ACUTE & CHRONIC LEUKEMIA

435 medicine teamwork

[Important | Notes | Extra | Editing file]

Lecture objectives:

- ⇨ Definition
- ⇨ Historic Perspective
- ⇨ Etiology and Risk Factors
- ⇨ Incidence
- ⇨ Classification
- ⇨ Comparison of Acute and Chronic Leukemia

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References: Doctors' Slides + Kumar + Step-up

No need to know the chemotherapy drugs and its details.

Leukemia

Osmosis videos are very helpful, u r recommended to watch them first video1,video2

- A group of malignant disorders affecting the blood and blood-forming tissues of: Bone marrow, Lymph system, Spleen.
- Occurs in all age groups. (ALL commonest seen in child) (males > females, 1-2:1)
- Results in an accumulation of dysfunctional cells because of a loss of regulation in cell division.
- Fatal if untreated! (Acute leukemia, المريض بيجيني على الطوارئ مش بالعيادة! .. Chronic: بيجيني المريض في العيادة ويكون اكتشاف المرض بالصدفة!)
- Often thought of as a childhood disease, BUT! The number of adults affected with leukemia is 10 times that of children! (extremely unlikely to see child with chronic leukemia, they usually have the acute form)

Etiology & pathophysiology:

- The etiology is unknown, it might be caused by: oncogenes mutation & tumor suppressor gene alteration, host factors, and environmental factors.
- Host factors:

  1- congenital chromosomal abnormalities → increase in patients with congenital disorders that have tendency for chromosomal abnormalities e.g. **Bloom's** syndrome, Fanconi syndrome, **Down's** & Klinefelter syndromes (30 times ↑ incidence of AL in child with Down's synd).

  2- Immunodeficiency: ↑ incidence of lymphoid leukemia & lymphoma (with hereditary immunodeficiency e.g. ataxia-telangiectasia & sex-linked agamaglobulinemia) → usually related to T & B lymphocyte gene rearrangement.

  3- Chronic bone marrow dysfunction (CBMD) syndrome have an ↑ risk of acute leukemic transformation.
- Environmental factors:

  1- Ionizing radiation: e.g. nuclear weapons in Hiroshima& Nagasaki. Both acute & chronic forms of leukemia including AML, ALL, CML were associated. ننتبه للصغار لما يروحون لعيادة الأسنان والأشعة اللي يتعرضون لها!

  2- Chemical drugs: e.g. **Benzene**, Chloramphenecol, Phenylbutazone and Cytotoxic alkylating chemotherapeutic agents (AML occur after tx with alkylating agents e.g. melphalan). The presence of RAS mutations in patients with AML has been associated with specific occupational exposure to chemicals.

  3- Viruses: The human T-cell leukemia-lymphoma virus-I (**HTLV-I**) has been implicated as a causative agent of adult T-Cell leukemia-lymphoma (now it has a vaccine, it is mandatory in the some countries). Another related virus **HTLV-II** has been isolated from patients with atypical hairy cell leukemia (CLL). The Epstein's Barr virus (**EBV**) has been linked to Burkitt's lymphoma.

Comparison of acute & chronic leukemia		
	Acute	**Chronic**
Types	1- Acute Lymphoblastic Leukemia (ALL) 2- Acute Myelogenous Leukemia (AML)	1- Chronic Lymphocytic Leukemia (CLL) 2- Chronic Myelogenous Leukemia (CML)
Age	All ages	Adults (old age usually)
Clinical onset	Sudden	Insidious (onset is more gradual)
Leukemic cells maturity	**Immature** (Large in size, >20% blasts either in peripheral blood or BM) Clonal proliferation of immature hematopoietic cells (the formation of blood or blood cells).	**Mature** forms of WBC
Anemia	Mild to severe	Mild
Thrombocytopenia	Mild to severe	Mild
WBCs	Variable	Increased
Organomegaly	Mild	Prominent

Myelogenous Leukemia:

- Leukemia characterized by proliferation of myeloid tissue (as of the bone marrow and spleen) and an abnormal increase in the number of granulocytes, myelocytes, and myeloblasts in the **circulating blood**. حطوا مليون خط على السيركليتنق بلود! لأنها first step to dx
- Myeloid tissue is a biologic tissue with the ability to perform hematopoiesis. It is mainly found as the red bone marrow in bones, and is often synonymous with this. However, myeloid can also be present in the liver and spleen. = myeloid tissue.
- A myelocyte is a young cell of the granulocytic series, occurring normally in bone marrow, **but not in circulating blood** (except when caused by certain diseases).
- Granulocytes are a category of WBC characterized by the presence of granules in their cytoplasm. They are also called polymorphonuclear leukocytes (PMN or PML) because of the varying shapes of the nucleus, which is usually lobed into three segments.
- The myeloblast is a unipotent stem cell, which will differentiate into one of the actors of the granular series.

