İzole Trombositopenili Hastaların Demografik ve Klinik Özellikleri

Demographic and Clinical Features of Patients with Isolated Thrombocytopenia

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ÖZ

GİRİŞ ve AMAÇ: *Trombosit sayısının 150.000/ mm³ altı trombositopeni olarak tanımlanmaktadır. İzole trombositopeni ise diğer serilerin (eritrosit ve lökosit) normal olup sadece trombosit değerinin düşüklüğü ile karakterizedir. Bu çalışmada izole trombositopeni nedeniyle hematoloji kliniğine başvuran hastaların etyolojik tanısı, klinik özellikleri ve kan parametrelerini değerlendirmeyi amaçladık.*

YÖNTEM ve GEREÇLER: *Ekim 2016 - Ocak 2018 tarihleri arasında kliniğimizde trombositopeni nedeniyle takip edilen hastaların dosyaları geriye dönük olarak tarandı. İzole trombositopeni saptanan 301 hasta çalışmaya dahil edildi. Patofizyolojik etyolojiye göre izole trombositopeni sınıflandırıldı. Primer immun trombositopeni (ITP) ile izole trombositopeniye yol açan diğer hastalıkların tam kan sayımı değerleri karşılaştırıldı.*

BULGULAR: *Hastaların 202'si kadın ve 99'u erkekti. 173 hastada artmış trombosit tüketimi, 45 hastada yalancı trombositopeni, 27 hastada trombosit sekestrasyonu(hipersplenizm), 3 hastada ise azalmış trombosit üretimine neden olan hastalıklar saptandı. 54 hastada trombosit değeri 100.000- 150.000 / mm³ arasında idi ve bu durumu açıklayacak herhangi bir patoloji yoktu. Primer ITP izole trombositopenili hastalarda en sık saptanan hastalıktı (%35,8) ve bu hastalarda trombosit sayısı diğer izole trombositopeniye yol açan hastalıklara göre anlamlı olarak daha düşüktü*

TARTIŞMA ve SONUÇ: *Çalışmamızda izole trombositopeninin en sık nedeni primer ITP, ikinci en sık neden yalancı trombositopeniydi. Diğer nedenler olarak ilaç ve enfeksiyon ilişkili, gestasyonel trombositopeni, kollajen vasküler hastalıklar ve hipersplenizm bulundu. Trombositopeni bir laboratuar bulgusudur ve çeşitli hastalıklarla ilişkili olabilir. İzole trombositopeniyi tanımlayabilen spesifik bir test yoktur. İlk önce periferik yayma ile gerçek ve yalancı trombositopeni ayrımı yapılmalıdır. Sonra da kapsamlı anamnez, fizik muayene ve diğer laboratuar testleri ile tanıya ulaşılmalıdır.*

Anahtar Kelimeler: *izole trombositopeni, demografik, immune trombositopeni*

ABSTRACT

INTRODUCTION: *Thrombocytopenia is defined as platelet count below 150.000/mm³. Isolated thrombocytopenia is characterized by low platelet count without any other abnormality of erythrocyte and leucocyte.This study aims to evaluate the etiological diagnosis, clinical features and blood parameters of patients who admitted to the hematology clinic due to isolated thrombocytopenia.*

METHODS: *The datas of patients who were diagnosed and followed up in our clinic between October 2016 and January 2018 for thrombocytopenia were screened retrospectively. 301 patients with isolated thrombocytopenia were included.İsolated thrombocytopenia was classified according to pathophysiological etiology.*

RESULTS: *Of the patients, 202 were female and 99 were male. We observed that decreased platelet causes were due to platelet consumption in 173 patients, pseudo-thrombocytopenia (PTCP) in 45 patients, platelet sequestration in 27 patients, and decreased platelet production in 3 patients. The platelet count was between 100 and 150,000/mm³ in 54 patients and there was no pathology to explain this condition. Primary ITP was the most common disorder (35,8%) and the level of platelet was significantly lower in these patients than in other isolated thrombocytopenia.*

