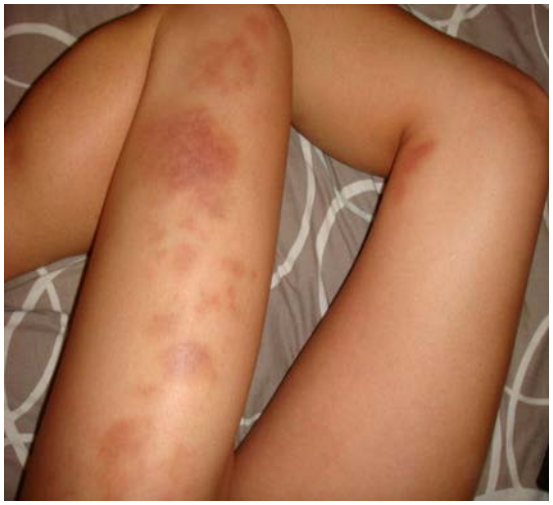
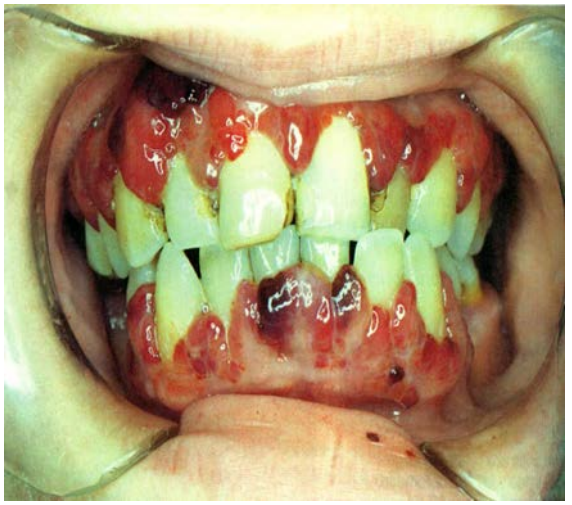
MS.4/ 1.Nov/*2015*.
Acute Leukemia: AML

Abdallah Abbadi

Case 9: Acute Leukemia

29 yr old lady complains of fever and painful gums for 1 week. She developed easy bruising and hemorrhagic spots on her trunk and limbs.





Physical findings

Spleen ++.Gum&

Skin shown.

Fever 40

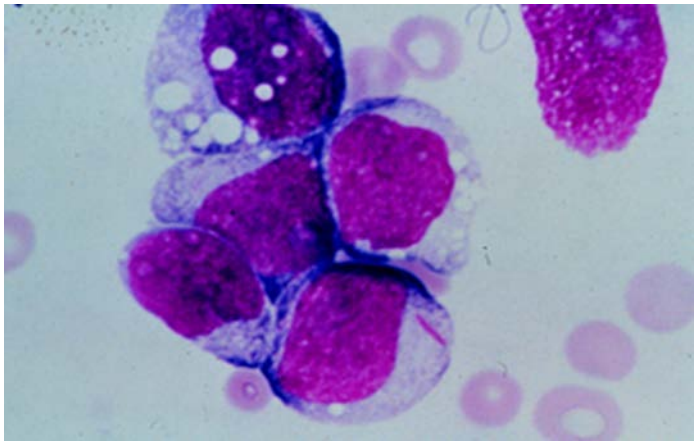
BP 100/70 P 102

Hb 9, WBC 54K

Blasts 80%, Plt 24K

PT 18/13, PTT 40/32,

Urine: RBC +3, WBC +++, Bacteria +++. Bld culture + E.Coli.



Common manifestations of acute leukemia

1-Manifestations of BM replacement

Anemia

Thrombocytopenia

Neutropenia

2-Infiltration of extra BM tissues:

LN, Gums, skin, CNS, others

3-Release of granules/ metabolites:

DIC/ gout, ARF

4-Hyperviscosity

AML- immunocytology

FAB	Immunological markers
M0	HLA-DR, CD33, MPO
M1	HLA-DR, CD13, CD33, MPO
M2	HLA-DR, CD13, CD33, CD15, CD34, MPO
M3	HLA-DR, CD33, CD15, MPO
M4	HLA-DR, CD13, CD14, CD15, CD33
M5	CD13, CD33, CD14, CD15, CD34
M6	CD13, CD33, glicophorin A
M7	CD41, CD61

