

Clinical and Laboratory Profile of Patients with Thrombotic Thrombocytopenic Purpura Seen at the University of Sto. Tomas Hospital: A Single Center Experience

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Abstract

Background: Thrombotic thrombocytopenic purpura (TTP) is considered a rare disease. In the Philippines, there are currently no local registry for such rare disease, thus clinical features that may be unique to the country is difficult to characterize.

Objective: To characterize the TTP patients seen in our institution based on the demographic, clinical and laboratory profile of these patients.

Results: A total of eight patients were described in this report. Median age was 38 years (range, 20-63) with a female predominance. All patients had neurologic symptoms and microangiopathic hemolytic anemia. Minor neurologic symptoms (confusion, headache and dizziness) were more frequently observed. Renal dysfunction (serum creatinine >1.4 mg/dL), fever (>38.0°C), and thrombocytopenia were observed in four patients (50%), seven patients

(87.5%), and six patients (75%), respectively. Patients underwent median of three sessions of Plasma Exchange (range, two to 38). Of the six patients who received therapeutic plasma exchange, five were discharged alive.

Conclusion: Fifty percent of the patients in this report presented with the classic pentad. This feature should be kept in mind as TTP is a true hematologic emergency. A high index of suspicion, prompt evaluation and treatment of patients are necessary because multi-organ thrombosis may not be reversible, if treatment is not urgently administered. Therapeutic Plasma Exchange is the management of choice and should be done immediately once TTP is recognized.

Keywords: Thrombotic Thrombocytopenic Purpura, Therapeutic Plasma Exchange

Introduction

In 1924, Eli Moschcowitz first reported thrombotic thrombocytopenic purpura (TTP) and is characterized by a pentad of findings that include microangiopathic hemolytic anemia, thrombocytopenia, renal failure, neurologic findings, and fever¹⁻². It is characterized by a widespread thrombi mainly composed of platelets in the terminal circulation of several organs.

Thrombotic thrombocytopenic purpura is considered a rare disease with reported incidence in the United States of approximately 4.5 per million per year, with a male: female ratio of 2:1.³ Worldwide incidence is difficult to ascertain due to lack of registry. In the Philippines, there are currently no local registry for such rare disease, thus clinical features that may be unique to the country is difficult to characterize.

The importance in recognizing and diagnosing acute TTP lies in the urgent requirement for treatment, specifically with Therapeutic plasma exchange (TPE) as it has been shown to reduce mortality in these patients.

The objective of this paper is to characterize the clinical and laboratory profile of patients with TTP seen in our institution.

Materials and Methods

A retrospective analysis of the clinical records of patients with thrombotic thrombocytopenic purpura (TTP) seen from January 2009 to March 2013 in a tertiary hospital was done. The data on demographic and laboratory profile were recorded and were analyzed. Current status of the patient was followed-up through phone or text message.

The statistical analyses included descriptive statistics (frequency and percentage of categorical variables and mean and standard deviation of continuous variable). Comparison of variables were done using T- test to compare two groups with numerical data, and Fisher's exact test to compare categorical data. A p value of <0.05 was considered statistically significant.

Results

A total of eight patients diagnosed with TTP in our setting from January 2009 to March 2013 with an average of 1.6 patients per year seen. The eight

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patients with TTP were predominantly female with a median age of 38 years (Table I).

All patients had microangiopathic hemolytic anemia and neurologic symptoms at the time of presentation (Figure 1). Thrombocytopenia at the time of presentation was seen in six of the patients; however, the two remaining patients eventually developed marked thrombocytopenia in their clinical course. Four patients had renal failure but only two of them required dialytic therapy. Neurologic symptoms were primarily minor with transient confusion predominating as a subtle symptom (Figure 2). Half of the population cohort presented with the classic pentad.

