Case Report

Thrombotic Thrombocytopenic Purpura (TTP), Successfully Treated with Plasma Exchange

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We report a case of a middle aged woman who developed TTP, was diagnosed on the basis of classical pentad of clinical features. She underwent 5 sessions of plasma exchange and was successfully treated with it. She did not develop any recurrence for a period of last 5 months. Thrombotic thrombocytopenic purpura (TTP) is a hematologic emergency. It is a multisystem disease that can cause rapid deterioration of the patient’s neurologic, renal, and hematologic status. TTP is an uncommon disease with a high mortality if misdiagnosed or untreated. Early diagnosis and aggressive treatment by therapeutic plasma exchange are necessary to reduce the risk of a fatal outcome.

Case Report

A 55 years old female patient presented in the department of accident and emergency with H/O sudden onset of right sided weakness, aphasia and high grade fever for 1 day. There was history of transient black outs in the last 1 week. On examination she was semi-conscious but responding to verbal stimuli. There was bruising around eyes i.e., black eyes which was caused by trivial trauma. Her temperature was 99.4F, blood pressure 140/90mm, pulse 90/min, respiratory rate 20/min. Patient was slightly pale, had no palpable lymph nodes and no sacral or pedal oedema. On G.I system examination liver and spleen were not palpable. The CNS examination revealed reduced muscle power of (4/5) on the right side with exaggerated reflexes on same side of the body.

Investigations at the presentation revealed Hb 7.9g/dl, TLC 9.6x10^4/ul, Platelets 11x10^4/ul, PT 12/12 sec, APTT 40.30 sec, BSL 130mg/dl, BUN 16mg/dl, Creatinine 2.4 mg/dl(0.6-1.2mg/dl), ALT 41 u/l(7-35u/l), AST 30 u/l (7-40u/l), T. Bili 0.8 mg/l (< 1.0 mg/l), LDH 1006 u/l (60-190u/l). An examination of the peripheral smear confirmed thrombocytopenia and revealed numerous schistocytes. Urine examination showed traces of proteins, no ketones & no glucose, WBC(5-8/hpf), RBC(numerous/hpf), CT scan of the brain was normal.

Patient was treated with mannitol infusion, omeprazole infusion 40mgBD, tab inderal 10mg TDS, and antibiotics (ceftriaxone 2 gm BD iv), but she did not improve. On day 3 the patient was unconscious, not responding to verbal stimuli, muscle power reduced to 3/5 on right side, an NG tube was passed for feeding and call was sent to haematologist for opinion. Labs at this stage revealed Hb 8.7g/dl, TLC 8.2 x10^9/l, PLTs 17000/ul, D. Dimers 1000-2000ng/ml [Normal value is <250ng/ml]. Autoimmune profile and viral markers for hepatitis B and C were negative.

A diagnosis of TTP was made, based on the pentad of features. This pentad consisted of the findings of altered consciousness, fever, microangiopathic hemolytic anemia, thrombocytopenia, and renal dysfunction. The definite diagnosis is based on assay of a cleaving protease ADAMTS -13, but its assay is not available in Pakistan so the diagnosis of TTP in our setting is a clinical diagnosis.

Plasma exchange (Plasmapheresis) was advised using 6-8 bags of plasma daily for 5 days, with continuous flow cell separator. Infusion was 250mg /day infusion was advised after each session of plasma exchange, for 5 days. Patient was comatose when the plasma exchange was started. Laboratory findings at the start of plasma exchange were: Hb 9.9 g/l, TLC 7.6 x10^9 /ul, PLTs 18 x10^9 /ul, PT 13/12 sec, APTT 29/30 sec, LDH 1006 u/l. After 5 sessions of plasma exchange patient’s condition improved and she became fully conscious and well oriented. One pint of fresh whole blood was also transfused daily.

Platelet count rose to 150x10^9/ul on 10th day of admission in the hospital. LDH levels went down to 500 U/l from the value of 1006 U/l at the presentation. Serum creatinine level went down from 2.7 mg/dl to 1.2 mg/dl. Patient was discharged on 12th day with oral steroids, and which were tapered and discontinued in the next 2 weeks. Low dose aspirin therapy was also started. Patient was followed up in haematology OPD and she is symptom free since a period of 5 months.

Discussion

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening multisystem disorder that is considered a true medical emergency. Moschcowitz first described TTP in 1924 when he noted that his 16-year-old patient had anemia; petechiae; microscopic hematuria; and at autopsy, disseminated microvascular thrombi. Since that time, the pathophysiology, etiology, and medical management of TTP has expanded. This life-threatening condition may have positive outcomes if recognized early and if medical intervention is initiated early. Abnormalities of plasma von Willebrand factor (VWF) have been recognized to be associated with thrombotic thrombocytopenic purpura (TTP) for over 20 years. Patients with chronic, relapsing
TTP have VWF multimers that are larger than normal, similar in size to those secreted by cultured endothelial cells. Recent observations have documented that a deficiency of a VWF-cleaving protease (termed ADAMTS13) may be responsible for the presence of these unusually large VWF multimers. Multiple mutations of the ADAMTS 13 gene can result in ADAMTS 13 deficiency and cause congenital TTP; autoantibodies neutralizing ADAMTS 13 protease activity have been associated with acquired TTP.

