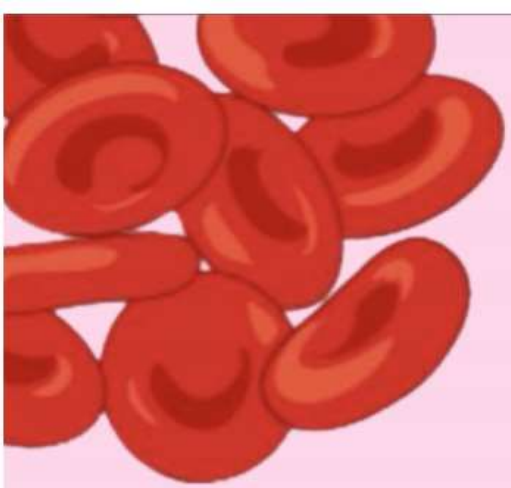


النادي الطبي

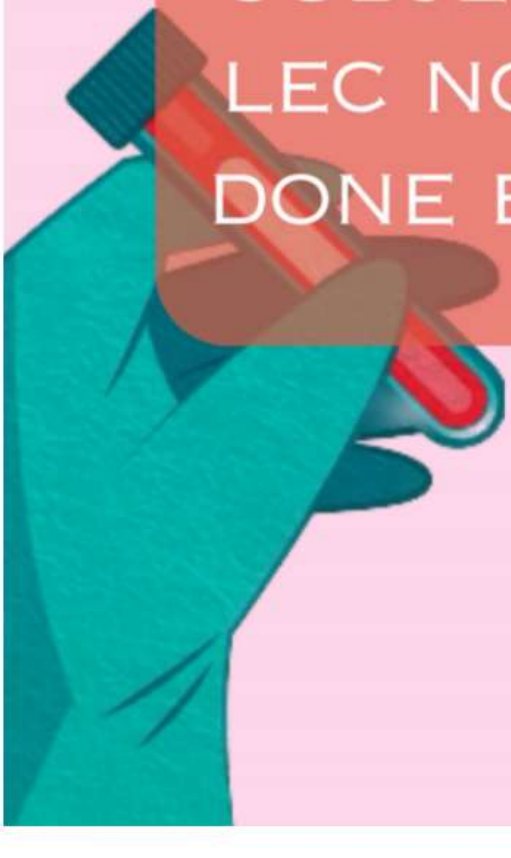
HEMATOPOIETIC & LYMPHATIC SYSTEM

-HAYAT BATCH-

SUBJECT : **Clinical Medicine**

LEC NO. : **2**

DONE BY : **Vein- Johainah Taha**



وَقُل رَّبِّ زِدْنِي عِلْمًا

"جميعنا نملك الكثير من العمل للقيام به، لا أحد يعلم ما هو القادم، لكن العمل بجد هو ما يُجمِّل مكانتنا."

ان شاء الله تكونوا بخير، قبل ما نبدأ بالمحاضرة، نصيحة كونوا دارسين محاضرة الباثو 5 ، ما تقرأوا المحاضرة و انتوا ما بتعرفوا شي عن محاضرة 5، هاي المحاضرة مكملة الها

اي شي عليه بكون بالاحمر بكون مهم،صدقاً كل شي مهم لانه الموضوع متكامل،
بس لو بدكم تأوتوا ادرسوا العلاج لأنه موضوع جديد

ما تنسوا تشكروا ربنا على نعمة الصحة 🙏 ربنا لك الحمد و الشكر دائماً و أبداً
و بسم الله نبدأ🙏

introduction

- cancer of blood cells in which neoplastic cells morphologically and immunophenotypically resemble B-lineage or T-lineage precursor cells (lymphoblasts)

- Leukemia refers to a disease arising in the bone marrow (medullary disease).

