British Journal of Medicine & Medical Research
4(1): 104-113, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Etiologic Evaluation of 1012 Patients Admitted with Thrombocytopenia

Mehmet Ali Erkurt[1*], Ilhami Berber[1], Ilknur Nizam[1], Emin Kaya[1], Mustafa Koroglu[1], Irfan Kuku[1] and Omer Kalaylı[1]

[1]Inonu University School of Medicine, Department of Hematology, Malatya, Turkey.

Authors' contributions

This work was carried out in collaboration between all authors. Author MAE designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors IB, IN and EK managed the analyses of the study. Authors MK, IF and OK managed the literature searches. All authors read and approved the final manuscript.

Research Article

Received 25th April 2013
Accepted 24th August 2013
Published 14th September 2013

ABSTRACT

Introduction: Thrombocytopenia is the situation where the number of thrombocytes is less than 150.000/ µL. This may result due to decreased thrombocyte production, increase in the destruction of thrombocytes and differentiation in distribution of thrombocytes. Hereditary and acquired diseases both contribute to the condition, but the acquired reasons are more common in older patients. In this study we aimed to present the patients' data with thrombocytopenia in the eastern Turkey and the underlying diseases that cause thrombocytopenia in order to contribute to literature.
Material and Methods: In this study, we retrospectively aimed to evaluate the etiology of thrombocytopenia at 1012 patients who admitted to Inonu University Medical Faculty Turgut Ozal Medical Center Hematology outpatient clinic, hematology service, emergency department and the ones who were consulted from other departments in the hospital. We collected data of patients for whom we searched the aetiology of thrombocytopenia as Department of Hematology.
Results: Total of 1012 patients, of whom 508 were female and 504 were male, were included to the study. The mean age was 51±20 years. The mean number of the thrombocytes was 64.28±43.05 /mL. The mean number of leucocytes was 13.89±32.71 /µL. The mean level of hemoglobin was 11.22±3.03 g/dL. Leukaemia, infections and the immune thrombocytopenias represented most of the cases, and the other reasons of

**Corresponding author: Email: erkurtali@hotmail.com;*

thrombocytopenia were drugs, chronic liver diseases, megaloblastic anemias, pseudothrombocytopenia, thrombotic microangiopathies and other diseases.
Conclusion: The reasons of thrombocytopenia may differ according to geographic distribution and step level of health centers. It's an expected situation for thrombocytopenia reasons that the high rate of infections can be accused in developing countries and malignant diseases to be the first reason in developed countries.

Keywords: Thrombocyte; thrombocytopenia; etiology.

1. INTRODUCTION

Thrombocytopenia is described as the thrombocyte count below 150.000 per microlitre. There are three major pathophysiological mechanism of thrombocytopenia: decreased production, accelerated destruction and sequestration [1]. Hereditary and acquired diseases contribute to thrombocytopenia, but acquired causes are more common with advancing age. In general, the patients with thrombocyte counts over 100.000 /µL are not expected to bleed even with major surgery. At thrombocyte counts between 50.000-100.000 /µL, bleeding may take longer than usual at the time of several traumas. Even in mild trauma, bleeding may be observed at thrombocyte counts between 20.000-50.000 /µL. If thrombocyte count is smaller than 20.000 /µL, spontaneous bleeding might be observed, and there is a risk of serious bleeding particularly at values lower than 10.000 /µL [2,3].

In clinical practice, the finding of thrombocytopenia is common and often casual. Only in the minority of cases it is found following bleeding or, in complete contrast, after thrombo-embolic events that can occur in the antiphospholipid syndrome and in heparin-induced thrombocytopenia [4,5].

Thrombocytopenia is not a disease but a symptom. For investigating causes of thrombocytopenia in patients, the etiology can be achieved by taking a good clinic history, physical examination and basic laboratory tests. Peripheral blood smear is the initial test for all patients with thrombocytopenia. Normally, 3 to 10 thrombocytes are seen in every area of high magnification. Whether thrombocytopenia is real or not can be distinguished with this test. Causes of thrombocytopenia have a wide range from temporary conditions to serious diseases [6,7].

