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Review Article

Immune Thrombocytopenic Purpura (ITP): A Comprehensive Review

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ABSTRACT
Immune thrombocytopenic purpura (ITP) is a condition where the body's immune system mistakenly attacks and destroys platelets, resulting in a decreased platelet count. This leads to the development of purpura on the skin and may cause bleeding episodes due to the presence of antibodies that target and damage platelets. Excluding the usual suspects helps in identifying the underlying causes of thrombocytopenia. The diagnosis of immune thrombocytopenia (ITP) relies on clinical suspicion and the presence of thrombocytopenia, as indicated on a normal peripheral smear. Bone marrow examination is performed in order to eliminate the possibility of leukemia, myelodysplastic syndrome or aplastic anemia. Circulating platelets become sensitized due to the presence of IgG autoantibodies. As a result, these cells are swiftly eliminated by antigen-presenting cells, such as macrophages, which are primarily found in the spleen, and occasionally in the liver or other parts of the monocyte-macrophage system. In response, the bone marrow increases the production of platelets. ITP frequently occurs in healthy individuals, including children and young adults, following a viral infection. Certain medications can also lead to immune thrombocytopenia, which is practically indistinguishable from idiopathic thrombocytopenic purpura. Children usually recover spontaneously within a few weeks or months, and splenectomy is rarely required. However, spontaneous remissions necessitating splenectomy in young adults are uncommon in the first several months following diagnosis. This article discusses the most frequent causes of ITP and outline an interdisciplinary diagnostic and therapeutic approach based on current research.

Key Words: Immune thrombocytopenia, Hematological diagnosis, Bone marrow examination, Treatment

INTRODUCTION

Immune thrombocytopenia (ITP) is one of the most common acquired bleeding disorders in paediatrics patients, with the incidence of symptomatic disorders ranging from approximately 3 to 8 per 100,000 children per year. Immune thrombocytopenia is a diagnosis of exclusion. It is characterized by immune-mediated accelerated platelet destruction and suppressed platelet production. ITP occurs as primary (isolated) ITP or as secondary ITP associated with other conditions such as autoimmune diseases and infections. The diagnosis is based on clinical suspicion and a normal peripheral smear except for thrombocytopenia. However, in many cases, a bone marrow examination is done to rule out leukemia, myelodysplastic syndrome, or aplastic anemia. According to the consensus recommendations, a bone marrow examination is not recommended in isolated thrombocytopenia, even if steroids are considered first-line treatment (recommendation grade 2C).[1]

Acute ITP is most common in children under 10 years of age, affects both male and female equally, and is most common in late winter and spring. Chronic ITP affects adolescents more often than young children, with women more often affected than men. Unlike acute ITP, it does not tend to be seasonal. Patients with chronic ITP are more likely to have underlying autoimmune disease, with up to one-third having clinical and laboratory manifestations of collagen vascular disease. Chronic ITP patients have fluctuating clinical course. The bleeding episodes may last days or weeks and may be intermittent. It is believed that platelet destruction in ITP involves autoantibodies directed against glycoproteins normally expressed on the platelet membrane. ITP is usually manageable with immunosuppressive therapy.[2,3] A similar form of autoimmune thrombocytopenia may also be associated with chronic lymphocytic leukemia, lymphoma, SLE, infectious mononucleosis, and other bacterial and viral infections. Some drugs can also cause immune thrombocytopenia that is indistinguishable from ITP.

The International Working Group defines ITP according to the following clinical stages:[4]

1. Newly diagnosed ITP is in the first three months post-diagnosis
2. Persistent ITP: 3-12 months duration
3. Chronic ITP: Greater than 12 months
4. Refractory ITP is the failure of splenectomy

ETIOLOGY

Immune thrombocytopenic purpura can be caused by infections such as human immunodeficiency virus (HIV), cancer (e.g., adenocarcinoma and lymphoma), and common variable immunodeficiency and autoimmune diseases such as systemic lupus erythematosus, autoimmune hepatitis, and thyroid disease.[5] IgG-mediated autoantibodies against platelet membrane proteins such as GP IIb/IIIa complex, GP Ib/IIa, and GP VIGP result in platelet destruction. Medications such as aspirin, amino salicylic acid, carbamazepine, cephalothin, digitoxin, phenytoin, acetazolamide, meprobamate, methyldopa, quinidine, rifampin and sulfamethazine have all been linked to autoimmune reactions.

