Acute Leukemia two types → Acute myeloid
→ Lymphoblastic.

aggresive & worst

ACUTE MYELOID LEUKEMIA (AML)

- Occur at all age groups, but more common in elderly
- Heterogenous, diagnosis is made by morphologic, immunophenotypic and karyotype studies → genetic mutation
- Prognosis depends most importantly on type of mutations (molecular and cytogenetic studies (Karyotype)
- Symptoms are accelerated, become significant within few weeks → Can kill Patient if not Treated.
- Symptoms are related to anemia, thrombocytopenia and neutropenia → Also: Bleeding & Infection (fatal)
  * because Blast (Leukemic cells) fill BM & destroy normal cells.
- Involvement of LN, spleen and solid organs is rare. When occurs, it is called myeloid sarcoma (acute monoblastic leukemia)
  → if go out Blood cause tumor in tissue

* AML prefere stay insid Blood Stream NOT in Tissue (opposite lymphoblastic Anemia)
Common in Viscera

PATHOGENESIS

- Mutations in genes of transcription factors required for maturation and differentiation of myeloblasts → maturation Arrest (cell stay as blast & can't move forward)
- Additional mutations in tyrosine kinase pathways (RAS) — Common
- Epigenetic mutation is common (20%); mutation is isocitrate dehydrogenase (IDH) produces an oncometabolite that blocks enzyme of epigenome and interferes with myeloblast differentiation — Change in DNA transcription (Regulation); Block to Transcriptional gen

Due to AML is Heterogenous we have 4 mains types of AML 👍

WHO-CLASSIFICATION

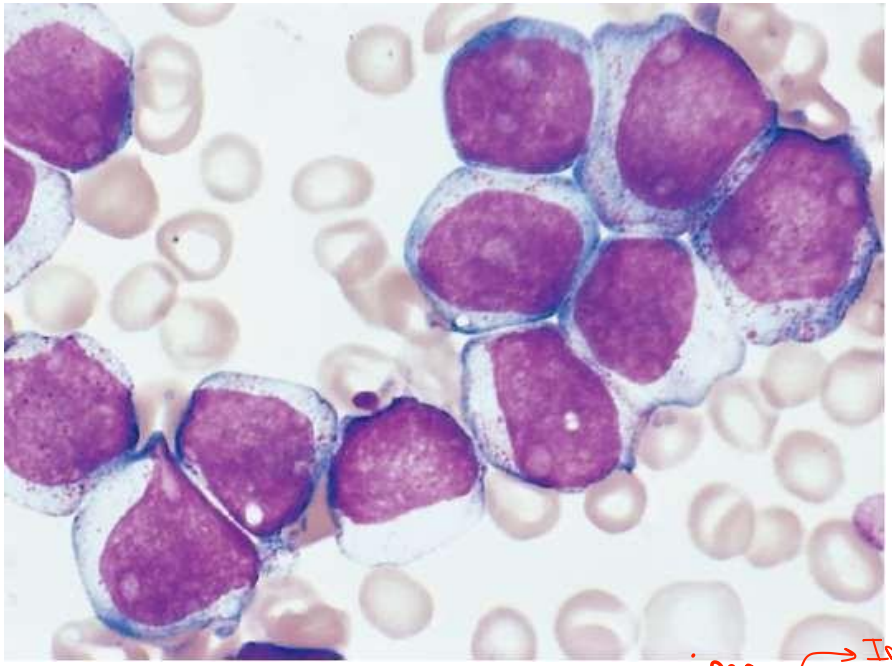
When Patient tre to another cancer previously, then have AML.

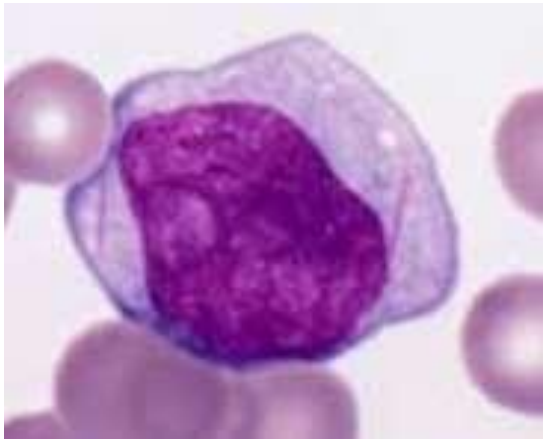
- **Therapy** related AML: occurs after treatment with chemo or radiotherapy (very bad Prognosis) Some acute leukemia follow Retreat with Chemo/radio Therapy. Because Chemo can cause mutation to BM cells.
- AML with recurrent cytogenetic mutation (translocation)
- AML with myelodysplasia: occurs de novo or complicates MDS (Morphology Examination)
- AML-Not otherwise specified if no MDS.

