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Reverse Angle: Immunological Evaluation of Patients with Idiopathic Thrombocytopenic Purpura: A Retrospective Cohort Study

Gökhan AYTEKİN[1], Eray YILDIZ[1], Fatih ÇÖLKESEN[1], Seda YILMAZ[1], Atakan TEKİNALP[1], Sinan DEMİRCİOĞLU[2], Şevket ARSLAN[1], Özcan ÇENELİ[2]

[1] **Necmettin Erbakan University, Meram School of Medicine, Department of Internal Medicine, Division of Allergy and Clinical Immunology, Konya, Turkey**
[2] **Necmettin Erbakan University, Meram School of Medicine, Department of Internal Medicine, Division of Hematology, Konya, Turkey**

Corresponding Author: Gökhan Aytekin ✉ ayteking@gmail.com

ABSTRACT

Objective: Primary Immune Thrombocytopenia (ITP, idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura) is an acquired thrombocytopenia caused by anti-platelet antibodies. The diagnosis of ITP may be challenging due to the various potential causes of thrombocytopenia, some of which are overlooked. Immunodeficiencies are also a rare cause of ITP. Although autoimmunity and, therefore, ITP are a common complication in primary immunodeficiency (PI) patients, there are not many publications in the literature that examine the frequency of PI in ITP patients and the immune abnormalities in these patients.

Materials and Methods: Forty-five patients with ITP (F: 37 [78.7%], M: 10 [21.3%]) were included in the study (age 42.9 ± 15.9).

Results: At least one antibody deficiency was detected in 7 patients (14.9%), and following further investigations, 2 patients (4.3%) were diagnosed with CVID, 3 (6.4%) with IgG deficiency, 1 (2.1%) with selective IgA deficiency and 1 (2.1%) with possible IgM deficiency. Immunoglobulin levels were normal while at least one abnormality was detected in 20 patients (42.6%) in peripheral lymphocyte subset analyses. The most common abnormality in this patient group was a reduced percentage of CD4+ T-cells (9 patients, 45% of patients with PLS abnormalities, 19.1% of all patients). CD3+ T-cell rates in 8 patients (17.8%), CD19+ B-cell rates in 6 (12.8%), CD3-CD16+56+ natural killer cell rates in 4 (8.5%), and CD4/CD8 cell ratios in 7 (14.9%) were reduced. In addition, the CD8+ T-cell rate in 8 patients (17%) was above the reference ranges.

Conclusion: Adult patients who are diagnosed with ITP may develop a variety of immunological abnormalities in addition to hypogammaglobulinemia. Therefore, clinicians should not overlook immunological evaluation in the etiological investigation of ITP and should closely monitor patients with immunological abnormalities.

Keywords: Hypogammaglobulinemia, idiopathic thrombocytopenic purpura, IgG

INTRODUCTION

Primary Immune Thrombocytopenia (ITP, idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura) is an acquired thrombocytopenia caused by anti-platelet antibodies (1). It is one of the most common causes of thrombocytopenia in otherwise asymptomatic adults. In an adult with suspected ITP, there are two major diagnostic concerns (2): These are distinguishing ITP from other causes of thrombocytopenia, which often have a similar clinical presentation but may require completely different treatment approaches, and determining whether the ITP is primary or secondary to a condition that might also benefit from treatment. The lack of a sensitive or specific diagnostic test for ITP and the large number of potential causes of thrombocytopenia, some of which may be overlooked, contribute to the challenges in diagnosing ITP. Therefore, it would not be wrong to say that ITP is a diagnosis of exclusion (2, 3). The pathogenesis of ITP is still not fully understood. While thrombocytopenia may be induced by an event

ORCID: Gökhan AYTEKİN / 0000-0002-9089-5914, Eray YILDIZ / 0000-0002-9596-1773, Fatih ÇÖLKESEN / 0000-0002-6595-1267, Seda YILMAZ / 0000-0002-7222-499X, Atakan TEKİNALP / 0000-0001-7937-4045, Sinan DEMİRCİOĞLU / 0000-0003-1277-5105, Şevket ARSLAN / 0000-0002-0343-0159, Özcan ÇENELİ / 0000-0003-2541-1335

