International Journal of Contemporary Pediatrics
*Goel N et al. Int J Contemp Pediatr. 2025 Apr;12(4):657-661*
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20250775

**Case Report**

# A case report of thrombotic thrombocytopenic purpura with positive ANA activity

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**Received:** 08 February 2025
**Accepted:** 06 March 2025

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## ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder, characterized by: consumptive thrombocytopenia, microangiopathic hemolytic anemia with the presence of schistocytes, renal impairment, neurological dysfunction and fever. A 12-years-old girl presented with TTP and had ADAMTS13 activity deficiency along with positive ANA activity. The child was planned for plasmapheresis but developed refractory seizures and pulmonary bleeding and succumbed to death. TTP with ANA positivity has a very fulminant course. Pulmonary involvement can be asymptomatic but has a poor prognosis with rapid clinical deterioration. A high index of suspicion is of utmost importance in low to middle-income countries settings as the facility of plasmapheresis is available at very few centers

**Keywords:** ANA, ADAMTS13, Plasmapheresis, Thrombotic thrombocytopenic purpura

## INTRODUCTION

Thrombotic mircoangiopathies (TMA) are a rare heterozygous group of disorders, characterized by microangiopathic hemolytic anemia (MAHA), peripheral thrombocytopenia and variable severity of organ dysfunction. TMA includes thrombotic thrombocytopenic purpura (TTP) that is characterized by central nervous system (CNS) involvement, hemolytic uremic syndrome (HUS) that is associated with severe renal involvement and can also be associated with various conditions such as pregnancy, cancer, chemotherapy, medications and human immunodeficiency virus (HIV).[1]

TTP is a life-threatening disorder that is characterized by: consumptive thrombocytopenia, MAHA with presence of schistocytes, renal impairment, neurological dysfunction and fever. However, this classical pentad is seen in only 40% patients.[2] Pathogenesis of TTP includes reduced activity of a von Willebrand factor (vWF)-cleavage protease (a disintegrin and metalloprotease with thrombospondin-1 like domains (ADAMTS13)) that leads to persistence of ultra large vWF multimers (ULVWF), causing platelet agglutination, microvascular thrombi formation, multi-organ dysfunction (MOD).[3] TTP has been found to be associated with some autoimmune disorder such as systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS) and some rare ones. The combined occurrence of TTP with SLE has shown worse prognosis as compared to isolated occurrence of either of them, therefore, a rigorous work up, accurate diagnosis and early initiation of treatment is required to improve the outcome of the patient.[4] Authors describe a case of a 12 years old girl with TTP with ANA positivity.

## CASE REPORT

A 12-years-old fully immunized and developmentally normal female, born out of a non-consanguineous marriage, was admitted to our hospital with complaints of intermittent high-grade fever and generalized weakness

for 3 weeks. There was no past history of bleeding manifestations, episodic pallor or jaundice, arthralgia, photosensitivity, shortness of breath, headaches or any other neurological manifestations at admission. On admission, she had fever (102.1F), normal blood pressure (50th to 90th centile for height and age), a Glasgow coma scale of 15/15 (E4V5M6), severe pallor, mild icterus and hepatomegaly (3 cm below the coastal margin) with no splenomegaly.

Considering the possibility of bacterial infections, broad spectrum iv antibiotics were started. Considering the possibility of hemolysis, a peripheral smear (PS) was sent. Bone marrow aspiration (BMA) was done to exclude malignancy considering bicytopenia with elevated uric acid, LDH and calcium levels. BMA showed megaloblastic changes and normal maturation of the myeloid lineage, with no atypical cells. Complete blood counts were suggestive of bicytopenia, with PS showing MAHA (Figure 1).

