ORIGINAL ARTICLE

Thrombotic Thrombocytopenic Purpura: A Single-Center Experience in Jordan

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ABSTRACT

Background: Thrombotic thrombocytopenic purpura is a relatively rare disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage. The early recognition is critical because it is an emergency condition requiring urgent therapeutic plasma exchange, which is a life-saving procedure and the cornerstone of the management.

Methods: A retrospective descriptive study was conducted at the Department of Medicine-Hematology at King Hussein Medical Center, Amman, Jordan, between June 2018 and July 2019. All patients from all departments who were diagnosed with Thrombotic thrombocytopenic purpura during the study period were enrolled. We obtained the information from all patients concerning demographic data, signs, and symptoms of presentation, and the results of investigations at admission and discharge. The number of plasma exchange sessions, days of hospitalization, usage of Rituximab, and outcome.

Results: 21 patients were enrolled, predominantly female (67%), the median age was 36.67 years. At diagnosis, 81% of patients showed neurological involvement. The median platelet count at presentation was 20.000/μL. All patients were anemic (mean HCT,25.42). Schistocytes were present in the peripheral blood film of all patients. The median number of plasma exchange sessions was 19 (range, 2–42), and the mean stay in hospital was 25 ± 11.6 days. Rituximab was administered to 11 patients (52%). A complete response was achieved in 62% (13/21) of patients, The mortality rate was 38% (8/21 patients). None of the patients' characteristics or laboratory results at presentation were significantly associated with mortality.

Conclusions: Although our study included a limited number of TTP patients, our findings revealed that our patients had poor prognostic factors and were less responsive to PEX than TTP patients in other countries. Our data also confirm a better survival rate in younger patients than in the elderly.

Key words: Thrombotic Thrombocytopenic Purpura, Jordan, Plasma Exchange, Rituximab.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a form of thrombotic microangiopathic anemia (TMA). This relatively rare disease characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and end-organ damage of varying severity due to ischemia resulting from thrombosis formation in small arteries, arterioles, and capillaries [1].TTP is distinguished from other types of TMA by a severe deficiency (<10%) of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a plasma protein that clears ultra-large von Willebrand factor (VWF) multimers. ADAMTS13 deficiency could be congenital, due to biallelic mutations in the ADAMTS13 gene, or acquired, like TTP. The accumulation of ultra-large VWF multimers causes platelet aggregation and adhesion in small vessels, leading to the formation of disseminated microthrombi, causing the clinical picture of TTP [2]. The global incidence of TTP is two cases per million people per year, with a median age of onset in the fourth decade of life. It is more common in females than in males, with a female: male ratio of 2–3:1 [3].

We conducted a one-year retrospective study at King Hussein Medical Center, a tertiary referral hospital in Amman, Jordan, to assess the incidence of TTP and analyze the clinical characteristics, clinical and laboratory examination results, treatments, outcomes, and prognosis of 21 TTP cases.

MATERIALS AND METHODS

This retrospective descriptive study was conducted at the Department of Medicine-Hematology at King Hussein Medical Center, Amman, Jordan, between June 2018 and July 2019. All patients from all de-

partments who were diagnosed with TTP during the study period were enrolled. The diagnostic criteria for TTP included the presence of MAHA [confirmed by anemia, >1% schistocytes on the peripheral blood film, and high lactate dehydrogenase (LDH)] along with thrombocytopenia, with or without end-organ damage. We excluded cases with elevated international normalized ratio and patients with malignant hypertension or metastatic malignancies. The study was approved by the ethical committee of the Royal Medical Services, Amman, Jordan. We obtained the information from all patients concerning demographic data, signs, and symptoms of presentation, and the results of investigations at admission and at discharge, including the number of schistocytes in the peripheral blood film, platelet count, hematocrit (HCT), white blood cells, creatinine, and LDH. The number of plasma exchange (PEX) sessions, days of hospitalization, usage of Rituximab (RTX), and outcome were also documented. Because a test to determine the level of ADAMTS 13 was unavailable at our hospital. Highly suspicious cases of TTP underwent emergency PEX, where 1.0–1.5 times the patient's plasma volume was replaced by type-specific fresh frozen plasma. Vascular access was obtained by the insertion of central venous catheters into the jugular or femoral veins. The weekly RTX dose was 375mg/m^{2}until complete response was achieved. Remission was defined as a clinical improvement in the general condition of the patient along with normalization of the platelet count, HCT, and creatinine, with no evidence of schistocytes in the peripheral blood film. Statistical analysis was performed using IBM SPSS Statistics 25.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive data were presented as the median, mean, and standard deviation, with the range and percentage where applicable. A P-value <0.05 was considered statistically significant.

