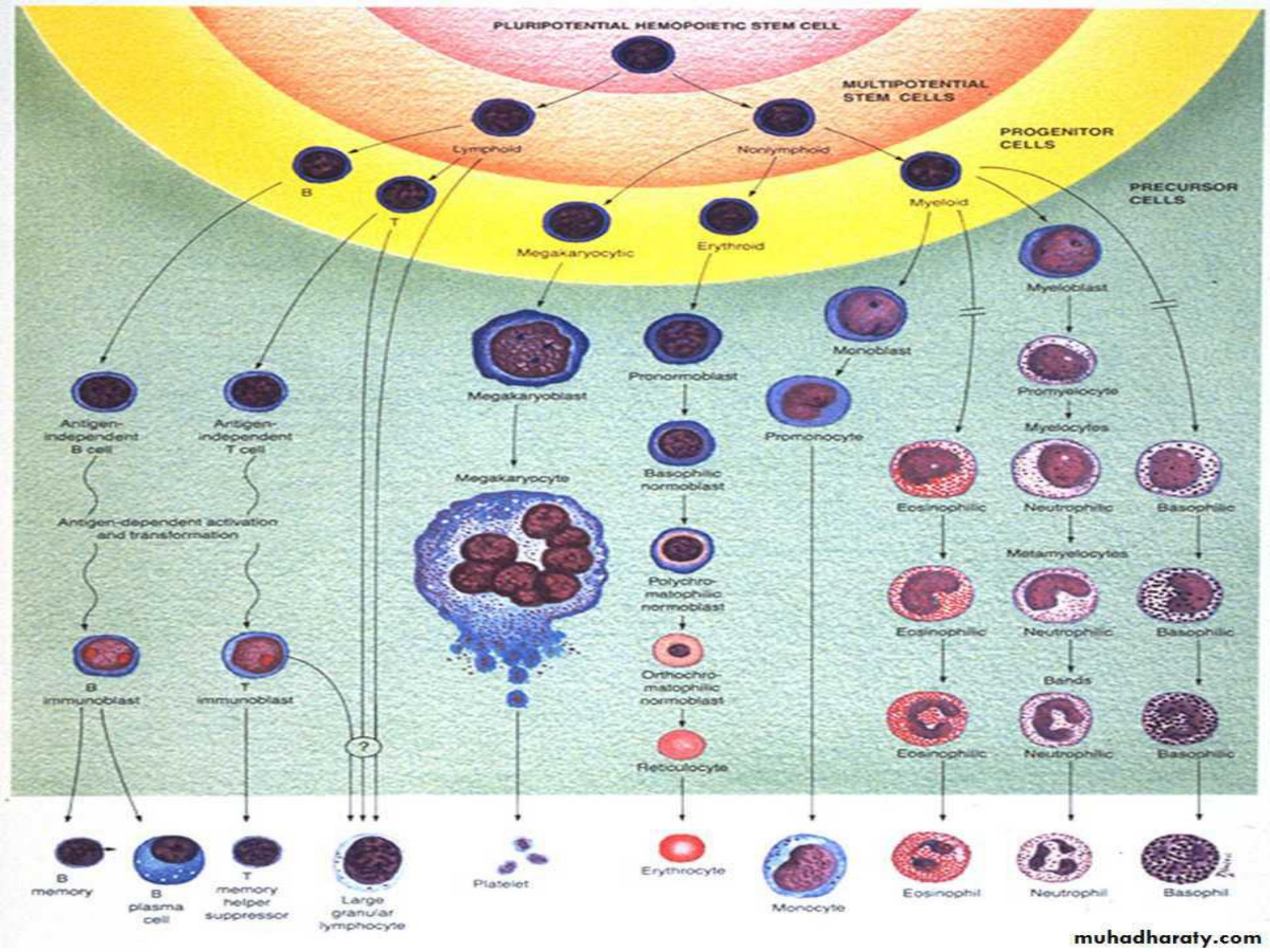
ACUTE LEUKEMIA

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

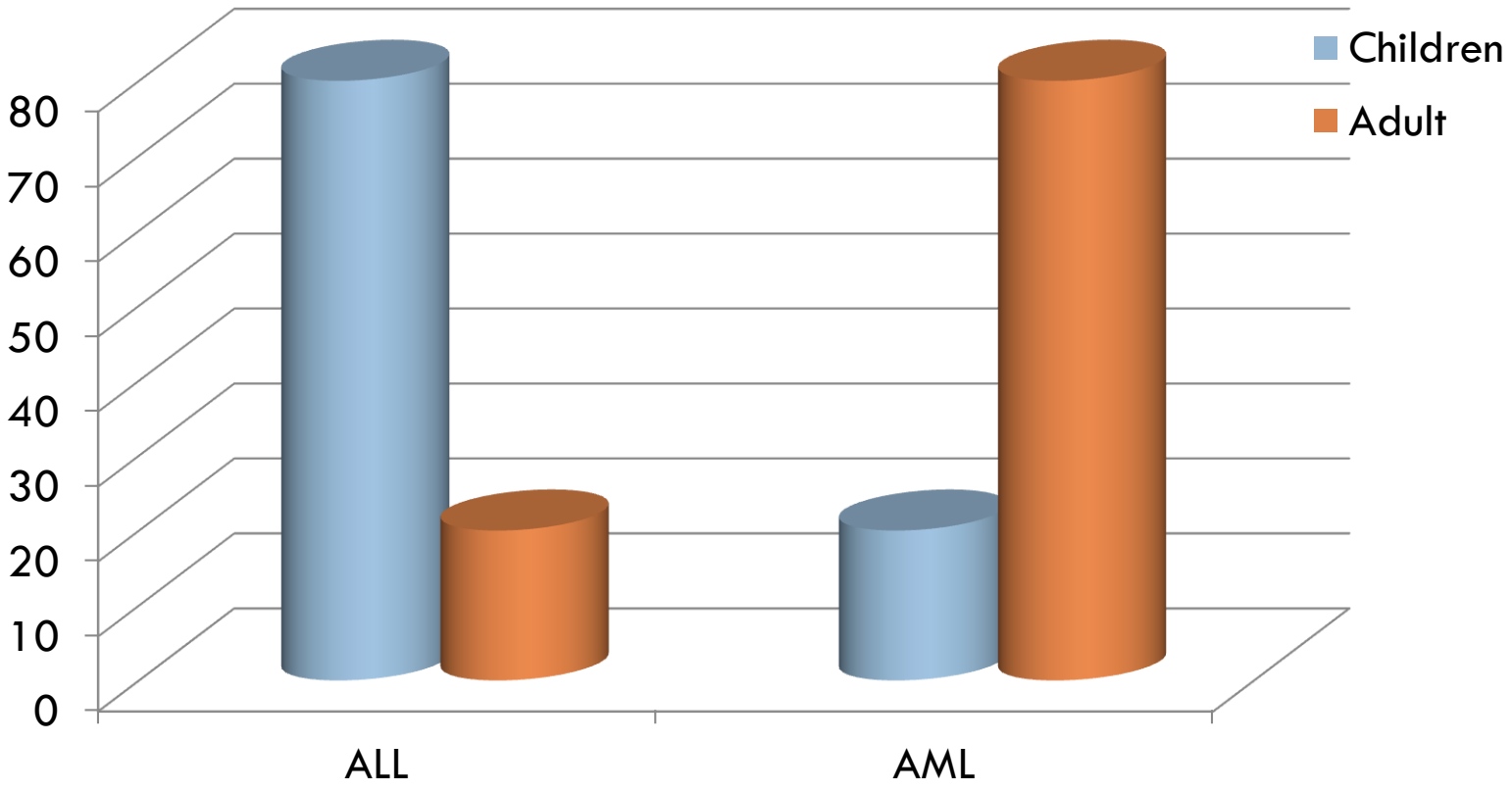
1. **Ionizing radiation**
   - Radiotherapy for ankylosing spondylitis
   - Diagnostic X - rays of the fetus in pregnancy
2. **Cytotoxic drugs:** Especially alkylating agents (myeloid leukemia , usually after a latent period of several years) Industrial exposure to benzene
3. **Retroviruses :**some cases 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.

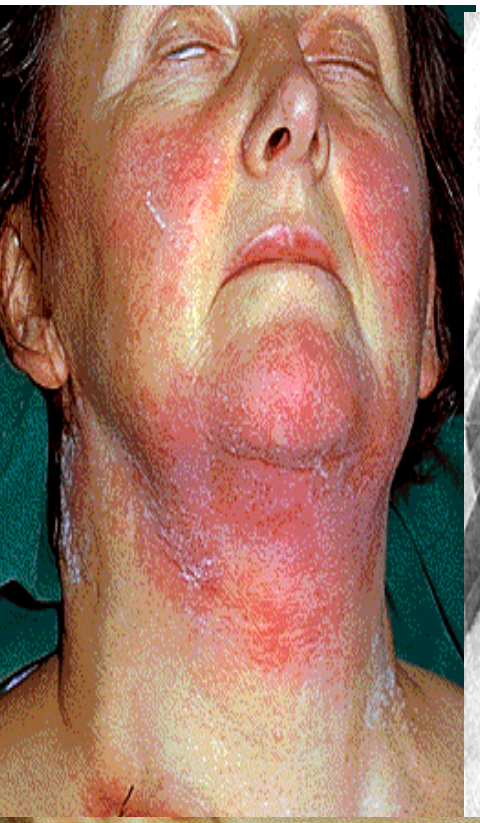
1. Bone marrow failure:

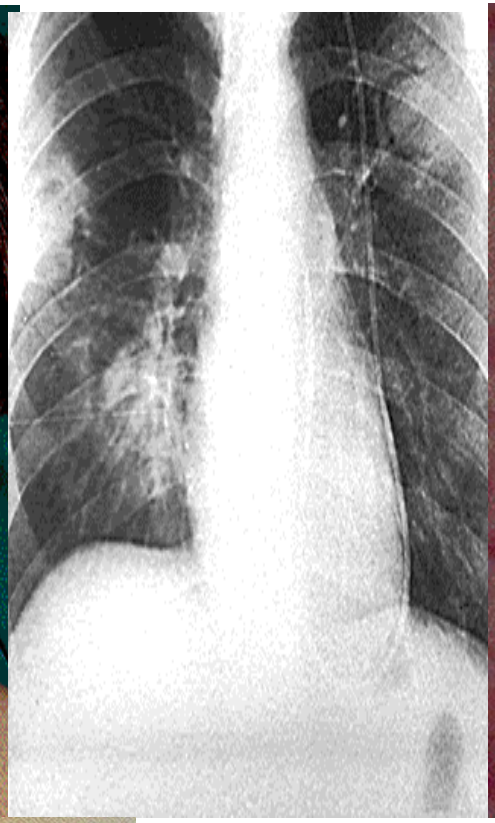
- **Anemia;** pallor, weakness, fatigue, lethargy, dyspnea on exertion, angina, and palpitation**.**
- **Neutropenia;** Infections due to reduced immunity, especially
- **Thrombocytopenia;** Bleeding manifestations into the skin;

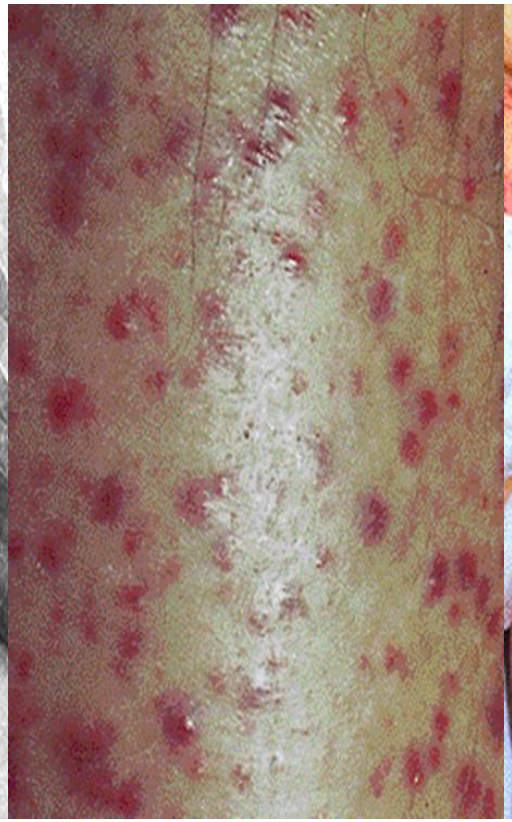
2. Organ and Tissue Infiltration by the leukemic cells:

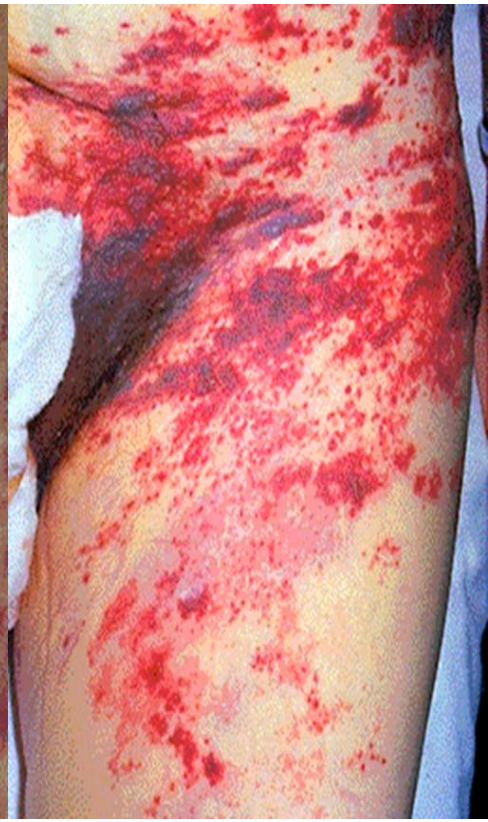
- Splenomegaly.
- Hepatomegaly.
- Bone pain.
- Arthralgia.

