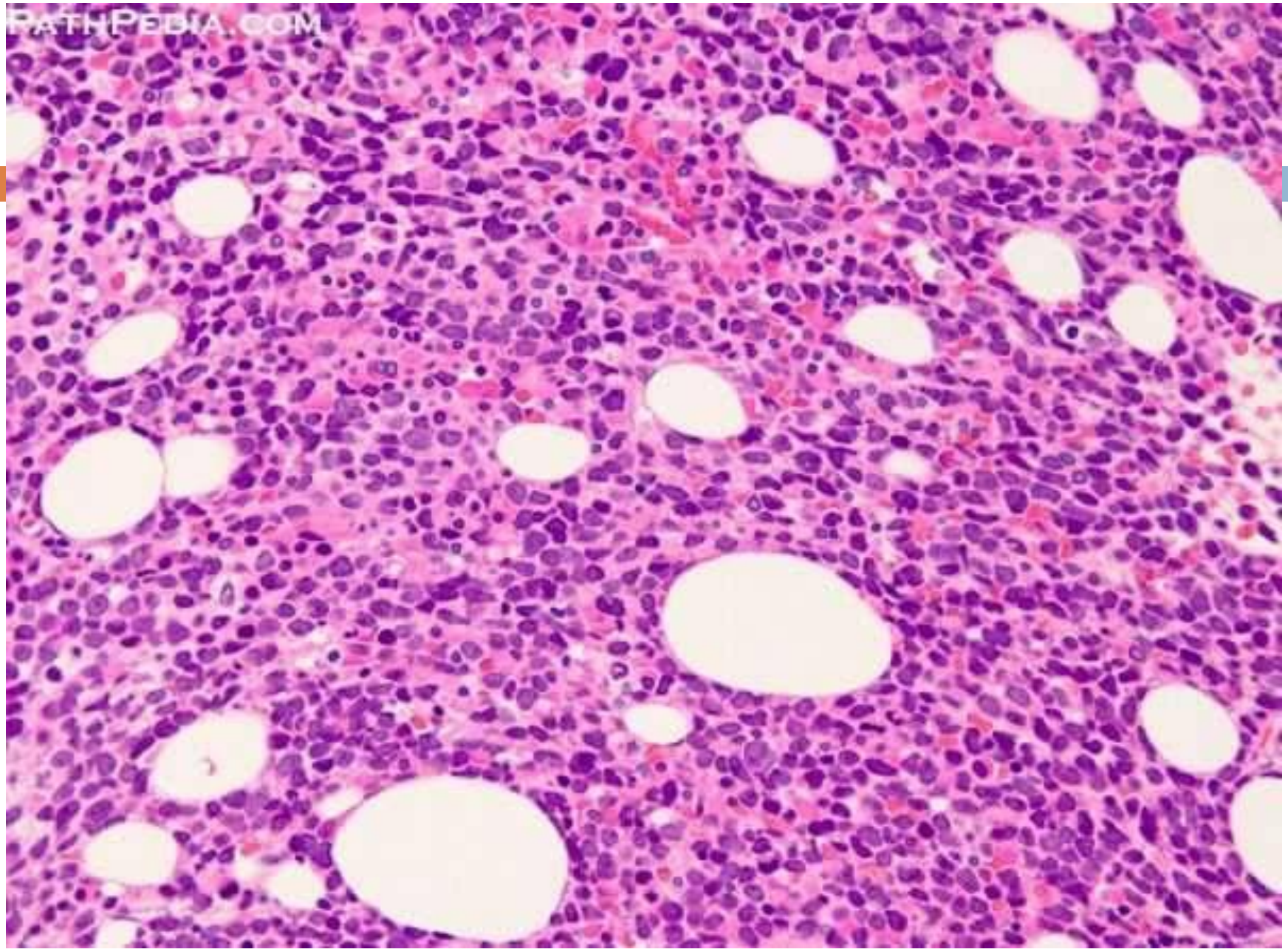

PATHPEDIA.COM

INVESTIGATIONS:

1. **Hematological;** BF & BM aspirate and biopsy

2. **Biochemical; may reveal,**

   ↑ S. uric acid

   ↑ S. LDH, and

   Hypercalcemia.

3. **Liver & Renal Function Tests;** are performed as a baseline before treatment begins.

INVESTIGATIONS

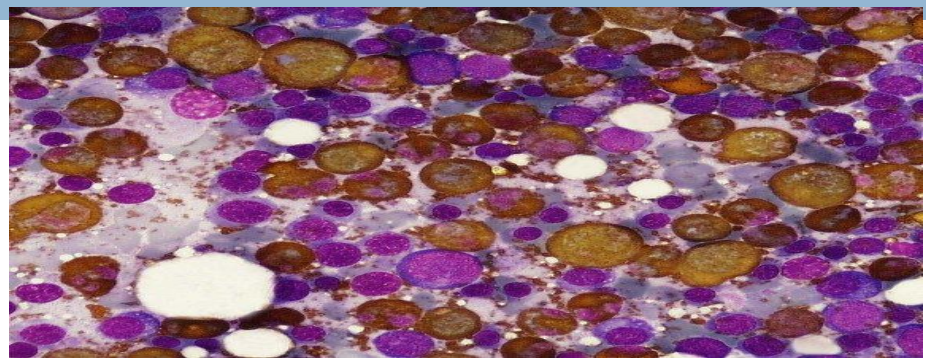
4. **Radiological Examination;** may reveal**,**
   - Lytic bone lesions.
   - Mediastinal widening caused by enlargement of the thymus &/or mediastinal LN enlargement (seen in T-ALL).