(4-6), a variety of immune disorders have been identified that may cause antibody production (7-9). Primary immunodeficiencies (PI) refer to immune disorders which predispose patients to frequent and recurrent infections, autoimmunity, lymphoproliferation, gastrointestinal diseases and malignancy (10). Approximately a quarter of these patients have autoimmune diseases, and in some patients, initial complaints are associated with these autoimmune conditions (11). The most common disorders are hematological cytopenias, such as immune thrombocytopenia and autoimmune hemolytic anemia (12, 13). Although autoimmunity and, therefore, ITP are common complications in PI patients, there are not many publications in the literature that examine the frequency of PI in ITP patients and the immune abnormalities in these patients. In addition, establishing an underlying immunological condition in ITP patients may be very important before a splenectomy.

MATERIALS and METHODS

Patients

The records of adult patients over 18 years of age who were evaluated due to acute ITP and who underwent an immune system assessment at the Hematology Department of Meram Faculty of Medicine at Necmettin Erbakan University until June 2018 were evaluated retrospectively. The study protocol was approved by the Ethics Committee of Necmettin Erbakan University, Faculty of Medicine. Informed consent was obtained from study participants.

The patients were diagnosed with ITP according to the American Society of Hematology guidelines (14).

Patients with diseases that would affect the immune assessment such as uremia, nephrotic syndrome, liver and/or renal insufficiency, HIV-AIDS, and patients who used drugs that would cause hypogammaglobulinemia such as anti-epileptic, anti-convulsant, or immunosuppressive agents were excluded. The records of 47 patients who complied with the study criteria were evaluated.

In addition to demographic data such as age, gender, family history of immunodeficiency in these records, complete blood count, serum immunoglobulin (IgG, IgA, IgM), and peripheral lymphocyte subset analyses were noted.

Serum immunoglobulin measurements were performed by particle-enhanced immunonephelometry using the Siemens BN II/BN ProSpec system. Lymphocyte subsets were measured using the BD FACSCanto II flow cytometer with an eight-color configuration with fluorescent-labeled antibodies.

Normal Ranges

Normal reference ranges for laboratory tests in the patients were 4 x 10^3/μl – 10 x 10^3/μl for white blood cells (WBCs), 1.5 x 10^3/μl – 7.3 x 10^3/μl for neutrophils, and 0.8 x 10^3/μl – 5.5 x 10^3/μl for lymphocytes (15, 16).

Normal ranges for immunoglobulins were 7 g/dl – 16 g/dl for IgG, 0.4 g/dl – 2.3 g/dl for IgM, and 0.7 g/dl – 4 g/dl for IgA (17). A tetanus antibody level of ≥ 0.04 IU/mL was considered sufficient (18).

In the evaluation of peripheral lymphocyte subsets (PLS) with the flow cytometric method, CD16-CD56 values of 5 – 31.3% were considered normal in males while values of 3.5 – 24.9% were considered normal in females. CD19 values of 6.3 – 20.8% were considered normal. CD3 values of 48 – 82.6% for men and 56.8 – 84.1% for women were considered normal. CD4 values of 23 – 52.6% for men and 26.9 – 55.5% for women were considered normal. Values of 12.8 – 40.2% for CD8 and 0.68 – 3.61 for CD4/CD8 were again considered normal (19).

Statistical Analyses

Statistical analysis was performed with the IBM SPSS Statistics Version 25 software package. Parametrically distributed values were expressed as mean ± standard deviation, and non-parametrically distributed parameters were expressed as median (interquartile range: minimum-maximum).

RESULTS

Baseline Demographic, Clinical, and Laboratory Parameters of the Study Population