Causes of thrombocytopenia vary according to geographical distribution and level of application centers. In literature, studies on the etiology of thrombocytopenia in adults do not have large patient numbers. The purpose of this study is to detect the underlying diseases at patients presented with thrombocytopenia and to present thrombocytopenic patients' data in Eastern Turkey to the literature.

2. MATERIALS AND METHODS

In this study, a total of 1012 patients who applied to Turgut Ozal Medical Center of Inonu University Medicine Faculty, at the level of outpatient hematology unit, hematology service, or who were consulted from emergency service and other hospital units, were evaluated retrospectively for etiology of thrombocytopenia between January, 2007 and December, 2011. Approval of University Ethics Committee was taken. Patients included into the study age were 18 years or older at the time of diagnosis. The age, sex, detailed medical histories,

physical examination and medications were recorded from files. Laboratory findings were recorded using an electronic database. Patients whose thrombocyte counts were lower than 150.000/ µL were described to have thrombocytopenia and were included in the study. Thrombocyte count was performed by Beckman Coulter LH 780 (Miami, FL, USA) which is a fully automated hematology analyzer system and it uses impedans method for thrombocyte count. Having thrombocyte counts lower than 100.000 /µLwas taken as a criterion for the diagnosis of immune thrombocytopenia, according to American Society of Hematology 2011[6]. Immune thrombocytopenia was diagnosed by exclusion of other causes of thrombocytopenia. The mean patient age, leucocyte, hemoglobin and thrombocyte counts were calculated.

2.1 Statistical Assessment

Statistical Package for Social Sciences version 15.0 for Windows was used as software for statistical analysis of research data. Measurable variables were presented as mean (X)± standard deviation (SD) and qualitative variables were presented with numbers and percentages.

2.2 Results

A total of 1012 patients who admitted with thrombocytopenia at diagnosis were included to the study. Of these, 508 patients were female (50.19%), 504 were male (49.81%). The mean age of patients was 51 years (47 for females, 54 for males). The mean thrombocyte count of patients was 64.28 /mL ± 43.05 (61.85/ mL for females, 66.72 /mL for males). The mean white blood cell number of patients was 13.89 / mL ± 32.7 (11.97/ mL for females, 15.82/ mL for males). The average haemoglobin was 11.22 g/dL ± 3.0 g/dL (10.85 g/dL for females and 11.6 g/dL for males) (Table 1).

Table 1. Characteristics of patients with thrombocytopenia

(Mean ± SD)	Female	Male	Total
Gender(number/%)	508(50.19%)	504(49.81%)	1012(100%)
Age	47±20	54±19.5	51±20
Platelets(/mL)	61.85±42.54	66.72±43.48	64.28±43.05
Hemoglobin (g/dL)	10.85±2.61	11.60±3.37	11.22±3.03
Leukocytes/µL	11.97±24.920	15.82±38.94	13.89±32.71
MCV (fL)	85.92±7.1	91.63±9.9	88.76±10.7

The numbers of affected patients and frequency of the diseases that caused thrombocytopenia are as follows:

Twenty one patients had thrombocytopenia due to EDTA antibody (2.1%), 5 patients had platelet satellitism (0.5%), 4 had giant thrombocytes (0.4%), where 86 patients had acute myeloblastic leukaemia (AML) (8.5%), 54 had acute lymphoblastic leukaemia (ALL) (5.3%), 21 had chronic lymphocytic leukaemia (CLL) (2.1%), 9 had chronic myeloid leukaemia (CML) (0.9%). Fourteen patients had aplastic anaemia (1.4%), 21 had different types of lymphomas (2.1%), and 12 had myelodisplastic syndrome (MDS) (1.2%). Twenty three patients had solid tumour metastasis (2.3%), 14 had multiple myeloma (1.4%), 6 had myelofibrosis (0.6%), where 2 had paroxysmal nocturnal hemoglobinuria (0.2%). Fifty one patients had megaloblastic anaemia (5.0%), 32 had chronic liver disease (3.2%), 27 had

