HEMATOLOGY

SYSTEM

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TOPICS

1- **Anemia – L دكتورة فردوس**
2- **Leukemia and lymphoma – L دكتورة أسيل**
3- **Septicemia – L دكتور سري**
4- **Bleeding disorder – S دكتورة فردوس**

السلايدات باللون الأسود وأي ملاحظة من الدكاترة أو سؤال امتحان باللون الأحمر

كل التوفيق ♥

ANEMIA

Definition : is a pathologic state resulting in an insufficient number of erythrocytes to deliver oxygen to organs and tissues.

Presentation: depends on the degree of anemia ,the rapidity with which anemia develops (Patients with chronic anemia are most likely asymptomatic) as well as the presence or absence of underlying end organ or vascular disease.

Symptoms of anemia : dyspnea , decreased exercise tolerance , palpitations , lightheadedness , fatigue and syncope.

Anemic patient ---look for reticulocyte count (RC)

- If it was high : then the patient has bleeding or hemolytic anemia
- If it was low or normal : then look for MCV (Based on mean corpuscular volume (MCV), anemia can be classified as microcytic (MCV < 80 µm3), normocytic (MCV = 80-100 µm3), or macrocytic (MCV > 100µm3).

Classification of anemia :

1- Anemia Due to Erythrocyte Underproduction or Maturation Defects

- Iron deficiency anemia
- Inflammatory anemia (anemia of chronic disease)
- Thalassemias

Microcytic anemia

- Anemia of kidney disease → NORMOCYTIC
- Cobalamin (vitamin b12) deficiency
- Folate deficiency

Macrocytic anemia

2- Hemolytic anemias

- Congenital hemolytic anemias:
  - Hereditary spherocytosis
  - Sickle cell syndromes
  - G6PD deficiency

- Acquired hemolytic anemia:
  - Immune – mediated hemolysis
  - Nonimmune hemolytic anemia

Anemia Due to Erythrocyte Underproduction or Maturation Defects

Iron deficiency anemia

Iron is an essential component of the hemoglobin molecule.In addition to its crucial role in oxygen delivery, iron is also necessary for DNA synthesis and cellular transport.

Hepcidin is the key protein in iron regulation. It's produced in the liver and it's a negative regulator f iron absorption.

كل ما زاد رح يقل ال absorbtion of iron

Its production increases with inflammation , and decreases in hypoxia, anemia and iron deficiency.

Hepcidin causes

1- internalization and proteolysis of ferroportin in the gut and macrophages causing inhibition of absorption from the gut .
2- inhibition of release from macrophages.

Causes of iron deficiency :

1- loss of iron(bleeding , menstruation , gastrointestinal bleeding)
   menstrual female who don't response to oral iron replacement , we should look foe gastrointestinal bleeding . Also any male patient at any age with iron deficiency , we should look to gastrointestinal bleeding / suspect colon cancer , peptic ulcer .
2- decrease intake (nutritional deficiency , decrease absorption : gastric bypass surgery , celiac disease, H. Pylori infection , autoimmune atrophic gastritis) .
3- increase iron requirement (pregnancy and lactation) .

Laboratory findings include

1- Microcytic with **ansiopoikilocytosis** , hypochromic RBCs with ↑red cell distribution width (RDW> 15%)
   - poikilocytosis : abnormal (different) shape of RBCs
   - anisocytosis : variation in RBCs size
2. ↓ferritin < 14 ng/ml ; ↑TIBC; ↓serum iron; ↓% saturation< 20%
   saturation (iron /total iron binding capacity *100)
3. ↑Free erythrocyte protoporphyrin (FEP)

ملاحظة : ال saturation بنعتمد عليها بالتشخيص بالحالات يلي بكون عنا ال ferritin عالي لأنه زي ما بنعرف ال ferritin يعتبر acute phase reactant برتفع أثناء ال infection وبالتالي بهاي الحالة ما بنعتمد عليه بالتشخيص .

Treatment :

Iron deficiency is treated with oral iron salts.**Oral ferrous sulfate** is the least expensive preparation with each 325 mg contains 65 mg of elemental iron.

frequent dosing ; 2-3 times daily increase hepcidin which will interfere with iron absorption. Therefore, it's better to give single daily dose or EOD(every other day).

Monitoring :
Iron replacement results in reticulocytosis within days , with an increase in hg concentration of 1 g/week.
iron replacement should be **continued 3-6 months after normalization of hg** , to replenish iron stores.
Parenteral iron : high iron requirements in dialysis patients , malabsorption.

Inflammatory anemia (anemia of chronic disease)
Causes: Chronic infections**,** Chronic rheumatological diseases and Malignancies.
increased inflammatory mediators :
>> increased hepcidin , decreased iron absorption
>> blunt erythropoietin response to anemia
Laboratory findings include
1. Normochromic , normocytic >> later microcytic hypochromic may develop (hepcidin effect).
2. ↑ ferritin, ↓ TIBC, ↓ serum iron, and↓ % saturation
3. ↑ Free erythrocyte protoporphyrin (FEP)
4. Low reticulocyte count (erythropoietin effect).

