Chapter 1

Introductory Chapter: Thrombocytopenia

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Additional information is available at the end of the chapter

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1. Thrombocytopenia

Normal platelet count in blood is 150,000–450,000/μL. Decreased platelet cell count (<150,000/μL) is called "**Thrombocytopenia**." Higher than normal platelet count is called "**Thrombocytosis**." Thrombocytopenia may be an incidental finding or patient can present with fatal hemorrhages. The causes of thrombocytopenia may vary from decreased production to increased destruction.

Platelets or thrombocytes are important blood cells like red and white cells. These are non-nucleated cellular fragments produced by megakaryocytes in bone marrow. On maturity of megakaryocytes, cytoplasm budding occurs releasing large number of platelets. Platelet production is controlled by a growth factor called "**Thrombopoietin (TPO)**." Life span of platelets is 10–14 days. Their count and functional status, both are important to maintain normal hemostasis. Bleeding does not occur usually if platelet count is >100,000/μL. Most of the patients bleed when platelet count falls to <10,000–20,000/μL. They can bleed at higher counts if there is associated functional defect with/without additional coagulation disorder.

Platelet surface has receptors for adhesive proteins like von Willebrand factor (VWF), fibrinogen, thrombin, collagen, and adenosine diphosphate (ADP). After tissue trauma, platelet adhesion occurs, activating platelets and forming platelet plug. This initiates coagulation process followed by clot retraction mediated by platelet contractile proteins and cytoskeleton.

Whenever low platelet count is reported in an asymptomatic patient, one must exclude pseudothrombocytopenia—a condition caused by the aggregation of platelets and resulting in false low count of platelets. Repeating the count along with careful look at peripheral smear can exclude this condition. Another cause of apparent thrombocytopenia is hypothermia. Platelets get transiently sequestrated in spleen, liver, and other organs in hypothermic patients. On rewarming, the platelets return to circulation. This phenomenon is also observed in cardiac patients undergoing surgery with hypothermic perfusion.

All patients having thrombocytopenia do not bleed. Etiology of thrombocytopenia is varied. It can be an incidental finding when patient is being investigated as routine health check-up or for some other disease. The patient with thrombocytopenia can be healthy looking, very sick looking as in sepsis or may be in terminal stages of life as in leukemia.

1.1. Immune thrombocytopenic purpura (ITP)

Major cause of acquired thrombocytopenia in childhood is the increased platelet destruction, which can be due to immune or nonimmune causes. One such important immune cause is immune thrombocytopenia which is also called as **immune thrombocytopenic purpura (ITP)**. It is the most common hematological autoimmune disorder. Antibodies produced target the membranes of platelet for accelerated destruction by phagocytes of reticuloendothelial cells, especially those of spleen. After binding of antibodies to platelet surface, circulating antibody-coated platelets are recognized by the Fc receptor on splenic macrophages, ingested and destroyed. The inhibition of megakaryopoiesis also contributes to thrombocytopenia. Usual clinical presentation of acute ITP is in 1–4 year-old child. There may be a history of preceding viral infection, 1–4 weeks before the onset of symptoms. There is a sudden onset of bleeding as generalized petechiae and purpura in otherwise healthy looking child. Gums and mucus membrane may be involved if associated with profound thrombocytopenia (platelet count <10,000/μL). About 80% of children with ITP have platelet count <20,000/μL. Severe bleeding is still rare. Some patients have still lower count <10,000/μL. Peripheral smear may show large platelets reflecting increased platelet turn over. Bone marrow examination is indicated in the presence of abnormal WBC count and unexplained anemia. Many patients with acute ITP have mild symptoms—petechiae and purpura. Treatment causes early rise of platelet count to safe level of >20,000/μL. Treatment options are: (1) No therapy in mild symptoms. (2) intravenous immunoglobulin (IVIG) 0.8–1.0 g/kg for 1–2 days. Response occurs in 95% patients in 48 hours. It is expensive and time consuming therapy. Patient may have headache and vomiting, indicating IVIG-induced aseptic meningitis. (3) Prednisolone therapy (1–4 mg/kg) usually for short periods until platelet count rises to >20,000/μL. This avoids the long-term side effects of corticosteroids use, like growth failure, osteoporosis, and hypertension. (4) Intravenous anti-D therapy in Rh positive patients. Intravenous anti-D therapy, at the dose of 50–75 μg/kg increases platelet count to >20,000/μL in 80–90% of patients in 48–72 hours. It induces mild hemolytic anemia. It gets bound to Rh positive RBC's, the complex binds to macrophage Fc receptors and interferes with platelet destruction thus raising platelet count [1]. Anti-D is not effective in Rh negative patients. Rarely, it may cause life-threatening intravascular hemolysis. It costs less and also has lesser side effects compared to IVIG. In 20% of patients of ITP, thrombocytopenia is persistent for more than 12 months. These patients are diagnosed as chronic ITP. In such patients, evaluation should be done for diseases like SLE, HIV, von Willebrand disease etc. Splenectomy is the best intervention for long-term results in chronic ITP [2] of such children. Medical therapy with the drugs such as IVIG, steroids, and anti-D used in acute ITP are also useful. Rituximab [3] monoclonal antibody directed against CD 20, has also shown good results. Four weekly doses of 375 mg/m^2 are given. Up to 60% of cases may respond. Thrombopoietic agents such as romiplostim [4, 5] and eltrombopag [6, 7] are also now approved by FDA to treat chronic ITP in adults.