الزبدة من الكلام كله، يقول لكم إنه الميلوجينس لوكيميا هي عبارة عن proliferation في myeloid tissue وزيادة غير طبيعية في الـ granulocytes, myelocytes, myeloblasts in the circulating blood لازم نعرف إنه في السركليتنق بلووود!! عشان كذا اسمها leukemia. + الميلوسايت هي خلية صغيرة منها تتكون الـmyelogenous WBC (زي ما تشوفون في الصورة) ، وهذي طبيعي نشوفها في البون مارو لأنه من هناك بتتكون عندي هذي الخلايا صح!! مو في السركليتنق بلود!!. النقطة الأخيرة يوضح لكم إن الميلوبلاست هي خلية جذعية، عندها القدرة إنها تكون أنواع من ال myelogenous WBC اللي تتميز بالـ granules.

Acute leukemia

Acute Myelogenous Leukemia (AML)

- Proliferation of myeloid tissue (BM & spleen) + abnormal increase in the number of granulocytes, myelocytes, myeloblasts in circulating blood.
- Predominant form of leukemia in neonatal period.
- 25% of all leukemias.
  - 85% of the acute leukemias in adults.
- Abrupt, dramatic onset (serious infections, abnormal bleeding)
- Uncontrolled proliferation of myeloblasts (hyperplasia of BM and spleen)
- Clinical presentation:
  - Symptoms related to pancytopenia: weakness, easy fatigue, SOB, infections, gingival bleeding, ecchymosis, epistaxis, menorrhagia.
  - Infrequent bone pain (sternum, long bones)
  - Onset: weeks to months.

Why there's pancytopenia?
Bc the bone marrow is Overcrowding by abnormal cells → Inadequate production of normal marrow elements

- Past medical history:
  - Prior hematologic disorders: Myelodysplastic syndrome, myeloproliferative disorder, Fanconi's anemia.
  - Prior chemotherapy and/or radiation therapy.
  - CHF & cardiac disease, prior transfusion or pregnancies, drug allergies, history of HSV infection.
- Physical exam:
  - Fever: almost always due to infection, small minority have fever related solely to underlying leukemia.
  - Skin: pallor, petechiae, ecchymoses, infiltrative lesions (leukemia cutis or granulocytic sarcoma)
  - Eye: retinal hemorrhages and/or exudates, pale conjuctivae.
  - Oropharynx: gingival hypertrophy (leukemic infiltration more w/ acute monoblastic leukemia), candidiasis, herpetic lesions.
  - Joints: polyarthritis, arthralgias, bone pain & tenderness.
- WHO Classification of AML:
  - AML with recurrent genetic abnormalities
  - AML with multilineage dysplasia
  - AML and MDS syndromes, therapy-related
  - AML, not otherwise categorized
- The prognosis is dependent on a range of key variables, the two main ones being age and cytogenetics

Acute Lymphoblastic Leukemia (ALL)

- Most common type of leukemia in children.
- 15% of acute leukemia in adults.
- Etiology:
  - Genetic syndromes: Down syndrome (both ALL & AML), Bloom syndrome, neurofibromatosis, schwachman syndrome, ataxia telangiectasia, Klinefelter's syndrome.
  - In utero exposure: ionizing radiation, related to MLL = inhibition of topoisomerase II: quinolones, flavonoids, catechins, podophyllin, benzene metabolites, estrogens, dipyrone (NSAID), mosquitocidal agent (Baygon)
- Clinical manifestations:
  - Bone marrow failure: Anemia, thrombocytopenia, neutropenia
  - Lymphadenopathy, hepatomegaly, splenomegaly
  - Bone pain, arthralgias (especially in children)
  - Infection, fever
  - Extramedullary spread: CNS involvement at diagnosis (5% children, 15% adults), Skin, Testes (10-15% boys)
  - **Mediastinal mass** (lymphoblastic lymphoma) or tissue mass (50% of T cell-ALL)
- Labs abnormalities:
  - Hyperuricemia, elevated LDH, tumor lysis: hyperkalemia, hyperphosphatemia, hypocalcemia.
  - Hypercalcemia → many infiltration, PTH-like substance.
- Immature lymphocytes proliferation in the bone marrow.
- Signs & symptoms may appear abruptly: fever, bleeding.
- Insidious with progressive weakness, fatigue.
- **Central nervous system manifestations**. you wont see CNS manifestation in AML!!! That's why treatment totally differs! A major difference between therapy for ALL and AML is the need for central nervous system directed therapy. Because Lymphocytes are smaller than myelocytes, myelocyte can't go to the hidden areas.. In ALL, give CNS prophylaxis!!!