Table I: Demographic and laboratory profile of patients with TTP at presentation

Demographical Features	
Age (median, y)	38 (20-63)
Sex (n,%)	
Males	2 (25%)
Females	6 (75%)
Laboratory Data (median, range)	
Hemoglobin, g/dL	72.5 (56-10.6)
Hematocrit, %	27.5 (17-31)
Platelet count, x109/L	28 (11-200)
LDH, U/L	2187 (918-3015)
Creatinine, mg/dL	1.18 (0.52-7.66)

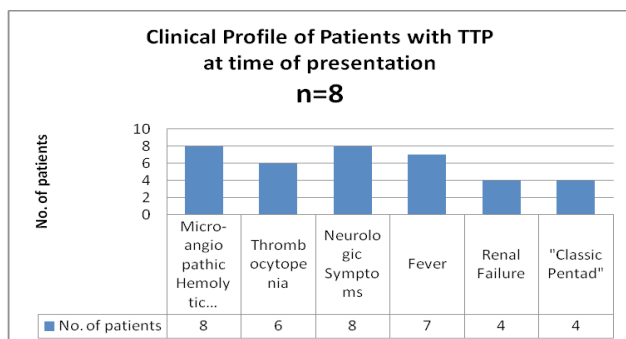


Figure 1: Clinical profile of patients with TTP at time of presentation

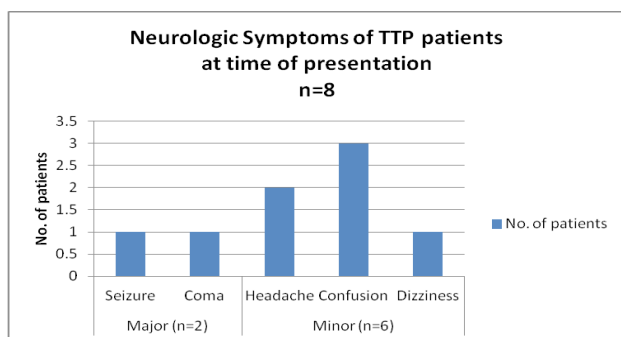


Figure 2: Neurologic symptoms of patients with TTP at time of presentation

Seven of the eight patients received plasma infusion as a "holding measure" until plasma exchange could be arranged (Table II). Only six of the patients eventually received TPE with a median number of three plasma exchanges. Half of the patients received steroids (two of these patients received high dose methylprednisolone with taper to oral prednisolone). Only one patient received further immunosuppressant in the form of rituximab and cyclophosphamide. Of the six patients who received TPE, five of the patients were discharged alive.

Table II: Therapy of patients with TTP

Therapy	No. of Patients
Plasma Infusion	7
Therapeutic Plasma Exchange	6
Number of Plasma Exchange (median, range)	3 (2-38)
Steroids (oral prednisolone and/or High Dose Methylprednisolone)	4
Rituximab	1
Other Immunosuppressive (e.g. Cyclophosphamide, Vincristine)	1

On further work-up for probable cause of TTP, half of the patients had no identifiable underlying condition (Figure 3). Two of the patients had TTP as the presenting manifestation of an occult underlying malignancy (breast cancer and disseminated signet ring carcinoma). Moreover, TTP was the presenting manifestation, as well of the patient with SLE.

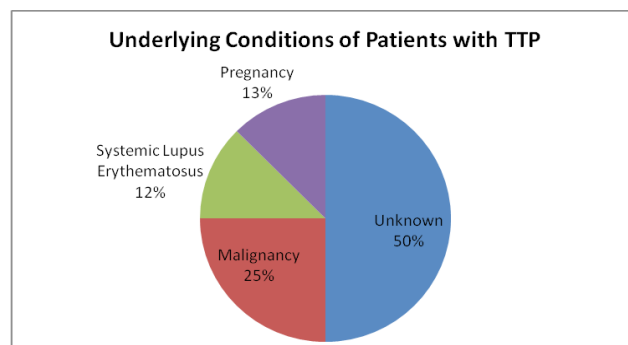


Figure 3: Underlying conditions of patients with TTP

There were three patients who died in this study cohort. Two of the three patients who died had an underlying malignancy, while the other one died of septic shock secondary to gram negative septicemia. Two patients were lost to follow-up.

