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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Clinical and Laboratory Findings in Various Reasons of Thrombocytopenia

Farklı Trombositopeni Sebeplerinin Klinik ve Laboratuvar Bulguları

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ÖZ

Amaç: Trombositopeni önemli bir kanama nedenidir. Bu çalışmada farklı nedenlere bağlı trombositopeniler ve onların hemostatik tabloya klinik ve laboratuar açısından yansımaları irdelenmiştir.

Metod: Çalışmaya 1993 ile 2011 yılları arasında Hacetttepe Üniversitesi Erişkin Hematoloji Bölümü'nde takip edilen 29 trombotik trombositopenik purpura (TTP), 36 immün trombositopenik purpura (ITP) ve 35 aplastik anemi (AA) hastası olmak üzere toplam 100 trombositopenik hasta dâhil edildi. Klinik özellikler ve laboratuvar sonuçları değerlendirildi.

Sonuçlar: Hastaların ortalama yaşları TTP grubunda 42.2 ± 19.5 yıl, ITP grubunda 40.1 ± 16.3 yıl ve AA grubunda 34.4 ± 14.7 yıl idi. AA grubunda kadın erkek oranı benzer iken TTP ve ITP grubunda kadınlar çoğunlukta idi. Tromboz, ateş ve sepsis TTP hastalarında daha fazla izlenirken, kanama ise tüm AA hastalarında izlendi. Tüm hasta gruplarında en fazla derialtı kanaması görüldü. TTP hastalarının tümünde mikroanjiyopatik hemolitik anemi (MAHA) ve trombositopeni mevcut iken 25 (%86.2) hastada ateş, 26 (%89.7) hastada nörolojik bozukluk, 16 (%55.1) hastada ise böbrek fonksiyonlarında bozukluk görüldü. TTP tanısı koyarken 5 kriteri de sağlayan 13 (%44.8) hasta; 4 kriteri sağlayan 12 (%41.4) hasta; 3 kriteri sağlayan 4 (%13.8) hasta bulunmaktaydı.

Sonuç: Trombositopenili hastaya yaklaşımda en önemli noktalar başvuru anındaki klinik ciddiyet ve altta yatan hastalıklardır. Trombositopeninin nedenini saptamada klinik yansımalar yardımcı olmakla beraber tanı koydurmakta yeterli değildir.

Anahtar Kelimeler: Trombotik Trombositopenik Purpura, İmmün Trombositopeni, Kazanılmış Aplastik Anemi, Trombositopeni

ABSTRACT

Aim: Thrombocytopenia is an important cause of bleeding. Different clinical conditions associated with thrombocytopenia and their reflections to the hemostatic table will be examined in this study.

Methods: A total of 100 patients with thrombocytopenia who were treated in Hacettepe University between 1993 and 2011, 29 with thrombotic thrombocytopenic purpura (TTP), 36 with immune thrombocytopenic purpura (ITP), and 35 with aplastic anemia (AA), were included in the study. Clinical features and laboratory values were reviewed.

Results: The median ages were 42.2 ± 19.5 years, 40.1 ± 16.3 years, and 34.4 ± 14.7 years in patients with TTP, ITP, and AA, respectively. The majority of patients were female in the TTP and ITP groups, but the female to male ratio was nearly equal in the AA group. Thrombosis, fever, and sepsis were more frequently seen in TTP. The most common bleeding type was subcutaneous bleeding in all patient groups. Among patients with TTP, twenty-five patients (86, 2%) had fever, 26 patients (89, 7%) had a neurologic disorder, and 16 patients (55, 1%) had renal dysfunction. Regarding the diagnostic criteria of TTP, 13 patients (44, 8%) met five, 12 (41, 4%) patients met four and 4 (13, 8%) patients met three criteria.

Conclusion: The severity of clinical presentation and underlying disorders are the most important points with which to approach patients with thrombocytopenia. Clinical reflections may help to identify the cause of thrombocytopenia but not sufficiently demonstrative for diagnosis.

Keywords: Thrombotic Thrombocytopenic Purpura, Immune Thrombocytopenia, Acquired Aplastic Anemia, Thrombocytopenia

