THROMBOTIC THROMBOCYTOPENIC PURPURA: OUR CLINICAL EXPERIENCE

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ABSTRACT

Objective: To assess clinical presentation and outcome of patients with thrombotic thrombocytopenic purpura (TTP) in our setup.

Study Design: Descriptive study.

Place and Duration of Study: Combined Military Hospital (CMH) Peshawar, from Feb 2016 to Aug 2017.

Patients and Methods: In a prospective design, patients diagnosed to be suffering from TTP, were included in this study. Detailed history along with physical examination and thorough investigation of all cases was carried out and collected on proformas. The diagnosis of TTP in our study was done by demonstration of significant schistocytes (more than 1 percent) on peripheral blood film. The patients were treated with steroids and plasma pheresis and in some cases with weekly Rituximab for 4 weeks. The patients were followed up in outdoor clinic on monthly basis.

Results: Being a very rare disease, only 11 patients suffering from TTP reported during the study period. They were followed prospectively with a mean duration of follow-up of 11.23 months (± SD 5.57). All patients (100 percent) had anaemia, thrombocytopenia and acute kidney injury. Fever was seen in 54.4% patients and 63.6% patients had neurological involvement. A likely secondary cause of precipitation of TTP was found in 54.5% cases. The mortality rate was 18.2 percent.

Conclusion: TTP is a challenging disease for intensive care specialists and can be fatal without effective treatment. A high index of suspicion followed by early diagnosis and prompt treatment can save life. Documentation of deficiency of plasma ADAMTS13 activity is not essential for the diagnosis of TTP and plasmapheresis is the treatment of choice.

Keywords: Pakistan Thrombotic microangiopathy, Plasmapheresis, TTP.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy (TMA). TTP results from either a congenital or acquired, severe deficiency of the enzyme ADAMTS13 activity, the specific von Willebrand factor-cleaving protease[1-3]. Low levels activity of this enzyme results in microthrombi formation which leads to endorgan ischemia and damage[3,4]. Central to the diagnosis of TMAs is thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and the clinical or histological effects of microvascular thrombosis. Early diagnosis and prompt treatment is the key to success in patients with TTP. The first-line therapy for acute TTP is based on daily therapeutic plasma exchange supplying deficient ADAMTS13, with or without steroids. Additional immune modulators targeting ADAMTS13 auto antibodies are mainly based on steroids and the humanized anti-CD20 monoclonal antibody rituximab. Novel therapies for TTP are still in preclinical phases[2,3]. Like most other diseases, data on TTP from Pakistan is lacking except for a few case-reports. The aim of our study was to describe our experience on TTP with clinical presentation and outcome in the local population.

PATIENTS AND METHODS

This descriptive study was conducted at the department of Critical Care Medicine, Combined Military Hospital (CMH) Peshawar from Feb 2016 to Aug 2017. In a prospective design, patients with symptoms suggestive of TMA, along with anemia and thrombocytopenia, were

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investigated and those confirmed by presence of significant number of schistocytes on the peripheral blood smear were included in the study. As it is a rare disease only eleven patients were selected with non-probability convenient sampling[5]. All patients underwent baseline investigations including blood complete picture, urea, creatinine, electrolytes, arterial blood gases, liver function tests, lactate dehydrogenase (LDH), chest X-ray, ultrasound abdomen and electrocardiography were carried out. For peripheral blood smear, slides were stained with leishman stain and were observed for schistocytes under oil-immersion lens. A minimum of 10 fields were observed by 2 Pathologists and a presence of more than 1 percent schistocytes were reported as diagnostic. Blood complete picture was carried out on automatic Sysmex (XP-100n KX-100) and chemistry on selectra (Netherland) fully automatic chemistry analyser. The data was collected on a pre-designed proforma. Anemia was defined as haemoglobin value of less than 13 gm/dl in males and 12.5 gm/dl in females. Thrombocytopenia was defined as platelet count of less than 150 x 10^9/L. Acute kidney injury was defined on the basis of acute kidney injury network (AKIN) criteria[6-8]. The patients were managed in main intensive care unit (ICU) of the hospital and then were shifted to lower level of care as their condition improved. All the patients underwent plasmapheresis and intravenous pulse methyl-prednisolone for three to five days followed by oral corticosteroids tapered off over three to six months. Rituximab was administered to selected patients, as IV infusion, 375 mg/m^2 once weekly for 4 weeks. Remission was defined by clinical improvement of the patient along with normalization of laboratory parameters which included resolution of renal function and correction of anemia and thrombocytopenia. The statistical analysis were carried out using the SPSS version 24. Descriptive data was summarized by calculating mean/median with standard deviation/ranges and calculation of percentages where applicable.