The patient's LDH was elevated with a gradual rise in serum bilirubin levels with a negative DCT. Baseline investigations are shown in Table 1. Her vitamin B12 and folate levels were within normal limits. By day 2 of admission, the child had developed complaints of persistent, progressive headaches. Considering the possibility of TMA, the PLASMIC score was calculated and it came out to be 7 (high risk for TTP). Serial investigations are shown in Table 2. The work up TTP and ANA was also sent as it was a female patient. The child was being planned for plasmapheresis and by the time she could be shifted, she started throwing seizures.

She was in status epilepticus and seizure could only be controlled by Midazolam infusion after securing airway. The child received one session of plasmapheresis; however, it could not be completed due to massive upper gastrointestinal bleeds. The child was shifted to PICU and planned for next session once bleeding is controlled and till that time FFP transfusion and immunosuppression was planned.

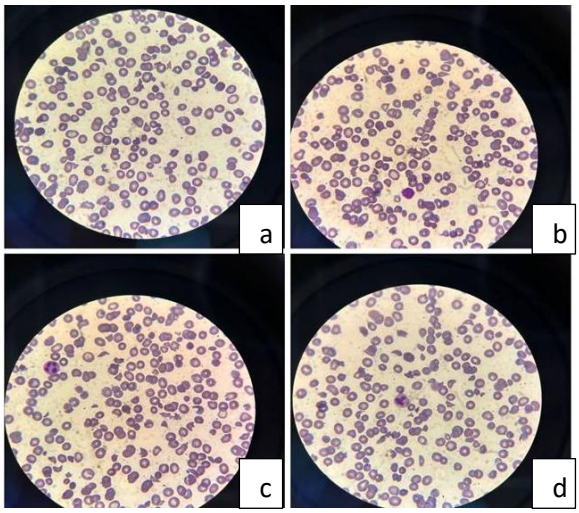


**Figure 1 (a-d): Peripheral smear showing microangiopathic haemolytic anaemia with schistocytes.**

However, after few hours of transferring in PICU she started having massive pulmonary bleed which could not be controlled and the child ultimately succumbs to her illness, owing to a massive hemorrhage. The pulmonary bleed was unusual in a suspected case of TTP. However, the report came after 48 hours and it showed markedly low ADAMTS13 activity (<0.2) (normal range: 60.6–130.6). The ANA levels also came out to be strongly positive. The fulminant course of this child along with involvement of pulmonary system can be due to underlying SLE in this child.

**Table 1: Baseline investigations.**

| Investigations | Patient's value | Reference value |
|---|---|---|
| **Hemoglobin (g/dl)** | 6.9 | 11.5-17.0 |
| **Total leukocyte count (TLC) (cells/cu.mm)** | 5200 | 4000-10,000 |
| **Differential leukocyte count (%) (N/L/M/E/B)** | 76.2/16.4/1.4/5.9/0.1 | |
| **MCV (cu.um)** | 97 | 77-86 |
| **RDWcv (%)** | 27.8 | 11-16 |
| **Platelets (cu.mm)** | 12000 | 150000-500000 |
| **Reticulocyte count (%)** | 8.3 | 0.5-2.5 |
| **Absolute reticulocyte count (cells/cu.mm)** | 327700 | 50000-100000 |
| **Peripheral smear** | Severe anemia with marked thrombocytopenia with presence of numerous fragmented RBC and schistocytes (5.6%) alongwith reticulocytosis suggestive of microangiopathic hemolytic anemia | |
| **Serum sodium (mEq/l)** | 144 | 135-145 |
| **Serum potassium (mEq/l)** | 2.7 | 3.5-5.5 |

Continued.