DISCUSSION AND CONCLUSION: *In our study, the two most common causes of isolated thrombocytopenia were primary ITP and pseudothrombocytopenia.We showed that other causes were drug and infection-related, gestational thrombocytopenia, collagen vascular diseases and hypersplenism. Thrombocytopenia is a laboratory finding and may be related to various disorders.There are no specific tests that can identify thrombocytopenia. True and false thrombocytopenia should be differentiated by peripheral smear.Then, the cause of isolated thrombocytopenia should be determined by comprehensive history, physical examination and laboratory tests.*

Keywords: *isolated thrombocytopenia, demographic, immune thrombocytopenia*

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INTRODUCTION

Thrombocytopenia is defined as a platelet count below 150.000/mm3. Thrombocytopenia could be a result of decreased platelet production , increased platelet consumption and platelet sequestration (abnormal platelet distribution) or combination of these. The examples of decreased platelet production are the congenital or acquired bone marrow failure syndromes (eg, hematologic malignancies ,aplastic anaemia, myelodysplastic syndromes, myelofibrosis, metastatic cancer to bone marrow , infections, vitamin B 12 and folate deficiencies), while increased platelet consumption is seen in circumstances such as immune mechanisms (eg, immune thrombocytopenia (ITP),drug -induced thrombocytopenia, infections such as HIV and connective tissue disorders) ; non-immune mechanisms (eg, disseminated intravascular coagulation and the thrombotic microangiopathies) (1-4). Splenic sequestration results from hypersplenism, which is characterized by redistribution of blood flow and platelets from the circulating pool to the splenic pool by congestive splenomegaly secondary to portal hypertension (2, 5-6).

It is known that multiple factors like increased destruction, decreased production and/or hypersplenism may contribute to the development of thrombocytopenia in many cases of thrombocytopenia, such as primary ITP, hepatitis C virus infection, and chronic liver disease (2,4-5).

Sometimes it is a challenge to determine the cause of thrombocytopenia especially in hospitalized patients with multisystemic disorders and multi-drug exposure where several mechanisms are in charge. In contrast, in outpatient cases, thrombocytopenia is often isolated and asymptomatic, also the specific causes are usually diagnosed easily (2).

Isolated thrombocytopenia which is known to be low platelet count without any other abnormality in the erythrocytes or leukocytes is usually a result of more limited disorders. The most common etiology is ITP. Other common causes include pseudothrombocytopenia and drug-induced thrombocytopenia (2). We aimed to retrospectively evaluate the diagnosis, demographic and clinical features of individuals who were referred to our hematology clinic because of isolated thrombocytopenia.

MATERIALS AND METHODS

Patients

In this retrospective study isolated thrombocytopenia patients aged over 18 who admitted to the Department of Hematology of Derince Education and Research Hospital between September 2016 and December 2018 were included to the study. Thrombocytopenia was defined as a platelet count <150.000 mm3. The following data were collected the from patients' electronic medical records: age, gender, complete blood count, peripheral smear, patients' past medical history and bleeding history, laboratory test results (eg. antinuclear antibody, anti-dsDNA, lactate dehyrogenase (LDH). The patients were diagnosed primary ITP according to the American Society of Hematology 2011 guidelines. Primary ITP is defined the platelet count was below 100000 / mm^3 in the absence of other causes or disorders in this guidelines (7). The study protocol was approved by the Institutional Ethics Committee (25.06.2020/ 2020-80).

Statistical Analysis

Statistical analyses were performed with SPSS version 21 (SPSS Inc, IBM, USA). Mean values of each parameters were reported with minimum-maximum values and standart deviation. Categorical data are presented as percentages and numbers. Independent samples T test was used for comparison between groups. All statistical analysis were two sided and significance was defined as $P < 0.05$.