RESULTS

Being a very rare disease, only 11 patients suffering from TTP reported during the study period[5]. The mean duration of follow-up was 11.23 months (±SD 5.57). The study population had a male predominance (82.8 percent) with a mean age of 39.8 years (±SD 12.67). All patients (100 percent) had anemia (mean lowest haemoglobin 7.02 ± SD 1.06), thrombocytopenia (mean lowest platelet count of 24 x 10^9 ± SD 13.49) and acute kidney injury (mean highest creatinine 388.82 ± SD180.49). Three of the patients (27.3 percent) with acute renal failure required haemodialysis temporarily. Fever at presentation was noted in 54.4 percent (6/11) and 63.6 percent (7/11) had neurological involvement. A complete pentad of clinical features was seen in 36.4 percent (4/11) patients. Schistocytes on peripheral blood smear were present in all cases with a mean value of 2.45 percent (range 1–4 percent). Mean highest LDH levels are 1239 u/L (±SD 314.29) (table). In one of the patients, the diagnosis was made post-mortem as he went into arrest soon on presentation and expired after multiple episodes of CPR. Treatment of the disease was carried out in 10/11 (90.9 percent) cases including plasmapheresis, IV methyl prednisolone and oral prednisolone. Plasmapheresis was carried out in all cases except one who expired at presentation, with mean of 5.9 (range 4-7) sessions. IV Methyl prednisolone was administered for three to five days with a mean of 4.6 doses (range 3-5) followed by oral Prednisolone. Rituximab was administered to three patients (27.3 percent). The mean ITC stay was 9.4 days (range 1-17). Kinetic description of haemoglobin, platelets and creatinine in response to treatment is shown in figure. According to this the platelet count is lowest at the start but slowly increases reaching a normal value on day 6, while there is a steady decrease in creatinine value but even by day 10 it does not touch the normal value. The hemoglobin concentration appears to remain static during this period but has a maximum dip till day 7 and then a steady increase. The mortality rate was 18.2 percent (2/11 patients),

one of the patients expired on presentation and the other one due to severe sepsis leading to septic shock and multi-organ dysfunction on ninth day of admission. The rest of the patients recovered completely with counts improving to normal value in all cases. The risk factor for TTP was unknown in 54.5 percent (6/11) cases. In the rest of the patients a likely risk factor was identified which included pregnancy, diabetic ketoacidosis, nephrectomy and craniotomy following head injury secondary to a road traffic accident. Pregnancy as a risk factor was present in 2 cases, in one TTP occurred post-partum and in the other after induced abortion, the rest of risk factors were present in one patient each.

Table: Comparison of patients of study group with George's study group[12].

Demographic/ clinical features	Our study population (n=11)	George's study population	
		ADAMTS13 <10% (n=51)	ADAMTS13 >10% (n=56)
Demographic			
Mean age (years)	39.82 (± SD 12.67)	41	57
Gender (% women)	17.2	80	57
Clinical features			
Neurologic abnormalities (%)	63.6	66	73
Renal abnormalities (%)	100	47	82
Complete pentad (%)	36.4	5	
Laboratory data			
Hematocrit	21.04 (± SD 3.06)	25	27
Platelet count (µL)	24000 (± SD 13490.73)	17000	43500
Creatinine (µmol/L)	388.82 (± SD 180.49)	97.2	291.7
LDH (units/L)	1239 (± SD 314.29)	1257	989
Clinical course			
Dialysis (%)	27.3	4	43
Death (%)	18.2	18	21
Plasma exchange Median (range)	5 (4-7)	19 (3-79)	9 (3-71)
Relapse	Nil	40	7

DISCUSSION

In 1966 a pentad of clinical and laboratory features was proposed as criteria for diagnosis of TTP. This included MAHA with fragmentation of RBCs in peripheral blood film, thrombocytopenia, neurological abnormalities, renal failure and fever[9]. However, subsequent studies demonstrated that last three criteria are not present in all patients[10,11]. So the presence of first two criteria was considered sufficient to make the presumptive diagnosis of TTP. In our study population in addition to MAHA and thrombocytopenia, renal involvement is seen in all cases. All the patients in our study group underwent plasmapheresis and received corticosteroids except one case whose diagnosis was made postmortem. The response to treatment was monitored with platelet count. An increased platelet count was anticipated after the second day of treatment, and the platelet count reached normal value on day 6 of treatment. In our study renal failure recovered more slowly than thrombocytopenia. Anemia was slow to develop and slow to recover. International data review also provided a similar trend[12]. The survival of patients with TTP depends on early diagnosis and prompt treatment and has not changed over almost 20 years since the introduction of plasmapheresis[13-15]. We had similar results in our study, with a survival rate

