Pathology of hematolymphoid system
Acute Leukemia
Histiocytic tumors

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* Most of disorders related to WBCs are neoplastic.

ACUTE MYELOID LEUKEMIA AML

Most aggresive

For diagnosis we depend on:
- Morphology
- Examine the antigens
- Karyotyp: Chromosomes

* Some mutations are common

- Occur at all age groups, but more common in elderly
- Heterogenous, diagnosis is made by morphologic, immunophenotypic and karyotype studies
  (Many Subtypes; ↳ Chromosomes)
- Prognosis depends most importantly on type of mutations (molecular and cytogenetic studies ↳ Karyotype)
- Symptoms are accelerated, become significant within few weeks → cytopenia because the bone marrow is filled with blasts instead of normal cells
- Symptoms are related to anemia, thrombocytopenia and neutropenia
- Involvement of LN, spleen and solid organs is rare. When occurs, it is called myeloid sarcoma (acute monoblastic leukemia)
  ↳ Solid mass → destruction

So they remain in the bone marrow or in the peripheral blood

PATHOGENESIS

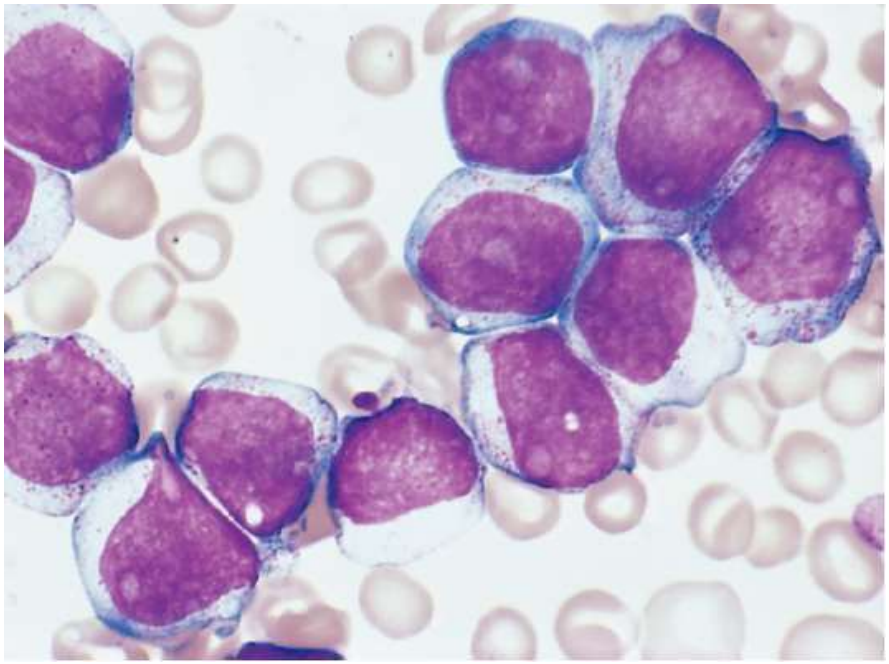
- Mutations in genes of transcription factors required for maturation and differentiation of myeloblasts
  - So they do not mature
- Additional mutations in tyrosine kinase pathways (RAS)
- Epigenetic mutation is common (20%); mutation is isocitrate dehydrogenase (IDH) produces an oncometabolite that blocks enzyme of epigenome and interferes with myeloblast differentiation

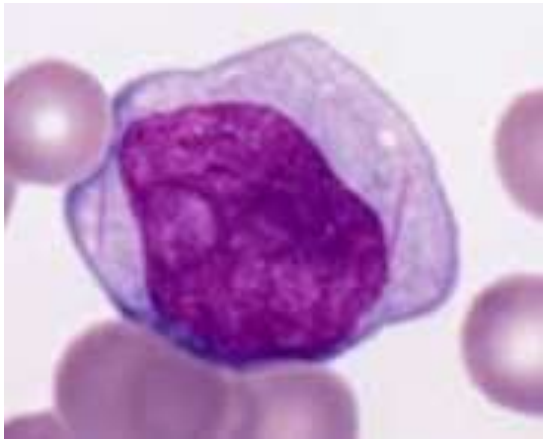
responsible for all the epigenetic mutations in all the DM.

WHO-CLASSIFICATION OF AML

- Therapy related AML: occurs after treatment with chemo or radiotherapy
- AML with recurrent cytogenetic mutation
- AML with myelodysplasia: occurs de novo or complicates MDS
- AML-Not otherwise specified

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





- 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

contain many enzymes mainly myloperoxidase

large nucleus

normal mature

فيه immature

Only seen in myeloblasts they are granules but with morphologic change (same content).

If it reaches >20%

* CD34: only expressed in blasts and it's negative in mature cells.
* We use the flowcytometry to check the presence of these antigens.

OUTCOME

- Generally poor, <30% responds to chemotherapy

Very poor prognosis

There are new therapies but still promising like Isocitrate dehydrogenase Inhibitors.

