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A CLEVER STROKE MIMIC: THROMBOTIC THROMBOCYTOPENIC PURPURA WITHOUT SCHISTOCYTES – A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Background: Thrombotic thrombocytopenic purpura (TTP) is a life-threatening hematologic emergency caused by ADAMTS13 deficiency, leading to microvascular thrombosis, haemolytic anaemia, thrombocytopenia, and end-organ damage. Neurological symptoms occur in up to 90% of cases and are frequently misdiagnosed as stroke. Prompt recognition and treatment reduce the mortality rate from over 90% to 10–20%.

Case presentation: A 70-year-old woman with no significant medical history presented with acute aphasia and right-sided facial and upper extremity numbness. Five days prior, she had experienced fatigue, headache, and bruising. On admission, she had stable vitals with mild aphasia and purpuric ecchymoses noted on examination. Laboratory findings revealed haemolytic anaemia (haemoglobin 7.8 g/dl, lactate dehydrogenase 875 U/l, total bilirubin 2.4 mg/dl), thrombocytopenia (35 $\times 10^9$/l), and unremarkable coagulation studies (partial thromboplastin time 30 sec, prothrombin time-international normalized ratio 1, fibrinogen 370 mg/dl, D-dimer 2.15 ng/ml). Peripheral smear showed no schistocytes but noted 2+spherocytes. Stroke was ruled out with brain magnetic resonance imaging/magnetic resonance angiography. Given the bicytopenia with possible haemolysis along with new neurological symptoms, TTP was considered in the differential diagnosis. A PLASMIC score of 5 suggested a high probability of TTP. Plasma exchange and corticosteroids were initiated within 5 hours of presentation. ADAMTS13 activity <1% confirmed the diagnosis 4 days after presentation. After five plasma exchange sessions, the patient's platelet count normalized and neurologic deficits resolved by discharge.

Conclusion: This case underscores the importance of considering TTP in stroke mimics, even in the absence of schistocytes, if clinical suspicion is high. Early recognition and initiation of treatment significantly improve patient outcomes.

KEYWORDS

Thrombotic thrombocytopenic purpura, stroke mimic, schistocytes

LEARNING POINTS

- Start plasmapheresis and high-dose steroids immediately for suspected thrombotic thrombocytopenic purpura (TTP), even if schistocytes are absent when clinical suspicions are high.
- Recognizing TTP's neurological symptoms mimicking stroke is crucial to avoid misdiagnosis and ensure timely treatment.

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INTRODUCTION/BACKGROUND

Acquired thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening autoimmune disorder characterized by autoantibodies against the ADAMTS13 protease. This condition leads to the accumulation of abnormally large von Willebrand factor (vWF) multimers. These multimers increase platelet adhesiveness, promoting the formation of microthrombi and resulting in severe thrombocytopenia[1].

Historically, TTP was nearly universally fatal, with a survival rate of approximately 10% before effective treatments were developed. However, with the advent of plasma exchange therapy and immunosuppressive treatments, survival rates in recent cohorts have improved to approximately 90%[1]. Despite these advances, early diagnosis remains challenging due to the rarity of the disease, with an annual incidence of about 1 case per million people[2].

Due to nonspecific neurological symptoms of TTP, patients with TTP are sometimes misdiagnosed as stroke, potentially missing the critical treatment window. While the presence of schistocytes on a peripheral blood smear serves as an important diagnostic clue for considering TTP, in rare cases this characteristic finding may be absent[1]. Here, we report a case of TTP without schistocytes.

CASE DESCRIPTION

A 70-year-old woman was transported to the hospital with acute-onset aphasia and right-sided sensory impairment as her chief complaints. Until 5 days before symptom onset, she had been in her usual state of health but then began experiencing fatigue. She subsequently developed a dull headache localized to the parietal region and mild subcutaneous bruising on her lower limbs, which were painless. She had no fever, chest pain, shortness of breath, gum bleeding, or haematuria.

On the afternoon of presentation, she experienced numbness on the right side of her face and body, along with difficulty in word retrieval. Her family brought her to the emergency department of a nearby hospital.

