HEMATOLYMPHOID SYSTEM BLEEDING DISORDERS

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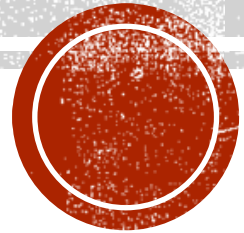


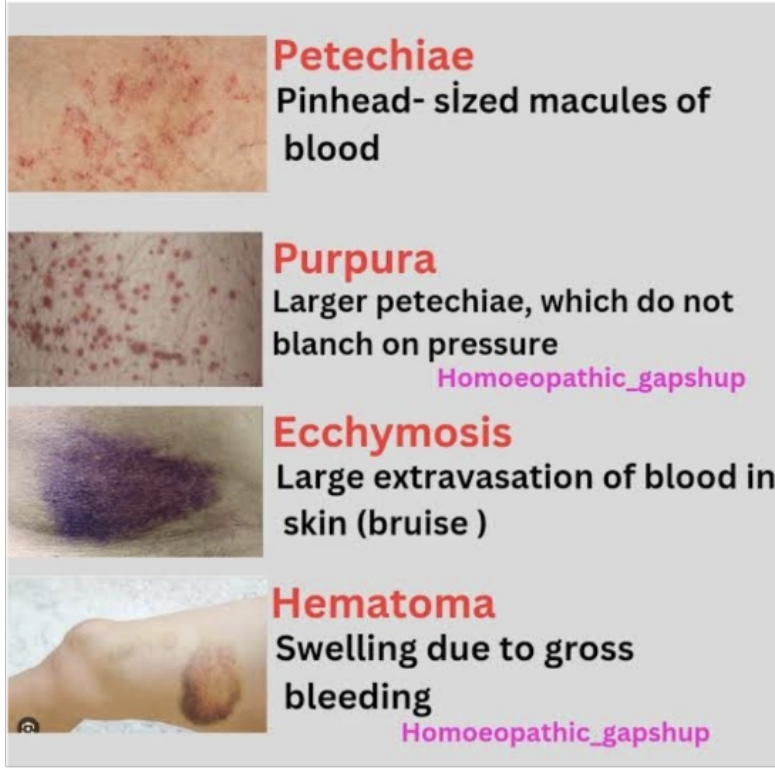
ABNORMAL BLEEDING

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

or combination

FRAGILE BLOOD VESSELS

- High corticosteroid (Cortisol / In Cushing Syndrome / In dermatologic diseases)
- Scurvy (vitamin C deficiency) (was common in old ages. Important for collagen structure in blood vessels)
- Vasculitis (autoimmune or infectious)
- Inherited disorders of connective tissue (weak CT tend to bleed)
- Patients develop spontaneous petechiae and ecchymoses in skin and mucous membranes (even in eye (conjunctiva); in skin superficial areas of body; large area bruises)
- Laboratory tests of platelets and clotting factors are normal



DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Emergency (at risk of dth)

