

Bleeding Disorders

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Hemostasis Physiology

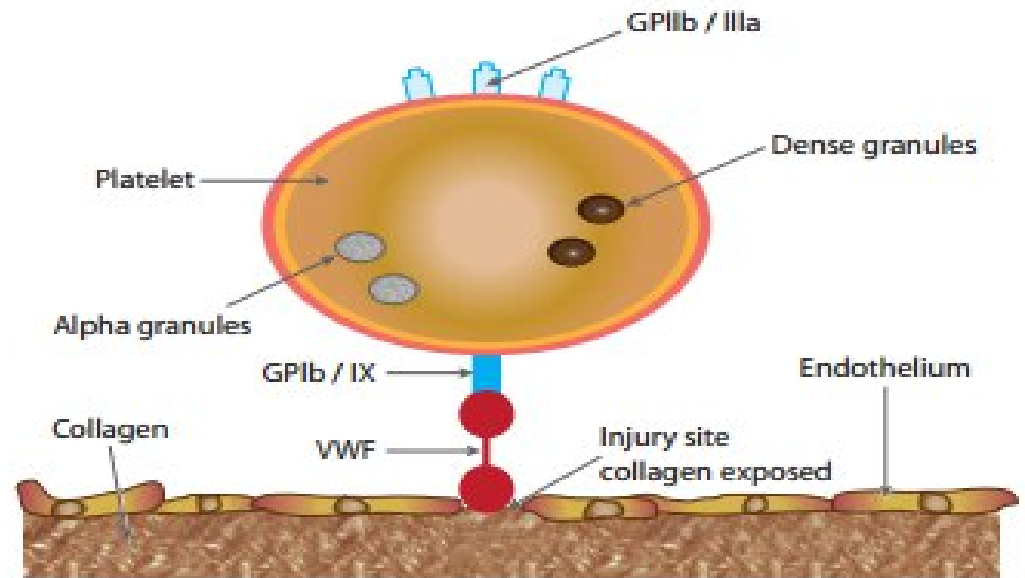
Hemostasis is a complex process in which multiple components of the blood clotting system are activated in response to vessel injury to control bleeding

It is composed of

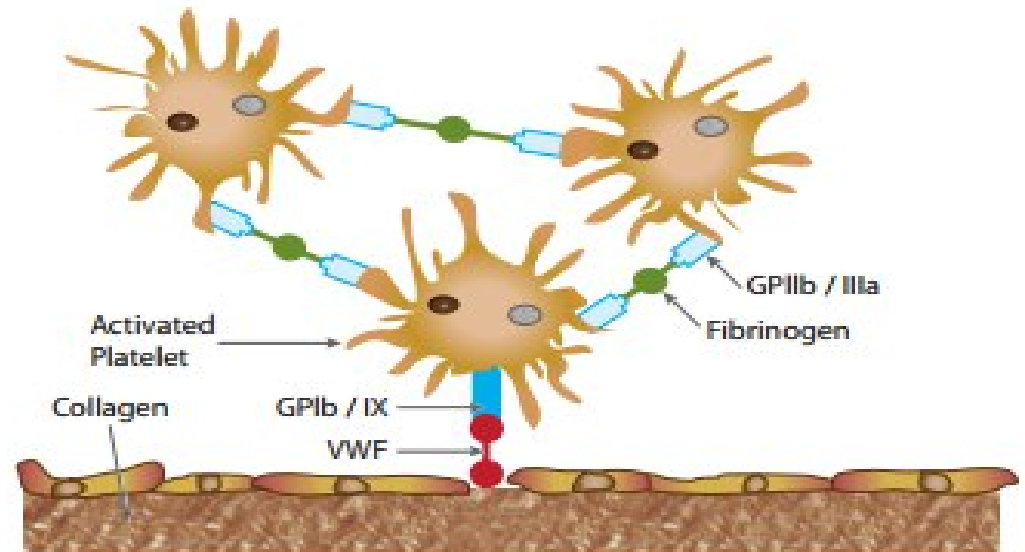
- 1 . Primary hemostasis
2. Secondary hemostasis
3. Fibrin clot formation and stabilization
4. Inhibition of coagulation

