Acute leukemias

Leukemias

Acute leukemias

- Acute lymphoblastic leukemia (ALL)
- Acute myeloid leukemia (AML)

Chronic leukemias

- Chronic myeloid leukemia (CML)
- Chronic lymphocytic leukemia (CLL)

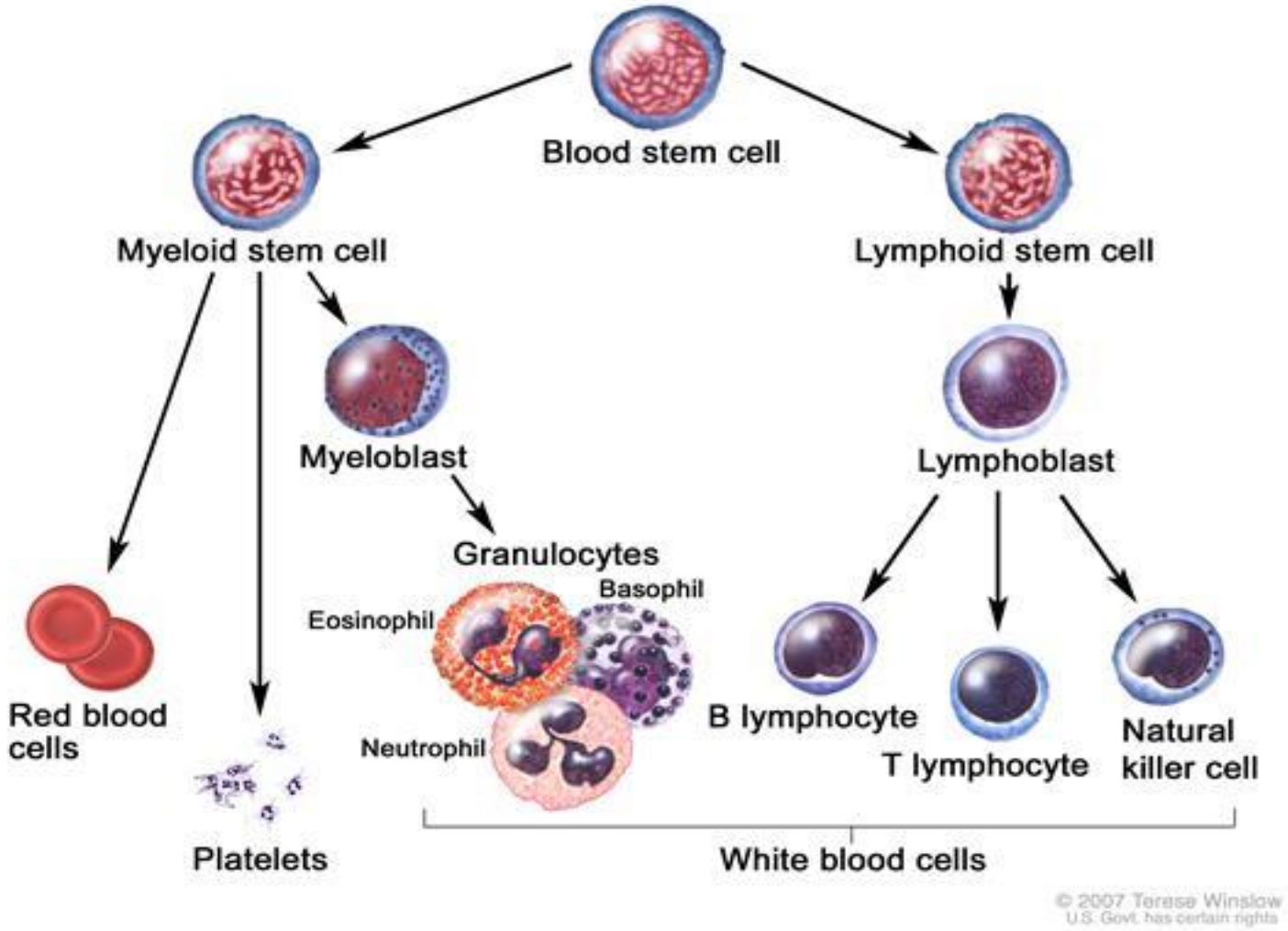
Acute leukemias

- Uncontrolled proliferation of blast (lymphoblast or myeloblast) cells in bone marrow.
- Normally in BM blast cells are < 5% of total cells.
- > 30% blasts (FAB classification) / >20% blasts (WHO classification – recent)

Acute lymphoblastic leukemia

- Clonal proliferation and accumulation of lymphoblasts in blood, bone marrow and other organs
- Disorder originates in single B or T lymphocyte progenitor
- Heterogenous disease with different biological subtypes

HEMATOPOEISIS



Acute lymphoblastic leukemia

- ~ 30% of all childhood malignancies. Most common malignancy.
- Incidence in adults : 20% of acute leukemias
- **ALL five times more common than AML.**
- **~ peak incidence age 2-5 years**
- **Boys > girls**

Acute Leukemia

Pathogenesis:

- **Ionizing radiation**
- **Alkylating agents**
- **Benzene**
- **Genetic disorders→Down's syndrome,ataxia Telengiectasia**

FAB classification

- French-American-British CFN – 1976
- Based on cell morphology & cell cytochemistry .