Anemia with kidney disease
- Relative deficiency of erythropoietin (synthesized in renal cortex in response to anemia and hypoxia)
- Low retic count , normocytic normochromic anemia
- **Burr cells** (echinocytes , erythrocyte with a small number of spicules of **uniform** size and distribution on the cell surface) in blood film only in case of **uremia** (late stage of kidney disease) .

هون حكت الدكتورة ضروري تميزوها عن ال spur cells وفيه بالسلايد صورة على كل وحدة منهم

Spur cells : acanthocytes, erythrocyte with a small number of spicules of ……..**variable** size an distribution on the cell surface / **in sever liver disease**)

- Microcytic features should raise the suspicion of iron deficiency (platelets dysfunction , angiodysplasia and peptic ulcer disease which may lead to GI bleeding).
- Patients with anemia of kidney disease who are not yet on hemodialysis with a hg level > 10 g/dl should not receive erythropoitic stimulating agents(ESA).
- Those with a hg < 10, should receive individualized ESA therapy based on symptoms , rapidity of anemia and transfusion needs (severe symptoms and needed recurrent transfusion ---we should use ESA)
- patients on hemodialysis , with a g level < 10 , should receive ESAs . **However , hg level should not exceed 11.5 g/dl (risk of HTN, volume overload and thrombotic events) .**

Thalassemia

- It's a disorder of erythrocyte production.
- Ineffective erythropoiesis (erythrocyte underproduction)
- Hemoglobin is a tetramer of 2 beta chains and 2 alpha chains which are produced in a balanced way.
- Genes responsible for alpha and beta chains production are located on chromosomes 16, 11 respectively.
- Imbalanced production results in impaired production of hemoglobin and ineffective erythropoiesis + hemolysis .
- Peripheral blood smear: microcytic hypochromic anemia , target cells , nucleated RBCs .
- **Unlike IDA; heterozygous thalassemia causes hypochromic microcytic anemia with normal to elevated RBC count and normal RDW.**
- Increased LDH , indirect hyperbilirubinemia , low haptoglobin level.

Alpha thalassemia

- Alpha globulin gene is duplicated on chromosome 16 >> several genotypes.
- Homozygous alpha thalassemia : **hydrops fetalis**
- A single gene mutation : **silent carriers , healthy**
- Two gene mutations : **alpha thalassemia trait**
  hg level around 10 g/dl , microcytosis , normal to elevated iron stores , normal hg electrophoresis , best diagnosed by direct sequencing of globin genes. Folate supplement (because folate deficiency due to ongoing hemolysis)
- Three gene mutations : **tetramer of beta chains called hemoglobin H** , can be identified in hg electrophoresis. More severe anemia , hg around 7-8 g/dl , seldom transfusion-dependent.

هدول المرضى رح يحتاجو transfusion بس لازم نكون حذرين وخصوصا ازا بدي أعطيه iron لما يكون عنده فيه نقص بالإضافة لوجود ال thalassemia لأنه هدول المرضى عندهم very good absorption of iron .

Beta thalassemia :

- More than 250 mutations have bee spectrum of the disease.
- **Beta thalassemia minor (trait):** microcytosis , hg level 10-12 g/dl, abnormal hg electrophoresis (increased hgA2 (alpha 2:gamma2) , sometimes increased hgF depending on the specific mutation.
- **Beta thalassemia intermedia :** hg 7 g/dl without need for transfusion.
- **Beta thalassemia major :**Homozygous beta thalassemia : severe symptomatic anemia diagnosed at early age. Transfusion dependent.
- Folate supplement , avoid iron supplements

Cobalamin deficiency

- Cobalamin is essential in DNA synthesis
- Its deficiency will result in megaloblastic anemia , ineffective hematopoiesis and as a result **intramedullary hemolysis** and **pancytopenia.**
- **causes of vitamin b12 deficiency :**
  - Diet : rare cause , only in strict vigans.
  - **Malabsorption** :most common cause;IBD, bacterial overgrowth , pancreatic insufficiency
  - Decreased bioavailability : age related gastric achlorhydria , PPI use.
    acid environment لازم يكون فيه good absorption ويصيرله bioavailable عشان يكون
  - Pernicious anemia : autoimmune antibodies against parietal cells or the intrinsic factor.
- Vitamin B12 deficiency is less common than folate deficiency and takes years to develop due to large hepatic stores of vitamin B12.
- **Presentation :**
  - weight loss , glossitis, anemia symptoms , lemon-yellow skin (anemia and jaundice secondary to hemolysis caused by ineffective erythropoiesis).
  - Severe deficiency can cause neurological manifestations (subacute combined degeneration of the spinal cord(posterior and lateral coluom)) even before anemia. Loss of vibration and proprioception , spastic ataxia , psychiatric symptoms (megaloblastic mania) which manifest as dementia , hallucinations and even frank psychosis.
- **Blood film :** oval macrocytic with hypersegmented neutrophils> 5 lobes , pancytopenia .
- Ineffective hematopoiesis and resulting intramedullary hemolysis : indirect hyperbilirubinemia , decreased haptoglobin and elevated LDH levels.
- Low reticulocyte count
- Low serum vitamin b12 , < 200
- Sometimes low normal levels don't indicate the level of tissue vitamin b12 , so to confirm diagnosis : elevated MMA (methylmalonic acid) , more sensitive , also elevated homocysteine levels.(in folate deficiency MMA is normal , homocysteine is elevated).
- **Treatment :** oral cobalamin 1000-2000 micrograms daily is the treatment of choice(even in pernicious anemia and malabsorption !) we don't need parenteral
- **Monitoring :**
  - Megaloblastic changes will be reversed within hours , reticulocytosis within days , hg level will increase 1 g/week .
  - Neuropsychiatric symptoms may not be reversed with replacement !
- **Inadequate response :** consider another diagnosis like **myelodysplasia.**

