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Recent Development of Nanomaterials for The Management of Immune Thrombocytopenia

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Abstract:

Immune thrombocytopenia (ITP) is caused by autoimmune platelet disintegration and has no known aetiology. Splenectomy, immunosuppressants, intravenous immunoglobulins, anti-D immunoglobulins, rituximab, thrombopoietin receptor agonists, corticosteroids, and other drugs can treat chronic ITP. Most people improve with existing treatments, although a small minority may develop resistance or not improve. Numerous processes suspected to contribute to ITP pathogenesis have been identified in recent years, and attempts are underway to create new treatments that target these pathways. Nanomaterials and other novel agents offer an alternative to transdermal drug delivery systems including patches, gels, sprays, and lotions, but transport mechanisms must be understood. Current ITP approaches and novel treatments are summarised below.

Keywords: Development, Nanomaterials, management, immune thrombocytopenia.

Introduction

Immune thrombocytopenic purpura (ITP) is a haematological condition marked by the presence of autoantibodies that enhance the immune system's destruction of platelets, resulting in consistently low levels of blood platelets. Inadequate platelet count might enhance bleeding as platelets play a vital role in blood clotting. This condition was formerly referred to as Werlhof's disease. This leads to the untimely breakdown of platelets by the reticuloendothelial system, which is mostly found in the spleen and sometimes in the liver. Patients may have mild mucocutaneous bleeding or life-threatening haemorrhage, or they may be asymptomatic. Within five years of being diagnosed with ITP, 15% of individuals are likely to develop severe bleeding that requires hospitalisation, even though only 5% of people have severe bleeding at

the time of diagnosis. It is crucial to acknowledge that the likelihood of experiencing serious bleeding differs in individuals with ITP. Patient with ITP who have a low platelet count, a history of bleeding, and specific comorbidities are more likely to experience severe haemorrhage. Acetazolamide, aspirin, digitoxin, methyldopa, sulfamethazine, cephalothin, rifampin, phenytoin carbamazepine, meprobamate, and quinidine are drugs that might cause the development of immune thrombocytopenic purpura (ITP) in certain persons by stimulating the creation of autoantibodies. One prominent view suggests that the development of autoantibodies against platelets is the main underlying cause of ITP (Piel-Julian et al., 2018; Adelborg et al., 2019; Provan et al., 2022).

1 Thrombocytopenia

Thrombocytopenia is indicated by a platelet count below 150,000/microL. The three primary causes of thrombocytopenia are reduced platelet production, increased platelet disintegration, and altered platelet distribution. Consider the potential of pseudothrombocytopenia. It is crucial. Although thrombocytopenia can be caused by both hereditary and environmental factors, the latter is more prevalent in elderly individuals. Thrombocytopenia is classified into three numerical phases. A moderate platelet count is between 50,000 and 100,000/microL, while a mild range is 100,000 to 150,000/microL. Low: 50,000 microliters or less; classified as acute. However, thrombocytopenia is typically not detected by clinical methods until the platelet count falls below 100,000/microL. The platelet counts of over two-thirds of adult patients are stabilised by the current treatments for chronic ITP, which include splenectomy, rituximab, corticosteroids, and thrombopoietin receptor agonists (TPO-RA). Conventional medications continue to be ineffective for a significant number of individuals, underscoring the urgent necessity for effective alternative medications. The immune response mechanism that

induces immune thrombocytopenic purpura (ITP) remains incompletely comprehended by researchers to this day (Zufferey et al., 2017; Chang et al., 2019).

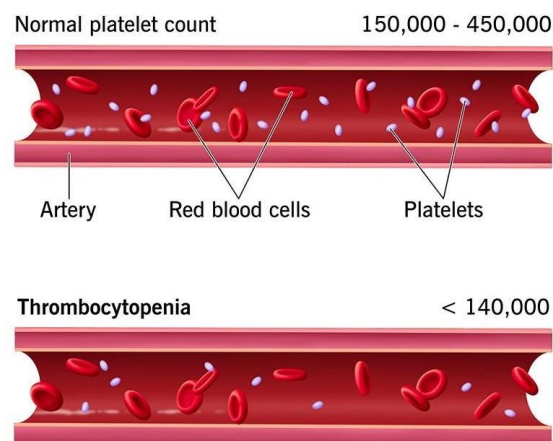


Figure 1 Thrombocytopenia

It was previously believed that thrombocytopenia could only be caused by the significant breakdown of platelets mediated by antiplatelet antibodies. But new research shows that T-cell cytotoxicity and decreased megakaryocyte synthesis are also involved in ITP production. Much progress has been made in understanding the multiple processes that contribute to the development of ITP, and new treatments targeting particular pathways are currently in the works. A summary of current and future ITP treatments as well as methods is the goal of this review (Perera et al., 2017; Sukumar et al., 2021).

