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Pathology HLS

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PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM – LECTURE 5

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Original Slides (black)
Modified (all colors but black)

Bleeding Disorders

- Pathologic bleeding occurs spontaneously or after trauma (prolonged bleeding).
- In normal physiology, in order to stop the bleeding; there should be an integration of the function of four main factors which are mentioned below

Caused by defect in either :

- Clotting factors
- Platelets
- Blood Vessels
- Endothelium

Blood Vessels-Related Bleeding

- Blood vessels bleeding can be associated with several diseases but there is no specific disease that affects blood vessels only.

Occurs in :

- Connective tissue diseases (a group of diseases that can be inherited or sometimes acquired, they can be associated with auto-immune diseases too like Rheumatologic diseases).
- Chronic steroid intake (it will weaken blood vessels and increase their chance of rupture).
- Systemic amyloidosis (amyloid protein will infiltrate any organ, it can cause physical damage to these organs including blood vessels)
- Vasculitic infections (there are some bacterial and fungal infections that can affect blood vessels such as spirochetes and some fungus. Those can result in vasculitis and sometimes aneurysm which in turn results in rupture and bleeding).
- Vitamin C deficiency (scurvy) (this is an almost outdated disease -it was common in the past but these days it is much less common-. Vitamin C is important for the structure of collagen in blood vessels and thus when it is deficient, it will weaken blood vessel and bleeding will occur).
- Patients develop spontaneous petechiae and ecchymoses in skin and mucous membranes (bleeding occurs in superficial parts of the body such as the skin. If the bleeding happened in a small area we call it petechiae, if the bleeding caused a large bruise then it's ecchymoses. Mucous membranes like in the oral cavity).

Platelets-Related Bleeding

- It can result from a numerical problem.
- Thrombocytopenia (ITP, AIDS) (it's basically a decrease in the number of platelets, the most common thrombocytopenia case is known as immune thrombocytopenia purpura. Also, AIDS patients suffer a damage to their megakaryocytes & blood in their bone marrow. This damage might lead to thrombocytopenia or in some cases thrombocytosis [paradoxically, their platelets are large in number, but they aren't functioning nor can function properly. This is common in myeloproliferative neoplasms]).
- Occasionally thrombocytosis (dysfunctioning) , with a chance of bleeding.

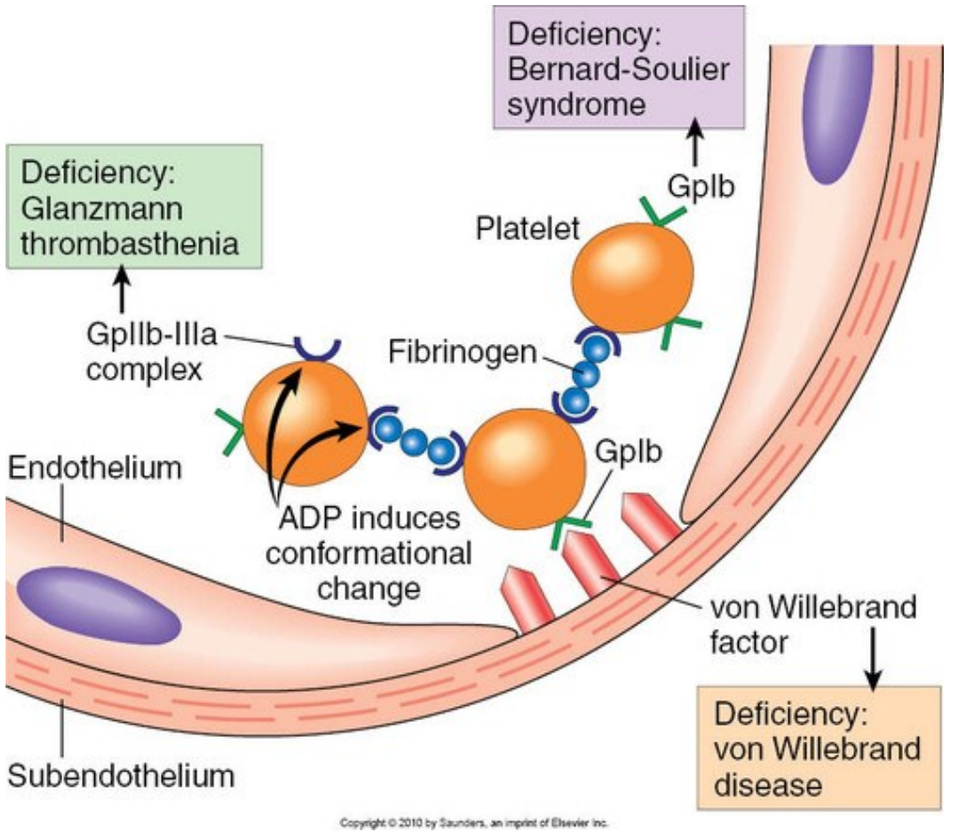
Platelets function tests: (other than counting their number)