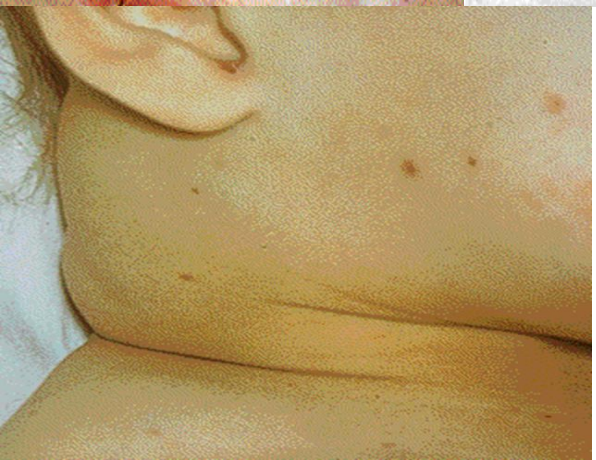
Skin infection Respiratory infection (Purpura) (Ecchymosis)





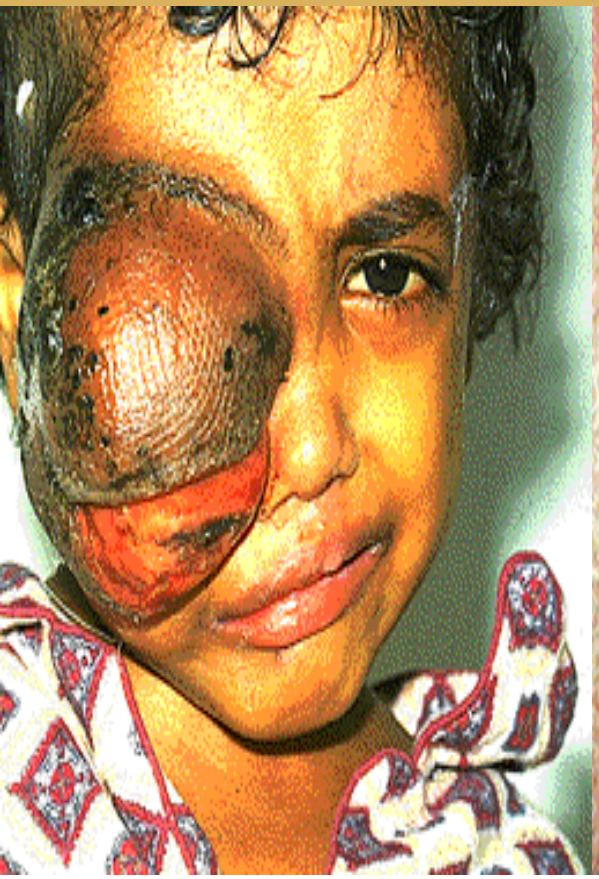




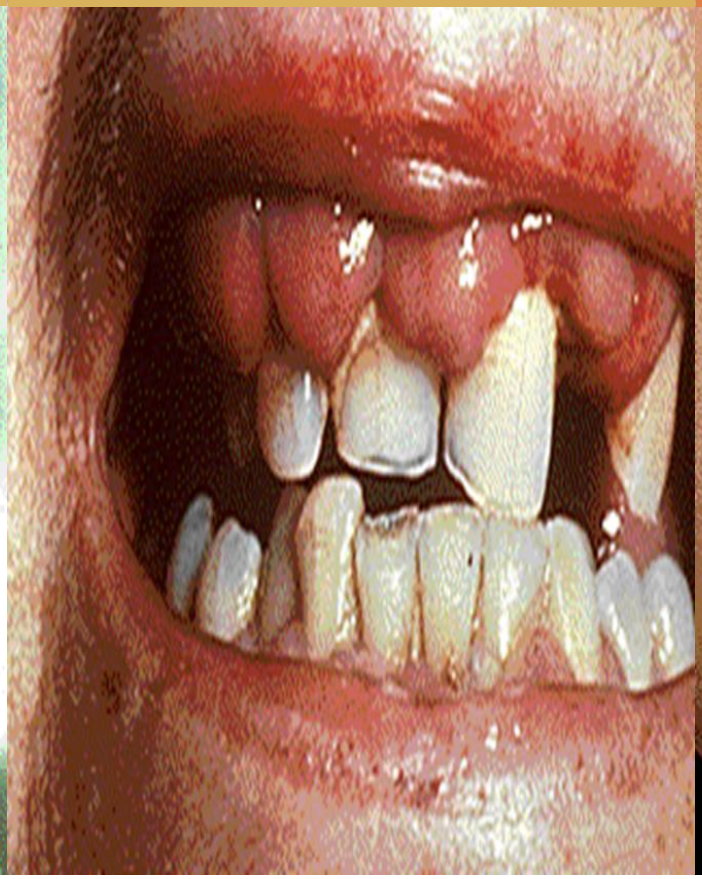


Lymphadenopathy

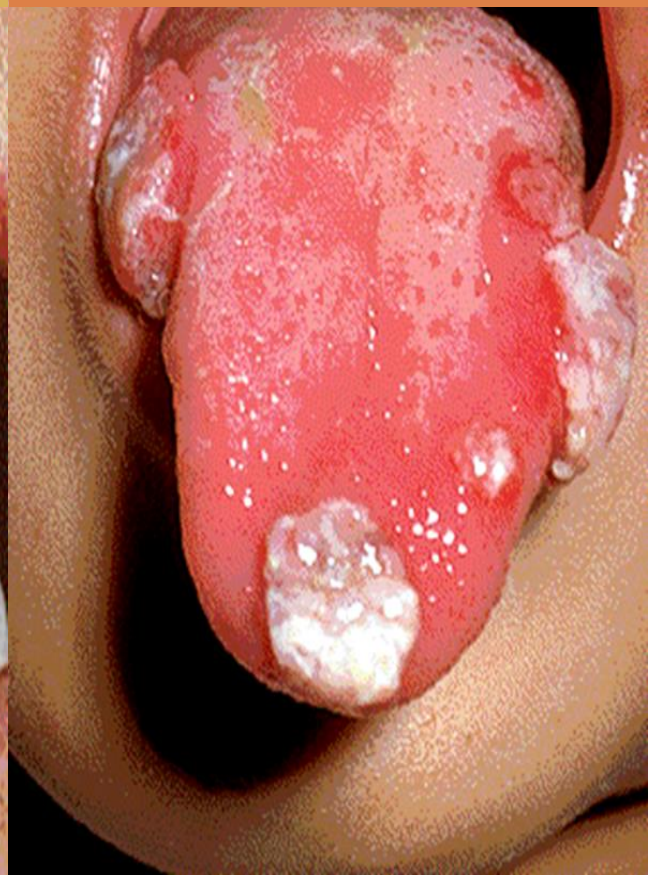
- Ocular infiltration



- Gum infiltration



Tongue infiltration

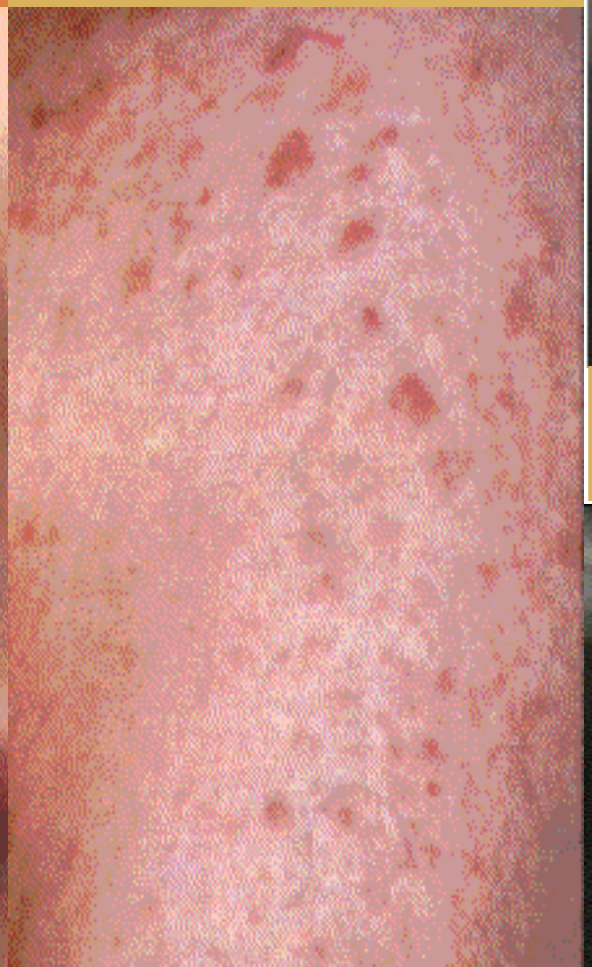


- **Skin infiltration**

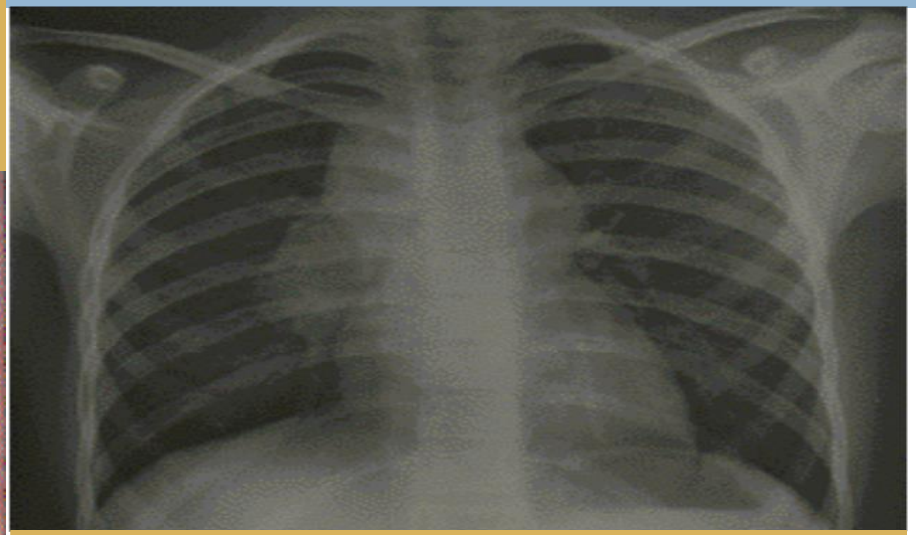
- **Mediastinal LN enlargement due to leukemic infiltration**

Nodular lesion

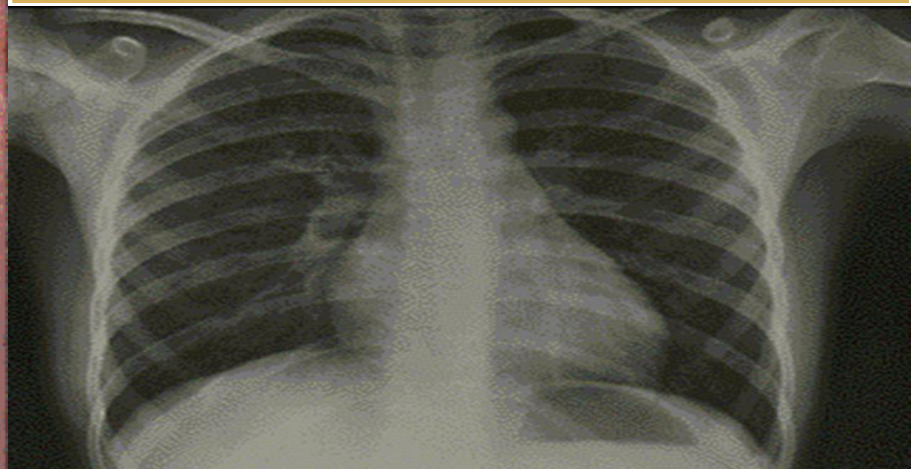
Raised erythematous lesion



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).

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.**

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**.**

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

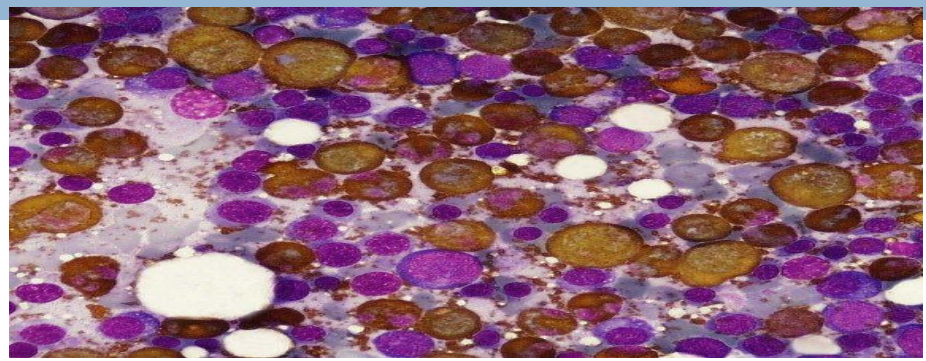
4. **Radiological Examination;** may reveal**,**
   - Lytic bone lesions.
   - Mediastinal widening caused by enlargement of the thymus &/or mediastinal LN enlargement (seen in T-ALL).

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

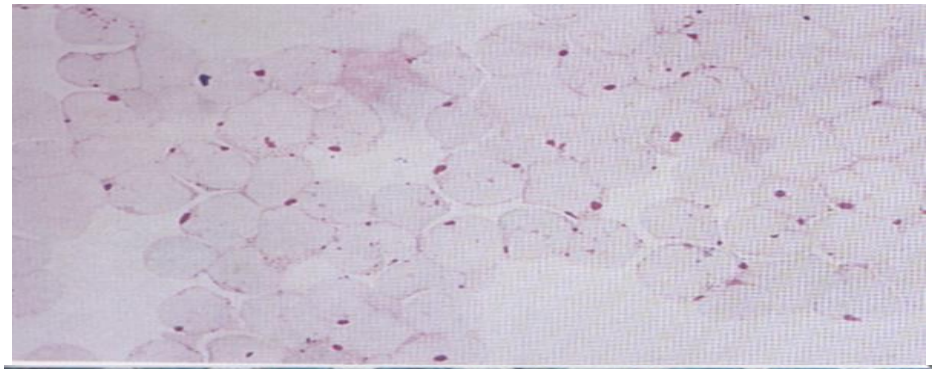
   CSF may show that the cerebrospinal fluid contains leukemic cells and indicates CNS involvement.

