Common Bleeding Disorders: Idiopathic Thrombocytopenic Purpura (ITP), Hereditary Hemorrhagic Telangiectasia and more

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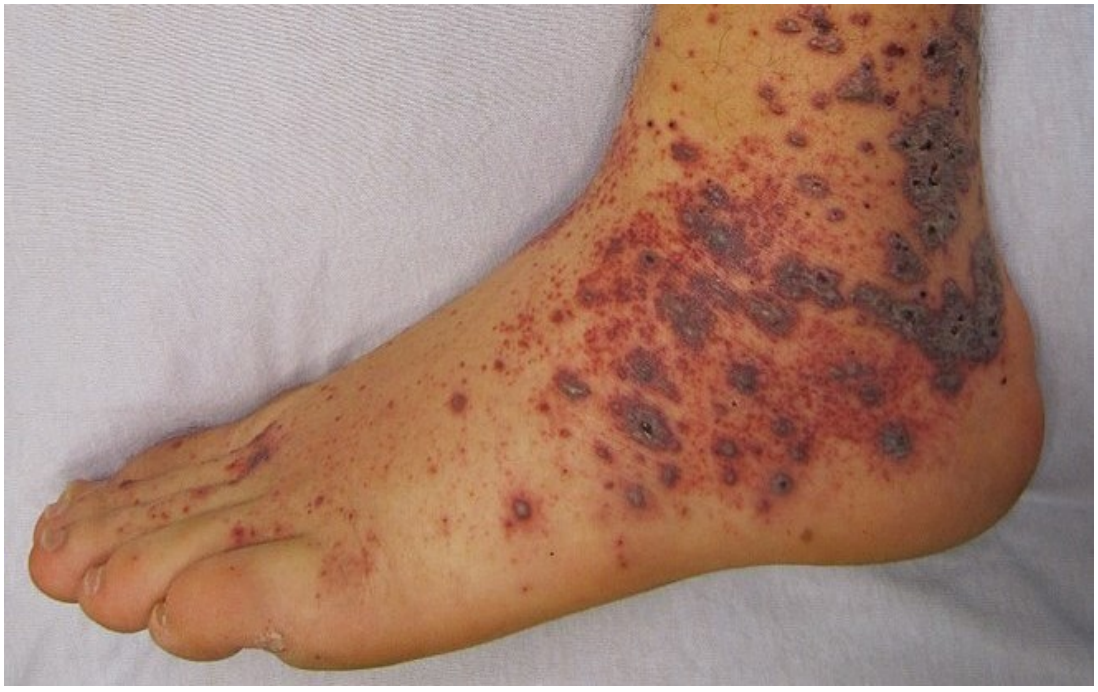
This article provides an overview of bleeding disorders caused by vessel wall abnormalities, platelet functional disorders, immune thrombocytopenic purpura, and thrombotic microangiopathies. These disorders share 2 common features: They are not caused by an abnormality in the clotting factors, and they present with bleeding without an effect on the international normalized ratio.



Classification of bleeding disorders

Bleeding disorders can be classified into the following categories.

Disorders of the vessel wall

1. Hereditary forms such as hereditary hemorrhagic telangiectasia and Ehler-Danlos syndrome
2. Acquired forms such as vitamin C deficiency, amyloidosis, and Henoch-Schönlein purpura

Disorders of clotting factor function

1. Hereditary forms such as hemophilia, von Willebrand disease, and dysfibrinogenemia
2. Acquired forms such as vitamin K deficiency and disseminated intravascular coagulopathy (DIC)

Disorders of platelet function

1. Disorders due to reduced bone marrow function/platelet production such as folate and B12 deficiency
2. Disorders of increased platelet consumption/platelet numbers such as DIC and idiopathic thrombocytopenic purpura
3. Disorders due to platelet function such as platelet adhesion disorders
4. Bleeding disorders due to vascular abnormalities

Definition and Overview

Defects in the blood vessels can cause vascular bleeding disorder. Patients develop petechiae, purpura, and bruising. Bleeding disorders due to vascular abnormalities rarely cause serious blood loss, except for hereditary hemorrhagic telangiectasia. The coagulation profile in bleeding disorders due to vascular abnormalities is normal. The diagnosis is usually clinical.

Gardner-Diamond Syndrome

This is a rare autoerythrocyte sensitization disorder that affects mainly women. Patients develop local pain followed by unexplained painful ecchymoses on the extremities. Although there may be a history of trauma, the ecchymoses typically occur distant from the site of trauma. Ecchymoses never occur on the back of the patient.

