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CASE REPORT

Therapeutic Plasma Exchange (TPE) Response in Thrombotic Thrombocytopenic Purpura (TTP): A Case Report

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ABSTRACT

Background: Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy. It derives from a severe deficiency of disintegrin-like metalloproteinase with thrombospondin motif type 1 member 13-regulates (ADAMTS13). This case report aims to describe how therapeutic plasma exchange (TPE) with steroids can improve good clinical outcomes in TTP.

Case Illustration: A 72-year-old male presented to the emergency department with complaints of fever persisting for 1 week. The patient also complained of a productive cough and shortness of breath. Patient was found apathetic (E3M6V4) and fever (38.1°C). Other vital signs were normal. Thorax examination revealed minimal bilateral basal crackles. Minimal pitting-edema was found in both lower extremities. Patient underwent complete blood count that indicates leukocytosis (shift to the left), thrombocytopenia, hypoalbuminemia, and impaired renal function tests. Chest X-Ray revealed pulmonary edema in both lungs and infiltrates with air-bronchogram in the right paracardiac area. Diagnosis of TTP was established based on history and physical examinations related to TTP pentad criteria (fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, and impaired renal function tests). Patient was then treated with TPE and steroids. Symptomatic treatments for the patient's complaints were given. Patient was then discharged from hospital after treatments.

Conclusion: This study provides a review of the expected course of treatment for patients with TTP. Treatment using TPE and steroids can increase platelet counts resulting in significant clinical improvements.

Keywords: Steroids; Therapeutic Plasma Exchange; Thrombotic Thrombocytopenic Purpura.

INTRODUCTION

A rare thrombotic microangiopathy known as thrombotic thrombocytopenic purpura (TTP) is characterized by severe thrombocytopenia, microangiopathy hemolytic anemia, and ischemic end organ injury as a result of microvascular platelet-rich thrombi.[1] TTP derives from a severe deficiency of the specific von Willebrand factor (vWF)–cleaving protease, disintegrin–like metalloproteinase with thrombospondin motif type 1 member 13–regulates (ADAMTS13).[1] Anti-ADAMTS13 autoantibodies are the most common cause of ADAMTS13 deficiency. It can also be inherited in a congenital form resulting from biallelic mutations in the ADAMTS13 gene.[2] 90% of instances of immune-mediated TTP (iTTP) appear in adulthood with 1,5-6 incidents per million annually. Variations in the annual incidence rate can most likely be attributed to national demographics. Across registries worldwide, there is consistency in women being two to three times more prone to develop iTTP. Childhood-onset iTTP is considerably less common, compromising approximately 10% of all cases.[1] TTP can be lethal without timely diagnosis and treatment, hence it is essential to diagnose TTP quickly in order to start prompt treatment. First-line treatment for acute TTP is daily therapeutic plasma exchange (TPE), with or without steroids, to provide depleted ADAMTS13. However, the evidence supporting steroid effectiveness in TTP treatment is still limited. Studies have shown similar outcomes whether or not steroid were used alongside TPE. Although former study did not answer the question of whether steroid increase the likelihood of remission compared to treatment without steroids, it suggests that high-dose steroid therapy can improve the management of TTP. There is a logical justification for using steroid to treat acquired TTP due to its autoimmune nature. Corticosteroids function by reducing the activity of the reticuloendothelial system and lowering the production of autoantibodies.[1]

Untreated TTP has a mortality rate of up to 90%. 75-90% people respond to plasma exchange overall. However, by using plasma exchange, the mortality rate decreases to 10-20%.[2] This case report aims to describe how therapeutic plasma exchange (TPE) with steroids can improve good clinical outcomes in TTP.

CASE ILLUSTRATION

A 72-year-old man came to the emergency room with a complaint of fever for the past week that has been continuous. Besides the fever, the patient also complained of a productive cough that he has had for the last five days. The sputum is greenish, thick, and not frothy. Occasionally, the patient experiences sudden shortness of breath before coughing. The shortness of breath improves when the patient expels the sputum. Sometimes, the patient also experiences headaches, which improve after taking pain relievers bought at a local store. During the illness, the patient feels weak and has a reduced appetite, resulting in decreased food and fluid intake. The patient denies other complaints such as rash, nosebleeds, bleeding gums, black stools, nausea, vomiting, and diarrhea. Five days ago, the patient was still able to urinate 4-5 times a day with a volume of approximately 200 ml of clear yellow urine. However, in the last two days, the frequency of urination has decreased to 1-2 times a day with a volume of approximately 200 ml of dark yellow urine. Physical examination revealed an apathetic consciousness (3/6/4), blood pressure of 130/89 mmHg, heart rate of 96 x/minute, respiratory rate of 21 x/minute, SpO2 of 99%, and a temperature of 38.1°C. There were no signs of anemia, jaundice, or lymphadenopathy. Examination of the chest revealed regular S1-S2 sounds, minimal bilateral basal crackles. Abdominal examination showed no tenderness but pain in non-specific quadrant of abdomen. There also showed no sign of ascites. Warm extremities with a capillary refill time < 2 seconds. There were no petechiae or purpura and no active bleeding in the mouth, nose, or rectum. Minimal edema was found in both lower extremities. Neurological examinations showed that no sign of paralysis, sensor impairment, or voluntary and involuntary movements.