- AML pts can present → having >70000 WBC + → can cause **leukostatic features** (cerebral hemorrhage, retinal hemorrhage, pulmonary hemorrhage) → there are myeloid cells occlude the vessels!! → DO LEUKOVARESIS!!!! (they may come with blindness bc of occluded BV)
- ALL pts can present with 15 yrs, with fever, feeling unwell, loss weight (vague symp) + lymphocytes 100,000!! → Do peripheral blood examination → there is lymphoBLASTs (but they wont occlude vessels)
- Myelocyte is big → don't go to hidden places (e.g. brain) → give systemic chemotherapy
Lymphocyte is small → can go to the hidden areas e.g. **brain + testis** !!! ☺ مهمة اقرؤوها!

Chronic leukemia

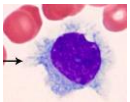
Chronic Myelogenous Leukemia (CML)

- Excessive development of **mature** neoplastic granulocytes in the bone marrow.
- Move into the peripheral blood in massive numbers.
- Ultimately infiltrate the liver and spleen.
- Chronic, stable phase followed by acute aggressive (Blastic) phase. Chronic transformed to acute → prog is very poor.
Philadelphia chromosome:
- Chromosomal abnormality causes chronic myeloid leukemia **t(9;22)**
- Genetic marker. (t(9;22) has a diagnostic value) CML يعني إذا مالقيناه نلغي
- The new 'fusion' gene BCR-ABL is capable of being expressed as a chimeric messenger RNA, which has been identified in cells from patients with CML

Chronic Lymphocytic Leukemia (CLL)

- The only leukemia that you can observe at early stage
- Production and accumulation of functionally **in**active but long-lived (no apoptosis), **mature**-appearing lymphocytes.
- **B** cell involvement (CD20 +ve)
- Lymph nodes enlargement is noticeable throughout the body → increase incidence of infection. There is abnormality with cell death → accumulation of not working cells! Loss function and became un-functioned!
- Complications from early-stage CLL is rare → Rx: watch and wait, no tx
  - May develop as the disease advances, if complication, then treat
  - Pain, paralysis from enlarged lymph nodes causing pressure.

❖ Hairy cell leukemia:



- Clonal proliferation of abnormal B cells Accumulate in the bone marrow and spleen.
- 2% of all adult leukemias, usually in males >40 yrs old
- chronic disease of lymphoproliferation → B lymphocytes that infiltrate the BM & liver.
- Cells have a hairy appearance.
- Symptoms from: **massive splenomegaly** → pancytopenia → infection → vasculitis.
- Tx: alpha-interferon, pentostatin, cladribine.

Unclassified leukemia:

- Subtype can't be identified.
- Malignant leukemic cells may have lymphoid, myeloid, or mixed characteristics.
- Frequently theses patients don't respond well to treatment (**poor prognosis**).

Differential Diagnosis of leukemia:

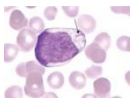
1- Aplastic anemia → Bone marrow fail totally to produce all cells, but RBCs will be maintained bc it is produced by other lymphoid tissue.
2- Myelodysplastic syndrome → BM produces cells but abnormal in shape & function.
3- Multiple myeloma.
4- Lymphoma
5- Sever megaloblastic anemia.
6- Leukemoid reaction. E.g. sepsis, has a very high WBC.

But if you have **myeloBLAST >20%**, forget about these DDx!! (: هذا هو الفيصل ما بين هذه الدفرنشيالز
U wont dx leukemia unless you have peripheral blood evaluation!