Evans syndrome is an ITP associated with autoimmune hemolytic anemia. Immune thrombocytopenic purpura is a diagnosis of exclusion and patients usually present with a history of mucocutaneous bleeding, sudden development of a petechial rash, or bruising.[6] Table-1 shows a list of causes and syndromes associated with ITP.

Table-1: Causes and syndromes associated with Immune thrombocytopenic purpura (ITP)

Infection	Immune alteration
Human immunodeficiency virus (HIV)	Antiphospholipid syndrome
Hepatitis C	Systemic lupus erythematosus
Cytomegalovirus	Evans syndrome
Varicella zoster virus	Hematopoietic cell transplantation
Bacterial	Chronic lymphocytic leukemia
	Common variable immunodeficiency
	Autoimmune lymphoproliferative syndrome

CLINICAL FINDINGS

ITP is diagnosed based on clinical findings. The most typical clinical manifestation in children includes a purpuric rash and easily bruising. About one-third of instances include bleeding from mucous membranes, such as nosebleeds or gingival bleeding. The gastrointestinal tract, vaginal mucosa, urinary tract, retina, and conjunctivae are additional areas where bleeding can occur. In acute ITP, the viral illness can trigger an immune response that leads to the destruction of platelets in the body, resulting in a decrease in platelet count. This can cause symptoms such as easy bruising and petechiae. Other than the signs of bleeding, the physical examination's findings are entirely normal. Negative examination includes the absence of lymphadenopathy and hepatosplenomegaly. Lymphadenopathy and/or hepatosplenomegaly should raise the consideration of other diseases, particularly leukemia, as these signs may indicate an underlying condition that needs to be investigated. Hyperbilirubinemia, pallor and splenomegaly are features of a concomitant hemolytic anemia, which can be seen in association with thrombocytopenia in Evans syndrome and other autoimmune diseases. In chronic ITP, the presentation is usually more gradual, with mild symptoms or no symptoms at all.

LABORATORY FINDINGS

Complete blood count (CBC) shows decreased platelet count (below $30x10^9$/L) for over three months. Peripheral blood smear shows large platelets and tiny platelet fragments (microparticles). Bleeding time is prolonged with normal PT and APTT levels. Mean platelet volume (MPV) and platelet distribution width (PDW), found in automated cell counters provide useful information in the evaluation of patients with ITP. The presence of numerous mega thrombocytes results in high MPV values. Platelet distribution width is also increased suggesting abnormal degree of platelet anisocytosis. Bone marrow examination shows normocellular marrow with increased numbers of megakaryocytes with focal loose clustering and in normal morphology and distribution (Figure-1). Megakaryocytes are not abnormally localized or clustered. However, in certain diseases or conditions such as myeloproliferative neoplasms, megakaryocytes can become abnormally localized or form clusters in the bone marrow. In Castelman–Kojima syndrome increased and clustered megakaryocytes have been described together with reticulin fibrosis. Coomb's test reveals anti-platelet antibodies that have been attached to the patient's platelets. However, it should also be noted that antibody analysis focal to the platelet glycoproteins IIb/IIIa, Ib/IX and Ia/IIa are of low sensitivity and seldom efficacious.[4]

Indirect Coomb's test uses a pool of normal donor platelets to detect free serum antibodies against platelets, usually anti-glycoprotein IIb/IIIa antibodies. Lymphocyte activation by autologous platelets, lymphocyte activation by platelet-antibody immune complexes, phagocytosis of platelet-associated IgG by competitive binding assays, radiolabeled Coombs antiglobulin tests, fluorescein-

labelled Coombs antiglobulin tests and ELISA are all tests that can detect anti-platelet antibodies.

In chronic ITP, the platelet count at presentation is generally between 20 and 70 x 10^9/L (20,000 and 70,000/mcL). Additional tests should be performed before making the diagnosis of chronic ITP, including evaluation for autoimmune disease and testing for anti-double-stranded DNA (anti-dsDNA), anti-Smith DNA, anti-cardiolipin, and anti-beta2 GP-I antibodies. SLE can be diagnosed by a high serum level of anti-Smith and anti-dsDNA antibodies. To rule out autoimmune thyroid disease, thyroid investigations are done, which have been linked to chronic ITP. A Coomb's test and measurement of the reticulocyte count are employed to exclude Evans syndrome (immune thrombocytopenia with autoimmune hemolytic anemia).