Cytochemistry

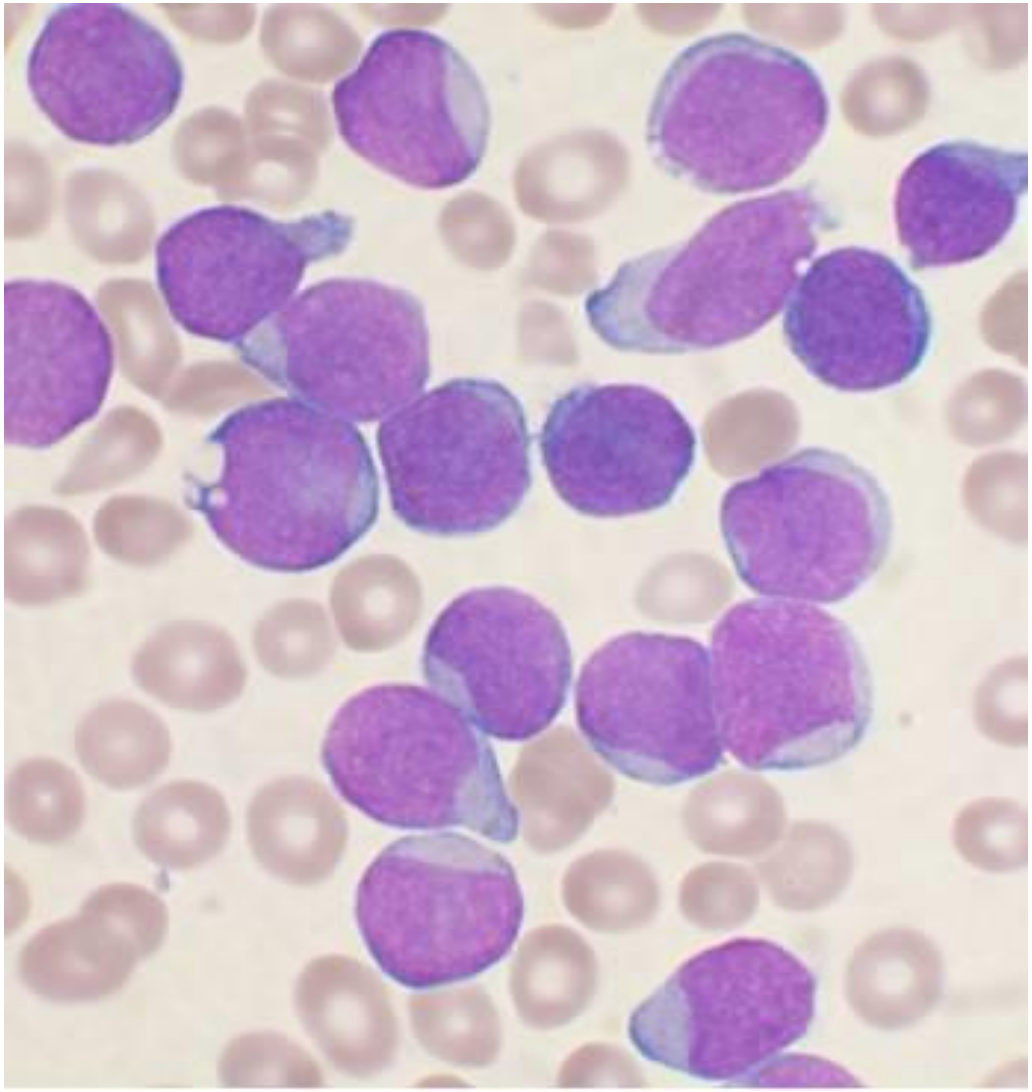
- Myeloperoxidase stain - Myeloid cells
- Sudan Black B- Myeloid cells
- Periodic acid schiff – Lymhoblasts (L1 type ALL)

Acute lymphoblastic leukemia (FAB classification)

