

Bleeding Disorders

Dr Mahmoud Shbair

CPBP

Fellowship of Pediatric Hematology and Oncology
Consultant Pediatric Hematologist and Oncologist

Thrombotic Microangiopathies

Excessive activation of platelets, which deposit as thrombi in small blood vessels.

A spectrum of clinical syndromes that includes **Thrombotic Thrombocytopenic Purpura (TTP)** and **Hemolytic-Uremic Syndrome (HUS)**

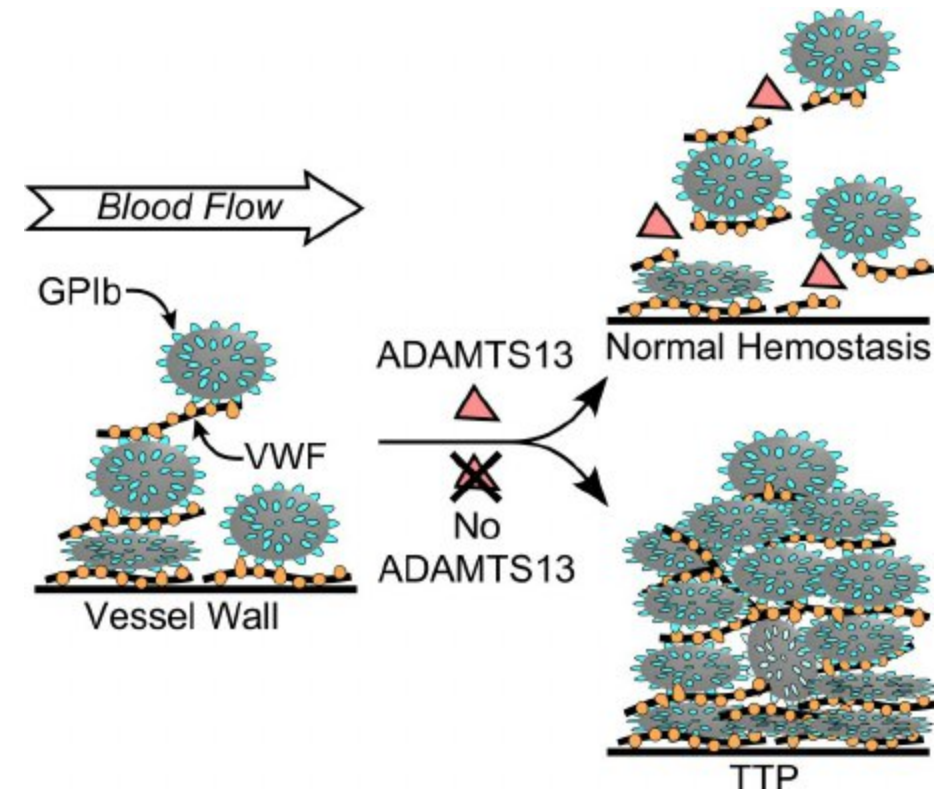
Laboratory tests of coagulation are usually normal

Thrombotic Thrombocytopenic Purpura (TTP)

Deficiency in a plasma ADAMTS13 enzyme which degrades very high-molecular-weight multimers of von Willebrand factor (vWF), leading to their accumulation and promoting platelet activation and aggregation.

Intravascular thrombi cause a microangiopathic hemolytic anemia and widespread organ dysfunction, in addition to thrombocytopenia

The deficiency of ADAMTS13 can be acquired (inhibitory autoantibodies) or less commonly inherited