of 81.8 percent. Oklahoma TTP-HUS registry data was analysed by George *et al*[12], table shows a comparison of our study population with George's study. George divided patients into 2 groups, patients with less than 10 percent ADAMTS13 activity in one group and more than 10 percent ADAMTS13 in another group. Renal involvement is high in our study population with all patients having deranged renal functions. Similarly, incidence of fever is high but neurologic involvement has almost similar frequency. The classic pentad of clinical features occurred in only 5 percent of cases of George's study group but in our population, it was seen in 36.4 percent of cases. The likely explanation of high incidence of fever, renal involvement and more frequency of classic pentad, may be due to late presentation of patients in our setup. A high incidence of fever might also be due to infections rather than disease itself. Although age is comparable in the two studies but there is a male predominance in our study population and female predominance in George's study. The laboratory data and mortality are comparable between the two studies. Our patients, in comparison, improved with lesser sessions of plasmapheresis and relapse of disease was not seen in any of our patients, this may be due to short follow-up period. The diagnosis of TTP in our study was done by demonstration of significant schistocytes (more than 1 percent) on peripheral blood film, as the assay for plasma ADAMTS13 activity and inhibitors are not freely available in our setup. A review of literature revealed that in appropriate clinical setting and in the absence of other known causes of TMA, a schistocytes count of more than 1 percent is strongly suggestive of diagnosis of TTP[16]. Documentation of severe deficiency of plasma ADAMTS13 activity is not essential for the diagnosis of TTP however severe acquired ADAMTS13 deficiency does define a subgroup of patients who appear to benefit from treatment with corticosteroids and other immuno suppressive agents and have high risk of relapse[9]. Furthermore, the pathologic changes in patients described as TTP or HUS are identical and initial treatment of all adult patients is plasma exchange[13,17,18]. A likely risk factor of TTP in our study was found in 45.5 percent cases. This included pregnancy, diabetic ketoacidosis and surgery. Pregnancy associated TMA is a rare disorder and is associated with significant maternal morbidity and mortality. It usually occurs antepartum or postpartum period[19-20]. Women who are either pregnant or in postpartum period make up 10 to 25 percent of TTP patients, suggesting the interrelationship between TTP and pregnancy[21]. The association of autoimmune diseases with TTP is well known and these can occur before, at the time of diagnosis

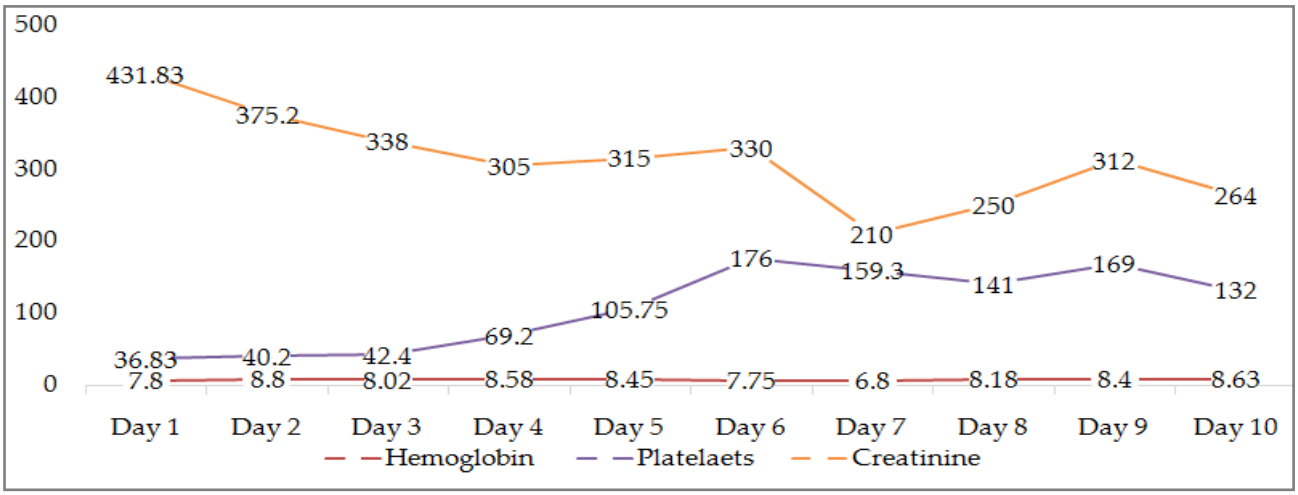

Figure: Kinetic of haemoglobin, platelets and creatinine in response to treatment.

and during follow-up of TTP. The most frequent autoimmune disorder reported is systemic lupus erythematosus, followed by Sjogren syndrome. It also includes type-I Diabetes Mellitus which was present in one of our cases[22-23]. The association of initial episode and relapse have also been established with surgery[23]. Three of our cases developed TTP post-surgery including following induced abortion, nephrectomy and craniotomy for head injury.

CONCLUSION

TTP is a challenging disease for intensive care specialists with very high mortality without effective treatment. A high index of suspicion followed by early diagnosis and prompt treatment can save many lives. Documentation of severe deficiency of plasma ADAMTS13 activity is not essential for the diagnosis of TTP, in the presence of appropriate clinical setting a schistocytes count of more than 1% is strongly suggestive of its diagnosis. In adult patients plasma exchange is the treatment of choice in acute settings.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any authors.

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