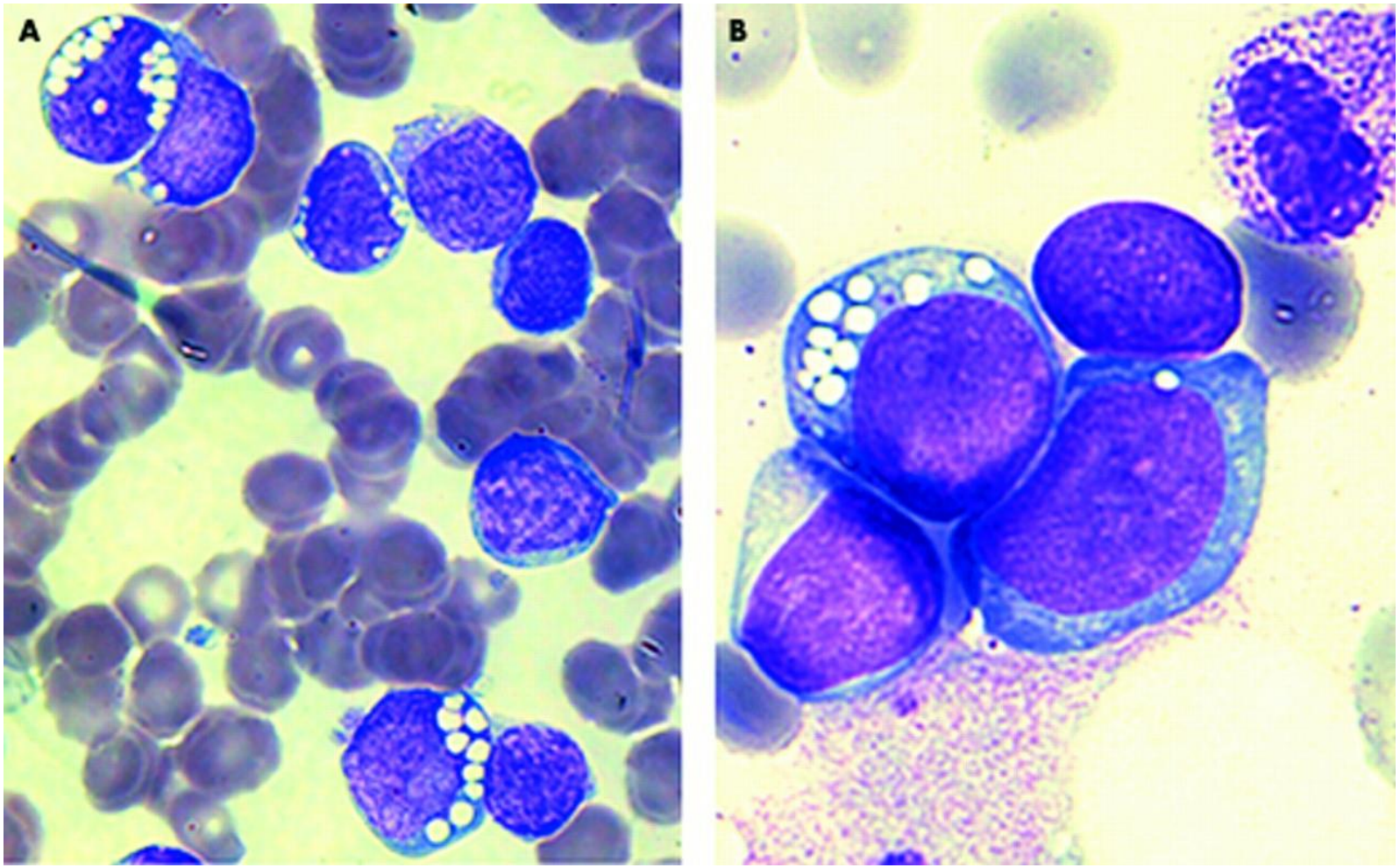
- **L1** : small lymphoblasts with coarse,condensed chromatin & inconsistent 1-2 punched out nucleoli. **75% cases**
- **L2** : large lymphoblasts of variable size with 1-2 **nucleoli. 20% cases**
- **L3** : large cells, fine chromatin, **vacuolated cytoplasm. 5% cases**

L1 type acute lymphoblastic leukemia

ALL L2 Type - PBS



ALL L3 Type – cytoplasmic vacuolation



WHO Classification-2001

Based on

Cell Morphology in PBS & BM.

