lec 1 : polycythemia.

Def : ↑ in total RBC mass

types: 1° ⇒ polycythemia vera / autonomous, spleenomegaly, ↓ Erythropoietin, ↑ B.M produc.

2° ⇒ ↑ hypoxia → ↑ erythropoietin ⇒ ↑ Erythropoiesis

- Relative polycythemia ⇒ secondary to ↓ plasma volume.
- absolute polycythemia ⇒ secondary to ↑ B/M produc. (true ↑ in RBC mass)

1° VERA

1) Mutation ⇒ TK - JAK2 ⇒ always active
2) less dependent on growth fac.
3) acts on signaling pathways
   → Receptor of erythropoietin
   → GF Receptor
4) panmyelocytosis (mainly Erythrocyte)
5) myeloprolifirative neoplasm.

2°

1) no spleenomegaly.
2) athelet ⇒ surreptitious.
3) adaptive ⇒ many reasons.
4) Alcohol ⇒ ↑ urination, ↓ respiration.
5) smoking
6) paraneoplastic (liver cancer, renal) ⇒ no hypoxia.
7) ↑ Erythropoietin ⇒ pgls

- Symptoms:

general:

1) cyanosis (زرقة), plethora (حمرة)
2) Headache + dizziness (hypertention).
3) ↑ viscousity + ↓ circulation ⇒ vission blurred, ischemia, cyanosis.
4) bleeding / Thromposis (problems in vWF).

VERA:

in addition to

1) pruritus (aquagenic)
2) peptic ulcer (↑ histamine)
3) gout ⇒ kidney stones, tophi, arthritis.
4) Chronic disease.
5) spent phase ⇒ after 10 years
   ⇒ B.M is fiprotic ⇒ shift to spleen.
6) Blast crisis ⇒ acute myeloid luekemia.

- Laboratory findings:

general: ↑ RBC count ① ↑ hematocrit ② ↑ Hg concent. ③

VERA: ⇒ ↑ Leukocytosis, ↑ Thrombocytosis.
↑ Hypercellu. B.M with panmyelocytosis.
↓ Erythropoietin.
⇐ JAK 2 mutation.

Lec 2: Anemia (General).

- Def: ↓ in oxygyn bind capacity 2° to ↓ RBC mass
  - ⇒ leads to hypoxia.
  - ⇒ measured by concent. of → Hg, → Hematocrit.

- Anemia ↑ Erythropoietin ⇒ causes Erythroid Heperplasia in B.M. (exept in renal failure or chronic inflamation) ?
  - if acute ⇒ prod. of Epo ↑ 5x
  - in sever cases ⇒ extra medullary Erythropoiesis.

Classificatio:

1) cause

① Blood loss

a) acute
- symptoms → ↓ intravas. volume.
- if > 20% lost ⇒ hypovolimic shock, death.
- if < 20% ⇒ interstesial fluid → intravascular (causes dilutional Anemia.) ⇒ (2-3) days.
  ⇒ (5-7 days) ↑ Erythropoietin.
- bleeding → internal ⇒ reuse of iron ✓
  → External ⇒ ↓ iron, ↑ complications.
- Morphology ⇒ normochromic, normocytic with veticulocytosis.

B) Chronic: $\frac{\text{rate RBC loss}}{\text{rate of produc}} > 1$
- mostly → GI, menestruation
- leads to iron dificiency anemia
- Morphology ⇒ hypochromic, microcytic, ↓ veticulocytosis.

② ↓ RBC product.

③ ↑ Distruction. (Chemolytic Anemia).

② Morphology:
- size, color, shape.
- hypochromic ⇒ ↓ Hg
- macrocytic ⇒ stem cell disease + maturation

Clinical features:

→ Headache, dizziness, fatigue, pallor

→ Adaptive: 1) Tachycardia
2) Tachypenea.
3) ↑ 2,3 bisphosphoglycerate

symptoms ⇒ special types:

1) chronic hemolytic anemia
⇒ ↑ belerubin leads to: Jaundice, gall bladder ston → black
red urin.

2) Extramedullary
⇒ spleenomegaly, hepatomegaly

3) Thalasemia major + sitle cell..
⇒ growth retardation.
⇒ bone deformity.
⇒ 2° hematochromatosis ⇒ (damage → heart, → Endo. glands.)

lec 3 : Anemia of low production.