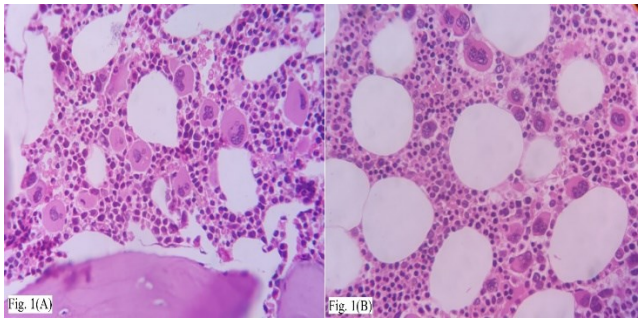

Figure-1: Bone marrow trephine biopsy specimen, immune thrombocytopenic purpura, showing megakaryocytes are increase in number with focal loose clustering having normal morphology (H & E × 40)

TREATMENT

The main indication for active therapy in patients with low platelet count is when there is acute bleeding or if emergent surgery is imminent. If there is no significant bleeding and the platelet count is above 30,000/dL, transfusion may be withheld.[4] Severe bleeding is seen in about 20% of children and 10% of adults, usually occurring when the platelet count falls below 30,000/dL. Cutaneous and mucosal bleeding may occur when the count is below 20,000/dL, while life-threatening hemorrhage, such as intracranial bleeding, typically occurs when the count is below 10,000/dL.

When treatment is necessary, one apheresis unit or 4 to 6 pooled platelet units may be given. Most children recover spontaneously without any long-term complications. Intravenous immunoglobulin (IV IgG) is the preferred treatment for severe cases, with a 5-day course of 400 mg/kg/d. This treatment leads to a response in over 70% of patients within 1 to 4 days, but the response is usually short-lived, often requiring repeated courses.

Patients with active bleeding require corticosteroids (Prednisone 1 mg/kg/day) to prevent further destruction of platelets. Approximately 60% of patients respond well to corticosteroid treatment within two weeks. However, it is important to note that the use of steroids in pregnant women during the first trimester carries a small risk of cleft palate. Dexamethasone (40 mg/day for 4 days) use in pregnancy can also increase the risk of abruptio placenta and premature rupture of fetal membranes.

Thrombopoietin Receptor Agonists (TPO-RAs): These drugs stimulate the production of platelets by binding to the thrombopoietin receptor on bone marrow cells. Examples of TPO-RAs include romiplostim and eltrombopag. They have shown to be effective in increasing platelet counts and reducing bleeding episodes in ITP patients. The standard treatment dose is 375 mg weekly for four weeks. These medicines stimulate the JAK-STAT pathway with subsequent megakaryocytic proliferation and platelet production.[7]

Monoclonal Antibodies: Monoclonal antibodies like rituximab and fostamatinib have been used in the treatment of ITP. Rituximab targets and destroys B cells, which are involved in the production of autoantibodies that attack platelets. Fostamatinib inhibits the activity of spleen tyrosine kinase (SYK), which decreases antibody-dependent phagocytosis of platelets.[7,8] The overall response rate was 43% within 12 weeks of therapy, and 18% have stable disease.[9,10] Responses can occur despite prior failures with thrombopoietins, rituximab, or splenectomy.

The drugs efgartigimod and rozanolixizumab are being tested for both ITP and myasthenia gravis.[7,11] They are antibody fragments that target the neonatal Fc receptor (FcRn), thereby inhibiting IgG recycling. IgG's half-life is shortened, bringing it down to normal or sub-pathogenic levels. Investigators have found response rates of 38% with efgaritigimod and 50% with Rozanolixizumab. Sutimlimab is a humanized monoclonal antibody against C1s, a complement pathway inhibitor.[12] In ITP, it decreases complement-dependent cytotoxicity, thereby decreasing platelet destruction.[7] Studies have revealed responses of 33%, many within days. However, their overall sample sizes were small. Rilzabrutinib is a Bruton Tyrosine Kinase-inhibitor (BTKI) with efficacy in the treatment of ITP.[7,10] It inhibits Fc (gamma) signal transduction causing a decrease in platelet phagocytosis and auto-antibody production. Studies have shown a response rate of about 40% to 50%, with minimal toxicity and a time to respond of about a week.

Immunosuppressive Drugs: Immunosuppressive drugs like azathioprine, mycophenolate mofetil, and cyclosporine are sometimes used in the treatment of ITP. These drugs work by suppressing the immune system and reducing the production of autoantibodies that attack platelets.