Cytochemistry

- Myeloperoxidase stain - Myeloid cells
- Sudan Black B- Myeloid cells
- Periodic acid schiff – Lymhoblasts (L1 type ALL)

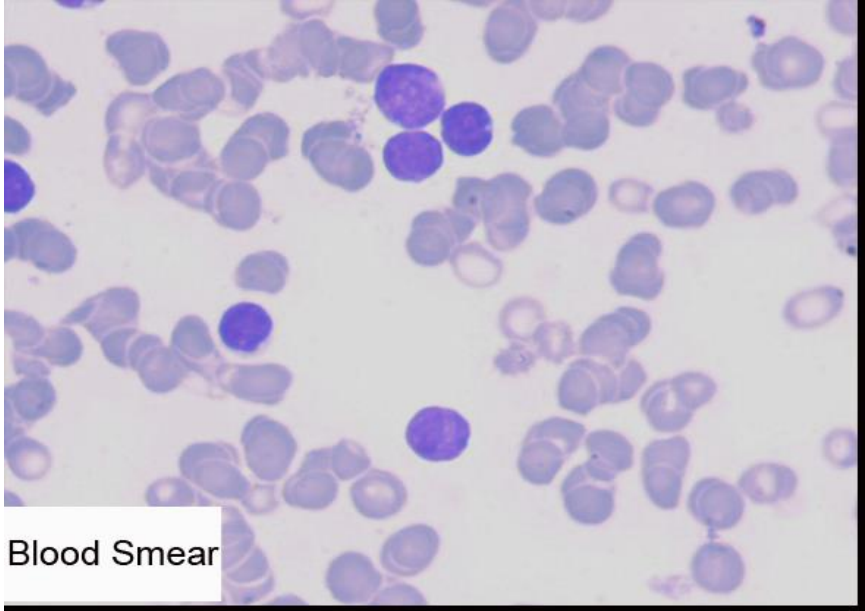
Immunophenotyping – McAntibodies against cell surface antigen / nuclear antigens (CD molecules)

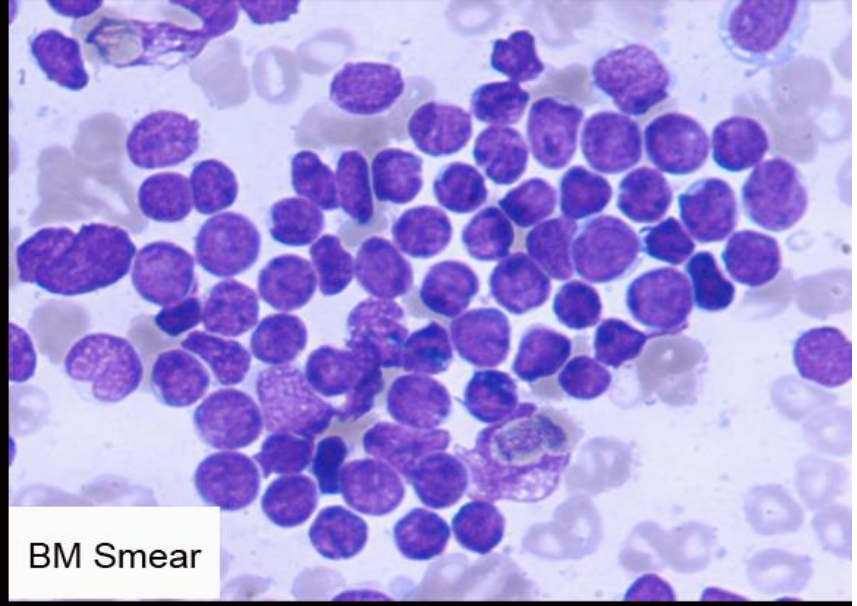
Molecular genetics – PCR, RT-PCR –fusion genes & products.

