Radiology Case Reports 20 (2025) 2995–2999

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Case Report

Fatal interplay between acquired thrombotic thrombocytopenic purpura and posterior reversible encephalopathy syndrome: a case report ☆

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ARTICLE INFO

Article history:
Received 10 February 2025
Accepted 22 February 2025

Keywords:
Thrombotic thrombocytopenic purpura
Posterior reversible encephalopathy syndrome
Microangiopathic hemolysis
Hypertensive crisis
Plasma exchange
ADAMTS13 deficiency

ABSTRACT

Acquired thrombotic thrombocytopenic purpura (TTP) is a rare haematological emergency characterised by severe ADAMTS13 deficiency, leading to thrombotic microangiopathy and multiorgan dysfunction. Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder associated with endothelial dysfunction, often secondary to uncontrolled hypertension or autoimmune conditions. We present a case of a 22-year-old male who presented with vomiting, headache, and right upper limb weakness, followed by a hypertensive crisis and generalised seizures. Initial investigations revealed severe thrombocytopenia, microangiopathic hemolytic anaemia, and acute kidney injury, raising suspicion for thrombotic microangiopathy. MRI findings confirmed PRES, while the presence of schistocytes and markedly reduced ADAMTS13 activity led to the diagnosis of acquired TTP. The patient was treated with plasma exchange, immunosuppressive therapy, corticosteroids, and antihypertensive agents. Despite aggressive management, the disease progressed to multiorgan failure, and the patient succumbed to the illness. This case highlights the fatal interplay between TTP and PRES, emphasising the need for early recognition and timely intervention. The coexistence of these 2 rare conditions presents a diagnostic and therapeutic challenge, underscoring the importance of prompt plasma exchange and immunosuppressive therapy in such critically ill patients.

☆ Competing Interests: The authors have declared that no competing interests exist.

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https://doi.org/10.1016/j.radcr.2025.02.094

Background

Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening thrombotic microangiopathy characterised by severe thrombocytopenia, microangiopathic hemolytic anaemia, and multiorgan dysfunction due to disseminated microvascular thrombosis [1]. The disease is caused by a severe deficiency of ADAMTS13, a von Willebrand factor-cleaving protease, leading to the accumulation of ultra-large von Willebrand factor (vWF) multimers and excessive platelet aggregation in the microcirculation [2]. The deficiency of ADAMTS13 can be congenital (Upshaw-Schulman syndrome) due to genetic mutations in the *ADAMTS13* gene or acquired, which is primarily due to autoantibody-mediated inhibition of ADAMTS13 activity [3]. Acquired TTP is the predominant form and is frequently associated with autoimmune diseases, malignancies, pregnancy, infections, and certain medications [1]. The incidence of acquired TTP is estimated to be 3–6 cases per million per year, with a higher prevalence among females and young adults [4]. Without appropriate treatment, the mortality rate exceeds 90%; however, with early intervention, including plasma exchange and immunosuppressive therapy, the survival rate improves significantly, exceeding 80% [5].

Neurological manifestations are common in TTP, occurring in over 50% of cases, and range from mild confusion to seizures and coma due to microvascular thrombosis and endothelial injury [6]. One of the severe neurological complications associated with TTP is posterior reversible encephalopathy syndrome (PRES), a disorder characterized by reversible vasogenic oedema due to endothelial dysfunction [7]. PRES is commonly associated with hypertensive encephalopathy, autoimmune disorders, renal dysfunction, and cytotoxic treatments and presents clinically with headaches, visual disturbances, altered mental status, and seizures [8]. Magnetic resonance imaging (MRI) findings typically demonstrate symmetrical hyperintensities in the parieto-occipital regions, consistent with vasogenic oedema [9]. The pathophysiology of PRES involves endothelial dysfunction, breakdown of the blood-brain barrier, and dysregulation of cerebral autoregulation, leading to vasogenic edema and neurological impairment [10].

The coexistence of TTP and PRES is rare but poses significant diagnostic and therapeutic challenges due to their overlapping pathophysiology, both involving endothelial dysfunction and microvascular injury. PRES in TTP may result from severe hypertension, endothelial damage, and thrombotic microangiopathy, leading to increased cerebrovascular permeability and oedema formation [11]. Studies have reported cases of PRES occurring in the setting of TTP, particularly in patients with hypertensive crises and acute kidney injury [12]. While PRES is typically reversible with blood pressure control and resolution of the underlying pathology, delayed recognition or persistent endothelial injury can lead to permanent neurological deficits or mortality [13].

