Thrombotic Thrombocytopenic Purpura in Oman: Disease Burden and Outcomes

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Abstract

Objectives: Thrombotic Thrombocytopenic Purpura (TTP) is a rare, life-threatening autoimmune disorder; limited information about this disease is available from the Middle East. This study aimed to provide background data on TTP epidemiology in Oman, including its clinical characteristics, disease course, and outcomes.

Methods: The study used a longitudinal retrospective observational design, drawing on data from the Royal Hospital and Sultan Qaboos University Hospital electronic databases. Patients who met the diagnostic criteria for TTP (January 2006 and December 2019) were included in the analysis.

Results: Fifty-four patients were diagnosed with TTP during the study period, and 13% (7/54) experienced a relapse. The incidence of TTP in Oman was found to be 1.8 cases per million population per year, and the disease was most commonly observed in females in their third to fifth decade of life. In 23 (42%) cases, the enzyme ADAMTS-13 was tested, enzyme deficiency was found in 6 patients, and acquired autoantibodies were found in 10 patients. Treatment modalities included steroids (94%), therapeutic plasma exchange (77%), rituximab (42%), and cyclosporin (18.5%). Morbidity caused by TTP in the study population included seizures in 14 (26%), confusion in 13 (24%), stroke in 10 (18%), coma in 2 (4%), and deranged kidney function in 25 (47%), with six patients requiring hemodialysis. Residual neurological deficits were observed in around 20% (2/10) of patients with stroke, while all patients with seizures had recovered. The case fatality rate during the study period was 13.2% (7/54) among all patients diagnosed with TTP, with a 30-day fatality rate of 9.2% (5/54) and a 90-day fatality rate of 13.2% (7/54).

Conclusions: Overall, the study indicated that TTP is a rare disease in Oman with a high proportion of neurological complications and is likely underdiagnosed.

Keywords: Oman, Thrombotic Thrombocytopenic Purpura (TTP), ADAMTS-13 enzyme, neurological complications, microangiopathic hemolytic anemia (MAHA).

Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is defined as a severe deficiency state of disintegrin and metalloprotease with thrombospondin type 1 motif, member 13 (ADAMTS-13). This enzyme cleaves ultra-large von Willebrand molecules and thus controls the thrombosis cascade.[1] A second trigger is usually required for this deficiency state to manifest clinically. TGF-β1 and interleukin-10 (IL-10) are

key regulators of immune homeostasis with anti-tumour effect.[2,3] Elevated plasma TGF-β1 levels play a role in the progression of TTP, leading to a procoagulant phenotype.[4] STAT3 was required for efficient IL-10-induced TTP expression.[5]

Conditions characterized by high flow, increased shear forces, and inflammatory state within tiny capillaries and arterioles usually trigger a clinical episode. Examples include infection, pregnancy, malignancy, systemic lupus erythematosus, toxins, and drugs.[6] Acquired TTP (aTTP) is more common than the congenital type. The reported case fatality rate in untreated cases is as high as 90% and between 10-20% in patients who receive aggressive treatment.[7]

With the advent of immunotherapy as a dominant modality in cancer treatment. TTP is one of the immune-related toxicities. Ipilimumab, a Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blocking antibody, has been widely used for cancer treatment.[8] The anti-CTLA-4 MoAb, ipilimumab, exerts a positive effect on relapsed Acute Myeloid Leukemia (AML).[9] TLR2 expression increased significantly in AML patients with mixed fungal and bacterial infection.[10] TLR2 ligand enhanced the antitumor efficacy of anti-CTLA-4 by increasing Fcγ receptor IV expression.[11]

Global data showed that the incidence of aTTP is around 3 per million population per year. In North America, the initial incidences of TTP plus hemolytic uremic syndrome (HUS) were reported to be 3.7-3.8 cases per million population annually.[7] In Europe, similar numbers were reported regarding the incidence and prevalence of aTTP. In the UK, the incidence of TTP was 1.2 cases per million population per year. The incidence of aTTP episodes in Germany was 2.1 cases per million population per year. In contrast to incidence, the global annual prevalence of TTP was estimated to be 10 per million population. Most studies showed female predominance in affected patients in their third to fifth decade of age. Around 10% of aTTP cases were in the pediatric age group.[7]