- Worse than ALL
- P53 mutation: worse outcome
- IDH inhibitors are new promising drugs

Subtype of AML

ACUTE PROMYELOCYTIC LEUKEMIA

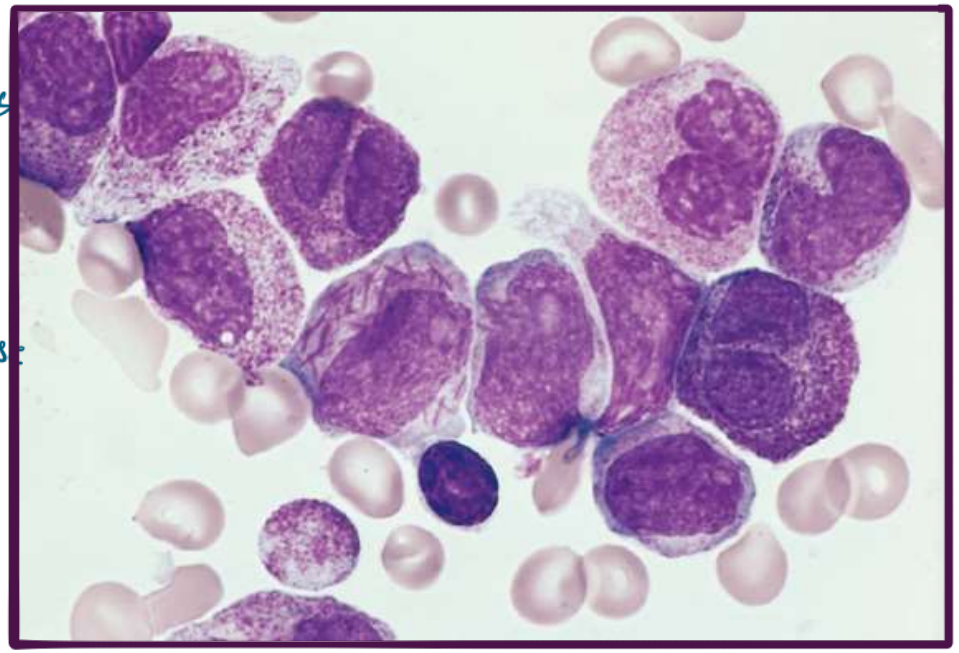
- Promylocyt is the stage of maturation that comes after myloblast.
- we don't find blasts → we find malignant promylocyte.

- Also called AML-M3 (They were designated by numbers)
- Maturation is arrested at promyelocyte stage
- Leukemic cells appear similar to promyelocytes (heavy cytoplasmic granules, numerous Auer rods, negative for CD34) (positive only in blasts.)
- 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. (special mutations that are not seen in any other leukemia) (promyelocyte)
- All trans-retinoic acid (ATRA), a vitamin A analogue, overcomes this block. Effect is synergistic with arsenic trioxide (degrades oncoprotein)
- Malignant promyelocyte secrete tissue factor, causing DIC

* Vitamine A is important for the maturation of leukemic cells.
* The mutation leads to the apperance of a chymeric protein that inhibits the usage of VIT.A for maturation.
* Treatment: Very large dose of VIT.A → force the chymeric protein to detach from the receptor (RARA).
* VIT.A that's used is alpha trans retinoic acid → which is a derivative with the same function.

* other treatmen is Arsenic trioxide : toxic was previously used as poisin.
* No Chemotherapy 2nd line
* patients develop DIC. because the promylocyte secrete TF. And patients die from DIC Not from the cancer itself.

* They are like the blasts but with neumerous granules.
* And Rods.
* May find 2nuclei because its malegnant.



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

PRECURSOR B AND T CELL NEOPLASMS

☆ Can appear in blood and bone marrow. and can appear in other tissues.
☆ Lymphocytes are every where.
☆ when it arise in tissues it's known as lymphoblastic lymphoma (Lymphoma).

- 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
  ↳ Can occure at any age
- Neoplastic cells are lymphoblasts, the most immature lymphoid cell. Aggressive neoplasms, express CD34 and TDT To distinguish lymphoblasts from leukoblasts.
- T-ALL is less common, presents in adolescents, involving thymus, more common in boys
- 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