The survival rate has improved from approximately 3% prior to the 1960s to 82%. Early plasma exchange initiation has beneficial outcomes. With early recognition of the clinical features, this life-threatening illness can be treated, with effective patient clinical responses in many cases.

Thrombotic microangiopathies TTP and hemolytic uremic syndrome (HUS) were once thought to have shared the same pathophysiological etiology; however, more recent findings suggest that TTP is a different entity than HUS. They are closely related disorders and are characterized by microvascular lesions with platelet aggregation. HUS is more common in children and is caused by strains of enterohemorrhagic Escherichia coli, especially E. coli O157:H7 carrying the Shigalike toxin. HUS is characterized by prominent renal involvement.

TTP is associated with pregnancy; diseases such as HIV, cancer, bacterial infection, and vasculitis; bone marrow transplantation; stem cell transplantation; and drugs. A study by Elizabeth F showed that 17 of 53 (32%) patients with idiopathic TTP have clinical and laboratory evidence of UTI.

In TTP microangiopathic hemolysis and platelet aggregation/hyaline thrombi are pathological lesions whose formation is unrelated to coagulation system activity. Platelet microthrombi predominate; they form in the microcirculation (i.e., arterioles, capillaries) throughout the body causing partial occlusion of vessels. Organ ischemia, thrombocytopenia, and erythrocyte fragmentation (i.e., schistocytes) occur. The thrombi partially occlude the vascular lumina with overlying proliferative endothelial cells. The endothelia of the kidneys, brain, heart, pancreas, spleen, and adrenal glands are particularly vulnerable to TTP. The liver, lungs, gastrointestinal tract, gallbladder, skeletal muscles, retina, pituitary gland, ovaries, uterus, and testes are also affected to a lesser extent. No inflammatory changes occur.

The classic pentad is rarely complete at presentation. Current clinical criteria for initiating therapy are (1) thrombocytopenia, (2) schistocytosis, (3) elevated serum LDH levels, and (4) absence of other disease entities that could explain the thrombocytopenia and microcytic hemolytic anemia. Early recognition and management are essential for patient survival. Key points in management of TTP are as follows:

- Use a device with a wide-bore, 2-lumen catheter at the femoral site. Use blood-cell separators so that the patient’s plasma is removed and replaced by fresh-frozen plasma (FFP). Start with a single plasma volume and exchange FFP at a rate of 40 mL/kg of body mass. A plasma exchange twice a day may be necessary for resolution of thrombocytopenia and neurologic complications if the response to the initial daily exchange is poor.
- Infusion of FFP (30 mL/kg) is used as a temporizing measure until the patient can be transferred to a facility where plasma exchange is available.
- The standard replacement fluid is FFP. However, success with cryosupernatant has been reported.
- Glucocorticoid-steroid and antiplatelet agents are used. Steroids often are administered prior to plasma exchange. Steroids have no proven added benefit over plasmapheresis alone, but some patients respond to high-dose prednisone (200 mg/d) alone, without plasma therapy.
- Antiplatelet agents are used, but hemorrhage is a concern and these agents’ benefit has not been proven. Aspirin and dipyridamole are recommended by some, but their use is controversial. Other antiplatelet agents (e.g., ticlopidine, prostacyclin) have variable outcomes.
- Splenectomy is performed occasionally to treat patients who do not respond to plasma exchange or that relapse chronically. Some patients benefit from splenectomy. The response may be due to the removal of the site of sequestration of the RBCs and platelets. Another possibility is that the spleen is a major site of microvascular occlusive lesions in severe TTP.
- Treatment of refractory or relapsing TTP includes vincristine. Vincristine is occasionally given to treat resistant cases. Dosing is 1 mg/m², with a maximum dose of 2 mg, given weekly.
- Supportive care for end-organ damage may be required. Hemodialysis is required occasionally for renal failure. Angiotensin-converting enzyme (ACE) inhibitors, nitroprusside, or esmolol may be required to control severe hypertension.
- Anticonvulsants, such as phenytoin, may be required for control seizures.
- Platelet-depleted packed RBCs may be necessary for severe hemolytic anemia.

1. Platelet transfusion is contraindicated because it is associated with rapid deterioration. The platelet aggregation worsens with platelet transfusions. In some studies, extensive platelet aggregates were found throughout the CNS on postmortem examination.
2. Desmopressin (DDAVP) is contraindicated because it acts by releasing ULVWF from the endothelium into the circulating blood.

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Conclusion
Early clinical diagnosis and exclusion of other causes of similar illness is very important. Understanding the pathophysiology of thrombotic thrombocytopenic purpura (TTP) is ongoing and too early to have clearly defined evidence-based standard therapeutic procedures that may be applicable for all patients. Intravenous (IV) plasma exchange, also called plasmapheresis, is the present standard of treatment for TTP. During the plasma exchange, the inhibitory antibodies are removed and the plasma is replenished with the deficient protease. Delay in starting the plasma exchange is correlated with treatment failure. If a delay is unavoidable, begin plasma infusion until the plasma exchange is available.

References