HEMATOLYMPHOID SYSTEM BLEEDING DISORDERS

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ABNORMAL BLEEDING

- Defined as spontaneous bleeding or prolonged bleeding after trauma
- Caused by abnormality in:
- 1) platelets
- 2) clotting factors
- 3) blood vessels – endothelial cells

↳ or a combination of abnormalities of the points above

Bleeding secondary to

FRAGILE BLOOD VESSELS

- High corticosteroid → like in cushing syndrome or when used excessively as a treatment
  - ↑ weak blood vessels
  - → commonly used as a treatment in dermatological diseases
- Scurvy (vitamin C deficiency) → was common in the old ages due to the scarcity of vitamin C in food → vitamin C is important for the collagen structure in the blood vessels
- Vasculitis (autoimmune or infectious)
  - → Vasculitis: inflammation of the blood vessel itself
- Inherited disorders of connective tissue
  - ↳ weak connective tissue
- Patients develop spontaneous petechiae and ecchymoses in skin and mucous membranes → ex. conjunctiva of the eyes
  - petechiae: minor bleeding in the skin & the superficial areas of the body
  - ecchymoses: ↳ Bruises → large areas
- Laboratory tests of platelets and clotting factors are normal

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

→ Emergency! → patients are at risk of death

- Systemic activation of coagulation system in the body
- Formation of myriads of thrombi in the microcirculation, may cause ischemia and microinfarction
  - ↳ myriads: innumerable / extremely numerous
  - ↳ small capillaries & arterioles not large vessels!
  - ↓ in any tissue in the body
- Followed by activation of fibrinolysis → dissolving thrombi
- Then patients become at risk of severe bleeding (consumed platelets and clotting factors) → And thats why DIC is also referred to as "Consumptive Coagulopathy"
- Patients develop thrombocytopenia, anemia and schistocytes
  - ↳ Because of the mechanical damage
  - ↳ Due to the numerous thrombi
  - ↳ Also called microangiopathic hemolytic anemia

↳ Remember:

Schistocytes form due to the mechanical damage of RBC's

PATHOGENESIS

Causes of DIC:

- 1) Release of tissue factor into the circulation (activates extrinsic pathway)
- 2) Widespread endothelial damage (causes release of tissue factor and expose the subendothelial von Willebrand factor) → causes platelet aggregation
  ↳ +collagen
- 3) Release of negatively charged substances in the circulation (activates intrinsic pathway) → seen in cases of physical damage of tissues, especially the brain

HIGH TISSUE FACTOR RELEASE

→ Bleeding in the placenta
→ Death of the baby
→ Leak of the amniotic fluid
→ association with DIC

Diseases conditions related to release of high amounts of tissue factors:

- From placenta, in obstetric complications
  - → factor III release
  - → especially in late pregnancies
- From certain cancer cells (acute promyelocytic leukemia, adenocarcinoma)
  - → The most important example
  - → any type
- Bacterial sepsis, bacterial toxins activate TF on monocytes, also monocytes secrete tumor necrosis factor and IL-1 that stimulate expression of TF on endothelium and inhibit thrombomodulin
  - → thrombosis inhibitor
  - → By releasing mucin which activates tissue factor

→ APL-associated DIC can kill the patient from bleeding rather than the tumor itself

→ Pancreatic adenocarcinoma is known for having frequent DIC in the body of the patient

WIDESPREAD ENDOTHELIAL DAMAGE

- Deposition of antigen-antibody complexes (systemic lupus erythematosus, vasculitis) (autoimmune diseases)
- Severe heat exposure (heat stroke, burn injury) → the patient can develop DIC
- Snake venom → Direct damage to the endothelial cells
- Certain infections (meningococci, rickettsiae, COVID19), this condition is called systemic inflammatory response syndrome → can lead to DIC & severe bleeding
  - infection → severe inflammation in the circulation → endothelial damage → the patient has high tendency to develop DIC → bleeding

ACTIVATION OF INTRINSIC PATHWAY

↳ Associated with physical damage of the tissue

- Massive tissue damage (trauma, surgery)
- Head injury
- Brain substance and collagen are negatively charged particles that are released in blood

↳ Brain is a soft tissue → its substances can be released easily in the circulation → activates the intrinsic pathway

* very important *

CLINICAL AND LABORATORY FINDINGS

due to the consumption of platelets & clotting factors (remember its name, consumptive coagulopathy)