1.1 Epidemiology of Thrombocytopenia

According to the latest consensus reached by the Thrombocytopenia International Working Group, the annual incidence of ITP differs between adults and children. Annual cases of ITP are anticipated to range from 2 to 7 per 100,000 individuals. There is an even split between the sexes in the two age ranges when these events take place: 20–30 and 60+. People of any age can get infected with ITP (Audia et al., 2017).

1.2 Diagnosis

Rather than being a sickness in and of itself, thrombocytopenia is a diagnostic condition. For complete information, it is recommended to consult patients who have experienced thrombocytopenia. In order to determine the root of a health problem, comprehensive analysis and laboratory testing are required. Further research is needed to fully understand certain aspects of the thrombocytopenia issue. Infection, pre-existing hematologic disease, non-hematologic diseases, a hereditary predisposition to haemorrhage and/or thrombocytopenia, recent live viral vaccination, inadequate dietary status, pregnancy, organ transplantation from a donor with a platelet alloantigen sensitization, and transfusions of platelet-containing

products into an allo-sensitive recipient can all lead to low platelet counts. Important things to know are alcohol use history and HIV risk factors. When treating asymptomatic patients with low platelet counts, doctors first and foremost want to rule out the possibility that the patient's low platelet counts are due to artifactual or "pseudo thrombocytopenia" rather than a real medical condition (Audia et al., 2017; Consolini et al., 2016).

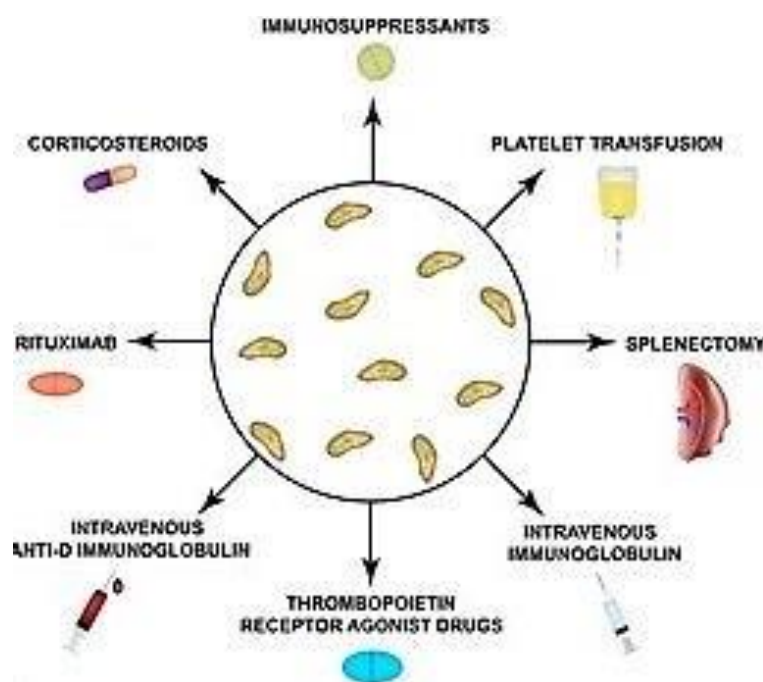


Figure 2 Diagnosis of Thrombocytopenia

Given the occurrence of congenital thrombocytopenia, it is also vital to investigate the family's medical history. Both episodes of bleeding and the administration of heparin can affect people with thrombocytopenia. Paroxysmal nocturnal hemoglobinuria and disseminated intravascular coagulation may be associated with the thrombosis clinic. Petechiae, purpura, bleeding gums, nosebleeds, significant menstrual bleeding, brain haemorrhage, and other symptoms can be found during a physical examination and used to diagnose thrombocytopenia. It is possible to successfully cure some symptoms produced by thrombosis as well. It is recommended that all patients who exhibit symptoms of thrombocytopenia get a peripheral blood smear test. Each part shows anything from three to 10 visible platelets when examined at a standard magnification. When it comes to diagnosing thrombocytopenia or helping patients rule out false positives, peripheral smears are invaluable (Bhattacharjee et al., 2020).