| Investigations | Patient's value | Reference value |
|---|---|---|
| **Serum bilirubin (mg/dl)** | 1.1 | 0.1-1.2 |
| **Alanine transaminase ((U/l)** | 31 | 4-36 |
| **Aspartate transaminase (U/l)** | 19 | 8-33 |
| **Serum urea (mg/dl)** | 19.2 | 5-20 |
| **Serum creatinine (mg/dl)** | 0.53 | 0.7-1.3 |
| **Total protein (g/dl)** | 8.1 | 6.0-8.3 |
| **Total albumin (g/dl)** | 5.1 | 3.5-5.5 |
| **Urine protein (dipstick)** | Negative | Negative |
| **Urine blood (dipstick)** | Negative | Negative |
| **Uric acid (mg/dl)** | 8.9 | 2.5-5.5 |
| **LDH (U/l)** | 2599 | 140-280 |
| **HIV ELISA** | Non-reactive | Non-reactive |
| **Anti HCV antibodies** | Negative | Negative |
| **HbsAg** | Negative | Negative |
| **International normalized ratio (INR)** | 0.86 | <1.4 |
| **Serum vitamin B12 (pg/ml)** | 752 | 160-950 |
| **Serum folate (ng/ml)** | 16 | 5-21 |
| **Calcium (mg/dl)** | 5.5 | 8.5-10.2 |
| **Phosphorus (mg/dl)** | 5.3 | 2.5-4.5 |
| **Direct coombs test** | Negative | Negative |
| **CPK (mcg/l)** | 47 | 30-135 |
| **CPK MB (IU/l)** | 16 | 5-25 |
| **D Dimer (mg/l)** | 0.51 | 0-0.5 |
| **Fibrinogen (mg/dl)** | 369 | 200-400 |
| **CRP (mg/dl)** | 0.85 | 0.3-1.0 |
| **ANA by IF** | 3+ | Negative |
| **ANA titre** | 1:320 | <1:80 |

N-neutrophils; L-lymphocytes; M-monocytes; E-eosinophils; B-basophils; MCV-mean corpuscular volume; RDWcv-red cell distribution width-coefficient of variation; LDH-lactate dehydrogenase; HIV-human immunodeficiency virus; ELISA-enzyme-linked immunosorbent assay; HCV-hepatitis C virus; CPK-creatine phosphokinase; CRP-c-reactive protein; ANA-anti nuclear antibodies

**Table 2: Serial investigations.**

| Investigations | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|
| **Hemoglobin (g/dl)** | 6.9 | 7.6 | 7.0 | 6.7 |
| **Total leukocyte count (cells/cu.mm)** | 5200 | 4290 | 6410 | 6320 |
| **Absolute neutrophils count (cells/cu.mm)** | 2070 | 1740 | 3730 | 2370 |
| **Platelets (cells/cu.mm)** | 12000 | 20000 | 12000 | 14000 |
| **Serum urea (mg/dl)** | 19.6 | 21.6 | 17.8 | 20.8 |
| **Serum creatinine (mg/dl)** | 0.53 | 0.40 | 0.45 | 0.48 |
| **Serum sodium (mEq/l)** | 144 | 142 | 142 | 137 |
| **Serum potassium (mEq/l)** | 2.7 | 3.6 | 4.4 | 4.0 |
| **Total serum bilirubin (mg/dl)** | 1.1 | 1.6 | 1.8 | 1.3 |

## DISCUSSION

We described a case who presented with fever, microangiopathic anemia with thrombocytopenia and had no signs or symptoms suggestive of central nervous system (CNS) involvement at the time of admission and did not develop acute renal failure throughout the course. Gradually, the child developed non-specific neurological symptoms, followed by refractory seizures and coagulopathy and ultimately died due to fulminant course of the disease. Investigations finally revealed low ADAMTS13 activity with ANA positivity. Our child was finally diagnosed as TTP with SLE and was planned for plasmapharesis, however, eventually succumb to illness.

Pulmonary symptoms are very rare in TTP. Subclinical manifestations could be present in some patients. However, few studies have been reported where patients with TTP exhibit abnormal chest X-ray findings, including diffuse or localized infiltrates, pleural effusions

or atelectatic changes. Pulmonary bleed in our case could be due to diffuse alveolar hemorrhage (DAH), that is a life-threatening complication and have been rarely reported to occur in TTP. There have been documented cases where intrapulmonary hemorrhage is the initial presentation of TTP. Autopsy studies have revealed that patients with TTP and associated pulmonary hemorrhage often have thrombi within the small vessels of the lung.

