HEMOLYTIC ANEMIAS

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PATHOPHYSIOLOGY

- RBC life span < 120 days — So they die earlier than the normal and the efficiency of O2 delivery less than normal
- Hypoxia triggers release of erythropoietin — Which will activate the bone marrow erythropoises
- Erythroid hyperplasia in bone marrow
- Peripheral blood reticulocytosis
- Extramedullary hematopoiesis in severe cases
- Hemoglobin is released in from damaged RBCs
- Serum haptoglobin: decreased (binds free Hg) in both intra and extravascular hemolysis
  - ↳ It will be consumed as it is bound to the HB and will be excreted in urin, this test can identify if the patient has hemolytic anemia when the haptoglobin decreased

CLASSIFICATION

Haptoglobin binding to the HB occurs in both extra vascular and intra vascular

- *Main site of hemolysis:* Inside blood stream or outside

More Common

- 1) Extravascular: occurs primarily in spleen (RBCs have abnormal shape or coated with antibodies, removed by macrophages, patients have jaundice, pigmented gall bladder stones, splenomegaly) As we know the HB will be converted to bilirubin

More obvious

- 2) Intravascular: inside blood stream (sudden release of Hg, patients have hemoglobinemia, hemoglobinurea, hemosiderinurea, iron deficiency)

Increase free HB → HB and hemosidren in urin → Cause red urin

As a result of hemosderinurea

There is no splenomegaly in the intravascular hemolysis

Another Classification

- *According to cause of hemolysis*
- Extracorpuscular (extrinsic factor) vs intracorpuscular

The defect maybe from inside the RBCs or outside

G6PD DEFICIENCY

- X-linked inheritance Appears early in life (more common in male, females need 2 mutations)
- Glucose 6-phosphate dehydrogenase deficiency
- Reduced production of glutathione, important for cell protection against harmful oxidants

G6PD normally found in all cells and its function to generate glutathione, and glutathione's function is to neutralise the oxidants which are molecules with high energy according to their free electrons and bcz of their energy they cause damage inside the cells

Those patients during normal situations (when they don't have stress) they suffer from mild hemolysis (without symptoms) but they have triggers of hemolysis (they have factors cause severe hemolysis for large number of RBCs

TRIGGERS OF HEMOLYSIS

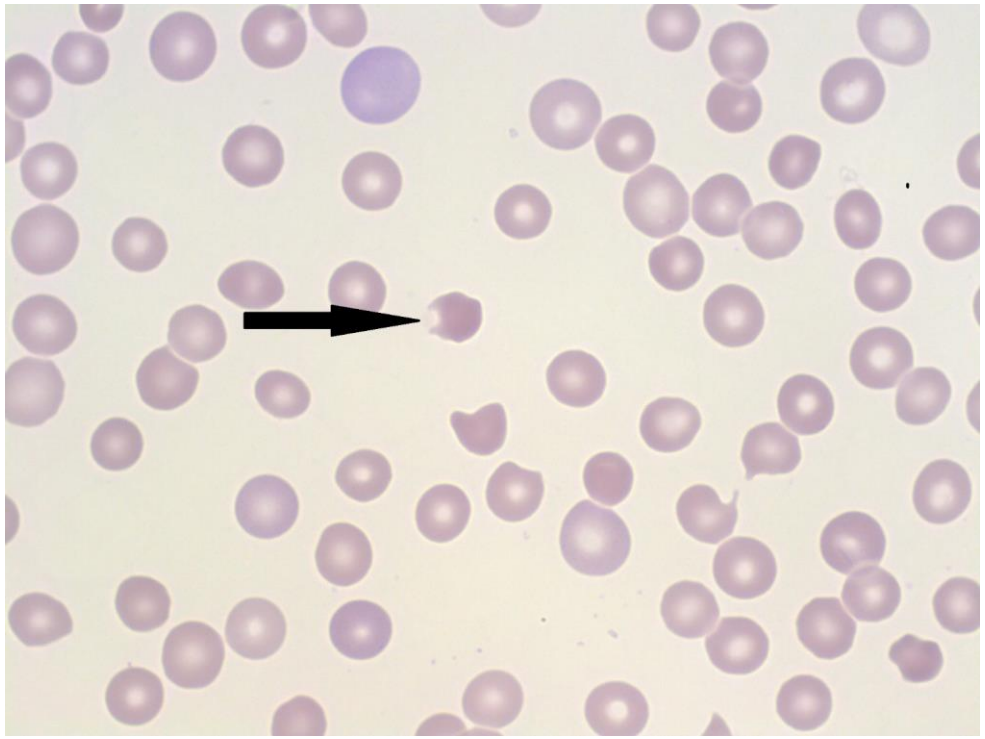
Which generate a large number of oxidants