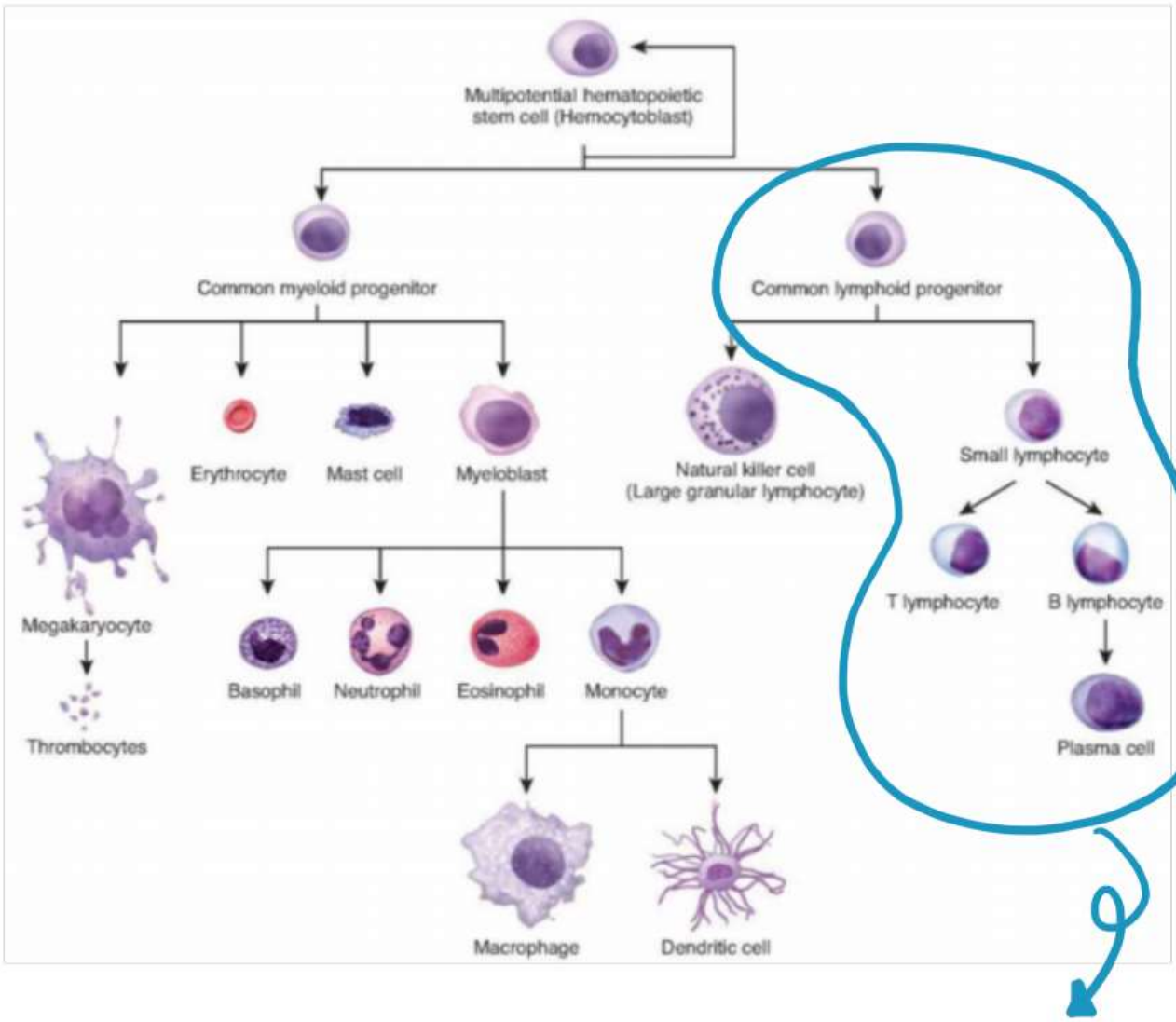
*In general, The most common site of leukemia in pediatric is (ALL) which is a malignancy in the bone marrow (the place where RBCs are formed and produced)

*It is also called an : Intramedullary disease

*So it's originate from the bone marrow

*hematopoiesis: The process of production of blood cells

*The most common blood test is the CBC (complete blood count), it measures blood cells such as WBCs, RBCs, platelets which are produced in the bone marrow

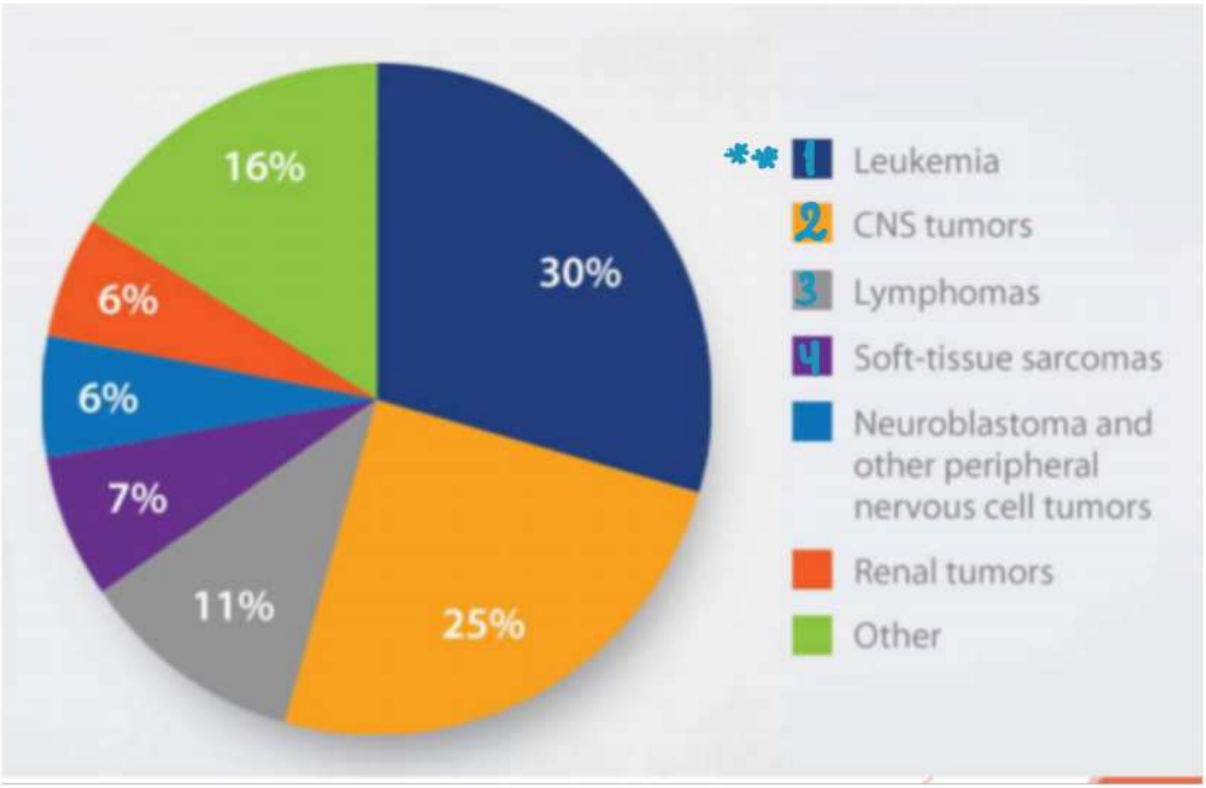


*Leukemia could happen in any stage of this maturation

*From common lymphoid progenitor down to mature T and B cells

- ALL is the most common cancer in children, with a peak incidence at age 2-5 years.

