PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM – LECTURE 5

Dr. Tariq Al-Adaily, MD د. طارق العديلي

Associate Professor

Department of Pathology

The University of Jordan

Email: TNALADILY@ju.edu.jo

School of Medicine

BLEEDING DISORDERS

- Pathologic bleeding occurs spontaneously or after trauma (prolonged bleeding)

Caused by defect in either:

- Clotting factors
- Platelets
- Blood vessels
- Endothelium

BLOOD VESSELS-RELATED BLEEDING

Occurs in:

- Connective tissue diseases
- Chronic steroid intake
- Systemic amyloidosis
- Vasculitic infections
- Vitamin C deficiency (scurvy)
- Patients develop spontaneous petechiae and ecchymoses in skin and mucous membranes

PLATELETS-RELATED BLEEDING

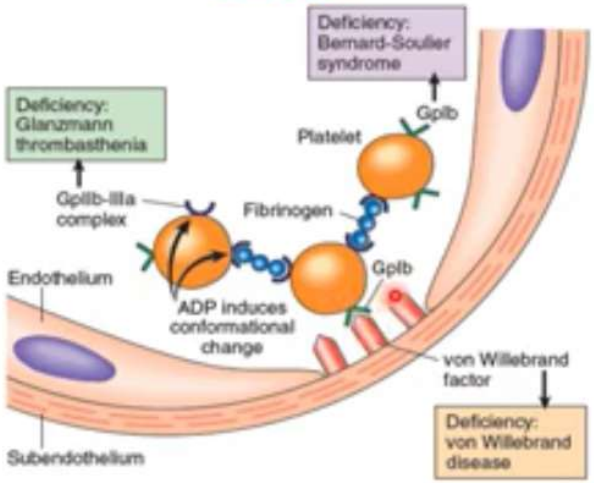
- Thrombocytopenia (ITP, AIDS)
- Occasionally thrombocytosis (dysfunctioning)

Platelets function tests:

- Bleeding time (obsolete)
- Platelets aggregation test
- Von Willibrand factor tests

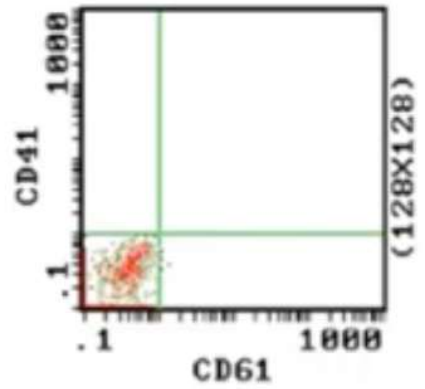
GLANZMANN THROMBASTHENIA

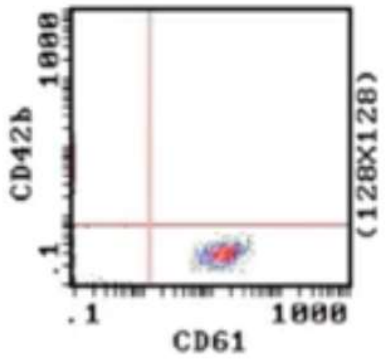
- Rare autosomal recessive
- Acquired (autoimmune disease)
- Deficiency /blockage of platelets glycoprotein IIb-IIIa (CD41/CD61 complex)
- Fibrinogen cannot bind platelets → prolonged hemorrhage



BERNARD SOULIER SYNDROME

- Very rare, autosomal recessive
- Deficiency is platelets membrane glycoprotein Ib (CD42b), which binds VWF
- Platelets are large, can show thrombocytopenia
- Diagnosis of Glanzmann and BS diseases: Flow cytometry





IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

- Patients have isolated thrombocytopenia (sometimes anemia of blood loss)
- Most bleeding occurs in skin, mucosal surfaces (petechiae and ecchymoses), also in GIT, urinary tract and CNS
- Acute ITP: affects children, commonly follows viral infection, self-limited
- Chronic ITP: affects middle age adults (F>M)
- IgG auto-antibodies against platelets membrane glycoprotein IIb/IIIa (chronic ITP)
- Coated platelets are engulfed by macrophages in spleen
- Splenomegaly is not always present, but patients benefit from splenectomy
- Peripheral blood shows large platelets, bone marrow shows increased number of megakaryocytes, spleen shows large aggregates of B-lymphocytes and plasma cells