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

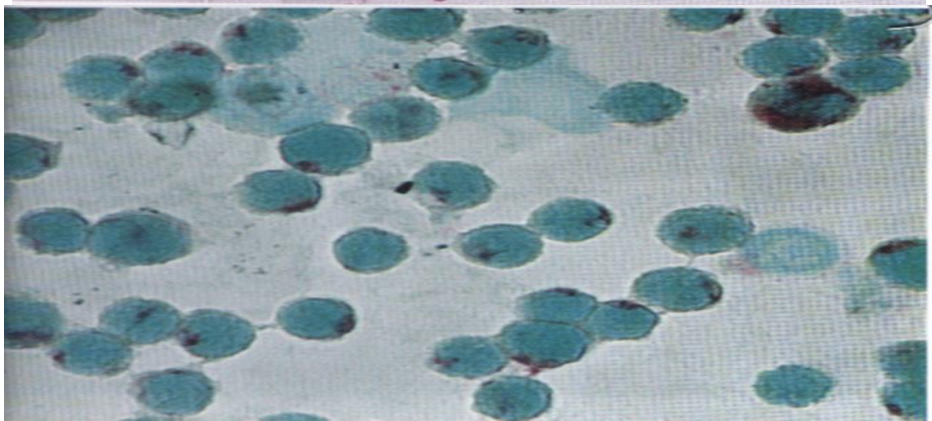
- Peroxidase :-
  - negative ALL
  - positive AML



- 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**.**

8. **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.

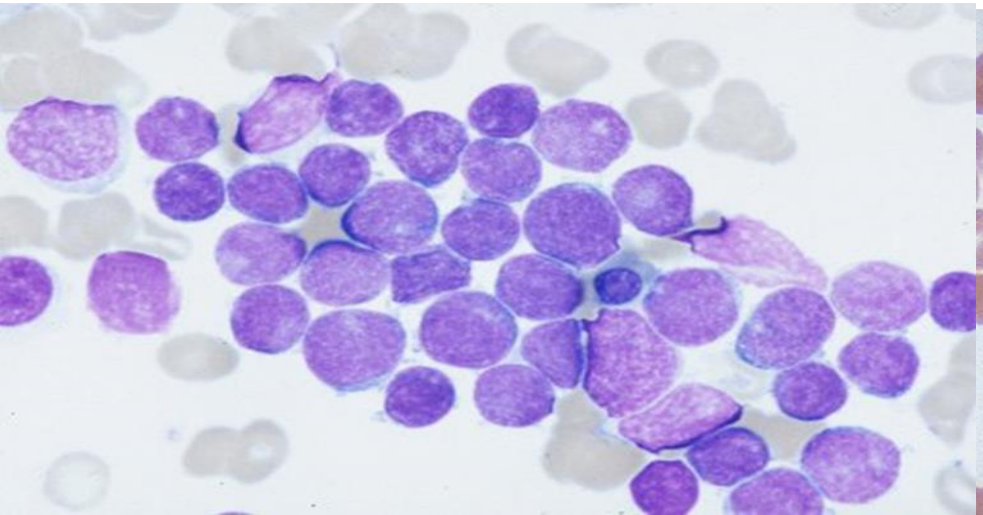
CLASSIFICATION is based on:

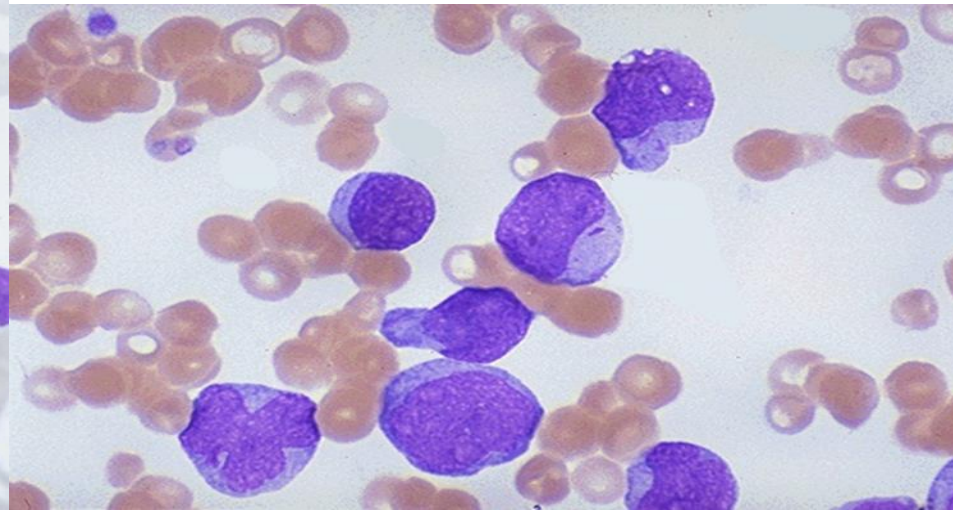
1. **Morphology of blasts.**
2. **Cytochemistry: SBB, PAS, MPO, …etc.**
3. **Immunophenotyping (by flowcytometry)**
4. **Genetic analysis includes : Cytogenetic techniques and Molecular genetic techniques**

- **(FAB)** classification is based mainly on morphology of the blasts, and on use of special stains (cytochemistry) and limited use of monoclonal markers in special situations (immunophenotyping).

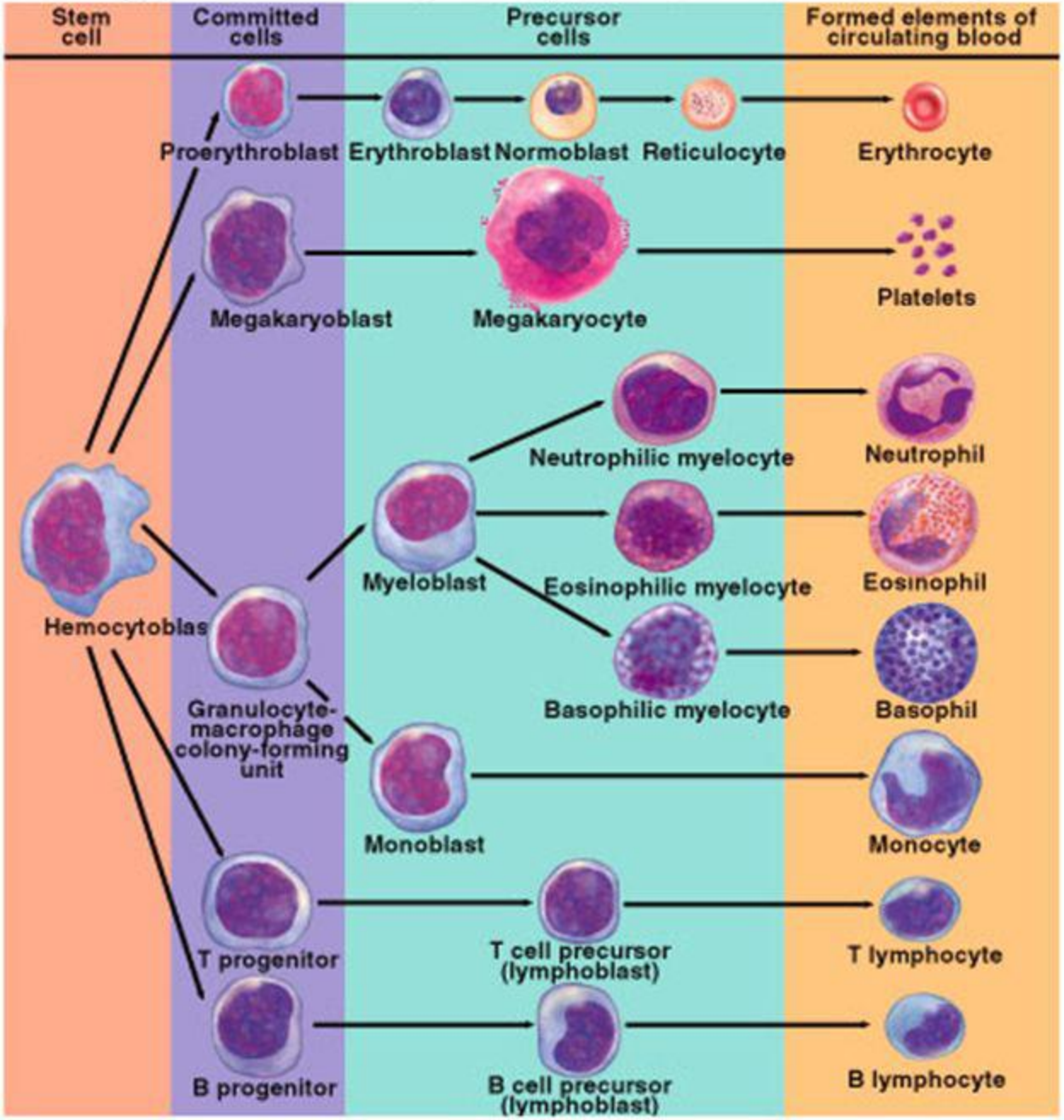
Differentiated AML from ALL

- **ALL(Lymphoblast)**
  - **Blast size** :small
  - **Cytoplasm**: Scant
  - **Chromatin**: Dense
  - **Nucleoli** :Indistinct
  - **Auer-rods**: Never present
- **AML (Myeloblast**
  - Large
  - Moderate
  - Fine, Lacy
  - Prominent
  - Present in 50%





Hemopoiesis



Acute myeloid leukemia

- four times more common than acute lymphoblastic leukemia (ALL) in adults.
- In children, the proportions are reversed, the lymphoblastic variety being more common.
- Considerable heterogeneity between cases, with respect to morphology, immunological phenotype, associated cytogenetic and molecular abnormalities and other.

- **Specific manifestation :**
  - Gum hypertrophy more common in certain subtypes of AML (monocytic AML M4 & M5)
  - Hepatosplenomegaly
  - Skins deposit
  - Lymphadenopathy
  - Renal damage
  - DIC : Disseminated intravascular coagulation, usually accompanied by skin and mucosal hemorrhage due to consumption of platelets and clotting factors, is a frequent presenting feature of acute promyelocytic leukemia