In the Arabic Gulf region, limited data has become available on TTP epidemiology. A very recent paper published by an expert panel reported that the incidence of aTTP is 1-2 and 5 - 6 per million person-years UAE, and Saudi Arabia (KSA), respectively.[12] In Kuwait, four cases of TTP were described in a study in 2011.[7] It was also reported that recurrent disease is rare. There needed to be more awareness about aTTP, access to rapid testing with ADAMTS13 enzyme, and new TTP treatments.[12] Moreover, expert consent from the Gulf region agreed that there is still a lack of published data on early diagnosis and treatment modalities of aTTP patients.[7]

Moreover, data from other Arab countries showed similar demographics. Two studies from Egypt reported 22 and 30 cases over 20 years with a mean age of 24 and a median of 46 years, with a female predominance of 65-73% and a case-fatality rate of 9-13%.[13,14] All adult cases with TTP had statistically significantly lower ADAMTS-13 levels due to an inhibitor. None had a miss-sense mutation in the enzyme.[15] Data from a single center in Jordan showed 21 patients, where 67% were females, 81% had neurological symptoms upon presentation, the mean age was 36, and the mortality rate was 38%.[16]

Given the above, this study was conducted to provide background data on TTP epidemiology and its description in the Omani population.

Methods

This cohort study was retrospective and was based on electronic records of patients with acquired or congenital TTP diagnoses from the Royal Hospital and Sultan Qaboos University Hospital. Patients were selected if, between January 2006 and December 2019, they were 12 years old or older and had one or more documented TTP episodes. Exclusion criteria included patients with incomplete data; and a diagnosis mimicking TTP, including severe sepsis, hypertensive crisis, human immunodeficiency virus (HIV), and Microangiopathic anemia in organ transplant patients.

Data gathered include demographics, clinical presentation, lab results, vital signs, procedures, medications administered, outcomes, and coded diagnoses. In addition, the blood bank logbook was used to identify all cases who underwent therapeutic plasma exchange in the two hospitals.

A TTP episode was defined as one or more inpatient stays with a Thrombotic Microangiopathy (TMA), an International Classification of Diseases (ICD),[12] and one or more Therapeutic Plasma Exchange (TPE) procedures during the same inpatient stay, or one or more documented ADAMTS13 test results less than 10%. In addition, relapse was defined as a new TTP presentation after 30 days of discharge from the initial episode.

Categorial variables were described as frequencies and percentages, while continuous variables were presented as mean (or median) with standard deviation (SD). Incidence was calculated by dividing the number of patients with a newly documented TTP diagnosis during a specific year by the total Omani population during that year, multiplied by 1 million. The data was analyzed using "IBM SPSS statistics" software version 29.0.00 (241), 2022. The medical research ethics committees at Royal Hospital and University Hospital reviewed and approved this study (SRC# 8/2018; MREC#2022).

Results

Fifty-four patients met the inclusion criteria during the study period. Considering that the total Omani population during the study period from 2006 to 2019 ranged from 1.9 to 2.5 million, with an average Omani population of 2.3 million.[17,18] The incidence of TTP was found to range from 0.5 to 3.6 cases per million per year with an average of 1.8 per million [Figure 1]. Our adult cohort population had an age of onset of TTP ranging from 1st year of life up to 79 years. Of note, congenital TTP cases had an age of onset in childhood. Interestingly, up to 61% of patients with TTP had their first presentation between the third to fifth decade of life. TTP in our study population predominated in females with a female-to-male ratio of 2.2:1. An onset of TTP in the postpartum period was observed in 6 patients [Figure 2]. The following clinical findings were documented during the acute presentation of TTP: fever (63%), petechiae/ecchymosis (35%), seizures (25%), headache (27%), confusion (24%), stroke (18%), and coma 3.7% [Table 1].