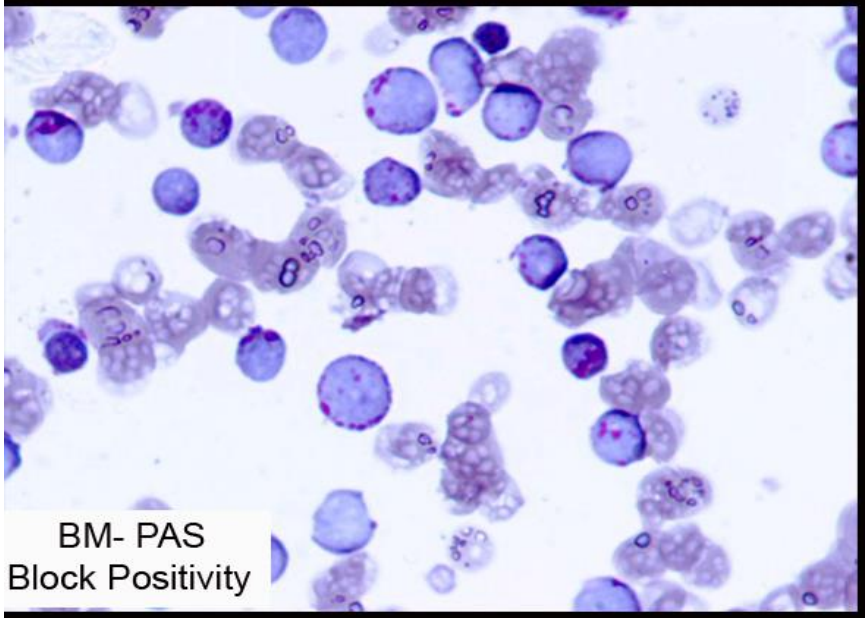
Cytogenetics

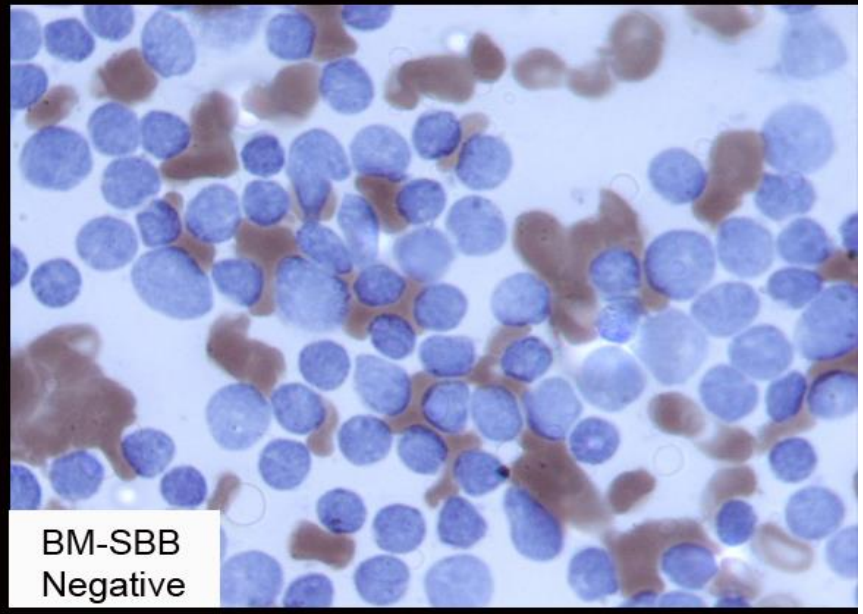
ALL-WHO Classification-2001

- **Precursor B ALL / Acute lymphoblastic lymphoma - 80% of cases**
- **Precursor T ALL / Acute lymphoblastic lymphoma - 15-20% of cases**









Acute Lymphoblastic Leukemia (ALL-L1)

Immunophenotyping

- Identification of CD molecules by McAbs.
- Immunocytochemistry
- Flow cytometry
- B cell markers→B cell ALL
- CD 10, 19, 20, 22.
- T cell markers →T cell ALL
- CD 3, 5, 7, 8 etc.

Stem cell marker

- **TdT is a protein expressed early in the development of pre-T and pre-B cells (seen in 90% ALL).**
- **CALLA (CD10) is an antigen found in 80% of ALL cases and also in the "blast crisis" of CML.**
- **CD 34 – stem cell marker**

Cytogenetics

- To see chromosomal abnormalities.
- Aneuploidy
- Hyperdiploidy - 50-67 chromosomes
- Hypodiploidy - < 45 chromosomes
- Tetraploidy- 92 chromosomes
- Monosomy- 45 chromosomes
- Chromosomal translocations & deletions.