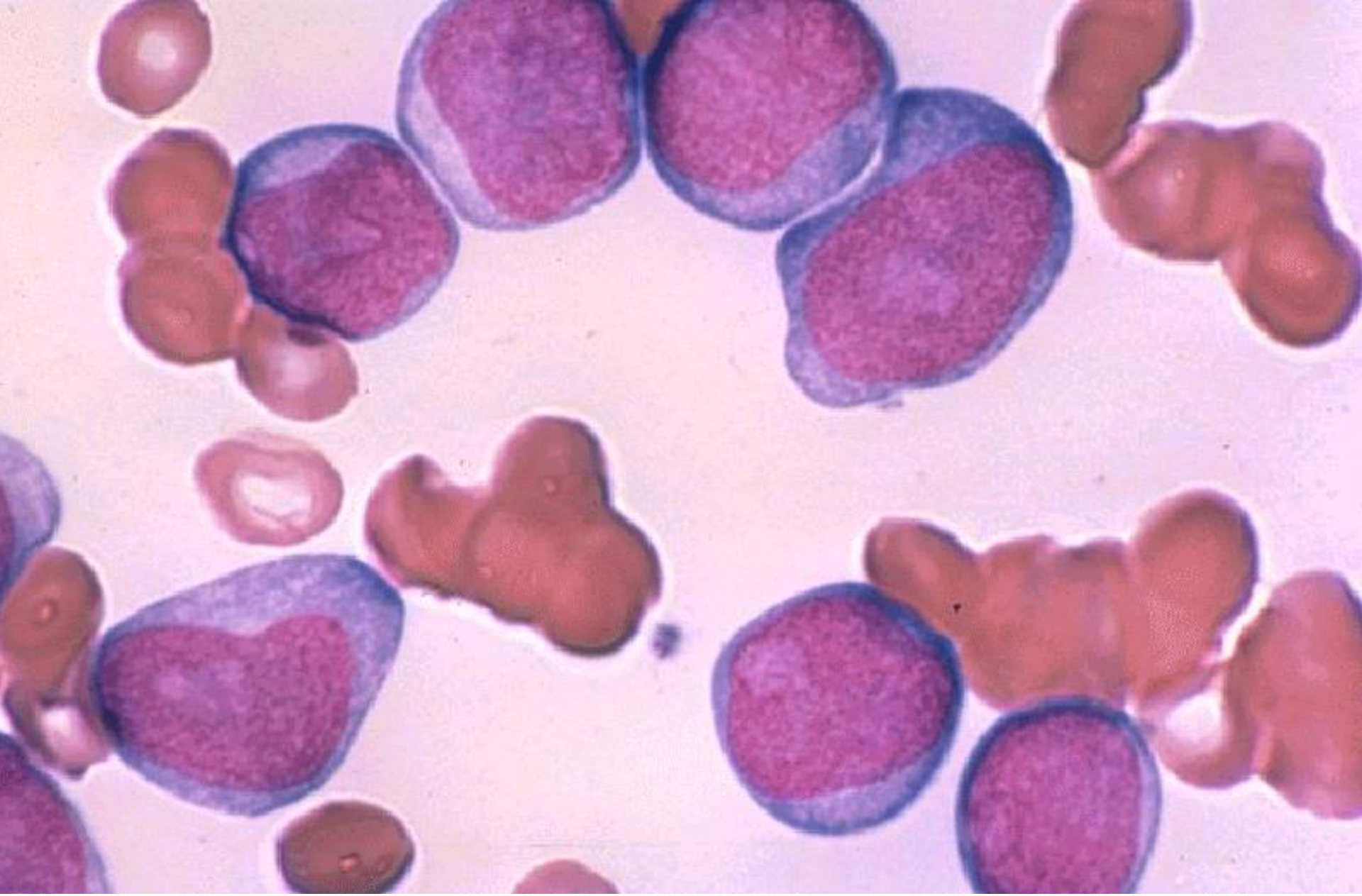
WHO Classification of AML

Acute myeloid leukemia (AML) and related neoplasms

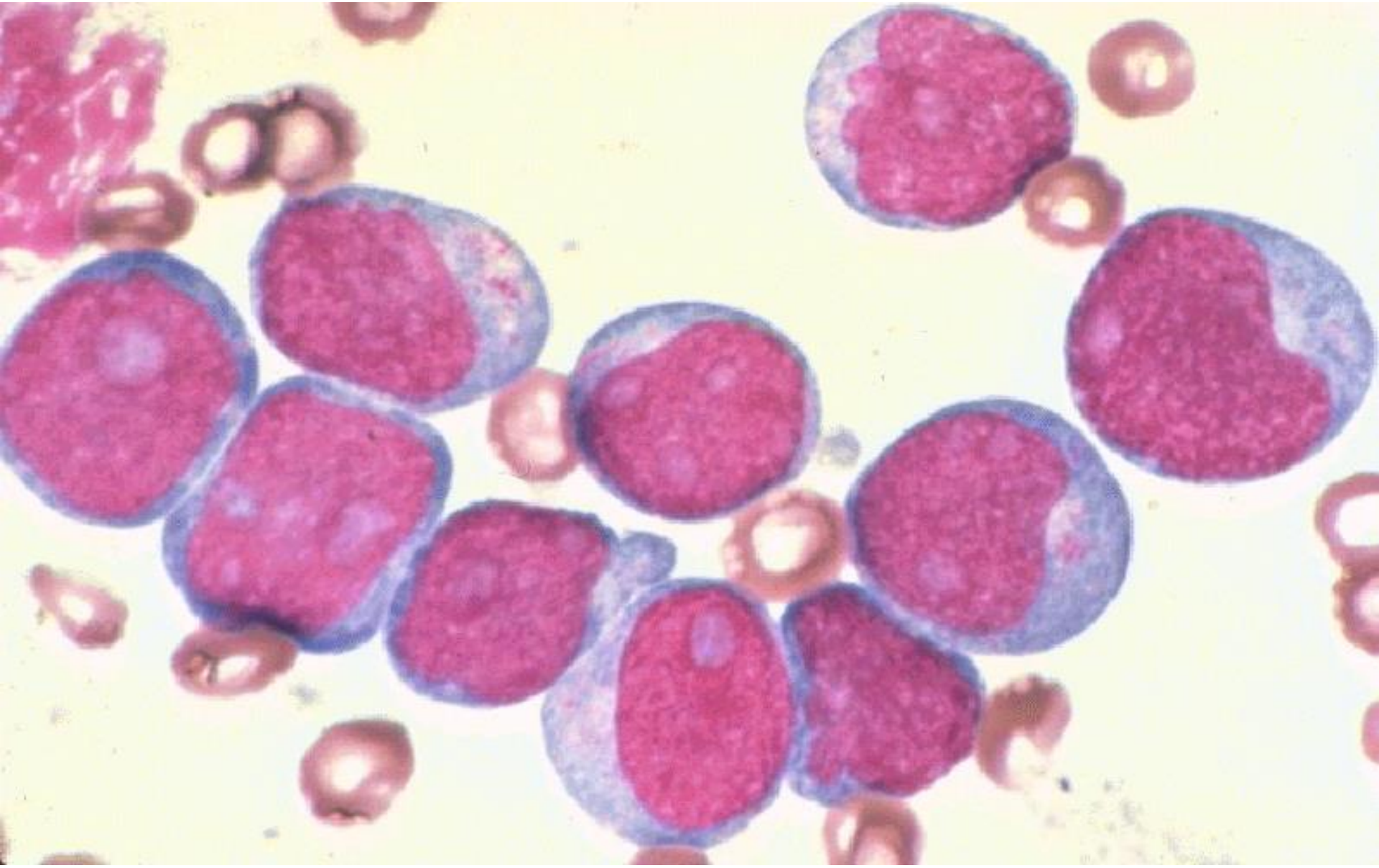
- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
  - APL with *PML-RARA*
  - AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
  - AML with t(6;9)(p23;q34.1);*DEK-NUP214*
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
  - *Provisional entity: AML with BCR-ABL1*
  - AML with mutated *NPM1*
  - AML with biallelic mutations of *CEBPA*
  - *Provisional entity: AML with mutated RUNX1*
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Pure erythroid leukemia
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis

French-American-British (FAB) classification of AML

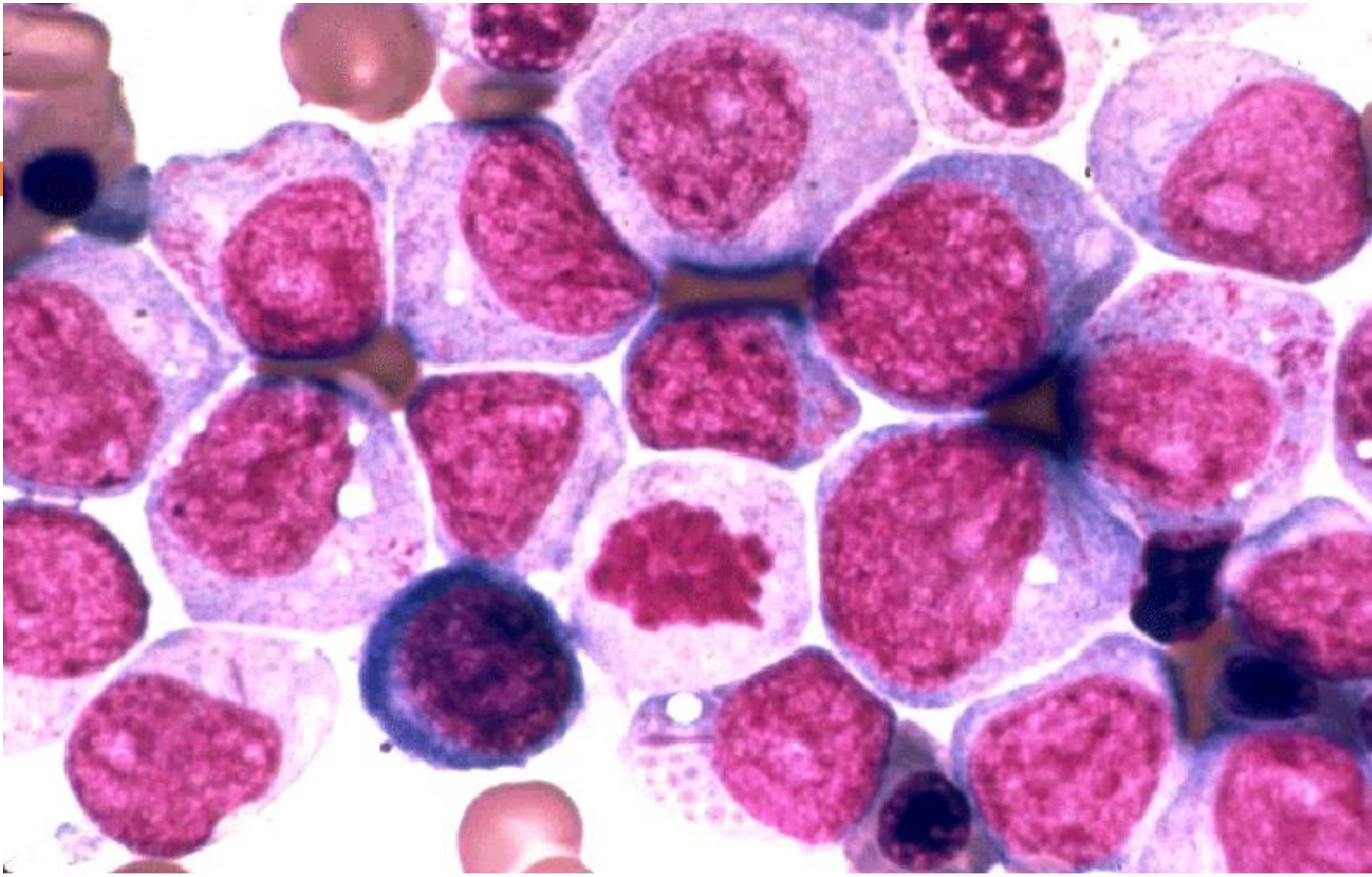
		Cytogenetics
M0	undifferentiated	
M1	Without maturation	
M2	With maturation	t(8; 21)
M3	Acute promyelocytic	t(15; 17)
M4	acute Myelomonocytic leukemia	inv(16)
M5	acute monoblastic (M5a) or monocytic (M5b) leukemia	
M6	acute leukemia with at least 50% erythroblasts in the bone marrow	
M7	Megakaryoblastic	



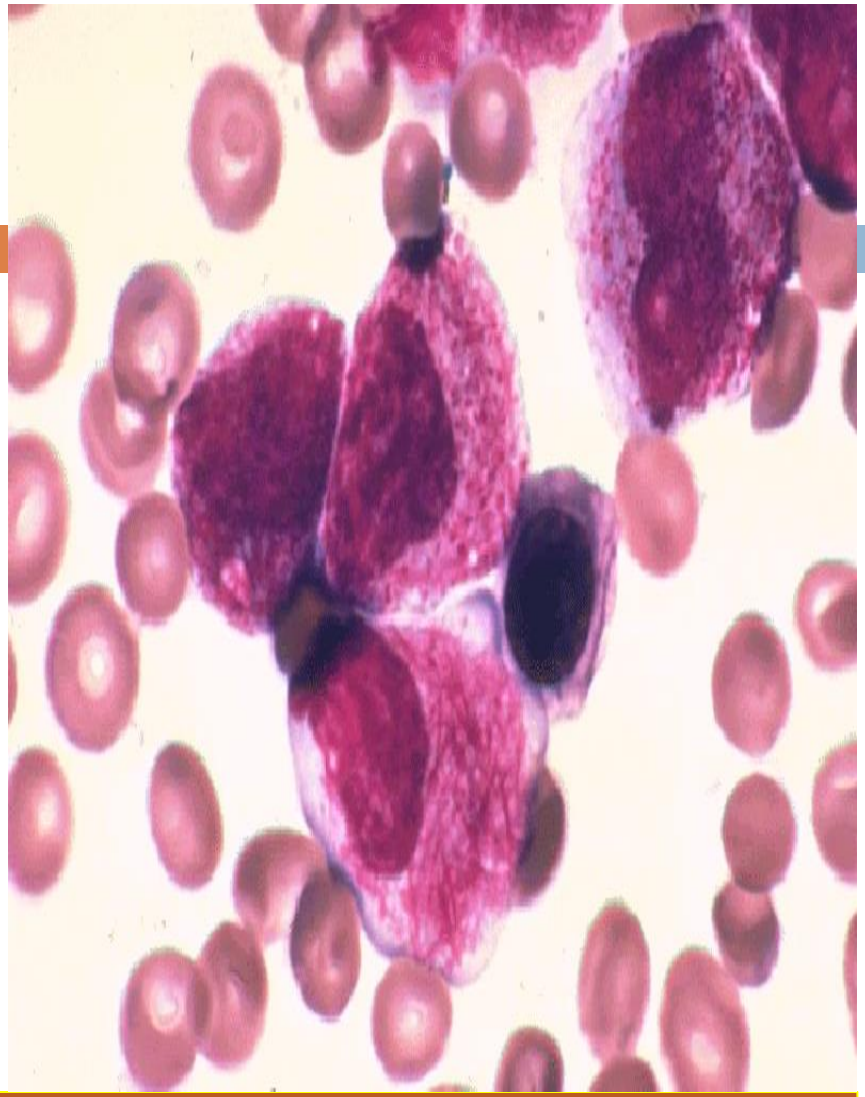
AML M0: with minimal evidence of differentiation