Single cell with very large number of chromosomes → It's a good prognosis

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

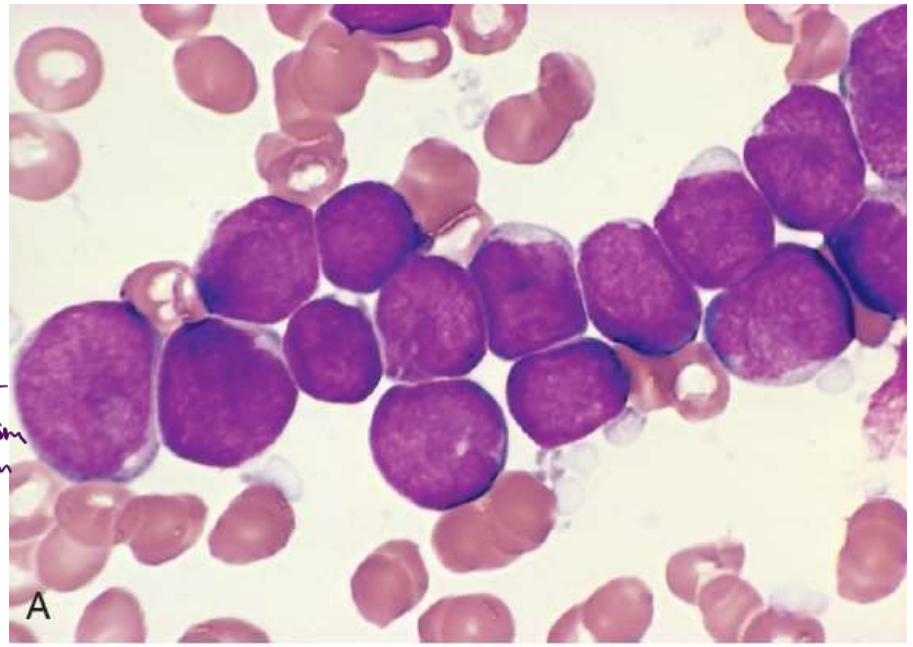
first mutation treated by targeted therapy

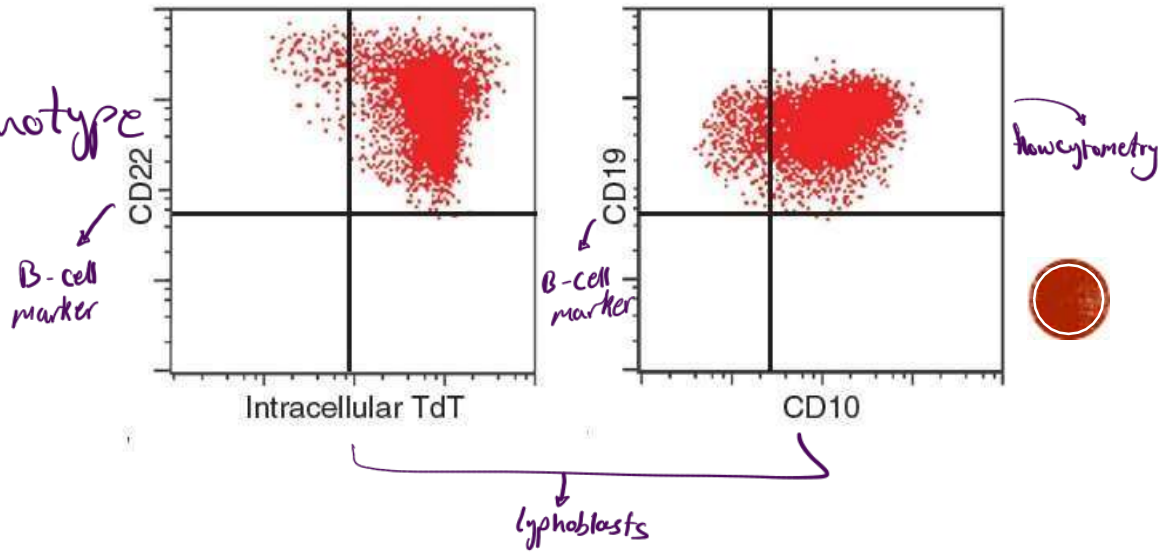
Philadelphia Chromosome was discovered firstly in Chronic CML myeloid leukemia.

- 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





CLINICAL FEATURES

- Anemia, thrombocytopenia
- Bone pain Common → felt with bones
- Lymphadenopathy and hepatosplenomegaly
- Testicular enlargement
- Mediastinal mass (T-ALL)
  - In thymus → compresion on heart and lungs
- CNS involvement harder treatment, chemotherapy in the spinal cord
- Damage to solid organs secondary to leukemic infiltration
  - like brain
- Favorable prognostic factors in B-ALL: hyperdiploidy, low WBC count, age between 2-10 years
  - better than AML
  - good prognosis
  - they response to chemo.
- Poor prognostic factors in B-ALL: age < 2 years, age in adolescents or adults, WBC count >100k

* There are many types of histiocytic tumors.
* This is the most common ↓

LANGERHANS CELL HISTIOCYTOSIS

- Neoplasm of dendritic cells
  - APC. They are simmiler to dendrites in nerves. in case of the disease → they become larg and swellowed like histocytes.
- Langerhans cells express CD1a and Langerin
- Langerin is a transmembrane protein, attached to Birbeck granules (tennis ricket shape under electron microscope)
  - cytoplasmic end
  - years befor they used to use the EM for diagnosis. Now we directly use antigens.
- Proliferating Langerhans cells appear large and vacuolated, similar to macrophages
  - They become neoplastic → that's why their shapes have changed.
- Pathogenesis: acquired mutation in serin/threonine kinase BRAF, leads to hyperactivity of this kinase
  - Seen in ① B-cell lymphoma ② LCH.

MULTISYSTEMIC LCH

everywhere in the body

- Occurs mostly in children less than 2 years
- Multiple cutaneous lesion, composed of LCs
- Hepatosplenomegaly and lymphadenopathy
- Pulmonary lesions — can also affect the heart
- 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