- Thrombocytopenia/prolonged PT and PTT/schistocytes
- Acute DIC (e.g. obstetric complication) shows ecchymosis (superficial hemorrhage), severe hemorrhage into body cavities → shock & death (& petechiae) (deep hemorrhage)
- Chronic DIC (e.g. cancer related) shows recurrent thrombosis → patients suffer from the ischemic impact
  - ex. pancreatic adenocarcinoma
- ----------
  - late complication of meningococcal septicemia
- Waterhouse-Friderichsen syndrome: meningococcous sepsis → DIC → adrenal hemorrhage → acute adrenal failure (no steroids, hypotension) → fatal! (caused by the bleeding not the infection)
- Sheehan syndrome: complicated labor → DIC → severe hemorrhage (+ electrolyte loss) → pituitary ischemia and necrosis → loss of pituitary function → affects the BP & lactation due to loss of prolactin

2 Rare & special situations

Absence of cortisol & mineralocorticoids which are essential for regulating electrolytes & blood pressure (BP)

ineffective circulation to the pituitary gland

grossly they show bleeding & hematoma

2 similar diseases

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) & HEMOLYTIC UREMIC SYNDROME (HUS)

- Widespread formation of platelets-rich thrombi in microcirculation → similar to DIC but with different mechanism
- NO activation of clotting factors (normal PT and PTT) → clotting system is preserved (in contrast to DIC)
- Leads to thrombocytopenia and tendency for bleeding
- Clinically: fever, thrombocytopenia, microangiopathic hemolytic anemia, renal failure and neurologic symptoms (the latter not present in HUS)

↳ small palpable pinpoint bleeding in the skin

↓ Due to thrombosis in small blood vessels

↓ Schistocytes

5 symptoms in TTP

4 symptoms in HUS

TTP

more common

- Congenital or acquired
- Deficiency in metalloproteinase ADAMTS13, normally negatively control vWF
- ADAMTS13 normally cleaves the precursor of vWF (large multimer molecule) into vWF. This multimer is capable of binding multiple platelets causing thrombosis

ADAMTS13 deficiency

↓

vWF multimer becomes dominant in the blood

ADAMTS13 is a circulating metalloproteinase synthesized primarily by the liver that cleaves ultra-large multimers of von Willebrand factor (vWF), thereby preventing excessive platelet aggregation. Inherited or acquired deficiencies of ADAMTS13 (the latter caused by autoantibodies) may lead to thrombotic thrombocytopenic purpura (TTP). This assay reports ADAMTS13 activity as a percentage of the activity seen in healthy individuals.

→ from Robbins pathology 11th edition

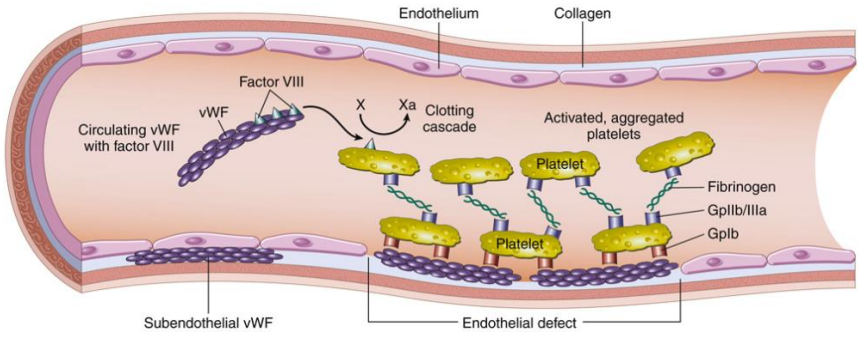
HUS

- Caused by E. Coli O157:H7 bacterial infection
- Food borne
- Bacteria secretes toxin that activates complement system and causes endothelial damage, mainly in kidneys → Not sepsis like in DIC

VON WILLIBRAND FACTOR → Vastly present in the circulation

- Endothelial cells are normally the major source of vWF
- It is also present in platelets granules and subendothelial area
- Facilitate platelets adhesion to damaged blood vessels
- It also stabilizes factor VIII → Free circulating vWF
  - → Carries Factor VIII
  - → Severe absence of vWF will affect the amount of factor VIII
- Precursor of vWF is a large multimer molecule
  - Activity of vWF is Examined by ristocetin aggregation test (ristocetin enhances vWF binding to platelets), if no aggregation → vWF deficiency

→ Endothelial stripping exposes subendothelial vWF → which binds the platelets to form the platelet plug