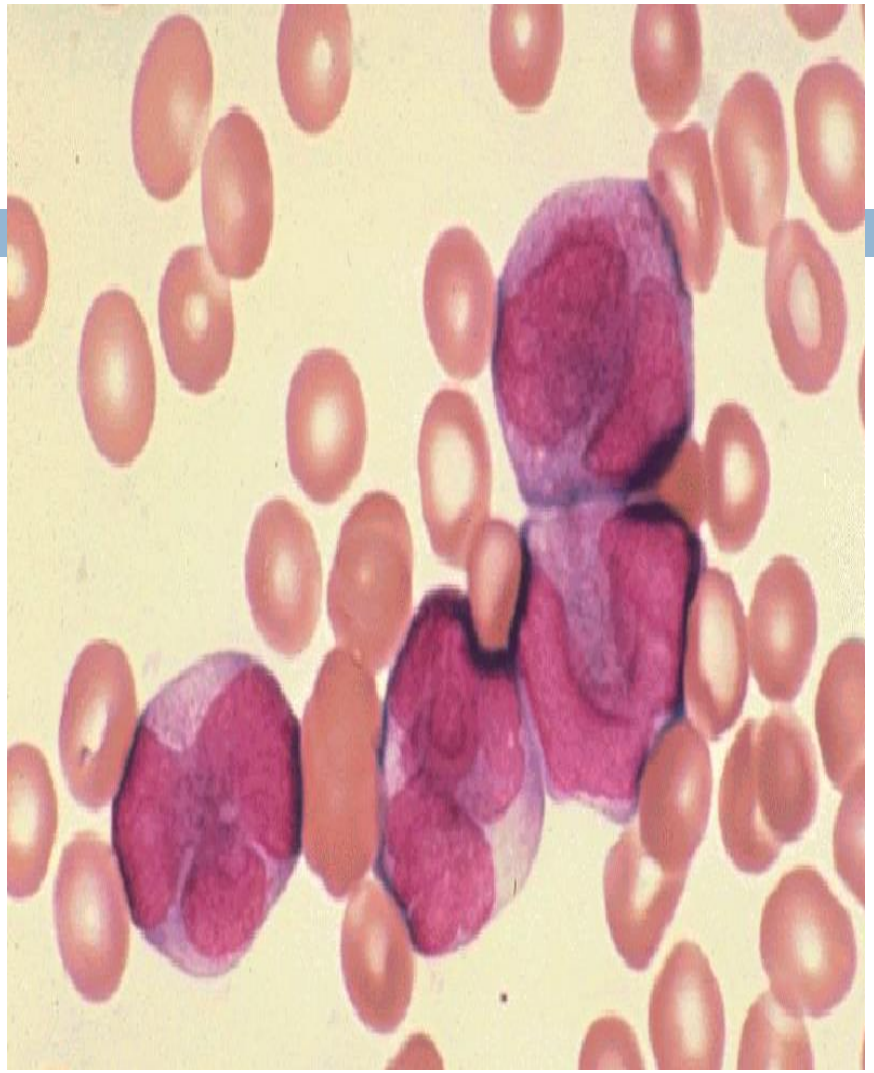
AML M1: without maturation



AML M2: with maturation



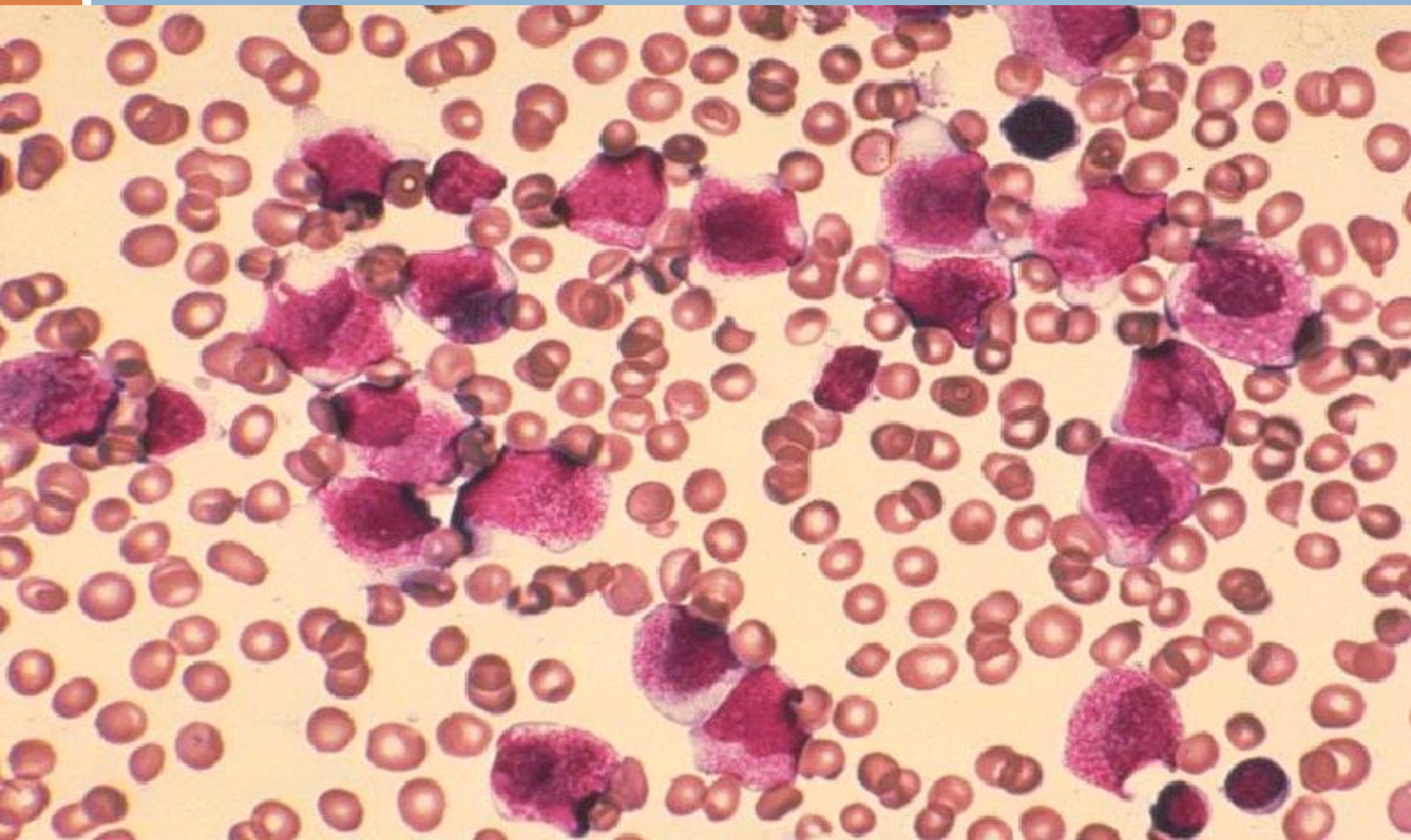
Classical M3 hypergranular

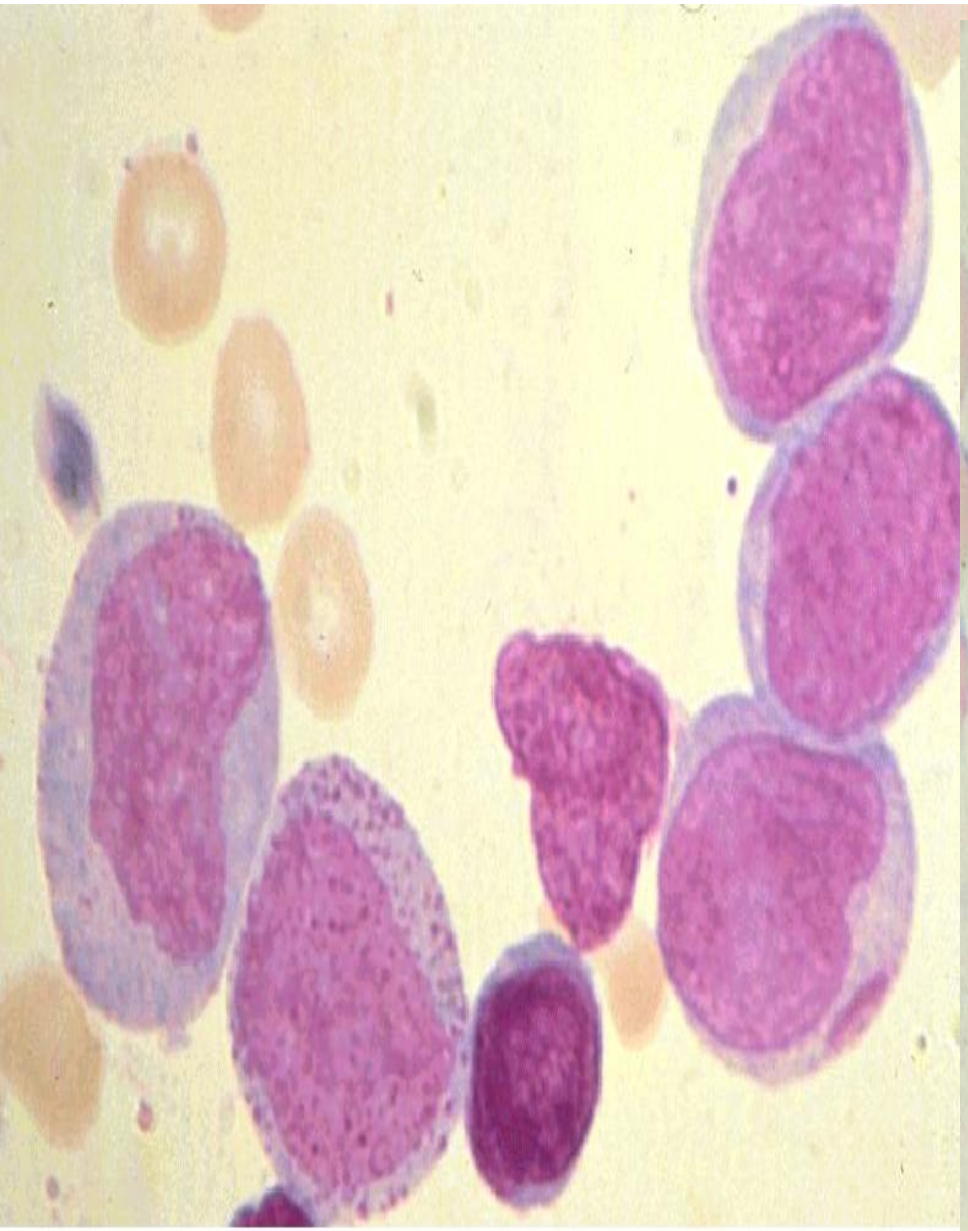


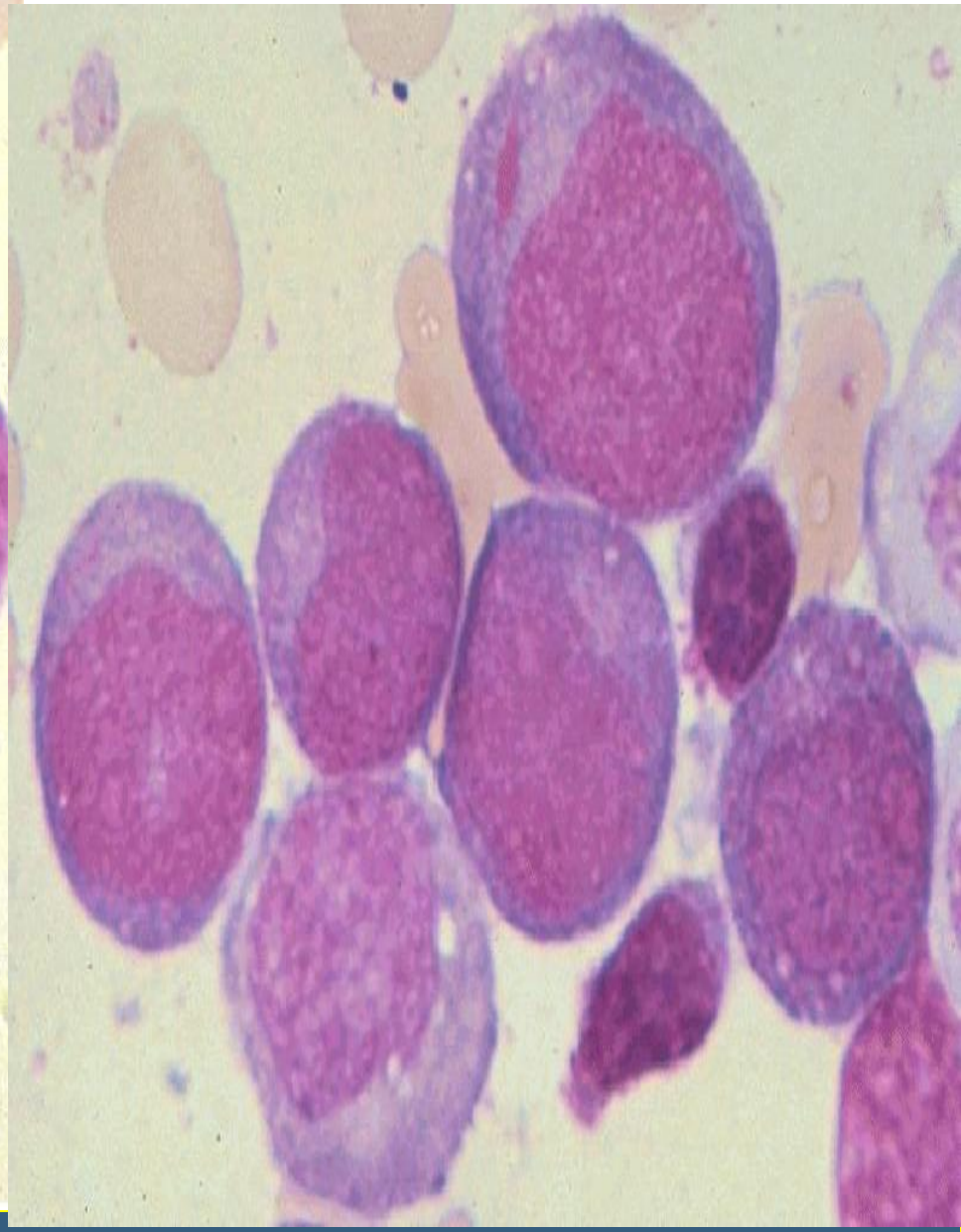
M3 variant hypogranular

AML M3: Acute Promyelocytic Leukemia

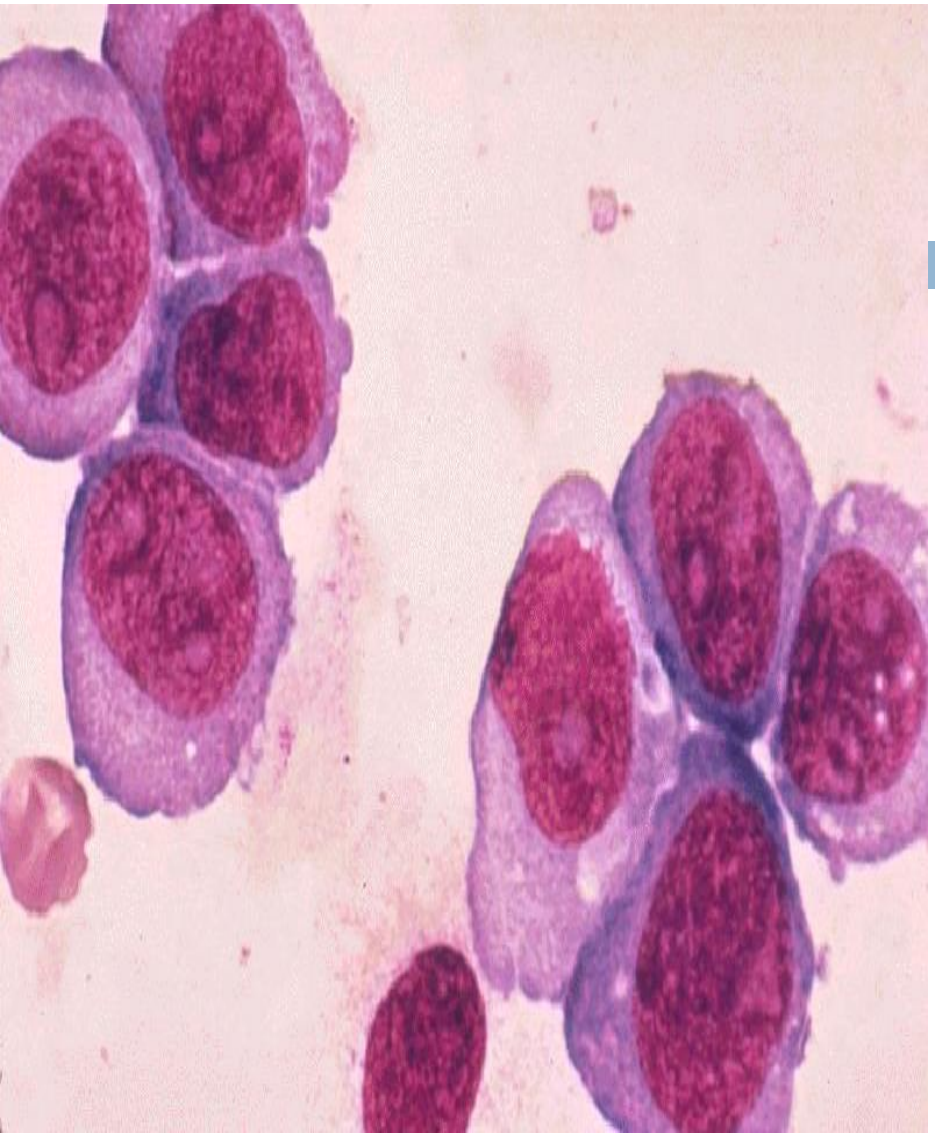
AML M3 (Classical)