Manifestation of TTP

Pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, and renal failure

Seriously fatal disease, high index of suspicion is important

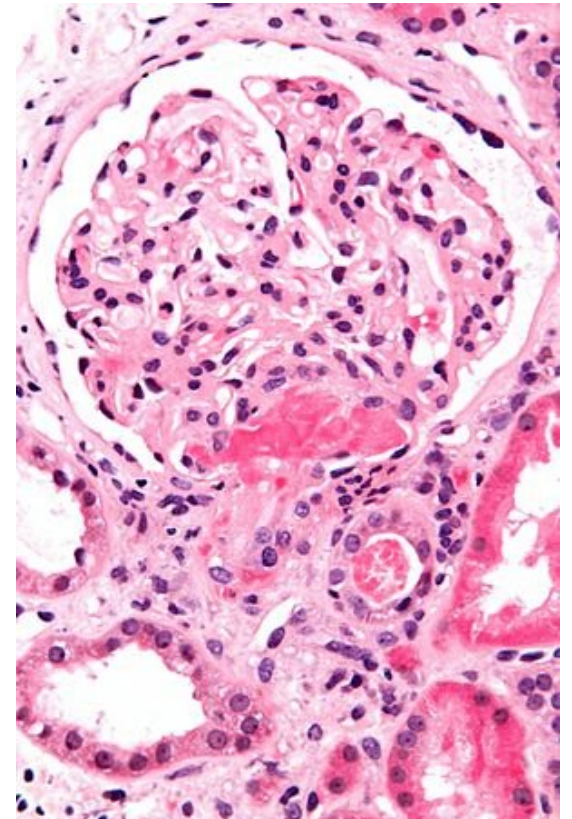
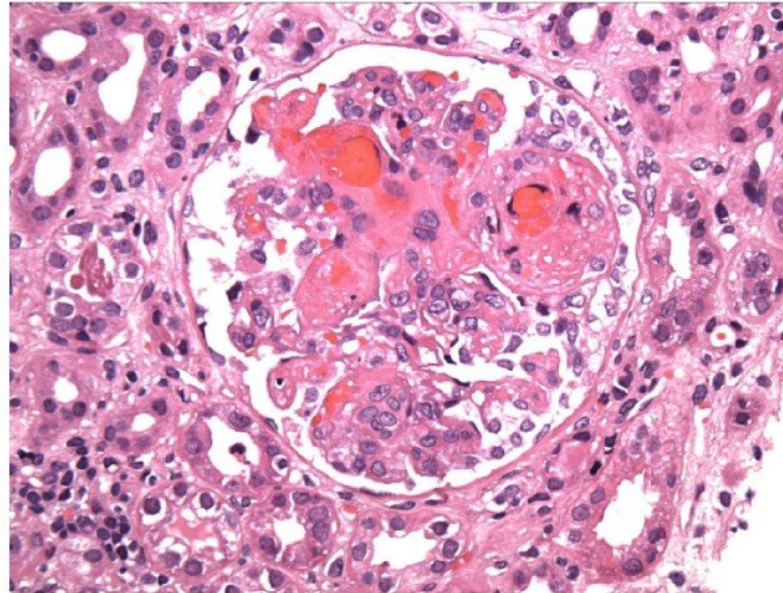
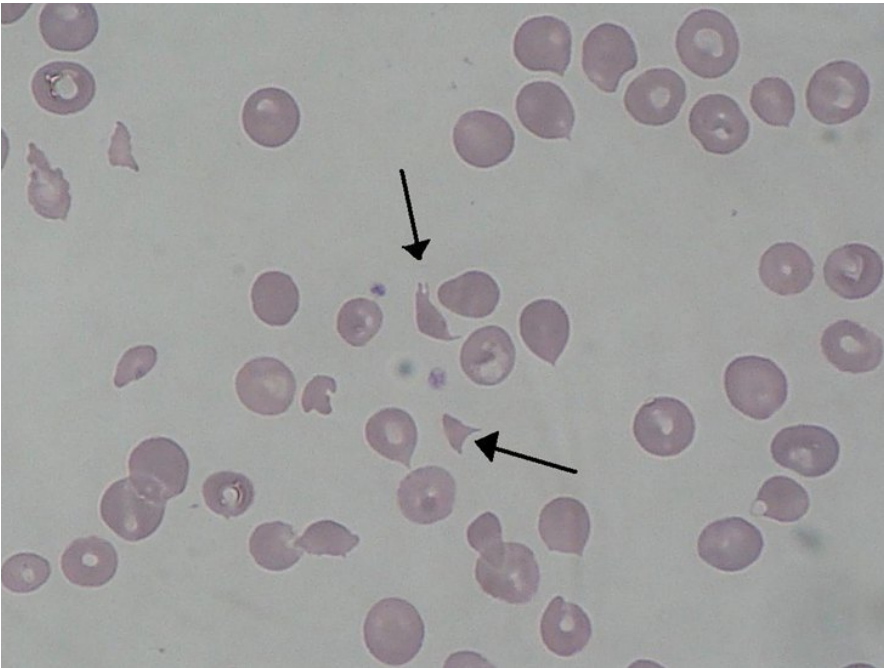
In hereditary form, onset is often delayed until adolescence and symptoms are episodic, factors other than ADAMTS13 (e.g., some superimposed vascular injury or prothrombotic state) must be involved in triggering full-blown TTP