Primary Hemostasis

- Vasoconstriction
- PLT adhesion
- PLT aggregation

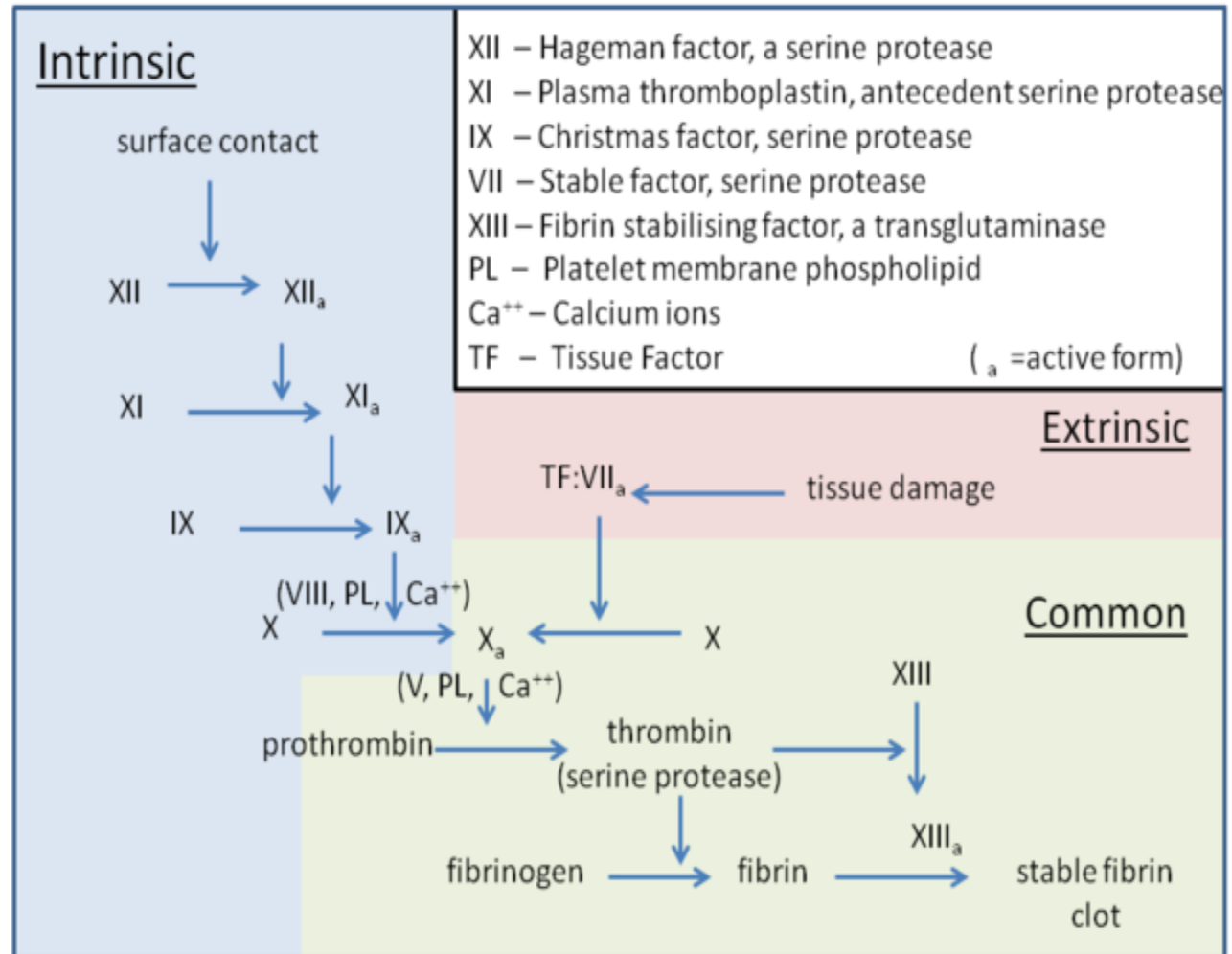


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Secondary Hemostasis fibrin clot stabilization

