

## A clinically suspected case of thrombotic thrombocytopenic purpura managed with therapeutic plasma exchange in Kathmandu Medical College Teaching Hospital

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**Keywords:** Thrombotic thrombocytopenic purpura, plasmapheresis, therapeutic plasma exchange



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### Abstract

Thrombotic thrombocytopenic purpura (TTP) is a life threatening thrombotic microangiopathy which may not present with the classic pentad of microangiopathic hemolytic anemia, fever, neurologic changes, thrombocytopenia and renal dysfunction. High level of clinical vigilance has to be rendered in suspected cases of TTP and therapeutic plasma exchange (TPE) must be started as soon as possible as this can be a lifesaving intervention. TTP is a category 1 recommendation for plasmapheresis as per the guidelines from American Society for Apheresis (ASFA). We present a case of 55 years old male who presented with abdominal pain, vomiting and fever and was clinically suspected as a case of thrombotic thrombocytopenic purpura. He received an intensive care treatment (endotracheal intubation with mechanical ventilation and renal replacement therapy) and after no improvement following fifth day of treatment, he was started on therapeutic plasma exchange (TPE). After two cycles of plasmapheresis, he had marked clinical improvement. Due to the cost unaffordability by the patient's family, further sessions of plasma exchange therapy could not be done. The patient was later discharged and followed up in outpatient basis.

### Introduction

Microangiopathic hemolytic anemia (MAHA) is a descriptive term for non-immune hemolytic anemia resulting from intravascular red blood cell fragmentation that produces schistocytes on the peripheral blood smear. Investigating thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) and other thrombotic microangiopathies often can pose challenge to the physicians. Primary thrombotic microangiopathies (TMA) comprises thrombotic thrombocytopenic purpura (TTP), Shiga toxin mediated hemolytic uremic syndrome (ST HUS), complement mediated TMA, drug induced TMA (DI TMA), metabolism and coagulation mediated TMA. Other disorders that can present with MAHA and thrombocytopenia are pregnancy-associated syndromes (eg, severe preeclampsia/HELLP syndrome), severe hypertension, systemic infections and malignancies and autoimmune disorders such as systemic lupus erythematosus.

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-

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threatening thrombotic microangiopathy characterized by systemic microvascular platelet aggregation, microangiopathic hemolytic anemia, severe thrombocytopenia, and organ ischemia linked to disseminated microvascular platelet rich-thrombi(1). TTP occurs due to deficiency of ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13). ADAMTS13 is the von Willebrand factor (VWF)-cleaving protease. A severe functional ADAMTS13 deficiency causes the blood accumulation of platelet-hyperadhesive ultra large VWF multimers, leading to the formation of platelet-rich micro thrombi within small arterioles. TTP can be congenital or acquired. Most of the cases of acquired TTP are idiopathic i.e. causes are not known. Most patients with idiopathic TTP have a deficiency in activity of ADAMTS13, and demonstrate an associated autoantibody. Other causes include drugs, pregnancy, infections, and malignancies.

The classic pentad of findings, consisting of thrombocytopenia, microangiopathic hemolytic anemia, fever, neurologic changes, and renal dysfunction, are seen in only a minority of patients. Thus, a high clinical index of suspicion is paramount because delay in recognition may adversely affect outcomes. Plasma exchange therapy using fresh frozen plasma is conducted to supplement ADAMTS13 and remove anti-ADAMTS13 autoantibodies in the patients with acquired TTP (2). The American Society for Apheresis (ASFA) in 2010, has given a category I recommendation for plasmapheresis/therapeutic plasma exchange (TPE) in patients with thrombotic thrombocytopenic purpura. Besides, corticosteroid therapy is often administered in conjunction with plasma exchange to suppress autoantibody production.

### Case Report

A 55 years old male presented with pain abdomen, vomiting and fever for five days and altered sensorium for one day. Abdominal pain was sudden in onset, present over his right lower abdomen, which increased in severity for the past two days. This was associated with low grade fever and vomiting which was non projectile, non- bile or blood stained.

There was no history of rash, diarrhea, joint pain, cough, chest pain, palpitations, loss of consciousness and abnormal body movements. There was no history of any prior drug intake. He had history of pre-diabetes and hypertension for which he was under lifestyle modification only.

On examination, patient had altered sensorium with Glasgow coma scale (GCS) of 12/15 (E2V4M6). His blood pressure was 90/60 mmHg, pulse 116/min and had axillary temperature of 102°F. His oxygen saturation was 90% on 2L/min with supplemental oxygen. Purpuric spots were noted in his oral mucosa. There was no evidence of focal neurological deficit. On abdominal examination, tenderness was noted on right iliac fossa with absent bowel sounds.

### Investigations on the first day of admission

His examination revealed hemoglobin 13.5 gm/dl, with total leucocytes count of 6500/cu mm, differential count of N88 L10 E2. His platelet count was low (15,000/cu mm) and had metabolic acidosis, increased serum urea (118 mg/dl) and creatinine (3.4 mg/dl). Alkaline phosphatase was markedly elevated (1045 U/L) but SGOT and SGPT were only slightly elevated. HIV, Hepatitis B and Hepatitis C were negative as per their respective rapid tests. The ultrasound examination of abdomen and pelvis was suggestive of mild hydronephrosis due to 9.7 mm calculus in right lower pole calyx and two 6-7 mm calculi in right distal ureter. Urine examination revealed red blood cells 8-10/HPF and pus cells 6-8/HPF. He had increased bilirubin (total bilirubin 5.1 and direct bilirubin 2.2 mg/dl), increased lactate dehydrogenase (LDH) (300IU/L), and negative direct antiglobulin (Coombs) test (DAT). However, in peripheral blood smear no schistocytes were found.