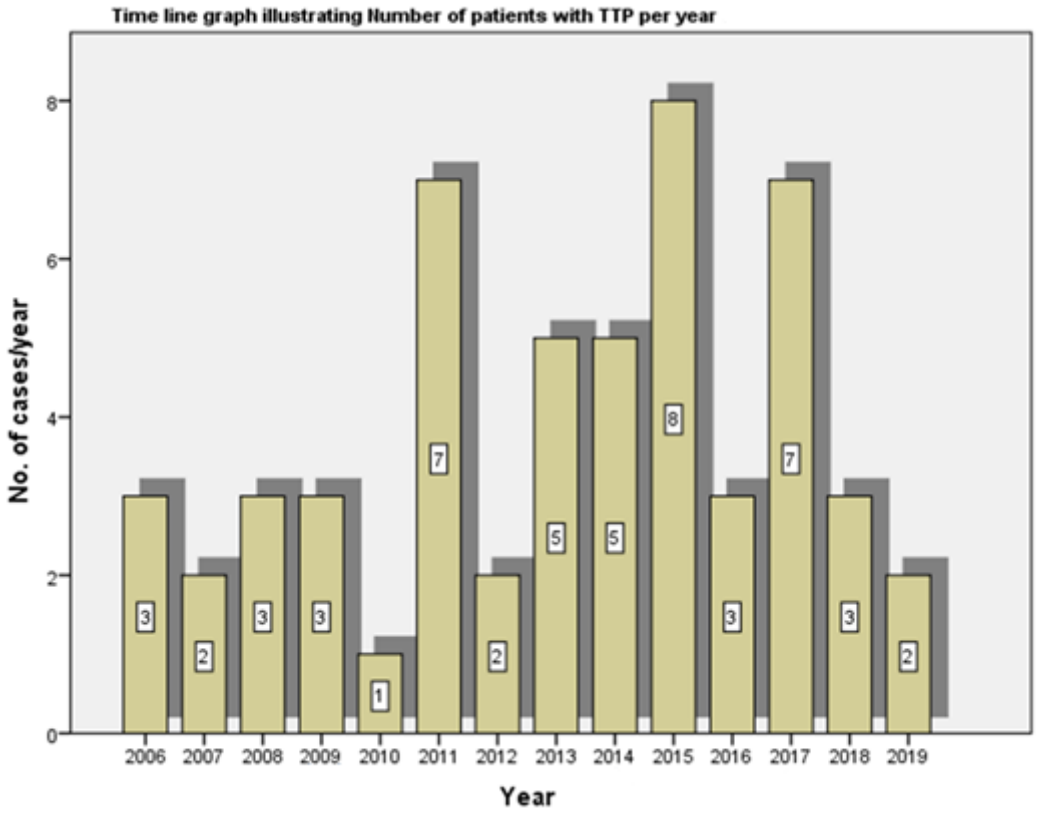

Figure 1: Number of TTP cases per year.

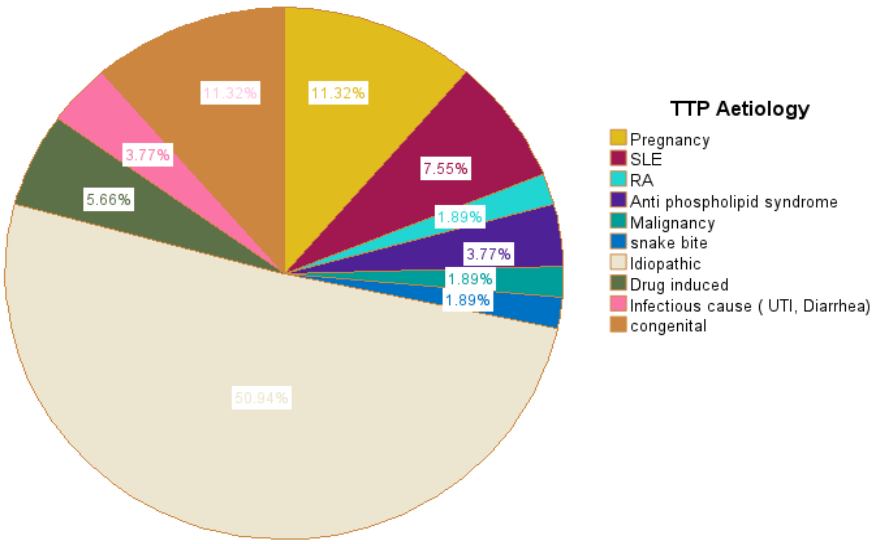

Figure 2: Etiology of TTP cases 2006 to 2019.

Table 1: Demographic characteristics of patients with TTP. Royal Hospital and Sultan Qaboos University Hospital. 2006-2019.