- ALL is classified by immunophenotype.
  - 80%-85% of childhood ALL is B-cell ALL.
  - About 15% of childhood ALL is T-cell ALL.



*Let's talk about the Incidence of malignancy in pediatric in general:

*The most common malignancy in pediatric is Leukemia,then CNS, then lymphoma.

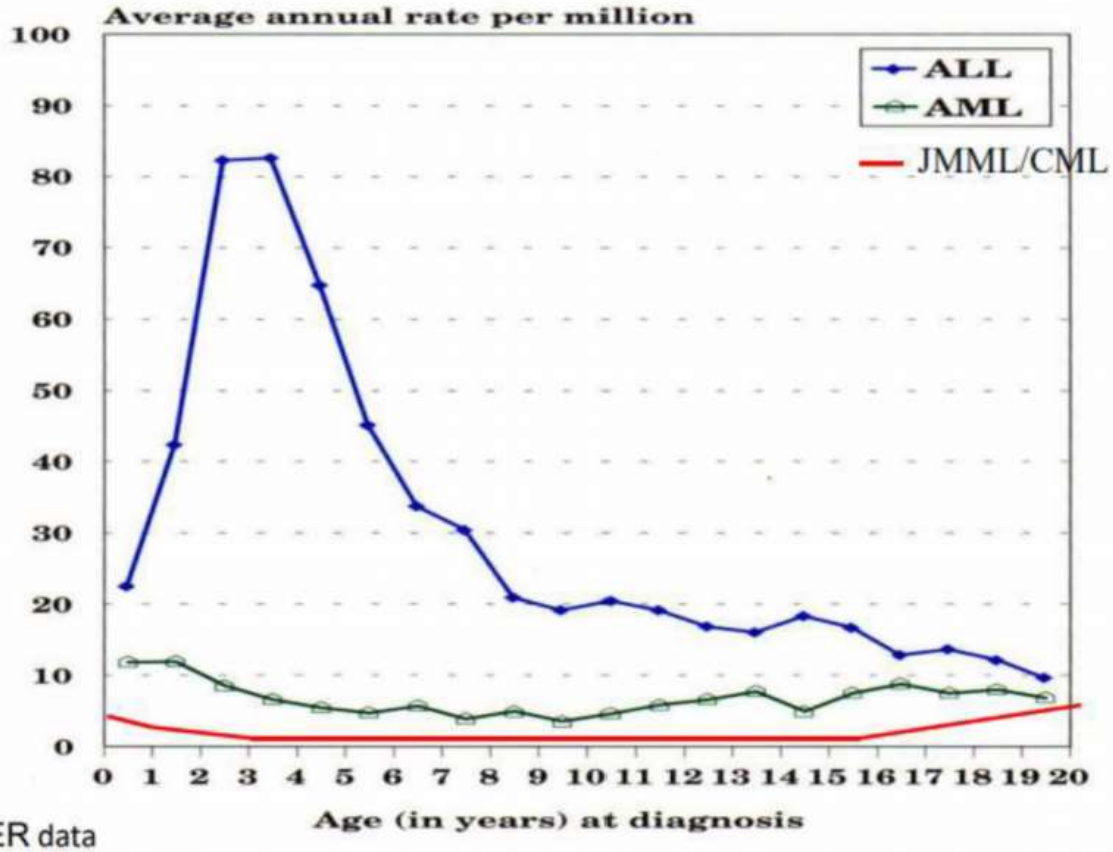
*And 80% of the leukemia are acute lymphoblastic leukemia

*And 80-85% of the are of B-Cell origin.

Incidence/Prevalence

- 41 per million children aged < 15 years in United States
- 17 per million adolescents aged 15-19 years

Age Specific Incidence of Leukemia



SEER data

*in general pediatric malignancy is UNCOMMON.
*ALL is between the age of 2-4

etiology

خلي ببالكم شغلة مهمة، كلمة Multifactor يعني في اكثر من سبب اجتمعوا و كانوا السبب بحصول لوكيميا مو شرط سبب واحد, مثال عامل وراثي مع تعرض لأشعة

- Multifactorial
- Risk Factors:
  - Radiation:
    - prenatal x-ray exposure
    - (CT) scan during childhood or adolescence associated with increased risk of leukemia or lymphoma
  - previous treatment with chemotherapy
  - inherited and familial risk factors
    - genetic syndromes with predisposition to ALL (Bloom syndrome, ataxia-telangiectasia, neurofibromatosis type 1, Fanconi anemia, Li-Fraumeni syndrome) + down syndrome
  - exposure to solvents or pesticides

مهم

Why Children get Leukemia??

1-Radiation (diagnostic or therapy):

*X-ray exposure through pregnency is not teratogenic but it can increase the risk of leukemia in children later.

*CT scan = 200 to 600 X-rays. So repeated CT scan is a risk factor for developing leukemia.