Treatment with plasma exchange

Thrombotic Thrombocytopenic Purpura (TTP)

Morphology

- Hyaline microthrombi are present in the arterioles and capillaries of end organs, such as the kidney, brain, and heart.
- Blood film reveals schistocytes (fragmented RBCs)



Hemolytic-Uremic Syndrome (HUS)

Another form of thrombotic microangiopathy.

Differs from TTP

- Absence of neurologic symptoms

- Prominence of acute renal failure

- Frequent occurrence in children

HUS occurs in either typical or atypical form.

Unclear basis of platelet activation.

Hemolytic-Uremic Syndrome (HUS)

Typical HUS

- Strongly associated with infectious gastroenteritis caused by *Escherichia coli* strain O157:H7, which elaborates a Shiga-like toxin
- Shiga-like toxin alters endothelial cell function and results in platelet activation and aggregation.
- Children and older adults are at highest risk.
- Bloody diarrhea, precedes HUS appearance by a few days
- With appropriate supportive care complete recovery is possible, but irreversible renal damage and death can occur in more severe cases

Hemolytic-Uremic Syndrome (HUS)

Atypical HUS

- Defects (inherited or acquired inhibitory autoantibodies) in complement regulatory proteins
- Excessive alternative complement pathway activation underlies the pathogenesis of this form of HUS that shows a remitting, relapsing clinical course
- Therapeutic antibodies that inhibit the activation of complement factor C5 are effective in preventing thrombosis in patients with inherited deficiencies

Other Thrombotic microangiopathies

Drugs (cyclosporine, chemotherapeutic agents)

Radiation, bone marrow transplantation

Other infections (HIV, pneumococcal sepsis)

Conditions associated with autoimmunity (systemic lupus erythematosus, HIV infection, lymphoid neoplasms)

Hemorrhagic Diatheses Related to Abnormalities in Clotting Factors

Bleeding due to coagulation factor deficiencies often occurs into

- The gastrointestinal and urinary tracts
- Weight-bearing joints (hemarthrosis)
- Deep muscular tissue

Hereditary deficiencies affect a single clotting factor

- vWF (von Willebrand disease)
- Factor VIII (Hemophilia A)
- Factor IX (hemophilia B)

Acquired deficiencies involve multiple coagulation factors

- Vitamin K deficiency (factors II, VII, IX, X and protein C)
- Disseminated intravascular coagulation

Von Willebrand Disease

Defective vWF

vWF function

- Platelet binding (via a PLT binding domain)
- Carrier molecule for FVIII (via a F VIII binding domain)

After synthesis, vWF undergoes multimerization to high and intermediate molecular weight multimers which are very much potent in adhering PLTs

Von Willebrand Disease

The most common inherited bleeding disorder of humans

- 1% by lab testing
- 1 per 500 symptomatic
- Wide variability in clinical expression is common

Most common symptoms related to defects in PLTs function

- Mostly mucocutaneous bleeding
- Epistaxis, easy bruising, oral bleeding, post-surgical (oropharyngeal) bleeding
- Menorrhagia and post-partum bleeding in females of childbearing age
- Bleeding in Joints in type 3

