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Review Article

Immune Thrombocytopenic Purpura in Patients with Inborn Errors of Immunity: A Narrative Review

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Abstract

Immune thrombocytopenic purpura (ITP) is one of the autoimmune disorders characterized by isolated thrombocytopenia due to immune-mediated platelet destruction. The pathogenesis of ITP is complex, involving autoantibodies against platelet glycoproteins (GPIIb/IIIa, GPIb/IX), excessive T helper1, T helper10, Thelper17 (TH1-TH0-TH17) polarization, Treg cell deficiency, and cytotoxic destruction of platelets. Cytotoxic CD8+ T-cell-mediated platelet lysis is evidenced by perforin/granzyme release in bone marrow biopsies. The diagnosis is based on excluding the other causes of thrombocytopenia, often following common viral infections. Immune thrombocytopenia can be categorized into primary and secondary groups. Secondary immune thrombocytopenia is linked with inborn errors of immunity (IEI). These errors are heterogeneous disorders with extensive clinical presentations, ranging from recurrent infections to immune dysregulation and autoimmunity. Studies have showed that autoimmune disorders are common manifestations among patients with IEI. Approximately 25-33% of IEI patients have autoimmunity disorders, including ITP, with ~20% of chronic ITP and 40% of pediatric Evans syndrome. Sometimes, patients with ITP may progress to primary immunodeficiency in the future because they may have an undiagnosed underlying IEI. Furthermore, the evaluation of patients with ITP for possible IEI, based on a history of recurrent infections and physical examinations, is essential. The prevalence of ITP is 16.2% in common variable immunodeficiency (CVID), 72% in Wiskott Aldrich syndrome (WAS), and high in autoimmune lymphoproliferative syndrome (ALPS) and LPS-responsive beige-like anchor (LRBA) / cytotoxic T-lymphocyte associated protein 4 (CTLA-4) deficiencies. IEI-associated ITP is often severe, chronic, and refractory, thus increasing morbidity. The treatments include corticosteroids, intravenous immunoglobulin (IVIG), rituximab, and targeted therapies like sirolimus. Recent studies highlight the genetic defects (e.g., FAS, CTLA4) that drive ITP, enabling precision medicine. This review study explains the recent advances in IEI-associated ITP, focusing on clinical features, pathogenesis, prevalence, and management. It also emphasizes early IEI screening for improved outcomes.

Keywords: Autoimmunity, Cytopenia, Immunologic deficiency syndromes, Immune thrombocytopenic purpura, Primary immunodeficiency diseases

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Introduction

Autoimmune disorders impose a significant burden on healthcare systems worldwide, affecting 3%-8% of the general population. Inborn errors of immunity (IEI) are heterogeneous disorders with extensive clinical presentations, ranging from recurrent infections to immune dysregulation and autoimmunity (1, 2). Immune thrombocytopenic purpura (ITP) is a hematologic autoimmune disorder characterized by a low platelet count, petechiae, purpura, and hemorrhagic events. It is caused by antiplatelet autoantibodies, with IgG autoantibodies sensitizing platelets for elimination by the reticuloendothelial system. The pathogenesis of ITP is complex, involving autoantibodies against platelet glycoproteins (GPIIb/IIIa, GPIb/IX), excessive T helper1, T helper10, Thelper17 (TH1-TH0-TH17) polarization, T regulatory (Treg) cell deficiency, and cytotoxic destruction of platelets. The diagnosis is based on excluding the other causes of thrombocytopenia, often following common viral infections (3-5). Inborn errors of immunity are a group of heterogeneous immunologic disorders affecting immune system components, with clinical presentations varying by genetic mutations (6, 7). Beyond recurrent infections, IEI patients are susceptible to malignancy, allergic diseases, and autoimmunity. Studies show that autoimmune disorders are common in IEI, with approximately 20% of patients with chronic autoimmune thrombocytopenia and 40% of pediatric Evans syndrome cases having a history of IEI. Autoimmunity in patients with IEI is caused by defects in T-cell tolerance and B-cell class-switch recombination. ITP may be the first presentation of IEI. Sometimes patients with ITP may progress to primary immunodeficiency in the future due to an undiagnosed underlying IEI. Furthermore, the evaluation of patients with ITP for possible IEI, based on a history of recurrent infections and physical examinations, is essential, particularly in cases of Evans syndrome where IEI prevalence is high (8-13). In this review, we aimed to investigate the recent advances in patients with IEI who have autoimmune thrombocytopenia. There are several investigations about the clinical presentations of ITP in patients with IEI. Table I shows, some studies with most important autoimmune findings in some primary immunodeficiency disorders.