1.2. Neonatal alloimmune thrombocytopenia (NAIT)

It is characterized by transient severe thrombocytopenia. Maternal antibodies are transferred from placenta and are directed against paternally inherited fetal antigens present on fetal/neonatal platelets. Newborn can have severe thrombocytopenia, with platelets as low as 10,000/μL on first day of life. There can be bleeding in the form of petechiae, hematoma, GIT bleed, and ICH. Utero bleeding can result in hydrocephalus, seizures or UID [2]. Immunophenotyping of maternal, paternal, and neonatal platelets along with tests for antiplatelet antibodies in maternal and/or or fetal serum can confirm the diagnosis. Severe NAIT (platelet count <30,000/μL) or severe bleeding can be transfused washed and/or irradiated maternal platelets. IVIG (1 g/kg × 2 days) or methyl prednisolone 2 mg/kg/day can also be used for transient relief [2].

1.3. Drug-induced immune thrombocytopenia

Some drugs cause immune thrombocytopenia more often. Two types of antibodies can be formed: drug dependent and drug independent. With former, thrombocytopenia subsides when drug is stopped. In case of drug independent antibodies, drug-induced antibodies and low platelet count may persist for longer making it difficult to exclude ITP. Treatment starts with stoppage of culprit drug. If drug-induced thrombocytopenia is severe, IVIG or corticosteroids may be used. Platelets may be transfused if life-threatening hemorrhage is anticipated.

1.4. Heparin-induced thrombocytopenia and thrombosis

This syndrome occurs in 1–5% of adults and is less common in children. Usually occurs 5–10 days after administration of heparin but can occur within hours if patient is already sensitized to heparin. Incidence is higher with higher dose of heparin, bovine heparin (compared to porcine heparin), and unfractionated heparin (compared to low molecular weight heparin (LMWH)) [8].

1.5. Thrombotic microangiopathic disorders

It is characterized by thrombocytopenia, capillary thrombosis, and microangiopathic hemolytic anemia. Thrombosis and ischemic necrosis may lead to multiple organ dysfunction and failure. Two important disorders are: thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS).

1.6. Thrombotic thrombocytopenic purpura (TTP)

In addition to the above-mentioned triad, TTP patient, usually an adult has fever, renal malfunction, and central nervous changes. Subtle shifting neurological signs such as aphasia, blindness and seizures may be there. Coagulation studies are usually nonconclusive. Blood urea nitrogen and creatinine are at times elevated. Treatment is plasmapheresis. Rituximab, steroids or splenectomy may be indicated in refractory cases.

1.7. Hemolytic uremic syndrome

It is a classical example of community-acquired acute kidney injury in children. Clinical features are common to TTP but are seen usually in young children, whereas TTP is disease of adults (rarely in adolescents). History of enteritis due to toxin producing *Escherichia coli* and *Shigella dysenteriae* precedes renal involvement. Pneumonia causing Pneumococci can also cause HUS. As diagnosis is usually clinical, renal biopsy is rarely needed. Anemia is initially mild but progresses. Platelet count is in the range of 20,000–100,000/μL. Coombs test is usually positive. Renal insufficiency is variable. It can progress to renal failure. With early diagnosis and prompt care, mortality is <5%, another 5% become dialysis dependent, and 30% may have persistent renal insufficiency in diarrhea-associated HUS. Mortality can be >20% in Pneumococci-associated HUS.

1.8. Kasabach-Merritt syndrome

Thrombocytopenia is associated with giant hemangioma of infancy. Hemangioma usually solitary may be present over extremities, neck or trunk. Sometimes hemangioma is retroperitoneal. It usually presents in the initial weeks of life, increases in size, and then regresses. Platelet count may be very low with the evidence of DIC. Mortality is 40%. Surgical removal is effective but sometimes not possible. Radiation therapy, vascular ligation/embolization, glucocorticoid therapy, interferon α, vincristine and propranolol are other alternatives.

1.9. Other causes

Infections like systemic bacterial and fungal infections, acute viral infections (e.g., infectious mononucleosis, dengue, and HIV), immunization with live virus vaccines like MMR, hemophagocytic lymphohistiocytosis, malaria, etc., and procedures such as ECMO, hemodialysis, apheresis, liver transplant, etc., can also be associated with thrombocytopenia by increasing their destruction. Dengue is frequently associated with thrombocytopenia. It occurs because of decreased production as well as increased peripheral destruction. Platelet dysfunction is also associated. Drugs like heparin, quinidine, antibiotics like rifampicin and vancomycin also cause thrombocytopenia. Platelets get trapped in enlarged spleen in splenomegaly, portal hypertension, Gaucher disease, etc., and cause low platelet count.

1.10. Thrombocytopenia caused by impaired platelet production

Patients having thrombocytopenia due to the decreased platelet production are more likely to have severe bleeding than those having low platelet count due to the increased platelet destruction. Common causes of decreased production are:

A. **Hereditary disorders:** Examples are congenital amegakaryocytic thrombocytopenia, thrombocytopenia absent radius (TAR) syndrome, Fanconi anemia, Bernard-Soulier syndrome, May-Hegglin anomaly, Gray platelet syndrome, and Wiskott-Aldrich syndrome etc.

B. **Acquired disorders:** This includes megaloblastic anemia (folic acid and vitamin B12 deficiency), aplastic anemia, myelodysplastic syndrome, sepsis, cytotoxic chemotherapy

for malignancy, replacement of platelet precursors in bone marrow by malignant cells—leukemia, neuroblastoma, rhabdomyosarcoma, etc.

Thrombocytopenia is quiet common finding in medical practice and is associated with variety of diseases. It can be a benign disorder as ITP in otherwise healthy child. Same patient can die if his intracranial hemorrhage is not managed properly. Thrombocytopenia can be associated with malignant diseases like leukemia, when daily monitoring of platelet count and proper management becomes essential. A patient of dengue can die of dengue hemorrhagic fever and can also recover completely if thrombocytopenia is managed properly. Thus, it is very important to be aware of thrombocytopenia, so that the affected patients can be adequately managed.

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