This case report presents a young male with acquired TTP complicated by PRES, manifesting as hypertensive encephalopathy and recurrent seizures. The case highlights the fatal interplay between these 2 rare conditions and underscores the importance of early diagnosis, aggressive plasma exchange, and immunosuppressive therapy. Despite the availability of effective treatment strategies, the presence of PRES in TTP significantly worsens prognosis, necessitating close monitoring and prompt intervention to improve clinical outcomes.

Case presentation

A 22-year-old male was brought to the emergency department by his relatives with complaints of recurrent vomiting, headache, and right upper limb weakness. The vomiting was nonprojectile, nonfoul-smelling, and nonbilious, containing food particles. The headache was described as dull in nature, localized to the bitemporal and occipital regions. The patient had no history of seizures, loss of consciousness, trauma, fever, recent infections, or similar complaints in the past. His medical and family history was unremarkable, with no known hereditary or autoimmune conditions. He was initially admitted to the neurology department for further evaluation.

On arrival at the emergency room, the patient was hemodynamically stable but hypertensive, with a blood pressure of 170/100 mmHg. His respiratory rate was 22 breaths per minute, and oxygen saturation was maintained at 99% on room air. The pulse rate was recorded at 88 beats per minute. Initial systemic examination findings were unremarkable for the cardiovascular, respiratory, and gastrointestinal systems. However, on neurological examination, the patient was drowsy but arousable. He followed verbal commands appropriately, and his Glasgow Coma Scale (GCS) score was 15/15. The pupils were bilaterally equal and reactive to light. The most notable finding was mild weakness in the right upper limb, while the rest of the neurological examination was within normal limits. Given his hypertensive state and neurological symptoms, a comprehensive diagnostic workup was initiated, and the patient was started on conservative management.

Laboratory investigations upon admission revealed anaemia with a haemoglobin level of 8 g/dL and thrombocytopenia with a platelet count of 0.70×10^6 cells/cumm. White blood cell counts were within normal limits. Biochemical analysis showed elevated urea (113 mg/dL) and creatinine (4.9 mg/dL), suggestive of acute kidney injury. The liver function tests showed mildly elevated alanine transaminase (ALT) levels at 80 IU/L, with normal aspartate transaminase (AST) and alkaline phosphatase levels. Serum LDH was significantly elevated at 1403 IU/L, raising suspicion of hemolysis. Urinalysis showed 2+ albuminuria, with a urine protein/creatinine ratio of 5.9 mg/mg and 24-hour urinary protein excretion of 8674 mg/day, indicating severe proteinuria. Electrolyte levels were within normal ranges, and the coagulation profile, including prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR), showed no major abnormalities. These findings pointed towards potential thrombotic microangiopathy, warranting further investigations.

On the second day of hospitalization, the patient developed 2 episodes of generalized tonic-clonic seizures. There was no preceding aura, and postictal confusion was noted following each episode. A computed tomography (CT) scan of the brain was performed immediately but showed no acute intracranial abnormalities Fig. 1. An electroencephalogram (EEG) revealed

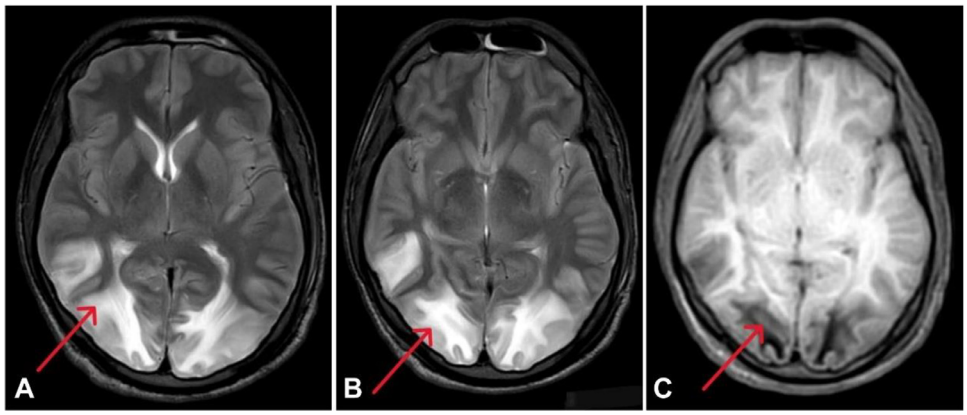

Fig. 1 – (A, B and C) MRI brain suggestive of hyperintensity involving cortical and subcortical, bilateral occipito-parieto-frontal areas, bilateral cerebellar hemisphere, pons on right side, right lentiform nucleus.

a diffuse spike-and-wave pattern consistent with generalized seizure activity. Given the hypertensive state and new-onset seizures, an MRI of the brain was conducted, which showed hyperintense lesions involving the cortical and subcortical regions of the bilateral occipito-parieto-frontal areas, cerebellar hemispheres, pons, and right lentiform nucleus. These findings were highly suggestive of PRES, a condition commonly associated with hypertensive encephalopathy and thrombotic microangiopathy.