KARYOTYPING : Chromosomal banding- Giemsa banding

FISH Technique

Complete karyotype

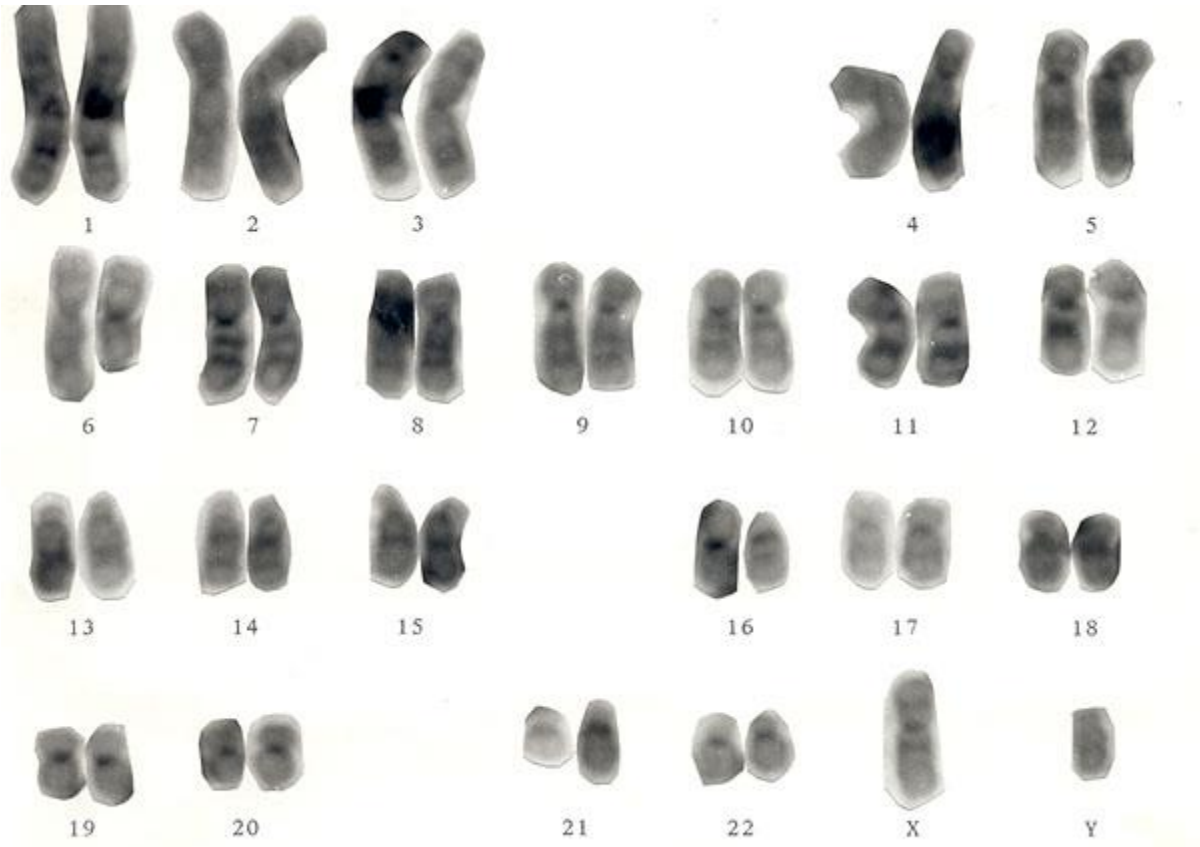


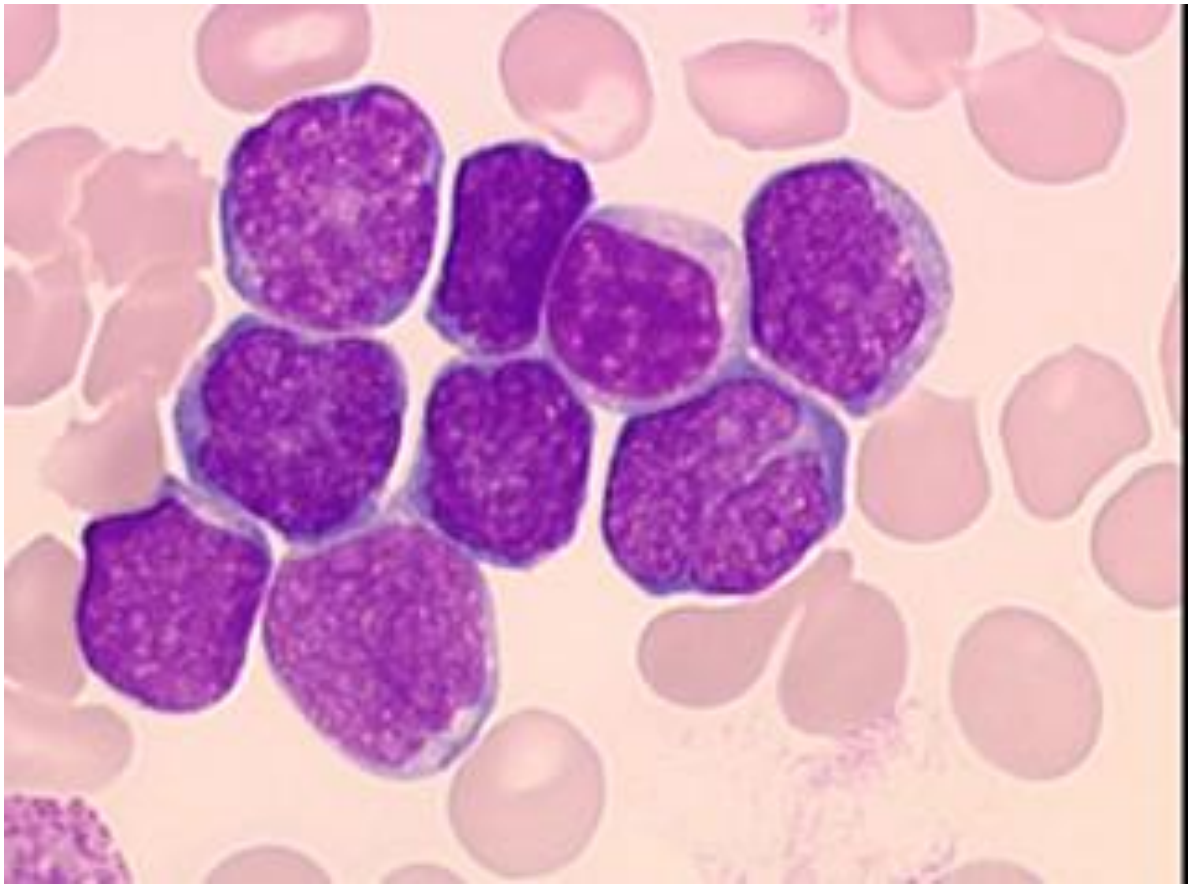
Figure 3: Complete karyotype of case 3

Immunophenotyping based BALL

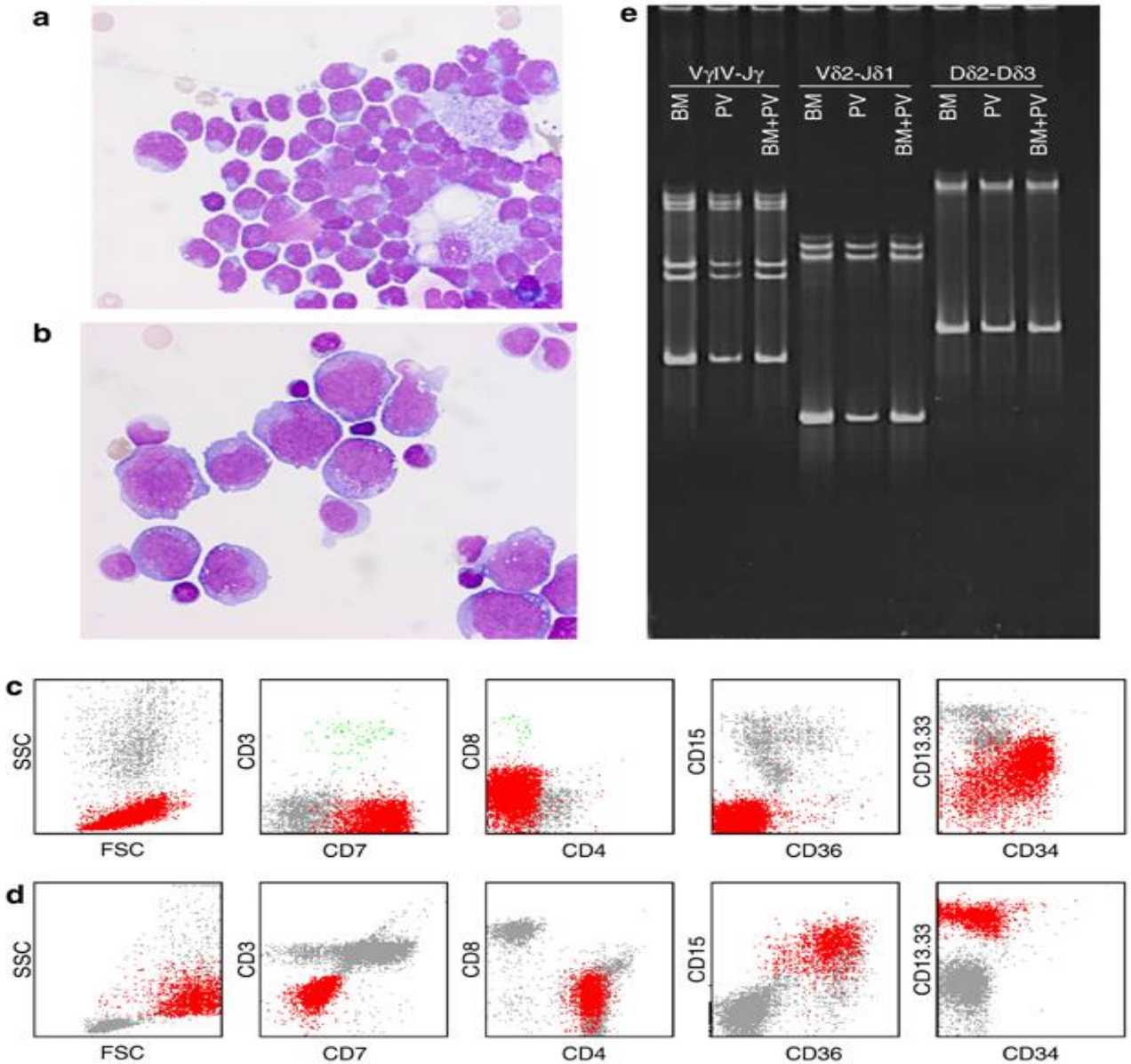
- Pro B – ALL – infants TdT+, CD10-, CD15+ worse prognosis.
- Pre B – ALL – 20% childhood ALL CD 10+ worse prognosis
- Common ALL- 60-70% childhood ALL CD10+ Good prognosis L1 Type
- B – ALL (eq to Burkitt's lymhoma)- surface & cyto Ig+,worse prognosis – L3 Type