5. **Lumber puncture for CSF examination;**

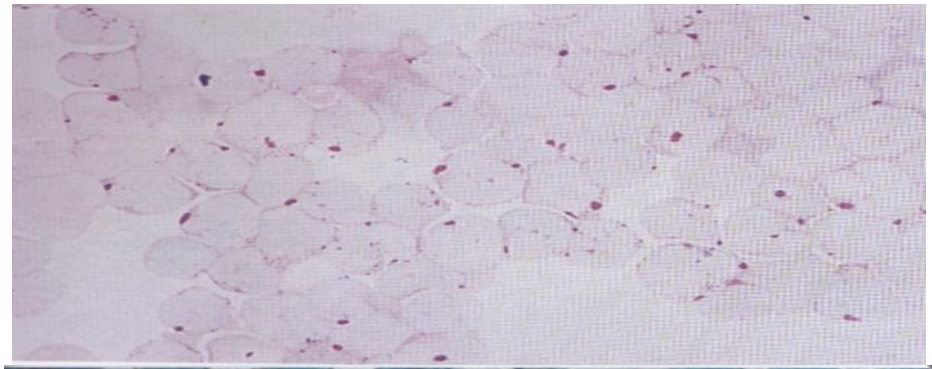
   CSF may show that the cerebrospinal fluid contains leukemic cells and indicates CNS involvement.

6. **Cytochemistry** ; is selective, when flow cytometric immunophenotyping is not readily and rapidly accessible

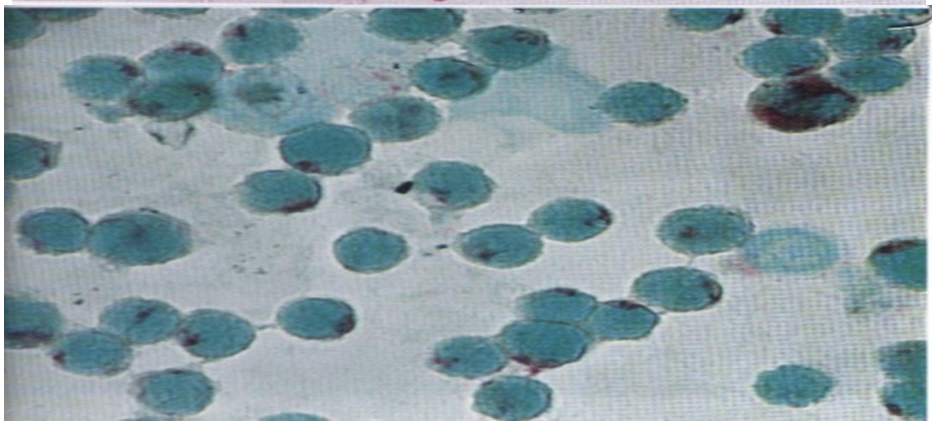
- Peroxidase :-
  - negative ALL
  - positive AML



- Periodic acid schiff
  - Positive ALL (block)
  - Negative AML



- c)Acid phosphatase :
  - focal positive
  - (T-ALL)



INVESTIGATIONS

7. **Immunophenotyping;** is indicated in all patients in whom the leukemia is not obviously myeloid**.**

- **Immunophenotyping in AL**
- **Immunophenotyping may be applied to detect**
  - ✓ **Specific surface membrane Ag.**
  - ✓ **Specific cytoplasmic Ag.**
  - ✓ **Specific intra-nuclear Ag.**
- **Flow cytometry: Is a technique by which a stream of cells that have been labeled with an antibody conjugated to a fluorescent dye flow past a detector and can be counted and sized. It is a rapid highly accurate and can detect several antigens on the same cells simultaneously and the strength of Ag expression.**

Table 20.2 Expression of cell-surface and cytoplasmic markers for the diagnosis of acute myeloid leukaemia and mixed-phenotype acute leukaemia.