→ general causes : Nutritional dificiency, chronic inflammation, B. M failure.

2) Anemia of inflammation/chronic disease

- hospitalized pts, cancer, chronic ifec. immune disease.

* ↑ IL-6
  ↓
  ↑ Hepcidin : → ① degrade ferroportin on macrophages so keeps Fe^{+2} inside them.
  ↳ ② ↓ erythropoietin.

* Lab. findings.

1) normal RBCs then hypochromic microcytic.
2) ↓ Reticulocytes, ↓ iron in serum
3) B. M iron stores ↑
4) ↑ serum ferritin. → cause it's an acute phase reactant.

1) Iron dif. Anemia → most common type
   → 10% developed coun-vie
   25-50% developing "
   [about the disease]

[About Iron]

* stored in : a) ferritin (soluble) in B.M liver spleen.
  b) homosiderin (insoluble)
  ↳ 15% - 20%
  ↳ granular, large iron, intracellular particle
  ↳ Light microscope ✓.

* transmmited by → transferrin. synthesized in Liver.
  ↳ ⅓ of it are saturated.

* Indicators : ser. Iron level ↓
  ser. ferritin level ↓
  Iron bind. capacity ↑
  ↳ B.M aspirate (earliest change)
  ↳ perl's prussian Blue ↓
  ↓ Reticulocyte Hg cont. CHr
  ↓ MRV as Mean Reticulocyte volu

3] MEGALOblastic Anemia.

1) cause ⇒ B12 or/& Folate dificiency.

- Both are required for the synthesis of Thymedine (DNA)

- problems in maturation & division.
→ may lead to apoptosis inside B.M.

Folate

⇒ in green veg. destroyed in cook.

⇒ minimal amount stored in body.

* Deficiency:

↓ Diet.

↑ Demand. (pregnency, chron. hemolytic anemia)

Methotrexate. (inhibit meta. + cell. usage)

alcohol, intestinal diseas, phynetoin., Beans.

Legume, phynetoin. (inhibit absorb.)

B-12

⇒ animal products

⇒ Bacteria in bowel.

⇒ Resist cook.

⇒ stored in liver.

* Deficiency:

1) Diet (vegeterians)

2) Defective absorbtion ⇒ most common.

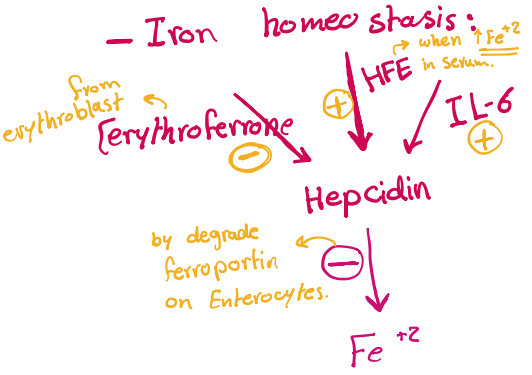
3) gastrectomy

4) Elderly ⇒ ↓ pepsin → ↓ absorbtion from food.

5) ↓ small bowel.

6) Metformin (B_{12})

7) Pernicious Anemia [causes vit. B-12 def. + megaloblastic anemia]
↳ autoimmune gastritis in which T cell & B cells attack Parietal cells (have the intrinsic Factor), thus prevent B-12 from binding and absorption.



* → low hepcidin ⇒ Iron defici.

→ very low hepcidin

- Thalasemia major ↳ ↑ erythroferrone.
- 1° hemochromatosis ↳ ↓ HFE

* Causes: 1) chronic blood loss 2) Diet / 3) ↑ Demand 4) Hypotransferrinemia 5) Enzymatic deficiency. 6) ↓ Absorption.

* Symptoms: 1) General sym. of Anemia 2) Restless leg syndrome 3) Hair loss / 5) Blue sclera 4) spooning finger nails. 6) Glossitis / Somatitis. 7) Cognitive impairment. 8) pica / 9) weak. immunity. 10) Chronic anemia.