	No. of patients	**Percentage**
Total No.	54	
Gender		
Females	37	68%
Males	17	32%
Female: Male ratio	2.2:1	
Age at onset		
< 20 yrs	9	16%
20-30 yrs	19	35%
30-40 yrs	8	14%
> 40 yrs	18	33%
Region		
Al Batinah	19	35%
Muscat	13	24%
Al Dakhlyia	7	13%
ASharqia	6	11%
Al Wosta	3	7.9%
Al Dhahira	1	1.9%
Al Buraimi	2	3.7%
Musandam	1	1.9%
Dhofar	2	3.7%

The titre of the ADAMTS-13 enzyme was measured in 23 patients (42%). The acquired form (deficient enzyme <10% with positive autoantibodies) was noted in 16 patients. Normal enzyme level was found in 7 patients. Three patients were found to have congenital TTP. They were from the Al-Wosta region. They responded to fresh frozen plasma infusion during relapses without therapeutic plasma exchange [Table 2].

Table 2: Summary of clinical presentation and laboratory results of patients with Thrombotic Thrombocytopenic Purpura in Royal Hospital, 2006-2019.

	Number of patients	**Percentage**
Clinical presentation		
Fever	34	63%
Petechiae/ecchymosis	19	35%
Seizures	14	25%

High Blood pressure	14	25%
Headache	15	27%
Confusion	13	24%
Postpartum period	6	11%
Stroke	10	18%
Coma	2	3.7%
Underlying malignancy	1	1.9%
Laboratory results on presentation		
Hb[1] level		
Mean	7.5 g/dl, (SD = 2.66)	
Range	5-10 g/dl	
Platelet count		
Mean	25 x 109 /L (SD=156.4)	
Range	3-120 x 10^9 /L	
ANA[3] titer > 1:60	10	18%
HIV[4]- positive Elisa test	0	
ADAMTS[4]- 13 tested.		42%
Deficiency	6	
Autoantibodies positive	10	
Deranged Coagulation (INR[5]>1.3)	0	
Deranged Renal function (creatinine (eGFR[6]< 90 ml/kg/min)	25	47%

Hb: hemoglobin; ADAMTS-13: a disintegrin and metalloprotease motif 13; INR: international normalized ratio; eGFR: estimated glomerular filtration rate.
[3]antinulclear antibodies[4];human immunodeficiency virus.

Treatment modalities received in this cohort study group were steroids (94%), TPE (77%), rituximab (42%), and cyclosporin (18.5%). One patient with a congenital deficiency of ADAMTS-13 received rituximab. Moreover, patients with congenital deficiency required fewer plasma exchange sessions (0 to 7 sessions) and had a shorter inpatient stay with a maximum of one-week duration. In comparison, up to 75% of patients with acquired ADAMTS-13 received rituximab, had a more prolonged inpatient stay, and required more TPE sessions (Range: 5-30) [Table 3].

Table 3: Treatment modalities of the studies patients 2006- 2019.

	Patients n (%)	**Patients' characteristics**
Steroids (Prednisolone, Methylprednisolone, or Hydrocortisone)	51 (94%)	
Top Up Fresh Frozen Plasma only	3 (5.5%)	Congenital TTP
Plasma exchange (PE) Mean= 8 sessions (SD=5.8) Range: 1-30 sessions	42 (77%)	
Rituximab	23 (42%)	
Cyclosporin	10 (18%)	It started as an adjuvant after rituximab and in cases post renal transplant.

Renal derangement and neurological deficits were common, but most were transient. Out of 25 patients with renal derangement on presentation, only nine had stage 2 – 3 chronic kidney disease, all of which continued to recover slowly as per the last follow-up visit after discharge. One patient experienced end-stage renal disease and was on regular hemodialysis. This patient presented in the postpartum period with low Hb was found to have severe renal derangement and received more than 30 sessions of TPE with prednisolone, rituximab, and cyclosporine. Two of the ten patients with neurological sequelae continued to have residual weakness, and both had connective tissue disease. The two patients with an initial acute presentation with coma recovered completely before discharge. All patients with seizures were free of fits and well-controlled on anti-epileptic medications [Table 4].

Table 4: Outcome of patients with TTP-related ischemic end-organ damage.