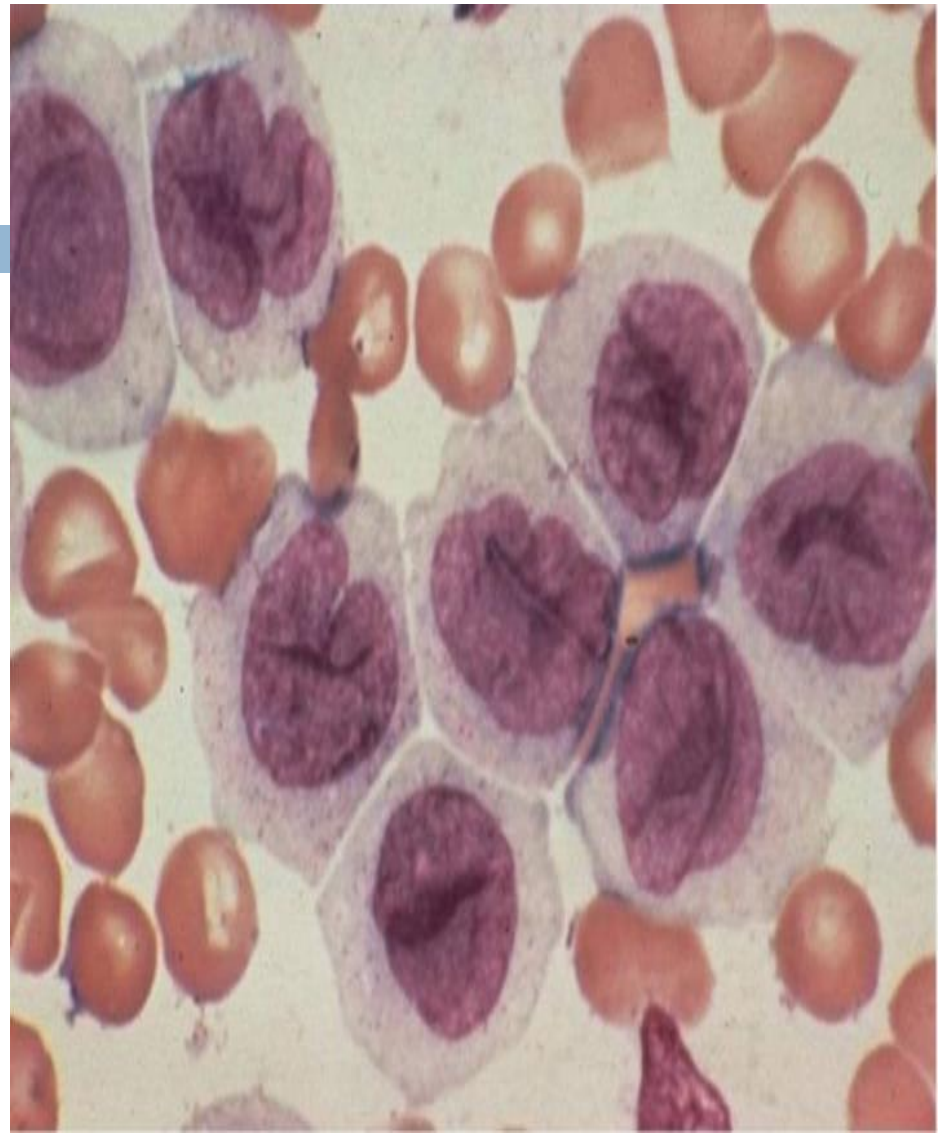




AML M4: acute myelomonocytic leukemia

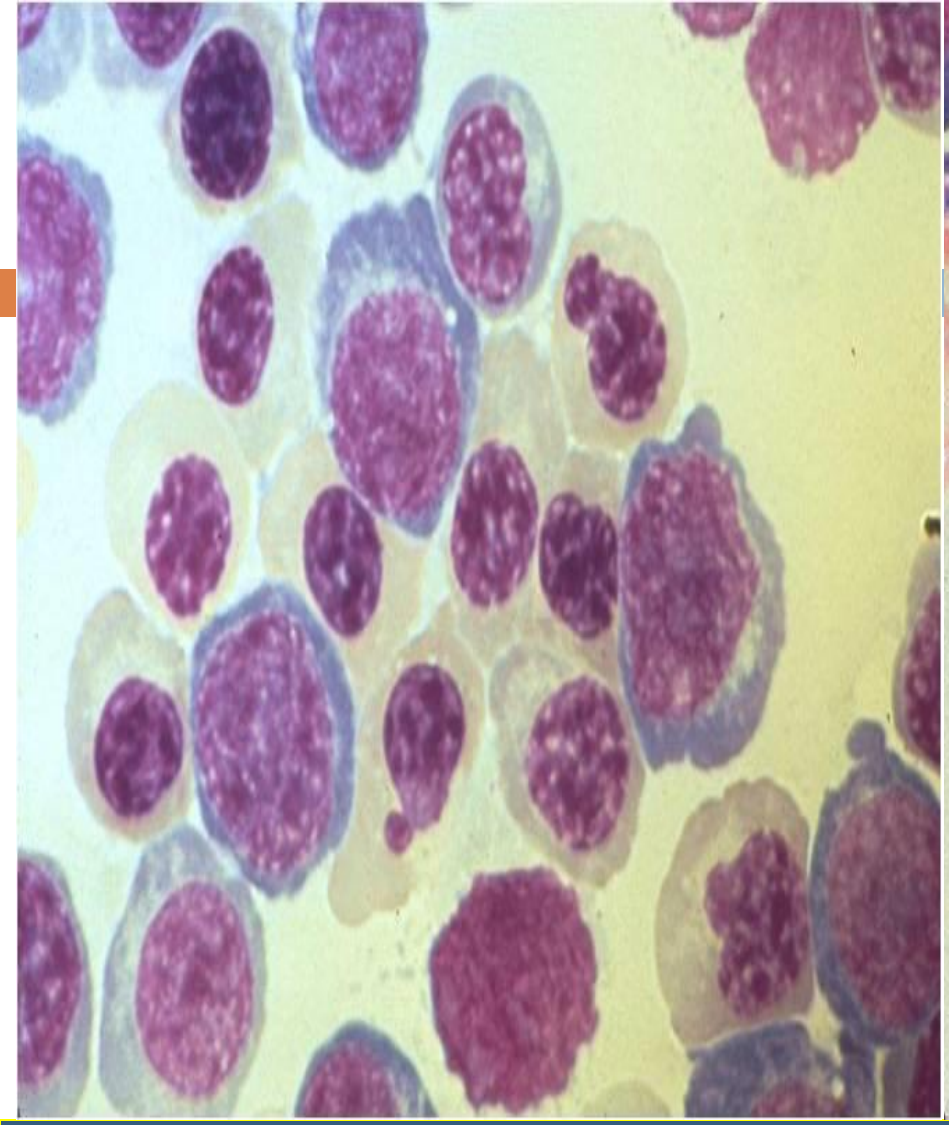


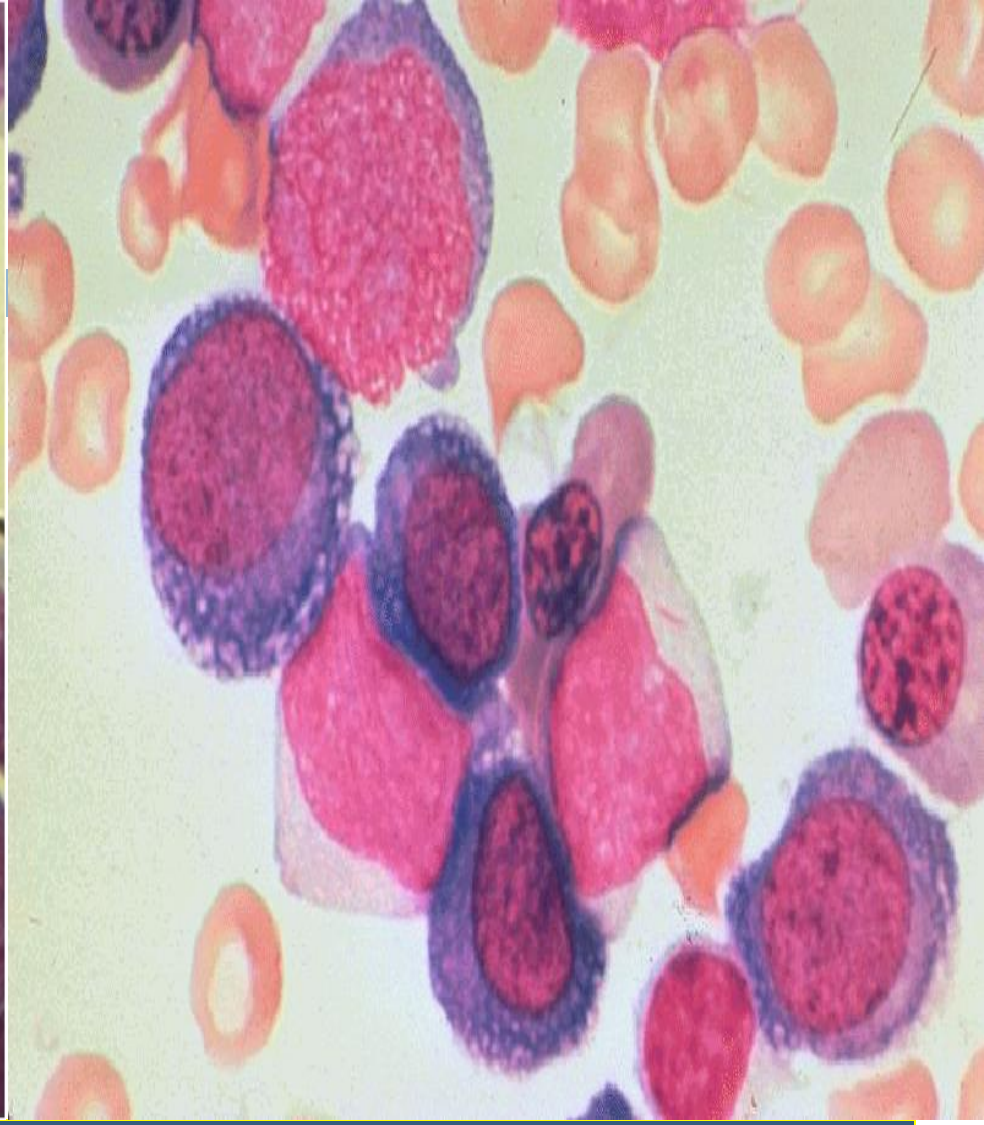
AML M5a



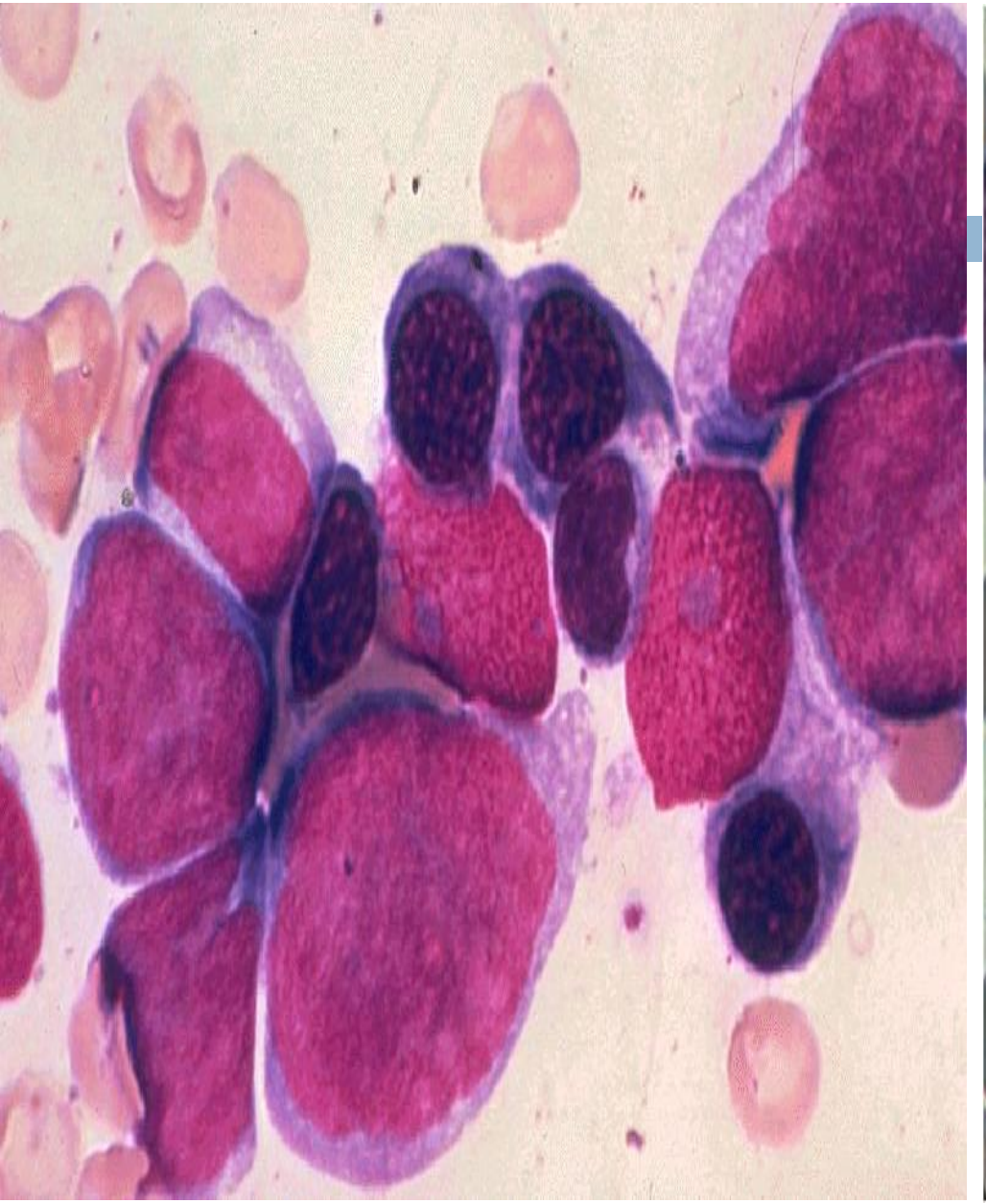
AML M5b

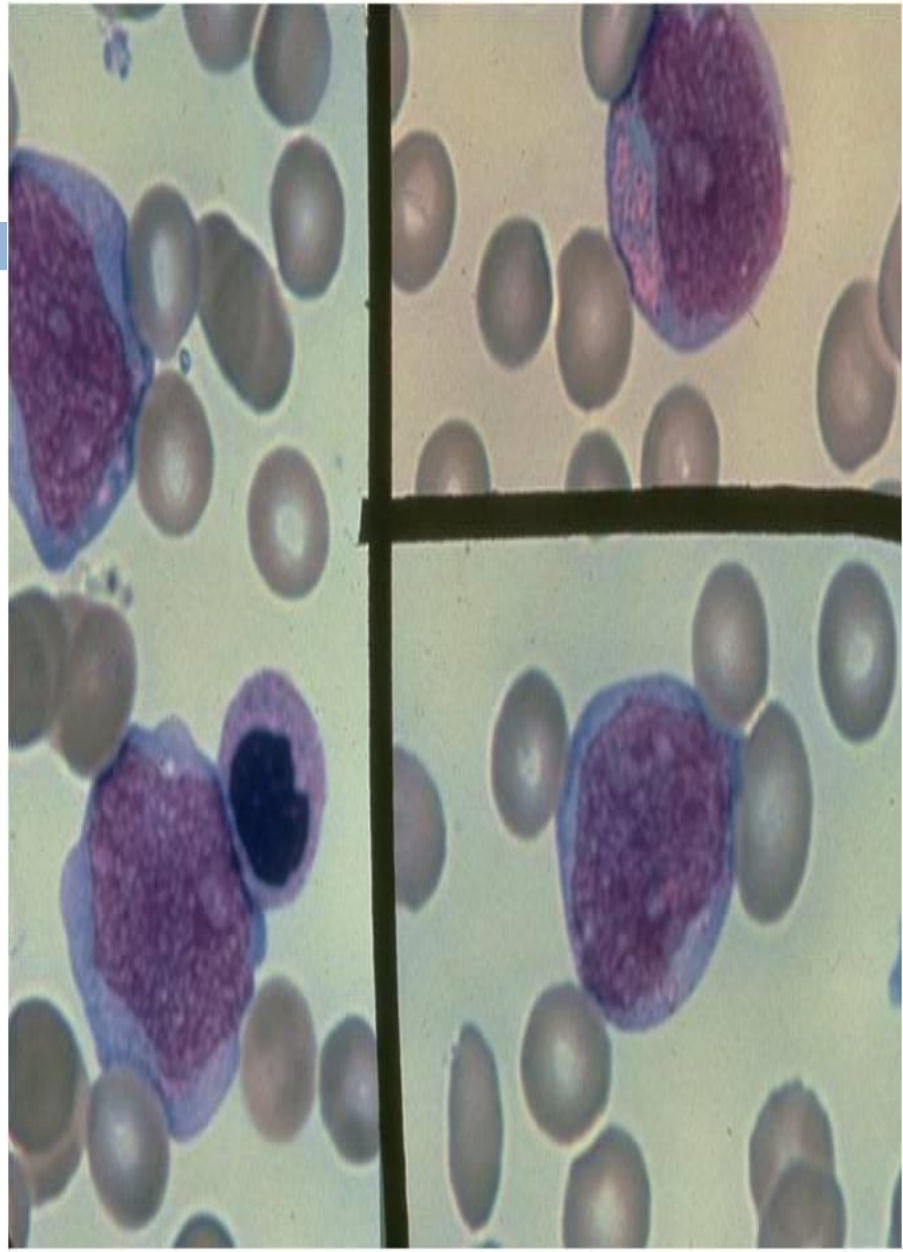
AML M5: acute monoblastic/ monocytic leukemia





AML M6: Acute erythroleukemia





AML M7: Acute megakaryoblastic leukemia

ALL

- Acute lymphoblastic leukemia represents **a clonal proliferation** of immature lymphocyte precursors. The cells may be B-cell precursors (~80 to 85% of cases) or T-cell precursors (~15 to 20% of cases)
- ALL is the **most common malignancy in childhood** and represents ~85% of childhood acute leukemia. ALL also occurs in adults but is uncommon (~15% of adult acute leukemia).