RESULTS

A total of 301 patients were enrolled to this study. Of the patients, 202 were female (67,1%) and 99 (32,9%) were male. The mean age of the patients was 44,89 ± 17,221 (range:18-87) years (in females and in males). The mean age of the female patients group (42.22 ± 16.215 years) was significantly lower than the male patients group (50.34 ± 17.99 years) ($p<0,0001$). Additionally, the mean hemoglobin level was significantly higher in males compared to females ($p<0,0001$). There was no significant difference between the mean platelet and leukocyte levels in the male and female patients. Patients with isolated thrombocytopenia were classified according to the etiological cause and pathophysiological mechanism. Classification of

patients with isolated thrombocytopenia according to etiologic cause is shown in Table 1. Fifty-four people had a platelet count between 100,000 and 150,000/mm3. Physical examination, laboratory findings (ANA, anti-ds DNA, sedimentation, LDH) and spleen size were within normal limits. Since their platelet value was over 100.000/mm3, they were not considered as primary ITP. Of the 54 people, 35 were women (64.8%) and 19 were men (35.2%). The median follow-up was 72 months (12-134 months). In this group of patients platelet levels remained above 100,000/mm3.

Table 1: Classification of patients with isolated thrombocytopenia according to etiologic cause

		Patients(n)	(%)
1)	Pseudo-thrombocytopenia	45	14,9%
a)	EDTA-Dependent	44	14,6%
	Pseudothrombocytopenia	1	0,3%
b)	Platelet Satellitism		
2)	Increased Platelet Consumption	173	57,4%
a)	Primary immune thrombocytopenia	107	35,8%
b)	Secondary	6	1,99%
	b1) Infections	25	8,3%
	b2) Gestational	13	4,33%
	thrombocytopenia[1]	17	5,65%
	b3) Autoimmune collagen	2	0,66%
	vascular diseases	2	0,66%
	b4) Drug-induced[2]		
	b5) Evans Syndrome		
	b6) Lymphomas		
3)	Decreased platelets production	3	0,99%
a)	Hereditary	2	0,66%
b)	Myelodysplastic Syndrome	1	0,33%
4)	Platelets sequestration (abnormal platelet distribution)	27	8,91%
5)	Unknown Cause[3]	54	17,81%

1Multiple mechanism: Physiological hemodilution, accelerated platelet destruction
2 usually immune mechanism, occasionally non-immune mechanism(especially linezolide)
3 In these patients, the platelet count was between 100 and 150.000 / mm3 and there was no pathology explaining this condition.

EDTA-dependent pseudothrombocytopenia (PTCP) was detected in 44 patients and thrombocyte satellitism was detected in one patient. One patient presented to our emergency department with chest pain and was diagnosed as myocardial infarction (MI). Immediately coronary angiography and anticoagulant therapy were planned for the patient. However treatment could not be started immediately due to the level of platelet 23.000/mm3. Pseudotrombocytopenia was detected in the patient by peripheral smear, and MI treatment of the patient was continued without delay.

In 29 patients, splenomegaly was detected in addition to thrombocytopenia. Fifteen out of 29 patients had splenomegaly due to chronic liver disease. Two patients had splenomegaly and thrombocytopenia due to splenic marginal zone lymphoma. One patient was diagnosed with metabolic storage disease. One patient had polycystic kidney-liver disease and splenomegaly. Although bone marrow biopsy was performed in 5 of the remaining 10 patients, no definitive diagnosis was made.

Increased platelet consumption was the most common pathophysiological mechanism causing isolated thrombocytopenia. Distribution of patients with secondary trombocytopenia by etiology is listed in Table 2. 107 patients were diagnosed with primary ITP. 79 of these patients are female (73.8%); 28 of them were male (26.2%). The female / male ratio was 2.8. All ITP with a mean age was 43,08± 17,19 years (range 18-83). The females were younger than the males (mean age 40,78 vs. 49,57 years, $p < 0.035$). We compared demographic and laboratory findings between primary ITP and pseudothrombocytopenia, splenomegaly/ thrombocytopenia,collagen vascular disorders.