1.3 Classification of Thrombocytopenia

Thrombocytopenia occurs due to three main pathophysiological mechanisms: sequestration, accelerated breakdown, and reduced production. The main reason for the commonly seen thrombocytopenia is rapid breakdown. At a certain juncture, the pace at which platelets were

breaking down surpassed the pace at which they were being produced. Platelet destruction can be caused by forces originating from outside or inside the cell. Thrombocytopenia, a disorder characterised by a low platelet count, occurs when megakaryocytes in the bone marrow are suppressed. This suppression can be caused by a lack of myelosuppressive medicines, radiotherapy, or aplastic anaemia (Koch et al., 2021). Megakaryocytic hypoplasia or aplasia without any other associated conditions is extremely uncommon. Megakaryocytic thrombocytopenia is a medical illness marked by the presence of macrocytosis, diserythropoiesis, and other abnormalities in the production of several cell types. It can either be present from birth or acquired later in life. Secondary thrombocytopenia, caused by increased splenic platelets, is distinguished by its capacity to distinguish between abnormal and normal platelets. Platelet levels are elevated in illnesses such as sepsis, preeclampsia, and immunological thrombocytopenia. Conversely, diseases such aplastic anaemia, which cause a decrease in platelet formation, lead to a notably high rate of platelet degradation.

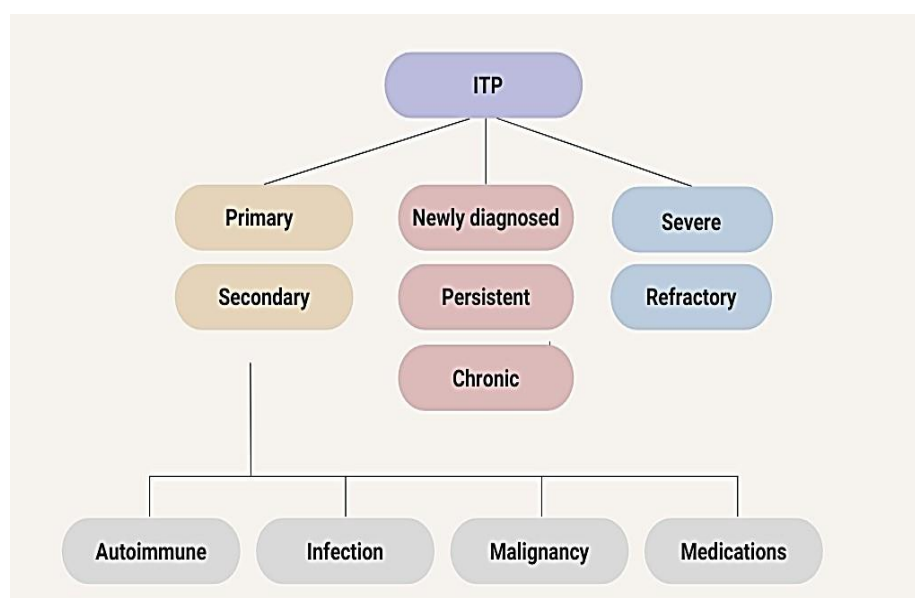


Figure 3 Classification of Thrombocytopenia

2 Treatment of Thrombocytopenia

Various approaches can be employed to treat thrombocytopenia, such as quitting the causative medicine, addressing the underlying infection, administering immunoglobulin G (IgG) replacement treatment, or utilising chemotherapy specifically tailored for chronic lymphoblastic leukaemia. Unfortunately, the origin of thrombocytopenia is still unclear, and its cause is only determined in a small percentage of patients. Moreover, the platelet count may not be necessarily modified due to the "curing" of the underlying medical disease that produced the ITP. Platelet transfusion can be used in cases of sudden bleeding to rapidly raise platelet

levels, particularly when the cause of low platelet count is not understood and is not considered to be related to the immune system. Platelet transfusion should only be used in cases of severe bleeding that could be life-threatening. It should be given after intravenous immunoglobulin to safeguard the platelets. Alternatively, the advantage could be insignificant or, at most, very temporary. In cases when the underlying cause of thrombocytopenia is not identified and there are no medical reasons to avoid it, corticosteroids may be used to raise the number of platelets in the blood. The primary cause of thrombocytopenia is the main aspect that determines the need for more specific treatment plans (Saluja et al., 2022, Porcelijn et al., 2018).

2.1 Initial therapy

The recommended initial treatment for asymptomatic adult patients newly diagnosed with ITP is to maintain a platelet count of $<20-30 \times 10^9/L$. The doctors advised that the treatment approach for each patient should incorporate distinct goals, such as the prevention of bleeding, the mitigation of toxicity, and the enhancement of quality of life (Rabbolini et al., 2017).