Three broad categories of von Willebrand disease are present

Von Willebrand Disease

Type 1 von Willebrand disease

- Autosomal dominant disorder
- Most common form accounting for 70% of cases
- Mild to moderate vWF deficiency i.e. quantitative
- Variable clinical expression but generally is associated with mild disease

Von Willebrand Disease

Type 2 von Willebrand disease

Qualitative defects in vWF with autosomal dominant inheritance, vWF is expressed in normal/near normal amounts

Associated with mild to moderate bleeding

Has 4 subtypes,

- Type 2A is the most common,
vWF is expressed in normal/near normal amounts but there is defective multimerization of the vWF molecules (multimers are absent from the plasma)
- Type 2B, Gain of function mutation in PLT binding domain of VWF
- Type 2M, Loss of function mutation in PLT binding domain (opposite of 2B)
- Type 2N, Loss of vWF binding function to FVIII

Von Willebrand Disease

Type 3 von Willebrand disease

- Autosomal recessive disorder
- very low levels of vWF and severe clinical manifestations.
- Markedly affects factor VIII half-life, so the bleeding characteristics resemble those seen in hemophilia.

Level of active vWF is reduced

Factor VIII may be secondarily affected resulting in PTT prolongation

The plasma level of active vWF, measured as the ristocetin cofactor activity

Hemophilia A (Factor VIII Deficiency)

Caused by mutations in factor VIII, inherited as an X-linked recessive trait
30% of patients have no family history; their disease is caused by new mutations

- Heterozygous females are affected by bleeding if the random inactivation of X chromosome involve the normal factor VIII allele

Three degrees of severity

- Severe HA: FVIII concentration < 1% of normal
- Moderate HA: FVIII concentration 2-5% of normal
- Mild HA: FVIII concentration 6-50% of normal

The marked heterogeneity in genetic lesions causes the variability in factor deficiency

The most severe deficiencies result from mutations that completely abolishes the synthesis of factor VIII.

Hemophilia A (Factor VIII Deficiency)

Clinical Features and Diagnosis

Easy bruising and massive hemorrhage after trauma or operative procedures

Spontaneous Joint hemorrhages (hemarthrosis)

Recurrent hemarthrosis leads to hemophilic arthropathy

Petechiae are characteristically absent

Prolonged PTT, normal PT

Factor VIII-specific assays are needed for diagnosis

Treatment involves recombinant factor VIII replacement, inhibitors is a challenging complication

Hemophilia B (Christmas Disease, Factor IX Deficiency)

X-linked recessive trait

A wide spectrum of mutations involving the gene that encodes factor IX produces disease with variable severity