Table 2. Distribution of patients with secondary thrombocytopenia by etiology diagnosis

Causes of Secondary immune thrombocytopenia	Patients (n)
1)Infections	6
a) EBV	2
b)HIV	1
c)HCV	1
d)Urosepsis	2
2) Gestational thrombocytopenia	25
3)Autoimmune collagen vascular disorders	13
a)SLE	8
b) Undifferentiated connective tissue disease.	5
4) Drug-induced	17
a) Colchine	4
b)Heparine	4
c)Linezolid	4
d)Carmazepine	3
e)Methotraxate	2
5) Evans Syndrome	2
6)Lymphomas	2
SLL	2

Abbreviation: EBV: Epstein-Barr Virus; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; SLE: Systemic Lupus Erythematosus; SLL: Small Lymphocytic Lymphoma

The platelet levels of primary ITP group was significantly lower than than the other 3 groups. All patients in the collagen tissue disorders group were female. Primary ITP and PTCP are more common in women, while splenomegaly/

thrombocytopenia is more common in men. The leucocyte levels of splenomegaly/ thrombocytopenia group was significantly lower than primary ITP group (p=0,0001) (Table 3).

Table 3. Comparison of primary ITP and disorders that caused isolated thrombocytopenia

	Primary ITP vs Pseudothrombocytenia	Primary ITP vs Splenomegaly /thrombocytopenia	Primary ITP vs Collagen Vascular Disease
Age(years) (mean)	43,08 vs 47,87	43,08 vs 49,52	43,08 vs 38,31
p value	0,15	0,095	0,229
Gender (n)	F:79 vs F:28 M:28 M:17	F:79 vs F:8 M:28 M:21	F:79 vs F:13 M:28 M :0
p value	0,17	**0,0001**	**0,0001**
PLT(mean)(x10^9/L)	42886,92 vs 61446,67	42886,92 vs 102103,45	42886,92 vs 78038,40
p value	**0,01**	**0,0001**	**0,01**
WBC(mean)(x10^9/L)	7194,39 vs 6671,21	7194,39 vs 5206,90	7194,39 vs 6400
p value	0,093	**0,0001**	0,157
Hb(gr/dl)	12,9 vs 13	12,9 vs 13,5	12,9 vs 12,7
p value	0,482	0,052	0,473

Abbreviations: ITP: Immune thrombocytopenia; F:Female ; M: Male ; WBC: White Blood Count;PLT: Platelet; Hb: Hemoglobin.

DISCUSSION

Thrombocytopenia is defined as a platelet count below the 2.5th lower percentile of the normal platelet count distribution. The third US National Health and Nutrition Examination Survey (NHANES III) was yielded potentially reference range for complete blood count. Results of this NHANES III support the classical cut-off value of 150.000 /mm3 as the lower limit of normal for thrombocytopenia (2,8).

Thrombocytopenia is a laboratory finding, not a disease. Etiologic causes of thrombocytopenia can be achieved by a careful history, physical examination and basic laboratory tests. All cases with isolated thrombocytopenia should be evaluated by peripheral smear. Thus the distinction between true and false thrombocytopenia can be clarified.