Complete blood count results showed an anemia, leukocytosis (shift to the left), and impaired renal function tests according to Table 1. Patient underwent peripheral blood smear evaluation with the result indicating normocytic normochromic anemia. From the thoracic examination, pulmonary edema was found in both lung fields and infiltrates with air-bronchogram in the right paracardial area.

Table 1. Complete Blood Count Results (source: primary data)

Parameters	Before TPE (21/12/23)	5 Days after TPE (28/12/23)
Haemoglobin (g/dl)	13.6	10.0
Haemotrocrite (%)	40	29
Leukocyte (10^3/µL)	15.9	9.0
Platelet (10^3/µL)	28	154
Erythrocyte (10^6/µL)	4.13	3.09
Albumin (g/dL)	3.0	3.0
Creatinine (mg/dL)	2.8	1.1
Ureum (mg/dL)	186	64
Patient's Clinical Condition		
Glassgow Coma Scale	E3M6V4	E4M6V5

The diagnosis of TTP in the patient was established based on clinical and objective examinations referred to as the "TTP pentad criteria". These criteria include fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, and kidney dysfunction as found in the patient.[3] Based on the examination results, the patient was diagnosed with TTP, sepsis that caused by pneumonia dextra, and acute kidney injury.

The patient is being treated by an internal medicine specialist and receiving the following therapy: Inj. Ampicillin Sulbactam 1.5 g/6 hours, Inj. Levofloxacin 750 mg/24 hours, Inj. Omeprazole 40 mg/12 hours, Inf. Paracetamol 1 g/8 hours, Inj. Ondansetron 4 mg/12 hours, Curcuma per oral 3 times a day, Sucralfate per oral 3 times a day, Domperidone per oral 3 times a day, PSDII per oral 3 times a day, N-Acetylcysteine per oral 3 times a day. The patient also underwent TPE procedures twice, which resulted in an improvement in the patient's platelet count, as well as urea and creatinine levels.

DISCUSSION

Thrombotic thrombocytopenic purpura (TTP) is a systemic thrombotic condition primarily affecting small blood vessels. TTP is linked to severe deficiency (less than 10%) of ADAMTS13 enzyme, which regulates the normal distribution of von Willebrand factor (vWF) multimers. ADAMTS13 produced by hepatic stellate cells, with its sole known function being the regulation of vWF multimers. Under normal conditions,

ADAMTS13 is in a latent, closed form, whereas vWF released by platelets and endothelial cells, is in a globular state. When ADAMTS13 activity is severely deficient (<10%), ULvWF (Ultra-Large von Willebrand Factor) multimers can accumulate, causing unregulated platelet adhesion and aggregation with thrombocytopenia and blockade of small vessels. This results in TTP, characterized by disseminated microthrombi and organ ischaemia.[1]

Initially, TTP was characterized by the pentad of severe thrombocytopenia, microangiopathic hemolytic anemia (MAHA), changes in mental status, kidney failure, and fever. Nonetheless, a presumptive diagnosis of TTP can now be made based on unexplained thrombocytopenia and MAHA alone. In our case, the patient experienced thrombocytopenia, altered mental status, impaired kidney function test, fever, and normocytic normochromic anemia suspicious of hemolytic process.[2]

Thrombocytopenia in TTP is caused by non-immunological platelet destruction. Endothelial damage leads to deposition of loose strands of platelets and fibrin in small blood vessels, which then damage passing platelets and red blood cells (RBCs), resulting in significant thrombocytopenia and anemia (microangiopathic anemia). Additionally, platelets are consumed within multiple small thrombi, further contributing to the thrombocytopenia. Multiple organs develop platelet-von Willebrand factor (vWF) thrombi, primarily at arterio-capillary junctions, a condition known as thrombotic microangiopathy. Organs particularly susceptible to this condition include the brain, gastrointestinal tract, and kidneys.[3,4]