WHO Classification of AML

- AML with recurrent cytogenic translocations
- AML with multi-lineage dysplasia
- AML and myelodysplasia, therapy related
- AML, not otherwise categorized

Cytogenetics abnormalities in AML

Prognostic Subgroup	Cytogenetic Abnormality
Favorable	- **t(15;17)/PML-RARA** - **t(8;21)** - **inv(16)/t(16;16)**
Intermediate	- Normal karyotype - t(9;11) - Gains of whole chromosomes or loss of Y chromosome
Unfavorable	- **t(6;9)** - **inv(3)/t(3;3)** - **Complex karyotype**

Promyelocytic leukemia M3

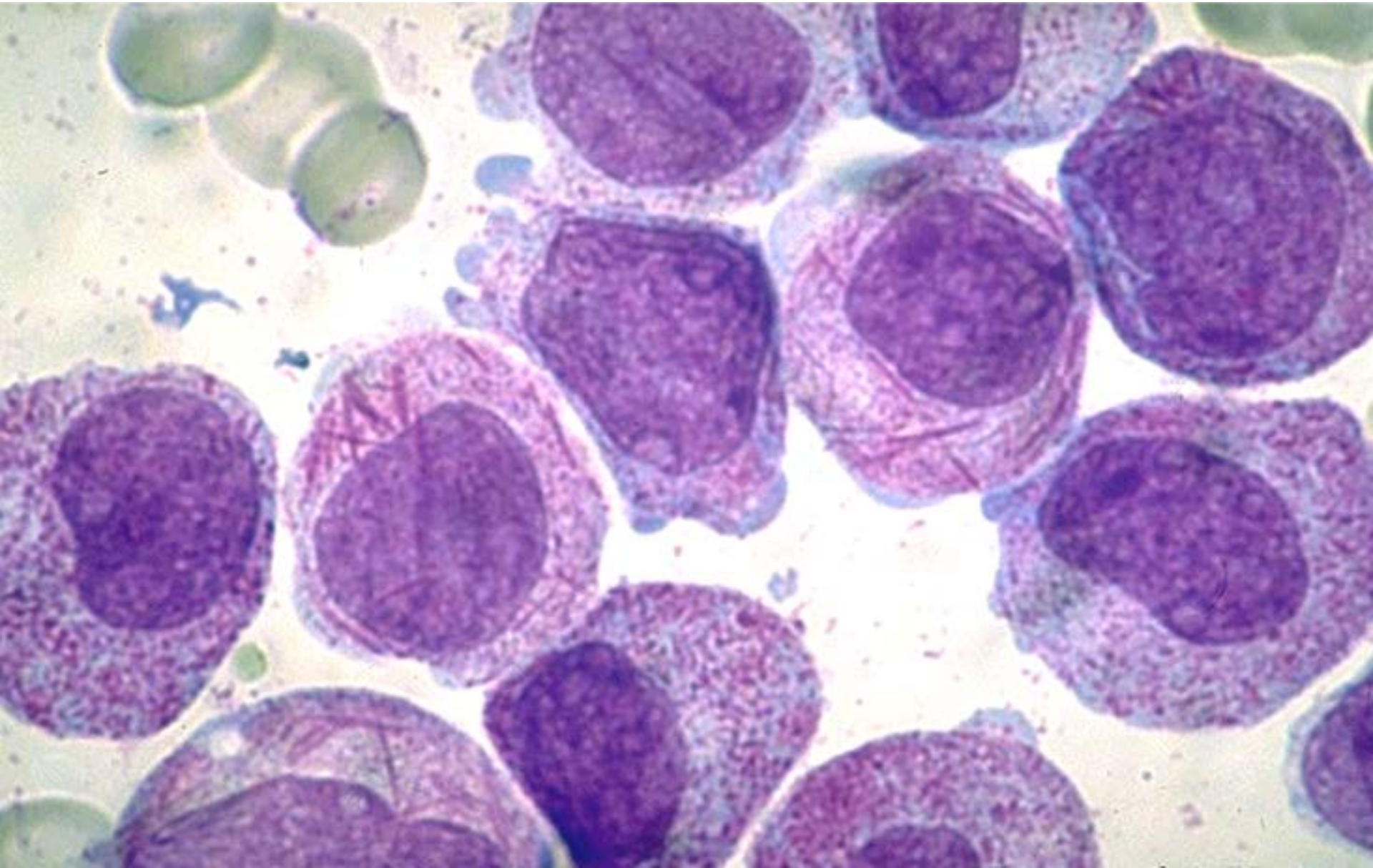
1. Associated with t (15;17) involving the retinoic acid receptor (RAR) gene .
2. Good prognosis category.
3. Commonly associated with **DIC**.