*Radiotherapy

*Chemotherapy

2-Inherited and familial disorders like down syndrom and the disorders above (حأوضح الكم كل مرض للإستزادة بالصفحة الجاية)

3-Exposure to solvents or pesticides, such as: Benzine, Radiation from nuclear bombs

4-Unknown cause: Most cases

الصفحة هاي للعلم فقط

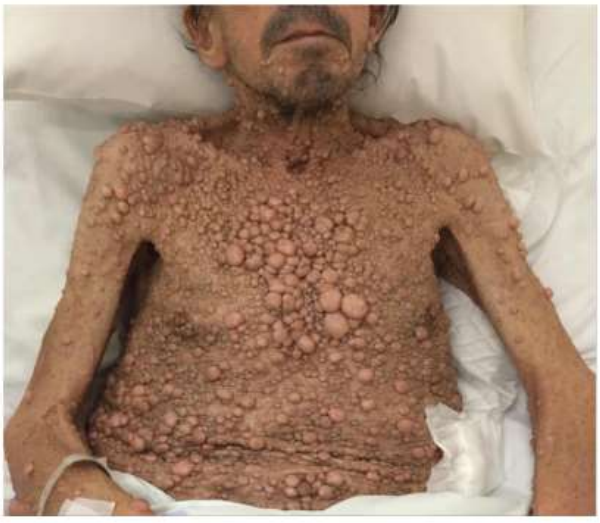
Bloom syndrome : A rare, inherited disorder marked by shorter than average height, a narrow face, a red skin rash that occurs on sun exposed areas of the body, and an increased risk of cancer.

Ataxia-telangiectasia (AT) is a rare inherited condition that affects the nervous system, the immune system and other body systems. It is characterized by ataxia (lack of coordination) due to a defect in the cerebellum (the part of the brain involved in coordinating the movement of muscles)

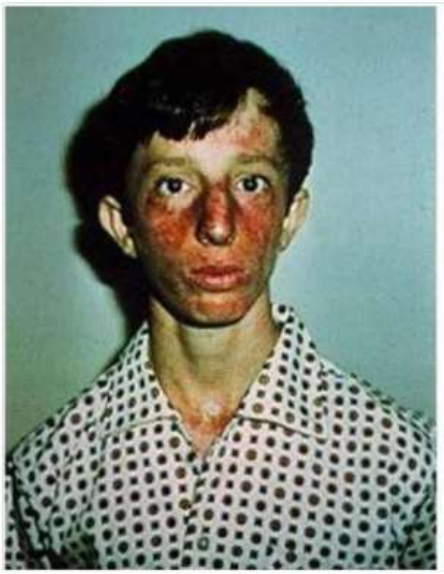
Neurofibromatosis type 1 (NF1) : is a genetic condition that causes tumours to grow along your nerves.

Fanconi anemia : is a rare disease passed down through families (inherited) that mainly affects the bone marrow. It results in decreased production of all types of blood cells. This is the most common inherited form of aplastic anemia. Fanconi anemia is different from Fanconi syndrome, a rare kidney disorder. (الجماعة الي بحفظوا الشكل تبع الامراض)

Li-Fraumeni syndrome : is a rare hereditary or genetic disorder that increases the risk you and your family members will develop cancer (breast mostly).



NF1



Bloom syndrome

Pathogenesis

هسا حنبدأ باثو 🦉🐵لو مو
دارسين باثو 5 كان الله بعونكم

- preleukemic cells acquire multiple genetic alterations:
  - ✳ disrupting genes that regulate hematopoiesis and lymphoid development (such as RUNX1 and ETV6) → t 12:21
  - constitutively activating tyrosine kinases (such as ABL1 mutations) → Philadelphia chromosome
  - activating oncogenes

- effects of leukemic transformation may include
  - arrested differentiation of lymphoblasts into B and T lymphocytes
  - increased cell proliferation To overcome the problem
  - decreased apoptosis

So, there is an accumulation of luekemic cells at the bone marrow that could grow over other normal myeloid proginator cells -> this effect RBCs, platelets and WBCs count
The patient will come with :

- replacement of bone marrow by ALL blasts

  - anemia, Low RBCs
  - thrombocytopenia,
  - neutropenia, Current infection
  - high to very high white blood cell count (> 100 x 109 cells/L)

Bot

Case حفظ لسؤال

They are high but inefficient so they could cause bleeding

Immunophenotype and Cytogenetics

- For diagnosis and prognosis
- Immune phenotype is defined by expression of cytoplasmic cluster differentiation (CD) markers
- precursor B-cell ALL (B-cell ALL) - defined by expression of cytoplasmic CD79a, CD19, HLA-DR
  - Example: common precursor B-cell ALL - about 75% of B-cell ALL characterized by :
    - CD10 expression and lack of surface or cytoplasmic immunoglobulin expression
    - frequently associated with favorable cytogenetics
    - best prognosis of any ALL subtype

بتتذكروا بالباثو حكينا في اشياء بتكون favorable و non

*Immunophenotype is a test to know the type of leukemia (lymphid-myeloid) and its origin (B-T) by checking the CD markers on the cell surface, by a process which is called the flow cutometric analysis.

*Cytogenic is a test to know the genetic alterations and the translocations of each cell (hyper/hypoploidy - translocation)

types of common genetic alterations in ALL

This is one of the initial tests

- high hyperdiploidy (51-65 chromosomes/cell or DNA index > 1.16)
- hypodiploidy (≤ 44 chromosomes/cell)
- Translocations
  - *ETV6-RUNX1* t(12;21) (p13.2;q22.1) cryptic translocation) ⇝ Very common 80% of ALL
  - *BCR-ABL1* t(9;22)(q34.1;q11.2) translocation) also called Philadelphia chromosome
  - *MLL* (KMT2A) rearranged t(v;11q23) translocation
- Deletions
  - *PAX5* deletion

*ETV6-RUNX1 is a major rule in prognosis, and is very common in ALL patients (80%)