This syndrome is seen in women with psychiatric disease. The diagnosis is a clinical one and psychiatric treatment usually solves the problem. The pathogenesis and mechanism of the disorder are not known.

Dysproteinemias and Vascular Purpura

Conditions characterized by abnormal protein content in the blood and immune or protein deposition in the blood vessel wall include:

- Amyloidosis
- Cryoglobulinemia
- Hypergammaglobulinemic purpura
- Hyperviscosity syndrome

The blood vessels can become fragile and start leaking blood. Patients present with purpura and the lesions are typically small in size (< 2 mm). Large lesions such as ecchymoses or bruises may be also seen in these patients.

The diagnosis of amyloidosis can be confirmed with a biopsy. Cryoglobulins can be detected by laboratory testing. Patients with cryoglobulinemia typically have hepatitis C. Patients with hypergammaglobulinemic purpura have a polyclonal increase in IgG on laboratory testing. Finally, patients with hyperviscosity syndrome have macroglobulinemia (elevated levels of IgA and IgG).

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome)

This is a hereditary disorder that is transmitted in an autosomal dominant fashion. There is a mutation in the receptor for transforming growth factor beta 1 and transforming growth factor beta 3, resulting in abnormal vessel formation in the skin, mucous membranes, and organs such as the lungs, liver, and brain.

The diagnosis is based on three main steps:

Step 1	A careful history and physical evaluation.
Step 2	Endoscopy or angiography to confirm e.g., gastrointestinal telangiectatic lesions
Step 3	Genetic testing to confirm the diagnosis and demonstrate a mutation in one of the previously mentioned genes

The treatment of hereditary hemorrhagic telangiectasia can be summarized as follows:

	Causes	**Treatment**
Nasal and gastrointestinal telangiectasias	Significant hemorrhage	Aggressively whenever bleeding
Vascular malformations in the brain	Stroke and bleed	Laser ablation, embolization, or surgical resection
Bleeding disorder	Chronic blood loss	Parenteral iron supplements

Surgical approaches to treat vascular malformations such as cerebral arteriovenous malformations are also used.

Bleeding Disorders Due to Functional Platelet Abnormalities

Definition and Overview

Bleeding disorders due to functional platelet abnormalities can be hereditary or acquired. The disorders of platelet function can be further classified into:

- Disorders of platelet adhesion
- Disorders of platelet secretion
- Disorders of platelet aggregation
- Disorders of platelet procoagulant activity
- Combined abnormalities of platelet function and number

For a platelet to be considered as normal functionally, it has to adhere to other platelets, secrete certain proteins for the activation of the clotting cascade and recruitment of more platelets and other cells, aggregate to other platelets, and have procoagulant activity. Moreover, the number of platelets available in the bloodstream needs to be appropriate for bleeding to not occur.

Acquired platelet functional abnormalities are caused by aspirin, antiplatelet therapy, or the use of nonsteroidal anti-inflammatory drugs.

Disorders of Platelet Adhesion

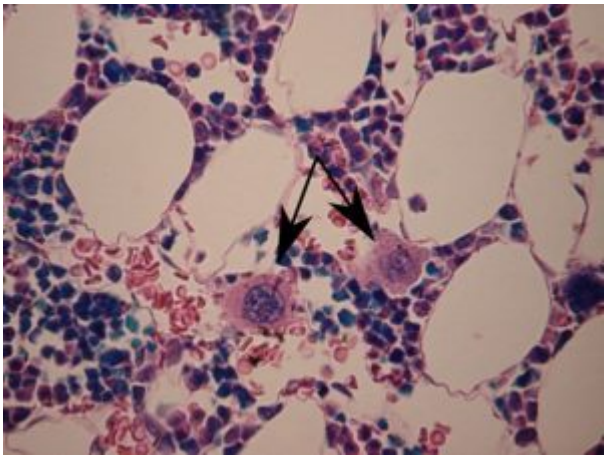


Image : “Two megakaryocytes are visible in this slide of bone marrow” by Wbensmith. License: CC BY-SA 3.0

Bernard-Soulier syndrome is a rare disorder of platelet adhesion that is characterized by a deficiency of glycoprotein Ib/IX. This protein is found on the surface of the platelet and is responsible for platelets sticking and clumping to each other. Children with this disorder present with bruises, frequent nosebleeds, and bleeding from the mouth and gums. Coagulation profile is normal; however, bleeding time is prolonged. The number of platelets may be low. On a blood smear, the platelets appear to be enlarged and do not clump to each other in response to ristocetin.