- Any Infection → Their metabolism produce oxidants
- Certain drugs: sulfonamides, nitrofurantoin, large dose of aspirin, vitamin K, primaquine (for malaria) — most imp. antibiotic.
- Fava beans (الفول)
- In all, large numbers of oxidants are generated, G6PD cannot neutralize them, causing hemoglobin denaturation and precipitate (Heinz bodies), damaging cell membrane and massive hemolysis of RBCs, 2-3 days after trigger

The Heinz bodies become solid (rigid area in the RBCs) when they reach the spleen the loss demorfmability

- Other cells lose demorfmability and partially phagocytosed inside spleen (bite cells)

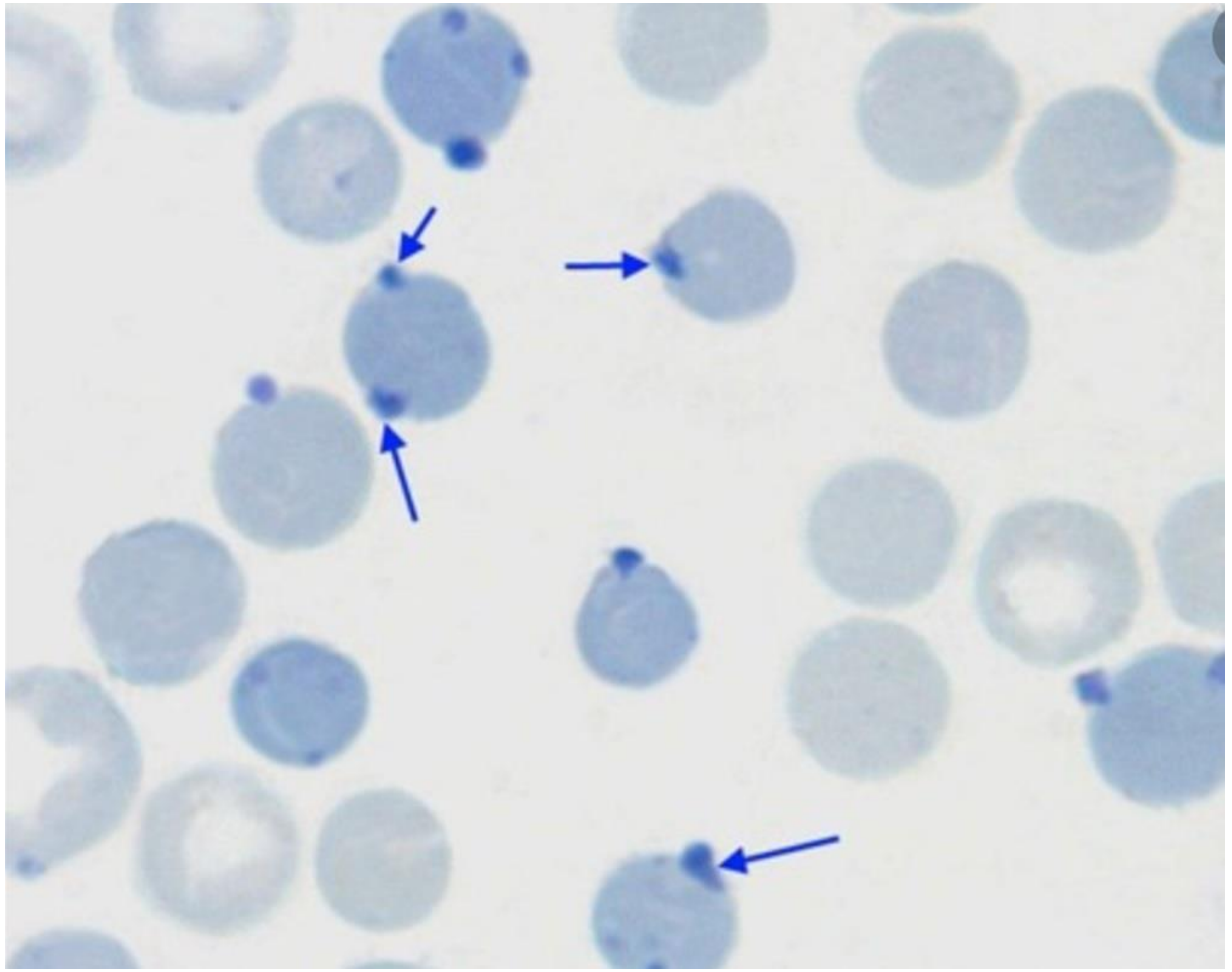
bite cells فبظهروا كانهم RBCs من ال rigid بعضوا الجزء ال macrophages هون ال