- T-ALL -10-15% childhood ALL, L2 Type, mediastinal mass+, splenomegaly, high TLC.
- Worst prognosis

T cell Type ALL



ALL- FLOW CYTOMETRY- Immunophenotyping



Cytogenetics

Cytogenetic translocations associated with specific molecular genetic abnormalities in ALL

Cytogenetic translocation	Molecular genetic abnormality	%
cryptic t(12;21)	TEL-AML1 fusion[6]	25.4% Good prognosis
t(1;19)(q23;p13)	E2A-PBX (PBX1) fusion[8]	4.8%
t(9;22)(q34;q11)	BCR-ABL fusion(P185)[9]	1.6% Bad
t(4;11)(q21;q23)	MLL-AF4 fusion[10]	1.6% Bad
t(8;14)(q24;q32)	IGH-MYC fusion[11]	
t(11;14)(p13;q11)	TCR-RBTN2 fusion [12]	

Signs and symptoms

- Nonspecific : fever, bleeding, bone pain, lymphadenopathy
- Musculoskeletal pain/ bony pain (leukemic infiltration of periosteum, aseptic osteonecrosis).
- Lympadenopathy : ~50% on presentation, nontentender, firm, rubbery & matted lymphnodes.
- Hepatosplenomegaly
- CNS LEUKEMIA

CNS Leukemia

- **Meninges may be involved.**
- **Cranial nerve involvement : nerve palsies.**
- **Nausea, vomiting, headache etc.**
- **CSF examination for leukemia cells**
- **Intrathecal chemotherapy required.**

PBS - Abnormalities

- Anemia → fatigue
- Thrombocytopenia → 75% have platelet count < 1 lac/cumm
- Half of the patients → bleeding e.g – nose, skin, mucosal.
- TLC:
- 50% have TLC < 10,000cells/cumm
- 20% have TLC > 50,000→ leukocytosis
- 40-90 % Cells are lymphoblasts

- **Aleukemic or subleukemic leukemia** → TLC shows leukopenia with some blast cells in PBS
- Confirm by bone marrow examination which would reveal > 20-30% blast cells

Bone marrow examination

- **Hypercellular bone marrow**
- **Erythroid , myeloid and megakaryocytes cells are replaced by leukemic cells**
- **Blasts >30-90%.**
- **Cytochemistry PAS +(L1), MPO -ve, SB-B -ve**
- **Immunophenotyping : Pro, Pre B, B or T cell lineage ALL.**
- **Karyotyping- chromosomal aberration.**

Risk group stratification

Bad prognosis

- WBC >50,000 L2, L3
- AGE >10 years or <1 year- Male
- Immunophenotype : precursor T cell & mature B cell ALL
- Treatment response : rapid reponse : favorable
- Slow response or failure of induction (>5% lymphoblasts)

Good prognosis

- WBC< 20,000 - L1
- AGE 2-8years- female
- Immunophenotype: early Pre-B ALL, CD10+.
- Treatment response :rapid

Cytogenetics

- Hypodiploidy (<45 chromosomes)
- T(9:22)
- Near tetraploidy (82-94 chromosomes)
- MLL/AF4 Fusion

- Hyperdiploidy (lymphoblasts with 50-67 chromosomes
- T (12: 21)
- TEL/AML1 rearrangement in precursor B-ALL
- Trisomies of chromosome 4,7 &10

TREATMENT

- **Induction chemotherapy**
- **Consolidation ,,**
- **Maintenance ,,**
- **CNS directed therapy**
- **Bone marrow transplantation: in patients who relapse after first remission after aggressive chemotherapy**

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%**