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders characterized by ineffective hematopoiesis, leading to dysplasia in one or more of the major blood cell lines

- Diagnosis of AML: 20% blasts (or more) in peripheral blood or bone marrow (of nucleated cells)

* Myeloblast





- Morphology: large cells, high N/C ration, fine granules in cytoplasm, fine chromatin, prominent nucleoli
- Auer rods: small pink rods present in cytoplasm, represent peroxidase enzyme
- Myeloblasts express CD34, myeloperoxidase (MPO), CD13, CD33
- Sometimes: monoblast, erythroblast, megakaryoblast

OUTCOME

- Generally poor, <30% responds to chemotherapy
  - Worse than ALL (Acute lymphoblastic leukemia)
  - P53 mutation: worse outcome
  - IDH inhibitors are new promising drugs

Prognosis

Bad Prognostic marker

* Subtype of AML *

ACUTE PROMYELOCYTIC LEUKEMIA (APL)

Leukemic cells are promyelocyte.

- Also called AML-M3
- Maturation is arrested at promyelocyte stage
- Leukemic cells appear similar to promyelocytes (heavy cytoplasmic granules, numerous Auer rods, negative for CD34)
- Carry recurrent mutation: t(15;17) fusion between PML gene (chrom 15) with alpha retinoic acid receptor (RARA) on chrom 17. Chimeric fusion gene produces a protein that blocks promyelocyte maturation by inhibiting the action of retinoic acid. (RARA)

Translocation

oncogen

* (Retinoic Acid is Vit. A) for cell maturation, so mutation block its receptor

* oncogen bind to (RARA) & blocks its transcription.

Treatment

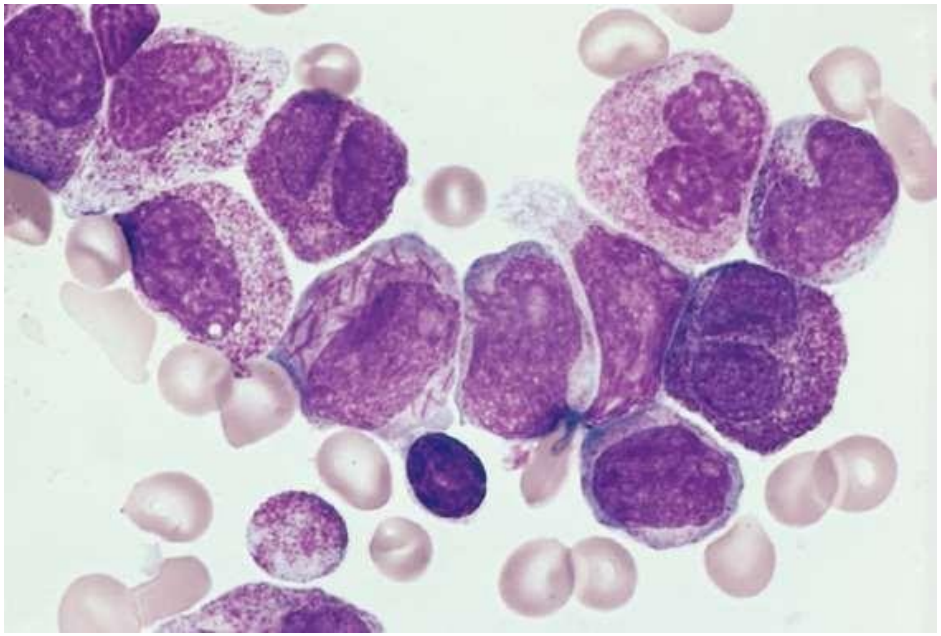
- All trans-retinoic acid (ATRA), a vitamin A analogue, overcomes this block. Effect is synergistic with arsenic trioxide (degrades oncoprotein)

& Induce maturation

- Malignant promyelocyte secrete tissue factor, causing DIC

Disseminated Intravascular Coagulation → leads wide spread Thrombosis then wide Bleeding & Die

* patient die from bleeding



- APL: malignant promyelocytes show numerous cytoplasmic granules and Auer rods. The nuclei are commonly cleaved.