liver transplantation (2.7%). May-Hegglin anomaly was observed at 1 patient (0.1%), Bernard solier disease at 1 patient (0.1%), Grey Platelet Syndrome at 1 patient (0.1%), Fanconi anaemia at 1 patient(0.1%), amegakaryocytic thrombocytopenia at 1 patient (0.1%), and Von Willebrand disease Type-2b at 1 patient(0.1%). A total of 151 patients were found to have idiopathic thrombocytopenic purpura (14.9%). Twenty five patients had gestational thrombocytopenia (2.5%), 7 had collagenous tissue diseases (0.7%), 13 had autoimmune haemolytic anaemia (1.3%). Twelve patients had heparin-induced thrombocytopenia (1.2%) and other drugs were the cause of thrombocytopenia at 82 patients (7.9%). Two patients had post transfusion purpura (0.2%). DIC was the cause at 31 patients (3%), where 14 patients were affected by thrombotic thrombocytopenic purpura (1.4%), and 13 had HELLP syndrome (1.3%). Massive blood transfusion was the reason at 8 patients (0.8%). Hypersplenism-induced thrombocytopenia was observed at 12 patients (1.2%). Eleven patients had cyclic thrombocytopenia (0.1%), and 11 had iron deficiency anaemia (1.1%). Infections were responsible for thrombocytopenia at 163 patients (16.1%) (Brucella Infections at 12 patients, EBV at 3 patients, HBV at 27 patients, HCV at 16 patients, HIV at 1 patient, Crimean-Congo-Hemorrhagic Fever at 2 patients, H. Pylori infection at 8 patients, Parvovirus at 6 patients, CMV at 3 patients, influenza infection at 47 patients, sepsis at 38 patients). In addition, no aetiology could be determined at 59 patients (5.8%). Distribution of the patients were shown in Table 2. The distribution of patients according to frequency were shown in Table 3.

Table 2. Ratio of the number of patients based on etiology

Disease	Number	Percentage (%)
1. Not real Thrombocytopenia		
a)Depending on EDTA	21	2.1
b)Platelet satellitism	5	0.5
c)Giant platelets	4	0.4
2. Reduced platelet production		
a)Megakaryocytic hypoplasia or suppression		
1. Leukemias		
I) AML	86	8.5
II) ALL	54	5.3
III) CLL	21	2.1
IV) CML	9	0.9
2.Aplastic anemia	14	1.4
3. Lymphomas	21	2.1
4. Multiple myeloma	14	1.4
5. Solid tumor metastasis	23	2.3
6. Myelofibrosis	6	0.6
8. Paroksismal nocturnal hemoglobinuria	2	0.2
b)Ineffective erythropoiesis		
1.Megaloblastic anemia	51	5.0
2.Myelodisplatic syndrome	12	1.2
3.Chronic liver diseases	32	3.2
4.Liver transplantation	27	2.7
c) Hereditary thrombocytopenias		
1.May-Hegglin anomaly	1	0.1
2.Bernard solier disease	1	0.1
3.Gri platelet syndrome	1	0.1

4.Fanconi anemia	1	0.1
5.Von Willebrand Disease Tip2b	1	0,1
6.Amegakaryocytic thrombocytopenia	1	0.1
3. Increased platelet destruction		
a) Immunological		
- Autoimmune		
1.Primer: Immune thrombocytopenia	151	14.9
2.Seconder:		
I) Infections	163	16.1
II) Gestational thrombocytopenia	25	2.5
III) Collagen tissue diseases	7	0.7
IV) Autoimmune hemolytic anemia	13	1.3
V) Drugs		
-HIT	12	1.2
-Other Drugs	82	7.9
-Post transfusion purpura	2	0.2
b) Nonimmunologic		
- Thrombotic microangiopathy		
1.Dissemine Intravascular Coagulation	31	3.0
2.Thrombotic Thrombocytopenic Purpura	14	1.4
3.HELLP Syndrome	13	1.3
- Other		
- Massive blood transfusion	8	0.8
4. Abnormal platelet distribution		
- Hypersplenism	12	1.2
5. Other		
--Cyclic thrombocytopenia	1	0.1
-- Iron deficiency anemia	11	1.1
6. Patients with undetectable	59	5.8
Total	1012	100