Folate deficiency

- **Causes** :
  - Malnutrition
  - Malabsorption : alcohol intake, IBD , celiac disease, amyloidosis
  - Increased demand : conditions with rapid cell turnover (pregnancy , psoriasis , hemolysis)
  - Drugs : causes decreased absorption or inhibit converting to active form ; **phenytoin , methotrexate , triamterene.**
- Folate deficiency develops within months, as body stores are minimal.
- **Presentation** is similar to vitamin 12 deficiency (except neuropsychiatric symptoms).
- **Diagnosis :** low serum folate , if normal can't be reliable , so elevated homocysteine level in suspected folate deficiency confirms the diagnosis . Good meal with good folic acid amount in it , can cause normal level of folic acid in serum .
- **Management :** oral folic acid 1-5 mg daily after exclusion of vitamin b12 deficiency.

Hemolytic anemias

- Ineffective erythropoiesis
- Immune injury mediated by immunoglobulins or complement
- Physical destruction by fibrin , valves and other intracirculatory devices.
- Symptoms depend on the severity of anemia and how acute the hemolysis is
- Pigmented gallstones (insoluble calcium bilirubinate) in chronic hemolytic anemias.
- Reticulocytosis (if stores are good), indirect hyperbilirubinemia , elevated LDH , elevated serum free hemoglobin, hemoglobinuria and decrease haptoglobin .
- Congenital vs acquired

- **Congenital :** hemoglobinopathies (sickle cell disease), disorders of the erythrocyte membrane (hereditary spherocytosis, hereditary elliptocytosis , hereditary pyropoikilocytosis), enzyme defects (G6PD deficiency) and the thalassemia syndromes.
- **Acquired :** drugs (penicillin , quinine , fludarabine ,bendamustine , methyldopa), immune mediated , micro or macroangiopathies , infections and physical agents.

Hereditary spherocytosis

- AD disorder
- Many gene mutations have been identified : alpha spectrin, beta spectrin , ankyrin , band 3 , protein 4.2
- Osmotic fragility (increased spherocyte fragility in hypotonic solution) , reduced surface area to volume ratio , splenic sequestration.
- Symptoms are variable : mild unrecognized anemia , symptomatic anemia(acute BM suppression after viral infection) , splenomegaly (rarely splenic infarction or rupture), calcium bilirubinate pigmented gallstones.
- Peripheral smear : spherocytes(round cells of uniform density without central pallor)
- Variable degrees of anemia ,hyperbilirubinemia , reticulocytosis , high MCHC.
- Diagnosis : osmotic fragility test , flowcytometry
- Folate supplement
- Splenectomy in severe hemolysis.

Sickle cell syndromes

- Homozygosity of a single point mutation in the beta globin gene >> abnormal hemoglobin S (under hypoxic conditions >> deformed erythrocytes that adhere to the endothelium of capillaries throughout the circulation.
- Hemolyzed erythrocytes release arginase , depleting the body from arginine which is an important precursor of nitric oxide
- Free hemoglobin scavenges nitric oxide
- This will lead to **vasoconstriction** and **platelet activation** which will lead to a more complicated clinical course.

• **Homozygous (HbSS) :** having the disease , **most severe**
• **Sickle cell trait (HbS)** : presence of one mutated and one normal chain; results in< 50% HbS in RBCs(normal , healthy person)
• **Coinheritance with HbC (Hb SC**) .
• **Coinheritance B- thalassemia (minor or major)** and **other hemoglobins which usually lead to milder disease than HbSS.**

لما يجي coinheritance مع ال b-thalasemia رح نشوف على ال blood film خلايا ال sikcles بالإضافة إلى ال target cells .

- **Complication :**

- Vaso-occlusive pain episode , Acute chest syndrome
- Aplastic crisis with parvovirus B19 infection of erythroid precursors
- Infection (encapsulated bacteria) due to functional asplenia (splenic tissue is present but dose not work well)

- Hyperhemolytic crisis , Multiorgan failure , Ischemic stroke Hepatic crisis , Cholelithiasis , Chronic kidney disease , proteinuria , Priapism (very painful and sustained erection), Pulmonary hypertention , Retinopathy , Osteopenia , osteoporosis , Avascular necrosis , Foot and leg ulcer.

ملاحظة :ال crisis يلي بتصير عند المرضى not enough treated and recognized in HCS عشان هيك طلع عنا ←

Strong recommendation from national institutes of health to manage and recognize these complication

هلأ الدكتورة حاطيتهم بجدول حكت اقرؤهم وذكرت منه إنه لما يجيوك هدول المرضى على الطوارئ بكون عندهم ألم شديد فلازم تبلشلهم ال opioid بسررعة .