Expression of markers for diagnoses	
Diagnosis of acute myeloid leukaemia (AML)	
Precursor stage	CD34, CD38, CD117, CD133, HLA-DR
Granulocytic markers	CD13, CD15, CD16, CD33, CD65, cytoplasmic myeloperoxidase (cMPO)
Monocytic markers	Nonspecific esterase (NSE), CD11c, CD14, CD64, lysozyme, CD4, CD11b, CD36, NG2 homologue
Megakaryocyte markers	CD41 (glycoprotein IIb/IIIa), CD61 (glycoprotein IIIa), CD42 (glycophorin 1b)
Erythroid marker	CD235a (glycophorin A)
Diagnosis of mixed phenotype acute leukaemia (MPAL)	
Myeloid lineage	MPO or evidence of monocytic differentiation (at least 2 of the following: NSE, CD11c, CD14, CD64, lysozyme)
B-lineage	CD19 (strong) with at least one of the following: CD79a, cCD22, CD10, or CD19 (weak) with at least 2 of the following: CD79a, cCD22, CD10
T-lineage	cCD3, or surface CD3

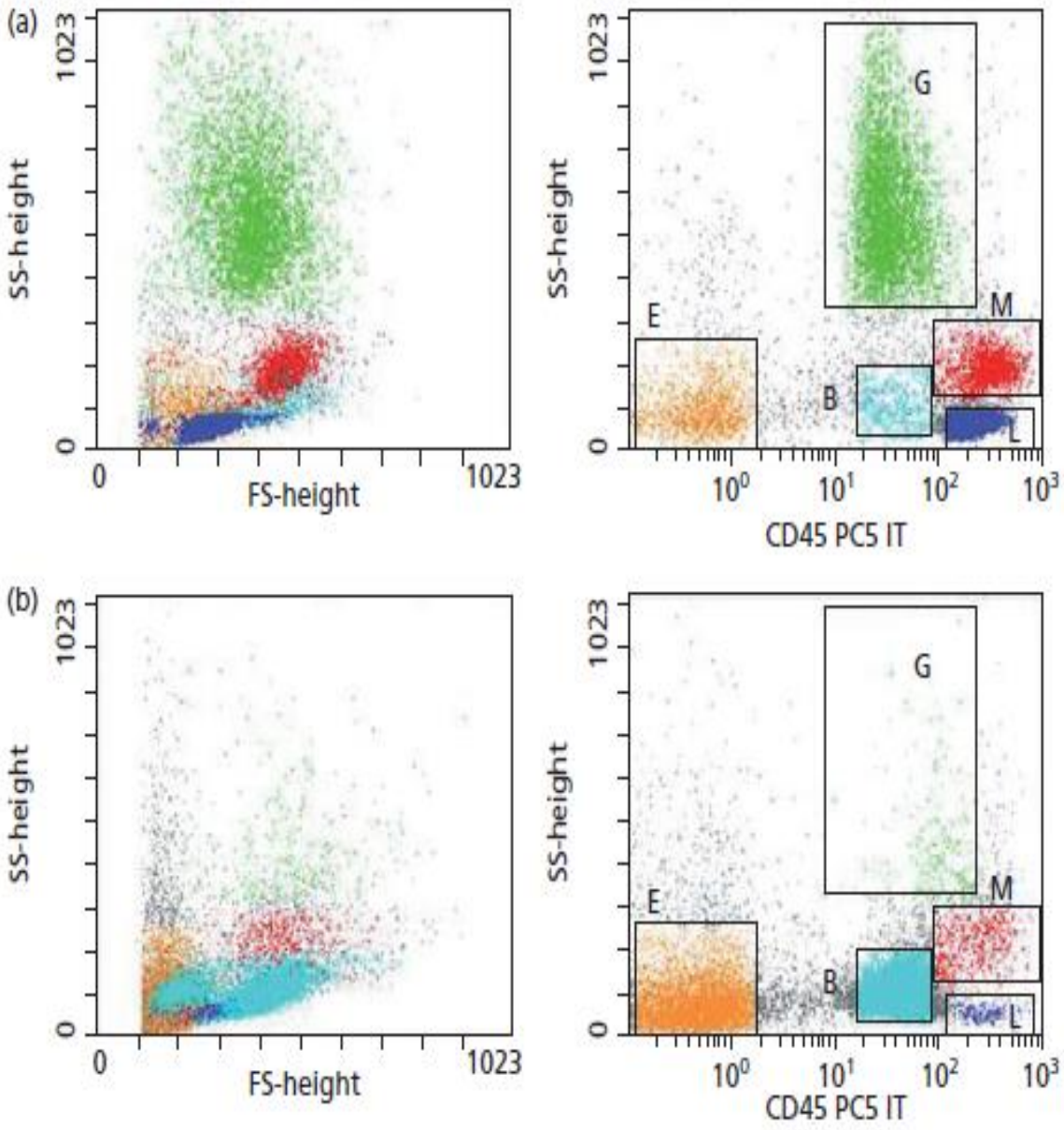


Figure 19.26 Flow cytometry immunophenotyping showing improvement of separation of populations by CD45 and sideways light scatter (SSC) gating. Forward light scatter (FSC) is also shown. (a) Normal bone marrow (left, SSC–FSC plot; right, SSC–CD45 plot); (b) acute myeloid leukaemia bone marrow (left, SSC–FSC plot; right, SSC–CD45 plot). G, granulocytes; M, monocytes; L, lymphocytes; E, erythrocytes; B, blasts. SSC–CD45 gating permits isolation of bone marrow blasts from all other populations, which is not possible by SSC–FSC gating.

7. **Cytogenetic analysis;** is essential in all patients, since knowledge of the karyotype is important for determining the prognosis and for choice of optimal treatment. Best performed on BMA


Thank you!