Of the six patients (two patients were lost to follow-up) evaluable for outcome measures, none of the baseline demographics, clinical and laboratory profile predicted outcome (Table III). Although patients who had lower platelet counts appeared to have a more favorable outcome (23.33 + 10.7 vs. 161.83 + 88.57, p 0.05), it did not reach statistical significance.

Table III: Relationship of Clinical and Laboratory Profile with Outcome

Parameter	Alive	Died	P value
Sex			1.00 (NS)
Age	42.67 + 21.59	45.33+ 22.03	0.89 (NS)*
Presence of Microangiopathic Hemolytic Anemia			1.00 (NS)
Presence of Neurologic Symptoms			1.00 (NS)
Presence of Renal Failure			1.00 (NS)
Presence of Thrombocytopenia			0.40 (NS)
Presence of Fever			1.00 (NS)
Hemoglobin (g/dL)	51.83 + 37.3	66.53 + 48.57	0.70 (NS)*
Platelet count, x109/L	23.33 + 10.7	161.83 + 88.57	0.05 (NS)*
LDH, U/L	2209.67 + 953.20	1415 + 560	0.28 (NS)*
Creatinine, mg/dL	3.3 + 3.8	1.11 + 0.5	0.38 (NS)*
Rose and Eldor Score§	4.67+ 0.58	3.33 + 1.15	0.15 (NS)*

* t-test is used, otherwise, fisher's-exact

§ The severity of the disease was assessed with the Rose and Eldor scoring system, which evaluates the platelet count, hemoglobin level, the serum creatinine level, and neurologic function⁴. Each category is given a score of 0 (normal findings), 1 (mildly abnormal clinical or laboratory findings), or 2 (markedly abnormal clinical or laboratory findings) on the basis of specific criteria; a total combined score of 4 or more indicates a diagnosis of severe thrombotic thrombocytopenic purpura. A platelet count of more than 100,000 per cubic millimeter is assigned a score of 0, a count of 20,000 to 100,000 per cubic millimeter a score of 1, and a count of less than 20,000 per cubic millimeter a score of 2. A hematocrit value of more than 36 percent is assigned a score of 0, a value of 27 to 36 percent a score of 1, and a value of less than 27 percent a score of 2. A serum creatinine level of less than 1.5 mg per deciliter (133mmol per liter) is assigned a score of 0, a level of 1.5 to 2.5 mg per deciliter a score of 1, and a level of more than 2.5 mg per deciliter a score of 2. A score of 0 is assigned if no neurologic deficits are present; a score of 1 if confusion, lethargy, or behavioral changes are present; and a score of 2 if a focal deficit, convulsions, stupor, or coma is present.

Discussion

The present report summarized all the cases of TTP presenting over a period of 4.25 years in our institution. The median age in our study is 38 years. This finding is comparable with Miller et. al epidemiologic study of TTP, which included three large populations in the United States, United Kingdom, and Canada, with a peak incidence between ages 30 and 50 years³. Likewise, the same peak age incidence was observed in South Korea in a study by Kim et. al, showing a median age of 47 years⁵. Both studies also noted a female predominance with a 2-3:1 ratio which was also observed in the present report.

Microangiopathic hemolytic anemia was seen in all patients in this study. This was also the observation in the study by Kim et. al and from the UK TTP registry⁶. Microangiopathic hemolytic anemia is expected to be seen in all patients as this is central to the pathogenesis of TTP. The pathophysiology of TTP has been clarified as an acute deficiency of von-Willebrand factor (VWF)-cleaving metalloprotease (ADAMTS13). ADAMTS13 deficiency results in the accumulation of ultra-large vWF multimers, which bind platelets, and leads to both thrombi in the microvasculature and thrombocytopenia. The micro thrombi then cause MAHA by shearing of red blood cells due to increased shear stress⁷.