*Favorable (good prognosis) : Hyperdiploidy + cryptic translocation

Clinical Presentation

- symptoms usually develop over days to weeks, less commonly over several months

↳ Because it's Acute not Chronic

- presenting symptoms and signs correlate with leukemic cell burden and extent of marrow infiltration (and resulting cytopenias)

① ②

The more leukemia cells we have in bone marrow the more cytopenias we have reflected as symptom on the patient

symptoms

↳ unexplained fever

- fever due to leukemia or neutropenia-related infection
- fatigue, lethargy, or pallor due to anemia → ↓ RBC, ↓ Hb
- bleeding, petechiae, or bruising due to thrombocytopenia
- ** bone or joint pain, limp
- splenomegaly, hepatosplenomegaly
- lymphadenopathy

Which are caused by infilteration

زهرة شبابي صارت جرجير من هالجامعة

The flower of my youth became arugula from the university.

oncologic emergencies at presentation

+ فيلم متذكرين المصطلحات.

السلايد مهمة جدًا عشان لتحت حنحكي عنهم

1. tumor lysis syndrome (نقاط عنه بالأسفل)
2. febrile neutropenia
3. leukostasis (due to hyperleukocytosis [white blood cell count > 100,000/mm3]), which may present with hypoxia, dyspnea (ضيق النفس), headache, somnolence (نعاس), confusion, or blurred vision, due to viscosity
4. severe thrombocytopenia or anemia
5. mediastinal mass compressing (تضغط) trachea or superior vena cava and causing respiratory distress or superior vena cava syndrome (more common in T-cell ALL)

هدول مجموعة من الsymptoms الخطيرة الي ممكن يظهروا حأشرح كل نقطة مع رقمها
(يرجى قراءته لانه مهم)

1- Tumer lysis usually happened at the begining of chemotherapy or spontaneously, when we have many malignant cells, they start to lyse continuosly, and that could lead :
*Hyperkalemia (خروج البوتاسيوم من داخل الخلايا الى خارجها) -> arrhythmia
*Hyperphosphatemia -> vomiting, cramps, nausia
*Hypoglycemia and seizure which can be the first presentation
*uricemia (increase uric acid)
*maybe: hyperglycemia and kidney failure

2- febrile fever due to current infection because of neutropenia

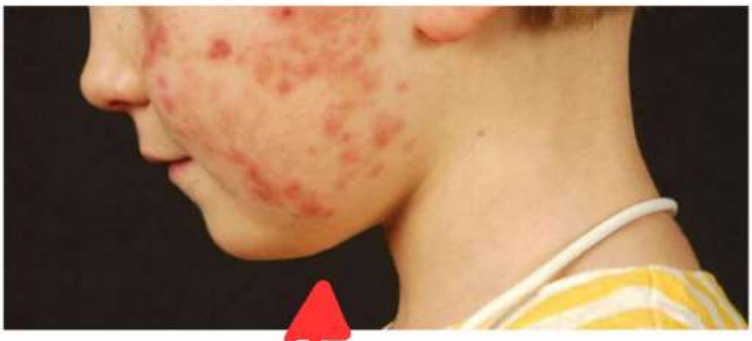
History

Ask about the risk factors

- Past Medical History
  - cancer predisposition syndromes
  - radiation exposure
  - chemotherapy
- Family history of leukemia To check if there is any translocation

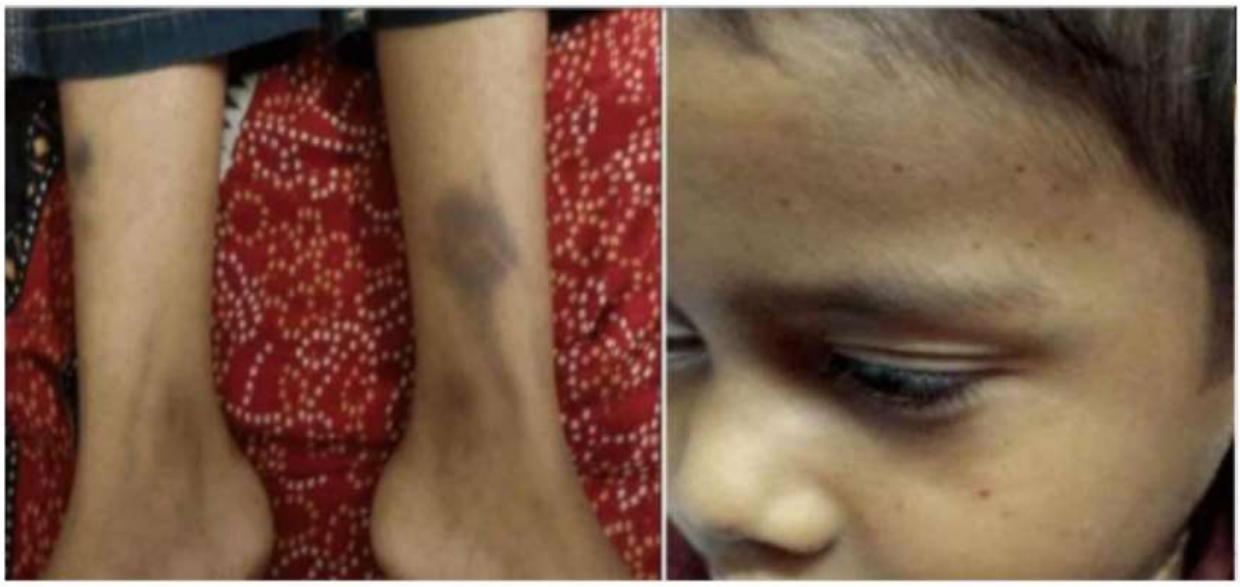
Physical exam

- General:
  - Fever
  - Lymphadenopathy
  - Pallor
  - Headache
  - respiratory distress