A clinically indistinguishable disorder from hemophilia A

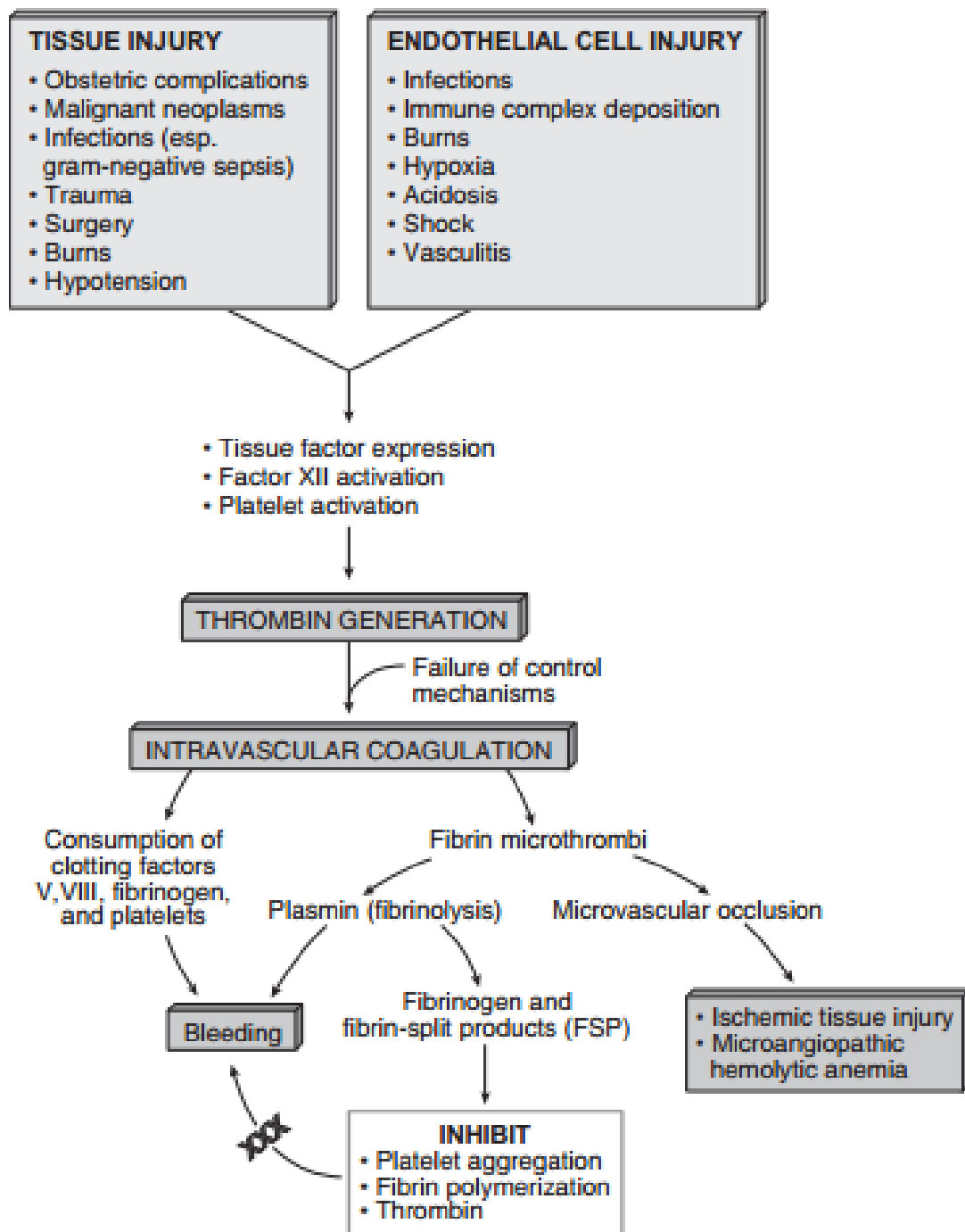
PTT is prolonged and the PT is normal

Diagnosed by assay of the factor levels

Disseminated Intravascular Coagulation (DIC)

DIC is a thrombohemorrhagic disorder characterized by the excessive activation of coagulation and the formation of thrombi in the microvasculature of the body, this happens through:

- Release of tissue factor and other procoagulants, into the circulation, sources include the placenta in obstetric complications, burns, severe trauma
- Widespread injury to the endothelial cells e.g. In sepsis, TNF induces endothelial cells to express tissue factor on their cell surfaces and increase adhesion molecules, mediating endothelial damage by oxygen species from leukocytes



The pathophysiology of disseminated intravascular coagulation (DIC)

DIC consequences

Widespread deposition of fibrin within the microcirculation leading to ischemia and microangiopathic hemolytic anemia

Consumption of platelets and clotting factors and the activation of plasminogen, leading to a hemorrhagic diathesis and accumulation of fibrin degradation products.

DIC Clinical Features

Onset can be acute or insidious based on underlying pathology

Common clinical presentations include microangiopathic hemolytic anemia, dyspnea, cyanosis, and respiratory failure, convulsions and coma, oliguria and acute renal failure; and sudden or progressive circulatory failure and shock

Diagnosis

- Clinical findings
- Low fibrinogen, high fibrin degradation products, low platelets and prolonged PT and PTT