The three pathways that make up the classical blood coagulation pathway



Hemostasis Physiology

Inhibition of coagulation

- Thrombin binds to the membrane receptor thrombomodulin and activates Protein C that binds protein S and inhibit factor V and VIII

Fibrinolysis

- Tissue plasminogen activator (t-PA) converts plasminogen to plasmin which breaks down cross-linked fibrin to several fibrin degradation products, the smallest of which is D-dimer

Tests of Hemostasis

Platelet counts

- Electronic particle counter and confirmed by blood smear

Bleeding time

- Older less specific test for PLT function, sometimes prolonged in vessel wall abnormalities

Tests of platelet function

- The ability of PLTs to aggregate in response to different agonists

Prothrombin time (PT)

- Assesses the extrinsic and common coagulation pathways

Partial thromboplastin time (PTT)

- This test assesses the intrinsic and common clotting pathways

Excessive bleeding can result from

1. Increased fragility of vessels
2. Platelet deficiency or dysfunction
3. Derangement of coagulation

**Primary
hemostatic
defect**

Bleeding Disorders Caused by Vessel Wall Abnormalities

Relatively common, do not usually cause serious bleeding, Platelet count, function and tests of coagulation (PT, PTT) are normal (unless affected by underlying disease e.g meningococemia)

Bleeding time may be increased

Most often, they present with small hemorrhages (petechiae and purpura), occasionally cause joints, muscles, menorrhagia,

- Infections e.g. meningococemia and infective endocarditis
- Henoch-Schönlein purpura
- Scurvy and the Ehlers-Danlos syndrome
- Hereditary hemorrhagic telangiectasia, autosomal dominant characterized by dilated, tortuous blood vessels with thin walls that bleed readily, bleeding can be serious

Bleeding due to Thrombocytopenia

Important cause of generalized bleeding

Normal PT and PTT that test coagulation

Involves small vessels involving the skin and the mucous membranes

Intracranial bleeding is serious complication

Causes of Thrombocytopenia

Decreased Production of Platelets

- Drug-induced: alcohol, thiazides, cytotoxic drugs
- Infections: measles, human immunodeficiency virus (HIV)
- Nutritional deficiencies: B12, folate deficiency
- Bone marrow failure
- Bone marrow replacement
- Ineffective hematopoiesis: Myelodysplastic syndromes

Causes of Thrombocytopenia

Decreased Platelet Survival

Immunologic destruction

Primary autoimmune

Chronic immune thrombocytopenic purpura

Acute immune thrombocytopenic purpura

Secondary autoimmune

Systemic lupus erythematosus, B-cell lymphoid neoplasms

Alloimmune: posttransfusion and neonatal

Drug-associated: quinidine, heparin, sulfa compounds

Infections: HIV, infectious mononucleosis (transient, mild), dengue fever

Nonimmunologic destruction

Disseminated intravascular coagulation

Thrombotic microangiopathies

Giant hemangiomas

Sequestration

Hypersplenism

Dilution

Transfusions

Neonatal Thrombocytopenia

Inherited forms include

- Wiskott-Aldrich syndrome: X linked recessive; affected boys have small platelets, eczema, and immunodeficiency
- Amegakaryocytic thrombocytopenia
- Thrombocytopenia-absent radius syndrome
- Fanconi anemia

Neonatal Thrombocytopenia

Acquired forms include:

- Neonatal alloimmune thrombocytopenia (NAIT):

Caused by alloimmunization to platelet antigens such as HPA-1a during pregnancy.

NAIT leads to destruction of fetal platelets, predisposing the fetus or neonate to intracranial hemorrhage.

