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Course Title: Wbcs and platelets disorders (MLT 4TH) Instructor: Saima hadi

Marks: 50

Attempt all questions .Each question carry 10 marks.

Q1. Write a note on Hodgkin lymphoma?

Lymphomas

Lymphomas are a bunch of diseases caused by malignant lymphocytes that accumulate in lymph nodes and cause the characteristic clinical features of lymphadenopathy.

Occasionally, they may spill over into blood ('leukemic phase') or infiltrate organs outside the lymphoid tissue.

The major subdivision of lymphomas is into

- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma

This is based on the histological presence of Reed-Sternberg (RS) cells in Hodgkin's lymphoma.

Pathogenesis

Hodgkin's disease may be a lymphoma during which RS cells are found within the disease tissue.

The characteristic RS cells, and the associated abnormal mononuclear cells, are neoplastic whereas the infiltrating inflammatory cells are reactive.

Immunoglobulin gene rearrangement studies suggest that the RS cell is of B-lymphoid lineage and that it is often derived from a B cell with a 'crippled' Immunoglobulin gene caused by the acquisition of mutations that prevent synthesis of full-length immunoglobulin.

The Epstein-Barr virus (EBV) genome has been detected in 50% or more of cases in Hodgkin tissue but its role in the pathogenesis is unclear.

Clinical features

The disease can present at any age but is rare in children and has a peak incidence in young adults.

There is 2: 1 male predominance.

The following symptoms are common.

1. Most patients present with painless, non-tender, asymmetrical, firm and rubbery enlargement of superficial lymph nodes.

- The cervical nodes are involved in 60-70% of patients,
- Axillary nodes in approximately 10-15%
- Inguinal nodes in 6-12%.

Retroperitoneal nodes are also often involved but usually only diagnosed by computed tomography (CT) scan. Cervical lymphadenopathy in a patient with

Hodgkin's lymphoma.

2. Clinical splenomegaly occurs during the course of the disease in 50% of patients. The splenic enlargement is seldom massive. The liver can also be enlarged due to liver involvement.

3. Mediastinal involvement is found in 6-11% of patients at presentation, particularly in young women. There may be associated pleural effusions or superior vena cava obstruction.

4. Cutaneous Hodgkin's disease occurs as a late complication in approximately 10% of patients. Other organs (e.g. bone marrow, gastrointestinal tract, bone, spinal cord or brain) may also be involved, even at presentation.

5. Constitutional symptoms are prominent in patients with widespread disease. The following Maybe seen:

(a) Fever approximately 30% of patients and is continuous or cyclic.

(b) Pruritus, which is often severe, occurs in approximately 25% of cases.

(c) Alcohol-induced pain in the areas where disease is present occurs in some patients;

(d) Other constitutional symptoms include

Weight loss, profuse sweating (especially at night), weakness, fatigue, anorexia and. Hematological and infectious complications.

Clinical staging

- The selection of appropriate treatment depends on accurate staging of the extent of disease.
- Staging is performed by thorough clinical examination together with chest X-ray and CT scan to detect intrathoracic, intraabdominal or pelvic disease.
- It is also used to monitor response to therapy.
- MRI scanning may be needed for particular sites.
- Bone marrow trephine is carried out in some centers and
- Liver biopsy may also be needed in difficult cases.

Staging of Hodgkin's lymphoma.

Stage I: indicates node involvement in one lymph node area.

Stage II: indicates disease involving two or more lymph nodal areas confined to one side of the diaphragm.

Stage III: indicates disease involving lymph nodes above and below the diaphragm.

Stage IV: indicates involvement outside the lymph node areas and refers to diffuse or disseminated disease in the bone marrow, liver and other extranodal sites.

The stage number in all cases is followed by the letter A or B indicating the absence (A) or presence (B) of one or more of the following:

Unexplained fever above 38°C, night sweats, or loss of more than 10% of body weight within 6 months.

Localized extranodal extension from a mass of nodes does not advance the stage but is indicated by the subscript E.

Q2.What is Hemostasis, also explain steps and clotting factors?

Hemostasis

Hemostasis is that the procedure of developing clots within the walls of damaged blood vessels and stopping blood loss while keeping blood within the fluid state within the vascular system. The process in which the body stop bleeding. Spontaneous arrest or prevention of bleeding form injured \ damage vessel by the physiological process.