- Skin The signs of thrombocytopenia
  - petechiae, purpura, or ecchymoses suggestive of bleeding diathesis
  - leukemic skin lesions (leukemia cutis)

+ skin rashes which are a non-branchable and not palpable



ecchymoses which is also a sign of thrombocytopenia

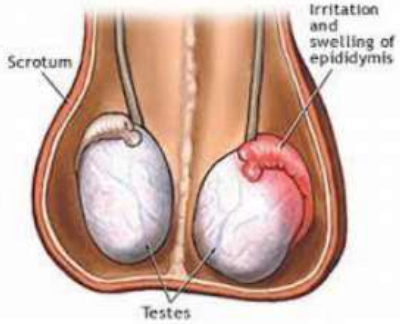
petechiae rash which is smaller than 2 mm in diameter and non blanchable
(لو ضغطت عليها ما بروح اللون)

- HEENT
  - orbital or tonsillar infiltration → Not Common
  - visual problems
  - cranial nerve palsy may indicate CNS leukemia

لـ مشاكل بالاحساس

- Chest
  - Respiratory distress more common with T-cell ALL
  - Assess for effusion and mediastinal mass

- Abdomen
  - splenomegaly and hepatomegaly
  - lesions suggestive of testicular infiltration
  - testicular swelling



Always if the man has a leukemia, we have examine their testes. because it's a common site of metastasis. Check if there is any enlargement or swelling.

diagnosis

- Typical signs or symptoms of ALL
- cytopenias, leukocytosis, and/or leukemia blast cells detected on blood smear
- bone marrow aspirate and biopsy and confirm diagnosis
  - morphologic identification of lymphoblasts on microscopy
  - flow cytometry to determine immunophenotype (شرحناهم)

- complete blood count with differential
- serum chemistry profile:

شرحناهم و حكينا كلهم بزيدوا الا Ca بنقص

- tumor lysis syndrome (TLS) panel including lactate dehydrogenase (LDH), uric acid, potassium, calcium, and phosphorous
- liver function tests, kidney function tests → To make a baseline before chemotherapy
- disseminated intravascular coagulation (DIC) panel including d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)

بنفحص ال (DIC) لانه حكينا بالباثو انه الmalignancy بزيد الDIC لهيك لازم اشيك عليه

- lumbar puncture concurrent with intrathecal chemotherapy

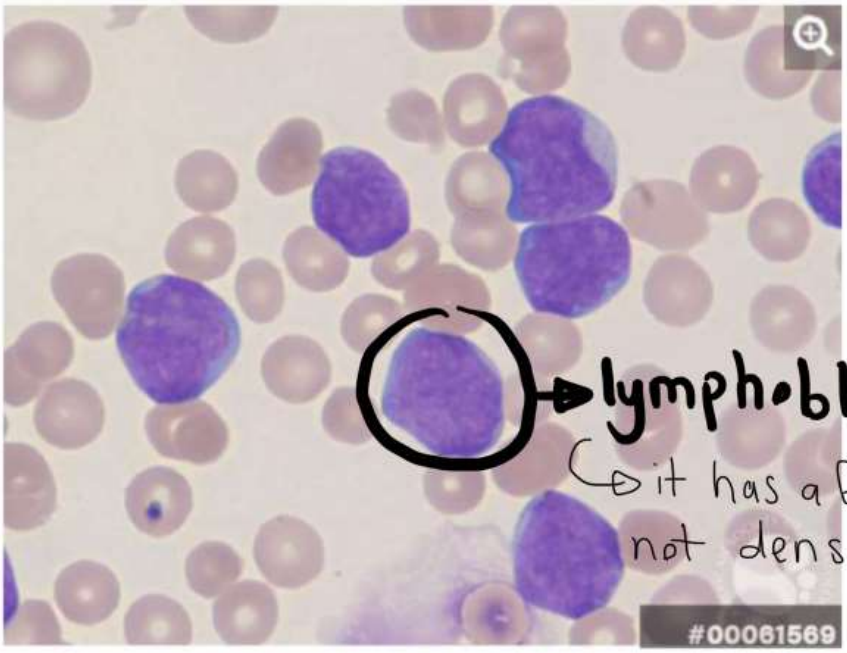
cerebral spinal fluid خزعة من

To see if there is any CNS involvement + we can give a chemotherapy in the same needle

- chest x-ray to rule out mediastinal mass
- scrotal ultrasound if suspected testicular involvement
- CT/MRI of head with contrast if neurologic symptoms

To detect any infilteration for the meninges

Peripheral blood film



لما تشوفوا هيك منظر عالسريع بتحكوا المريض معه لوكيميا

Differential Diagnosis

يعني امراض غير اللوكيميا و الهم نفس الاعراض
حسيت من نبرة صوت الدكتورة انهم مو كثير مهمين 🤣

(SLE)

- systemic lupus erythematosus or other rheumatological disorders
- viral infections such as Epstein-Barr virus (EBV) infection and parvovirus infection may cause hematologic abnormalities similar to acute leukemia[3]
- systemic-onset juvenile idiopathic arthritis
- benign proliferation - normal precursor B-cells (hematogones) in bone marrow may increase with viral infection, chemotherapy, or bone marrow transplant (leukemoid reaction)
- other blastic hematopoietic neoplasms
  - acute myeloid leukemia (AML)

الحمدلله على نعمة الصحة 🙏 الله يحمينا يارب من شر المرض

Management

هسا بدنا نحكي عن فترة العلاج (مهم)