At presentation, her right-sided sensory impairment had improved, but she exhibited mild aphasia with word-finding difficulties. Her vital signs were stable, and no apparent neurological deficits were observed. A non-contrast computed tomography (CT) scan of the head showed no acute intracranial abnormalities and CT angiography did not reveal any major vascular occlusion. Her National Institutes of Health Stroke Scale (NIHSS) score was 1. Blood tests showed haemoglobin at 8 g/dl and platelet at 20,000/µl. Given the suspicion of a stroke, she was transferred to our hospital for further neurologic evaluation and treatment. Upon arrival at our hospital, her vital signs were as follows: blood pressure 117/63 mmHg, heart rate 88 bpm, respiratory rate 19 breaths per minute, body temperature 37.2°C, and oxygen saturation 97%. On physical examination, she was well-nourished, alert, and did not exhibit signs of acute distress. Neurologically, she remained alert with mild aphasia, showing some difficulty with fluency, but her right-sided sensory impairment had resolved, and her NIHSS score remained 1. Motor strength was symmetric at 5/5 in all extremities, deep tendon reflexes were normal, sensory function was intact, and cranial nerve examination showed no abnormalities.

On skin examination, multiple subcutaneous bruises with a purpuric distribution were noted on both the upper and lower extremities. The rest of the examination, including cardiovascular, respiratory, gastrointestinal, and genitourinary assessments, was unremarkable.

Initial laboratory tests *(Table 1)* revealed anaemia with a haemoglobin level of 7.8 g/dl and thrombocytopenia with a platelet count of 35 ×10^3/µl. Renal function and coagulation studies were within normal ranges. The total bilirubin level was elevated at 2.4 mg/dl and lactate dehydrogenase (LDH) was 876 IU/l, suggestive of haemolytic anaemia. A peripheral blood smear showed spherocytes, but no schistocytes were observed *(Fig. 1)*. Brain magnetic resonance imaging (MRI) did not reveal any findings indicative of cerebrovascular disease. Despite the absence of schistocytes, TTP was suspected given the presence of stroke-like symptoms, possible haemolytic anaemia, and thrombocytopenia. The patient's PLASMIC score was calculated as 5. Given the poor prognosis associated with untreated TTP, immediate treatment was initiated.

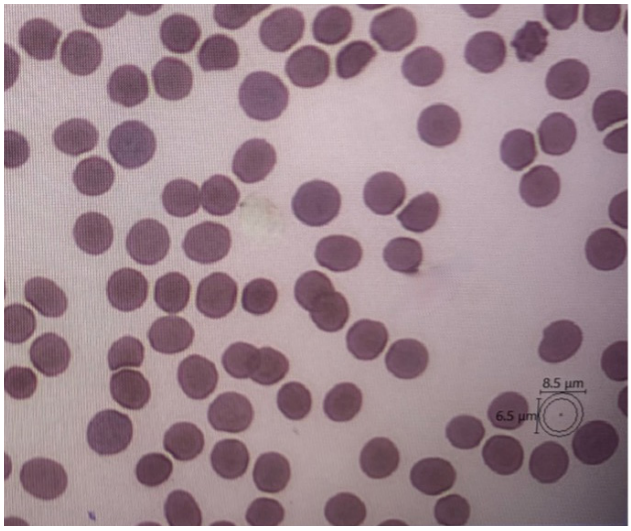
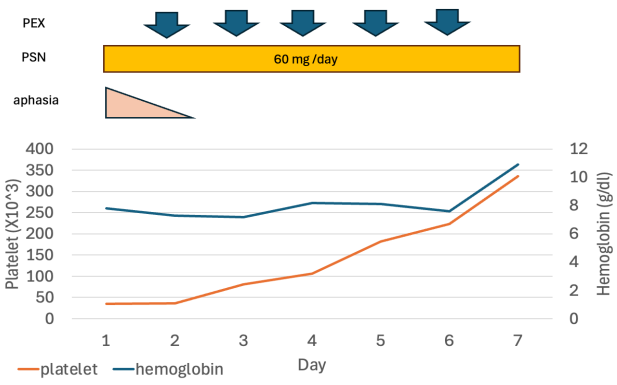


Figure 1. Peripheral blood smear.



Abbreviations: PEX, plasma exchange; PSN, prednisone.

Figure 2. Clinical course.