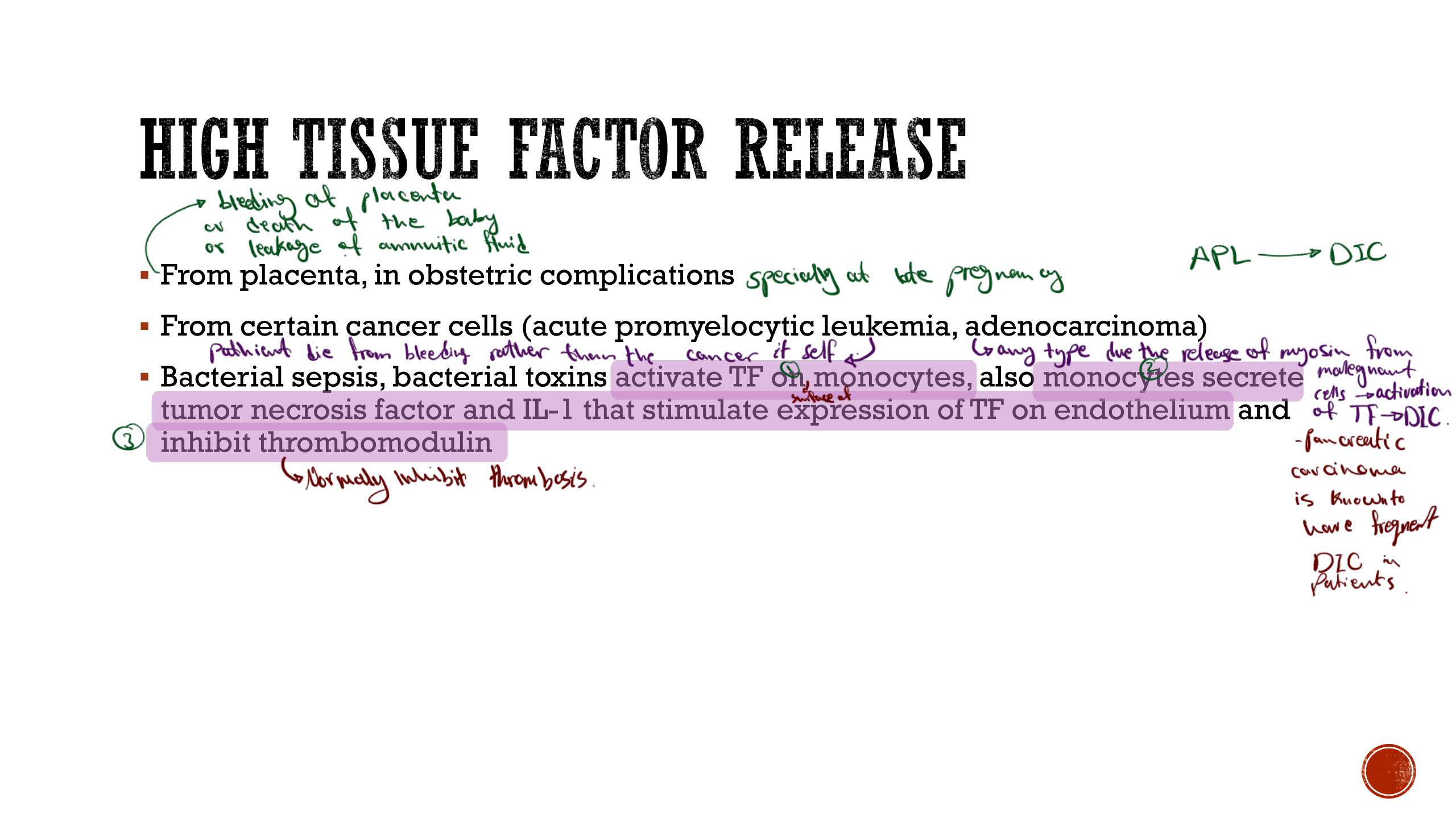
- Systemic activation of coagulation system in the body
- Formation of myriads of thrombi in the microcirculation, may cause ischemia and microinfarction
- Followed by activation of fibrinolysis 1st formation of thrombi 2nd dissolved
- Then patients become at risk of severe bleeding (consumed platelets and clotting factors) → consumptive coagulopathy.
- Patients develop thrombocytopenia, anemia and schistocytes
  - ↳ Microangiopathic hemolytic anemia ↗

PATHOGENESIS one of the three mechanisms:

- 1) Release of tissue factor into the circulation (activates extrinsic pathway) Increased
- 2) Widespread endothelial damage (causes release of tissue factor and expose the subendothelial von Willebrand factor) 2nd any activation of the EX. pathway
  once the endothelium is streped out → exposure of the vWF → platlet activation
- 3) Release of negatively charged substances in the circulation (activates intrinsic pathway) seen in physical damage to the tissue specially the brain.

HIGH TISSUE FACTOR RELEASE

- From placenta, in obstetric complications
- From certain cancer cells (acute promyelocytic leukemia, adenocarcinoma)
- 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



WIDESPREAD ENDOTHELIAL DAMAGE

- Deposition of antigen-antibody complexes (systemic lupus erythematosus, vasculitis)
- Severe heat exposure (heat stroke, burn injury)
- Snake venom
- Certain infections (meningococci, rickettsiae, COVID19), this condition is called systemic inflammatory response syndrome

ACTIVATION OF INTRINSIC PATHWAY

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

CLINICAL AND LABORATORY FINDINGS

- Thrombocytopenia, prolonged PT and PTT, schistocytes
- Acute DIC (e.g. obstetric complication) shows ecchymosis, severe hemorrhage into body cavities
- Chronic DIC (e.g. cancer related) shows recurrent thrombosis
- ----------
- Waterhouse-Friderichsen syndrome: meningococcous sepsis → DIC → adrenal hemorrhage → acute adrenal failure (no steroids, hypotension)
- Sheehan syndrome: complicated labor → DIC → severe hemorrhage → pituitary ischemia and necrosis

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

Small pinpoint bleeding in skin

- Widespread formation of platelets-rich thrombi in microcirculation
- NO activation of clotting factors (normal PT and PTT) The clotting system is preserved
- Leads to thrombocytopenia and tendency for bleeding which can be fatal
- Clinically: fever, thrombocytopenia, microangiopathic hemolytic anemia (schistocytes), renal failure and neurologic symptoms (the latter not present in HUS)

TTP

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

precursor of vWF is a large multimer molecule composed of many vWF monomers.