- Bleeding time (obsolete) we can test the function of thrombocytes using bleeding time test. We make a small cut in the superficial part of the body (the ear for example), and we wait until the bleeding stops. This test is obsolete and rarely used these days.
- Platelets aggregation test (we add a material known as Ristocetin, it's an antibiotic and it can cause an artificial aggregation in the presence of VWF. Adding Ristocetin means that platelets do not aggregate, only then can we know that one of the tests got an abnormal result (it's either that platelets aren't functioning well or VWF is missing, that's why we do these tests simultaneously – if VWF was there then the problem is with the platelets-).
- Von Willibrand factor tests (this factor is essential for the function of platelets, that's why we usually do these 2 at the same time (these 2 = Platelets aggregation & Von Willibrand factor))

Glanzmann Thrombasthenia

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

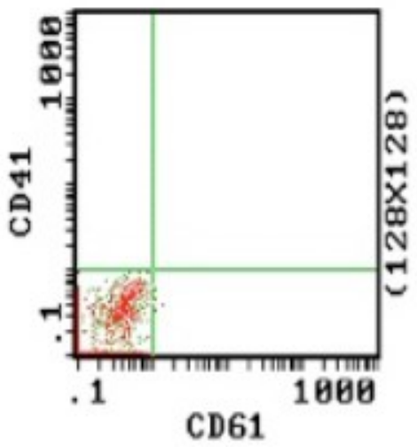
VWF is located beneath the endothelium so whenever the endothelium is damage and removed, VWF will be exposed and it'll bind the platelets using glycoprotein Ib so the platelets plug would anchor at that site.
If it was deficient then the platelets can't bind the defective place (to form the plug) and the patient will suffer a haemorrhage.



Bernard Soulier Syndrome

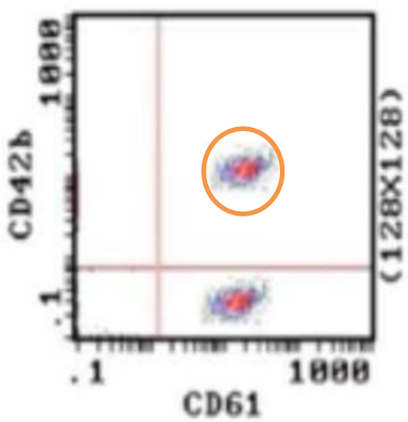
- Very rare, autosomal recessive
- Deficiency is platelets membrane glycoprotein Ib (CD42b) which binds VWF.
- Platelets are large, can show thrombocytopenia (this is a structural abnormality)
- Diagnosis of Glanzmann and BS diseases: Flow Cytometry (this test examines the antigen found on the surface of the fluid cells (I guess the doctor meant cells found in the plasma ?)

CD41 & CD61



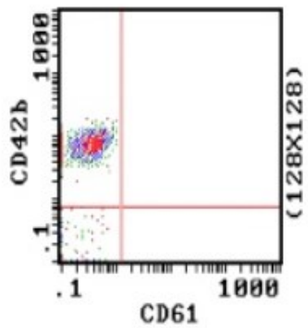
In this figure, the platelets aren't moving anywhere (just like you while studying this lecture), platelets aren't going to either of the marker's direction, so they are deficient of both markers
(Glanzmann disease)

CD42b & CD61



In this figure, the platelets are moving to the CD61 marker area, which means they are normal, while CD42 is deficient. If the platelets were normal then it should be located as shown
(Bernard Soulier Syndrome)