* CD 34 -ve .

PRECURSOR B AND T CELL NEOPLASMS

Acute Lymphoblastic Leukemia (ALL).

Commonly involve viscera

In lymph node

- Lymphoblastic lymphoma when occurs in solid tissue (T>B) *
- Acute lymphoblastic leukemia when circulates peripheral blood and involve bone marrow (B>T)
- B-ALL is the most common childhood malignancy
- Neoplastic cells are lymphoblasts, the most immature lymphoid cell. Aggressive neoplasms, express CD34 and TDT*
- T-ALL is less common, presents in adolescents, involving thymus, more common in boys

⊕ To BM it Involve Thymus.

- B-ALL tends to disseminate to solid organs (brain, testis, spleen)

PATHOGENESIS

- Mutations in transcription factors for genes responsible for maturation of blasts

* In B-LL, mutation in PAX5 gene

- Mutations in RAS signaling and tyrosine kinase proteins promoting cell survival

* Most childhood B-ALL have hyperdiploidy (>50 chromosomes) and t(12;21), involving ETV6 and TUNX1 genes, creating new transcription factor

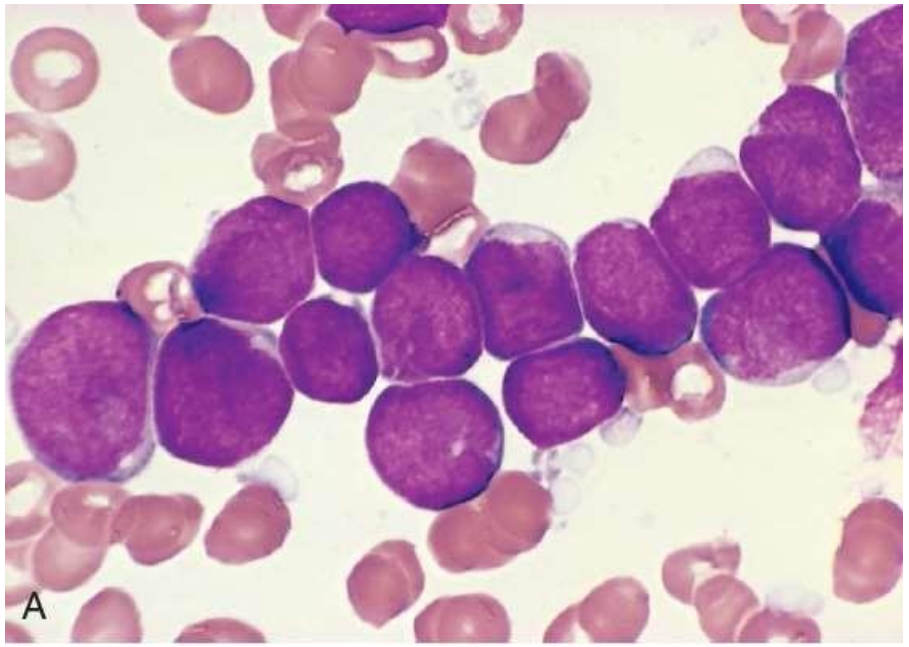
- Adult B-ALL exhibits t(9;22) between ABL and BCR genes, similar to chronic myeloid leukemia, creating a new tyrosine kinase protein (imatinib)

Cause, cell proliferation ← → Drug

- T-ALL shows mutation in NOTCH1 gene (70% of cases), PTEN gene (tumor suppressor) and CDKN2A (promotes cell cycle)

MORPHOLOGY OF ALL

- Blasts are large, high N/C ration
- Chromatin is open (pale)
- Nucleolus sometimes present
- Cytoplasm is not granular