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INTRODUCTION

Thrombocytopenia is defined as a platelet count of lower than 150 000 per micro liter of blood. The degree of thrombocytopenia may be subdivided into mild (100 000 - 150 000 /microL), moderate (50 000 – 99 000 /microL) or severe (<50 000 /microL) due to the platelet count (1). Various conditions could be associated with thrombocytopenia, which have risks ranging from life-threatening to no risk at all. Physicians should focus on probable causes and weigh up the consequences of thrombocytopenia such as risk of bleeding, thrombosis, and other complications. Outpatients may be asymptomatic and a common diagnosis is immune thrombocytopenic purpura (ITP). Certain conditions have medical emergency. In some disorders such as thrombocytopenic purpura (TTP) or heparin-induced thrombocytopenia, immediate action is essential (2). The first approach to patients with thrombocytopenia must be the severity of disease. Bleeding among its clinical features is the most important complication. Control of bleeding is crucial in patients with thrombocytopenia. However, bleeding has a direct proportion with platelet count. Secondly, underlying disorders should be determined. Many diagnostic tests should be performed. Accurate and rapid identification of cause is essential in terms of thrombocytopenia, especially in conditions such as TTP and disseminated intravascular coagulation (DIC), because life-saving procedures should be started promptly in these conditions. The most important example is plasmapheresis in TTP. It does not come in to mind easily if the patient has no demonstrative features. The diagnosis of TTP is as easy if the classic pentad is present. Plasmapheresis should be initiated immediately in the presence of clinical suspicion (3).

Generally, three distinct mechanisms or combinations of these mechanisms cause thrombocytopenia (4). First, bone marrow could be insufficient to make platelets. Cancer infiltrating marrow and aplastic anemia (AA) are the most common examples of paucity of bone marrow. Secondly, damage of platelets via autoimmune pathways or non-autoimmune pathways such as infections, medicines, mechanical devices or clotting. Lastly, enlargement of the spleen may lead it to withhold many platelets, which is also called sequestration. For example, thrombocytopenia would be seen in cirrhosis and myelofibrosis due to splenic enlargement.

Two of the common causes of thrombocytopenia are AA and ITP. AA is not just anemia. It is characterized by marrow failure due to stem cell disorder and peripheral pancytopenia. It may be congenital but is most commonly acquired. All three cell lines could be decreased; however, thrombocytopenia and neutropenia would be more problematic. Supportive treatments such as transfusions or stimulating factors are essential. Substantially, the exact treatment is hematopoietic cell transplantation if age is appropriate and a compatible donor has been found (5). Unlike AA, ITP is an autoimmune destruction of platelets. The diagnosis of ITP should be made by excluding other causes of thrombocytopenia. Treatment is not recommended even if the platelet count does not fall below 10 thousand per micro liter in cases of non-bleeding table. If there is bleeding, replacement of thrombocytes and treatment is essential regardless of the number of platelets. Intravenous immunoglobulin and steroids have been main therapies (6). Thrombotic thrombocytopenic purpura is a rare cause of thrombocytopenia, which is characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, fever, neurologic disorder, and renal dysfunction. The criteria for diagnosis was revised in 2006 (7). If a patient has MAHA and thrombocytopenia with or without organ involvement (i.e. renal, neurologic) and without any apparent cause, TTP should be suspected. If there is a mutation in ADAMTS-13 (a disintegrin and metalloproteinase with a

thrombospondin type 1 motif, member 13), von Willebrand factor (vWf) cleaving enzyme, congenital TTP will occur. Antibodies to ADAMTS-13 will result in acquired TTP (8). After plasma exchange in these kinds of disorders, survival improved to 80% from 10% (9).

In this study, we aimed to evaluate the importance of thrombocytopenia and clinical reflections of thrombocytopenia due to ITP, AA, and TTP.

MATERIALS AND METHODS

Study Design and Patient Selection

We retrospectively analyzed 100 patients with thrombocytopenia who were diagnosed as having ITP, AA or TTP and were treated in the Department of Hematology of Hacettepe University Hospital between 1993 and 2011. Age, sex, detailed physical examination, and history including the last medical history was recorded after reviewing the patients' files. Clinical features such as bleeding, thrombosis, fever, neurologic findings, and sepsis; laboratory values such as hemoglobin, platelet count, urea, creatinine, lactate dehydrogenase (LDH) and mean platelet volume (MPV) were noted. For each group, laboratory findings were compared at the time of admission to the hospital and at the time of discharge. Diagnosis of TTP is made clinically and only requires thrombocytopenia and MAHA without another clinically apparent etiology. Absence of neurologic signs or platelet count being greater than 150 000 /mm³ on two consecutive days is adequate to consider a response in patients with TTP. Remission means normal platelet count for 30 days after the last plasmapheresis.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS v. 20.0). The analysis of categorical variables was performed using Fisher's exact test or Chi-square test. The non-parametric Mann-Whitney U or Kruskal-Wallis test were performed for continuous variables, if applicable. In all statistical analyses, $p<0.05$ was considered statistically significant.

RESULTS

Demographic Characteristics

A total of 100 patients with thrombocytopenia, 29 with TTP, 36 with ITP, and 35 with AA were included in the study. The median ages were 42.2 ± 19.5 years, 40.1 ± 16.3 years, and 34.4 ± 14.7 years in patients with TTP, ITP, and AA, respectively. In terms of age, there were no statistical differences between all groups ($p= 0.21$). The majority of patients were female in the TTP and ITP groups, but the female to male ratio was nearly equal in the AA group.