Splenectomy: Although splenectomy has been a long-standing treatment for ITP, newer surgical techniques and minimally invasive approaches have made the procedure safer and more effective. Splenectomy involves the removal of the spleen, which is responsible for the destruction of platelets in ITP. Removing the spleen can help increase platelet counts and reduce bleeding episodes.

Combination Therapies: In some cases, a combination of different treatments may be used to manage ITP. For example, a TPO-RA may be combined with an immunosuppressive drug or a monoclonal antibody to achieve better outcomes.

Newer Drugs under trial for ITP[13]
Daratumumab is an IgG1k monoclonal antibody that has been approved for use in multiple myeloma (MM). It has also shown potential in treating refractory post HSCT Evans syndrome patients. However, the current status of its under-research trial for immune thrombocytopenia (ITP).

Mezagitamab (TAK-079) is another anti-CD38 antibody that is an IgG1 monoclonal antibody. It has shown promising results in various trials. It binds to CD38 at a concentration of 0.7 nM and targets plasma cells, plasmablasts, NK cells, and activated T/B cells. In a monkey model of collagen-induced arthritis, it has demonstrated efficacy comparable to dexamethasone. In a study involving healthy humans, single low doses of Mezagitamab resulted in a significant reduction in NK cells (97%-99%) with recovery by day 6-8. It also led to a 90% decrease in plasmablasts within 2 days, with recovery by day 29-59. Additionally, there was a reduction in IgG, IgA, and IgM levels, which recovered by day 78. However, the current status of Mezagitamab trials in ITP is under research evaluation.[13]

DIFFERENTIAL DIAGNOSIS

Drug-induced thrombocytopenia: Certain medications, such as heparin, quinine, and certain antibiotics, can cause immune-mediated destruction of platelets.

Thrombotic thrombocytopenic purpura (TTP): This is a rare condition characterized by the formation of blood clots in small blood vessels, leading to platelet consumption and subsequent thrombocytopenia.

Hemolytic uremic syndrome (HUS): Similar to TTP, HUS is characterized by the formation of blood clots in small blood vessels, leading to platelet consumption and subsequent thrombocytopenia. It is often associated with gastrointestinal infections, particularly Escherichia coli (E. coli) infection.

Disseminated intravascular coagulation (DIC): DIC is a condition characterized by widespread activation of the clotting cascade, leading to the formation of blood clots throughout the body. This can result in platelet consumption and subsequent thrombocytopenia.

Sepsis: Severe bacterial infections can lead to immune-mediated destruction of platelets.

PROGNOSIS

The prognosis of immune thrombocytopenic purpura (ITP) varies depending on several factors, including the underlying cause, age, overall health, and response to treatment. In general, the prognosis for ITP is considered good, with most individuals experiencing spontaneous remission within a few months to a year.

Acute ITP, which is the most common form in children, often resolves on its own without any long-term complications. Approximately 80% of children with acute ITP recover within 6 months, even without treatment.

Chronic ITP, which lasts for more than 6 months, can be more challenging to manage. However, with appropriate treatment, most individuals with chronic ITP can achieve remission or maintain a stable platelet count. The prognosis for chronic ITP is generally favorable, with the majority of individuals living normal, healthy lives. However, some individuals may require ongoing treatment or experience occasional relapses.

COMPLICATIONS

In rare cases, ITP can be severe and lead to life-threatening bleeding complications. This is more common in older adults or individuals with other underlying medical conditions. However, with prompt medical intervention and appropriate treatment, the prognosis for severe ITP can still be favorable.

It is important for individuals with ITP to work closely with their healthcare providers to manage their condition and monitor their platelet counts regularly. With appropriate medical care and lifestyle adjustments, most people with ITP can lead normal lives and have a good prognosis.

CONCLUSIONS

Immune thrombocytopenic purpura is an autoimmune disorder characterized by the destruction of platelets by autoantibodies. Management of ITP involves the use of corticosteroids, immunoglobulins, and other immunosuppressive agents as first-line treatments. It also explores the use of splenectomy, rituximab, and other therapies for refractory cases. The paper acknowledges the limitations of current management strategies and highlights the need for further research to develop more effective

treatments. It also emphasizes the importance of individualized treatment plans based on the patient's specific etiology and clinical presentation. At present, there is no cure for Immune Thrombocytopenic Purpura.

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