- Prominent Auer rods.

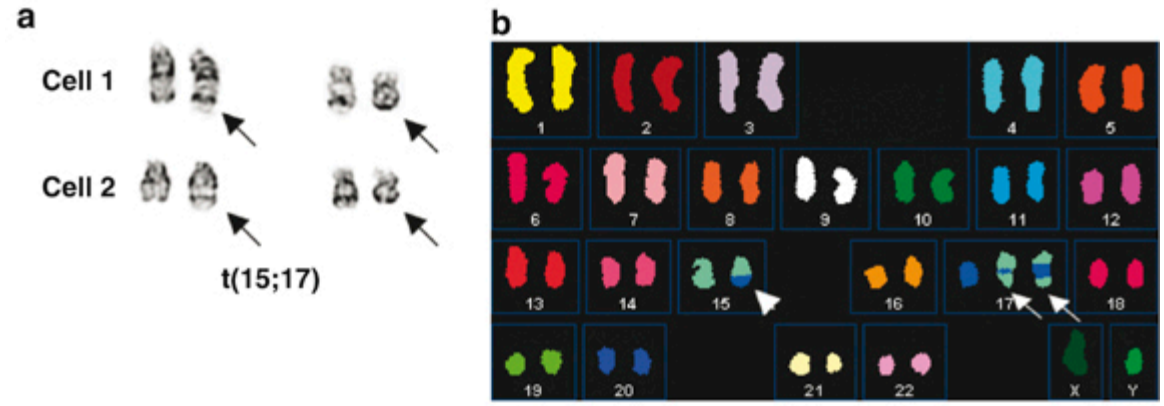
WHO Classification of Acute Myelogenous Leukemia (AML)

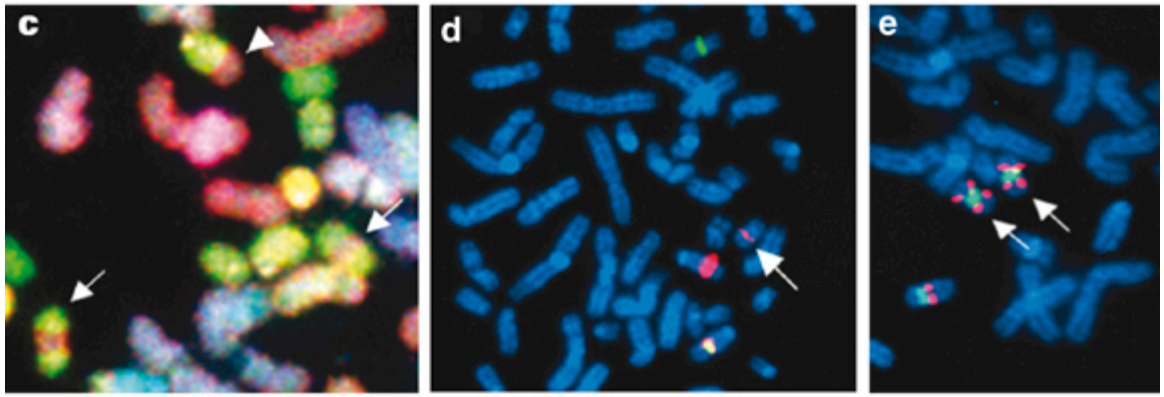
Class	Prognosis
I. AML with Recurrent Chromosomal Translocations	
AML with **t(8;21)**(q22;q22); CBFa/ETO fusion gene	**Favorable**
AML with **inv(16)**(p13;q22); CBFb/MYH11 fusion gene	**Favorable**
AML with **t(15;17)**(q22;q21.1); PML/RARa	**Favorable**
AML with t(11q23;variant)	Poor
II. AML with Multilineage Dysplasia	
With prior **myelodysplastic** syndrome	Very poor
Without prior myelodysplastic syndrome	Poor
III. AML, Therapy-Related	
Alkylating **agent related**	Very poor
Epipodophyllotoxin related	Very poor
IV. AML, Not Otherwise Classified	
Subclasses defined by extent and type of differentiation (M0-M7)	Intermediate