* Morphology: 1) poikelocytosis 2) target cell ⊙ 3) hypochromia 4) microcytic. 5) ↓ Reticulocytes. 6) ↑ Erythropoietin (not effective) 7) Thrombocytosis. (shift)

* ⇒ not exectreal rather it shields from skin or mucosa.

hem → red meat 20%

non-hem → vegetable 1%

Functions of B-12 (rather than DNA):

synthesis:
1) myelin sheath
2) neurotransmmiters (epi., norepi.)

3) destruction of homocystien → Toxic to neurons.

4) Recycling of tetra hydro folate ← يساعد اخوه الفولات

* there is no relation btw. the degree of neuronal damage with the degree of Anemia.

Morphology: Macroovalocyte? كبيرة بيضاوية

it takes longer time to mature.

Symptoms: 1) general
2) Glossitis (beefy tounge)
3) Mild Jaundice.
4) severe: pancytopinea.

⇒ B-12 Deficie.

1) postero lateral spinal cord columns degenerate
↳ loss of proprioseption, paresthesia.
2) nephropathy الكلى التهاب
3) neuropsychotic ... تنميل

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5) Anemia of renal disease:

- ↓ EPO ⇒ ↓ RBC produc. ⇒ ↓ retic. count
- x correlate with kidney func. [serum creatinine]
- pts with uremia → bleeding (platelet func.?)
  ↳ echynocytes (Burr cells)
  ↳ الحواف بارزة

4) Aplastic Anemia:

- damage to multipotent stem cell.
- hematopoietic stem cells are depleted.
- leads to pancytopienia
- all age groubs.

* pathogenesis:

→ Extrinsic:
1) Ag cross reactiv., T cell attack stem cells. Evidence: imm.sup. drugs restore B.M. in 70% of cases.
2) drugs ⇒ chloramphenicol, gold injec. pregnancy, NSAIDs, hepatitis V.
3) Mostly idiopathic.

→ intrinsic:
* 10% have telomerase defect, which leads to early death of stem cells.
* genitic. altered stem c. attrack Tcell

* Lab. find.:
→ blood: pancytopenia, normochromic, Macrocytic.
→ B.M: ↑fat, ↓ stem cells.

* special types of B.M failure.

→ Fancon's Anemia:
1) rare
2) inherited
3) defect in DNA repair protien
4) early in life → Aplastic Anemi
↳ acute Leukemi

→ Pure Red cell Aplasia:
1) Absence of Erythroid cell. in BM
2) → inherited: Diamond-Blackfan
→ Acquired: autoimmune
parvovirus. B 19

6) Anemia of Liver Disease:

1) Multi. fact.
2) ↓ clotting factors ⇒ bleeding varices.
3) ↓ transferrin synth.
4) acanthocyte (spur cell)

---

7) of hypothyroidism:-

* Thyroid H. ⇒ ↑ Erythropoiesis
  ↳ ↑ EPO

* normochromic, macrocytic.

---

8) Myelo dys plastic Anemia:

1) acquired neoplastic, mutation in stem cells.
2) old age
3) prolonged survival + defect. maturation, cells stay in B.M.
4) refractory
5) macrocytic
6) neutropinea, Thrombocytopinea.

lec 4 : Hemolytic Anemia

* Pathophysiology: hypoxia ⇒ ↑ EP ⇒ ↑ erythropiosis (extramedullary in seve cases).

↑ Retic. , hemoglobin is releasd from damaged RBC.

↓ haptoglobin (cause it becomes bound), erythroid hyperplasia in B.M.

* classification: ① ⇒ Extravascular ⇒ in spleen by Macrophages.
  * site.
  ⇒ Jaundice, spleenomegally, pigmented gallbladder stones.

② ⇒ intravascular (inside Blood stream) ⇒ sudden Hg release, hemoglobinurea, hemosiderin urea.
iron deficiency, hemoglobinemia.

*cause : ⇒ extra capsular (extrinsic factors), intra capsular.

⟹ causes of hemolytic Anemia:

1) G6PD Deficiency: [Trigger induced.]

* X- linked inherited
* G6PD ⇒ glutathion ⇒ protects against oxidants.
* Trigers: 1- infections., 2. drugs: sulfonamides, primaquine, ↑ dose of aspirine, nafrofurantoin.
  3- Fava beans.

