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"Platelets Deficiency: The Silent Threat of Thrombocytopenia"

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ABSTRACT

A decrease in the platelet count in blood is a common feature of thrombocytopenia, hematological disorders. Homeostasis is maintained by Thrombocytes, or platelets, which are responsible for stopping bleeding after injury. This process is essential. A blood count below 150,000 per micro-liter is typically considered a diagnosis of the disease, known as thrombocytopenia, when platelets are present in measurable amounts within the range of 140,000 to 450000 per blood cell. Thrombocytopenia may cause severe bleeding, which can range from mild bruising and Petechiae (Red spot) to life-threatening complications. The risk of bleeding increases as platelet counts decrease, necessitating prompt diagnosis and treatment. Thrombocytopenia is associated with pre-eclampsia and high liver enzyme levels during pregnancy.

Keywords: Thrombocytopenia, hematological disorder, Thrombocytes, HELLP,Platelets.

INTRODUCTION :

Thrombocytopenia may be an incidental finding in patient which can present with fatal hemorrhage. The cause of Thrombocytopenia may vary from decreased production to increased destruction. It is a hematological condition characterized by an abnormally low platelets count, which predisposes individuals to bleeding's complications. This condition can arise from various etiologies , including bone marrow disorder , autoimmune diseases , infection and the use of certain medications. The clinical manifestation of thrombocytopenia range from asymptomatic cases to severe bleeding episodes , depending on the underlying cause and the degree of platelets depletion. [3,10,20]

Whenever low platelet count is reported in an asymptomatic patient , one must exclude pseudo- thrombocytopenia -a condition caused by the aggregation of platelets and resulting in false low count of platelets. [5,10]

Sometimes all patients having thrombocytopenia do not bleed. Etiology of thrombocytopenia is varied. It can be incidental findings when patients is being investigated as routine health check-up or for some other disease.The patients with thrombocytopenia can be healthy looking , very sick looking as in sepsis or may be in terminal stages of life as in leukemia. It can be congenital or acquired.[5,11,21]

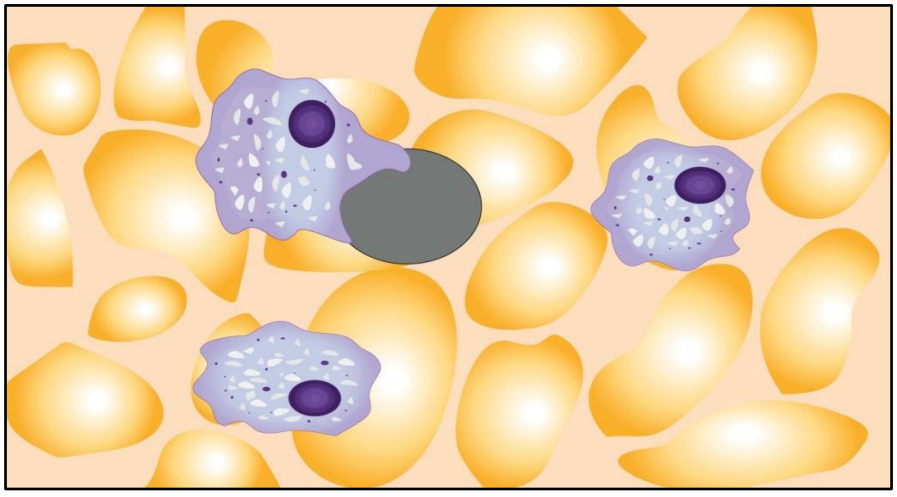


Figure 1: Thrombocytopenia blood smear

Algroithm for Thrombocytopenia Evaluation

Sequential Flow chart for Thrombocytopenia development and evaluation is shown in **Figure 2**.