Parameter	Result	Reference range
Complete blood count		
WBC (10^3/µl)	8.32	3.84-9.84
Hemoglobin (g/dl)	7.8	13.7-17.5
Hematocrit (%)	23.4	40.1-51
MCV (fl)	96.3	79.4-98.4
Platelets (10^3/µl)	35	151-424
Biochemistry		
BUN (mg/dl)	21	6.0-23
Creatinine (mg/dl)	0.8	0.6-1.4
T-Bil (mg/dl)	2.4	0-1.2
D-Bil (mg/dl)	0.4	0-1
AST (IU/l)	25	0-40
ALT (IU/l)	13	0-41
ALP (IU/l)	75	35-129
Coagulation		
PTT (sec)	30	25-35
PT (sec)	11.5	11-13.5
INR	1	0.8-1.2
Anaemia workup		
Iron (µg/dl)	95	30-160
TIBC (µg/dl)	306	228-428
Ferritin (ng/ml)	748	22-300
LDH (IU/l)	876	135-250
Hp (mg/dl)	<10	30-200
Reticulocyte (%)	6.11	0.64-2.26
Coombs, direct	-	-
Vit B12 (pg/ml)	276	232-1245
Folate (ng/ml)	11.6	>3.1
Hcy (µmol/l)	13.6	<15
MMA (nmol/l)	187	<370

Abbreviations: WBC, white blood cells; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; D-Bil, direct bilirubin; Hcy, homocysteine; Hp, haptoglobin; INR, International normalized ratio; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; MMA, methylmalonic acid; PT, prothrombin time; PTT, partial thromboplastin time; T-Bil, total bilirubin; Vit B12, vitamin B12.

Table 1. Laboratory data.

High-dose corticosteroids and plasma exchange therapy were initiated within 5 hours of admission *(Fig. 2)*. By hospital day 3, her aphasia improved, and her platelet count normalized. An ADAMTS13 assay prior to treatment initiation came back 4 days later with activity <1%, an anti-ADAMTS13 antibody level of 51 U/ml, and a positive ADAMTS13 inhibitor, confirming a diagnosis of acquired TTP.

The patient underwent five consecutive sessions of plasma exchange therapy. Her platelet count remained stable after the completion of plasma exchange, and she was discharged on hospital day 7.

DISCUSSION

This case highlights the complexity of diagnosing TTP, particularly when it mimics acute stroke and lacks the classic finding of schistocytes on a peripheral blood smear. Historically, TTP was clinically defined by the "pentad" of fever, microangiopathic haemolytic anaemia (MAHA), thrombocytopenia, neurological impairment, and renal dysfunction. However, studies demonstrate fewer than 10% of acute TTP patients present with all five features[2]. Currently, the presence of thrombocytopenia and MAHA, in the absence of an alternative explanation, is sufficient to strongly consider TTP or another thrombotic microangiopathy (TMA).

The differential diagnosis for this case was extensive. Given the neurological symptoms and initial imaging findings, acute ischemic stroke or transient ischemic attack (TIA) was initially suspected. However, imaging did not reveal findings of an infarct, the patient lacked major risk factors for TIA, and the presence of thrombocytopenia and haemolytic anaemia could not be explained by a cerebrovascular event. Consequently, TTP became the leading consideration.

The presence of schistocytes on a peripheral blood smear is highly sensitive for the diagnosis of TTP, with most studies reporting schistocyte percentages ≥1% in all confirmed TTP cases. However, the specificity is lower, as schistocytes can also be seen in various non-TTP conditions such as sepsis, metastatic carcinoma, renal failure, and in neonates, often in conjunction with other red cell abnormalities like target cells or elliptocytes. One study found that a schistocyte percentage >0.55% had a sensitivity of 74.2% and specificity of 79.2% for TTP, highlighting its moderate diagnostic accuracy[3]. Therefore, while the presence of schistocytes is a key, diagnostic feature of TTP, it must be interpreted in the context of clinical findings and laboratory parameters such as thrombocytopenia, elevated LDH, and absence of significant coagulopathy to avoid misdiagnosis.

When schistocytes are absent, diagnosis must rely on clinical presentation, markers of haemolysis (elevated LDH, low haptoglobin, and reticulocytosis), and specific testing such as ADAMTS13 activity. The absence of schistocytes does not rule out TMA but highlights the need for an integrated clinical and laboratory approach. The PLASMIC score is a clinical tool developed to stratify the likelihood of TTP among

Table 2. Literature review.