### Clinical progression with interventions

He was admitted in medical intensive care and started on empirical intravenous antibiotics (ceftriaxone, doxycycline and metronidazole) to provide coverage for possible urinary as well as intra-abdominal infection. Methylprednisolone was administered suspecting vasculitis or thrombotic microangiopathy as a possibility. He was transfused four pints of platelet rich plasma (PRP) and his platelets after the transfusion was 24,000/cu mm.

On third day, his platelet count was 24,000/cu mm. Four pints of PRP was transfused which resulted in platelet counts of 27,000/ cu mm. His hemoglobin fell to 10.6 gm/dl. Antibiotics were upgraded to meropenem and ticoplanin as the patient developed healthcare associated pneumonia evidenced by inspiratory crackles and bilateral non-homogenous opacities on chest X-ray. He became tachypneic and was kept under continuous positive airway pressure (CPAP) overnight.

On fourth day, he was unable to maintain oxygen saturation despite high flow oxygen and his GCS fell to 8/15. He was subsequently intubated and kept under mechanical ventilation (volume control-assist control mode) with vasopressor support. He underwent first session of hemodialysis due to persistent rise in urea and creatinine levels (205 mg/dl and 3.5 mg/dl respectively) and decreased urine output. After further six pints of platelet rich plasma transfusion, his platelets was 30,000/cu mm. On fifth day, he had second session of renal replacement therapy.

### Further investigation reports

D-dimer levels were high 2.99 mg/L. C3 and C4 levels within normal range. P-ANCA, C- ANCA, Anti GBM antibodies were negative. ANA titre was non-significant. Pro-calcitonin levels were high. Rapid tests and thick/thin smears for malaria were negative. Blood test for infectious diseases such as kala-azar, leptospirosis, scrub typhus, dengue and brucella were negative. His tracheal aspirate, urine and blood culture revealed no growth. Influenza A and B tests were negative.

### Initiation of therapeutic plasma exchange

On day 6, based on the history of fever, altered mental status, low platelets count, increased lactate dehydrogenase, falling hemoglobin level and acute kidney injury, a clinical diagnosis of thrombotic thrombocytopenia was made. Decision to start on therapeutic plasma exchange was made.

The right internal jugular line for renal replacement therapy was used. 30–40 mL/kg of plasma (1–1.5 plasma volumes) were removed at each procedure and replaced with 1/4th diluted 20% human albumin solution with 0.9% saline and fresh frozen plasma. The filtration plasmapheresis technique was used where blood was passed through a filter to separate the plasma components from the larger cellular components. The advantage of filtration technique was, a large filter could be easily added to the existing continuous veno-venous hemodialysis circuit without much interruption to patient care.

### Results after therapeutic plasma exchange

After first session of TPE, his platelet count increased to 55,000/cu mm. After second session of TPE, his platelets count further increased to 75,000/cu mm. Patient's general condition improved and inotropes support was tapered down. His platelet counts was on increasing trend with 9th day count of 109000/cu mm, 10th day count of 198000/cu mm and 11th day count of 289080/cu mm and didn't fall thereafter.

Patient was extubated on day 14 and he did not need any further hemodialysis sessions. He was stepped down from intensive care unit and was discharged on 30th day of admission.

### Discussion

The word plasma pheresis is derived from the greek word "apheresis" which means "to take away". Plasmapheresis is an apheresis procedure which separates and removes the plasma component from a patient(3). The term plasma exchange is used when plasmapheresis is followed by replacement with fresh frozen plasma infusion. Plasmapheresis can be done either by centrifugation or filtration method. We used the filtration plasmapheresis technique where blood was passed through a filter to separate the plasma components from the larger cellular components.

The diagnosis of thrombotic thrombocytopenic purpura can often be challenging because of the lack of specific diagnostic criteria and variety of presentations. TTP can present without the full pentad; up to 35% of patients do not have neurological signs at presentation and renal abnormalities and fever are not prominent features. As the concern of TTP was strong in the case, we resorted to plasma exchange while the diagnostic evaluation continued. ADAMTS 13 activity could not be measured as the test was unavailable in our setting. Peripheral smear did not have schiocytes or fragmented red blood cells (RBC). The peripheral smear was examined by a general pathologist instead of hematologist or a doctor who specialized in TMA syndromes. Patient did not consent for renal biopsy and after recovery the biopsy was not deemed necessary. Even just two sessions of plamapheresis caused the marked improvement in the clinical condition of the patient. Further session could not be carried out due to financial constraints.

### Acknowledgement

We would like to extend our sincere thanks and appreciate the efforts of Professor. Dr. Arpana Neopane and her team who provided valued support in the intensive care treatment of the patient.

### Consent

Written informed consent was obtained from the patient for the publication of this case report.

### Conclusion

Diagnosis of TTP, TMA and MHA can often be difficult. Sometimes, not all diagnostic criteria can be met. TTP has a high mortality rate, and there is significant room for improvement in numerous areas of patient care. A trial of therapeutic plasma exchange, when the clinical ground is strong can be a lifesaving treatment modality. However, the high financial burden and unavailability of plasmapheresis service in tertiary hospitals may be the reasons why such interventions could not be effectively implemented in country like Nepal.

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