Sheet No.
9

PATHOLOGY

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ACUTE MYELOID LUKEMIA

general features:

-it is a tumor of hematopoietic progenitors caused by acquired oncogenic mutations that impede differentiation, leading to the accumulation of immature myeloid blasts in the marrow

-it is a very aggressive neoplasm, so it is one of the worst cancers a human being can be affected with.

- Occur at all age groups, but more common in elderly
- Heterogenous (many forms of disease depending on many various genetic mutations present across different genes or genetic loci), diagnosis is made by morphologic, immunophenotypic and karyotype studies

  -karyotype studies: Karyotypic study: It studies the mutations at the level of chromosomes (cytogenetic) and genes (molecular), these studies are added by WHO classification because prognosis depends most importantly on the type of mutation, before WHO classification, (FAB classification) they relied only on the morphology and immunophenotype
- Prognosis depends most importantly on type of mutations (molecular and cytogenetic studies
- Symptoms are accelerated, become significant within few weeks
- Symptoms are related to anemia, thrombocytopenia, and neutropenia, the accumulation of myeloid blast in the BM induces BM failure leading to anemia…
- Involvement of LN, spleen, and solid organs is rare. When occurs, it is called myeloid sarcoma (acute monoblastic leukemia), which is a subtype of AML. Monoblast tends normally to differentiate into a macrophage in tissues, so in this leukemia, they tend to go into solid organs and at that setting we call it myeloid sarcoma (tissue tumor of AML).

PATHOGENISIS:

- **Mutations in genes of transcription factors required for maturation and differentiation of myeloblasts**
- **Additional mutations in tyrosine kinase pathways (RAS) => prolonged survival**
- **Epigenetic mutation is common (20%); mutation is isocitrate dehydrogenase (IDH) produces an oncometabolite that blocks enzyme of epigenome and interferes with myeloblast differentiation**
- **Epigenetic mutation: A mutation that affects the function of the DNA without any changes in the codons**

WHO-CLASSIFICATION

- **1-Therapy related AML: occurs after treatment with chemo or radiotherapy**
- **occurs after treatment with chemo or radiotherapy. For instance, if the patient has a breast cancer and she received chemotherapy, she will have a risk for AML later on, so, we call it therapy related AML, the prognosis is very poor**
- 2- **AML with recurrent cytogenetic mutation**

If the patient doesn't have a history of chemo or radiotherapy, then we test the cytogenetic mutation, we won't go deeply with them since they are many and complicated, you just need to understand that some cytogenic mutations if they are positive then we call it as AML with this cytogenetic mutation, prognosis is different according to which the mutation occurs.

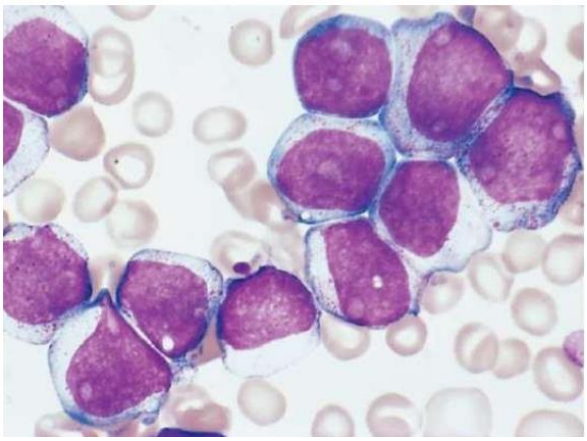
- **3-AML with myelodysplasia: occurs de novo or complicates MDS**

If the patient doesn't have these two, then we check for the presence of myelodysplasia (the abnormal shape of hematopoietic stem cells), if it is present then we call it AML with myelodysplasia.

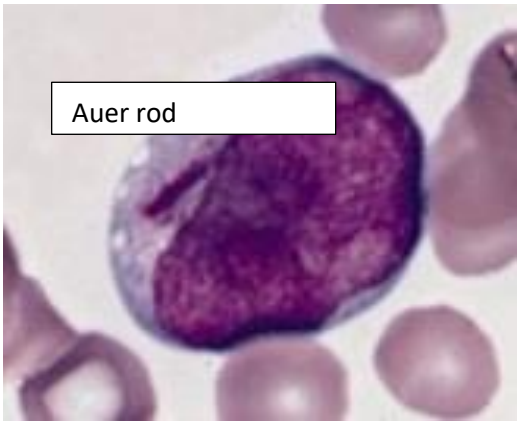
- **Patients with MDS can progress to AML. AML with myelodysplasia occurs either de novo and this is a very bad disease**

-when we examine the BM morphology, the hematopoietic stem cells look very abnormal, OR it can be a complication of MDS (less aggressive than the de novo one).