2.1.1 Corticosteroids:

Oral corticosteroids are the first choice of treatment for people with chronic ITP, unless there is a reason to avoid corticosteroids or a requirement for a faster increase in platelet count due to sudden bleeding. Oral prednisone is the most commonly prescribed corticosteroid. It is taken by mouth at a dose of 0.5-2 mg/kg/day for a duration of 2-3 weeks. The medicine should be gradually reduced in dosage with the goal of completely stopping its use within a period of 6-8 weeks. The initial response rate ranges from seventy to eighty percent; yet, the long-term remission rates are below average and the relapse rates are significant. Administering Dexamethasone at a larger dosage has also been proposed as a method to increase the overall amount of corticosteroid delivered within a short period of time. Based on a comprehensive analysis of nine randomised studies, it was shown that there was no discernible disparity in the long-term rates of response and overall platelet response after six months between the administration of high-dose dexamethasone and oral prednisone. In contrast, the group treated with dexamethasone showed a greater overall increase in platelet count and experienced fewer negative side effects after 14 days. The choice of treatment should be based on the unique attributes of each patient, as both forms of corticosteroids are effective (Laghmouchi et al., 2021; Swinkels et al., 2018).

2.1.2 Anti-D immunoglobulin:

Anti-D immunoglobulin specifically targets the D antigen of the Rh blood group system. It works by competitively binding to Fc receptors on macrophages, blocking the breakdown of antibody-coated platelets by erythrocytes coated with anti-D. Therefore, it is exclusively

accessible to those with Rh-positive blood type and an intact spleen. It is typically advised to give a solitary intravenous infusion with a dose of 50 to 75 µg/kg, and a reaction should be noticed within 48 hours. In general, the rate at which people respond is around 65%, and this response usually lasts for a period of three to four weeks. Although the use of anti-D immunoglobulin therapy is not very common, there have been reports of severe intravascular hemolysis that can be life-threatening, which has caused a lot of concern (Kohli et al., 2019).

2.2 Second line treatments

Most individuals with ITP exhibit a positive response to first therapies, such as intravenous immunoglobulin (IVIG) or glucocorticoids. Nevertheless, a significant number of cases necessitate further therapy as a result of the challenges associated with sustaining long-term results. These individuals may be contemplating a splenectomy as a surgical alternative or pharmaceutical therapy, such as rituximab or TPO-RA (Laghmouchi et al., 2021).

2.2.1 Rituximab:

Rituximab, a chimeric monoclonal antibody that particularly targets CD20 on B lymphocytes, has been proposed as a viable therapy option for ITP due to the significant role B cells play in its development. Anti-CD20 targeted therapy effectively eliminates CD20+ B cells and reduces the formation of anti-platelet antibodies. Studies on ITP have shown that the standard dose of rituximab has resulted in response rates of 20-30% after 2-5 years and 60-80% after 6-12 months. In addition, we assessed the effectiveness and safety of administering low-dose rituximab in order to ascertain its lack of adverse reactions. The comprehensive study found that the total response rate for ITP patients who received low-dose rituximab was 63%, while the full response rate was 44%. Rituximab therapy, when administered at low levels, exhibits a favourable safety profile and demonstrates efficacy (Swinkels et al., 2018).

2.2.2 Splenectomy:

Splenectomy is a successful treatment because the spleen is where platelets are primarily destroyed and where anti-platelet antibodies are produced. Around 70-80% of patients who undergo splenectomy get a prolonged positive response to chemotherapy for a duration of at least six months. Additionally, 60-70% of patients maintain this response for a period of five years or more. However, the inclination towards this method is declining because of the possibility of problems and the existence of efficient non-surgical therapeutic alternatives. The use of laparoscopic splenectomy is favoured over open splenectomy due to its decreased occurrence of procedural problems. Moreover, the risk of infection in instances of sepsis and venous thromboembolism is elevated by 2.1% and 2-4 fold respectively following a splenectomy. Once chronic ITP has been definitively diagnosed, the option of splenectomy

should only be entertained, taking into account the potential long-term complications associated with surgery and the chance of spontaneous remission of ITP during the initial year of diagnosis (Kohli et al., 2019).