Steps

3 steps involve in hemostasis….

I. Vasoconstriction
II. Hemostatic plug\ platelet plug formation
III. Coagulation of blood

i) Vasoconstriction

Vasoconstrictors are the drugs that constricts the blood vessels and thereby control tissue perfusion. They are added to LA to oppose the vasodilatory action of local anesthetic agent.

ii) Hemostatic plug\ platelet plug formation

Disturbance of the endothelium exposures subendothelial von willebrand factor (vWF) and collagen, which help platelet adherence and activation. After activation of platelets it leads to an affected shape change (from small rounded discs to flat plates with spiky protrusions that markedly increased surface area), also because the release of secretory granules. Within minutes the secreted products recruit additional platelets, which undergo aggregation to make a primary hemostatic plug.

iii) iii) Coagulation of blood

In the era of 19th century, a German pathologist Rudolf Virchow in 1860 (Nichols & Bowie, 2001) defined thrombi (blood clots) and their tendency to embolize. Platelets were discovered, and their function was recognized, alongside discovery of the different components of the coagulation process. The recent understanding of the biochemical procedures of coagulation began within the 1940s, when Paul Owren (1947) recognized that a bleeding diathesis during a girl couldn't be explained by the 4-factor concept, positing that she lacked a fifth clotting factor in her plasma. Throughout the 1940s and 1950s, several more coagulation factors were discovered. Coagulation factors were designated by roman numerals. The numeric system that

was adopted assigned the amount to the factor consistent with the sequence of discovery and to not the purpose of interaction within the cascade.

Clotting factors

There are three essential steps in clotting factors: In response to separation of the vessel or damage to the blood itself, a posh cascade of chemical reactions occurs within the blood involving quite a dozen blood clotting factors. The net result's formation of a posh of activated substances collectively called prothrombin activator. The prothrombin activator catalyzes change of prothrombin into thrombin.

CONVERSION OF PROTHROMBIN TO THROMBIN

Clot Retraction and Expression of Serum. Within a couple of minutes after a clot is made, it begins to contract and typically expresses most of the fluid from the clot within 20 to 60 minutes. Platelets are necessary for clot retraction to occur. Therefore, failure of clot retraction is a sign that the amount of platelets within the circulating blood could be low.

Hemophilia A

The hemostatic abnormality in hemophilia A is caused by a deficiency or a defect of factor VIII. Factor VIII was thought to be produced by endothelial cells and not by the liver, as most coagulation factors are. The defective gene is located on the X chromosome (F8 gene). Hemophilia A can manifest in women. Normal homeostasis requires a minimum of 30% antihemophilic factor activity. Severe sorts of the disease occur when the extent is a smaller amount than 1% of normal.

Clinical Findings

Patients with severe hemophilia (less than 1% of factor VIII) may experience severe, spontaneous bleeding. The common soft tissues are Hemarthrosis, ecchymoses.

Laboratory Tests

The Screening tests that demonstrate lengthy aPTT, normal PT, and normal platelet count (except in some cases of von Willebrand disease) show a problem in the basic way.

Hemophilia B.

The chrismas disease of hemophilia B, factor IX is short or defective. Hemophilia B is inherited as an X-linked recessive trait (F9 gene). Similar to hemophilia A, the disorder manifests

primarily in males. Clinical manifestations of the two disorders are identical. The result of screening laboratory test is similar for both tests. Specific factor assays for Christmas factor establish the diagnosis. Purified Christmas factor products are recommended for the treatment of minor and major bleeding

Clinical Findings

In the more severe sorts of the disease, during which antihemophilic factor levels are low, hemarthroses and dissecting intramuscular hematomas are a part of the clinical picture. Serious bleeding can occur in these patients after trauma or surgical procedures.

Laboratory Tests

Screening laboratory tests may show prolonged aPTT, normal or slightly reduced platelet count, normal PT, and normal TT. Additional laboratory tests are needed to determine the diagnosis and sort of Willebrand disease. These contains ristocetin cofactor activity, ristocetin-induced platelet aggregation, immunoassay of vWF, multimeric analysis of vWF, and specific assays for antihemophilic factor.