Clinical manifestations:

• **Clinical manifestations related to problems caused by:**	
✓ Leukemic cells infiltrate patient's organs: - Splenomegaly, hepatomegaly, lymphadenopathy, bone pain, meningeal irritation (ALL), oral lesions (chloromas: solid collection of leukemic cells occurring outside BM)	✓ Bone marrow failure: - Overcrowding by abnormal cells → Inadequate production of normal marrow elements → Result in: Anemia, thrombocytopenia, decrease number & function of WBCs.

Diagnostic studies: (for prognostic & diagnostic purposes)

1- To diagnose & classify	2- To identify cell subtype & stage
- Peripheral blood evaluation (CBC & blood smear) - Bone marrow evaluation → Increased cellularity, reduced erythropoiesis, reduced megakaryocytes + Replacement by blast cells >20% - **Best Initial Test** 1st step to dx any pt with hematological dis → peripheral blood smear looking for abnormal cells احفظها زي اسمك.	- **The Most Accurate Flow-cytometry** (to know the phenotype, flow cytometry is the method of detecting specific CD subtype associated with each type of leukemia) Morphologic, histochemical, immunologic, and cytogenic methods. - The presence of **Auer rods** is consistent with a diagnosis of **AML** 

Treatment:

Collaborative Care

- Goal is to **attain remission** (when there is no longer evidence of cancer cells in the body)
- **What is Remission?** The main aim of treatment for ALL is to **give a remission**. This means that the abnormal, immature white cells or blasts can no longer be detected in the blood or bone marrow, and normal bone marrow has developed again. For many people with ALL the remission lasts indefinitely and the person is said to be **cured**.

Collaborative Care (cont.)

1 - Chemotherapy treatment	a. Induction therapy -all pts
	• Attempt to induce or bring **remission**. • Seeks to destroy leukemic cells in the tissues, peripheral blood & bone marrow. • Patient may become critically ill (provide psychological support as well)
	b. Intensification therapy -like consolidation, same drugs but at higher dose
	• **High**-dose therapy. • May be given after induction therapy. • Same drugs at higher doses and/or other drugs.
	c. Consolidation therapy
	• Started after remission is achieved. • The purpose is to eliminate remaining leukemic cells that may not be evident.
	d. Maintenance therapy –only in ALL not AML
	• **Lower** dose of the same drug.

2- Combination therapy	• Mainstay treatment • **3 purposes:** ✓ ↓ drug resistance ✓ ↓ drug toxicity to the patient by using multiple drugs with varying toxicities ✓ Interrupt cell growth at multiple points in the cell cycle

Bone marrow & stem cell transplantation

- Goal: Totally eliminate leukemic cells from the body using combinations of chemotherapy with or without total body irradiation.

- Eradicates patient's hematopoietic stem cells. → Give him one of strongest chemotherapy ever!! You will make his bone marrow ZERO!!! RBC, WBCs, plt… = zero
  Many pts die in this procedure ☹
  Aim to destroy any remnant of blast and then to receive the new one.
- Replaced with those of an HLA-matched (Human Leukocyte Antigen)
  - Sibling (is a brother or a sister; that is, any person who shares at least one of the same parents)
  - Volunteer
  - Identical twin
  - Patient's own stem cells removed before

★One might wonder wether to proceed directly to bone marrow transplant (BMT) after remission or only give more chemotherapy?
if the prognosis is poor then go straight to BMT, but if the prognosis is good give more chemotherapy.the best indicator of prognosis in *acute leukemia* is cytogenetics or assessing specific chromosomal characteristics found in each pt.
[GOOD cytogenetics=less chance of relapse=more chemotherapy]
[BAD cytogenetics=more chance of relapse=immediate BMT]
(MASTER THE BOARDS)

Case مهم تقرؤونها

- 17 years old lady presented to the ER with CBC: WBCs 50,000, HGB 10, PLT 15000 + abnormal circulating blasts 30%
- How to proceed with diagnosis and tx?
    - Diagnosis & risk stratification: لازم أسوي كل شيء هنا!
        1- Peripheral blood for:
            a. morphology → abnormal blasts.
            b. Peripheral blood flow-cytometry → 30% blasts with CD33, CD34 +ve.
        2- BM biopsy for:
            a. Morphology (myeloblasts)
            b. Flow-cytometry (50% blasts express M antigens)
            c. Molecular (FLT 3-ITD +ve) (to know what is the causative agent causing leukemia)

Peripheral blood film will tell u just blast, wont tell u which type of AML it is…

Then how to approach the pt with suspected leukemia????