The potential pathophysiology of TTP leading to diffuse alveolar hemorrhage (DAH) is believed to involve capillary injury, followed by the adherence of platelets and fibrin to the vascular endothelial cells. This process increases vascular permeability, resulting in non-cardiogenic pulmonary edema. Thomas et al., reported a case of 68-years-old male with polymyositis who presented with hemoptysis and was found to have TTP.[5] In a retrospective review of 14 patients diagnosed with TTP from 2004 to 2012 at a community hospital in Scranton, pulmonary bleed in the form of hemoptysis was found in 7% patients amongst other respiratory findings, most common being dyspnea.[6] DAH is associated with worse outcomes.

TTP can be classified as 'congenital' which is rare and occurs due to congenital absence of ADAMTS activity or as 'acquired', which occurs more frequently and may be due to auto antibodies or due to some factors having inhibitory effect on it.[7] Mild to moderate ADAMTS13 deficiency may occur in conditions other than TTP and can occur in severe sepsis, systemic inflammation and in pregnant women with HELLP syndrome. Nguyen et al, reported decreased ADAMTS13 activity in patients with severe sepsis, suggesting the role of elevated inflammatory cytokines in decreasing the ADAMTS activity.[8] Patients with SLE may have aberrant activation of auto reactive lymphocytes.

Plasma exchange (PLEX) has been found to be most effective for treating a patient with TTP. It removes the pathological autoantibodies, cytokines and harmful undesired substances. PLAX may also be proven beneficial for SLE related complications other than TTP such as neurolupus, alveolar hemorrhage and severe lupus nephritis as reported by Pugnoux et al.[9]

It is still unclear whether we could predict severe ADAMTS13 deficiency through clinical examination. Coppo P et al, reviewed which factors could predict severe ADAMTS deficiency. Patients with a significant deficiency in ADAMTS13 were younger, had lower platelet counts and creatinine levels and more frequently tested positive for antinuclear antibodies (ANA) at diagnosis with a significant p value<0.001, similar to our case.

Chronic renal failure was more common in patients with detectable ADAMTS13 activity (19.2% vs. 1.1%, p<0.001). Multivariate logistic analysis showed that patients with severe ADAMTS13 deficiency were more likely to have ANA (Odds Ratio (OR) 4.81, 95% confidence interval (CI) 1.5–15.4), lower platelet counts (OR 0.98, 95% CI 0.96–1) and lower creatinine levels (OR 0.99, 95% CI 0.98–0.99) compared to those with detectable ADAMTS13 activity (p<0.01, 0.14 and <0.01, respectively).

The presence of ANA, platelet counts <31×10^9/l and creatinine levels<2mg/dl identified patients with severe ADAMTS13 deficiency with 52% sensitivity and 97% specificity. These criteria had a high positive predictive value (98.2%) for severe ADAMTS13 deficiency and a negative predictive value of 39.5%. our patient also had positive ANA levels (1:320+), significant severe thrombocytopenia and creatinine values were not elevated.[10]

TTP has occasionally been observed in individuals with systemic lupus erythematosus (SLE). Since SLE and TTP present with similar clinical symptoms, TTP might be overlooked in SLE patients without thorough and detailed examinations. The most effective treatment for TTP is currently plasma exchange. Our case highlights that TTP is rare and life-threatening and hence, requires the sharp suspicion so that plasma exchange can be imitated at the earliest.

## CONCLUSION

TTP should be kept in the differential of bicytopenia specially if not associated with any atypical cells in peripheral smear. Plasmapheresis is life saving and therefore a high index of suspicion should be kept so that necessary arrangements can be done timely. TTP with ANA positivity has aggressive course.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Goel N, Chawla A, Prabhakar P. A case report of thrombotic thrombocytopenic purpura with positive ANA activity. Int J Contemp Pediatr 2025;12:657-61.