*↑oxidants ⇒ Hg denaturates ⇒ Heinz bodies ⇒ RBC (their membrane) distruc. by spleen. (2-3 days after trigger).

* Morphology ⇒ Bite Bodies. (indented defect in c.m).
* supravital special stain: Heinz bodies ⇒ dark spots attached to C.M. (condinsed denatured)

2) Immune (acquired) hemolytic anemia:

* Ab ⇒ RBC cell membrane protiens. ⇒ detected by coombs test:

→ Direct coombs test: antibodies against auto-Ab.

→ indirect ≠ : RBC serface protiens in serum.

* 2 types:

1) Warm type.

- IgG Ab.
- 37°c

* Mecanism: IgG binds RBC. ⇒
⇒ Macrophage (in spleen) bind Fc portion of IgG thus "بتنقيها"
⇒ RBC becomes spherocyte (changes its structure after ضربة)
⇒ destroyed by spleen.

* Causes:
- 60% idiopathic, - 25% SLE,
15% drugs: (α-methyldopa, penicillin).

* variable severity.
* small round hyperchromatic spherocytes.

2) Cold type:

- IgM Ab (bind 5 RBCs) ⇒ low affinity!
- peripheral blood.

* IgM Ab bind RBC (leads to) ⇒ C3b & C3b from complement system bind to RBCs too as a respones ⇒ IgM dettech 😐 letting C3b&C3d bound. ⇒ Splenic Macrophages remove these RBCs.

* Raynaud phenomena: IgM binds 5 RBCs ⇒ making agglutination ⇒ bloking small blood capillaries in fingers & toes (أطراف)

* 2 types:

- transient: (acute) in recovery of infection by: mycoplasma pneumonia., mononucleosis (mild, self limited).
- chronic: in B-cell lymphoma or idiopathic, persistant.

3) Hereditary spherocytosis:

- Autosomal Dominant, sometimes recessive.
- mutation in RBC cell membrane skeleton (proteins).
- mostly ankyrin, band 3 or spectrin.
- ↓ surface area, loss of biconcavity, becomes smaller sphere.
- unstable cells, keeping loosing parts, littile amount of cytoblasm is lost.
- severity is variable, some pts are asymptomatic! ⇒ depend on type of mutation.

* pathogenesis: Entraped by small vessels in spleen, engulfed by hesto cytes so degraded Extravascular.

* corrected by spleenectomy. (removal of spleen).

* normal amount of Hg (normal MCH)

* ↑ MCHC

* ↑ fragility of spherocytes in hypotonic solution (↑ osmotic fragility)

4) Paroxysmal (sudden) Nocturnal (at night) Hemoglobinurea.

- Rare, acquired
- mutation in B.M stem cells. (all are effected).
- mutation in **PIGA** gene ⇒ ↓PIG protien: structural prot. that anchors many others.
- degradation of RBCs, to lesser extent WBCs & Platelets inside Blood.
- Thrombosis: when platelets lyse they secrete thier content. وبيقى عمل

* Mechanism:-

→ complement sys. attacks RBC creating pores, how? RBCs normally have CD55 & CD59 attached to PIG

→ During night: CO_2↑, ↓ Blood PH ⇒ ↑ complement sys. activity. ⇒ more hemolysis.

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5) Traumatic hemolysis:-

Go Back to كمان مرة slides

(☺ . صفحة مش محررة)

Lec 5: Hemoglobinopathies

Normal Hg in Adults: 95% Hg A ($\alpha 2 \beta 2$), 3% HgA2 ($\alpha 2 \delta 2$), شقفة HgF

1) Thalasemia:
↓ production of Hg chains (α or β), ↑ production to the another, results in unpaired chains ⇒ instability & hemolysis.

- inherited, Autosomal recessive.
- resistant to malaria falciparum.
- ↑ Middle East, South East Asia, Africa.

✱ Genatics

1) α-chain
- encoded by 2 genes on chromos. 16 = 4 genes. (2 genes على كل اليل)
- mutations ⇒ deletion.
  - → < 2 genes ⇒ silent
  - → 4 genes ⇒ death (hydrops fetalis) ← بكون عندهم تلاث انواع الطبيعي: Hg ↑ HgBarts + HgH +
  - → 3 genes ⇒ Hg-H disease:
    - Extra β-chains → tetramer → Hg-H
    - Extra γ-chains → Hg Barts
    - Both have high affinity towards Oxygen.