RESULTS

Because TTP is an extremely rare disease, only 21 patients were identified during the study period. The patients were predominantly female (14/21, 67%), and the median age was 36.67 ±13.76 years. Our hospital only treats adult patients, so the age range was 20–62 years old. The presenting symptom was a headache in 6, fever in 4, and bleeding in 10 patients (ecchymosis and petechial rashes,5; epistaxis,2; rectal bleeding,1; gum bleeding,1; and hematuria, 1). At diagnosis, 81% (17/21) of patients showed neurological involvement (headache,12; seizure, 1; hallucination, 2;and disorientation, 2). The duration of presenting symptoms before diagnosis was 5.1 days (range, 3–21 days). The pentad of clinical features of TTP((i.e, neurological symptoms, fever, acute renal failure, anemia, and thrombocytopenia) was only documented in two patients (9%). Patient Characteristics at the Time of Diagnosis summarized in Table 1. The median platelet count at presentation was 20.000/μL(range, 6000–82,000/μL). All patients were anemic (mean HCT,25.42 ± 5.27g/dL; range, 18–37 g/dL). There were five (23%) patients who presented with renal impairment. The highest creatinine level in the TTP patients was 7.2mg/dL (mean, 1.49 ± 1.61). One patient with acute renal failure required hemodialysis. LDH was elevated above the upper limit of normal in all patients (mean LDH, 2900 ± 1483 U/L; range, 698–6120). Schistocytes were present in the peripheral blood film of all patients, with>5%schistocytesseen in 5/21 (24%) cases, while 1%–5% schistocytes were documented in 12/21 (57%) patients.

The risk factors of TTP were unknown, except in six cases (29%), of whom five were pregnant and one who had mild HIV. All patients in our study received PEX.

Table 1: Patient Characteristics at the Time of Diagnosis (n=21)

Demographic/ clinical Features	Study population
Demographic	
Mean age(years)	36.67 ±13.76
Sex (%female)	67%
Clinical features	
Neurologic abnormalities (%)	81%
Bleeding	48%
Renal abnormalities (%)	23%
Complete pentad (%)	9%
Clinical course	
Complete response (%)	62%
Death (%)	38%
Plasma exchange sessions (range)	19 (2–42)
Rituximab need	52%

Table 2: Laboratory results at the time of diagnosis and at discharge

Laboratory data	Admission (n=21)	Discharge (n=13)	Normal range
WBC count	4.5	7.6	4-10x109/L
Hematocrit	20%	36%	F 36-48%/M 45-52%
Platelet count (μL)	20,000/μL	210.000/μL	150,000-400,000 /μL
Creatinine (mg/dL)	1.5 mg/dl	2.16 mg/d	0.72-1.25 mg/dL
LDH (units/L)	2900 U/L	310 U/L1	125-220 U/L
Shistocytes %	6%	0%	nill
T.bilirubin	4.6 mg/dL	1.2 mg/dL	0.2-1.2 mg/dL

The median number of PEX sessions was 19 (range, 2–42), and the mean stay in hospital was 25 ± 11.6 days (range, 3–42). One to four doses of RTX were administered to11 patients (52%) who were refractory to PEX and one patient with relapsed disease. A complete response was achieved in 62% (13/21) of patients, all of whom had a platelet count >210,000/μL at discharge. We used a platelet cut-off value of>150,000/μL to define a complete response and>100,000 to define a partial response. Thus, all patients who responded achieved a complete response, and no partial responses were noted. The mean patient age was 35.5 years and 43.9 years in patients who achieved a response and failed to respond, respectively, but this was not statistically significant (P=0.1). The creatinine level on admission and at discharge was 1.49 ± 1.61 mg/dL and 2.16 ± 2.43 mg/dL, respectively. Thus, complete remission and mortality were not associated with acute renal failure at presentation. One patient (1/13, 8%) who achieved a complete response relapsed after 4 months, complete response was achieved again following 10 sessions of PEX with RTX, and he was discharged 3 weeks after admission. The mortality rate was 38% (8/21 patients), with four patients dying within the first week and the remainder dying 1 week after commencing PEX treatment. Death was due to septic shock and multi-organ failure in three cases and gastrointestinal bleeding in three cases. One patient died from intracranial hemorrhage and one from diffuse alveolar hemorrhage. None of the patients' characteristics or laboratory results at presentation were significantly associated with mortality.