• The only potential cure : allogenic bone marrow transplantation (not studied well)

• **Hydroxyurea** (increases fetal hemoglobin level , increases nitric oxide production.). Reduces subsequent acute pain crisis, reduces the risk of stroke and acute chest syndrome , prolongs survival .

• **Painful crises :** oral glutamine (NAD precursor), P selectin inhibitor crizanlizumab (prevent cellular adhesion)

G6PD deficiency

- X-linked disease
- More than 160 mutations
- Two variants (G6PD A : mild form , G6PD Mediterranean-acute episode of hemolysis (favism))
- Partial protection against malaria infection
- G6PD is essential in pentose-phosphate pathway , reduction NADP to NADPH >> reduce oxidative stress)
- Triggers of hemolysis : drugs , fava beans , naphthalene
- Peripheral smear : bite cells , Heinz bodies (denatured hemoglobin)on supravital stain.

ال Heinz body بالعادة ال spleen رح يتخل منهم بس بالمرضى يلي عندهم splenectomy رح نشوفهم

- Diagnosis :
  1- fluorescent spot test to detect NADPH(+ve : lack of fluorescence, not in acute hemolysis) .

لأنه في حالات ال acute رح تكون الخلايا ال old كلها صارلها hemolysis وبالتالي يلي ضايل عندي هي الخلايا ال new يلي لسا الانزي فيها موجود بكمية منيحة .

  2- qualitative G6PD enzyme activity and subtyping (more specific) - routine test for each new born .

Immune – mediated hemolysis :

- Antibody binds to erythrocyte >> complement and phagocyte mediated RBC destruction.
- The lab hallmark : **+ve direct coomb's test**

- Warm antibodies (igG , reacts at body temp.) vs cold antibodies (IgM , react at cooler temp.)
  - **Warm autoimmune hemolytic anemia:**
- Primary vs secondary to drugs (penicillin , methyldopa), lymphoproliferative disorders (CLL), diseases with disordered immune regulation (SLE).
- Spherocytes on blood film
- Management : steroids , IVIG , rituximab , splenectomy (effective in 70% of patients)
  - **Cold agglutinin disease :**
- Blood film : erythrocyte agglutination , markedly elevated MCV
- Causes : lymphoproliferative disorders , infections (mycoplasma , EBV infection)
- Management : avoidance of cold exposure(mainstay of tt)
- Steroids , IVIG, and splenectomy are seldom effective
- Rituximab , fludarabine or combination has demonstrated activity in some case series.

Nonimmune hemolytic anemia:

1- Microangiopathic hemolytic anemia :

- Blood film : fragmented RBCs (shistocytes)
- Erythrocyte destruction resulting from shearing as they circulate through fibrin strands.
- Occurs with **TTP , HUS , malignancy , DIC(PTT is prolonged) , hypprtensive crisis , drugs (cyclosporine, mitomycin , gemcitabine), eclampsia**
- Often accompanied by thrombocytopenia , kidney impairment , CNS disturbance. Especially in TPP have neurological manifestation with fever and kidney impairment.

2- Macroangiopathic hemolytic anemia :

- Prosthetic valves
- LVAD (left ventricular assist device)

3- Paroxysmal nocturnal hemoglobinuria (PNH) :

- Lack proteins on the erythrocyte surface. يلي بمنعو أنه الخلايا تتهاجم من الكومبلمنت سستم
- Acquired mutations in the PIGA gene that persists in bone marrow stem cells.
- **CD55 , CD59** protects erythrocytes from complement mediated destruction.
- Presentation : episodic hemolysis, marrow aplasia and thrombosis (unclear etiology) .
- Higher risk for leukemia and myel dysplasia .
- Diagnosis : flowcytometry (absence of cd55 cd59)
- - Management : folate supplementation , steroids , eculizumab (a novel monoclonal antibody to C5 , inhibition of terminal complement cascade thus inhibits hemolysis , reduces thrombotic complications and improve quality of life , meningococcal vaccine before use)

4- Hemolysis associated with chemical and physical agents :

- Arsenic , elevated serum copper , bite of brown recluse spider , severe burns

5- Hemolysis from infections :

- Malaria , babesiosis , clostridia , bartonella

Approach to a patient with anemia

- **History taking**
- **Physical examination**
- **Investigations:**
  - **CBC** along with the **peripheral blood smear** (blood film) can give valuable clues to the diagnosis
    By CBC determines degree of anemia , Hb level and involvement of othe lines WBC, PLATELET …
  - Macrocytic , microcytic , normocytic to narrow the differential diagnosis.
    SO look to MCV
  - In addition to the CBC, the **reticulocyte count** provide clue to the diagnosis; A normal bone marrow will produce more reticulocytes in response to anemia or hypoxia.In contrast , patients with vitamin b12, folate or iron deficiency or those with marrow diseases such as myelodysplasia or aplastic anemia , Cannot produce adequate reticulocytes in response to anemia.
  - **bone marrow aspirate and biopsy** can be helpful in the diagnosis of anemia, especially in assessing stem cell disorders like aplastic anemia, dysmyelopoitic syndromes and acute leukemia.
  - The presence of combined cytopenias increases the likelihood of a primary marrow disorder.