Clinical and Laboratory Features

Thrombosis, neurologic findings, fever and sepsis were seen more frequently in TTP. Bleeding was seen all AA patients. There was no sepsis or neurologic findings with ITP. No patients in the AA group had neurologic findings. Six of 29 patients with TTP had thrombosis in multiple sites. In TTP patients, pulmonary thromboemboli, cranial thrombosis, portal vein thrombosis, deep vein thrombosis, thrombosis in descending aorta and hepatic vein thrombosis were detected in 2, 3, 1, 1, 1, and 1 patients, respectively. Clinical reflections of all three conditions were seen in Table 1. The most common bleeding was subcutaneous bleeding in all patient groups. The classification of bleeding sites is shown in Table 2. Values at admission to hospital and the last values were noted in each group. Some of the changes of these values were statistically significantly different. Laboratory findings are reported in Table 3.

Thrombocytopenia and MAHA was present in all patients with TTP.

Table 1. Clinical features of ITP, AA, and TTP groups				
	ITP (n=36)	**AA (n=35)**	**TTP (n=29)**	***P***
Thrombosis (n, %)	2 (5.6)	1 (2.9)	6 (20.7)	0.03
Bleeding (n, %)	23 (63.9)	35 (100)	19 (65.5)	<0.001
Fever (n, %)	1 (2.8)	23 (65.7)	25 (86.2)	<0.001
Sepsis (n, %)	0 (0)	4 (11.4)	12 (41.4)	<0.001
Neurologic findings (n, %)	0 (0)	0 (0)	26 (89.7)	<0.001

Table 2. Bleeding sites of all three groups			
	ITP (n=36)	**TTP (n=29)**	**AA (n=35)**
Subcutaneous (n,%)	18 (50)	14(48.3)	29 (82.9)
Gastrointestinal (n,%)	0 (0)	2 (6.9)	4 (11.4)
Pulmonary (n,%)	0 (0)	1 (3.4)	0 (0)
Genitourinary (n,%)	0 (0)	2 (6.9)	2 (5.7)
Intracranial (n,%)	0 (0)	2 (6.9)	4 (11.4)
Mucosal (n,%)			
Vaginal	4 (11.1)	4 (13.8)	6 (17.1)
Epistaxis	0 (0)	0 (0)	5 (14.3)
Mouth-gum	3 (8.3)	1 (3.4)	5 (14.3)
Multiple mucosal	2 (5.6)	2 (6.9)	8 (22.9)

Additionally, 25 (86.2%) patients had fever, 26 (89.7%) patients had neurologic findings, and 16 (55.1%) patients had renal dysfunction. Thirteen (44.8%) patients met five criteria for the diagnosis of TTP, 12 (41.4%) patients met four, and 4 (13.8%) patients met three criteria. Eleven of 29 patients had an underlying disorder that lead to TTP and 18 of 29 patients had none, thus the latter were considered as idiopathic TTP. Among the patients with secondary TTP, 4 had systemic lupus erythematosus (SLE), 3 had hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome, 1 patient had gastric adenocarcinoma with bone marrow metastasis, and 1 patient had Burkitt's lymphoma. Apart from these, one case was dependent upon the use of cyclosporine after renal transplantation, and another patient underwent bone marrow transplantation with a diagnosis of acute lymphoblastic lymphoma and was also using cyclosporine.

Table 3. Laboratory findings of the three groups				
		ITP	**TTP**	**AA**
Hemoglobin (g/dL)	Admission	13.4	8.6	7.3
	Last	12.6	10.2	9.5
		p=0.01	*p=0.009*	*p<0.001*
Platelet count (x10³/μL)	Admission	17	25	13
	Last	222	186	68
		p<0.001	*p<0.001*	*p<0.001*
Creatinine (mg/dL)	Admission	0.6	1.2	0.8
	Last	0.7	0.8	0.9
			p=0.03	
LDH (U/L)	Admission	499	1641	444
	Last	381	614	428
			p<0,001	
MPV (fL)	Admission	8.8	8.3	7.3
	Last	8.5	7.9	7.4

Treatment

The median number of plasmapheresis sessions was 17 (range; 2-127) in patients with TTP. There was no relation between session count and remission. Twenty-one of 29 patients showed response; 8 patients did not respond (72%). Two patients died of relapsing disease despite initially responding to plasmapheresis, along with 8 (34%) unresponsive patients. In these patients, a median of 7 (range; 0-100) units of platelets and 6 (range; 0-25) RBC replacement units were administered. Other therapeutics used in patients with TTP in our study are represented in Table 4. Patients with ITP and AA were treated with appropriate treatment protocols.