2) β-chain.
- Single gene on chromo. 11 ⇒ 2 genes.
- point mutations ⇒ results are inpredictable.
- β = normal / β^0 = no produc. / β^+ = ↓ produc.
- types:
  1. β / β^0 ⇒ silent / no symp.
  2. β^+ / β^+ ⇒ Thalasemia intermedia.
  3. β^0 / β^+ ⇒ Thalasemia major. [Cooly anemia]
     - ↳ Extra α-chains ⇒ hemolysis of RBC in spleen + Erythroid precursors in B.M, why? [ineffective Erythropoie]
     - α-chain don't form tetramer as β-chains فلهذا تكون الـ hemolysis بكل الاماكن.

✱ Morphology:
⇒ hypochromic microcytic anemia (as in iron defic. anemia), Target cells (in any abnormal Hg synth.), Basophilic stippling [ribosomes]

- in thal. major ⇒ 1) in blood: ↑ poikelocytosis, nucleated RBCs.
  2) in B.M: ↑↑↑↑↑ Normoblast, hemosiderosis (cause of repeated transfusion).

✱ Clinical symptoms:

1) Thal. trait = minor = carrier ⇒ No sympt., premarital test is important, normal life span
2) Thal. intermedia (المشكلة β-chain) & Hg-H (المشكلة α-chain) ⇒ moderate symp., no need to blood transfusion (regular).

3) Thal. Major ⇒ - sympt. start after age of 6 months.

- persist. anemia symp., - skeletal abnormalities
- growth retardation.
- ameloirated by regular blood transfusion.
- in 2nd & 3rd decades of life ⇒ 1) syst. hemochromatosis (fatal)
  2) related organ damage.

Diagnosis:

- Hg electrophoresis test

→ all β-thal : ↑ HgA2 , ↑ HgF

→ Thal. Major: X HgA or very low amount.

→ HgH disease ⇒ HgH + Hg Barts

→ α-thal carrier or minor ⇒ no abnormality is found, Genitic test is available (بتيجي فيه)

2) Sickle Cell Anemia:

- most common familial hemolytic anemia worldwide.
- Africa, African American, Middle East, Saudi Arabia.
- substitution ? ⇒ glutamic acid (hydrophilic) → valine (hydrophobic), in β-chain
- Autosomal co-dominance: → heterozygous: HgS + HgA >> carrier.
  → homozygous: only HgS
  ] in electrophoresis
- Resistant to malaria falciparum.

Pathogenesis: deoxy. HgS → polymaris longitudinaly → distorting cell shape → creating sikle shape.

- it's reversable by reoxy., however with repetition RBC becomes sickle shaped perm.
- HgA in carriers + HgF in newborn inhibits HgS polym.
- ↑ dehydration, ↑ acidosis, ↑ [HgS] ⇒ ↑ sickling.

- The presence of α-Thalasemia with sickle cell anemia ⇒ ↓ sickling.
☺ يعني اعراضهم أخف

* Longer time to pass through capillaries, removed by macrophages in spleen, Adhere to endothelial cells ⇒ thrombus.

Clinical features:

⇒ dependent on sickle cell fraction: Chronic, moderate-sever hemolytic anemia ⇒ after age of 6 months, worsening by repeated sudden attacks.

⇒ independent on sickle cell fraction: Vaso-occlusive crisis ⇒ organ infarction, associated with: sys. infection, inflamation, dehydration acidosis.

- Hand-foot syndrome, stroke, myocardial infraction, retinopathy, Autospleenectomy, acute chest syndrome.
- Aplastic crisis → infection by Parvovirus B19 → worsening Anemia → self limited.
- ↑ susceptibility to encapsulated Bac. (pneumococcus, salmonella) after spleenectomy.

⇒ carriers ⇒ Asymptomatic.

Lab. findings:

1) blood smear: target cells + sickled cells
↳ it's normal in sickle cell trait.

2) in sickling test ⇒ adding hypoxic agents تثبيط اوكسجين

3) Hg electrophoresis.