Ethylene-diamine-tetra-acetic acid (EDTA) is commonly used as an anticoagulant for hematologic tests in laboratory medicine (9). Pseudothrombocytopenia (PTCP) is spuriously the detection of low platelet counts by automated blood counter device despite normal platelet number in peripheral smear. The most important cause of PTCP is EDTA-dependent agglutination. Other rare reasons are platelet satellitism, platelet-leucocyte aggregates, other anticoagulant-dependent agglutination or presence of giant platelets (10). EDTA-dependent PTCP is a rare condition in general population. The prevalence rate of EDTA-dependent PTCP was reported between 0.1-0.13% in general population and approximately 1% in hospitalized paitents (11-13). In contrast, the rate of PTCP was found to be 15.3-17% in the outpatient clinic .In both studies , PTCP was the second most common cause for isolated thrombocytopenia (14,15). We demostrated that when we excluded the group of 100.000-150.000/mm3 patients whose clinical and laboratory findings are normal, PTCP was the second cause with isolated thrombocytopenia. We showed that the rate of PTCP was 14,9 % in our study.

In a study of Bizzaro; observation of 112 cases with EDTA- dependent PTCP showed that the mean age of PTCP was 55.7 years and F/M ratio was 1.6 and also there were no clinical manifestation of disease in the patients during the 5-year (6 months-10 years) follow-up period. This study also confirms that EDTA-dependent PTCP is not pathological significance (16). In our study, the mean age of PTCP patients was 47.87 years, which was lower than Bizzaro's study and F/M ratio was 1,64. EDTA-dependent pseudothrombocytopenia should be kept in mind. Identification of this clinical entity prevents redundant laboratory testing, medical interventions and / or treatments.

Immune thrombocytopenia is an autoimmune disease characterized by immunologic destruction of otherwise normal platelets. Primary ITP was defined as a platelet count less than 100x109/L in the absence of any underlying cause by an International Working Group (IWG) consensus panel (7 ,17,18).

This threshold of 100.000 plt value is preferred rather than 150x109/L based on the following data. The healthy individuals with a platelet count between 100 x109/L and 150 x109/L had only 6,9% chance of developing a persistent platelet count below 100 × 109 / l over a 10-year period. (19). The reference values of platelet counts in healthy individuals in non-Western countries were found to be lower from international data (20-21). This threshold level also prevents to be misdiagnosed

with ITP in most women with gestational thrombocytopenia, a well-known physiological phenomenon (18,22).

In our study, 17.81% of patients with isolated thrombocytopenia had level of platelet between 100-150,000 mm3. The physical examination and laboratory results of this group were normal. A platelet level below 100,000 mm were not detected in this group in an average follow-up period of 72 months according to past medical records.

The incidence of primary ITP in adults is 3.3 / 100,000 per year. Although it is more common in women among young adults, it is seen equally in women and men over 65 years of age (23). In our study, we revealed that primary ITP was the most common cause of isolated thrombocytopenia (35,8%). In our study, 73,8 % of primary ITP patients were women. The mean age with primary ITP in female was 40,78 years.

Primary ITP is diagnosis of exclusion. Since there is no definitive diagnostic test, a comprehensive medical history and physical examination should be done and the causes of secondary ITP should be excluded. The secondary ITP include various diseases such as rheumatological diseases (systemic lupus erythematous, antiphospholipid syndrome), lymphoproliferative diseases (chronic lymphocytic leukemia, B-cell lymphomas), Evans Syndrome;, drug-related thrombocytopenia, common immune deficiency syndromes, HCV, HIV (7,24). Secondary ITP approximately accounts for 18-20% of ITP (24, 25). In our study, approximately 20% of the patients were diagnosed with secondary ITP additionally gestational thrombocytopenia and drug-induced thrombocytopenia were the leading etiological causes.

In conclusion, thrombocytopenia is a laboratory finding which associated with various diseases.In our study, the most common cause of isolated thrombocytopenia was primary ITP and the second cause was PTCP. Among the secondary ITP causes include gestational thrombocytopenia, drug-induced thrombocytopenia and collagen vascular disorders, respectively. When faced with thrombocytopenia, the clinician should initially distinguish between "pseudothrombocytopenia" and true thrombocytopenia by peripheral smear. Then drug and infection-related thrombocytopenia, hypersplenism and obstetric causes should be excluded. After all the secondary causes are eliminated; primary ITP could be diagnosed.

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