Disorders of Platelet Secretion

Disorders of platelet secretion include alpha-granule deficiency, dense granule deficiency, and abnormal granule secretory mechanism.

Patients with a platelet secretion abnormality have:

- Impaired platelet adhesion
- Aggregation
- Repair of blood vessels after injury

Disorders of Platelet Aggregation

Glanzmann thrombasthenia

Glanzmann thrombasthenia arises from abnormal glycoprotein IIb and IIIa, which are required for proper platelet adhesion. The platelets only adhere to ristocetin. The disease can be classified into a severe form, in which no glycoproteins can be detected, or a mild form, with reduced levels of glycoproteins in circulation.

The rare disorder Glanzmann thrombasthenia presents with impaired platelet aggregation. Patients with this disorder may present with life-threatening bleeding. Platelets fail to plug to the site of an injury. There is a deficiency in the glycoprotein IIb/IIIa.

Combined Abnormalities of Platelets’ Number and Function

Some rare hereditary disorders affect platelets’ function and number. These include:

- May-Hegglin anomaly
- Alport syndrome
- Wiskott-Aldrich syndrome

The main cause of bleeding in these disorders is related to thrombocytopenia, not platelet dysfunction.

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is a heterogeneous disease that is characterized by increased platelet clearance and insufficient platelet production. Tissue macrophages are responsible for platelet destruction in ITP. The process of destruction occurs in the spleen.

The destruction of platelets in ITP appears to be facilitated by the presence of IgG immunoglobulins; hence the term “immune.” Infection with hepatitis C, human immunodeficiency virus, or *Helicobacter pylori* can contribute to the production of these antibodies. The management of ITP revolves around corticosteroids, mainly prednisolone. After the cessation of prednisolone, some patients with ITP may develop cytopenias.

Patients with ITP who do not respond to prednisolone should receive one of the following treatments as second-line therapy:

- Ciclosporin
- Cyclophosphamide
- Oral high-dose dexamethasone
- Parenteral methylprednisolone
- Danazol
- High-dose intravenous immunoglobulin

Romiplostim and eltrombopag are thrombopoietin receptor agonists. They stimulate the production of platelets from the bone marrow and are both licensed for the treatment of ITP. If all of the above treatment options fail to treat the thrombocytopenia, splenectomy might be considered.

Thrombotic Microangiopathies

These disorders present with microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury. The pathogenesis of thrombotic microangiopathies (TMA) includes vascular damage, arteriolar and capillary thrombosis, and endothelial cell abnormalities.

The following table summarizes the most common TMA syndromes, their characteristics, and management:

Name	Etiology	Clinical Features	Treatment
Complement-mediated TMA	Mutations in CFH, C3, CD46 or other complement genes	Occurs in children. Acute kidney injury is common.	Plasma infusion or exchange. Anti-complement therapy.
ADAMTS13 deficiency mediated TMA	ADAMTS13 mutations	Occurs in children. Presents with ischemic organ injury. Acute kidney injury is rare.	Plasma infusion.
Coagulation mediated TMA	DGKE, PLG, or THBD mutations	Occurs in infants. Presents with acute kidney injury.	Plasma infusion.

Acquired Thrombotic Thrombocytopenic Purpura (TTP)	Autoantibody inhibition of ADAMTS13	Uncommon in children. Presents with ischemic organ injury. Kidney injury is rare.	Plasma exchange and immunosuppressive therapy.
Shiga toxin-mediated TMA	Enteric infection with Shiga toxin-producing strains of *Escherichia coli* or *Shigella dysenteriae*	Common in young children. Presents with acute kidney injury. Outbreaks are common.	Supportive care is needed.
Drug-mediated TMA: Immune reaction OR Dose-related reaction	Immune reaction example: quinines. Dose-related reaction involves the inhibition of vascular endothelial growth factor.	Sudden onset of symptoms with acute kidney injury. OR Gradual onset of renal failure over weeks to months.	Removal of drug and supportive care.
Complement-mediated TMA	Antibody inhibition of complement factor H.	Acute kidney injury. Seen in children and adults.	Plasma exchange, immunosuppression, or anti-complement therapy.

References

Canadian hemophilia society: http://www.hemophilia.ca/en/bleeding-disorders/platelet-function-disorders/types-of-platelet-function-disorders/#c451

Chosamata B. The management of immune thrombocytopenic purpura. *Malawi Medical Journal*. 2015;27(3):109-112.

The New England Journal of Medicine: http://www.nejm.org/doi/full/10.1056/NEJMra1312353

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