Complete blood counts revealed impaired renal function tests. Estimated glomerular filtration rate (eGFR) based on serum creatinine was 23 mL/min/1.73 m^2 which is classified as renal failure. Serum creatinine decreased from 2.8 mg/dL before the first TPE to 1.1 mg/dL after the second TPE. The complement system is overactivated in TTP which can lead to host tissue injury with the kidney being the main target organ. Cugno *et al.*[5] showed that the complement system may be involved in the pathophysiology of TTP. Complement regulatory gene variants may have affected the endothelial susceptibility to injury in the presence of ultralarge vWF multimers.The condition of renal impairement is also explained by

the thrombotic microangiopathy, characterized by an unusually large number of vWF and platelet microthrombi in renal capillaries and arterioles as the most likely mechanism. Variants of complement regulatory genes may also have affected the endothelial vulnerability to injury in the presence of ultralarge vWF multimers.[6]

In this case, the patient experienced abdominal pain as the main complaint, which is a sign and symptoms of gastrointestinal ischemia due to microthrombi formation. Based on former studies, gastrointestinal ischaemia is also present in 35% of patients and can manifest as abdominal pain, nausea, and diarrhea. Altered mental status in the patient is also correlated with brain ischemia, with neurological symptoms affecting about 60% of patients and can vary widely from mild confusion or altered sensorium to stroke, seizures, or coma. Most cases with TTP develop neurological symptoms due to the interaction between platelets and vascular endothelium, leading to severe coagulation dysfunction.[7]

The patient was also diagnosed with sepsis due to pneumonia, where TTP is often triggered by bacterial or viral infection, which can be the cause of fever and leukocytosis in patients. Sepsis as a life-threatening organ dysfunction caused by excessive host response to infection may correlate with ADAMTS13 dysregulation. The extent of reduced ADAMTS13 antigen levels and activity appeared strongly associated with sepsis severity and prognosis. The mechanism is still unclear. However, it has been suggested to be a consequence of reduced synthesis, degradation by thrombin, consumption by massive amount vWF, or impaired proteolytic activity in the presence of inflammatory mediators.[8,9]

Plasma exchange is the first-line therapy which can delete vWF multimers and anti-ADAMTS13 antibodies. Immunosuppressive therapy such as steroids in combination with TPE might improve renal outcomes showed significant improvement rather than TPE alone in patients with kidney disease.[10]

Patient was given TPE treatment immediately after being diagnosed with TTP. For TTP, TPE is used daily until platelet count > 150 x 10^9/L and resolution of non-fixed neurologic symptoms then continues for two more sessions then stops. Recovery of ADAMTS13 activity to >10% within 7

days is associated with clinical response. TPE alone can be a life-saving procedure and should be provided to all patients with a suspected TTP but the initiation of TPE and corticosteroids in all patients regardless of the availability of ADAMTS13 testing has significantly reduced the mortality and morbidity.[11]

Platelet counts in this patient after TPE treatment were increased significantly. The principle of TPE is to separate and filter out the patient's plasma components through extracorporeal circulation and discard the patient's abnormal plasma components, thereby removing pathogenic substances, metabolites, and toxins in the patient's plasma. TPE can remove pathogenic factors in blood circulation and improve immune function. One estimated plasma volume (often 40 mL/kg of body weight) is the recommended volume of exchange for each therapy. Treatment ought to be administered once every day. TPE does not require tapering and can be terminated quickly upon remission.[11] Pan *et al.*[12] found that the platelet counts of the patients after plasma exchange were significantly increased. The results show that plasma exchange has a good curative effect on TTP patients.

Corticosteroid was used in conjunction with TPE. Corticosteroids operate by decreasing the activity of the reticuloendothelial system as well as decreasing autoantibody production. This should be initiated as soon as possible in all patients with unexplained hemolytic anemia and thrombocytopenia with a normal coagulation profile.[14] Additional therapies added comprise vincristine, cyclosporine, cyclophosphamide, and rituximab. These are usually used as adjuvants if corticosteroids and TPE fail as first-line treatments. It has been demonstrated that rituximab and glucocorticoids can reduce the amount of time needed for therapeutic plasma exchange. Rituximab works well on refractory and relapsed TTP patients and targets B-lymphocytes. The immunosuppressive medications vincristine, cyclophosphamide, and cyclosporine have mediocre effectiveness. For this reason, they are usually given concurrently with other secondary therapies in refractory cases or when first-line therapy has failed. Typically, hemolysis markers are checked daily.[10] 90% of cases of thrombotic thrombocytopenic purpura end in death if treatment is not received. Early intervention (corticosteroids and

plasma exchange) reduces mortality to 15%. The likelihood of unfavorable results increases with the length of time a patient delays receiving therapy. Death is considerably decreased by early diagnosis and treatment with plasma exchange and corticosteroids. The main cause of death can be coronary thrombosis, which can result in rapid death, congestive heart failure, and an acute myocardial infarction.[15]

CONCLUSION

Thrombotic thrombocytopenic purpura (TTP) can be treated using therapeutic plasma exchange (TPE). TPE in combination with steroids can increase platelet counts significantly and make good clinical improvements.

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