Factor XI Deficiency Factor XI deficiency, an autosomal recessive inherited condition sometimes referred to as hemophilia C, is more prevalent in the Ashkenazi Jewish population but found in all races. Treatment of bleeding in individuals with the combined deficiency requires antihemophilic factor concentrate and FFP. Some patients with proaccelerin deficiency also are lacking the proaccelerin normally present in platelets and should need platelet transfusions also as FFP.

Factor VII Deficiency Inherited factor VII deficiency is a rare autosomal recessive disorder. Bleeding is uncommon unless the level is less than 3%. Bleeding is usually delayed because clots form normally but are vulnerable to fibrinolysis. Umbilical stump bleeding is characteristic, and there's a high risk of intracranial bleeding. Replacement can be accomplished with FFP,

Q3.Explain Hemophilia its types, symptoms, and lab diagnosis?

Hemophilia

Hemophilia A and B are similar in both clinical and pathological features, the difference being in the deficient factor. Both are sex-linked recessive disorders resulting in inherited deficiency of the clotting factor or synthesis of a defective clotting factor. Males are affected and females are carriers.

Hemophilia A (factor VIII deficiency)

Hemophilia A is the most common hereditary X- linked recessive disease with a reduction in the amount or activity of factor VIII. About 30% of hemophiliacs have no family history and may be due to acquired mutations.

Factor VIII serves as a cofactor for factor IX in the activation of factor X in the coagulation cascade (Fig. 33.2). Reduced amount or activity of factor VIII is associated with lifethreatening bleeding. Bleeding is due to both inadequate coagulation and inappropriate clot removal (fibrinolysis).

Mode of Inheritance

Hemophilia is transmitted as sex-linked recessive disease and the genes for factor VIII are located on the long arm of the X-chromosome. Hemophilia does not clinically manifest when there is a normal copy of X-chromosome. Males with a defective/mutant factor VIII gene (hemophiliac gene) on their single X chromosome (XH) suffer from hemophilia. Heterozygous females are carriers and do not express the full clinical disease because of the paired normal X-chromosome. However females with two copies of the defective XH chromosome may rarely suffer from hemophilia.

Risks of transmission to children:

When female is a carrier and male is normal (carrier female and normal male) The 25% of children may be normal male, 25% normal female, 25% female carrier and 25% may be hemophiliac male With normal female and the hemophiliac male (normal female and hemophiliac male): Hemophiliac male does not transmit the disorder to his sons, since he donates only a normal Y chromosome to his son and not the defective XH chromosome. A hemophiliac male always passes on his abnormal XH chromosome to all his daughters and thus all daughters will be asymptomatic carriers. When female is a carrier (asymptomatic,

heterozygous) and male is hemophiliac (carrier female and hemophiliac male): There are chances of 25% of children may be female carrier, 25% hemophiliac females, 25% normal male and 25% hemophiliac male. When female is hemophiliac and male is normal (hemophiliac female and normal male): The 50% children will be female carriers and 50% may be male with hemophilia. Note: Female hemophiliac usually do not survive beyond puberty.

Clinical Features

Clinical severity depends on the level of Factor VIII activity with normal range expressed as 50-200% (Table 36.3). Moderate to severe deficiency of factor VIII presents with easy bruising and massive bleeding following trauma or operative procedures.

- Frequent and spontaneous hemorrhages occur into the joints and are known as hemarthrosis.
- Recurrent bleeding into the joints will lead to crippling deformities.
- Patient may also present with spontaneous or post-traumatic bleeding into soft tissues.

Petechiae observed in platelet and vascular disorders are not seen in hemophilia.

Laboratory Findings

- Bleeding time: Normal.
- Clotting time: Prolonged.
- Platelet count: Normal.
- Prothrombin time: Normal.
- Activated partial thromboplastin time (APTT): Increased (normal 30-40 seconds) Prolongation of APTT is dependent upon the severity of deficiency of factor VIII.
- Factor VIII assay: This is essential for the diagnosis, to assess the factor VIII levels and severity of disease. Factor VIII function is assessed by conducting coagulation assays with mixtures of patient plasma and factor VIII-deficient plasma.

Carrier detection: DNA markers are used as screening tests to detect female carriers and prenatal diagnosis of affected fetuses.