- Additional causes: birth asphyxia, necrotizing enterocolitis, and thrombosis

Chronic Immune Thrombocytopenic Purpura (ITP)

Autoantibody mediated destruction of
platelets

Either

- Primary (idiopathic)

Secondary immune thrombocytopenia causes
has to be excluded

- Secondary: systemic lupus erythematosus, HIV infection, and B-cell neoplasms such as chronic lymphocytic leukemia

Chronic ITP Pathogenesis

The autoantibodies, mostly of the IgG class, most often against platelet membrane glycoproteins IIb-IIIa or Ib-IX

Antiplatelet antibodies act as opsonins that are recognized by IgG Fc receptors expressed on phagocytes, leading to increased platelet destruction.

Autoantibodies may also bind to and damage megakaryocytes, leading to decreases in platelet production that further exacerbate the thrombocytopenia.

ITP MORPHOLOGY

The spleen is

- Enlargement of the splenic follicles, with prominent reactive germinal centers.
- **Congestion of the sinusoids and Foamy histiocytes** are seen in the red pulp. The foamy appearance is secondary to accumulation of phospholipids from **phagocytosed platelets**.

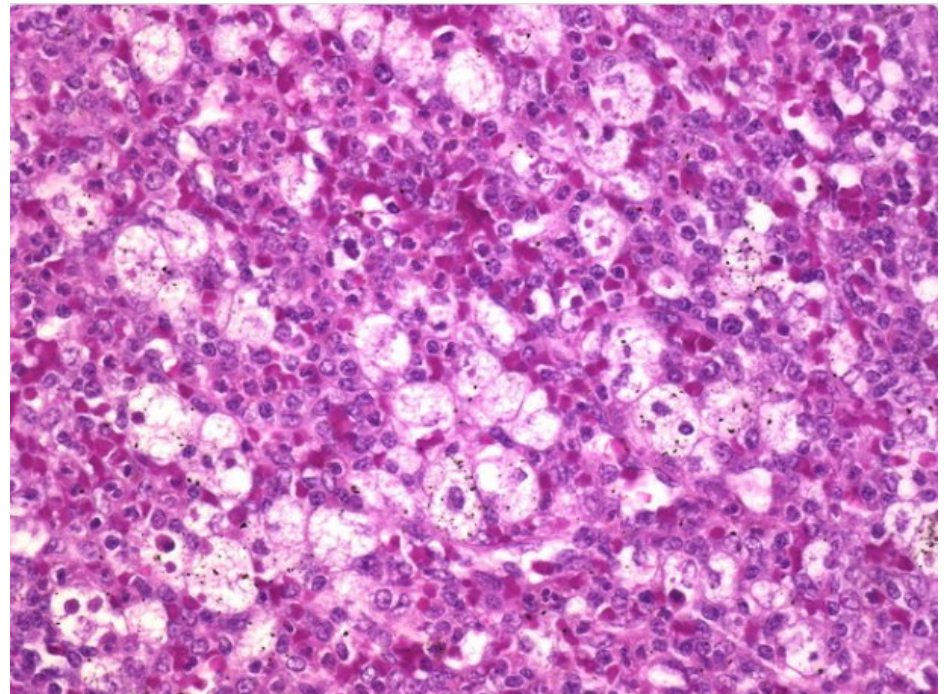
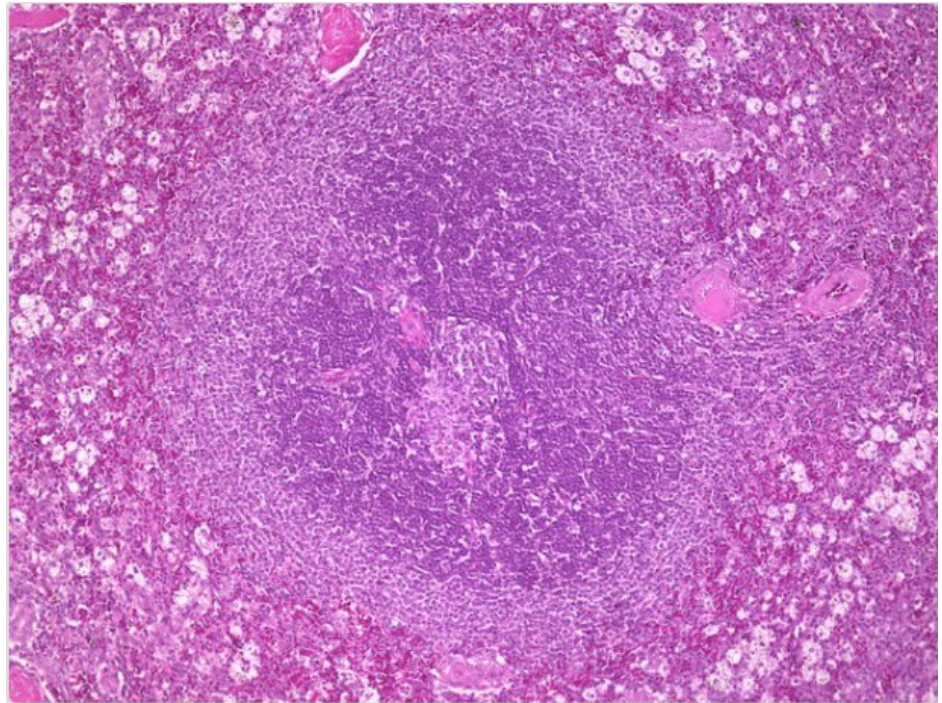
The bone marrow