Leukemia and lymphoma

Leukemia

Acute leukemia (AML , ALL)

is a hematologic malignancy characterized by infiltration of the bone marrow, blood, and other tissues by uncontrolled proliferation and abnormal delayed differentiation of clonal myeloid or lymphoid precursor cells, exceeding 20% of the bone marrow or blood.
In adults, acute myeloid leukemia (AML) is more common than acute lymphoblastic leukemia (ALL).

1- Acute Lymphoblastic Leukemia (ALL)

- ❖ ALL is more common in children and adolescents than in adults.
- ❖ Although ALL in children is often curable, survival in adult patients (older than 19 years) remains inferior despite the adoption of pediatric ALL regimens.

❖ **ALL presents** with malaise, bleeding, infections, bone pain, or a combination of these symptoms, with a small subset (<10%) having symptomatic central Nervous system involvement at diagnosis.

May cause bone marrow depression /pancytopenia(Anemia, thrombocytopenia/ bleeding , neutropenia- infection) + **CNS manifestation**.

❖ In adults, 75% of ALL is of B-cell lineage.

❖ mature **B-cell ALL** can present as extramedullary disease, including gastrointestinal or testicular involvement.

❖ A mediastinal mass with wheezing and stridor or skin involvement can be the presenting features of **T-cell ALL**. T-cells maturation occur in Thymus .

يعني رح يكون عند المريض أعراض ال pancytopenia مع أعراض بسبب ال mediastinal mass زي ال
ورح يكون عنده برضه dyspnea widened mediastinum

❖ ALL is classified by immunophenotype, cytogenetics, and molecular abnormalities.

❖ The most important cytogenetic abnormality in adult ALL is the **Philadelphia chromosome t (9,22)** , found in 20% to 30% of patients.

❖ Philadelphia chromosome-positive ALL had **a poor prognosis.**

ال Philadelphia chromosome أكتر اشي بنشوفه بال CML بس الفرق انه وجوده بال CML بكون good prognosis بينما وجوده بال ALL يعتبر bad prognosis .

❖ Treatment regimens are complex. Regimen backbones include **vincristine, anthracycline, corticosteroids, and L-asparaginase.**

❖ Unlike in AML, **central nervous system prophylaxis** is essential during ALL therapy.

• Relapse may occur without targeted treatment for CNS -Localized treatments used (Radiation, Intrathecal chemotherapy) .

❖ Adult survivors of childhood leukemia **face higher risks** of secondary cancer, cardiovascular disease, and the metabolic syndrome (high BMI, truncal Obesity , dyslipidemia, insulin resistance, and hypertension) compared with age-matched controls.

❖ Screening for lipid profile, diabetes, and hypertension is recommended.

❖ Echocardiography to screen for left ventricular dysfunction should be performed at intervals of 3 to 5 years, particularly if **anthracycline** exposure was high or if chest radiation was used. Anthracycline cause dilated cardiomyopathy.

❖ Female survivors have a higher risk of myocardial dysfunction(MI) during pregnancy.

❖ High-dose glucocorticoids, typical of ALL regimens, pose a risk for osteopenia.

❖ The cumulative incidence of secondary cancer after radiation therapy for childhood ALL reaches 11% at 30 years; tumors include skin cancer, thyroid and parotid tumors, sarcomas, and brain tumors.

❖ Cranial radiation also increases the risk for stroke and neurocognitive defects.

2- Acute Myeloid Leukemia

❖ AML typically manifests with anemia, thrombocytopenia, or functional neutropenia secondary to bone marrow replacement with abnormal myeloblasts.

❖ Petechiae, epistaxis, and other mucosal **hemorrhages** occur when the platelet count dips below 20,000/RL (20 x 109/L).

❖ Symptoms of **anemia** vary more with patient's age and comorbidities.

❖ Although the leukocyte count is typically elevated, the absolute neutrophil count tends to be low, which confers an increased risk of **infection**.

❖ Cytogenetic and molecular classification of AML has gained increasing importance in recent years.

❖ In the 1970s, a group of French, American, and British leukemia experts divided AML into subtypes, **M0 through M7**, based on the type of cell the leukemia develops from and how mature the cells are. This was based largely on how the leukemia cells looked under the microscope after routine staining.

❖ Subtypes M0 through M5 all start in immature forms of white blood cells. M6 AML Starts in very immature forms of red blood cells, while M7 AML starts in immature forms of cells that make platelets.

The most important one is M3 - Acute promyelocytic leukemia (APL)

❖ Acute promyelocytic leukemia, characterized by poorly differentiated leukocytes with distinctive primary granules that contribute to coagulopathy.

❖ Chromosomal translocation t (15;17).

❖ Many patients achieve cure with <u>all-trans retinoic acid</u> **(ATRA),** which targets the underlying defect in cell differentiation.

