CASE REPORT

Thrombotic Thrombocytopenic Purpura with Delayed Hematological Manifestations in an Atypical Stroke : A Case Report

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disease which is often missed because of its heterogeneous presentation. A 55-year-old female presented with an atypical stroke; concurrent acute ischemic stroke and intracranial bleed with normal initial laboratory investigations. Ten days later, clinical and biochemical evolution revealed a diagnosis of TTP, representing an uncommon and atypical presentation of the condition. With prompt diagnosis and extensive workup, immediate treatment was delivered. This case highlights the challenges of diagnosing delayed and atypical presentation of TTP and stroke and its management in resource-limited settings when plasma exchange is not readily available; due to financial constraints or certain contraindications. Thus, we commenced plasma infusion and intravenous steroids, which led to sustained biochemical and clinical improvement. It highlights the critical role of prompt diagnosis, emphasizing the integration of clinical expertise, and strategic problem-solving to overcome challenges in resource-limited settings and deliver optimal outcomes in complex cases.
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INTRODUCTION

Thrombotic microangiopathy (TMA) is a rare disease characterized by microangiopathic haemolytic anaemia, platelet aggregation, and multi organ failure. Thrombotic thrombocytopenia purpura (TTP) is a severe form of TMA and is associated with severe or functional deficiency of ADAMTS13 enzyme. Prompt diagnosis is crucial, as when left untreated, the mortality rate is close to 90%. TTP is further classified into congenital TTP (cTTP) or acquired TTP (aTTP). cTTP, also known as hereditary TTP, is caused by pathogenic variants in the ADAMTS13 gene causing ADAMTS13 deficiency. aTTP or immune-mediated TTP, is due to ADAMTS13 deficiency mediated by autoantibodies due to underlying causes, such as infection, malignancy, vasculitis, and autoimmune diseases (1). However, autoantibodies in TTP are often idiopathic and may not be linked to any underlying causes. Here, we present an intriguing case of a patient with an atypical stroke who later developed delayed hematological manifestations, including thrombocytopenia and microangiopathic hemolytic anemia (MAHA). This case underscores the importance of maintaining a high index of suspicion for TTP in stroke patients, highlighting unique diagnostic and therapeutic challenges.

CASE REPORT

A 55-year-old woman with a five-year history of diabetes, hypertension, and stage III CKD presented with sudden right-sided weakness, speech loss, and facial asymmetry, despite strict adherence to her medications and follow-ups. Examination revealed right-sided hemiparesis and global aphasia with a National Institute of Health Stroke Scale (NIHSS) score of 24. Urgent magnetic resonance imaging (MRI) of the brain revealed an acute left high parietal infarct with concurrent right-sided posterior parietal intraparenchymal haemorrhage (Figure 1). Magnetic resonance angiography (MRA) showed a left-sided middle cerebral artery (M2 segment) with medium vessel occlusion (MeVO) (Figure 2). Intravenous (IV) thrombolysis was contraindicated due to presence of intracranial haemorrhage. Mechanical thrombectomy was not attempted, as the cause of the intraparenchymal haemorrhage was uncertain, thus she was admitted for post stroke rehabilitation.