- risk stratification
  - patient characteristics, leukemic cell characteristics (immunophenotype, cytogenetics), and response to initial treatment are used to predict risk of treatment failure
  - Treatment according to risk-group-specific protocols that may include more intensive therapy and/or increased supportive measures

اول خطوة بالعلاج هي اني احدد المريض بأي risk group:
Low risk / intermediate risk / high risk / very high risk

after 1 month we should stratified the patient on some characteristics such as the age, gender, race, and syndromes

توضيح نقطة 1 و الي هي مهمة كثير:
لازم نحدد هل الوكيميا Tcell او Bcell لانها رح تفرق معي بال Risk group ، الTcell اخطر مثلا (بالسلايدات الجاية حنحكي شو الاشياء الخطيرة و شو الشغلات المو خطيرة)

و في نقطة مهمة ، و هي انه لازم اقيم الresponse تبع الinitial treatment كيف هو بعد 1month ، لو ما كان في response هاد شي risky

طيب ليش احنا بنعمل هدول القروبات ؟ لا نه لكل قروب في طريقة علاج خاصة فيهم، و مدة للعلاج تحدد بحسب الrisk group

وانا أفرغ

prognostic factors in ALL include

مهمين

Higher risk group

- unfavorable prognosis
  - Age<1year and >10 years
  - white blood cell (WBC)> 50000 → Important in initial presentation
  - CNS or testicular involvement
  - T-cell
  - hypodiploidy (≤ 44 chromosomes per cell)
  - Philadelphia chromosome (*BCR-ABL1* fusion or Ph+ or t(9;22)(q34;q11.2)
  - *MLL* (*KMT2A*) rearrangement (t(v;11q23.3))
  - intrachromosomal amplification of chromosome 21 (iAMP21)
  - high minimal residual disease (MRD) (≥ 0.01%) following induction therapy → After 1 month their initial response is low
  - Down syndrome
  - obesity
  - black race and Hispanic ethnicity
  - male gender

Favorable prognostic factors

- Age: 1 to < 10 years
- Girls
- B-cell ALL
- No CNS or testicular involvment
- high hyperdiploidy (51-65 chromosomes/cell or DNA index > 1.16)
- *ETV6-RUNX1* (t(12;21)(p13.2;q22.1) cryptic translocation)
- *ERG* deletion
- Response to treatment

management of newly diagnosed ALL

- chemotherapy is mainstay of treatment
- treatment regimens consist of 4 major components
  1. induction therapy (also called remission induction)
  2. consolidation therapy (also called intensification)
  3. central nervous system (CNS)-directed therapy
  4. Maintenance → To allow normal marrow to grow again
- HSCT is generally reserved for children with induction failure* or very high risk for relapse

حنشرح عن تعريف كل وحدة بالسلايدات الجاي

كل مرضى الALL بنبدأ معهم chemotherapy و بعد شهر لازم اشوف كيف الresponse

High and good response → Curable but needs a long time treatment

هسا حنحكي عنه بالتفصيل بالادوية و الخطوات بالترتيب

If there is no response and the chance to cure and survive is low → HSCT haematopoietic stem cell transplantation

1

remission induction

- goal is to achieve complete remission (no clinical or molecular evidence of disease)
- 4-6 weeks مهم
- 3- or 4-drug regimen consisting of vincristine, L-asparaginase, and a corticosteroid, with or without an anthracycline + intrathecal chemotherapy
- if remission not achieved, additional chemotherapy is given and, if complete remission is subsequently achieved, hematopoietic stem cell transplant (HSCT) may be indicated
- if remission achieved treatment continues to consolidation phase

2

consolidation therapy

- begins after complete remission is achieved
- regimens generally lasts 6-9 months مهم
- combination of cyclophosphamide, cytarabine, mercaptopurine, methotrexate, corticosteroids, vincristine, and intrathecal chemotherapy
- high risk of treatment-related adverse effects

الله يعافينا و يعافيكم، هاي اصعب مرحلة عند مريض السرطان، بفقد شعره و بتعب كثير و بتبدأ أعراض الأدوية تظهر عليه

*In this stage, we'll see the following in the patient :

1- sever thrombocytopenia
2- sever anemia
3- infection

3/

CNS-directed therapy

كل المرضى لازم اعمل الهم هاي الخطوة سواء صار معهم involvement in CNS or not ضروري احميهم

- indicated in all children
- starts during induction, and may continue through maintenance
- intrathecal chemotherapy (methotrexate alone → CNS1, or triple therapy with methotrexate, cytarabine, and hydrocortisone → CNS 2+3)
- CNS-directed systemic chemotherapy (dexamethasone, L-asparaginase, and methotrexate) are standard in all children.
- cranial radiation is used infrequently and is generally reserved for children with highest risk of CNS relapse

4/

Maintenance

- continues until ALL has been in complete remission for 2-3 years
- mercaptopurine orally daily, methotrexate orally or parenterally weekly along with pulses of vincristine and a corticosteroid (prednisone or dexamethasone)

*This pase (1.5 to 2 years)

*During this phase the normal bone marrow start to grow again and start to synthesise blood comonent

المريض ببدأ يستعيد شعره الي فقده و ببدأ يرجع لوضعه الطبيعي و جسمه ببدأ يرجع لوضعه الطبيعي
بس مع هيك لازم يلتزم بالادوية المذكورة لاحميه من المرض لحتى ما يرجع اله

complications

- Oncologic Emergencies شرحناهم
  - **tumor lysis syndrome** - usually occurs in response to therapy, but can occur spontaneously in children with high presenting white blood cell (WBC) count[3]
  - Leukostasis (WBC > 100,000/mm^3)
  - febrile neutropenia
  - severe thrombocytopenia or anemia **Normal platelt count 150000-450000**
  - mediastinal mass (common in T-cell ALL), tracheal compression or superior vena cava syndrome[3]