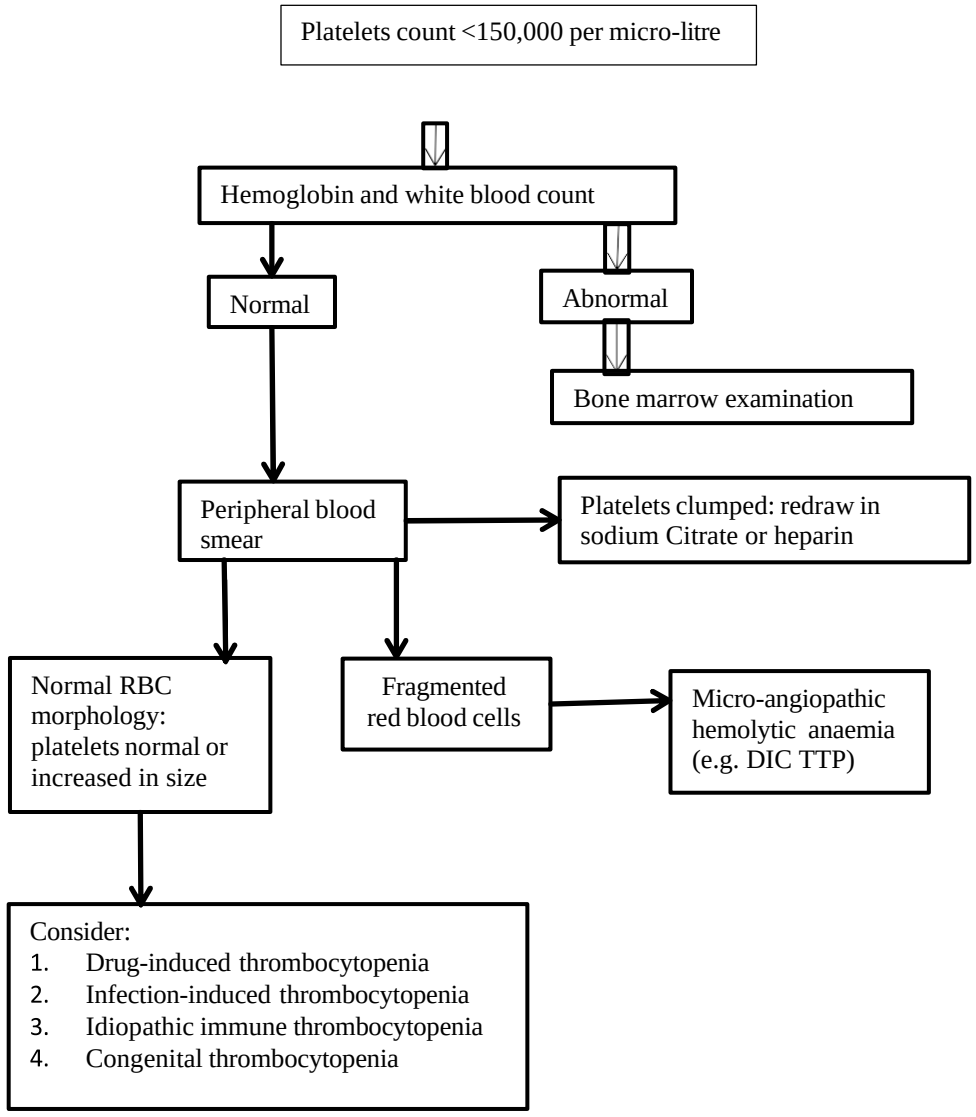


Figure 2: Algroithm for Thrombocytopenia Evaluation

Immune Thrombocytopenia

A low platelet count caused by an imbalanced interplay between regulatory and effective immune cells leads to increased platelet clearance and impaired thrombopoiesis in immune thrombocytopenia (ITP), an acquired condition. With an incidence ranging from 1.7 to 3.9 per 100,000/year and a prevalence ranging from 9.5 to 23.7 per 100,000 adults, it is a very frequent condition that affects both adults and children.In older individuals, the incidence is flipped, with women experiencing a higher prevalence than men. It affects roughly 5–10 out of 100,000 children annually.[7,10,18]
The International Working Group on ITP has defined ITP as either primary or secondary, depending on whether there is an evident precipitating trigger or a predisposing disease. ITP can be either a temporary or chronic disorder.Primary ITP, which is typified by isolated thrombocytopenia, affects 80% of newly diagnosed adults. Secondary ITP is brought on by or linked to another illness, such as a chronic infection (e.g., Helicobacter pylori, HIV, HCV, or CMV), a haematological condition (chronic lymphocytic leukaemia, large granular lymphocytic leukaemia, lymphoma, or autoimmune lymphoproliferative syndrome), or after receiving medication such as quinidine and heparin.[7, 10]