3 Nanomaterials for The Management of Immune Thrombocytopenia

Recent developments in nanotechnology and nanomaterials have made possible the use of nanoparticles including metallic nanoparticles, micelles, polymeric nanoparticles, quantum dots (QDs), and others in brain research and studies, thereby expanding the horizons of biomedical science. Nanoscale materials have unique molecular properties that allow them to interact with biological systems. Among these characteristics include a tiny size, high stability, and a surface-to-volume ratio that can be uniform or modified to vary. Neurotoxicity, nausea, anaemia, hair loss, and gastrointestinal irritation are some of the potential side effects of using chemotherapy and medicines. Nanoparticles made of metals like silver, gold, and magnetic metal oxides encase pharmaceuticals to solve problems with medicine delivery. Treatments for a variety of neurological disorders (NDs) have made extensive use of nanomaterials throughout the last decade. Significant advances in nanotechnology have been made by researchers in the area of nanomedicine, particularly in the neurosciences. An overview of the many types of nanomaterials and their applications in neurology is provided in this article (Kohli et al., 2019, Neunert et al., 2017).

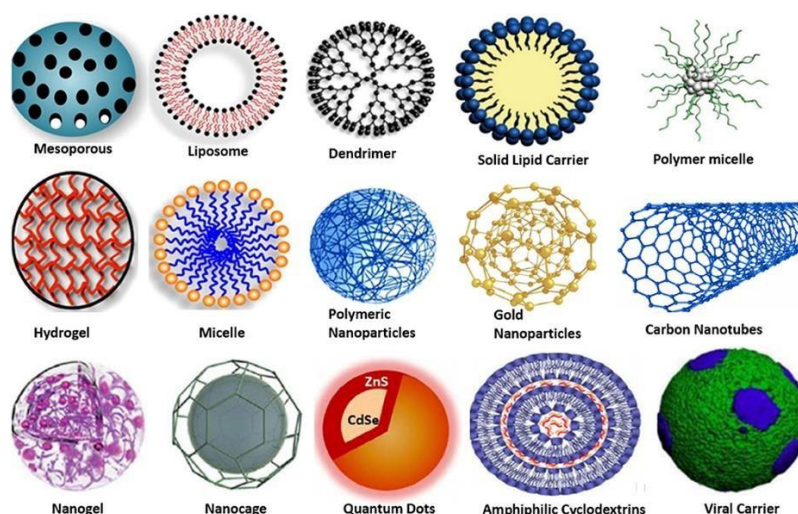


Figure 4 Nanomaterials for the management of immune thrombocytopenia

3.1 Metallic Nanoparticles

In the field of biomedicine, metallic nanoparticles have demonstrated remarkable efficacy. Synthesis and functionalization with groups that enable conjugation with medicines, antibodies, and ligands are currently feasible processes for these materials. There are new possibilities for biotechnology, magnetic separation, and medication delivery as a result of

these functionalization and alterations. Furthermore, numerous imaging models have been advocated for throughout the years, including CT, MRI, PET, ultrasound, optical imaging, and SERS. Images of many different diseases can be better captured with the help of these models. In recent years, nanomaterials have found widespread use in the evaluation, imaging, and therapy of numerous illnesses. Regardless, there are a number of ways in which nanoparticles might cause lysosomal dysfunction, oxidative stress, and autophagy, rendering them neurotoxic and detrimental to the CNS (Altomare et al., 2016).

3.2 Quantum Dots

Unique nanoparticles known as quantum dots (QDs) have a diverse array of therapeutic applications for neurological diseases. When employed in nanoparticles, quantum dots (QDs) demonstrate exceptional selectivity and sensitivity. A plethora of research has been published that examines the use of quantum dots (QDs) in the diagnosis and treatment of Alzheimer's disease (AD). QDs have been demonstrated to be capable of crossing the blood-brain barrier (BBB); however, additional research is necessary to determine their potential for injury (Neunert et al., 2017).