Common variable immunodeficiency

Common variable immunodeficiency (CVID) is a primary immunodeficiency presented with recurrent sinopulmonary infections. Alongside infections, autoimmune disorders such as autoimmune cytopenia, hemolytic anemia, neutropenia, and ITP may be initial manifestations (21-24). CVID patients with only infections have better prognoses than those with autoimmune, autoinflammatory, neoplastic, or lymphoproliferative disorders, which increase morbidity and mortality (25). ITP in CVID involves autoantibodies, autoreactive T cells, and splenic macrophages (26, 27). Studies suggest that microRNA-142 and microRNA-155 contribute to CVID complications in murine models, though human evidence is lacking (28). In a study, a detailed clinical spectrum of 623 CVID patients was evaluated. The non-infectious presentations were 68.1%, and autoimmune complications were 32.2% (13). Usually, CVID patients have a significant diagnostic delay. Clinical presentation may be delayed to the age of 20 to 50, although it may occur at any age. As research shows, CD21low B cells are essential predictors of autoimmune cytopenia in CVID (29, 14). Autoimmune thrombocytopenia is diagnosed earlier in patients with both CVID and thrombocytopenia, compared with CVID patients without autoimmunity. These patients also exhibit delayed clinical presentations of immunodeficiency. In a study by Somasundaram (14), 20 patients with CVID-related ITP and 20 with ITP without CVID were enrolled.

The immunological and clinical manifestations of both groups were evaluated. As it was found, the bleeding scale was higher at initial presentations in the patients with CVID-related ITP; however, the remission rate was higher, and they required less treatment.

Corticosteroids and interavenous immunoglobulin (IVIG) are the first-line treatment in patients with autoimmune cytopenia. In refractory cases, splenectomy is an alternative modality. Rituximab is another successful option limiting splenectomy in immunodeficient and immunocompetent cases (26). Recent data suggest Janus kinase (JAK) inhibitors for refractory cases in refractory inflammatory conditions (30-32).

X-linked agammaglobulinemia (XLA)

The prevalence of autoimmunity in patients with X-linked agammaglobulinemia is generally low, due to reduced antibody production. However, rare cases of XLA presenting with chronic immune-mediated thrombocytopenia have been reported (29).

DCLRE1C gene mutation

Artemis deficiency is a severe combined immunodeficiency caused by mutation in the DCLRE1C gene. The impairment in DNA repair and the blocking of immunity maturation lead to T-, B-, NK+ immunologic phenotype and radiosensitivity. Among 5373 IEI patients registered in Iran, nine patients from nine families had mutations in the DCLRE1C gene. Autoimmunity was identified in two patients; one had autoimmune thrombocytopenia and celiac disease, while the other had juvenile idiopathic arthritis (30). In another study, fifteen patients with Artemis deficiency were included, two of whom had autoimmune hemolytic anemia. Furthermore, autoimmune cytopenias, such as autoimmune thrombocytopenia, can emerge as a clinical manifestation of Artemis deficiency (33, 34).

Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome (WAS) is a rare IEI that presents with recurrent sinopulmonary infection, bleeding tendency due to thrombocytopenia, and atopic dermatitis. It is caused by genetic mutation in the Wiskott-Aldrich syndrome protein (WASP). It is inherited by an X-linked pattern. Gene mutations range from mild to severe (6, 35). Patients with WAS are susceptible to malignancy and autoimmunity. The increased incidence of autoimmunity in patients with WAS is associated with Treg cell dysfunction, impaired positive selection of self-reactive B cells, and production of several autoantibodies. Immune-mediated platelet consumption, ineffective thrombopoiesis, and intrinsic platelet abnormality are pathophysiologic mechanisms of thrombocytopenia in WAS patients (36, 37). Twenty percent to seventy-two percent of these patients have clinical manifestations of autoimmunity. Dysfunction of WASP in WAS can lead to megakaryocyte abnormality, small platelet formation, and microplatelets. These cells were recognized by autoantibodies and are removed by the reticuloendothelial system. Also, according to some studies, megakaryocytes have an increased tendency to cell death and changes in maturation pattern (20, 38). Forty percent of mice-deficient WASP have antiplatelet antibodies (39). Antiplatelet antibodies have a poor correlation with autoimmune thrombocytopenia. Therefore, autoimmune thrombocytopenia is difficult to diagnose in the setting of thrombocytopenia, which is a characteristic of WAS. Autoimmune thrombocytopenia can exacerbate the thrombocytopenia that is a characteristic of WAS. The presentation of autoimmune thrombocytopenia is a sudden decline in platelet count with or without bleeding. After transfusion of platelets in these patients, the platelet count does not increase. Sudden platelet decline, spontaneous and significant increase in petechiae, bruising, and bleeding are the manifestations of autoimmune thrombocytopenia (35). X-linked thrombocytopenia (XLT), X-linked congenital neutropenia, and WAS are the WAS-related disorders. All of them have pathogenic variants in WASP and can present with variable hematopoietic cellular disorders. A case report explained a male neonate with severe thrombocytopenia and platelet dysfunction. This patient had a novel mutation in the WAS gene. He had severe thrombocytopenia and normal mean platelet volume. As it was concluded, in cases of severe thrombocytopenia at birth, WAS-related disorders should be evaluated. The therapeutic approach related to WAS is particularly challenging, especially in cases

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where thrombocytopenia at birth is severe (40). Thrombocytopenia is a universal presentation of WAS/XLT, and the risk of bleeding is a significant challenge. Managing non-immune thrombocytopenia in patients with WAS is a definitive therapy (hematopoietic stem cell transplantation and gene therapy). In the absence of hematopoietic transplantation, supportive therapy, high-risk activity avoidance, and avoidance of platelet transfusion as far as possible to prevent autoimmunity is essential. For patients with autoimmune thrombocytopenia, the therapies to consider are glucocorticoid, high-dose IVIG, rituximab, and splenectomy (35, 36, 41).

Autoimmune lymphoproliferative syndrome (ALPS)

ALPS is an inborn error of immunity caused by the mutations in the genes that regulate cell apoptosis. It does not have any pathognomonic test for diagnosis; however, according to 2010 criteria, patients should exhibit double-negative α/β T cells greater than 1.5% of the total lymphocytes or at least 2.5% of the total T cells in circulation. They also have elevated levels of soluble FAS ligand (sFASL greater than 200 pg/ml), IL-10, and vitamin B12. The other findings are elevated levels of IgG, IgA, IgE, and high concentration of autoantibodies such as anti-platelet antibody, anti-neutrophil antibody, anti-nuclear antibody, and rheumatoid factor. Apoptotic defects in the pathway of FAS/FASL components (FAS-FASL-FADD-CASP8-CASP10) are the leading cause of ALPS.

However, some patients have clinical and laboratory findings similar to ALPS patients without genetic defects in FAS/FASL pathways (ALPS-like disorders). Also, some patients (20%) with ALPS presentations do not have identifiable genetic mutations. The most important clinical manifestations are lymphoid hyperplasia, lymphadenopathy, hepatosplenomegaly, and autoimmune hematologic defects, for example, autoimmune thrombocytopenia, autoimmune hemolytic anemia, and lymphoma. The most prevalent autoimmune complications in patients with ALPS are autoimmune hemolytic anemia and then autoimmune thrombocytopenia (18, 42, 43). Kaya et al, showed that screening of ALPS can be helpful for patients with lymphoma and thrombocytopenia at diagnosis and those who have nonmalignant organomegaly with immune thrombocytopenic purpura. They found that thrombocytopenia, anemia in patients with lymphoma, lymphadenopathy, and splenomegaly in patients with immune cytopenia are predictive factors for ALPS. In another study, Palmisani et al. (44, 45) compared the classical ALPS patients with mutations in FAS, FASL and CASP10 genes to ALPS patients with undetermined gene mutations (approximately one-third of patients with clinical presentations of ALPS do not have defined genetic mutations). Different cytopenias were seen in both patient groups. However, lymphocytopenia and autoimmune neutropenia were more frequent in the patients with no defined genetic mutations. In the ALPS-FAS/CASP10 patients, optimal control was achieved through first (IVIG and corticosteroids) and second (rapamycin and mycophenolate mofetil) line treatments, while the others needed more than two therapeutic lines. The treatments of patients with a definitive diagnosis and a probable diagnosis of ALPS are similar. The first-line management is based on autoimmunity, complications, and lymphoproliferation. Autoimmune cytopenia and especially autoimmune hemolytic anemia can be treated with mycophenolate mofetil and a short course of corticosteroids. Immune thrombocytopenia was treated with corticosteroids accompanied by a high dose of IVIG. However, rituximab is an option in the case of treatment failure. Sirolimus is another agent that can be used for ALPS patients. Hematopoietic stem cell transplantation is the choice of treatment for patients with severe cytopenia, immunodeficiency as well as those prone to malignancy (43, 45, 46, 47).