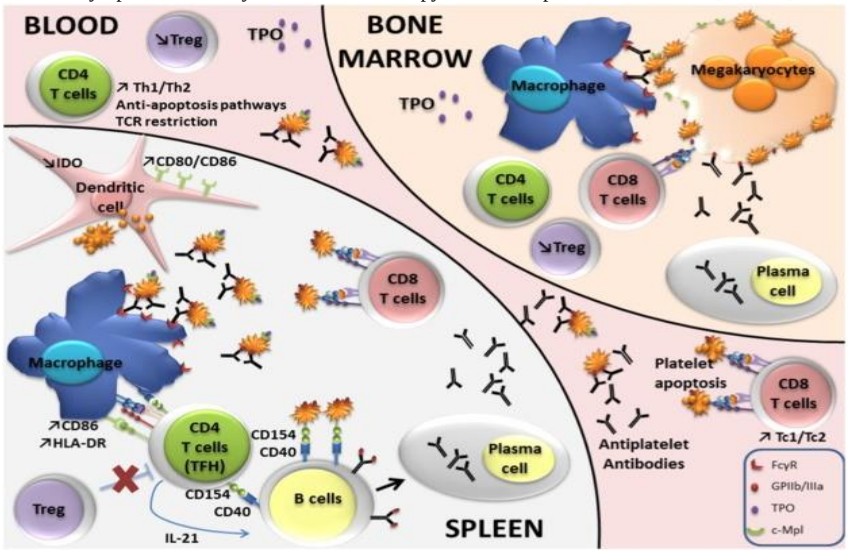
For newly diagnosed ITP patients, corticosteroids are still the primary line of treatment; nevertheless, immunosuppression should be minimised, a lesson that was especially more important during the COVID-19 pandemic. There is strong evidence to support the use of more recent medications as a follow-up treatment, including fostamatinib, rituximab, and thrombopoietin receptor agonists (TPO-RAs).[7,10,19]

Pathogensis

Immunocompromised autoimmune disease (ITP) presents an exceedingly complex pathogen. Various mechanisms, including defective thrombopoiesis, T-cell-mediated platelet destruction, and peripheral platelets destruction caused by antiplatelet antibodies, are responsible for the development of primary ITP. Every pathogenic process contributes to the development of thrombocytopenia.

Peripheral platelet destruction in the blood, spleen, and liver leads to peripheral thrombocytopenia and an immunological response against megakaryocytes, as well as reduced bone marrow production. A lack of regulatory T-cells in the spleen, blood, and bone marrow, as well as deficiencies in B and T cells that result in defective auto-antibody generation and aberrant T cell responses, contribute to the persistence of this autoimmune response.

It's possible that the pathophysiology of secondary ITP is similar to that of primary ITC. However, specific mechanisms have been found to differ in certain types of secondary lymphocytes. Antigen mimicry is a mechanism that involves antibodies against invasive proteins in interacting with specific epitopes on GPs, leading to thrombocytopenia caused by HIV, Helicobacter pylori, and Hepatitis C infections. [7,13,14].



.Figure 3: Pathogenesis of acute thrombocytopenia

Due to Decreased or defective production of platelets from bone marrow:

It is usually related to bone marrow problem.This can be due to various causes, including bone marrow failure or suppression[1] , inherited disorders , acquired conditions such as Myelodysplastic syndrome or leukemia , infection like HIV or hepatitis and certain medication like chemotherapy or antibiotics. Diagnosis involve a complete blood count to determine platelets count , a bone marrow biopsy to assess marrow function and morphology , and additional tests to rule out underlying conditions.[12]

Treatments focuses on addressing the underlying causes , supportive care like platelets transfusion , medications to stimulate platelets production , and in severe cases , bone marrow transplantation . Prompt diagnosis and treatments are crucial to prevents bleeding complication and ensure effective managements of thrombocytopenia resulting from decreased platelet production in the bone marrow.[8,12]

Drug induced Thrombocytopenia

Sulfasalazine which is commonly used in RA show modest side effect and cause of thrombocytopenia in approximately 10% of patients . Methyl-dopa which is alpha analogue of dopa the precursor of dopamine (DA) and NA is one of the first rationally designed anti-hypertensive develop thrombocytopenia in few patients. Cotrimoxazole given along with diuretics has caused higher incidence of thrombocytopenia. Sirolimus which is also called as rapamycin is medication used to prevent organ transplantation rejection can suppress bone marrow , mainly causing thrombocytopenia.[2,4,10,21]

Table 1: List of drugs responsible for Drug induced Thrombocytopenia [21]

Medication/substance.	**Drug class.**	**Proposed mechanism of Action.**
1) Alcohol	Ethanol	Suppression of Megakaryocytes production
2) Heparin	Anti-coagulant	Platelets factor 4 / heparin antibody
3) Gold salt	Anti-rheumatic	Auto-antibody
4) Hydrochlorothiazide	Anti-hypertensive	Suppression of Megakaryocytes production