Complications of Hemophilia

- Deforming arthritis and contractures: The most frequent complication is deforming arthritis due to repeated bleeding into the joints. Organization and fibrosis of intramuscular hematomas results in contractures of involved muscles.
- Anemia: Excessive, spontaneous or repeated bleeding may result in anemia.
- Causes of Death
- Intracranial hemorrhage: Severe deficiency of factor VIII may result in spontaneous, fatal intracranial hemorrhage.
- Prolonged bleeding: Rarely, prolonged bleeding following surgical procedures may be fatal.

Hemophilia B (Christmas disease, Factor IX Deficiency)

Both factor VIII and IX together activate factor X in coagulation cascade. Thus, severe factor IX .deficiency is clinically indistinguishable from hemophilia A. It is also inherited as an X-linked recessive trait and presents with variable clinical severity. Assay of factor IX should be done to diagnose Christmas disease (named after the first patient). Recombinant factor IX is used for treatment.

Clinical Features

Clinical features are usually milder than those of hemophilia A. In both the diseases, hemarthrosis is the common presentation. Treatment is by infusion of purified or recombinant Factor IX.

Laboratory Findings

Similar to hemophilia A

- Bleeding time: Normal
- Clotting time: Prolonged
- Platelet count: Normal.
- Prothrombin time: Normal.
- •Activated Partial Thromboplastin Time (APTT): Increased (normal 30-40 seconds).
- Factor IX assay: Factor IX is decreased.

Q4 .Describe Von Wille Brand disease?

Von Willebrand

Von Willebrand disease (VWD) may be a genetic disease caused by missing or defective Willebrand factor (VWF), a clotting protein. VWF binds antihemophilic factor, a key clotting protein, and platelets in vessel walls, which help form a platelet plug during the clotting process. VWD is the most common bleeding disorder. It is carried on chromosome 12 and occurs equally in men and women.

Symptoms

People suffering from Von Willebrand disease have frequent nosebleeds, easy bruising and excessive bleeding during and after invasive procedures, like tooth extractions and surgery. Women often experience menorrhagia, heavy menstrual periods that last longer than average, and hemorrhaging after childbirth.

TYPES

There are three main types of VWD based on qualitative or quantitative defects in VWF. A fourth type, acquired VWD, is not hereditary.

Type 1 VWD is found in 60%-80% of patients. People with type 1 VWD have a quantitative deficiency of VWF. Levels of VWF within the blood range from 20%-50% of normal. The symptoms are usually mild.

Type 2 VWD is found in 15%-30% of patients. People having type 2 VWD have a qualitative deficiency in their VWF. Type 2 is broken down into four subtypes: type 2A, type 2B, type 2M and type 2N, depending on the presence and behavior of multimers, molecular chains of VWF. Symptoms are mild to moderate.

Type 3 VWD is found in 5%-10% of patients. People with type 3 VWD have a quantitative deficiency of VWF. There symptoms are severe, and include spontaneous bleeding episodes, often into their joints and muscles.

Acquired VWD. This type of VWD in adults results after a diagnosis of an autoimmune disorder, like lupus, or from heart condition or some sorts of cancer. It can also occur after taking certain medications.

DIAGNOSIS

When VWD is suspected, plasma of a patient must be investigated for quantitative and qualitative deficiencies of VWF. This is achieved by measuring the quantity of VWF during a VWF antigen assay and therefore the functionality of VWF with a glycoprotein (GP)Ib binding assay, a collagen obligatory assay, or a ristocetin cofactor motion (RiCof) or ristocetin induced platelet agglutination (RIPA) assays. Factor VIII levels also are performed because antihemophilic factor is sure to VWF which protects the antihemophilic factor from rapid breakdown within the blood. Deficiency of VWF can then cause a discount in antihemophilic factor levels, which explains the elevation in PTT time. A platelet aggregation assay will show an abnormal response to ristocetin with normal responses to the opposite agonists used. A platelet function assay may give an abnormal collagen/adrenaline closure time, and in most cases, a traditional collagen/ADP time. Type 2N may be considered if factor VIII levels are disproportionately low, but confirmation requires a "factor VIII binding" assay.