Table 3. The distribution of patients according to frequency

Diseases	Number	Percentage(%)
1. Leukemias	170	16,8
2. Infections	163	16,1
3. Immune thrombocytopenia	151	14,9
4. Medications	94	9,1
5. Thrombotic microangiopathy	58	5,7
6. Megaloblastic anemia	51	5,0
7. Chronic liver diseases	32	3,2
8. Pseudothrombocytopenia	30	3,0
9. Liver Transplant	27	2,7
10. Gestational thrombocytopenia	25	2,5
11. Solid tumor metastases	23	2,3
13. Lymphomas	21	2,1
14. Aplastic anemia	14	1,4
15. Multiple myeloma	14	1,4

16. Autoimmune Hemolytic Anemia	13	1,3
17. Myelodysplastic Syndrome	12	1,2
18. Hypersplenism	12	1,2
19. Iron deficiency anemia	11	1,1
20. Massive blood transfusion	8	0,8
21. Connective tissue diseases	8	0,8
22. Myelofibrosis	6	0,6
23. Hereditary thrombocytopenias	6	0,6
24. Paroxysmal nocturnal hemoglobinuria	2	0,6
25. Post transfusion purpura	2	0,2
26. Cyclic thrombocytopenia	1	0,1
27. Patients with undetermined etiology	59	5,8
Total	1012	100

2.3 Discussion

In severe thrombocytopenia, life-threatening bleeding may be occur, so detecting the cause of thrombocytopenia and its treatment may be life-saving. To investigate the cause of thrombocytopenia, medical history, physical examination and basic laboratory tests should be the preliminary steps.

In 16.8% of 1012 patients admitting to our clinic with thrombocytopenia, the reason was leukaemia and it was the most frequent reason of thrombocytopenia. Infections were at the second major cause with a frequency of 16.1%. Immune thrombocytopenia was found to be the third most frequent reason with a frequency of 14.9%. This must be due to the fact that our centre is one of the biggest tertiary centres in Eastern Anatolia serving for about 6 million people and complicated cases are referred to us.

Thrombocytopenia at leukemia can develop as a result of cytotoxic therapy or when the disease progresses to the accelerated and blastic phases. Acute leukaemia accounted for 83% of patients with leukaemia. In a patient with severe thrombocytopenia and bleeding, the physician should think of leukaemia and make the necessary evaluation for early diagnosis.

Infections are among the main diseases that cause thrombocytopenia. Thrombocytopenia is observed most frequently after viral infections. During infections, bone marrow thrombocyte production is suppressed beside the immunological thrombocyte destruction. While two thirds of patients with bacteraemia may have mild or moderate thrombocytopenia, one third of patients may develop severe thrombocytopenia (<50.000 /µL) [8]. At our series, 23% of infection cases had sepsis. The incidence of thrombocytopenia should be considered for the patients in intensive care unit with sepsis. Krishnan et al. had a study about patients with thrombocytopenia in intensive care unit and they reported that those with thrombocytopenia had a higher mortality rate than those without thrombocytopenia [9]. Dealing effectively with the infection may reduce the incidence of patients presenting with thrombocytopenia.

The most common cause of isolated thrombocytopenia is immune thrombocytopenia [10,11]. Our series had similar results.

At drug-induced thrombocytopenia (DITP), severe thrombocytopenia can occur immediately after the first administration of antithrombotic agents that block fibrinogen binding to platelet GP IIb-IIIa, such as abciximab, tirofiban, and eptifibatide [12,13]. At our series, the frequency

of DITP was found as 9.1%. In our patients, the most common causative drug for thrombocytopenia was heparin (1.2% of all cases). Among the drug-related thrombocytopenia, heparin-induced thrombocytopenia (HIT) deserves particular attention [14,15]. The cancer patients who were receiving chemotherapy were not included into the study.

Splenomegaly, immune thrombocytopenia and inadequate thrombopoietin production are the causes of thrombocytopenia in chronic liver disease [16]. Hermos et al. published an article on the longitudinal course of thrombocyte count in a large series of patients with non-hepatitis C-related chronic liver disease, severe thrombocytopenia occurred in a modest proportion of patients 13.4% [17]. At our series, 5.9% of the patients hadthrombocytopenia due to chronic liver disease.

Thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, HELLP syndrome, disseminated intravascular coagulation (DIC) are called thrombotic microangiopathies [18]. At our series, thrombocytopenia due to thrombotic microangiopathy was found to have a frequency of 5.7%.

At our series, 5% of the patients admitting with thrombocytopenia had megaloblastic anaemia.On the contrary of common belief, two –thirds of patients were men and they were young. Megaloblastic anaemia is the one of the most important cause of pancytopenia [19]. For this reason, if a patient presenting with thrombocytopenia has pancytopenia, the physician should suspect megaloblastic anaemia.

The first thing to exclude when thrombocytopenia has been found incidentally, in the absence of clinical symptoms, is the possibility of a pseudo-thrombocytopenia due to in vitro agglutination of thrombocytes in blood collected in to tubes containing EDTA [20]. This event occurs in about one case in every 1.000 healthy individuals and has no clinical significance. It is also important to exclude the so-called "platelet satellitism", due to adhesion of thrombocytes to polymorphonuclear cells [21]. At our series, pseudothrombocytopenia rate was found as 3%. First step of differential diagnosis for thrombocytopenia is to determine whether it's pseudothrombocytopenia or not.

Mechanisms of gestational thrombocytopenia are not clear. The differential diagnosis between primary immune thrombocytopenia and gestational thrombocytopenia is important. [22,23]. Pregnancy rate at our series cases was found as 2.5%. Patients with gestational thrombocytopenia typically had thrombocyte counts above 70. 000 /µL. It occurs at the last period of pregnancy (3rd trimester) and resolves spontaneously after birth.

Thrombocytopenia due to iron deficiency anaemia rate was found as 1.1% at our series. Iron deficiency anaemia is usually the cause of relative thrombocytosis. However, some studies reported that iron deficiency anaemia may also cause thrombocytopenia [24,25].

In the literature, there is one study about investigating aetiology of thrombocytopenia in adults [26]. Bone marrow examination may be performed to all patients who have unexplained aetiology of thrombocytopenia. In our study, bone marrow examination was performed to approximately one third of patients.

As a result of several studies investigating the aetiology of pancytopenia, socioeconomic status and developmental levels of countries have different results [19,27,28]. In our study, we included the patients who have not only isolated thrombocytopenia, but also

thrombocytopenia accompanying bicytopenia and pancytopenia. Causes of thrombocytopenia like pancytopenia may change with geographical distribution and level of application centres. But there's no study to evaluate the relation between thrombocytopenia and developmental levels of countries in the literature. Our results suggest that there may be a relationship.

Infections and nutritional thrombocytopenia are common for aetiology of thrombocytopenia in developing countries. In developed countries, the elderly population rate is higher. Therefore, we can think that malignant diseases are common in developed countries. A large number of patients admit to our centre because it's an important tertiary health centre in Eastern Anatolia. Thus, causes of thrombocytopenia are quite variable. For clarifying this issue, both in developed and in developing countries, more studies which include higher number of patients should be performed.

CONSENT

All authors declare that 'written informed consents' were obtained from all patients (or other approved parties) for publication of this article.

ETHICAL APPROVAL

All authors hereby declare that all actions have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

The authors have no financial or personal relationships referenced to this study.

REFERENCES

1. Goldstein KH, Abramson N. Efficient diagnosis of thrombocytopenia. Am Fam Physician. 1996;53:915-920.
2. Jensen R, Macy P. Thrombocytopenia-Common Etiologies and Laboratory Evaluation. Clinical Hemostasis Review. 2003;17:1-6.
3. Veneri D, Franchini M, Randon F, Nichele I, Pizzolo G, Ambrosetti A. Thrombocytopenias: a clinical point of view. Blood Transfus. 2009;7:75-85
4. Diz-Küçükkaya R, Hacihanefioglu A, Yenerel M, et al. Antiphospholipid antibodies and antiphospholipid syndrome in patients presenting with immune thrombocytopenic purpura: a prospective cohort study. Blood. 2001;98:1760-4.
5. Warkentin TE. An overview of the heparin-induced thrombocytopenia syndrome. Semin Thromb Hemost. 2004;30:273-83.
6. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117:190-207.
7. Doyle B Porter DL. Thrombocytopenia. AACN Clin Issues 1997;8:469-480.
8. Bithell TC. Miscellaneous form of thrombocytopeni. In Lee GR, Bithell TC, Foerster J et al (eds): Wintrobe's Clinical Hematology. 9 th ed. Lea & Febiger, Philadelphia 993;p.1363.