هاي الخلايا بكون فيها specific granules موجودة في ال cytoplasm ومهمة لأنها بتعمللنا coagulopathy يعني بالعادة
بيجس المرضى عندهم DIC , فمثلا بيجيك مريض عمره 50 سنة عنده fatigue , SOB, bleeding وعملتله CBC لقيت
ال WBC تقريبا 60000 وكلهم myeloblast وال Hb عندك 6 فهون بتحط ببالك ال M3 .
-مرضى ال M3 همه أكتر مرضى رح تلاقي عندهم ال D-dimer ,PTT ,PT مرتفعين ورح تلاقي ال low fibrinogen
وبالاضافة إلى thrombocytopenia .
-ال ATRA هو عبارة عن vit. A derivative مهم لل differentiation of myeloblast فلما يصير فيه
translocations رح يصير عنا abnormal differentiation وبالتالي بتصير ال m3 .

Diagnosis: Myeloblasts are usually seen in the peripheral blood smear>20 % but may be absent despite unequivocal bone marrow infiltration.

peripheral blood smear shows an immature granulocyte with a rod-shaped inclusion body (Auerrod) characteristic of acute myeloid leukemia , large nucleus and scant cytoplasm .

في حال ما طلع معنا على ال blood smear خلايا ال myeloblast هاد ما بستبعد تشخيص ال leukemia خصوصا ازا
كان عنده clinical manifestation عشان هيك لازم أعمل ال BM- biopsy بتكون more specific .

❖ **The treatment** of AML consists of induction therapy with an **anthracycline** (such as daunorubicin) and infusional **cytarabine**.

❖ The goal is to ablate the bone marrow, eliminating the blasts, although this transiently destroys the normal hematopoietic cells as well. Cells are expected to recover after a period of aplasia, which extends for **3 to 4 weeks**, during which time the patient is supported by transfusions (erythrocytes and platelets) and prompt antibiotic treatment of neutropenic fever.

❖ Complete response is achieved in 60% to 85% of patients younger than 60 years.

الفكرة بال ttt إنه نعمل ablation لل BM ونشيل ال abnormal cells بس ك side effect رح ينشال معها ال normal hematopoietic cells فرح يصير عنا sever pancytopenia لهيك خلال عاي الفترة بكون بعالج المريض symptomatic ttt فمثلا بعطيه ال RBC عشان أحسن ال erythrocyte وبعطيه ال platelet عشان ال DIC ولو كان عنده sever neutropenic بنعطيه prophylactic antibiotics .

-هلأ ال induction therapy بتاخد من 3 الى 4 أسابيع وبعد هيك ال BM ببلش يصنع ال normal cells وبصير عنا recovery .

Chronic leukemia : (CLL ,CML)

ال CML هاي بعتبروها وحدة من ال myeloproliferative disorder
بينما ال CLL فهاي صاروا يصنفوها من ضمن ال lymphoid malignancy

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Lymphoid Malignancies

❖ **Lymphoma classified into Hodgkin and non-Hodgkin lymphoma.**

❖ Epidemiology : the incidence of non-Hodgkin lymphoma **rises with increased age** the incidence of Hodgkin lymphoma shows a **bimodal age distribution**, with an early peak in the second and third decades of life, then a decline, followed by a sustained increase with older age.

يعني هدول المرضى عندهم 2 peak وحدة بتصير بين عمر 10-20 / 20-30 والتانية بتصير عند عمر ال 50 وما بينهم بتقل ال incidence

وبالتالي المريض الكبير بالعمر مثلا 60 سنة رح يكون عنده risk لل non – Hodgkin لأنه هي بتزيد مع العمر وبنفس الوقت عنده ال risk لل Hodgkin لأنه هاد عمر ال second peak الهم .

Risk factors

❖ Most cases seem sporadic.

❖ familial clustering can be seen, with an increased relative risk in first degree relatives.

❖ Patients with both congenital and acquired immunosuppression (such as HIV infection, organ transplantation, or an inherited immunodeficiency) are at greater risk.

بال organ transport رح يكون ال risk الهم بعد سنة لأنهم رح يكونوا اخدين جرعة عالية من ال immunosuppressan

❖ **Various viral infections are also associated with increased risk. Epstein-Barr virus** is associated with Burkitt lymphoma,seen in African pediatric patients, as well as some cases of Hodgkin lymphoma.

❖ Human T-cell lymphotropic virus type 1 **(HTLV-1)** is associated with T-cell leukemias and lymphomas.

❖ **Hepatitis C virus** is associated with an increased risk of lymphoma, particularly splenic marginal zone lymphoma.

❖ **HIV infection** is associated with an increased risk of principally B-cell lymphomas, typically with aggressive histology, more advanced stage, more B symptoms, and a higher risk of extranodal and central nervous system involvement.

❖ Kaposi sarcoma herpesvirus **(human herpesvirus 8)** is associated not only with Kaposi sarcoma but also with primary effusion lymphoma.

❖ Patients with autoimmune rheumatic disorders, such as Sjogren syndrome, systemic lupus erythematosus, and rheumatoid arthritis, have an increased risk of non-Hodgkin lymphoma. The strongest association is with Sjogren syndrome and extranodal marginal zone lymphomas.

Evaluation and Diagnosis

❖ **Enlarged lymph** nodes are the most common sign of lymphoma

❖ The size, distribution, or persistence of enlarged lymph nodes or systemic symptoms raises concern for lymphoma.