LPS-responsive beige-like anchor (LRBA) deficiency and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) haploinsufficiency

The haploinsufficiency of CTLA-4 and the deficiency of LRBA are IEI disorders with similar clinical presentations. LRBA has a vital

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role in the regulation of CTLA-4. Furthermore, most individuals with LRBA deficiency have defects in CTLA-4 expression (20). LRBA deficiency is an autosomal recessive IEI caused by mutation in the LRBA gene that encodes the LRBA protein. The LRBA protein is a cytosolic component that contributes to vesicle trafficking and CTLA-4 receptor turnover in Treg cells. The biallelic mutations in the LRBA gene can lead to immune dysregulation. This condition was previously categorized under CVID (48). The clinical presentations of LRBA deficiency are frequent infections, chronic diarrhea, autoimmune disorders, organomegaly, hypogammaglobulinemia, and growth retardation (50). In a systematic review, the clinical presentations of LRBA and CTLA-4 deficiency were compared. Among the manifestations of CTLA-4 deficiency, autoimmunity was 43%, while, in the patients with LRBA deficiency, autoimmunity was 31%. The autoimmune presentation was the most common in CTLA-4 and LRBA deficiency. The median age of the first autoimmune presentation in the patients with CTLA-4 and LRBA deficiency was 6.5 and 3 years, respectively. The most common manifestations of autoimmune disorders among the patients with LRBA and CTLA-4 deficiency were immune thrombocytopenic purpura, autoimmune hemolytic anemia, and autoimmune neutropenia. The immunosuppressive management of these patients included biologic agents and glucocorticoids. The patients with CTLA-4 and LRBA deficiency were both responsive to this therapeutic approach. Some studies have also shown that hematopoietic stem cell transplantation, as another treatment, is not associated with significant clinical outcomes (19, 49-52).

Other IEI associated with ITP

Additional IEI linked to ITP include activated PI3Kδ syndrome (APDS), where AICs are frequent (76%), with ITP common due to PIK3CD/PIK3R1 mutations (53, 54). STAT3 gain-of-function mutations cause multiorgan autoimmunity, including ITP in ~40% of the cases (55, 56). Kabuki syndrome and DiGeorge syndrome also feature ITP as part of immune dysregulation (57-58). In selective IgA deficiency, ITP occurs in ~5-10% of the cases (59, 60). Other disorders like chronic granulomatous disease (CGD) and hyper-IgE syndrome have been shown to be associated with ITP in rare cases (61, 62). Additionally, deficiencies in complement components (e.g., C1q deficiency) may predispose ITP due to impaired immune regulation (63, 64).