Heparin - Induced Thrombocytopenia

Heparin-Induced Thrombocytopenia (HIT) is a rare but potentially life-threatening complication of heparin therapy. It occurs when the body's immune system mistakenly identifies heparin as a threat and produce antibodies against it. These antibodies then bind to platelets , leading to their activation , aggregation , and removal from the circulation , resulting in a low platelets count (thrombocytopenia).[4,6,10]
One study showed that patients who developed heparin-induced thrombocytopenia had a 20% in hospital mortality rate. Regardless of thrombosis developments .[2 ,10,19,21]

Infection-induced Thrombocytopenia:

Infection-induced thrombocytopenia is a condition where a bacterial or viral infection leads to a low platelets count , increasing the risks of bleeding and bruising . This occurs when the immune system mistakenly attacks and destroys platelets , or when the infection directly suppresses platelets production in the bone marrow. Common causes include sepsis , meningitis , pneumonia, , hepatitis , and CMV . It include the symptoms like fever , fatigue , bleedings , and petechiae. Diagnosis involves a platelets count , blood smear , and infectious diseases workup.[23]

Human Immunodeficiency Virus (HIV) Infection.

In person infected with HIV , thrombocytopenia may occur during the acute retro-viral syndrome coincident with fever , rash , and some throat. However , thrombocytopenia may also be a acquired immunodeficiency syndrome(AIDS) , occurring late in the course of HIV infection. HIV- related thrombocytopenia is particularly likely to occur in people who abuse drugs[22].

Inherited Thrombocytopenia

Inherited thrombocytopenia refers to a group of rare genetic disorders characterized by a low platelets count , which can increases the risks of bleeding and bruising. These conditions are caused by mutations in genes responsible for platelets production , function or survival. Example include Bernard-Soulier syndrome , Glanzmann thrombocytopenia , and wiskott-Aldrich syndrome.Symptoms include easy bruising, nosebleeds , and bleeding gums[8] .

A. Autosomal recessive thrombocytopenia

Genetic disorders called autosomal recessive thrombocytopenia are caused by genetic mutation in genes involved in platelet production, function or both. These disorders are rare. In humans, disorders are passed down through autosomal recessive inheritance with two copies of a modified gene required for each parent, and carriers with one mutated gene typically do not show symptoms. CAMT, TAR, and MYH-9 are all types of autosomal recessive thrombocytopenia. The clinical manifestations of each type differ, including abnormalities like low platelet count, ischemic megakaryocytes, and skeletal defects. The symptoms of autosomal recessive thrombocytopenia may include extended bleeding, mild bruising, and skin irritation. Diagnosis involves a complete blood test, platelet count analysis, blood tests, genetic testing, or family history evaluation. Treatment options are available depending on the severity and type of illness, including platelet transfusion, medication to stimulate platelets, anti-coagulant agents to minimize bleeding, and bone marrow transplantation in severe cases. Autosomal recessive thrombocytopenia can result in elevated rates of bleeding, anemia, infection, and skeletal abnormalities when not treated. [8].

B. Autosomal dominant thrombocytopenia.

Autosomal dominant thrombocytopenia are a group of rare genetic disorders characterized by low platelet count and impaired blood clotting or both. These disorder result from mutation in genes responsible for platelet production , function or both , and are inherited in an autosomal dominant pattern . this means that a single copy of the mutated gene is enough to cause the condition.[8] There are several types of autosomal dominant thrombocytopenia disorders , including MYH-9- Related disorders , Bernard-Soulier syndrome , and platelet disorder with associated myeloid malignancy and immunodeficiency . MYH9-Related disorder affect the platelet function and size, while Bernard-Soulier syndrome is characterized by large platelet size and thrombocytopenia.
Symptoms may include prolonged bleeding , easy bruising , petechiae , nosebleeds , and heavy menstrual bleeding. Diagnosis involve a complete blood count with platelet count , blood smear analysis , genetic testing and family history evaluation.Treatment option vary depending on the specific disorder and severity , they may include platelet transfusion , medication to stimulate platelet production , anti-fibrinolytic agent to reduce bleeding and bone marrow transplantation in severe case. Managing these disorder requires a multidisciplinary approach , involving hematologist , geneticists and other specialists.[8]