HEPARIN-INDUCED THROMBOCYTOPENIA

- 5% of patients receiving unfractionated heparin
- IgG antibody develops, against platelet factor-4 on platelets membrane in a heparin-dependent pattern, causing platelets aggregation and thus thrombosis
- Can also develop in low-molecular weight heparin

THROMBOTIC MICROANGIOPATHIES

- Includes thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)
- TTP: fever, microangiopathic hemolytic anemia, thrombocytopenia, neurologic deficits and renal failure
- HUS: similar symptoms, dominance of renal failure, no neurologic symptoms, common in children
- In both diseases, the small circulation in the body is filled with platelets-rich microthrombi, without activation of clotting factors (PT and PTT are normal)

THROMBOTIC MICROANGIOPATHIES

- TTP: deficiency in ADAMTS13, a plasma protein required for vWF. The precursor of vWF is a large multimer that is capable to bind many platelets causing aggregation
- HUS: enterohemorrhagic E.Coli in the gut produces shiga-toxin that reaches kidneys and causes endothelial damage and thrombosis
- Blood film: schistocytes, thrombocytopenia

COAGULATION DISORDERS

- Diseases related to clotting factors
- Inherited, or more commonly acquired
- Vitamin K deficiency: decreased synthesis of factors II (prothrombin), VII, IX, X
- Liver disease
- DIC
- Warfarin
- Auto antibodies (single or multiple factors)

CLOTTING FACTORS-RELATED BLEEDING

- Prothrombin time (PT): assess extrinsic (factors V, VII) and common pathways (factors X, prothrombin or fibrinogen)
- Partial thromboplastin time (PTT): assess intrinsic (factors XII, XI, IX, VIII, V) and common pathways
- In addition to deficiency, an autoantibody (inhibitor) can interfere with the function of clotting factors
- Mixing study: adding a normal serum to patient's serum then repeating PT and PTT tests. If they are corrected, then the patient has true deficiency. If not corrected, then the patient has an inhibitor antibody

VON WILLIBRAND DISEASE

- Autosomal dominant
- Most common inherited bleeding disorder (1% of population)
- Spontaneous bleeding from mucous membranes, wounds and menorrhagia
- VWF is synthesized in endothelium (Weibel-Palade bodies), also present beneath endothelium, inside platelets
- It also circulates the plasma, carry factor VIII
- After endothelial damage, subendothelial VWF binds platelets through glycoprotein Ib, forming platelets plug
- Ristocetin agglutination test: it activates vWF to bind GPIb causing platelets clump.

VON WILLIBRAND DISEASE

- vWD causes a compound defect: non-functional platelets and deficiency in factor VIII
- Symptoms are mainly related to platelets defects, except in homozygous state (resembles hemophilia A, prolonged PTT)
- Type I vWD: most common, decreased levels of serum vWF
- Type IIA: absent high-molecular weight multimers of vWF
- Type IIB: the high molecular weight multimers have very short half life and are hyper functioning, consuming platelets, patients have mild chronic thrombocytopenia

HEMOPHILIA A

- X-linked inheritance, AKA classic hemophilia
- Reduced factor VIII
- Can affect females (random inactivation of X)
- 30% of cases appear as a new mutation
- Mild deficiency results in excessive bleeding after trauma
- Severe, life-threatening bleeding occurs if level drops <1% of normal level
- 10% have normal level but non-functioning factor
- Bleeding tends to occur in deep tissues with mechanical stress (joints, body cavities). Patients develop deformity in joints
- Skin petechiae is absent
- Prolonged PTT, corrected by mixing study
- Specific assay test is available

HEMOPHILIA B

- AKA Christmas disease
- Deficiency in factor IX
- X-linked
- Much less common than hemophilia A
- Clinically similar to hemophilia A
- Prolonged PTT, corrected by mixing study
- Factor assay test is available

ENDOTHELIAL-RELATED BLEEDING

- Widespread endothelial damage causing release of tissue factor, a prothrombotic agent, causing disseminated intravascular coagulation (DIC)
- Rapid consumption of clotting factors (prolonged PT, PTT) and platelets, exceeding replacement process
- Patients then develop life-threatening bleeding
- Peripheral blood shows schistocytes, anemia and thrombocytopenia
- Causes of DIC:
- Endothelial damage: septicemia and viremia, snake venom, complicated labor, advanced cancer, severe trauma, snake venom, severe inflammation (acute pancreatitis)