Reference	Age (years)	Sex	Clinical features	Platelets (×10⁹/l)	Haemoglobin (g/dl)	LDH (U/l)	PLASMIC score	ADAMTS13 activity (%)	Treatment	Response
Fava et al.[11]	33	F	Confusion, coma, seizure, fever	24	5	N/A	7	N/A	TPE, GC	Remission
Tsai et al.[12]	36	F	CVA	6	7	N/A	7	<10	TPE, GC, RTX	Remission
Downes et al.[13]	40	F	CVA	239	9.3	296	6	11	TPE	Remission
Downes et al.[13]	42	F	CVA	207	10	N/A	5	12	TPE	Remission
Daram et al.[5]	66	F	Fever, confusion, blurred vision, fatigue, dark urine, petechiae	29	11.7	691	5	N/A	TPE	Remission
Imanirad et al.[6]	40	F	MI, CVA	34	11.7	558	7	<5	TPE, GC	Remission
Imanirad et al.[6]	25	F	CVA	27	9.4	510	7	<5	TPE, RTX	Remission
Imanirad et al.[6]	68	F	Asymptomatic	27	7.4	4764	7	<5	TPE, GC, RTX, splenectomy	Remission
Imanirad et al.[6]	58	F	CVA	14	8	1800	7	<5	TPE, GC, RTX	Remission
Idowu et al.[7]	48	F	CVA	97	11.1	238	5	16	TPE	Remission
Decker et al.[8]	43	F	CVA, Asthenia, gait disorder	17	12.9	454	6	<5	TPE, GC	Remission
Yu et al.[9]	47	F	CVA	50	9.8	629	5	<1	TPE, RTX	Remission

Abbreviations: CVA, cerebrovascular accident; F, female; GC, glucocorticoid; LDH, lactate dehydrogenase; N/A, not available; RTX, rituximab; TPE, therapeutic plasma exchange.

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patients presenting with thrombotic microangiopathy and to guide the initiation of therapeutic plasma exchange (TPE). A literature review of 12 studies involving 970 patients demonstrated that a PLASMIC score ≥5 has excellent sensitivity (99%) and negative predictive value (99%) at a TTP prevalence of 35%[4].

A review of 12 published cases of TTP without schistocytes on peripheral blood smear highlights the diagnostic challenge *(Table 2)*[5-9]. All patients were female, with ages ranging from the 30s to the 70s, and presented with characteristic clinical features of TTP, including neurological symptoms (e.g., confusion, seizures, stroke), fever, and systemic complaints such as fatigue or visual disturbances. Despite the absence of schistocytes, a hallmark of MAHA, all cases exhibited laboratory evidence of haemolysis, such as elevated lactate dehydrogenase, low haptoglobin, indirect hyperbilirubinemia, and/or reticulocytosis. While most cases had severely decreased ADAMTS13 activity, the clinical diagnosis of TTP was supported by the constellation of findings and favourable response to TPE. PLASMIC scores were retrospectively estimated when sufficient data were available, and most patients appeared to fall into the intermediate to high-risk categories. All patients received TPE along with adjunctive immunosuppressive therapy and achieved clinical remission. These cases underscore that the absence of schistocytes does not exclude the diagnosis of TTP and should not delay empiric treatment in patients with otherwise supportive clinical and laboratory findings.

In TTP, approximately 30% of patients may not initially exhibit haemolytic anaemia, likely because platelet aggregation and microvascular thrombosis precede overt red cell fragmentation, which typically occurs under high shear stress[8]. Nevertheless, patients without schistocytes who received TPE achieved remission, although relapse rates remained high, emphasizing that early recognition and treatment are critical. Similarly, in a retrospective study of 886 allogeneic transplant recipients with post-transplant diarrhoea, 80 had histologic evidence of intestinal TMA, yet only 46% demonstrated >2 schistocytes per high-power field[10]. The absence of schistocytes in transplant associated-TMA may result from localized endothelial injury, red cell extravasation rather than fragmentation, bone marrow suppression, or variability in smear interpretation. These findings stress the importance of maintaining a high index of suspicion for TMA in patients with suggestive clinical and laboratory features, even when schistocytes are not present.

CONCLUSION

This case highlights the diagnostic challenge of TTP, particularly when it mimics acute stroke in the absence of schistocytes. Despite the initial suspicion of cerebrovascular disease, the combination of thrombocytopenia, haemolytic anaemia, and ADAMTS13 deficiency confirmed the diagnosis. Early plasma exchange and corticosteroids resulted in a favourable outcome.

Clinicians should consider TTP in stroke-like presentations, even without schistocytes, and rely on an integrated clinical and laboratory approach for timely intervention while awaiting confirmatory ADAMTS13 testing. Given the risk of recurrence, long-term monitoring is essential. This case underscores the importance of early recognition and treatment in improving patient outcomes.

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