1- **peripheral blood morphology** (I wanna determine which subtype of leukemia this 30% myelobblast!!

هل ممكن يجيني المريض بدون ميولوبلاست أو بدون أي بلاست؟ ايه ممكن! البلاست بتكون في البون مارو!!!! سو أنا بسوي برفرال بلود مورفولوجي وبون مارو..

بس قبل البون مارو بسوي flow cytometry

أكلم اللاب وأقول للباثولوجست يجي من بيته عشان يشوف،

2-**flow -cytometry**

= myeloblast!!!يحدد لي شكل الميلوبلاست CD33 or CD34

So we can diagnose with peripheral blood morphology and flow cytometry but I have to go next day for **bone biopsy**, bc peripheral blood morph and flow cytometry wont tell me if there is no blast in blood but there is in the bone!!

!!لازم اسوي بون مارو بيوبسي حتى لو طلعت لي البلاست في البلود

- Treatment:
    - ★ Goals:
        1- **Remission induction** (chemo for 28 days) حتتنوم، مش حتروح للبيت
        2- Response assessment (Day 28)
        3- Consolidation (chemo/SCT)
        4- Maintenance only in ALL not AML!!

نقطة ١: هل أعطيهم الكيمو في كل الـ٢٨ يوم؟ لا!!! والا موّتّ المريض في ثلث المدة هذي! أجل وش أسوي؟ أعطي الكيمو ٧ أيام بس. ثم أنتظر، لأن العمر النصفي للplt: 10dys, RBCs 120, WBC 1-3 dys

بعدين أنتظر هذي الفترة (٢١ يوم الباقية) وأشوف كيف الاستجابة اللي بتكون عبارة عن: destroying all cell lines

so what is the MAX day of response? 28th day.

* من الأشياء المهمة اللي تصير مع الكيمو والترانزبلانت، هو العقم مدى الحياة، خصوصًا مع ALL لأنهم ياخذون aggressive chemo .. فإذا ما ناقشت المريض عن العقم في هالحالة، يعتبر واحد من أهم الأشياء اللي تدخل في الإثكس! فلما يتزوج بعدين وما نقول لهم يجيني بعدين ويرفع علي قضية ☺ منب رايقة أنا بعد ☺

نقطة ٢،٣،٤:

I have to do baseline bone marrow biopsy, Take BM biopsy after 28 dys then compare!! So how I can interpitate?

Leukemic blast is < 5% !مبااااارك = called complete response, remission

After that I enter to consolidation

AML → chemotherapy

ALL →stem cell transplant(ALL is treated and cured by chemo 'especially in children it can be cured'!!! After chemotherapy are finished, the pt receives a stem cells transplant to restore the bone marrow) ,

After that maintenance, only in ALL (خفيف، ياخذه في البيت)

MCQs

1- A 47-year-old woman presents to clinic concerned about her recent ill health. She has noticed over the last three months that she has been suffering from headaches, fatigue and recurrent infections. She notes she has rarely been to the doctor before and otherwise leads a healthy lifestyle. She decided to see a doctor when she noticed petechial rashes appearing on her arms. On examination there is no organomegaly and blood tests reveal an MCV of 105, a pancytopenia with the bone marrow appearing hypocellular on biopsy.?

a. Chronic myeloid leukaemia
b. Myeloproliferative disorder
c. Aplastic anaemia
d. Acute lymphoblastic anaemia

2- A 65-year-old man presents to you reporting he has become increasingly worried about his lack of energy in the last 2 weeks. He mentions he has been increasingly tired, sleeping for long periods and has suffered from fevers unresponsive to paracetamol. He became increasingly worried when he noticed bleeding orginating from his gums. A blood film shows auer rods, hypogranular neutrophils and stains with Sudan black B. The most likely diagnosis is?

a. Acute lymphoblastic leukaemia
b. DiGeorge syndrome
c. Disseminated intravascular coagulation
d. Acute myeloid leukaemia

3- A 5-year-old girl presents with her parents who have become concerned about the small petechiae and ecchymoses on her skin. An abdominal examination reveals hepatosplenomegaly. You suspect an acute leukaemia. The most appropriate initial investigation for diagnosis is?

a. Chromosomal analysis of bone marrow cells
b. Electron microscopy
c. Flow cytometry
d. Direct microscopy of bone marrow cells

Answer key:

1 (C) | 2 (D) | 3 (D)

Not convinced? Check the link