- Bite cells: appears are indented defect in part of cell membrane of RBCs

And when they reach spleen another time they will be destroyed cuz they have abnormal shape

Patients have extra vascular hemolysis (remember the G6PD is the cause)



- Supravital special stain highlights Heinz bodies as membrane-bound, dark spots representing condensed and denatured Hg

CLINICAL TYPES Of G6PD deficiency

- Symptoms of ~~intravascular~~ Extravascular hemolysis
- G 6PD-A type: modest decrease in amount of G 6PD, bone marrow compensate by producing new RBCs Not complete absent of enzyme so they have lower glutathione
- G6PD-Mediterranian: qualitative defect of enzyme (low function), more severe symptoms The production is normal but they have functional deficiency of enzyme
- Females: can have symptoms if random inactivation affects the normal X-chromosome

Still they can show the disease

one mutation ويا اما two mutations يا اما بصير عندهم

inactive بصير second X chromosome بس

Here the antigen is normal and the problem is the antibodies which deal with Ag as a foreign

IMMUNE HEMOLYTIC ANEMIA

Acquired not inherited

- The presence of auto-antibody against RBC membrane protein
- These antibodies are detected by Coombs test The diagnosis

We have 2 methods

- Direct Coombs test: RBCs of patient are incubated with antibodies that target normal human antibodies (RBCs will agglutinate)

The blood converts to clot instead of liquid

- Indirect Coombs test: patients' serum is added to "test RBCs" that have certain surface proteins (identify the type of antigen)

Synthetic RBCs

Serum contains autoantibody

In both methods the blood will convert to clot (agglutination will occur)

In immune hemolytic anemia we have 2 types and the more common is the warm one

WARM TYPE

Those RBCs are coated by abnormal IgG and when reach the spleen, the IgG will bind to the FC receptors on the macrophages, then IgG will detach result in loss of part of RBCs cell membrane كانّه سحب معه طرف منه

- High affinity auto-antibody (mostly IgG type) The active autoantibody
- Binding occurs in core circulation (37°C) warm عشان هيك اسمه
- Removed by macrophages in spleen
- spherocytes develop, then destroyed by spleen (extravascular hemolysis)

As a result of losing part of membrane

- 60% are idiopathic, 25% associated with systemic lupus erythematosus, 15% by drugs (α-methyldopa, penicillin)

Anti hypertensive

- Severity of anemia is variable, most patients have mild chronic anemia and splenomegaly And they will develop jaundice and stones

COLD TYPE

Here when the IgM coat the RBCs, some complement proteins from the complement system will bind to the RBCs

When the RBCs reach the core circulation (37) the IgM will detach but the complement proteins still bind to the RBCs

The RBCs become spherical in shape and destroyed in the spleen

- Low-affinity autoantibody (IgM)
- Binding occur in peripheral areas of body (<30°C)
- After IgM binding, few C3b and C3d molecules bind RBCs
- When RBCs return to core circulation, IgM dissociates, but C3b stays, identified by splenic macrophages and removed
- IgM binds 5 RBCs, thus creating in vivo agglutination, might block small capillaries in fingers and toes causing Raynaud phenomenon

Causing ischemia

تثليج الأصابع

Clinically we have 2 types of the cold

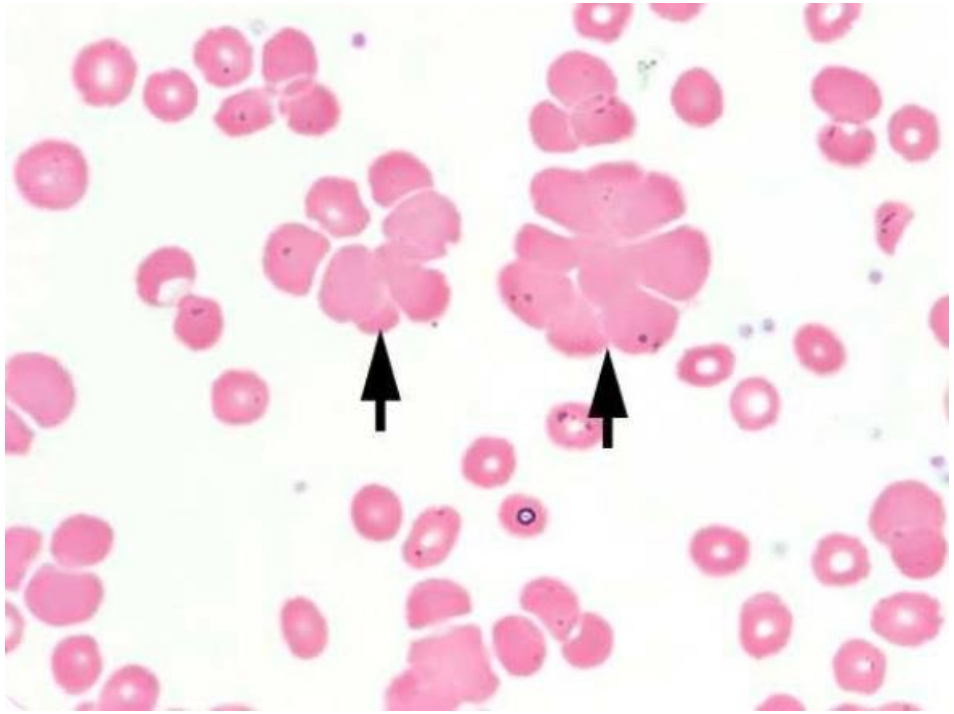
- Transient forms of cold-IHA occur in recovery of infections by mycoplasma pneumonia and infectious mononucleosis (mild, self-limited)