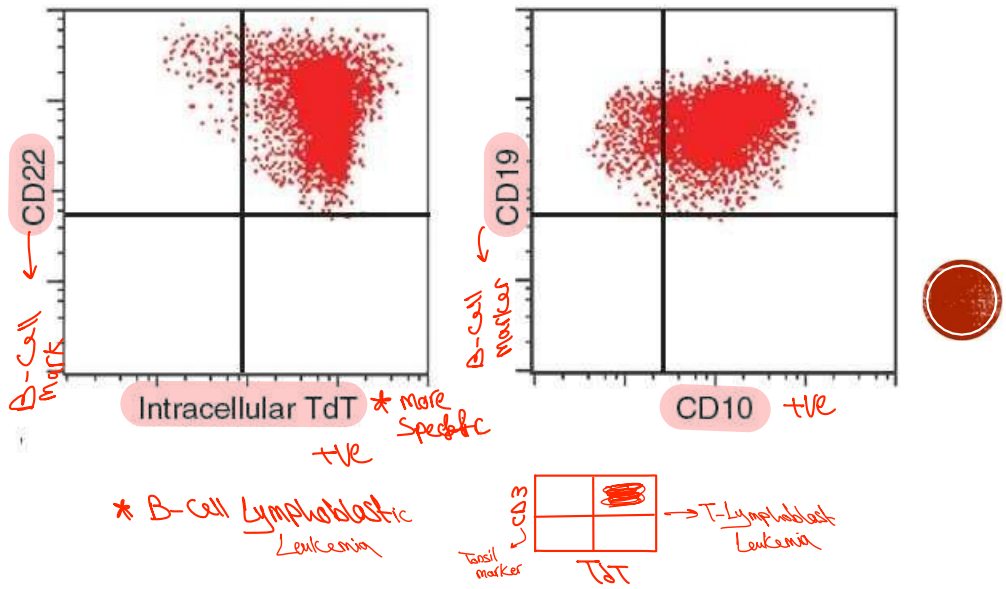


→ * Differences Between Lymph/Myelo Blast !

* Lymph → has minimal Cytoplasm & No granules or Auer rods

* Sever case → Immunophenotype to examin markers & Ag.

Myelo ← * CD34 in both



CLINICAL FEATURES

- Anemia, thrombocytopenia & Neutropenia → fatal
- Bone pain
- Lymphadenopathy and hepatosplenomegaly
- Testicular enlargement boy
- Mediastinal mass (T-ALL)
- * CNS involvement
- Damage to solid organs secondary to leukemic infiltration
- Favorable prognostic factors in B-ALL: hyperdiploidy, low WBC count, age between 2-10 years
- Poor prognostic factors in B-ALL: age < 2 years, age in adolescents or adults, WBC count >100k

* Response to chemotherapy → Leave leukemia

LANGERHANS CELL HISTIOCYTOSIS

Tumor

- Neoplasm of dendritic cells
- Langerhans cells express CD1a and Langerin
- Langerin is a transmembrane protein, attached to Birbeck granules (tennis ricket shape under electron microscope)
- Proliferating Langerhans cells appear large and vacuolated, similar to macrophages
- Pathogenesis: acquired mutation in serin/threonine kinase BRAF, leads to hyperactivity of this kinase

Clinicaly we have 2 forms → multiSystemic LCH
2 → uniSystem LCH

MULTISYSTEMIC LCH

- Occurs mostly in children less than 2 years
- Multiple cutaneous lesion, composed of LCs
- Hepatosplenomegaly and lymphadenopathy
- Pulmonary lesions
- Osteolytic lesions
- Extensive bone marrow infiltration leads to pancytopenia
- Treated with chemotherapy

UNISYSTEM LCH

- AKA eosinophilic granuloma
- Affects a single organ, most commonly bone, then skin, lung, stomach
- Can be unifocal or multifocal
- Unifocal is commonly asymptomatic, can cause pain
- Mulfocal unisystem disease presents in children, commonly affects calvaria bone, extends to pituitary gland causing diabetes insipidus, exophthalmous (Hand- Schuller-Christian triad).
- Proliferating LCs are admixed with numerous eosinophils, lymphocytes, plasma cells and neutrophils
- Treatment: unifocal: surgical excision, multifocal: chemotherapy, sometimes spontaneous regression