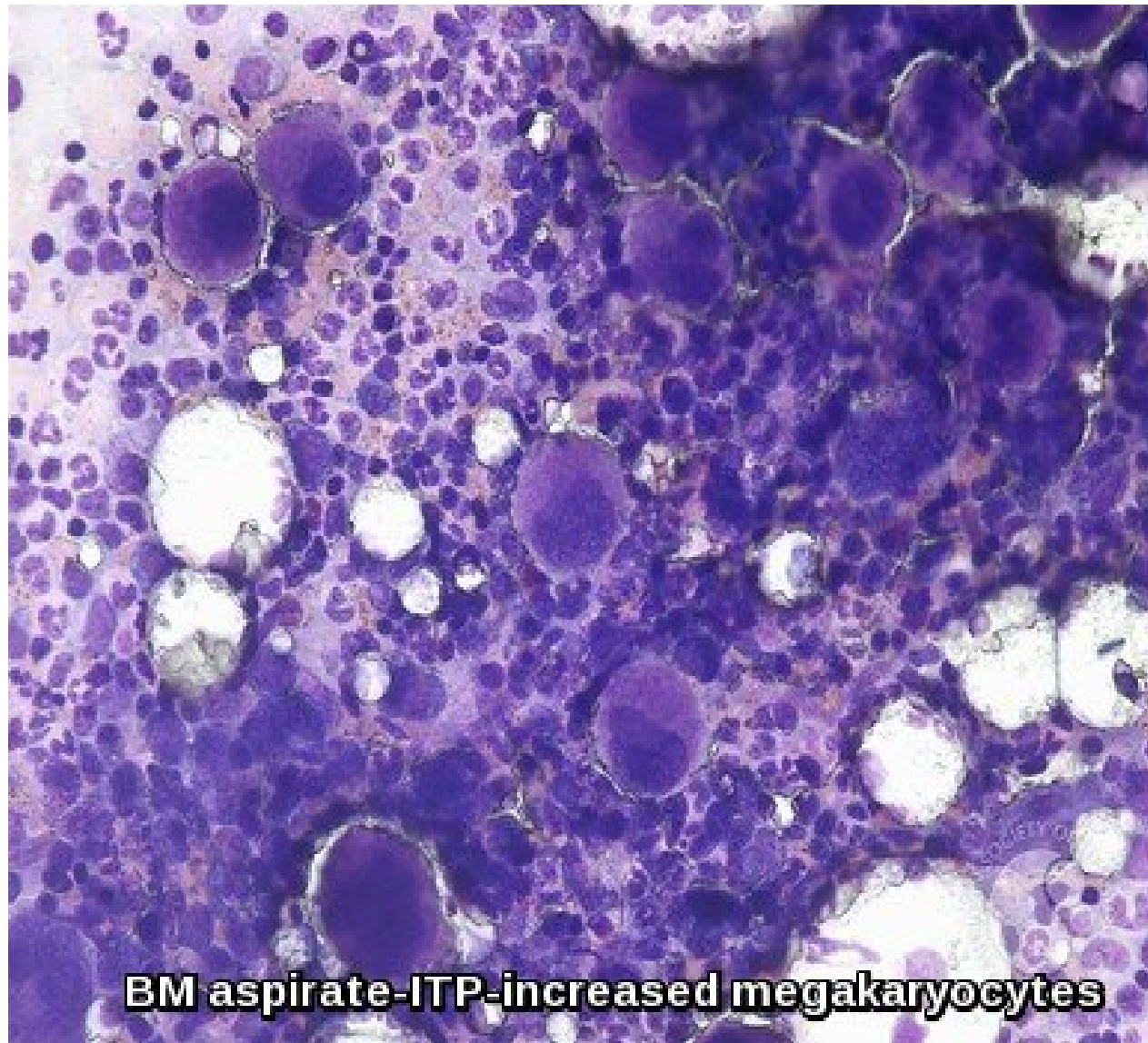
- **A modestly increased number of megakaryocytes**, some are apparently immature, with large, nonlobulated, single nuclei.
- The importance of bone marrow examination is to rule out thrombocytopenia resulting from bone marrow failure or other primary bone marrow disorders.