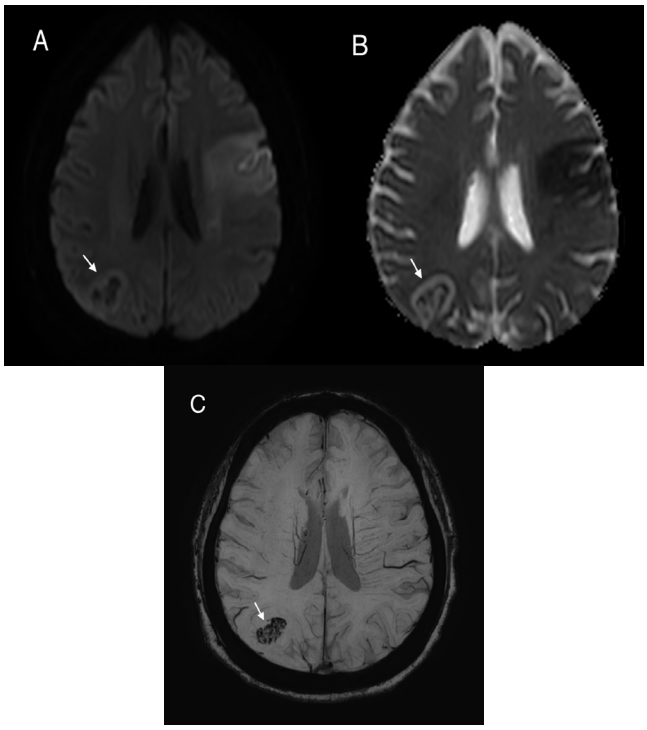

Figure 1: Axial sections of the brain MRI, showing the diffusion weighted imaging (DWI) (Figure 1A), apparent diffusion coefficient (ADC) (Figure 1B), and susceptibility weighted imaging (SWI) (Figure 1C) sequences, demonstrating DWI high signal intensity at the left parietal region with corresponding low signal intensity on ADC, in keeping with an acute infarct. At the right posterior parietal region (white arrows on all three panels), there is concurrent typical acute intraparenchymal hemorrhage signal changes, which was confirmed on SWI (Figure 1C).

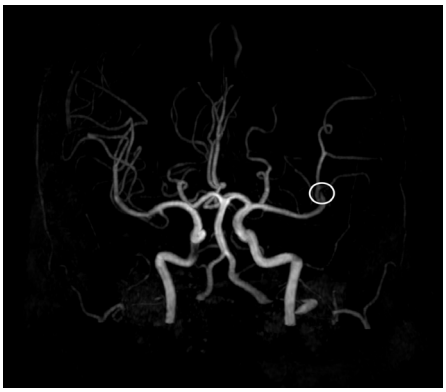

Figure 2: Magnetic resonance angiography (MRA) image showing a truncated left middle cerebral artery (M2 segment), in keeping with medium vessel occlusion (white circle).

At day 10 of admission, her clinical condition deteriorated with features of sepsis. Vital signs showed a temperature of 37.9°C, blood pressure of 140/70 mmHg, and a pulse rate of 110 beats per minute. Blood investigations revealed a drop of haemoglobin from 9.1 to 5.1 g/dl; and her platelet counts dropped from 294,000 µL to 12,000 µL. Her renal function showed acute on chronic kidney injury (AoCKD) with an increase of creatinine levels from 176 to 324 µmol/L. C-Reactive Protein (CRP) was raised at 219 mg U/L. Her total bilirubin level was 59 mg/dL, with an indirect bilirubin predominance of 32 mg/dL. The transaminases level and coagulation profiles were within normal range. Her lactate dehydrogenase (LDH) was raised 1174 U/L, and reticulocyte count was elevated at 9%. An urgent full blood picture revealed MAHA with 6.3% schistocytosis.

A diagnosis of TTP was made, as evidenced by MAHA, thrombocytopenia, neurological deficits and AoCKD. The clinical findings of tachycardia and fever, as well as raised CRP hinted the possibility of aTTP. She was treated for hospital-acquired infection with broad spectrum antibiotics and worked up for secondary causes such as malignancy and occult infections. ADAMTS13 activity level was sent to confirm clinical diagnosis of TTP.

She was transferred to the intensive care unit (ICU) and was transfused with red blood cells cells and fresh frozen plasma at a rate of 15mls/kg for three days. In total she received 900 mls (3 units of fresh frozen plasma) per day for three days at an infusion rate of 10-50mls/min. Although plasma exchange was initially considered, it had financial implications which the patient and

family was not able to bear. She was instead given IV methylprednisolone one gram daily for three days. By day three of ICU admission, her blood parameters improved where her haemoglobin increased from 7.1g/dl to 9.1g/dl, platelet counts raised from 96,000 to 146,000 µL, and reticulocyte count dropped from 4.56 % to 3.48 %. Within the following days, her platelets returned to normal level (>150,000 µL) and remained stable until her discharge.

Other extensive work-up for TMA to exclude infections and malignancy were negative, which included stool sampling for enterohemorrhagic Escherichia Coli, tumour markers, and a computed tomography (CT) scan of the thorax, abdomen and pelvis. The CT scan showed right renal and splenic hypodense lesions with cervical nodules which could be secondary to infection or metastasis. A positron emission tomography (PET) scan was done and flurodeoxyglucoes (FDG) hypermetabolism was seen at the left level four cervical node. A cervical node biopsy was pursued, unfortunately, as the lesion was small, the yield was unsatisfactory. Consequently, laboratory analysis revealed the absence of ADAMTS13 enzyme activity, which is in keeping with severe ADAMTS13 deficiency confirming the diagnosis of TTP (normal values is >10%). The patient fortunately continued to improve and was discharged home on a tapering dose of oral prednisolone.