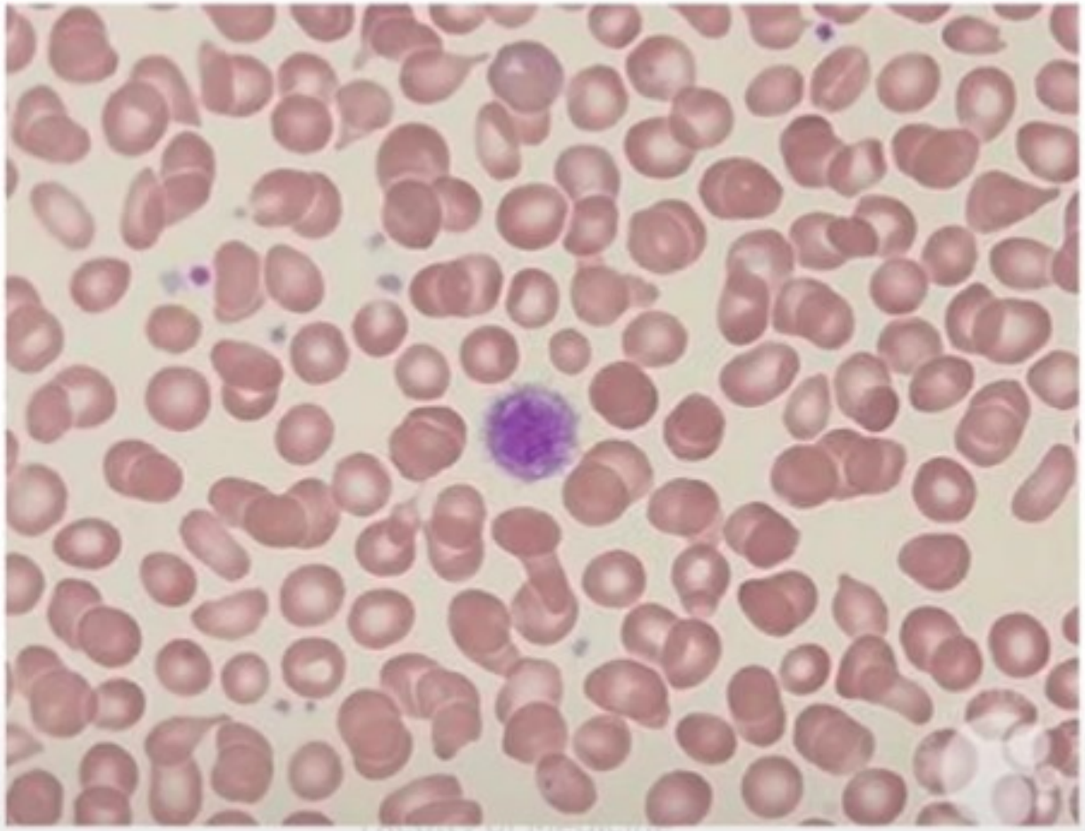
Extra : what do you think is going on here ?



Immune Thrombocytopenic Purpura (ITP)

- Purpura means bleeding in the skin
- Patients have isolated thrombocytopenia (sometimes anaemia 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 biopsy shows increased number of megakaryocytes (they are intact and found in high numbers to compensate for the thrombocytopenia), spleen shows large aggregates of B-lymphocytes and plasma cells (we can see these if we do a splenectomy, and examine a section under the microscope. B-lymphocytes and plasma cells are responsible for secreting this auto-antibody)

This slides wasn't in the pdf version, but it was in the recorded lecture, so you might as well check it



- ITP: thrombocytopenia, mean platelets volume (MPV): high

Heparin Induced Thrombocytopenia

- It's acquired (induced)
- 5% of patients receiving unfractionated heparin (heparin is used as an anticoagulant –stops coagulation & prevents it- . There are 2 forms of platelets :
  1. Large form known as the unfractionated form
  2. Improved form which takes only the active site of the heparin and its known as fractionated heparin or low-molecular weight heparin
- For an unknown reasons, Heparin induces the synthesis of IgG antibody that will be targeted against platelet factor-4 on platelets membrane in a heparin-dependent pattern, causing platelets aggregation (after IgG binds to antigens on the surface of platelets) and thus thrombosis (they cross react the platelets to form a spontaneous thrombus)
- So, the patient has a paradoxical case of thrombocytopenia with thrombosis. Same thing occurs in PNH –paroxysmal nocturnal hematuria- with the exception that in PNH, the platelets are lysed and torn which causes the release of their content, thus promoting the occurrence of a thrombus. But in Heparin induced thrombocytopenia, the antibody will cross react platelets together to form a thrombus .
- Can also develop in low-molecular weight heparin. (rare and much less common)