كتير مهم نعرف ال change of LN وأكثر سبب لل lymphadenopathy هو ال viral infection ولو بدنا ناخد كيس
مثلا واحد عنده small, painful LN , from few day هاد عالأغلب يكون benign على عكس واحد
عنده اياها من 3 أو 4 أسابيع وكانت progressive وكمان painless وما كان فيه دليل على infection فهاي بالغالب رح تكون malignant

❖ Systemic symptoms **(B symptoms)** indicates the presence of one or more of the following**: fever, drenching night sweats, or unexplained weight loss.**

❖ CT scan of the chest, abdomen, and pelvis**(CT-CAP)** can assess palpable lymph nodes not amenable to physical examination .

❖ **Diagnosis is generally established based on lymph node biopsy**. An **excisional biopsy** is often preferable to **a core needle biopsy**(FNA) as it may.
better determine nodal architecture.

❖ **Flow cytometry** on cytology can demonstrate B-cell or T-cell markers, as well as features consistent with monoclonality.

ازا ما لقينا فيها BM involvement ما في داعي نعمل BM biopsy

Staging

❖ Lymphomas are staged I to IV based on the **number of sites of disease** and the presence of **extranodal involvement**.

❖ Staging involves physical examination, CT scans, and PET scans in most patients.

❖ Lymphoma stages are also designated **A or B**; *A indicates no systemic symptoms are present*, and *B indicates the presence of one or more of the B symptoms.*
A(1,2,3,4) / B (1,2,3,4)

Stage 1 : single LN region
Stage II : two or more LN regions on same side of diaphragm
Stage III: LN regions on both sides of diaphragm , include spleen or localized.
Stage IV: diffuse extralymphatic disease (liver, BM, lung , skin)

Hodgkin Lymphoma

❖ Hodgkin lymphoma represents approximately 10% of lymphomas and is curable in most, but not all, patients.

❖ It has a bimodal incidence, although it most commonly presents in young adults.

❖ Presentation with mediastinal, cervical, and supraclavicular involvement is particularly common for the nodular sclerosing subtype .

❖ Patients may also present with B symptoms, although that is more commonly seen in elderly patients with more advanced disease.

❖ Pruritus may also be a presenting symptom

❖ **The diagnosis** is established with a lymph node biopsy specimen showing **Reed-Sternberg cells.**

❖ Reed-Sternberg cells are large and either are multinucleated or have a bilobed nucleus ("owls eye" appearance) with prominent eosinophilic inclusion-like nucleoli. They can be seen with light microscopy in biopsies from individuals with Hodgkin lymphoma. They are usually derived from B lymphocytes. When seen against a sea of B cells, they give the tissue a "starry sky" or "motheaten" appearance. The absence of Reed-Sternberg cells has very high negative predictive value for Hodgkin disease.

❖ The number of Reed-Sternberg cells and variability in the composition of the infiltrate lead to pathologic subtypes, including nodular sclerosis(most common) , mixed cellularity, lymphocyte predominant(best prognosis) , and lymphocyte depleted (worst prognosis) .

❖ More than 90% of patients present with "classic" Hodgkin lymphoma pathology and, even with early-stage disease, receive chemotherapy because this has been shown to result in higher cure rates.

❖ The doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen is most commonly used.

Non-Hodgkin Lymphomas

B-Cell lymphomas

1- **Indolent B-Cell Lymphomas-** (slow progression , asymptomatic , ttt only in late stage , less effective response to chemotherapy)
- Follicular Lymphoma
- Mucosa-associated Lymphoid Tissue Lymphoma
- Chronic Lymphocytic Leukemia
- Hairy Cell Leukemia

2- **Aggressive B-Cell Lymphomas-** very rapid , high response to chemotherapy
- Diffuse large B-cell lymphoma
- Burkitt lymphoma
- Mantle Cell Lymphoma

T-cell lymphomas

- Cutaneous T-Cell Lymphoma
- Peripheral T-Cell Lymphoma, Not Otherwise Specified
- Anaplastic Large Cell Lymphoma
- Angioimmunoblastic T-Cell Lymphoma

Follicular Lymphoma

❖ Follicular lymphoma is the most common indolent B-cell lymphoma.

❖ They demonstrate lymph node architecture with a follicular morphology.

❖ They arise from the germinal center B cells of the lymph node.

❖ They characterized by the presence of a 1(14:18) translocation that causes an overexpression of the BCL2 oncogene.

❖ Many patients are not symptomatic at diagnosis and in some cases do not require therapy for many years. just follow up

❖ **Histologic transformation,** most typically to a **diffuse large B-cell lymphoma**, occurs in approximately 30% of patients with follicular lymphomas and is associated with an aggressive course and poor prognosis.

❖ Transformation may be suggested by a change in the clinical pattern of disease with new systemic symptoms or rapid progression of a localized area of disease, a rise in serum lactate dehydrogenase, or markedly higher areas of standardized uptake values on PET scans.

❖ **New biopsy** is required to establish that transformation has occurred.

عشان نعرف لأي type تحولت

Mucosa-associated Lymphoid Tissue Lymphoma

❖ Mucosa-associated lymphoid tissue (MALT) lymphoma is an extranodal Marginal zone lymphoma.

❖ Gastric MALT lymphoma may be the best known, particularly given its common association with Helicobacter pylori infection.