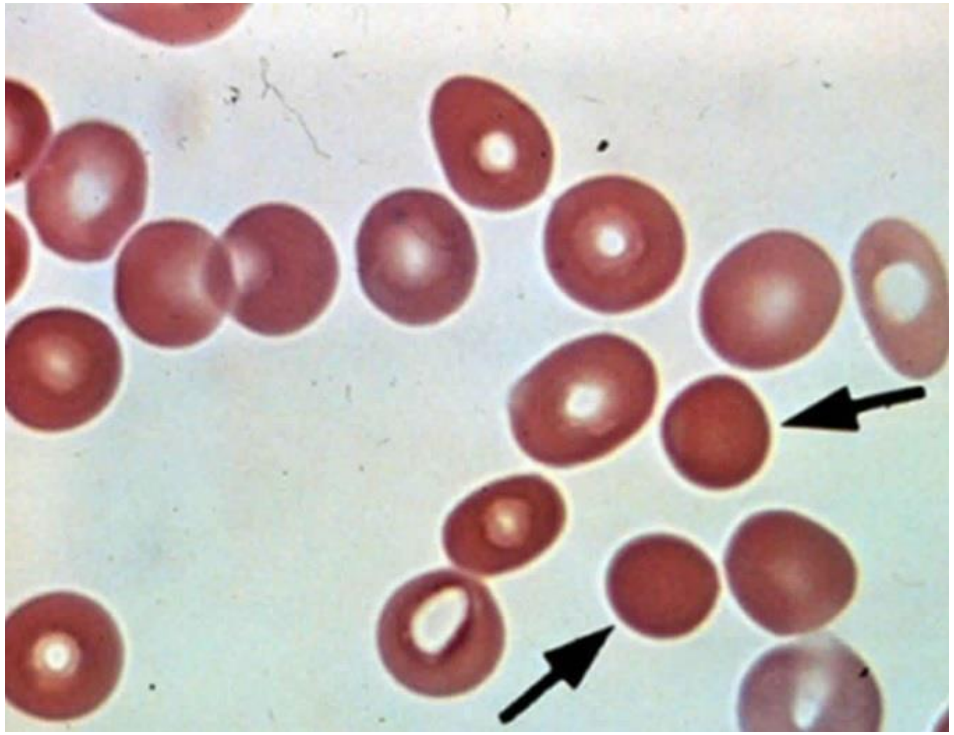
Or Epstein Barr virus

- Chronic persistent form occur in B-cell lymphoma or idiopathic

In cold type we can see agglutinated RBCs not seen in worm one cuz the IgM is large and can bind 5 RBCs

They don't show the central pallor cuz they are not biconcave





- Left: RBC agglutination: RBC clumps in different directions
- Right: spherocytes appear as small, round hyperchromatic RBC

HEREDITARY SPHEROCYTOSIS

Extravascular

- Autosomal Dominant, sometimes recessive
- Mutation is RBC cell membrane skeleton
- Most commonly affects ankyrin, band 3 or spectrin The mesh work proteins
- Cell membrane becomes unstable, keeps losing parts of it as the RBC age
- Little amount of cytoplasm is lost
- With decreasing surface area, the RBC loses it normal biconcave morphology and becomes a smaller sphere

PATHOGENESIS

- Spherocytes are nondeformable زي الكرة ما بتقدر تطعجها
- Entrapped in small vessels in spleen, engulged by histiocytes and destroyed (extravascular hemolysis)
- If spleen is removed, spherocytes persist in peripheral blood, thus, anemia is corrected
- The degree of anemia is variable (depends on the type of mutation)
- Some patients are asymptomatic, while others might have severe hemolysis