The peripheral blood smear **reveals abnormally large platelets** (marco or megathrombocytes), which is a sign of accelerated thrombopoiesis.

ITP

Spleen, germinal
center and foamy
histiocytes





BM aspirate-ITP-increased megakaryocytes

ITP- macrothrombocyte



Chronic ITP Clinical features

Adult women younger than 40 years, F:M 3:1

Insidious onset, mucocutaneous bleeding

Petechiae and ecchymoses, easy bruising, nose bleeds, bleeding from the gums, and hemorrhages into soft tissues from relatively minor trauma.

May manifest first with melena, hematuria, or excessive menstrual flow

Intracranial hemorrhage, serious but rare in treated patients.

Chronic ITP Clinical features

Splenomegaly and lymphadenopathy are uncommon in primary disease

low platelet count, normal or increased megakaryocytes in the bone marrow, and large platelets in the peripheral blood are presumptive evidence

Treatment include glucocorticoids, intravenous immunoglobulin, anti-CD20 antibody (rituximab) and splenectomy , drugs that mimic the effects of thrombopoietin (so-called TPO-mimetics), splenectomy.

Acute Immune Thrombocytopenic Purpura

Childhood illness with equal frequency in both sexes

Abrupt onset, often 1 to 2 weeks after a self-limited viral illness triggering the development of autoantibodies

Self-limited, usually resolving spontaneously within 6 months.

Glucocorticoids or intravenous immunoglobulin treatment for severe thrombocytopenia.

Chronicity in 20% of children following a course similar to adult chronic ITP

Drug-Induced Thrombocytopenia

Drugs can induce thrombocytopenia through direct effects on platelets and secondary to immunologically mediated platelet destruction

The drugs most commonly implicated are quinine, quinidine, and vancomycin

Heparin-induced thrombocytopenia (HIT) has a distinctive pathogenesis and occurs in 5% of persons receiving heparin and is of two types

Heparin-induced thrombocytopenia (HIT)

Type I thrombocytopenia

- Rapidly after heparin therapy
- Little clinical importance

Type II thrombocytopenia,

- Less common
- Greater clinical significance and severity,
- Five to 14 days after heparin therapy begins
- Caused by antibodies that recognize complexes of heparin and platelet factor 4
- Often leads to life threatening venous and arterial thrombosis