Forty-five patients with ITP (F: 37 [78.7%], M: 10 [21.3%]) were included in the study (age 42.9 ± 15.9). The mean age of the patients was 42.87 ± 15.9 years while the mean leukocyte count was 8734.0 ± 3835.1 cells/mm^3 and the mean platelet count was 37148.9 ± 29735.01 cells/mm^3. Mean IgG, IgM and IgA values of the patients were 12.5 ± 4.92 g/l, 1.16 ± 0.83 g/l and 1.81 ± 0.84 g/l, respectively. There were 7 patients (14.9%) with at least one antibody deficiency, 5 patients (10.6%) with low IgG levels, 2 patients (4.3%) with low IgA levels, and 3 patients (6.4%) with IgM

deficiency. Patient 1 had panhypogammaglobulinemia. Patient 4 had low IgG and IgM levels. These patients were diagnosed as CVID according to the ESID criteria following further evaluation (20). Patient 2, Patient 5 and Patient 6 had only low IgG levels. These patients were regarded as having an IgG deficiency (21). Patient 7 had low IgA levels. This patient was regarded as having selective IgA deficiency according to relevant criteria (22). Patient 3 had low IgM levels. The patient whose IgG subsets could not be assessed was regarded as having possible selective IgM deficiency according to the relevant diagnostic criteria (23). High IgG levels (17.3 – 31 g/l) were detected in 6 patients (12.6%) while high IgM levels (2.53 – 4.81g/l) were detected in 4 patients (8.5%). Baseline demographic, clinical, and laboratory parameters of the study population are summarized in Table I.

Peripheral Lymphocyte Subset Analyses

The percentage of $CD3^+$ T lymphocytes, $CD3^+CD4^+$ T lymphocytes, $CD3^+CD8^+$ T lymphocytes, $CD19^+$ B lymphocytes and $CD3^-CD16^+56^+$ natural killer cells in the patients were 65.2 ± 10.5%, 34.5 ± 10.3%, 30.4 ± 10.1%,

Table I: Baseline demographic, clinical, and laboratory parameters of the study population.

	Total (n=47)
Gender (female), n (%)	37 (78.7)
Age	42.87 ± 15.9
Leukocyte count (4000-10000 /mm³)	8734.0 ± 3835.1
Platelet count (/mm³)	37148.9 ± 29735.01
Lymphocyte count (/mm³)	2312.8 ± 1291.9
Lymphopenia (≤800/mm³), n (%)	13 (27.7)
Hemoglobin (g/l)	13.25 ± 1.85
Ig G (7-16 g/L)	12.5 ± 4.92
Ig M (0.4-2.3 g/L)	1.16 ± 0.83
Ig A (0.7-4 g/L)	1.81 ± 0.84
CD 3 (%)	65.2 ± 10.5
CD 4 (%)	34.5 ± 10.3
CD 8 (%)	30.4 ± 10.1
CD 4/CD 8	1.3 ± 0.77
CD 19 (%)	13.1 ± 6.2
CD16-56 (%)	10.8 ± 7.2
Number of patients with at least one antibody decrease, n (%)	7 (14.9)
Number of patients with low Ig G, n (%)	5 (10.6)
Number of patients with high Ig G, n (%)	6 (12.6)
Number of patients with low Ig M, n (%)	3 (6.4)
Number of patients with high Ig M, n (%)	4 (8.5)
Number of patients with low Ig A, n (%)	2 (4.3)
Number of patients with at least one abnormality in peripheral lymphocyte subsets, n (%)	21 (44.7)
Number of patients with low CD 3, n (%)	8 (17.0)
Number of patients with low CD 4, n (%)	9 (19.1)
Number of patients with low CD 8, n (%)	1 (2.1)
Number of patients with high CD 8, n (%)	8 (17.0)
Number of patients with low CD 19, n (%)	6 (12.8)
Number of patients with high CD 19, n (%)	5 (10.6)
Number of patients with low CD 16-56, n (%)	4 (8.5)
Number of patients with low CD4/CD8, n (%)	7 (14.9)

13.1 ± 6.2% and 10.8 ± 7.2%, respectively. The mean CD4/CD8 ratio was 1.3 ± 0.77. Immunoglobulin levels were normal while at least one abnormality was detected in 21 patients (44.7%) in peripheral lymphocyte subset analyses. The most common abnormality in this patient group was a reduced percentage of $CD4^+$ T-cells (9 patients, 42.9% of patients with PLS abnormalities, 19.1% of all patients). $CD3^+$ T-cell rates in 8 patients (17.8%), $CD19^+$ B-cell rates in 6 (12.8%), $CD3^-CD16^+56^+$ natural killer cell rates in 4 (8.5%), and CD4/CD8 cell ratios in 7 (14.9%) were reduced. In addition, the $CD8^+$ T-cell rate in 8 patients (17%) and $CD19^+$ B-cell rate in 5 (10.6%) were above the reference ranges (Table II).