LABORATORY FINDINGS

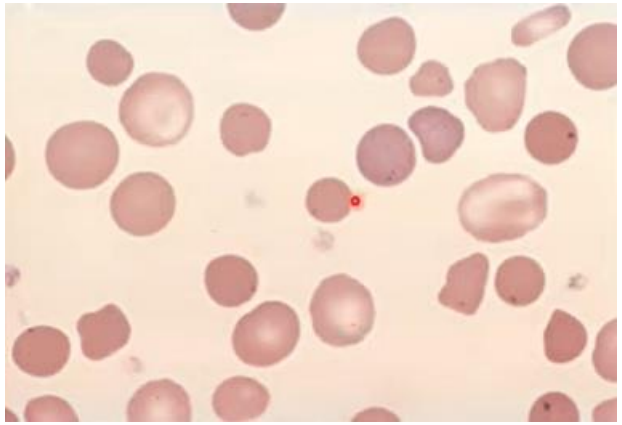
- Appearance of spherocytes in peripheral blood
- Spherocytes have a smaller size (low MCV)
- Little cytoplasm is lost, normal amount of Hg (normal MCH)
- MCHC is increased Cuz the MCH / MCV will give bigger number
- Spherocytes show increased fragility when put in hypotonic solution (increased osmotic fragility)

Third test

hypotonic وبنضيف عليه the patient's blood بنجيب

solution وبنصير نخففه اكثر وأكثر ونشوف لحد وين يصير lysis ال

fragility ال يزيد ورح يتحملوا ما رح spherocyte ف



They don't show central pallor

Intravascular hemolysis

Means sudden

PAROXYSMAL NOCTURNAL HEMOGLOBINUREA

Means at night

- Rare, acquired disease Acquired mutation in the stem cells but it comes late in life
- Mutation in PIGA gene, results in deficiency in phosphatidylinositol glycan (PIG), a structural protein on cell membrane that anchors many other proteins Which are CD55 and CD59
- Mutation occurs in bone marrow stem cell (leukocytes, RBCs and platelets are all affected)

PATHOGENESIS

- Complement system: circulating proteins that are part of immune system. They are activated (C5b-C9) and attack cell membrane to create pores, causing lysis
- Blood cells protect themselves by membrane proteins CD55 and CD59, that are normally attached to PIG

From the complement system

- In PNH: RBCs, and to a lesser degree WBCs and platelets, are spontaneously lysed inside blood

Patients will develop anemia, leukopenia and thrombocytopenia

Why it occur more at night?

- During sleep, ↑CO2, ↓ blood PH, more active complement system, more hemolysis
- Thrombosis is common

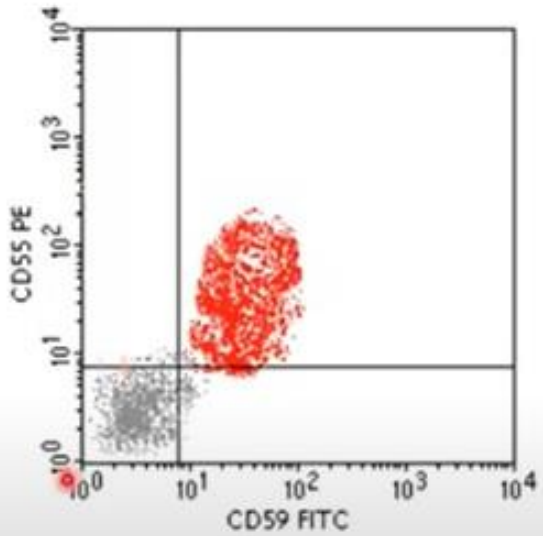
هسا لما يصر lysis ل platelet رح يطلعوا كلشي جواتهم من ضمنهم ADP ويعملوا thrombosis

صح المرضى بيجوا ب anemia بس بموتوا من ال thrombosis

How to diagnose the PNH

The red population is normal

The gray population in PNH



- Flow cytometry study: the red population shows expression of CD55 and CD59, while the gray one is negative for both (PNH clone)

TRAUMATIC HEMOLYSIS

- Direct physical force, or turbulence causing lysis of RBCs
- Prosthetic heart valves
- Repetitive physical pounding (marathon, boxing, marching)
- Disseminated thrombi (microangiopathic hemolytic anemia)
- Hallmark of traumatic hemolysis: schistocytes

بتكون ممزوعه وبطلع عنا
different shapes of RBCs