Further evaluation included a peripheral blood smear, which demonstrated the presence of schistocytes, reinforcing the suspicion of a thrombotic microangiopathic process. A differential diagnosis of thrombotic TTP was considered, given the constellation of microangiopathic hemolytic anaemia, thrombocytopenia, and neurological involvement. Additional autoimmune and haematological workups were performed to confirm the diagnosis. The patient tested positive for antinuclear antibodies (ANA) with a speckled pattern at a titer of 1:1000. ADAMTS13 activity was markedly reduced to 9%, confirming acquired TTP. Other autoimmune markers, including anti-dsDNA and complement levels, were within normal limits. Direct and indirect Coombs tests were negative, ruling out autoimmune hemolytic anaemia. The absence of recent infections, negative antineutrophil cytoplasmic antibodies (ANCA), and lack of hereditary disease further supported the diagnosis of acquired TTP rather than a hereditary thrombotic microangiopathy. Peripheral smear with Giemsa stain shows schistocytes in Fig. 2.

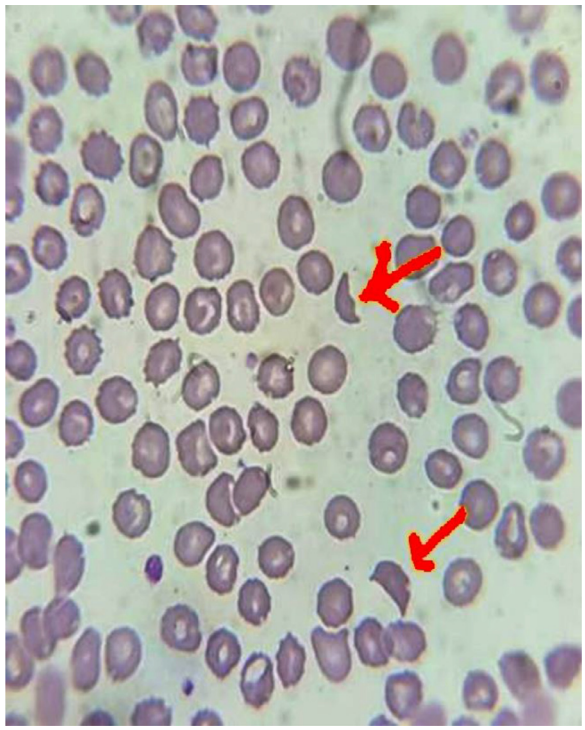

Fig. 2 – Peripheral smear with Giemsa stain shows schistocytes (arrows).

Given the life-threatening nature of TTP, the patient was promptly started on targeted treatment. Blood pressure was aggressively controlled using antihypertensive medications. Anticonvulsant therapy was initiated with intravenous levetiracetam at a dose of 1 g daily for 7 days. Immunosuppressive therapy with rituximab (375 mg/m^2 weekly for 4 weeks) was administered due to its proven efficacy in acquired TTP. Additionally, corticosteroid therapy was initiated with intravenous methylprednisolone at 1 g daily for 3 days, followed by oral prednisolone at 60 mg daily, which was gradually tapered over the subsequent week. Given the severity of the condition, 3 cycles of plasma exchange with fresh frozen plasma were performed, along with 2 sessions of heparin-free hemodialysis to manage acute kidney injury. Despite aggressive treatment and supportive care, the patient's condition continued to deteriorate, and he succumbed to multiorgan failure on the tenth day of hospitalization.

This case highlights the challenges associated with diagnosing and managing acquired TTP, particularly when complicated by PRES and renal dysfunction. Early recognition and initiation of plasma exchange, immunosuppressive therapy, and blood pressure control are crucial in improving patient outcomes. However, refractory cases remain difficult to manage,

emphasizing the need for continued research into advanced therapeutic strategies for TTP.

Discussion

Thrombotic TTP is a life-threatening thrombotic microangiopathy characterized by severe deficiency of ADAMTS13, a von Willebrand factor-cleaving protease, leading to widespread microvascular thrombosis, hemolytic anaemia, thrombocytopenia, and multiorgan dysfunction [14]. PRES, on the other hand, is a neurotoxic state often associated with hypertensive crisis, renal dysfunction, and endothelial injury, resulting in cerebral vasogenic edema and neurological deterioration [13]. The coexistence of these 2 rare conditions presents a significant diagnostic and therapeutic challenge, as seen in the case of a young male with acquired TTP complicated by PRES, culminating in fatal multiorgan failure.

