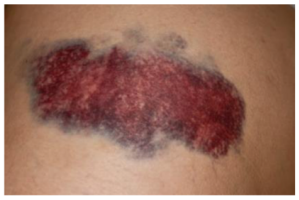
Lecture '1'

Abnormal bleeding

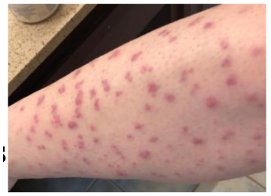
spontaneous bleeding or prolonged bleeding after trauma

- Caused by abnormality in:
- 1) platelets
- 2) clotting factors
- 3) blood vessels – endothelial cells

fragile blood vessels



ecchymoses



petechiae

1. High corticosteroid
2. Scurvy (vitamin C deficiency)
3. Vasculitis inflammation of the blood vessels (autoimmune or infectious)
4. Inherited disorders of connective tissue

- Patients develop spontaneous petechiae and ecchymoses in skin and mucous membranes, result from small blood vessel ruptures
- Laboratory tests of platelets and clotting factors are normal (because the problem is in the blood vessels)

disseminated intravascular coagulation (DIC)

imp!

FATAL

- 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
- Then patients become at risk of severe bleeding (consumed platelets and clotting factors)
- Patients develop thrombocytopenia,anemia and schistocytes

pathogenesis

هلأ أسباب العرض.

activation of the extrensic and exirnsic pathway.

1) Release of tissue factor into the circulation (activates extrinsic pathway)

)Widespread endothelial damage (causes release of tissue factor and expose the subendothelial vonWillebrand factor

3) Release of negatively charged substances in the circulation (activates intrinsic pathway)

1 high tissue factor release

Placenta , cancer , Bacterial.

- From placenta,in obstetric complications
- 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
- From certain cancer cells

1. acute promyelocytic leukemia,malignant cells secrete tissue factor
2. Adenocarcinoma,

2 Widespread endothelial damage

SLE inflamation

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

3 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 (DIC)

- Thrombocytopenia are consumed)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

2 special situations. "rare" نادر نوعم

- Waterhouse-Friderichsensyndrome:meningococcous sepsis→DIC→adrenal hemorrhage →acute adrenal failure (no steroids,hypotension)
- Sheehan syndrome:complicatedlabor→DIC→severehemorrhage→pituitary ischemia and necrosis

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Now 2 similar diseases :-

Thrombotic thrombocytoenic parpura (TTP) & hemolytic uremic syndrome (HUS)

Widespread formation of platelets-rich thrombi in microcirculation

- NO activation of clotting factors (normal PT and PTT) ⟶ (DIC) مومتل ال
- Leads to thrombocytopenia and tendency for bleeding
- Clinically: fever, thrombocytopenia, microangiopathic hemolytic anemia, renal failure and neurologic symptoms (the latter is not present in HUS)

Just in (TTP)

5 symptoms – 1 in (HUS)

* TTP

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

* 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

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Von willbrand factor

- 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 factorVIII so any problem in vWF will affect VIII amount. 8
- Precursor of vWF is a large multimer molecule
- Examined by ristocetin aggregation test (ristocetin enhances vWF binding to platelets), if no aggregation → vWF deficiency

extra.

In the ristocetin aggregation test, ristocetin is added to a blood sample. Ristocetin facilitates the binding of vWF to platelets. If there is no aggregation in response to ristocetin, it suggests a potential vWF deficiency

Von willbrand disease

- Autosomal dominant
- Most common inherited bleeding disorder (1% of population in US)
- Affects platelets function (dominant symptom) and coagulation (factorVIII)
- Patients present with ecchymosis , easy bleeding and menorrhagia
- In homozygous disease, factorVIII 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

A → VIII
B → IX

- X-linked disease
- Most common cause of inherited serious bleeding
- Deficiency in factor VIII (prolonged PTT) [but PT is normal]
- 70% have a family history,30% appears as a new mutation
- Severe disease occurs when the level of factorVIII drops to 1% of normal level (spontaneous bleeding)
- Mild deficiency:bleeding occurs after trauma or surgery
- In 10% of patients:normal level but abnormal function
- Bleeding occurs in body cavities (joints,abdomen,chest),no petechiae
- Hemophilia B: identical to hemophilia A,less common,factor IX deficiency

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Thrombocytopenia

- 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 when we have a highly marked thrombocytopenia
- Thrombocytopenia may occur in the setting of increased platelets destruction (bone marrow shows increased megakaryocytic activity) or decreased production from bone marrow
- HIV infection causes thrombocytopenia (both increased destruction and decreased megakaryocytic survival)

Pin Point.

Immune thrombocytopenic purpura (ITP)

- Acute ITP is seen in children after viral infection (self-limited)
- Chronic ITP is commonly seen in middle-age women
- An autoimmune disease and it neeeds a 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 normal or even proliferating megakaryocytes

extra.
These antibodies target these specific platelet glycoproteins, leading to platelet destruction and reduced platelet counts in the blood.

Heparin induced thrombocytopenia

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

Past Papers :-

3-10 years old child with petechial hemorrhage, what is the disease?
a. Von-willebrand disease
b. Accidental Aspirin
c. Disseminated intravascular coagulation d. Hemophilia
answer: a

-A patient was found to have mild anemia and abundant schistocytes. All of the following tests are important to explain the cause of schistocytes EXCEPT:
a. History of violent exercise b. History of food poisoning
c. Abnormal PT and PTT tests d. High level of ADAMTS13
e. Presence of thrombocytopenia

A 4-year-old boy presents with recurrent joint pain involving the knees and hips. He had always bruised easily, and recently the parents had seen blood in his urine. A presumptive diagnosis of classic hemophilia (hemophilia A) is made, and coagulation blood tests are performed. Which of the following is the most likely set of findings of coagulation screening tests?
(A) Normal bleeding time, platelet count, and thrombin time; prolonged PT and APTT.
(B) Normal bleeding time, platelet count, thrombin time, and APTT; prolonged PT.
(C) Normal bleeding time, platelet count, thrombin time, and PT; prolonged PTT.
(D) Normal platelet count and thrombin time; prolonged bleeding time, PT, and APTT.
(E) Prolonged bleeding time, PT, APTT, and thrombin time; decreased platelet count.

A 35-year-old woman presents with fever, fatigue, mucocutaneous bleeding, and changing neurologic signs. Laboratory examination reveals thrombocytopenia, anemia, and reticulocytosis, as well as increased concentrations of creatinine and urea nitrogen. Examination of a peripheral blood smear reveals many fragmented circulating red cells (helmet cells and schistocytes). The most likely diagnosis is:
(A) Bernard-Soulier disease.
(B) DIC
(C) ITP.
(D) TTP.
(E) von Willebrand disease

Done by: Dana megdady