VON WILLIBRAND DISEASE

- Autosomal dominant → Most patients have the heterozygous disease
  → Homozygous disease is more severe
- Most common inherited bleeding disorder (1% of population in US) → very common, even more than hemophilia
- Affects platelets function (dominant symptom) and coagulation (factor VIII) → But not platelet count
- Patients present with ecchymosis (or petechiae), easy bleeding and menorrhagia
- In homozygous disease, factor VIII deficiency becomes severe enough to resemble hemophilia A disease → Bleeding in the body cavities not only in the skin
- Type 1: most common, modest reduction of vWF level
- Type 2A: the precursor of vWF is not synthesized, too
- Type 2B: the precursor of vWF is unstable → abnormally hyperactive with very short half-life, capable of binding to multiple platelets causing thrombocytopenia as well → Reduction of vWF level
  → clinical picture similar to TTP

we have to ask about the older siblings & uncles from the maternal side to check if the mother is a silent carrier

HEMOPHILIA A

*Bleeding in the skin → platelet defeciencies (ecchymosis & petechiae)

*Bleeding in body cavities → clotting factors defeciencies

- X-linked disease → affects males more than females
- Most common cause of inherited serious bleeding → more serious than vWF disease
- Deficiency in factor VIII (prolonged PTT) → But the PT is normal
- 70% have a family history, 30% appears as a new mutation
- Severe disease occurs when the level of factor VIII drops to 1% of normal level (spontaneous bleeding) → life-threatening

Naturally, we have a huge reserve of factor VIII

symptoms appear when the level of factor VIII drops below 20%

- Mild deficiency: bleeding occurs after trauma or surgery
- In 10% of patients: normal level but abnormal function → affects normal growth
- Bleeding occurs in body cavities (joints, abdomen, chest), no petechiae nor ecchymosis
- Hemophilia B: identical to hemophilia A, less common, factor IX deficiency → rare

→ may appear at the circumcision (earliest surgery of the males)

THROMBOCYTOPENIA

- Defined as platelets count below 150,000 cell/uL → It is not a must to have bleeding tendency
- Increased risk of bleeding occurs when count drops below 50,000
- Spontaneous bleeding: <5,000
- Bleeding occurs in superficial parts of body (skin, mucous membranes), called petechiae and ecchymosis
- Larger hemorrhage occurs in brain → other body cavities are usually preserved in marked thrombocytopenia
- Thrombocytopenia may occur in the setting of ① increased platelets destruction (bone marrow shows increased megakaryocytic activity) or ② decreased production from bone marrow
- HIV infection causes thrombocytopenia (both increased destruction and decreased megakaryocytic survival)

Resembles cold type IHA which also occurs post-infection

IMMUNE THROMBOCYTOPENIC PURPURA

Palpable pinpoint bleeding in the skin

↳ Isolated thrombocytopenia

- Acute ITP is seen in children after viral infection (self-limited) → sensitization of the platelets in an abnormal way → consumption by the spleen
- Chronic ITP is commonly seen in middle-age women → requires therapy
- Formation of autoantibody (IgG) against glycoprotein IIb/IIIa or Ib/IX complexes → Detected in 80% of patients
- Splenic histiocytes remove coated platelets and destroy them
- Splenomegaly is NOT prominent, but patients benefit from splenectomy → Differs from hemolytic anemia
- Bone marrow shows proliferating megakaryocytes
  - ↳ In contrast to myelodysplastic syndrome (MDS) where megakaryocytes are abnormal

HEPARIN-INDUCED THROMBOCYTOPENIA

(HIT)

- Moderate to severe thrombocytopenia affects 5% of patients receiving heparin after 1-2 weeks of therapy
- Formation of IgG antibody that binds factor-4 in a heparin-dependent manner, resulting in platelets activation and thrombosis (consumptive thrombocytopenia)
- Mostly seen in high-molecular weight heparin

→ Affects the coagulation system

→ It is unknown how exactly

→ Doesn't affect the platelets

unless in HIT

formation of a platelet plug within circulation

→ thrombosis + thrombocytopenia

→ In pharmacology, their are two forms of heparin:

1) high-molecular weight heparin
2) low-molecular weight/fractionated heparin
   - → The modified / better form using the active subunit
   - → Still can cause HIT but much less common than HMW heparin

يا حليم، يا ودود، ياذا العرش المجيد، يا مبدئ يا معيد، يا فعالاً لما تريد، أسألك بعزك الذي لا يُرام، وملكك الذي لا يُضام، وبنورك الذي ملأ أركان عرشك، أن تغيث غزة، وتلطف بأهلها، اللهم اجعل لهم من كل ضيق مخرجاً، ومن كل هم فرجا، ومن كل بلاء عافية، اللهم استر عوراتهم، وآمن روعاتهم، واحفظهم من بين أيديهم ومن خلفهم !!
اللهم عجل بالفرج لهم، وبشرهم بما يفرحهم ويحيي أرواحهم !!