❖ H. pylori-associated gastric MALT lymphoma should be treated with antibiotics and proton pump inhibitors initially. very high cure rate

معلومة مهم نركز عليها : إنه هو النوع الوحيد من ال malignancy يلي رح يكون علاجه عن طريق ال antibiotics

Chronic Lymphocytic Leukemia

❖ Chronic lymphocytic leukemia (CLL) is generally easy to diagnose because it manifests as an increase in absolute lymphocytes on complete blood count.

❖ The lymphocytes are predominantly small and mature appearing, although they may be fragile and form **"smudge cells"** on the peripheral smear.

❖ Flow cytometry using peripheral blood is essential in establishing the diagnosis and will reveal B-cell antigens (CDI9, 20, and 23), coexpression of CD5 (normally a T-cell marker), and <u>low levels of a monoclonal surface immunoglobulin</u>(increase risk of infection) .

بالعادة رح يكونوا asymptomatic ولما نعمل ال CBC رح نلاقي ال WBC مرتفعة جدا وأتوّ من 80% همه lymphocyte وعلى ال blood smear رح تشوف ال smudge cells .

❖ **CLL** and **small lymphocytic lymphoma** represent the same disease, with the designation as leukemia or lymphoma based on the dominant clinical manifestation in either peripheral blood and marrow or nodal involvement, respectively.

❖ Both CLL and small lymphocytic lymphoma are treated the same.

❖ CLL is now grouped more with the lymphomas than with the leukemias in treatment centers.

❖ CLL is typically an indolent disease, patients with low-stage, asymptomatic chronic lymphocytic leukemia can be observed without therapy for decades.

❖ Patients with CLL are prone to infection, in part related to commonly associated hypogammaglobulinemia.

❖ Patients with CLL and small lymphocytic lymphoma may also develop autoimmune cytopenias such as immune thrombocytopenic purpura and autoimmune hemolytic anemias.----indication of ttt

❖ **Transformation** to a **large cell lymphoma (known as Richter transformation)** occurs in about 5% of patients with CLL and small lymphocytic lymphoma and is generally associated with a poor prognosis and refractory disease.

Richter transformation بنسميه lymphoma إلى leukemia تحول من

Diffuse Large B-Cell Lymphoma DLBL

❖ Diffuse large B-cell lymphoma represents approximately 30% of non-Hodgkin lymphomas.

❖ Patients often present with symptomatic **enlarging lymphadenopathy** in the neck or abdomen.

❖ Approximately 40% may have symptoms or signs of **extranodal disease**, and one third have **systemic symptoms**(B symptoms) .

❖ **Biopsy** specimens show diffuse effacement of normal nodal architecture by large, atypical lymphoid cells with prominent nucleoli and basophilic cytoplasm.

❖ **Flow cytometry** reveals B-cell antigens, and most patients have monoclonal surface immunoglobulin.

❖ Sixty percent of patients have advanced (stage III or IV) disease at diagnosis, and standard therapy is **R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone).**

❖ Patients with poor prognostic features, such as elevated serum lactate dehydrogenase level, extensive tumor burden, and poor performance status, may **receive more aggressive initial therapy**.

Burkitt Lymphoma

❖ Burkitt lymphoma is remarkable for its extremely rapid growth.

❖ **The endemic form** occurs primarily in Africa, is a common cause of childhood cancer, and is associated with Epstein-Barr virus infection. Patients may present with a large jaw mass .

❖ **The sporadic form** is more typically seen in the United States, occurs at a somewhat later age, and is more likely to present with abdominal or pelvic involvement.

❖ A third variety of Burkitt lymphoma is the **immunodeficiency-associated form** and occurs in HIV infected patients.

❖ **MYC gene** activation is characteristic of this lymphoma.(8:14)

❖ Various aggressive multi-agent chemotherapy regimens with rituximab have been associated with **high cure rates**.

❖ Early signs of the **tumor lysis syndrome** are often present in patients with Burkitt lymphoma even before treatment is initiated and should be anticipated because the tumor is quite chemosensitive .

Tumor lysis syndrome lead to :

• Hyperkalemia (arrhythmias)
• Hyperphosphatemia → hypocalcemia
• Hyperuricemia

Hairy cell leukemia

• Rare chronic B-cell malignancy _ Express CD19, CD20, CD22
• Peripheral smear: hairy cells
  - Lymphocytes
  - Hair-like cytoplasm projections
• Massive splenomegaly
• BRAF mutation

Septicemia

بالنسبة لهاي المحاضرة شرحها دكتور سري ، والدكتور كان يقرأ قراءة ما ضاف أي اشي فرح أحط رابط السلايدات هون
https://drive.google.com/file/d/1iZtiJJPpgyLHXOKNi5cUwPN_AEYmX_9m/view?usp=sharing

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bleeding disorder and anticoagulation seminars

بهاد السمينار الدكتورة ما علقت الا على INR إنه normally لازم يكون أقل من 1.1 ولكن ال target إنه أوصله ل 2-3 بكون فقط في أدوية ال vit.k+ antagonist زي ال warfarin

وهي رابط السيمينار :

https://drive.google.com/file/d/16wxQMiIk2CiIhd5gkN8Ow-YhhQGHJuy3/view?usp=sharing