Thrombotic Microangiopathies

- There are 2 main diseases that result in this syndrome and that includes thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS).
- Note that there's a difference between thrombotic thrombocytopenic purpura & idiopathic thrombocytopenic purpura. In TTP we notice a thrombosis everywhere in the body which results in thrombocytopenia because platelets are consumed in forming these thrombi.
- HUS patients have a different pathogenesis, but they end up with similar findings
- TTP : fever , microangiopathic hemolytic anemia, thrombocytopenia, neurologic deficits and renal failure. (patients have a pentad – 5 symptoms / 5 findings - . But, not all of these are prominent, most patients have 3-4 symptoms with the 5th symptom being absent or present but in a minor condition)
- HUS : similar symptoms, dominance of renal failure, no neurologic symptoms, common in children (while TTP can affect any age)
- In both diseases, the small circulation in the body is filled with platelets-rich microthrombi, without activation of clotting factors they are intact and not active (PT and PTT are normal).
- The thrombi in both diseases are small and they obstruct small circulation, causing thrombocytopenia

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 .
- ADAMTS13 converts the precursor of vWF into vWF, so if ADAMTS13 is missing, vWF will stay in its precursor form. vWF normally has a short half life but the precursor form persists in the blood and its capable of binding many platelets together forming a spontaneous thrombus.
- HUS : enterohemorrhagic E.Coli in the gut produces shiga-toxin that reaches kidneys (it's more concentrated there) and causes endothelial damage and thrombosis.
- E.Coli appears in contaminated food
- Blood film (In both diseases) : schistocytes (direct physical damage to the RBCS which results from the small thrombi) , thrombocytopenia.

Coagulations Disorders

- Diseases related to clotting factors.
- Inherited, or more commonly acquired.
- Vitamin K deficiency : decreased synthesis of factors II (prothrombin), VII, IX ,X (it's acquired, can be due to dietary reasons but usually it's related to drugs, like warfarin. Vitamin K is present in large amounts in green leaves. Remember the year 1972 (1 = 10, 9 , 7 ,2)
- Liver disease liver is responsible for synthesizing these factors
- DIC in this disease, there's a consumption of all clotting factors
- Warfarin which blocks the synthesis of clotting factors that need Vitamin K
- Auto antibodies (single or multiple factors) these autoantibodies bind one or more of these factors so the patients won't have a TRUE deficiency, it's just that these factors can't function.

Clotting Factors-Related Bleeding

- Prothrombin time (PT) : assesses extrinsic pathway factors (V, VII) and common pathways (factors X, prothrombin II or fibrinogen)
- Partial thromboplastin time (PTT) : assesses intrinsic pathway factors (XIII, XI, IX, VIII, V) and common pathways . So the main difference is in factor VII
- In addition to deficiency, an autoantibody (inhibitor) can interfere with the function of clotting factors.
- If we conducted these tests and the patients' results were as the following :
  1. Prolonged PT & normal PTT → deficiency in either factors V or VII
- Mixing study (it helps us differentiate between a true deficiency of factors and the presence of autoantibodies – inhibitors-) : adding a normal serum to patient's serum then repeating PT and PTT tests . If they are corrected, then the patient has true deficiency (a corrected result means we added the deficient factor, that's why it's a true deficiency) . If not corrected, then the patient has an inhibitor antibody (because the inhibitor will block the new added factors)

Von Willibrand Disease

- It's a disease of clotting factors
- Autosomal Dominant , it has many subtypes
- most common inherited bleeding disorder (1% of population)
- Spontaneous bleeding from mucous membranes (superficial parts), wounds and menorrhagia (excessive menstrual bleeding)
- VWF is normally widespread and vast in amounts.
- VWF is synthesized in endothelium (Weibel-Palade bodies), also present beneath endothelium (as an anchoring protein) , inside platelets.
- It also circulates the plasma, carry factor VIII
- After endothelial damage (in which endothelial cells are damaged and torn away) , subendothelial VWF becomes exposed and binds platelets through glycoprotein Ib (CD42b) forming platelets plug.
- Ristocetin agglutination test : it activates vWF to bind GPIb causing platelets clump (the previous test can be done in vitro by adding the Restocetin)