9. Krishnan J, Morrison W, Simone S, Ackerman A. Pediatr. Implications of thrombocytopenia and platelet course on pediatric intensive care unit outcomes. Crit Care Med. 2008;9:502-5.
10. Kaya E, Erkurt MA, Aydogdu I, Kuku I, Ozhan O, Oner RI, Ulutas O. Retrospective analysis of patients with idiopathic thrombocytopenic purpura from Eastern Anatolia. Med Princ Pract. 2007;16:100-6.
11. Nugent D, McMillan R, Nichol JL, Slichter SJ. Pathogenesis of chronic immune thrombocytopenia: increased trombosit destruction and/or decreased trombosit production. Br J Haematol. 2009;146:585.
12. George JN, Aster RH. Drug-induced thrombocytopenia: pathogenesis, evaluation, and management. Hematology Am Soc Hematol Educ Program. 2009;153-8.
13. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, Vondracek T. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med. 1998;129:886-90.
14. Franchini M. Heparin-induced thrombocytopenia: an update. Thromb. J. 2005;3:14.
15. Warketin TE. Heparin-induced thrombocytopenia: pathogenesis and management. Br J Hematol. 2003;121: 535-55.
16. Kajiwara E, Akagi K, Azuma K, et al. Evidence for an immunolocigal basis of thrombocytopenia in chronic liver disease. Am. J Gastroenterol. 1995;90:962.
17. Hermos JA, Altincatal A, Weber HC, et al. Thrombocytopenia and bleeding in Veterans with non-hepatitis C-related chronic liver disease. Dig Dis Sci. 2013;58:562-73
18. Moake JL. Mechanisms of diseases: thrombotic microangiopathies. N Engl J Med 2002; 347: 589-600.
19. Carmel R. Megaloblastic Anemias: Disorders of Impaired DNA Synthesis. Ed. Greer JP, Foerster J, Rodgers GM, Paraskevas F, Glader B, Arber DA, Means RT. Wintrobe's Clinical Hematology.12th ed. Lippincott Williams & Wilkins Co. Philadelphia. 2009; pp 1144-1173.
20. Mant MJ, Doery JC, Gauldie J, Sims H. Pseudothrombocytopenia due to platelet aggregation and degranulation in blood collected in EDTA. Scand J Haematol. 1975;15:161-70.
21. Peters M, Heyderman RS, Klein NJ. Platelet satellitism. N Engl J Med. 1998;339:131-2.
22. McCrae KR. Thrombocytopenia in pregnancy. Hematology Am Soc Hematol Educ Program. 2010;2010:397-402.
23. Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. Blood. 2013 3;121:38-47.
24. Kuku I, Kaya E, Yologlu S, Gokdeniz R, Baydin A. Platelet counts in adults with iron deficiency anemia. Platelets. 2009;20:401-5.
25. Berger M, Brass LF. Severe thrombocytopenia in iron deficiency anemia. Am J Hematol. 1987;24:425–428.
26. Pembrey RG, Handley DA, Kimber RJ. Causes of thrombocytopenia in a hospital population. A six-months survey of 7,750 patients. Med J Aust. 1971 Mar 13;1:5838.
27. Savage DG, Allen RH, Gangaidzo IT, Levy LM, Gwanzura C, Moyo A, Mudenge B, Kiire C, Mukiibi J, Stabler SP, Lindenbaum J. Pancytopenia in Zimbabwe. Am J Med Sci. 1999 Jan;317:22-32.

28. Kumar R, Kalra SP, Kumar H, Anand AC, Madan H. Pancytopenia--a six year study. J Assoc Physicians India. 2001;49:1078-81.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=215&id=12&aid=2004