DISCUSSION

In adult patients, ITP is diagnosed by ruling out a wide range of secondary causes of thrombocytopenia. Immunodeficiency syndromes are also among the causes of secondary immunodeficiency and should be kept in mind during etiologic investigations. Although autoimmunity and cytopenias are well-known and well-defined complications in immunodeficiency patients (11, 12, 24, 25), the number of studies investigating immunodeficiency syndromes or immunological abnormalities in adult ITP patients in the literature are limited.

Table II: Summary of Immunological Abnormalities in Patients with Idiopathic Thrombocytopenic Purpura.

	Low IgG	Low IgM	Low IgA	Low CD3	Low CD4	Low CD8	High CD8	Low CD4/8	Low CD19	High CD19	Low CD16-56
Patient 1	X	X	X				X				
Patient 2	X								X		
Patient 3		X									
Patient 4	X	X									
Patient 5	X									X	
Patient 6	X										
Patient 7			X						X		
Patient 8				X						X	
Patient 9											X
Patient 10									X		X
Patient 11				X	X			X	X		
Patient 12					X		X	X		X	
Patient 13					X				X		
Patient 14				X	X			X			
Patient 15					X		X	X			X
Patient 16							X	X			
Patient 17				X	X						
Patient 18					X		X	X			
Patient 19							X				X
Patient 20						X					
Patient 21							X	X			
Patient 22					X						
Patient 23				X						X	
Patient 24				X	X						
Patient 25				X							
Patient 26							X		X		
Patient 27				X							
Patient 28										X	

In the present study, at least one antibody deficiency was detected in 7 patients (14.9%), and following further investigations, 2 (4.3%) were diagnosed with CVID, 3 (6.4%) with IgG deficiency, 1 (2.1%) with selective IgA deficiency and 1 patient (2.1%) was diagnosed with possible IgM deficiency.

CVID is a hypogammaglobulinemia condition characterized by inaccurate/inadequate differentiation of B cells that predispose patients to infections, autoimmunity, lymphoproliferation, granulomatous diseases and malignancy (26). Autoimmune conditions are diagnosed in a quarter of CVID patients and are the first reason for admission in many patients (25). Autoimmunity is also considered an indicator of immune dysregulation, and immune dysregulation manifests itself most commonly with ITP and autoimmune hemolytic anemia (AIHA) (12). In a retrospective study of 326 CVID patients, Wang et al. reported that 35 patients (11%) had a history of ITP and AIHA, 19 of which had an episode of thrombocytopenia and hemolytic anemia before receiving a CVID diagnosis (11). Bolileau et al. identified autoimmune cytopenia in 55 of 311 CVID patients (25). In another study assessing 990 CVID patients, autoimmune cytopenia was identified in 101 (10.2%) whereas, ITP was detected in 73 (7.4%) (27). Rahiminejad et al. identified primary immunodeficiency in 38% of patients in a population of pediatric and adult patients with chronic ITP (28). In a study of 21 patients with autoimmune thrombocytopenia and CVID, only 4 (19%) had been diagnosed with CVID before ITP and 13 (62%) had been diagnosed with CVID at least 6 months after ITP. In 4 patients (19%), these two conditions were concomitant (12). In our current study, the diagnosis of CVID in 2 patients (4.3%) is also important in terms of showing that CVID is a key factor in the etiology of ITP.

Selective IgG deficiency refers to conditions that are accompanied by IgG deficiency and frequent respiratory tract infections but do not fully meet the CVID criteria (21). Antibody responses to memory cells, switched memory B cells, vaccines and infections in patients with IgG deficiency are considered to be better than in CVID patients, and unlike CVID, where a B cell defect is considered to be prior to germinal center maturation, a B cell defect is considered to be after germinal center maturation (29). Although autoimmunity in these patients is not as frequent as in CVID, the detection of IgG deficiency at a rate of 6.4% in our study suggests that autoimmunity should be kept in mind in patients with IgG deficiency. In addition, these patients should be closely monitored for other possible primary immunodeficiency symptoms.