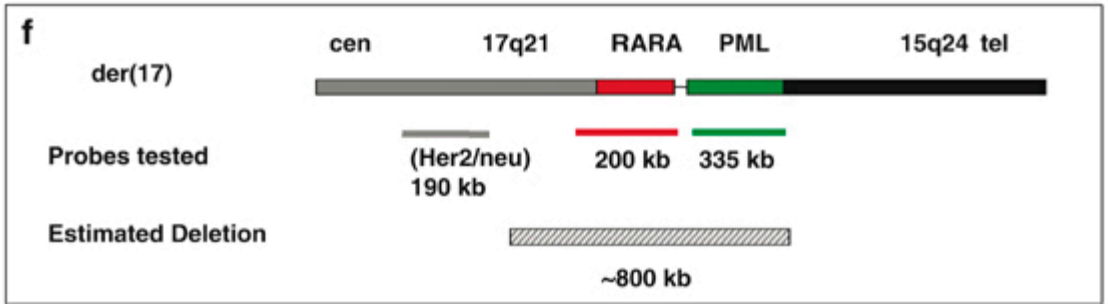
Auer rods in AML



t(15;17) translocation in AML







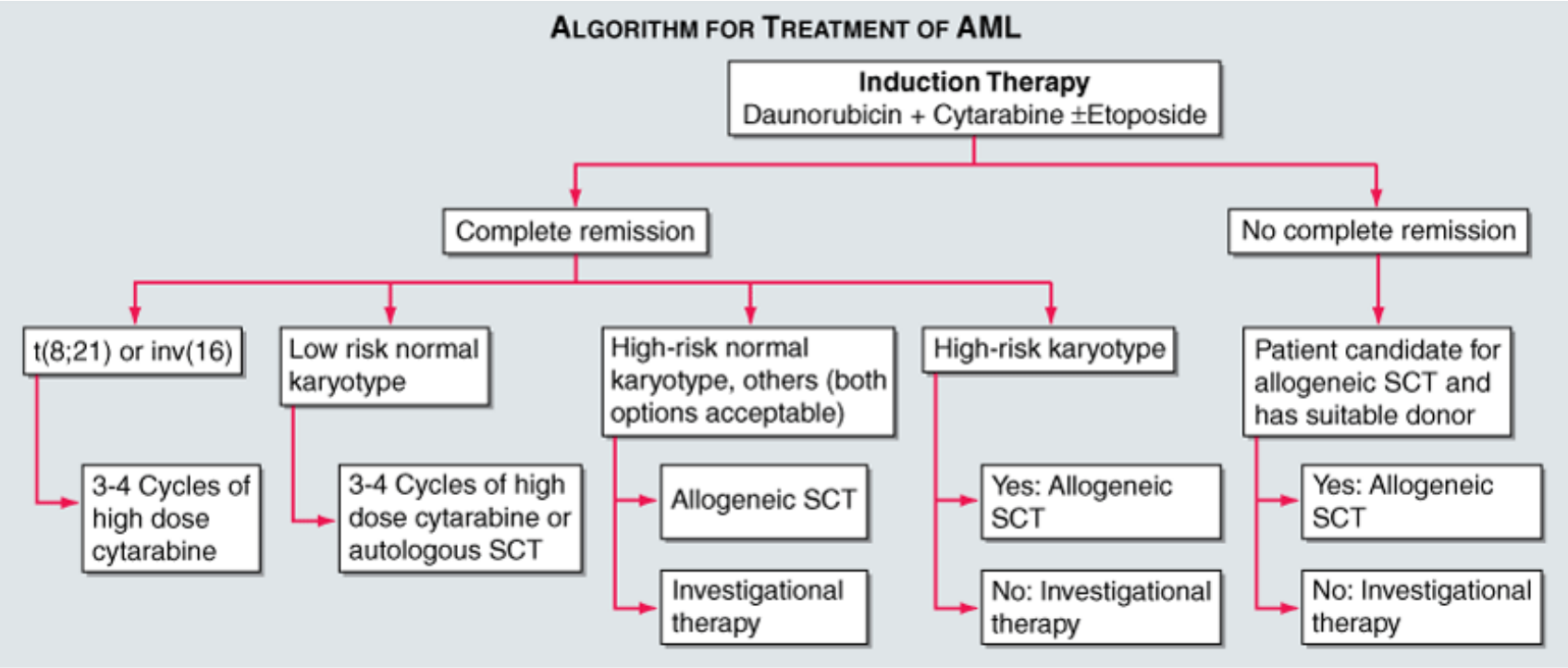
M4: Myelomonocytic leukemia

- With inverted 16 and associated eosinophilia this is a good prognostic category
- Associated with leukemia cutis.
- CNS disease may occur.

M5: Monocytic leukemia

- Commonly associated with skin and soft tissue disease.
- Gingival hyperplasia
- CNS disease may occur.

Treatment



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Treatment aml/m3

- **Tretinoin (all tran retinoic acid)** is an oral drug that induces the differentiation of leukemic cells bearing the **t(15;17)**; it is not effective in other forms of AML.
- APL is responsive to **cytarabine** and **daunorubicin**, but about **10**% of patients treated with these drugs die from **DIC** induced by the release of granule components by dying tumor cells.

ATRA Syndrome

- Tretinoin does not produce DIC but produces another complication called the ***retinoic acid syndrome***.
- *Occurring within the* first 3 weeks of treatment, it is characterized by **fever**, **dyspnea**, **chest pain**, **pulmonary infiltrates**, **pleural** and **pericardial effusions**, and **hypoxia**.
- The syndrome is related to adhesion of differentiated neoplastic cells to the pulmonary vasculature endothelium.
- Glucocorticoids, chemotherapy, and/or supportive measures can be effective.
- The mortality of this syndrome is about **10**%.

Other ATRA side effects

- Nasal stuffiness, dry red skin, transient elevations in serum aminotransferases and bilirubin, and hypertriglyceridemia can occur, but rarely require an alteration in treatment.

Case 9 B

A 19 yr old male has been complaining of fatigue, joint pain for 2 wks. He was admitted because he had a high fever.P/E he looked ill and pale, with Temp 40, BP 100/70, p 104, he had generalized LN enlargement, badly infected tonsil. His spleen was enlarged.Hb 9.5g/dl, plts 45k, WBC 90k: blasts 88%, other cells 12%.LDH 1600, Uric acid 13, Ca 7, PO4 5, Creat 3, K, 6.1, PT, PTT,TT, Nml.