Thrombocytopenia was also essentially found in all patients as reported by Kim et. al and the UK TTP registry. Thrombocytopenia is indeed expected in almost all cases of TTP due to increased platelet

binding in the endothelium. However, in this study, two out of the eight patients presented with a normal platelet count with a rapid decline during the clinical course. These two cases were eventually investigated to have an occult malignancy, one with breast cancer and one with disseminated signet ring carcinoma. Both patients were found to have metastatic disease to the bone marrow. A plausible explanation of the initial normal platelet count is that patients with disseminated cancer have higher levels of Vascular Endothelial Growth Factor (VEGF) compared to healthy controls⁸. In cancer patients, a high B-VEGF concentration was associated with a high platelet count. Besides stimulating proliferation of tumor blood vessels, VEGF also increases vascular permeability possibly contributing to tumor cell extravasation and metastasis formation.

Neurologic symptoms were observed in 100% of the patients in this cohort which is a bit higher than observed by Kim et. al (61.5%) and the UK TTP registry (78%). However, all three studies showed minor neurologic symptoms were predominantly observed, particularly confusion.

Renal failure was observed in 50% of cases in this study which is comparable with the 40% incidence of renal failure in the UK TTP Registry. Renal failure was significantly higher at 76.9% in Kim's study. The renal manifestations of hematuria, proteinuria, and mild impairment of the clearance function in TTP are consistent with the focal and segmental distribution of micro thrombi most commonly observed at pathological examination⁹. Current evidence indicates that renal function impairment is mild and transient

in most cases of acquired TTP. Renal failure may become more apparent when the course of TTP is protracted. Severe renal dysfunction occurs mostly in association with other causes of renal failure.

Fever was seen in 87.5% of this set of patients which is higher than observed in Kim's study (44.2%) and the UK TTP Registry (21%). Even if the patient eventually diagnosed and died with gram negative septicemia is to be censored, the incidence of fever in this cohort is still higher.

Fifty percent of the patients in this study presented with the classic pentad. A classic review by Ridolfi et. al reported that 98% percent of TTP patients had microangiopathic hemolytic anemia, 83% had thrombocytopenia, 84% had neurologic symptoms and 76% had renal failure¹⁰. This further supports that the diagnostic pentad is not present in all patients at all times. Currently, the diagnostic criterion of TTP is reduced to a dyad of thrombocytopenia and microangiopathic hemolytic anemia (defined by negative findings on direct antiglobulin test, red blood cell fragmentation, and evidence of accelerated red cell production and destruction) with no clinically apparent alternative explanation for thrombocytopenia and anemia¹¹.

For several decades, TTP was considered a severe and frustrating therapeutic dilemma. In 1965, a series reviewed by Amorosi et. al of 271 patients showed a 90% mortality rate for patients diagnosed with TTP¹². A landmark trial by Rock et. al, in 1991 showed that plasma exchange is more effective than plasma infusion in the treatment of TTP and the study showed the mortality of TTP patients dropped to 29%¹³. Thus, the availability of effective treatment has created urgency for establishing the diagnosis, and this urgency has required decreased stringency of diagnostic criteria, from the classic pentad of clinical features to the current dyad mentioned previously. In this cohort of patients, five out of the six patients who received therapeutic plasma exchange were discharged alive. One of the patients discharged eventually died due to underlying disseminated breast malignancy within 30 days after discharge. The mortality rate in this series is 25% (as measured from admission to hospital discharge).

The observations and interpretations made in this study may be limited to the small number of patients. However, due to the rarity of the disease, to the best of our knowledge, this is the largest cohort of patients with TTP reported in the Philippines. A multicenter registry of TTP patients is recommended to ascertain the epidemiologic data.

Conclusion

Thrombotic thrombocytopenic purpura is indeed one of the true hematologic emergencies. A high index of suspicion, prompt evaluation and treatment of patients are necessary because multi-organ thrombosis may not be reversible, if treatment is not urgently administered. Therapeutic Plasma Exchange is the management of choice and should be done immediately once TTP is recognized. Although TTP is associated with high mortality per se, mortality may still be related to the underlying condition and comorbidities.

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