Early Complications

Through chemotherapy

- toxicities of chemotherapeutic agents
- cytopenias and infection
- osteonecrosis
- * DVT → **Very common** ← الدكتورة اهتمت فيه
- Pancreatitis
- peripheral neuropathy
- depression[4]

Late Complications

After finishing the chemotherapy

- complications common after cranial radiation:
  - neurocognitive deficits — In patient taking radiation
  - neuroendocrine abnormalities such as growth hormone deficiency and precocious puberty → Common
  - obesity and metabolic syndrome

complications related to management

- hypercoagulopathy/stroke - asparaginase
- peripheral neuropathy - vincristine — Numbness, weakness, unability to walk
- osteonecrosis and bone mineral density deficits - long-term corticosteroid exposure, asparaginase
- cardiotoxicity - anthracyclines
- secondary malignant neoplasms - chemotherapy (such as anthracyclines, oxazaphosphorines, and epipodophyllotoxins), radiation
- infertility - alkylating agents (such as cyclophosphamide), radiation

*All chemotherapy cause

GI effects

Nausia

Vomiting

Bone Marrow suppression

Prognosis

- overall prognosis in newly diagnosed childhood ALL[1]
  - remission achieved in about 98%
  - reported survival in children and adolescents aged 1-18 years
    - 5-year survival > 90%
    - long-term event-free survival about 85%
  - complications due to cancer treatment may persist or develop months to years after therapy

Quiz Time

1- A patient had blasts with immunophenotype Cd13+, membrane Cd19+, Cd79a+, and cytoplasmic Cd22+, Cd10- and Cd20-. The most likely diagnosis is:
a. Early precursor B ALL
b. Common ALL
c. Late pre-B ALL
d. Mixed phenotype acute leukemia
Answer : A

2- structural abnormalities in childhood All associated with a poor outcome include the following, except:
a. t(9;22) BCR/ABL
b. t(1;19) E2A/PBX1
c. t(4;11) MLL/AF4
d. t(1;14) TAL1/TCR
e. All of the above
Answer : E

3- Children with following genetic diseases are at increased risk of, all except:
a. Down syndrome
b. Neurofibromatosis type 1
c. Bloom syndrome
d. Ataxia telangiectasia
e. Retinoblastoma
Answer : E

4- All of the following statements concerning acute lymphocytic leukemia (ALL) are true EXCEPT:
A- Most cases (about 85%) are derived from T-cell progenitors
B- Staging of ALL is based on bone marrow biopsy and cerebrospinal fluid examination
C- Chromosomal abnormalities are identified in most cases of ALL
D- Exposure to medical radiation is associated with an increased incidence of ALL
Answer : A

1

11. Which of the following chromosomal abnormalities in acute lymphoblastic leukemia of childhood carry a favorable outcome?

A. t(12;21)
B. t(4;11)
C. t(9;22)
D. hypodiploidy
E. 11q23

2

12. You are meeting with parents of 10-year-old child who recently develops acute lymphoblastic leukemia (ALL); the mother has a concern about risk of CNS relapse. Which of the following is **LEAST** likely to increase the risk of CNS relapse in children with ALL?

A. first traumatic lumbar puncture (LP)
B. T-cell leukemia
C. cranial nerve involvement at the time of diagnosis
D. presence of lymphoblast in the CSF at any time during treatment
E. age of more than 10 year at the time of the diagnosis

3

13. Children with ALL who carry poor outcome include all the following **EXCEPT**

A. age younger than 1 year and older than 10 year
B. T-cell immunophenotype
C. hyperdiploidy chromosomal abnormality
D. initial leukocyte count of > 50,000
E. poor response to initial therapy

4

14. Which of the following chromosomal abnormalities of childhood ALL carries the highest risk of relapse despite intensive chemotherapy?

A. t(9;22)
B. t(4;11)
C. hypodiploidy
D. t(1;19)
E. t(12;21)

5

17. You are evaluating a 9-year-old boy child with ALL who recently develops testicular relapse; an important statement that should be mentioned to his parents is

A. testicular relapse occurs in the majority of boys with ALL
B. it usually occurs during the course of therapy
C. such relapse occurs as painful swelling of oneor both testes
D. the diagnosis is confirmed by ultrasonography of the affected testis
E. the majority of affected boys can be successfully retreated, and the survival rate is good

6 21. A healthy 20-day-old male neonate with Down syndrome appears pale; examination reveals a palpable liver 6 cm below the right costal margin and palpable spleen 3 cm below the left costal margin; lab findings include: hemoglobin, 8.8 g/dl; platelets count, 55000/mm3; white blood cell count, 18700/mm3 with 10% blast cells; bone marrow examination is consistent with acute leukemia.
Of the following, the **BEST** approach for the management is

A. intensive chemotherapy
B. low dose chemotherapy
C. pulses of chemotherapy
D. bone marrow transplantation
E. close follow up

7 28. Metabolic derangement secondary to tumor lysis syndrome is commonly encountered after starting chemotherapy in children with malignancy; it include all the following **EXCEPT**

A. hyperuricemia
B. hypernatremia
C. hyperkalemia
D. hyperphosphatemia
E. hypocalcemia

Answers :-

1. A
2. طالب مرهق
3. C
4. B
5. E
6. E
7. B