Selective IgA deficiency is the most common primary immunodeficiency. Two thirds of the patients have been reported to be asymptomatic (30, 31). However, 20-30% of patients develop an autoimmune disease during the follow-up of patients at immunology clinics (32). In one study, the frequency of IgA deficiency in chronic ITP patients was reported to be 5% (20). In our study, the prevalence of selective IgA deficiency was 2.1% in adult acute ITP patients.

Truly selective IgM deficiency is a very rare immunodeficiency associated with recurrent infections, atopy and autoimmunity, and refers to low IgM levels and the absence of other immunological abnormalities. IgM deficiency in which the IgG subset or specific antibody response is not known is considered a possible IgM deficiency (33). In our study, low IgM levels were detected in one patient and this patient was regarded as having a possible IgM deficiency since IgG subsets were not studied. Goldstein et al. identified autoimmune diseases in 14% of patients with sIgM deficiency (33). ITP, Hashimoto's thyroiditis, systemic lupus erythematosus and autoimmune glomerulonephritis were the most common autoimmune diseases (34-36).

In our study, we detected at least one abnormality in peripheral lymphocyte subsets although immunoglobulin levels were normal in 21 patients (44.7%). The most common abnormality in this patient group was a reduced percentage of $CD4^+$ B cells (9 patients, 42.6% of patients with peripheral lymphocyte subset anomalies, 19.1% of all patients).

In a study of 125 pediatric ITP patients, Wu et al. reported that the $CD3^+$ T cell rate in acute ITP patients was 55.44% ± 14.31% (37). In our study, this rate was 65.2 ± 10.5%. In another study, the $CD3^+$ T-cell rate in ITP patients was lower compared to healthy individuals and reached values similar to those in healthy individuals after treatment (38). In our current study, the $CD3^+$ T-cell rate was low in 8 patients (17%) and was one of the most common flow cytometric abnormalities. Liu et al. demonstrated that this rate was reduced in ITP patients, which was associated with clinical improvement (39).

El-Rashedi et al. reported that the $CD8^+$ cell rate was higher and that the $CD4^+$ T-cell rate was decreased

in both acute and chronic ITP patients compared to the control group (40). However, Li et al. found that the $CD4^+$ T-cell rate and the CD4/CD8 cell ratio were decreased in ITP patients compared to healthy individuals (38). Furthermore, the CD4+/CD8+ cell ratio has been shown to improve with treatment (40-42). In our current study, the most common flow cytometric abnormalities were decreased $CD4^+$ T cell rates in 9 patients (19.1%) and decreased CD4/CD8 ratio in 7 (14.9%) while the increase in $CD8^+$ T-cell rates in 8 (17%) consistent with these data.

$CD3^-CD16^+$ $CD56^+$ natural killer cells are very important in establishing an immune response against viral infections. NK cells have an inhibitory effect on antibody production and play a significant role in B cell regulation (43). Therefore, it is not surprising that the NK cell rate decreases in autoimmune diseases (44). This reduction is more noticeable in patients with acute ITP (45). Decreased NK cytotoxicity has also been shown in chronic ITP patients (46). In our study, was low NK cell rate in 4 patients (8.5%).

Wu et al. reported a $CD19^+$ B cell rate of 19.47% ± 6.93% in patients with acute ITP (37). In our study, this rate was found to be 13.1 ± 6.2%. Zahran et al. demonstrated that the $CD19^+$ B cell rate increased in pediatric ITP patients (47). B cells are the source of anti-platelet antibodies, and B cells producing antibodies to glycoprotein IIb-IIIa have been shown to be increased in ITP patients (48). In addition, the reduction of NK cells which have an inhibitory effect on B cells in ITP patients may have caused an increase in $CD19^+$ B cells (43). In our study, the $CD19^+$ B-cell rate above the reference range in 5 patients (10.6%).

The retrospective design of the study and the small size of the study population were the most significant limitations. In addition, the evaluation of IgG subsets may have caused possible IgG subset deficiencies to be overlooked.

In conclusion, adult patients who are diagnosed with ITP may develop a variety of immunological abnormalities in addition to hypogammaglobulinemia. Therefore, clinicians should not overlook immunological evaluation in the etiological investigation of ITP and should closely monitor patients with immunological abnormalities.

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None

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

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