No. of patients (%)	**Treatment**	**Patients' characteristics**

Neurological deficits			
Stroke	10 (18%)	Plasma exchange, Steroids	2 patients had a residual neurological deficit on discharge.
Seizures	14 (25%)	Levetiracetam, Plasma exchange Steroids	All were controlled with anti-epileptics on discharge. 2 patients passed away with TTP 2 patients with connective tissue disease, SLE, APLS 1 patient has drug-induced TTP
coma	2 (3.7%)	Plasma exchange, steroids	recovered
Kidney disease			
CKD[3]	9 (16.5%)	plasma exchange, steroids, haemodialysis	Half the case has CKD stage 2-3 recovering based on the last clinic record. 3 cases have connective tissue disease, SLE, RA, and APLS. 1 case had a snake bite.
Mortality	7 (13%)		Non-Hodgkin's lymphoma Vasculitis Confusion and aspiration pneumonia 3 cases of Advanced age, multi-organ failure Post BMT, GVHD, TTP

ESRD: end-stage renal disease; HD: hemodialysis; CKD: chronic kidney disease.

Relapse was recorded in 7 patients (13%), and these occurred 1 to 7 years after the initial episode of TTP with a mean of 3.5 years (SD=2.8). This study showed a case fatality rate of 9% (5/54) at 30 days and 13% (7/54) at 90 days. Among patients who died, the age ranged from 13 to 87 years, with a mean of 46 years (SD=30.1).

Discussion

This study evaluated the incidence, treatment modalities, and clinical outcomes of TTP in the Omani population over a decade from 2006 to 2019. The incidence of TTP in Oman was found to be 1.8 per million population per year, which is lower than global data, and in other Gulf countries, the incidence was recorded to be 3 - 6 cases per million population annually. This suggests that TTP is an underdiagnosed disease.

TTP onset in the postpartum period was observed in 6 patients. Many case series reported that pregnancy is a precipitating factor for acute episodes of TTP-HUS. The association between pregnancy and the increased concentration of procoagulant factors, decreased activity of ADAMTS-13, reduced fibrinolytic activity, and loss of endothelial cell thrombomodulin has been well-described. These changes progress in severity throughout pregnancy, with the maximum abnormalities observed at delivery and during the immediate postpartum period.[19,20]

Although most patients received the appropriate conventional therapy, mortality and stroke were high at 13% and 18%, respectively. This indicates late diagnosis and calls for early diagnosis, prompt, effective treatment, and adoption of new novel therapies to improve outcomes. Like other Gulf countries, the relapse rate observed in this study is lower than globally reported. The rate in this study was 13% over a follow-up period of 14 years compared to 30-50% globally.[7,21-23] Moreover, the relapse of TTP was more common in congenital TTP than acquired TTP.

Recent data reported survival rates of over 95% in patients receiving the latest recommended standard of care of TPE, immunosuppression, and the novel monoclonal therapy caplacizumab. Caplacizumab was approved for TTP treatment in combination with steroids and TPE in 2018 in Europe and 2019 in the USA.[12] Its recent approval and unavailability in the Gulf region explain why none of the patients in our cohort received caplacizumab during the captured period. Therefore, our study findings reflect the outcome of conventional therapies.

Literature shows that the consequences of TTP can last beyond the acute episode. For example, a study from the United Kingdom found that TTP patients reported impairments in quality of life, cognitive function, psychological well-being, and physical functioning.[12] Similarly, our study showed that TTP was associated with significant comorbidities, many of which have been precipitated by TTP, such as kidney dysfunction and neurological symptoms.

The study generally strengthens the evidence that research and treatment gaps exist for TTP in Oman. However, the study was limited by the retrospective retrieval of data recorded electronically for medical purposes rather than research. In addition, ADAMTS-13 needed to be more readily available and was required to be outsourced abroad.

The study provided background information on TTP in Oman. It showed that Oman has a lower incidence of TTP than other Arabian Gulf countries and to global data. Therefore, it is likely underdiagnosed. Additionally, there was regional clustering of congenital TTP in the AlWosta governate, where genetic counseling would be effective. Finally, this analysis from Oman found a high case fatality rate and morbidity in patients with TTP, despite treatment with TPE and immunosuppression, highlighting the need for rapid diagnosis by increasing awareness and easy access to ADAMTS-13 testing.

Disclosure

The authors declare no conflicts of interest. No funding was received for this study.

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