HIV-Associated Thrombocytopenia

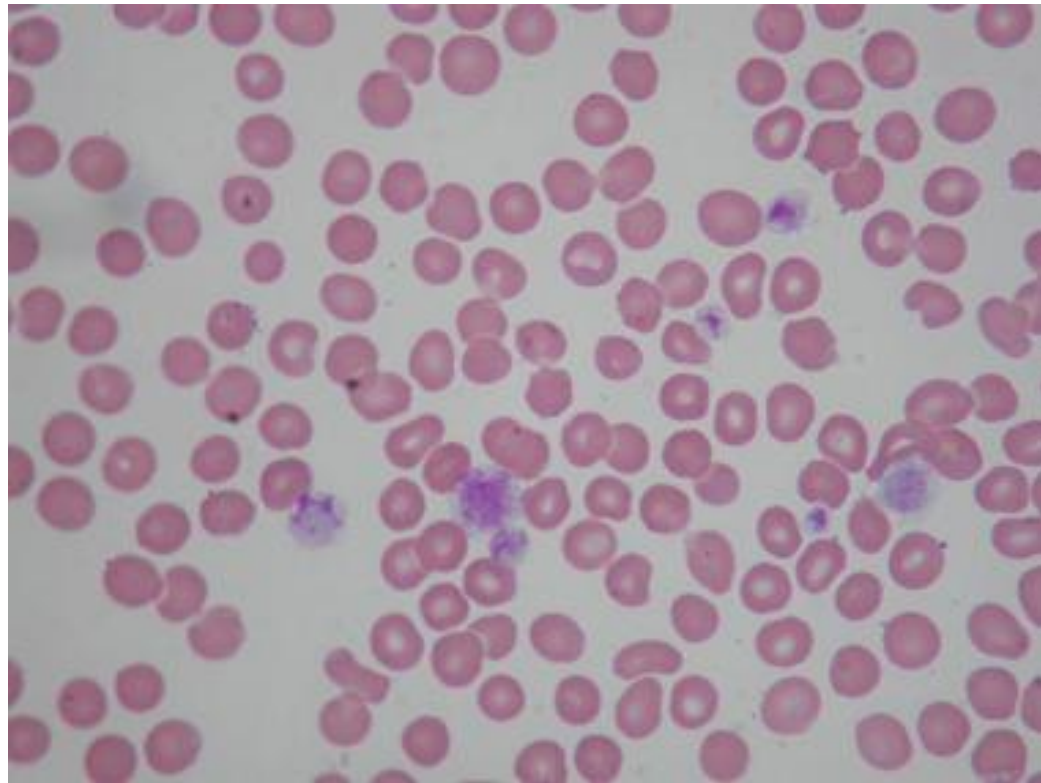
Thrombocytopenia is one of the most common hematologic manifestations of HIV infection

- Impaired platelet production: CD4 receptors are found on megakaryocytes
- Increased destruction: B-cell hyperplasia and dysregulation

Bleeding Disorders Related to Defective Platelet Functions

Bernard-Soulier syndrome

- Also known as giant platelet syndrome
- Is an autosomal recessive disorder, defect in the membrane glycoprotein complex GPIb/IX or GPV that binds vWF
- Examination of the blood reveals thrombocytopenia and circulating giant platelets.
- The disease becomes symptomatic during childhood with ecchymoses, epistaxis, and gingival bleeding. During later ages, the disease is manifested by menorrhagia and gastrointestinal bleeding



Bleeding Disorders Related to Defective Platelet Functions

Glanzmann thrombasthenia

- Is an autosomal recessive disorder
- Defect in the glycoprotein complex IIb/IIIa, which binds fibrinogen
- Platelets fail to aggregate or retract, leading to impaired hemostasis.
- Patients present shortly after birth with mucocutaneous or gingival hemorrhage, epistaxis, or bleeding after circumcision.

Bleeding Disorders Related to Defective Platelet Functions

Acquired PLT dysfunction

- Aspirin and NSAID: inhibit cyclooxygenase that synthesizes thromboxane A₂ and prostaglandins, both mediators play an important roles in platelet aggregation and subsequent degranulation
- Uremia: pathogenesis of platelet dysfunction involves defects in adhesion, granule secretion, and aggregation.