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Table I: Summary of the key findings from the selected studies on ITP in IEI

Study (reference)	Country	Total IEI patients	% with ITP	Most important findings
Ho et al., 2020 (14)	USA	623 (CVID)	16.2%	Autoimmunity in 33.2% of CVID; ITP associated with higher morbidity; genetic defects in 10-30%
Somasundaram et al., 2023 (15)	Germany	20 (CVID-related ITP)	100% (selected cohort)	Higher bleeding at presentation in CVID-ITP; higher remission, less treatment needed; elevated sIL-2R
Cortesi et al., 2022 (4)	Italy	N/A (review)	N/A	ITP in IEI severe/refractory; mechanisms: tolerance defects, apoptosis issues; targeted therapies key
Hadjadj et al., 2019 (16)	France	N/A (pediatric ES)	65% genetic	High genetic basis in pediatric Evans syndrome; immune genes variants
Taskin et al., 2024 (10)	Turkey	82 (IEI with AIC)	40.2% ITP	AIC initial in 54.9% IEI; refractory in IEI; CVID, ALPS common
Bousfiha et al., 2022 (17)	Morocco	769	14% AIC (ITP included)	AIC in 14%; polyautoimmunity 47%; CVID most associated
Hafezi et al., 2021 (18)	Iran	780 (ALPS/ALPS-like)	High in ALPS (second most common after AIHA)	AIC in ALPS: AIHA > ITP; genetic defects in 80%
Jamee et al., 2021 (19)	International (review)	212 LRBA, 222 CTLA4	31-43% autoimmunity (ITP common)	ITP/AIHA most auto in LRBA/CTLA4; median onset 3-6.5 years
Sudhakar et al., 2021 (20)	India	N/A (WAS review)	20-72% autoimmunity	Autoimmunity in WAS due to Treg dysfunction; ITP exacerbates thrombocytopenia

Note: N/A indicates not applicable or not cohort-based cases.

Discussion

This narrative review explains current knowledge about ITP in the field of IEI, highlighting its prevalence, mechanisms, and management. Immune thrombocytopenic purpura stands out as a prominent autoimmune manifestation, marked by immune-mediated platelet destruction leading to thrombocytopenia. Approximately 20% of patients with chronic autoimmune thrombocytopenia and up to 40% of pediatric Evans syndrome cases are associated with underlying IEI. Notably, ITP can often be the initial presenting feature of IEI, underscoring the critical need for early screening in patients with ITP, particularly those with a history of recurrent infections or unusual clinical findings. The prevalence of ITP is notably high in specific IEI conditions, such as CVID at 16.2%, WAS ranging from 20-72%, and ALPS as well as LRBA/CTLA-4 deficiencies. ITP in these contexts is frequently severe, chronic, and refractory to treatment, contributing to increased morbidity and mortality. The underlying pathogenesis involves anti-platelet autoantibodies, Treg deficiencies, and impaired apoptosis, particularly evident in ALPS and LRBA/CTLA-4 deficiencies. Recent advances in genetic screening have identified key mutations, such as those in FAS, CTLA4, and LRBA genes, paving the way for precision medicine approaches with targeted therapies like sirolimus, rituximab, and JAK/STAT inhibitors.

Genetic testing is also recommended for early diagnosis, enabling targeted therapies like JAK/STAT inhibitors or hematopoietic stem cell transplantation (HSCT) to prevent complications (17, 38, 65-67). The limitations of this study are its narrative nature and lack of

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systematic search or meta-analysis, which has potentially introduced a selection bias. Also, the study was limited to English-language publications. Many of the reported cohorts are small or retrospective, limiting robust prevalence estimates. Future research should focus on larger, prospective studies and genetic screening programs.

Conclusion

Inborn errors of immunity encompass a diverse group of disorders characterized by a wide range of clinical manifestations, including recurrent infections, malignancies, and autoimmune conditions. ITP can often be the initial presenting feature of IEI. Early diagnosis through comprehensive evaluation of infection history, physical examinations, and genetic testing is essential to mitigate complications and enhance patient prognosis. The standard treatments, including corticosteroids and IVIG, remain first-line options, while HSCT offers a potential solution for refractory cases to improve long-term outcomes. Future research should prioritize large-scale, prospective studies and expanded genetic screening to deepen the understanding of the interplay between IEI and ITP, ultimately fostering the development of more effective therapeutic strategies. A suggestion is routine IEI evaluation in refractory thrombocytopenia, especially pediatric patients with infections or positive family history.

Availability of Data

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

Ethical Considerations

This is a narrative review and did not involve human or animal subjects; therefore, ethical approval was not required.

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Authors' Contributions

A. Kh: Methodology, investigation, data curation, writing the original draft, review, and editing.

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Conflict of Interest

The author declares no conflict of interests regarding this research.

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