- If no one of these is present, then it is AML-Not otherwise specified(according To the old classification)



- 4-AML-Not otherwise specified
- Diagnosis of AML: 20% blasts in peripheral blood or bone marrow (of nucleated cells), remember: normally we don't see blasts peripherally



Morphology:

Myeloblasts are similar to lymphoblasts but they are larger and have more amount of cytoplasm (in comparison to lymphoblasts), high N/C ratio, fine granules in cytoplasm (granulocyte progenitor cells) in contrast to lymphoblasts :which don't have granules, fine chromatin (pale), prominent nucleoli (more than lymphoblast)

- Auer rods: small pink rods present in cytoplasm, represent peroxidase enzyme ▪Myeloblasts express CD34, myeloperoxidase (MPO), CD13, CD33
- ▪ Sometimes: monoblast, erythroblast, megakaryoblast
- They are negative for TdT and CD10.
- Sometimes we see other cell lines: monoblast, erythroblast, megakaryoblast
- **Outcome:**
- Generally poor <30% responds to chemotherapy, (also recurrent rate is high)
- Worse than ALL
- P53 mutation: worse outcome
- IDH inhibitors are new promising drug

ACUTE PROMEOLYCYTIC LUKEMIA:

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 (chrom15) with alpha retinoic acid receptor (RARA) on chrom17. Chimeric fusion gene produces a protein that blocks promyelocyte maturation by inhibiting the action of retinoic acid.**
- **All trans-retinoic acid (ATRA), a vitamin A analogue, overcomes this block. Effect is synergistic with arsenic trioxide (degrades oncoprotein)**
- **After giving the patients this treatment, promyelocytes will keep differentiating into baso, eosion-phils and mainly neutrophils, then they die by the end of their short life spans.**
- **-arsenic is toxic in high doses, but this type of treatment requires low dose.**
- **Malignant promyelocyte secrete tissue factor, causing DIC**
  We have a special situation in which malignant promyelocytes secrete tissue factor, causing DIC, so the patient might die from DIC even before suffering from the leukemia.

- **APL: malignant promyelocytes show numerous cytoplasmic granules and Auer rods**
- **The nuclei are commonly cleaved**
- **The nuclei are commonly cleaved (we call it "figure of eight" because it is similar to the number 8 in English).**

PRECURSOR B AND T CELL NEOPLASMS

*note: Precursor neoplastic cells are the most immature lymphoid cells [lymphoblasts

*and notice that it is lympho-BLASTIC not lympho-CYTIC, which was SLL or CLL

-chronic LL→lymphocytic

-acute LL→lymphoblastic

1-Lymphoblastic lymphoma when occurs in solid tissue (T>B)

2- Acute lymphoblastic leukemia when circulates peripheral blood and involve bone marrow (B>T), it is aggressive & progresses rapidly.

*remember that we cant differentiate between B and T cells under Microscope, it needs surface markers study.

- **B-ALL is the most common childhood malignancy(important)**

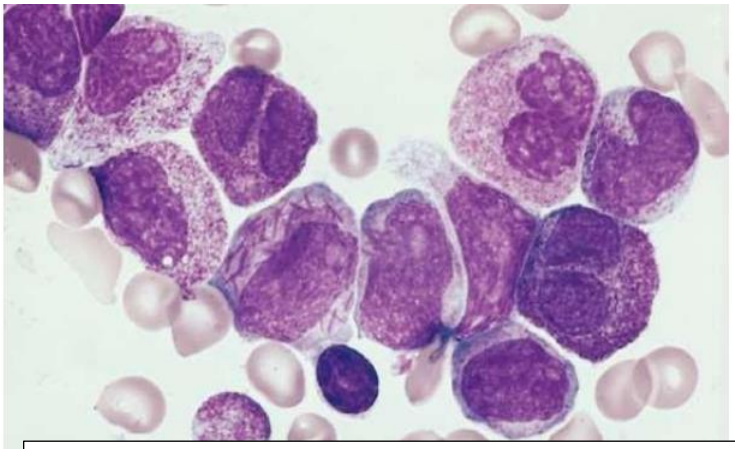
-extra-note: the 2nd common is CNS tumors and neuroblastoma.

- **Neoplastic cells are lymphoblasts, the most immature lymphoid cell.**

Aggressive neoplasms, express CD34 [membrane marker] and TDT [nuclear].

-so if the cell was -ve TDT, it is confirmedly a mature cell.

- **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)** because the lymphocyte normally circulates the blood then resides in tissues, these do the same.