C. X-linked Thrombocytopenia.

X-linked thrombocytopenia is a rare genetic disorder characterized by low platelet count and impaired blood clotting . it affect males and females , although males are more severely affected due to their single X chromosome. This disorder is caused by mutations in the GATA1 gene , located on the X chromosomes , and is inherited in an X-linked recessive pattern , this means that males , who have one X chromosome , are more likely to express the condition , while females , who have two X chromosome are typically carriers but may exhibit mild symptoms. Incidence of X-Linked thrombocytopenia is estimated to be 1 in 1000,000 to 1 in 500,000 births , with affected population including males and females, although males are severely affected. The symptoms of X-Linked thrombocytopenia may include prolonged bleeding , easy bruising , petechiae , nosebleeds , and heavy menstrual bleeding. Diagnosis involve a complete blood count with platelet count , blood smear analysis , genetic testing and family history evaluation. Treatment option vary depending on the specific disorder and severity , they may include platelet transfusion , medication to stimulate platelet production. X-Linked thrombocytopenia requires a multidisciplinary approach , involving hematologist , geneticists and other specialists.genetic counseling is essential for families affected by X -linked thrombocytopenia to understand the risks and make informed decision.Early diagnosis and

personalized managements are crucial to preventing complication and improving outcomes . with proper care , individual with X-Linked thrombocytopenia can lead active and fulfilling lives.[8]

Treatments :

Treatment of immune thrombocytopenia (ITP) aims to increase Platelet count , reduce bleeding risk , and improve quality of life . The patients with a platelet count below 30,000 per cubic millimeter need treatment , and a platelet count of 50,00 per cubic millimeter is sufficient to assure safety . it has been generally accepted since 1977 that glucorticosteroid should be the first-line treatment for ITP [11,15]. Once the diagnosis is made , treatment should be initiated immediately. Standard Prednisolone 1 to 1% mg er kg per day was administered in 3 to 4 divided doses to mimic to body's natural cortisol circadian rhythm and reduce the risk of insomnia and other side effect. Glucocorticoids should not be used long-term due to various side effect such as hyperglycemia , infection , glaucoma , osteoporosis etc.[5,9,12,14,17] For refractory cases , second line treatment are employed , including rituximab , a monoclonal antibody targeting CD20- positive B cell and thrombopoietin receptors agonist (TPO-RAs) , such as romiplostim which stimulates platelet production. Additional treatment include azathioprine , cyclosphosphamide and vinca alkaloids . supportive care includes transfusion , antifibrnolytics and local wound care to manage bleeding complications[5,9,12,15,16,17]. In severe cases , emergency treatment like high-dose corticosteroids , IVIG , and platelet transfusion may be necessary.[5,12,15]

CONCLUSION :

Thrombocytopenia is a common disorders with myriad underlying causes. Careful attention to clinical history and physical examination , supplemented by carefully selected laboratory tests , is critical for
accurate and timely diagnosis. Because some rare causes of thrombocytopenia are immediately life- threatening , physicians should be familiar with both common and UN-common etiologies.

Effective managements of thrombocytopenia requires:[8]

I. Accurate diagnosis through comprehensive testing and evaluation .
II. Understanding of the underlying causes, including inherited and acquired forms , bone marrow failure and immune-mediated thrombocytopenia.
III. Timely intervention with appropriates treatment options , such as platelet transfusion , medications and bone marrow transplantation .
IV. Ongoing monitoring and managements to prevents complication and optimize outcomes.
V. Continued research and education to improve our understandings of the condition and uncover new treatments.

By taking a comprehensive and multidisciplinary approach to thrombocytopenia , healthcare professional can provide optimal care and improves the lives of individuals affected by thrombocytopenia.

Advance in medical research and collaborative efforts , however , offer hope for improving treatment outcomes and enhancing patient care . ongoing investigation into the novel therapies , including monoclonal antibodies and gene therapies , hold promise for addressing unmet needs.[9] Personalized medicine approach , tailored to individual patient characterized , have shown potential in optimizing treatment efficacy and minimizing side effect. Early diagnosis and intervention significantly improves outcomes , underscoring the importance of awareness and education among healthcare providers and patients.

Multidisciplinary care teams , comprising hematologists , primary care physicians , and specialized nurses , play a vital role in ITP management. Regular monitoring adjustments to treatment plans , and attention to pyschosocial needs ensure comprehensive care. The development of biomarkers for diagnosis and treatment response will revolutionize ITP managements. Comparative effectiveness research and international registries facilitate knowledge sharing , informing best practice and guiding future research .[18]

In conclusion , immune thrombocytopenia presents ongoing challenges , but collective efforts and emerging research held improved treatment outcomes and enhanced quality of life for affected individuals. Continued collaboration , innovation , and patients-centered care will drive progress , reducing morbidity and improving survival rates. Through perseverance and dedication , the medical community can transform the lives of those affected by ITP. , fostering hope , and improved well-being. [6]

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