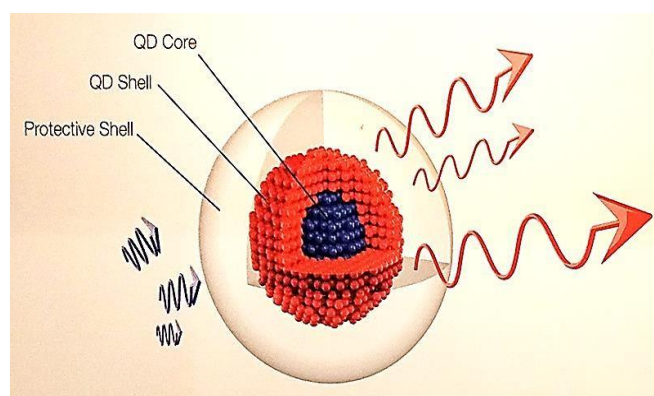


Figure 5 Quantum Dots

3.3 Dendrimers

Optical dendrimers are highly advantageous in the field of neuroscience applications because they possess the combined benefits of particle-defined structures and functionalized surfaces. The most recent breakthrough involving dendrimers is the development of an MRI contrast agent that enhances the visualisation of blood circulation. Dendrimers are very versatile polymeric structures that exhibit distinct physicochemical properties, like those of biomolecules, as extensively evidenced. Therefore, dendrimers are utilised as agents with antiviral, antibacterial, and anticancer properties. Moreover, the unique way in which host-guest binding motifs interact plays a crucial role in the transportation and precise delivery of drugs. Dendrimers can be employed as glycol carriers to specifically target tissues for the

diagnosis and treatment of malignant diseases. In addition, they offer vaccine antigens, specifically peptides (Altomare et al., 2016)

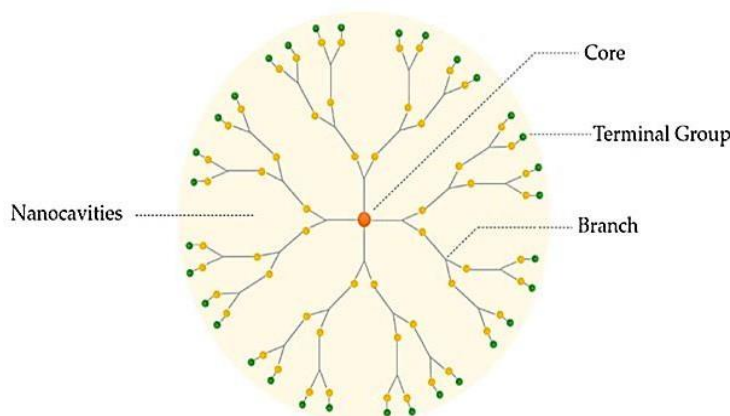


Figure 6 Dendrimers

3.4 Carbon Nanotubes

The inherent mechanical, electrical, and physico-chemical properties of carbon nanotubes, a type of nanomaterial, are attracting attention. The application of surfactants to carbon nanotubes reduces their toxicity to cells, thereby reducing the cells' adhesion to the nanotubes. During the production of carbon nanotubes using metal catalysts, the occurrence of free radicals, peroxidative reactions, DNA damage, and inflammations impedes their use in the diagnosis and treatment of neurological diseases (Liu et al., 2023).



Figure 7 Carbon Nanotubes

4 Summary and Conclusions

Thrombocytopenia can only be effectively treated if the underlying pathophysiological reasons that produce it are understood. In certain cases, such as TTP, heparin-induced thrombocytopenia, acute leukaemia, or severe ITP, prompt diagnosis and investigation may be life-saving. It is possible to learn a lot about potential medical conditions and therapies by doing a thorough physical examination and collecting a thorough medical history. It is crucial to be quite meticulous when analysing the peripheral blood smear. A brief therapy trial can help get to the bottom of things when coming up with a differential diagnosis is tough. In the absence

of a family history, distinguishing between ITP and hereditary thrombocytopenia may prove difficult. When this occurs, intravenous immunoglobulin infusion is usually helpful for ITP, but it won't help with inherited thrombocytopenia. Novel therapeutic techniques for patients with thrombocytopenia, especially in the case of ITP, have recently made considerable advancements (Neunert et al., 2019; Neunert et al., 2015). Several diagnostic and therapeutic technologies and treatment processes, including thrombopoietin and rituximab, are necessary for effective approaches to challenging disorders. There are numerous potential causes of thrombocytopenia, making the differential diagnosis and treatment of the condition complex. A particular diagnostic test does not exist for several thrombocytopenias, including ITP. However, it may take many months for the results to be revealed if a molecular test is utilised as the last examination for a suspected illness. No universally accepted diagnostic tool exists for ITP at this time that can reliably foretell how a patient will react to rituximab or splenectomy. It is essential to identify and eliminate the root causes of thrombocytopenia in order to manage the condition successfully through the use of preventive measures and focused treatments. In order to compare various therapy options and determine which ones are safest and most effective, clinical trials are crucial. Considering the efficacy and safety of long-term maintenance treatment options for patients with chronic illnesses is crucial, as is keeping an eye out for any curative outcomes (Zain et al., 2019; Aljarad et al., 2018; Gafter-Gvili et al., 2023).

Acknowledgements

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