Don't underestimate with these large cells, they are a good question for the lab part😊

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)(Philadelphia chr) between ABL and BCR genes, similar to chronic myeloid leukemia CML, creating a new tyrosine kinase Protein(poor prognosis)→treated with imatinib**

-- (imatinib): is an antibody drug that blocks this tyrosine kinase

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

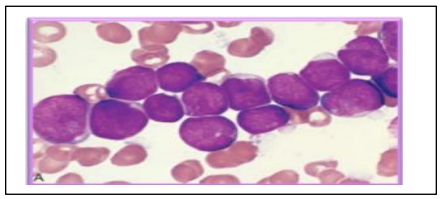
-B-LL→PAX5

-T-LL→NOTCH1

-Interesting info:

Philadelphia chromosome is the first discovered translocation abnormality in human cancer, and Imatinib is the first targeted therapy used in cancer.

MORPHOLOGY OF ALL



▪ **Blasts are large, high N/C ration**

▪ **Chromatin is open (pale)**

▪ **Nucleolus sometimes present**

-INDICATION FOR THE IMMATURATION.

▪ **Cytoplasm is not granular**

-so, we could differentiate between MLL and ALL by the amount of granules and cytoplasm

In ALL→the cytoplasm is just a rim and almost no granules**.**

---if the specimen taken from the patient is aspirate(fluid), we test it with flow-cytometry

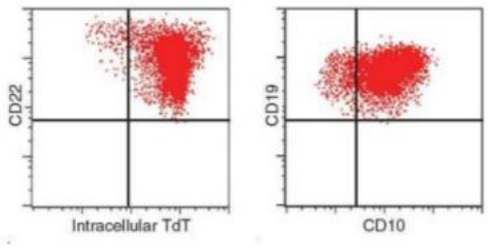
-if biopsy(tissue)→we examine it immunohistochemically.

-flow cytometry confirms if these are lymphoblasts and specifies the type B or T

• CD22 & CD19 are B-cell markers

• CD10 is present in lymphomas of follicular origin and immature cells

• TDT is an immature lymphoblast marker



CD22,20,19 +VE so it is b cell

-tdt or CD10 +ve it is immature lymphoblast

So the Dx is B-LL

CLINICAL FEATURES

▪ **Anemia, thrombocytopenia**(secondary to destruction of the bone marrow)
• **Bone pain**
• **Lymphadenopathy and hepatosplenomegaly**
• **Testicular enlargement**
• **Mediastinal mass (T-ALL)**
• **CNS involvement**→in contrast to AML, ALL shows CNS manifestation, which is important for treatment, hence the drug will be administered intrathecally through spinal cord.
▪ **Damage to solid organs secondary to leukemic infiltration+**neutropenia+very low Hb.
▪ **Favorable prognostic factors in B-ALL: hyperdiploidy, lowWBC count, age between 2-10 years**
▪ **Poor prognostic factors in B-ALL: age < 2 years, age in adolescents or adults,WBC count >100k**

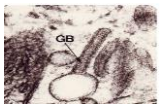
LANGERHANS CELL HISTIOCYTOSIS(LCH)

-The term histiocytosis is an "umbrella" designation for a variety of proliferative disorders of dendritic cells or macrophages. Some, such as very rare histiocytic lymphomas, are highly malignant neoplasms. Others, such as most histiocytic proliferations in lymph nodes are completely benign and reactive. Between these two extremes lie a group of relatively rare tumors comprised of Langerhans cells, the Langerhans cell histiocytoses.
-Langerhans cells are immature dendritic cells found in the epidermis; similar cells are found in many other organs, and they function to capture antigens and display them to T cells.
-in this disease, the LCs which are APCs tend more resemble macrophages(histiocytes)→So called histiocytosis.
▪ **Neoplasm of dendritic cells**

▪ **Langerhans cells express CD1a and Langerin**

▪ **Langerin is a transmembrane protein, attached to Birbeck granules (tennis racket shape under electron microscope)**

-in the past, they used to diagnose based on morphology so under microscope, they resembled tennis ricket shape



extra

▪ **Proliferating Langerhans cells appear large and vacuolated, similar to macrophages**

▪ **Pathogenesis: acquired mutation in serin/threonine kinase BRAF,leads to hyperactivity of this kinase**

-Remember! we discussed this kinase mutation in Hairy Cell Leukemia,and it is common in solid tumors as well as melanoma.

-Langerhans Cell Histiocytosis is a solid tumor and it develops in tissues, so it is not a leukemia.

-There are 2 major categories of LCH:

1)MULTISYSTEMIC LCH

-more severe

- Multisystemic ---> the patient has the disease in multiple -organs.

▪ **Occurs mostly in children less than 2 years**

▪ **Multiple cutaneous lesion(as masses), composed of Langerhans Cells.**

▪ **Hepatosplenomegaly and lymphadenopathy**

▪ **Pulmonary lesions→are common(bad symptom)**

▪ **Osteolytic lesions→** these cells proliferate in the bone in numerous areas, similar to plasma cell myeloma but in plasma cell myeloma, they are functional neoplastic cells which cause bone erosion while the multisystemic LCH only causes physical destruction to the BM (reabsorption and destruction).