DISCUSSION

TTP is life-threatening disease, however, with recent understanding of its pathogenesis, the presence of thrombocytopenia and MAHA alone, without an alternative explanation, should prompt the diagnosis of TTP. The reported prevalence is approximately ten cases per million people annually worldwide (1).

TTP is associated with a deficit in ADAMTS13 activity, defined as a level that is less than 10%. ADAMTS13 is a von Willebrand factor cleaving protease, the deficit of which produces massive intravascular platelet aggregation, subsequent microvascular thrombosis, red blood cell fragmentation, ischemic organ damage, consumptive thrombocytopenia and haemolytic anaemia. Microthombi may be deposited at end organs such as the brain, kidney, myocardium and liver; leading to multi-organ failure. A retrospective monocentric study done by Renaud et al. showed that diagnostic delay is highly prevalent in TTP, with a significant impact on short-term neurological outcomes (2).

The spectrum of neurological deficits in TTP can be overwhelming, however, the most common manifestations are headache, encephalopathy, seizures, and focal neurological deficits (3). Although there have been case reports reporting the occurrence of ischemic stroke in TTP, the occurrence of haemorrhagic strokes is relatively uncommon. Our case is especially unique, with the patient with an atypical presentation ; concurrent ischemic and haemorrhagic strokes with a delayed hematological response, serving as a fresh reminder to neurologists to not miss this clinical syndrome.

Therapeutic plasma exchange (TPE) with replacement of plasma remains the cornerstone of treatment for TTP, performed daily until features related to organ impairment resolve with hematological recovery. In most cases of aTTP, the use of steroids is advocated as an adjunct to TPE. It is noteworthy to be reminded that despite medical advancements, data from prospective, randomized, and controlled trials are limited, thus international guidelines serve more as a recommendation and that treatment of TTP should be tailored to each individual patient at the discretion of the treating physician.

The challenge in our patient was the atypical nature of the stroke - concurrent ischemic and haemorrhagic multiterritorial strokes with initial imaging pointing to atherosclerosis in virtue of vessel occlusion. However, several days later biochemical parameters prompted the suspicion of TTP. Although there is an abundant literature describing on ischemic stroke in TTP, along with success in treatment with IV thrombolysis and TPE, the data on cerebral haemorrhage is limited. Some reported good outcome with plasma exchange, but these patients were younger and had no metabolic comorbidities (4). Case reports on older patients presenting with cerebral haemorrhage (i.e. intracranial bleed, subdural haemorrhage and subarachnoid haemorrhage) and TTP showed forlorn outcomes (5). These patients succumbed to death within hours, regardless of optimal treatment. The pathophysiology of cerebral haemorrhage is complicated, involving primary and secondary brain injury, oxidative stress, neuroinflammation and neurotoxicity.

Initiation of TPE was considered, however, financial limitation was a hurdle in our institution. Referral to another government center was deferred as she was not safe for transfer due to her current clinical condition. Therefore, we decided to treat her with fresh frozen plasma at 15mg/kg for a total of three days. She was also started on IV methylprednisolone 1000 mg per day for three days, that was subsequently tapered down to oral prednisolone. The rationale of steroid use was as an adjunctive treatment to TPE in patients with aTTP. Prompt diagnosis and treatment facilitated a rapid biochemical recovery, with her platelet levels approaching normal by day three post-treatment, eliminating the need for further use of FFP. Despite not receiving TPE, the patient had a favourable clinical outcome. At one-month follow-up in the clinic, her NIHSS score was stable at 15, with no clinical deterioration or biochemical evidence of recurrence.

CONCLUSION

In conclusion, plasma infusion maybe an alternative treatment modality when plasma exchange is not available, due to certain contraindications or lack of adequate supply of safe plasma. This case underscores the importance of carefully weighing the risks and benefits of treatment options while considering TTP as a potential cause of stroke, especially in atypical presentations. Managing a critically ill patient with limited resources presented significant challenges, particularly for a life-threatening condition like TTP, which often requires resource-intensive treatments such as plasma exchange. These challenges were compounded by the need to balance medical constraints with the patient's and family's preferences and expectations, creating a complex ethical dilemma. Open communication with the family was essential to align their hopes with realistic outcomes, while navigating financial limitations and addressing multifaceted management issues. This serves as a poignant reminder of the need for patient-centered care that integrates clinical expertise, ethical sensitivity, and practical problem-solving in resource-constrained settings.

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