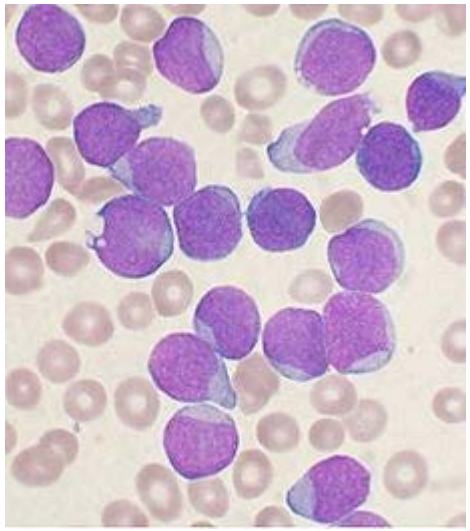
Flow

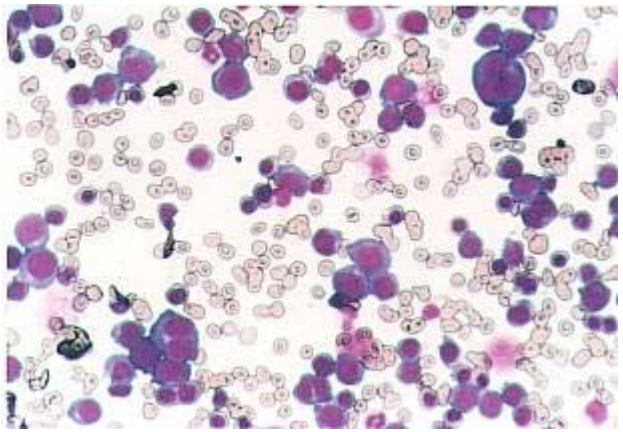
CD19(+),Tdt(+),

CD10(+),CyIg(-),

Karyotyping normal

PAS +++





Common manifestations of acute leukemia

1-Manifestations of BM replacement

Anemia

Thrombocytopenia

Neutropenia

2-Infiltration of extra BM tissues:

LN, Gums, skin, CNS, others

3-Release of granules/ metabolites:

DIC/ gout, ARF

4-Hyperviscosity

Biology of Adult Acute Lymphoblastic Leukemia

Classification:

- Morphologic Features
- Immunophenotyping

Morphologic subtypes of acute lymphoblastic leukemias (FAB classification)

Subtype	Morphology	Occurrence (%)
L1	Small round blasts clumped chromatin	75
L2	Pleomorphic larger blasts clefted nuclei, fine chromatin	20
L3	Large blasts, nucleoli, vacuolated cytoplasm	5

Immunologic classification of acute lymphoblastic leukemias

B- lineage (80%)	Markers
Pro-B	CD19(+),Tdt(+),CD10(-),CyIg(-),
Common	CD19(+),Tdt(+),CD10(+),CyIg(-),
Pre-B	CD19(+),Tdt(+),CD10(+),CyIg(+),SmIg(-)
Mature-B	CD19(+),Tdt(+),CD10(±),CyIg(±),SmIg(+)
T-lineage (20%)	
Pre-T	CD7(+), CD2(-), Tdt(+),
Mature-T	CD7(+), CD2(+), Tdt(+),

Chromosomal/molecular abnormalities with prognostic significance in ALL

Better prognosis

- normal koryotype
- hyperdiploidy

Poor prognosis

- t (8; 14)
- t (4; 11)

Very poor prognosis

- t (9; 22); BCR/ABL (+)

Risk classification in ALL

1. Standard risk
2. High risk
3. Very high risk

High-risk ALL

1. Pre - T
2. Pro - B
3. Age > 35 years,
4. WBC > 30 G/L in B-ALL
   > 100 G/L in T-ALL
5. No remission after 4 weeks of induction therapy

Very high-risk ALL

Chromosome Philadelphia - positive or BCR/ABL (+)

In ALL the choice of treatment-strategy depends on:

1. Risk qualification
2. Immunophenotype of leukemic cells
    - T lineage,
    - early B lineage,
    - mature B lineage,
3. Age and biological condition
4. Goal of treatment

Remission induction therapy in ALL

1. Antineoplastic treatment
   a/Drugs: prednisone, vincristine, asparginase, cyclophosphamide
   duanorubicin/adriablastin/epirubicin,
   cytosine arabinoside,
   b/Treatment duration: 4-8 weeks
   c/ No of courses: 1- 2
2. CNS prophylaxis
3. Supportive care
4. Treatment of complications

Post-remission therapy in standard-risk ALL

1. **Chemotherapy**

   a/. Maintenance therapy: 6-mercaptopurine,

   methotrexate - for 2-3 years.

   b/. Intensification treatment periodically

   repeated: daunorubicin/adriablastin,

   prednisone, vincristine, cyclophosphamide.

2. CNS prophylaxis

Post-remission therapy in high-risk ALL

1. Intensification treatment: amsacrine, mitoxantrone, idarubicine, high dose cytosine arabinoside, high dose methotrexate, high dose cyclophosphamide.
2. Hematopoietic stem cell transplantation
   - high-dose therapy
   - reduced intencity conditioning

Post-remission therapy in very high risk ALL

- High-dose therapy (reduced-intencity ?) + allogeneic stem cell transplantation

Treatment results in ALL

- **Adults**
  - **Complete remission (CR)** **80-85%**
  - **Leukemia-free survival (LFS)** **30-40%**

- **Children**
  - **Complete remission (CR)** **95-99%**
  - **Leukemia-free survival (LFS)** **70-80%**