Treatment

The Treatment of Von Willebrand disease depends on the analysis and severity.. There are a couple of coagulation factor concentrates that are rich in VWF, and are recommended for patients with VWD. These therapies are given by intravenous infusion. In December 2015, the US Food and Drug Administration (FDA) approved Baxalta's Vonvendi®, the first recombinant VWF product. Unlike other products, it contains VWF only, not VWF and factor VIII.

Causes

The usual cause of von Willebrand disease is an inherited abnormal gene that controls von Willebrand factor — a protein that plays a key role in blood clotting. When you have low levels of this protein or it doesn't work because it should, small blood cells called platelets cannot stay together properly nor attach themselves normally to the blood vessel walls when an injury has occurred. This interferes with the clotting process and can sometimes cause uncontrolled bleeding. Many people with Willebrand disease even have low levels of antihemophilic factor, another protein that helps in clotting. Factor VIII is involved in another inherited clotting disorder called hemophilia. But unlike hemophilia, which mainly affects males, von Willebrand disease affects males and females and is usually milder. Rarely, Willebrand disease can develop later in life in people that didn't inherit an abnormal gene from a parent. This is

known as acquired von Willebrand syndrome, and it's likely caused by an underlying medical condition.

Q5.Explain Hemolytic uremic syndrome and its types?

Hemolytic uremic syndrome

Hemolytic uremic syndrome (HUS) may be a condition that results from the abnormal premature destruction of red blood cells. Once this process begins, the damaged red blood cells start to clog the filtering system within the kidneys, which can eventually cause the life-threatening renal failure related to hemolytic uremic syndrome. Most cases of hemolytic uremic syndrome develop in children after two to 14 days of diarrhea — often bloody — thanks to infection with a particular strain of Escherichia coli (E. coli).

Signs and symptoms

- Bloody diarrhea & Vomiting
- Abdominal pain
- Pale skin
- Fatigue and irritability
- •The Fever, may usually not high or may not be present at all
- Blood in the urine
- Decreased urination or blood in the urine
- One of the symptom is swelling of the entire body, hands, or feet

Typical and Atypical-HUS

Typical

- Infection by Shiga toxin-producing bacteria E coli serotype O157:H7 is the cause .Mostly with diarrhea often bloody diarrhea (D+HUS).

Atypical

- Atypical HUS (non–Stx-HUS) is rare.
- As the name implies, infection by Stx-producing bacteria is not the cause, and disease may occur year-round without diarrhea (D-HUS).The familial form is associated with genetic abnormalities.

Pathophysiology Stx-associated HUS

- After ingestion, Stx– E coli closely adheres to the epithelial cells of the gut mucosa by means of a 97-kd outer-membrane protein (intimin).
- Shiga Toxin is transfer by polymorphonuclear neutrophils (PMNs) in the blood, because Stx rapidly and completely binds to PMNs when incubated with human blood.
- the receptor expressed on glomerular endothelial cells has 100-fold higher affinity than of PMN receptor
- Infiltrates of inflammatory cells and production of cytokines such as IL-8 and tumor necrosis factor contribute to the cytotoxic damage in glomerular and renal tubular cells.
- Endothelial damage leads to the release of prothrombotic-, vasoactive-, and platelet-aggregating substances that cause platelet activation with the subsequent formation of thrombi.
- Erythrocyte damage primarily occurs in the renal microvasculature.
- This toxin attach to endothelial cells of the microvasculature of the glomerulus and exerts a direct toxic effect.

Lab Daignoses

- CBC
- TLC Increase 50000 – 60000/uL
- Hb Decrease
- Platlets Decrease
- P Smear
- Fragmented Rbcs e.g
- Schistocytes,
- Helmet cells,
- WBC differential may reveal a left shift (i.e., immature WBCs, including bands, myelocytes, metamyelocytes).
- Chemical Test
- BUN and creatinine levels are elevated.
- Uric acid level may be increased
- Protien and albumin levels may be mildly decreased.

- LDH & Bilerubin Elevated.
- Decreased plasma levels of clotting factors V and factor VIII
- Increased activated partial thromboplastin time (aPTT) and prothrombin time (PT)
- Increased D-dimer and fibrinogen-degradation products (FDP)
- Levels of serum haptoglobin which binds hemoglobin, are decreased.
- Stx may be detected using specific antibody testing, gene studies, and enzyme-linked immunosorbent assay (ELISA).