DISCUSSION

The early recognition of TTP is critical because it is an emergency condition requiring urgent therapeutic PEX, which is a life-saving procedure in TTP.PEX is the cornerstone of TTP management. Before the era of PEX, the mortality rate was >90%. PEX has dramatically improved the prognosis of TTP, with a remission rate >90%. Daily PEX allows for the repletion of ADAMTS13 and the removal of autoantibodies against ADAMTS13 [4].In recent years, the introduction of humanized anti-CD20 Rituximab in refractory and relapsed TTP made a breakthrough in TTP management and led to further improvement in the prognosis of the disease. Recently, many trials involving RTX in frontline management along with PEX showed significantly shorter hospitalizations, better patient response, and less recurrence than those who were treated with PEX alone [5].Our study is one of the few studies focusing on TTP management in Jordan. The sample size of 21 patients was relatively large, considering the rarity of the disease; however, the incidence of TTP in Jordan has not been documented. Our study findings affirmed the results of other cohorts regarding the female predominance of TTP, with over two-thirds of TTP patients being female [6]. The median age for our patients was 36.7 years, which was relatively younger than the patients in other studies and could be attributed to the population of Jordan being younger than those in Western countries [7]. Bleeding was the most common presenting symptom in our cohort, followed by headache and then fever. All patients who presented with bleeding symptoms had a mild degree of hemorrhage, mostly presenting as ecchymosis and petechial rashes, although epistaxis, rectal bleeding, gum bleeding, and hematuria were also observed. Neurological symptoms were documented in 81% of patients, of whom seven had severe neurological symptoms, like severe headache, hallucination, disorientation, and seizure. The classical pentad of TTP was documented in a minority of patients, consistent with other case series [8]. The mean presenting platelet counts in our cohort was 20,000/μL, which was very low in comparison with most previous series, reflecting the higher degree of TTP severity in our patients [9]. The mean HCT was 25.4 g/dL, which was again considered lower than most series [10]. The proportion of patients with renal involvement was relatively lower than in previous reports [11]; it was documented in five of our patients, of whom only two had moderate to severe renal impairment. This could be related to our patients seeking early medical care, resulting in the detection of TTP in the early stages. The high LDH level reflects the degree of hemolysis, with a high level related to a larger proportion of schistocytes in the peripheral blood [12]. MAHA with red blood cell fragmentation (i.e., schistocytes) is the most important criterion for presumptive TTP diagnosis [13], it was observed in of all our TTP patients. Few patients had a predisposing factor of TTP (five patients were pregnant and one patient had HIV). Although pregnancy-associated TTP is a rare disorder with significant mortality and morbidity that usually occurs post- or antepartum [14], it made up 24% of our cohort. This could be attributed again to the high percentage of the young population in Jordan (68% are below the age of 30)[15]. TTP treatment involves PEX along with steroids. The introduction of PEX resulted in a decline in the mortality of TTP patients from 90% to <20% and is usually based on the replacement of 1.5 times the patient's plasma volume [16]. In our study, all patients received PEX within few hours of diagnosis. TTP is one of the highest emergency conditions in medicine because it carries high mortality if PEX is delayed [17]. In our study, the response to PEX was based on the normalization of the platelet count and the resolution of MAHA based on the absence of schistocytes in the peripheral blood film. A complete response was confirmed in 62% of our patients, which was lower than previously reported. The mean platelets count at discharge

was 210,000/μL in contrast to 20,000/μL at admission. None of our patients achieved a partial response (defined as a platelet count of 100,000–150,000/μl). Laboratory results at the time of diagnosis and discharge documented in Table 2. The mean age of patients who achieved a complete response was 35.5 years, while in patients who failed to respond, the mean age was 43.9 years. Although this suggested that younger patients tended to have a higher rate of response than older patients, the association was not statistically significant (P =0.1). None of the presenting factors (age, sex, HCT, platelets, bilirubin, creatinine, LDH, percentage of schistocytes on the peripheral blood film, or presenting symptoms) was statistically significant to predict a response. Our PEXprotocol is 1.5 plasma volumes daily until normalization of the platelet count. In our study, the median number of PEX sessions was 19, which was relatively higher than previous reports in other countries [18]. The reason for the high number of sessions in our study was because PEX was continued until the platelet count was>150,000/μl, while in other institutions, PEX was discontinued when clinical symptoms resolved and the platelet count reached a predetermined level that was lower than ours of150,000/μL. RTX is a monoclonal antibody targeting CD20 on B-lymphocytes, resulting in a reduction of antibodies directing against ADAMTS13.RTX is used in refractory and relapsed cases of TTP, and it has a high response rate in these subset groups. However, there are few trials on the effectiveness of RTX in TTP treatment [19]. The standard weekly RTX dose is 375mg/m^2.RTX was administered to 52% of our patients, and a maximum of four weekly doses was administered in two cases. The mortality rate in our study was 38%, which was higher than the20% mortality rate in the Canadian Apheresis Study Group trial and the 21.3% mortality reported by Shamseddine et al [20,21].In our study, half of the fatalities occurred early within 1 week of diagnosis.

Our study has several limitations. First, the small sample size made it difficult to empower the small differences between subgroups. Second, the follow-up period was short, so the recurrence rate was underestimated. Third, a test to determine the plasma level of ADAMTS13 was unavailable at our institution. While this is not essential for TTP diagnosis, a severe deficiency of ADAMTS13 increases the suggestion of TTP in the presence of clinical symptoms and schistocytes on the peripheral blood film.

CONCLUSIONS

Although our study included a limited number of TTP patients, our findings revealed that our patients had poor prognostic factors and were less responsive to PEX than TTP patients in other countries. Our data also confirm a better survival rate in younger patients than in the elderly.

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