▪ **Extensive bone marrow infiltration leads to pancytopenia**

▪ **Treated with chemotherapy**

-survival is around 5 yrs.

2)UNISYSTEM LCH

-AKA eosinophilic granuloma

▪ Affects a single organ, most commonly bone, then skin, lung, stomach

- This disease is heterogeneous: it comes in a single organ but with different medical conditions.
- It affects the bone (MOST COMMONLY and usually in children), then skin, lung (in old adults and usually smokers), and stomach.

▪ Can be unifocal or multifocal but within the same organ.

▪ Unifocal is commonly asymptomatic, can cause pain:
(we do an x-ray for a child and we see a small osteolytic lesion in the bone) and sometimes it can cause pain.

▪ Multifocal uni system disease presents in children, commonly affects calvaria bone(skull bone), extends to pituitary gland causing diabetes insipidus (patients will urinate like they have diabetes) and also, due to neural damage, it will result in exophthalmous (Hand-Schuller-Christian triad).

--This triad :(1) osteolytic lesion (2) diabetes insipidus (3) exophthalmos is called Hand-Schuller-Christian triad. This is a rare situation.

▪ Proliferating LCs are admixed with numerous eosinophils(hence the name comes from: eosinophilic granuloma), lymphocytes, plasma cells and neutrophils under the microscope.

- This reminds us of Hodgkin Lymphoma, but in the HL there are a few cancerous cells, while in the eosinophilic granuloma there are numerous cancerous cells.

▪ Treatment: unifocal: surgical excision,
multifocal: chemotherapy, sometimes spontaneous regression(and this is a rare phenomenon in cancer. It could regress on its own and it could be related to the activation of the immune system that removes this tumor)

DONE

TO RECAP:

SUMMARY

MYELOID NEOPLASMS

Myeloid tumors occur mainly in adults and fall into three major groups:

- **AML**
  - Aggressive tumors comprised of immature myeloid lineage blasts, which replace the marrow and suppress normal hematopoiesis
  - Associated with diverse acquired mutations that lead to expression of abnormal transcription factors, which interfere with myeloid differentiation

SUMMARY

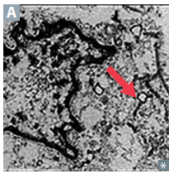
LYMPHOID NEOPLASMS

- Classification is based on cell of origin and stage of differentiation
- Most common types in children are ALLs/lymphoblastic lymphomas derived from precursor B and T cells
- Most common types in adults are non-Hodgkin lymphomas derived from germinal center B cells

Acute Lymphoblastic Leukemia/Lymphoma

- Highly aggressive tumors that manifest with signs and symptoms of bone marrow failure, or as rapidly growing masses
- Tumor cells contain genetic lesions that block differentiation, leading to the accumulation of immature, nonfunctional blasts

Langerhans cell histiocytosis



Collective group of proliferative disorders of Langerhans cells (antigen-presenting cells normally found in the skin). Presents in a child as lytic bone lesions and skin rash or as recurrent otitis media with a mass involving the mastoid bone. Cells are functionally immature and do not effectively stimulate primary T cells via antigen presentation. Cells express S-100 and CD1a. Birbeck granules ("tennis rackets" or rod shaped on EM) are characteristic A.

PAST PAPERS:

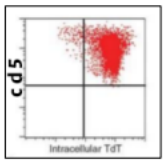
Q6. not associated with fibroblast:

Answer: AML

Q9. t(15,17) is associated with all of the following except:

Answer: Splenomegaly

Q4. What type of cancer does this flow cytometry represent:



Answer: Notch1

40. Wrong about AML

Answer: It occurs at all age groups, but more common in children

43. Wrong about B-ALL

Answer: CD3 is the marker for it

48. Which of the following is expressed in Langerhans Cell Histocytosis?

Answer: Langerhans cells express CD1a

Chromosomal translocations

TRANSLOCATION	ASSOCIATED DISORDER	NOTES
t(8;14)	Burkitt (Burk-8) lymphoma (c-*myc* activation)	The Ig heavy chain genes on chromosome 14 are constitutively expressed. When other genes (eg, *c-myc* and *BCL-2*) are translocated next to this heavy chain gene region, they are overexpressed.
t(11;14)	Mantle cell lymphoma (cyclin D1 activation)	
t(11;18)	Marginal zone lymphoma	
t(14;18)	Follicular lymphoma (*BCL-2* activation)	
t(15;17)	APL (formerly M3 type of AML)	
t(9;22) (Philadelphia chromosome)	CML (*BCR-ABL* hybrid), ALL (less common); Philadelphia CreaML cheese	