Table 4. Treatment modalities in patients with TTP		
	Remission n=21	**Unresponsive n=8**
Number of plasmapheresis session (range)	2-127	7-44
Steroid (n/%)	21 (72.4)	7 (24.1)
Pulsed steroid (n/%)	2 (6.9)	1 (3.4)
Cyclosporine (n/%)	4 (13.8)	0 (0)
Cyclophosphamide (n/%)	4 (13.8)	1 (3.4)
IVIG (n/%)	6 (20.6)	1 (3.4)
Vincristine (n/%)	5 (17.2)	3 (10.3)
Rituximab (n/%)	1 (3.4)	0 (0)
Splenectomy (n/%)	2 (6.9)	0 (0)

DISCUSSION

The clinical presentation and first laboratory findings help in the differential diagnosis of thrombocytopenia. In addition, the differential diagnosis may sometimes be compulsive. For example, thrombosis is not unique to TTP and thrombotic risk is not associated with the platelet count. It might be seen in the course of other thrombocytopenic conditions. Disseminated intravascular coagulation, heparin-induced thrombocytopenia, antiphospholipid syndrome, and TTP are the best known conditions concurrently associated with thrombocytopenia and thrombosis. Occasionally it looks like a double-edged sword and can be very difficult to manage (10). Although it is not demonstrative, neurologic findings with thrombocytopenia should indicate TTP. There were no neurologic findings in the ITP and AA groups in our study. Fever and sepsis might be seen in many conditions, especially infectious conditions. Bleeding is directly proportional to platelet count (11). Patients with AA had lowest platelet count and it is ordinarily expected that all of patients with AA had bleeding.

Changes in laboratory values were as expected. However, in the case of MPV, if there is destruction of platelets such as ITP or TTP, MPV could be found to increase, whereas if there is a production defect such as in AA, MPV could be found to decrease or be unchanged (12). In a study, among 175 patients with thrombocytopenia of unknown cause, 84 had bleeding (13). MPV values in these patients with bleeding symptoms were found significantly lower. MPV values of fewer than 8 fL identified a 7-fold increased risk of bleeding. In our study, patients with AA had lower MPV than in the other two groups, and it was found statistically different. This result is similar to findings in the literature.

We highlight a curious cause of thrombocytopenia, TTP. MAHA and thrombocytopenia is sufficient for a diagnosis of TTP. The frequency of criteria for diagnosis of TTP was similar to the literature in this study (14). ADAMTS 13 activity and inhibitor testing was not used because of the retrospective study design. These tests may be useful for diagnosis today. The immediate commencement of plasmapheresis is crucial and the response to plasmapheresis is generally good. The response rate to plasmapheresis and mortality in the present study were similar to other studies conducted in our country (15). As in the literature, other agents were used in our study and response rates were in line with the literature. However, antibodies such as rituximab were rarely used in our retrospective analysis. Recent studies have shown that rituximab has high response rates in refractory cases (16). New diagnostic tools such as ADAMTS13 activity and inhibitor testing and novel agents for treatment such as rituximab are promising in TTP (17).

Our study has some limitations. The retrospective nature is the first limitation of our study. Due to the retrospective analysis, survival results were not ideal and the correlation between time of diagnosis and onset of treatment was unapparent. The selection of patients might be a second limitation of our study. Our hospital is a third-line health institution, so the time for patients

with uncommon diagnosis to reach our hospital could be long. In total, 29 patients with TTP were found between 1993 and 2011. Therefore, the number of patients with TTP was low for our institution. There were many patients with ITP and AA in the period during which the study was conducted. However, patients in the ITP and AA groups were selected according to the accessibility of patient files. Selection bias of these groups may have occurred. Although distinct causes of thrombocytopenia should not be compared, they might be evaluated in terms of clinical reflections. There was no direct comparison between groups in our study. Demographic data were revealed simply. On the other hand, the number of patients was not sufficient to display characteristics of diseases. The low number of patients was another limitation of our study.

Herein, in the context of clinical and laboratory parameters, we aimed to evaluate two commonly seen thrombocytopenic conditions, ITP and AA, and also a rare disorder, TTP. Physicians should not focus on only one cause of thrombocytopenia, the cause may sometimes be hard to identify, as in TTP. Generally, but not always, patients with ITP are asymptomatic. Bleeding is seen in patients with AA. Patients with TTP may present with diverse clinical pictures such as fever, thrombosis, and organ failure. This rare cause of thrombocytopenia has to be kept in mind because if therapeutic plasma exchange is initiated promptly, the disorder would probably resolve.

The severity of clinical presentation and underlying disorders are the most important points with which to approach patients with thrombocytopenia. Clinical reflections may help to identify the cause of thrombocytopenia but not sufficiently demonstrative for diagnosis.

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Compliance with Ethical Standards:

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