- The highest incidence of ALL is **between 1 and 5 years** of age. There is a slight male predominance.
- There is a marked increase in risk of ALL in children with **trisomy 21 (Down syndrome**) and following exposure to ionizing radiation.

- **Specific manifestation** with Acute lymphoblastic leukemia :
  - ✓ bone pain, arthritis
  - ✓ lymphadenopathy
  - ✓ hepatosplenomegaly
  - ✓ mediastinal mass
  - ✓ testicular swelling
  - ✓ meningeal syndrome

2016 WHO classification of ALL

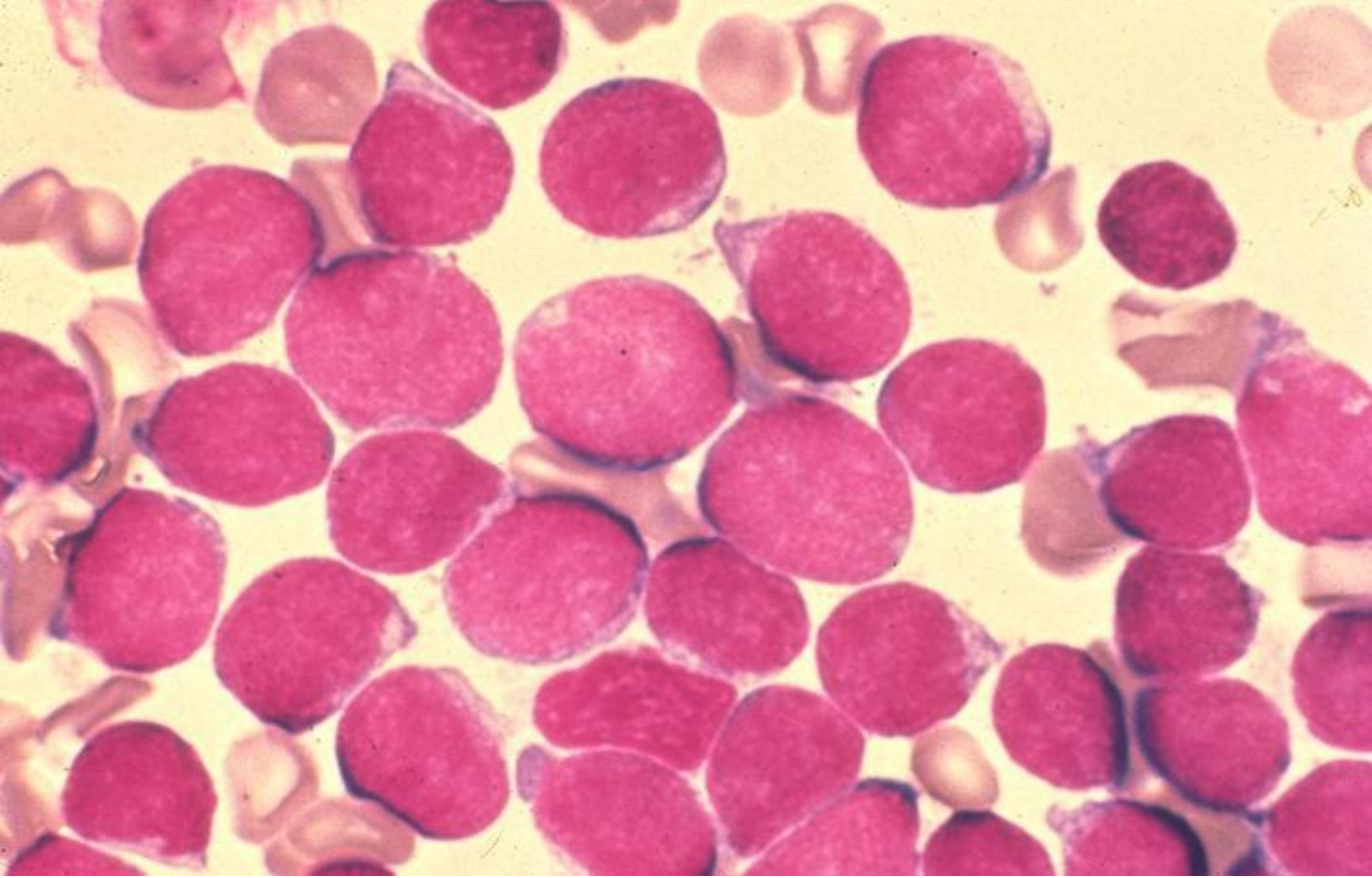
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

1. WHO classification

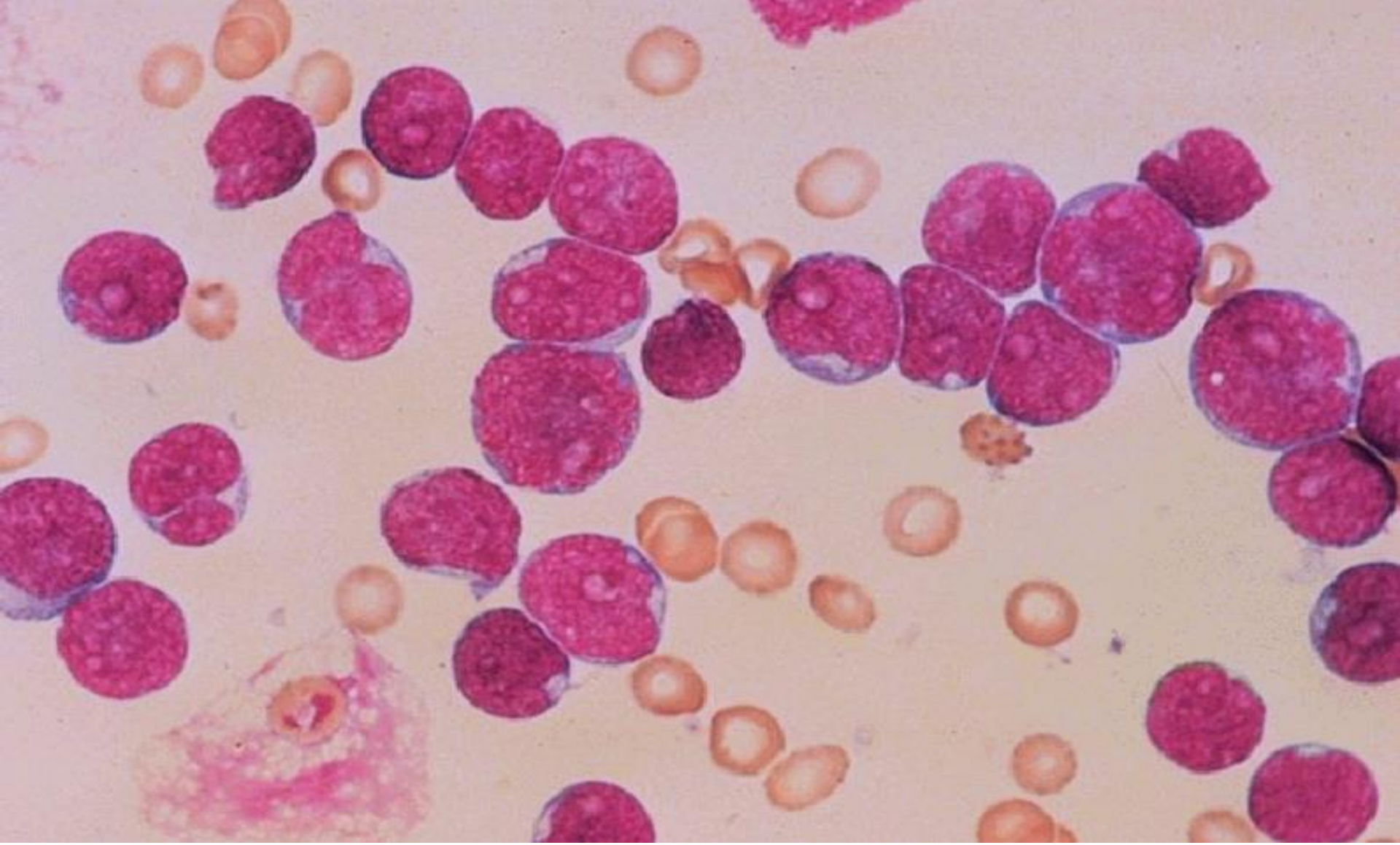
French-American-British (FAB) classification of ALL