Von Willibrand Disease

- vWD (when vWF is deficient) causes a compound defect : non-functional platelets (they can't aggregate in the absence of vWF and the patient will suffer superficial bleeding) and deficiency in factor VIII (this occurs in severe cases. As we mentioned earlier, vWF carries factor VIII)
- symptoms are mainly related to platelets defects, except in homozygous state which is considered a severe form due to a markedly decreases in vWF (resembles hemophilia A (the patient will have a clinical syndrome similar to hemophilia where bleeding occurs in body cavities not in superficial areas like the skin) , prolonged PTT (decreases in factor VIII))
- Type I vWD : most common, Decrease levels of serum vWF → non-functioning platelets
- Type IIA : absent high-molecular weight multimers of vWF → the precursor isn't there, and patients with this subtype don't have multimers.
- Type IIB : the high molecular weight multimers have very short life and are hyper functioning, consuming platelets, patients have mild chronic thrombocytopenia → multimers are there but they have an abnormal function causing an alternate problem of consuming platelets because multimers bind many platelets and thus causing mild persistent thrombocytopenia
- The pathogenesis of Type IIB is similar to that of TTP. But, in TTP the case is widespread and severe while in Type IIB, multimers consume some platelets causing mild thrombocytopenia without the formation of a thrombi

Hemophilia A

- 2nd most common inherited bleeding tendency
- X-linked inheritance (mainly a disease of males but it can affect females) , AKA classical hemophilia
- Reduced factor VIII
- Can affect females (random inactivation of X)
- 30% of cases appear as a new mutation. In 70% there's a family history coming from the mother's side (uncles or brothers).
- Mild deficiency (normally we have an excess amount of factor VIII, that's why symptoms appear when there's a marked deficiency – 20% of the normal amount is present for example-) results in excessive bleeding after trauma (symptoms and bleeding mainly appear after a trauma like major surgeries. Males can undergo a surgery early on in their life like undergoing a circumcision. If that male suffers from hemophilia, he'll develop excessive bleeding after surgery)
- Severe, life-threatening bleeding (and possibly death) occurs if level (of factor VIII) drops < 1% of normal level
- 10% have normal level but non-functioning factor
- bleeding tends to occur in deep tissues (soft tissues –muscles-) with mechanical stress (joints, body cavities). Patients develop deformity in joints due to repetitive bleeding
- This bleeding is more problematic than the one related to platelets.
- scan petechiae is absent
- prolonged PTT, corrected by mixing study (because there is no inhibitor)
- specific assay test is available (it's a new test that investigates factor VIII presence and functionality)

Hemophilia B

- AKA Christmas disease
- Deficiency in factor IX (intrinsic pathway)
- X-linked
- Much less common than hemophilia A
- Clinically similar to hemophilia A if the deficiency is mild then the patient will have excessive bleeding after a major trauma while if the deficiency was severe then the patient might have a life-threatening bleeding.
- Prolonged PTT, corrected by mixing study
- Factor assay test is available it's done to differentiate it from hemophilia A

Endothelial-Related Bleeding

- Widespread endothelial damage causing release of tissue factor, a prothrombotic agent, causing disseminated intravascular coagulation (DIC)
- This disease will cause a formation of a microthrombi in the entire body, these thrombi will consume clotting factors and platelets, thus the patient suffers from a thrombosis everywhere. But paradoxically, patients complain from bleeding because there are no clotting factors, they were all consumed in the formation of the thrombi (this is the difference between DIC and microangiopathic haemolytic anaemias – TTP & HUS-)
- Rapid consumption of clotting factors (prolonged PT, PTT) and platelets, exceeding replacement process.
- Patients then develop life-threatening bleeding
- Peripheral blood shows schistocytes (in TTP, PT & PTT results are normal) , anemia and thrombocytopenia
- Causes of DIC :
- Endothelial damage causes the secretion of a tissue factor (which can be secreted from elsewhere also) : septicemia and viremia, snake venom, complicated labor (there's a production of a tissue factor from the placenta), advanced cancer (the most notorious is a type of acute leukemia known as acute pro-myelocytic leukemia. These malignant blasts secrete the tissue factor in large amounts. Also, epithelial tumors might contain immune mucin which circulates in the blood activating the tissue factor to cause DIC) , severe trauma (surgeries) , snake venom, severe inflammation (acute pancreatitis (severe inflammation in the abdomen))