HUS

Different than DIC : no sepsis

- Caused by E. Coli O157:H7 bacterial infection
- Food borne
- Bacteria secretes toxin that activates complement system and causes endothelial damage, mainly in kidneys

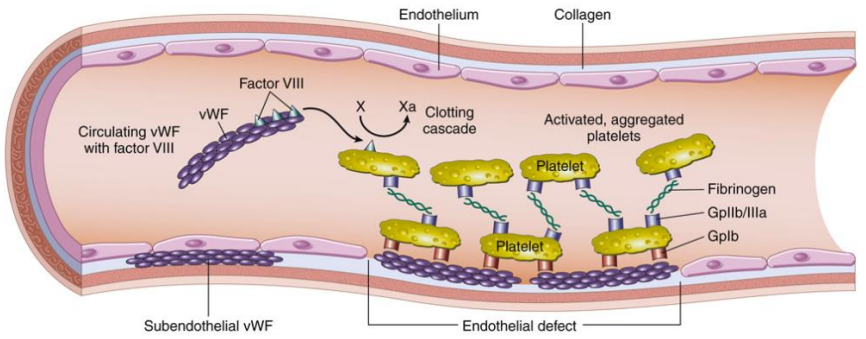
VON WILLIBRAND FACTOR

→ Some are free circulating
→ Some are subendothelial

→ Vastly present in the circulation.
→ It's firstly bellow the endothelial cells

- 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 → Sever absence of vWF will affect the Factor XIII.
- Precursor of vWF is a large multimer molecule circulating in blood
- Examined by ristocetin aggregation test (ristocetin enhances vWF binding to platelets), if no aggregation → vWF deficiency

in labs:



VON WILLIBRAND DISEASE

→ platlet count is normal but not functioning.
→ develop petichea and echymosis

- Autosomal dominant
- Most common inherited bleeding disorder (1% of population in US)
- Affects platelets function (dominant symptom) and coagulation (factor VIII)
- Patients present with ecchymosis, easy bleeding and menorrhagia
- In homozygous disease, factor VIII deficiency becomes severe enough to resemble hemophilia A disease
- 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 with very short half-life, capable of binding to multiple platelets causing thrombocytopenia as well

HEMOPHILIA A

- X-linked disease → more common in males.
- Most common cause of inherited serious bleeding more serious than vWD
- Deficiency in factor VIII (prolonged PTT) while PT is normal
- 70% have a family history, 30% appears as a new mutation
  - ask for maternal uncles : It's X linked
- Severe disease occurs when the level of factor VIII drops to 1% of normal level (spontaneous bleeding) symptoms appear when it drops to 20% of normal level
  - life threatening
- Mild deficiency: bleeding occurs after trauma or surgery
  - mainly boys → first surgery is circumcision → the disease appears at that time.
- In 10% of patients: normal level but abnormal function
  - functional difficiency with abnormal PTT.
- Bleeding occurs in body cavities (joints, abdomen, chest), no petechiae
  - abnormal joints so can't grow normally
- Hemophilia B: identical to hemophilia A, less common, factor IX deficiency
  - rare

THROMBOCYTOPENIA

It's not a must to have symptoms or bleeding tendency.

- Defined as platelets count below 150,000 cell/uL
- 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 in case of marked thrombocytopenia.
- Thrombocytopenia may occur in the setting of increased platelets destruction (bone marrow shows increased megakaryocytic activity) or decreased production from bone marrow

Body cavities are preserved.

- HIV infection causes thrombocytopenia (both increased destruction and decreased megakaryocytic survival)

IMMUNE THROMBOCYTOPENIC PURPURA

Most important

Pin point

Isolated thrombocytopenia.

- Acute ITP is seen in children after viral infection (self-limited)
  - ↳ Sensetization of platlets in abnormal way → destruction in the spleen *Little bit simmilar to the cold type hemolytic Anemia
- Chronic ITP is commonly seen in middle-age women
  - ↳ Autoimmune needs specific therapy.
- Formation of autoantibody (IgG) against glycoprotein IIb/IIIa or Ib/IX complexes
- Splenic histiocytes remove coated platelets and destroy them
- Splenomegaly is NOT prominent, but patients benefit from splenectomy
- Bone marrow shows proliferating megakaryocytes

detected in 80% of patients

* Two types of heparin:
① high molecular weight → commonly used → cause this side effect
② low molecular wight → fractionated heparin → may cause it but to much lesser probability

HEPARIN-INDUCED THROMBOCYTOPENIA HIT

↳ function on coagulation system not on platlets.

- 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

→ unkown exactly how heparin induce this binding
→ formation of a platlet plug within the blood stream
→ IgG binds multible platlets and form a thrombus
→ Thrombocytopenia + Thrombosis.
→ consumbtive thrombocytopenia.
→ Similar to paroxismal Nocturnal Hemoglobinurea.