TTP is predominantly caused by autoantibody-mediated inhibition of ADAMTS13, leading to the accumulation of ultra-large von Willebrand factor (vWF) multimers and subsequent platelet aggregation, microvascular thrombosis, and end-organ damage [15]. The classic pentad of TTP includes thrombocytopenia, microangiopathic hemolytic anaemia, neurological symptoms, renal dysfunction, and fever, though not all patients present with the full spectrum of symptoms at the time of diagnosis [15]. The presence of schistocytes on the peripheral smear, elevated lactate dehydrogenase (LDH), and reduced ADAMTS13 activity are hallmark diagnostic findings, as seen in this patient.

PRES is a neurological syndrome characterized by vasogenic edema due to endothelial dysfunction, typically precipitated by acute hypertension, sepsis, renal failure, or autoimmune diseases [16]. The imaging findings of bilateral cortical and subcortical hyperintensities in the occipito-parieto-frontal regions, cerebellum, and brainstem on MRI are diagnostic for PRES, as observed in this case [17]. The pathophysiology of PRES in TTP is thought to be related to dysregulated cerebral autoregulation, resulting in hyperperfusion, endothelial dysfunction, and breakdown of the blood-brain barrier [18]. The presence of PRES in TTP is associated with poor prognosis, often due to concurrent systemic involvement.

The cornerstone of TTP treatment includes emergent plasma exchange (PEX), which removes circulating autoantibodies against ADAMTS13 and replenishes the deficient protease, thereby preventing further microvascular thrombosis [19]. Corticosteroids, such as methylprednisolone and oral prednisolone, are frequently used to suppress autoantibody production. Rituximab, an anti-CD20 monoclonal antibody, has been increasingly used as an adjunct therapy in refractory or relapsing TTP cases due to its efficacy in depleting B-cells and reducing autoantibody formation [20]. In this case, despite early initiation of plasma exchange, immunosuppressive therapy with rituximab, and blood pressure control, the disease progressed rapidly, resulting in multiorgan failure.

Acute kidney injury (AKI) in TTP results from thrombotic microangiopathy-induced endothelial damage in the renal microvasculature. Proteinuria, hematuria, and elevated creatinine levels are commonly observed, with severe cases requiring renal replacement therapy [21]. The presence of massive proteinuria (8674 mg/day) in this patient highlights the extent of renal involvement, further complicating disease management. Additionally, the marked elevation of inflammatory markers such as serum ferritin and procalcitonin suggests a systemic inflammatory response, which has been associated with worse outcomes in thrombotic microangiopathies [22].

Despite aggressive therapeutic interventions, the prognosis of TTP complicated by PRES remains poor, particularly in cases with severe neurological and renal involvement. Studies have shown that early diagnosis and prompt initiation of plasma exchange significantly improve survival, but mortality remains high in patients with multiorgan failure [23]. Future research should focus on optimizing treatment strategies for refractory TTP cases, particularly exploring the role of novel targeted therapies such as caplacizumab, a vWF-directed monoclonal antibody, which has shown promise in reducing the burden of microvascular thrombosis and improving outcomes in severe TTP [24].

This case highlights the complex interplay between TTP and PRES, emphasizing the need for early recognition, aggressive plasma exchange, and close hemodynamic monitoring. Clinicians must maintain a high index of suspicion for PRES in TTP patients presenting with acute neurological deterioration, as a timely intervention may prevent irreversible cerebral damage. The rapid progression to multiorgan failure in this patient underscores the fatal potential of this rare combination, warranting further research into advanced therapeutic strategies for severe thrombotic microangiopathies.

Conclusion

This case underscores the complex and fatal interplay between acquired TTP and PRES, 2 rare but life-threatening conditions. The presence of severe thrombocytopenia, microangiopathic hemolysis, and neurological deterioration should prompt early suspicion of TTP, particularly in the setting of hypertensive crisis and renal dysfunction. PRES, as a neurological complication, further exacerbates the clinical course, leading to increased morbidity and mortality. Despite timely initiation of plasma exchange, immunosuppressive therapy, corticosteroids, and antihypertensive management, the rapid progression of the disease in this patient resulted in multiorgan failure and death. This case highlights the importance of early recognition, aggressive treatment, and close monitoring in patients with thrombotic microangiopathies to improve survival outcomes. Future research is needed to explore novel therapeutic strategies for refractory TTP cases, particularly when complicated by PRES and acute kidney injury.

Patient consent

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

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