L1	blast cells small, uniform high nuclear to cytoplasmic ratio
L2	blast cells larger, heterogeneous; lower nuclear to cytoplasmic ratio
L3	vacuolated blasts, basophilic cytoplasm (usually B-ALL)

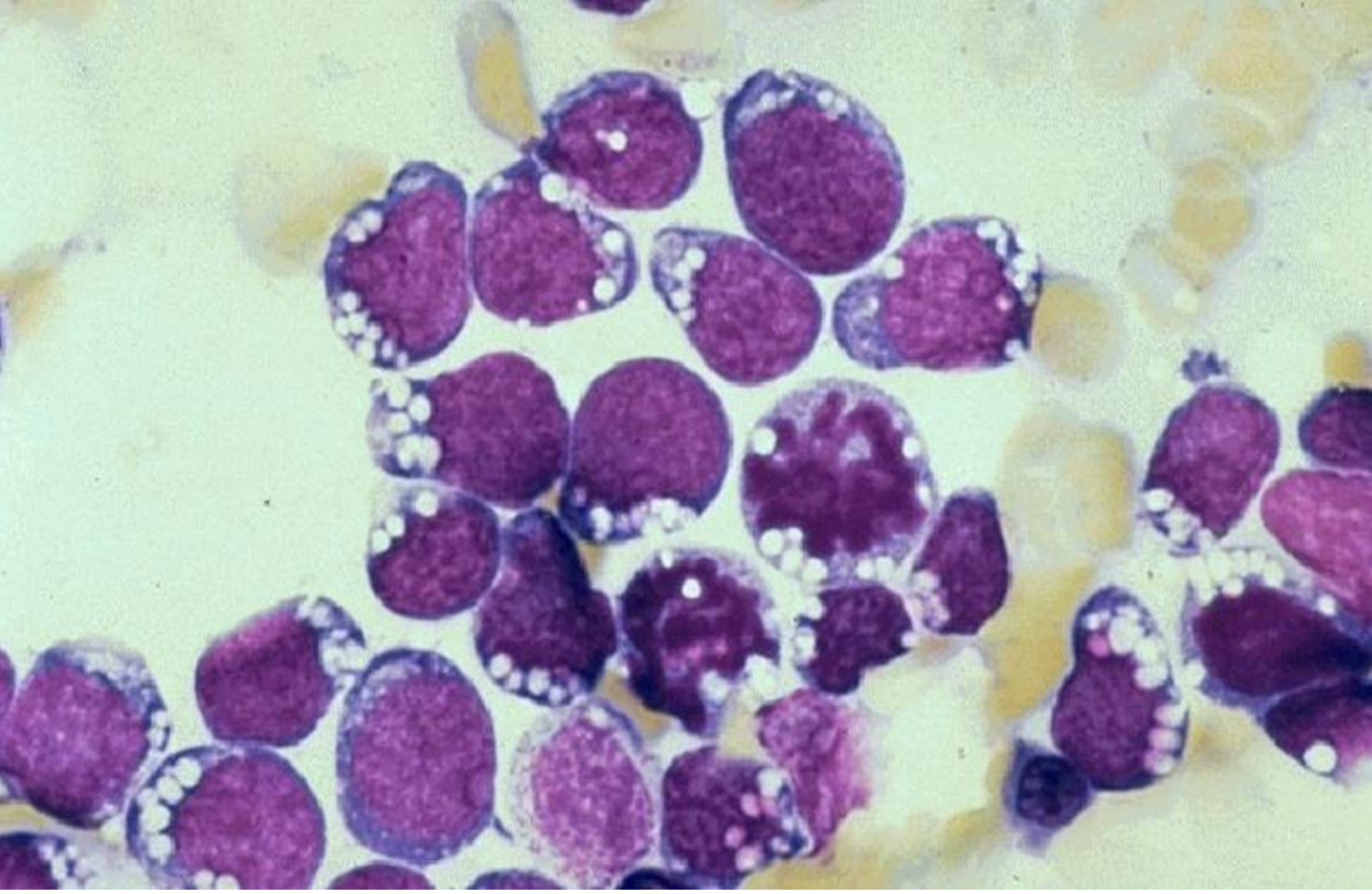
- The FAB classification based strictly on morphology. The L3 type consists of mature B cells (not precursors) and corresponds to blood involvement by Burkitt's lymphoma.



ALL L1 subtype: monomorphic blasts, majority small, high N/C ratio, scanty cytoplasm, small or inconspicuous nucleoli



ALL-L2 subtype: heterogeneous blasts, variable sizes & N/C ratios, with more prominent nucleoli & nuclear membrane irregularities



ALL-L3 subtype: monomorphic large blasts with prominent nucleoli strongly basophilic vacuolated cytoplasm

Management

1. Central venous catheter inserted to :

- facilitate blood product
- adm. of chemotherapy and antibiotics
- frequent blood sampling

2. Blood support :-

- **platelet con.** for bleeding episodes or if the platelet count is <10x109/l with fever .
- **fresh frozen plasma** if the coagulation screen results are abnormal **.**
- **packed red cell** for severe anemia (caution : if white cell count is extremely high).

Management

3. **Prevention and control infection**
   - barrier nursed
   - Intravenous antimicrobial agents if there is a fever or sign of infection
4. **Physiological and social support**

Treatment of acute leukemia

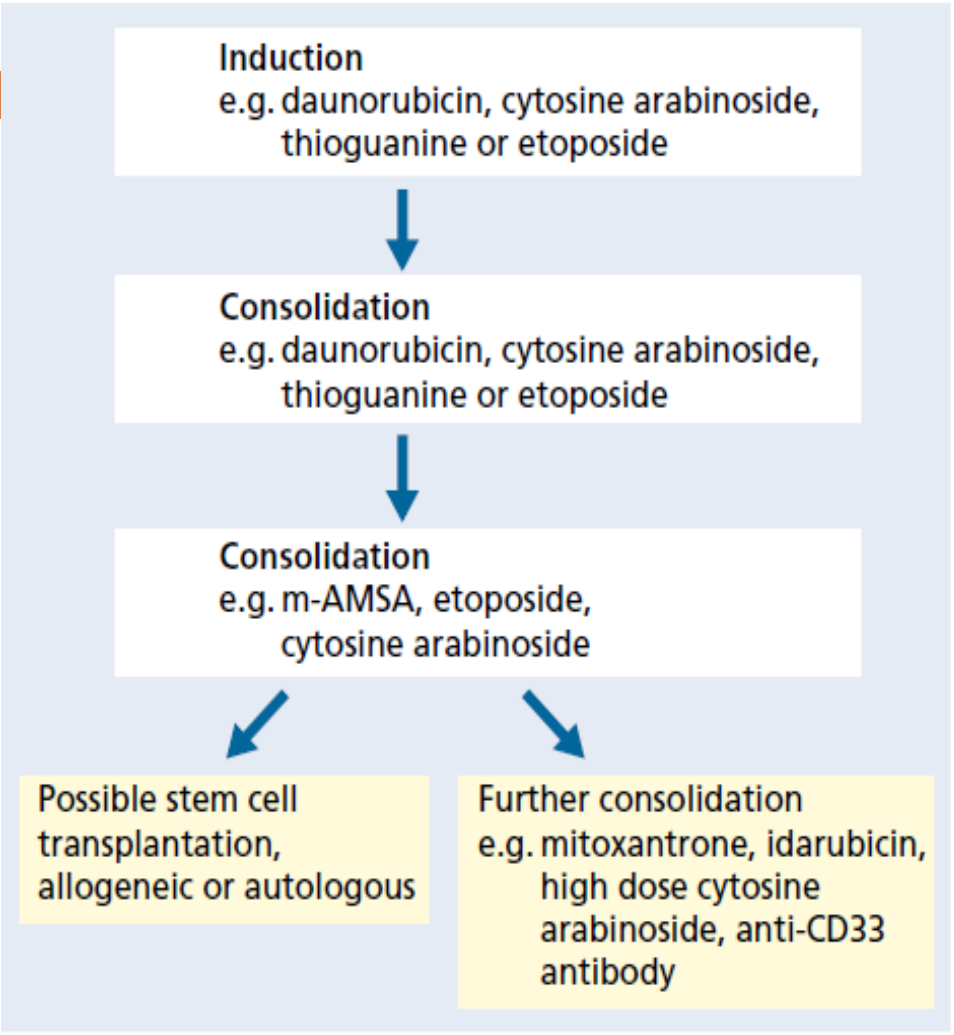
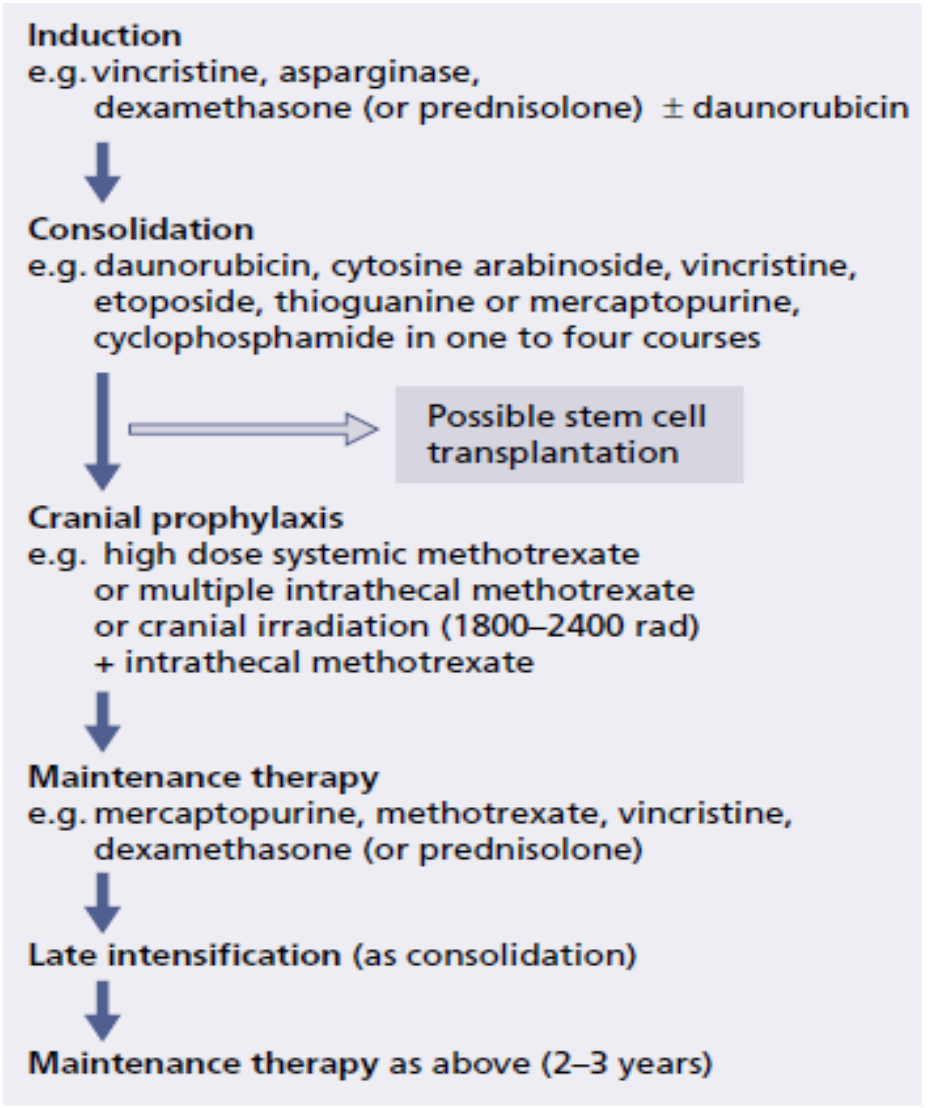


Figure 13.9 Acute myeloid leukaemia: flow chart illustrating typical treatment regimen.



(a)

Figure 17.6 Acute lymphoblastic leukaemia (ALL).

Outcome in adult acute leukemia

Disease/risk	Risk factors	survival
Acute myeloid leukaemia		
Good risk	Promyelocytic leukaemia t(15;17) t(8;21) inv 16 or t(16;16)	76%
Poor risk	Cytogenetic abnormalities −5, −7, del 5q, abn(3q), complex (> 5)	21%
Intermediate risk	AML with none of the above	48%
Acute lymphoblastic leukaemia		
Poor risk	Philadelphia chromosome High white count > 100×10^9/L Abnormal short arm of chromosome 11 t(1;19)	20%
Standard	ALL with none of the above	37%


Thank you!