Thrombotic Thrombocytopenic Purpura in Dengue Fever

Tze Yuan Tee[1], Rizna Abdul Cader[2]

[1] Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia.
[2] Department of Nephrology, Internal Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia.

Corresponding Author:
Rizna Abdul Cader, MD. Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre. Jalan Yaacob Latif, Bandar Tun Razak 56000 Cheras, Wilayah Persekutuan Kuala Lumpur, Malaysia. email: rizna_c@hotmail.com.

ABSTRAK

Purpura trombositopenik trombotik adalah kondisi medis yang jarang tetapi mengancam jiwa. Pengenalan dini dan pengobatan purpura trombositopenik trombotik penting terutama pada pasien yang tidak datang dengan pentad klasik untuk mengurangi angka kematian yang tinggi. Di sini, kami menggambarkan kasus pasien yang tidak memenuhi fitur pentad klasik purpura trombositopenik trombotik yang diinduksi oleh demam berdarah. Gambaran darah lengkap awal pasien tidak memiliki semua ciri khas anemia hemolitik mikroangiopati tetapi ada sel darah merah yang terfragmentasi. Namun, bahkan sejumlah kecil sel darah merah yang terfragmentasi dalam darah tepi harus mengingatkan dokter tentang kemungkinan diagnosis purpura trombositopenik trombotik bersama dengan gejala lainnya. Lebih lanjut, tanda dan gejala purpura trombositopenik trombotik dan demam berdarah dapat tumpang tindih seperti demam, trombositopenia, defisit neurologis yang menyerupai ensefalopati dengue, dan cedera ginjal akut yang diinduksi dengue.

Keywords: *acute kidney injury, ADAMTS13, dengue fever, plasma exchange, thrombotic thrombocytopenic purpura.*

ABSTRACT

Thrombotic thrombocytopenic purpura is a rare but life threatening medical condition. Early recognition and treatment of thrombotic thrombocytopenic purpura is important especially in patients who do not present with the classic pentad to reduce the high mortality. Herein, we describe a case of a patient who does not fulfil the classic pentad features thrombotic thrombocytopenic purpura that was induced by dengue fever. The patients' initial full blood picture did not have all the typical features of microangiopathic haemolytic anaemia but there were fragmented red blood cells. However, even a small number of fragmented red blood cells in the peripheral blood should alert physicians of the possible diagnosis of thrombotic thrombocytopenic purpura together with other symptoms. Furthermore, signs and symptoms of thrombotic thrombocytopenic purpura and dengue fever can overlap such as fever, thrombocytopenia, neurological deficit mimicking dengue encephalopathy and dengue induced acute kidney injury.

***Keywords*:** *acute kidney injury, ADAMTS13, dengue fever, plasma exchange, thrombotic thrombocytopenic purpura.*

INTRODUCTION

Thrombotic thrombocytopenic purpura is a rare condition caused by spontaneous platelet aggregation when ultra large multimers of von Willebrand factor are not cleaved appropriately in the absence of ADAMTS13.[1] The incidence of thrombotic thrombocytopenic purpura in the United States is 4 to 6 per million of the population per year whereas in the United Kingdom, it is 6 cases per million per year.[1] The classical pentad of thrombotic thrombocytopenic purpura are thrombocytopenia, fever, neurological symptoms, renal dysfunction and microangiopathic haemolysis. Thrombotic thrombocytopenic purpura can be idiopathic, autoimmune related or secondary. Secondary thrombotic thrombocytopenic purpura could be due infections, malignancy, drug induced or pregnancy associated. Infections associated with thrombotic thrombocytopenic purpura include human immunodeficiency virus, *Mycoplasma pneumoniae*, *Legionella pneumophila* and hepatitis C. There are a few published case reports of dengue fever with thrombotic thrombocytopenic purpura and is becoming an increasingly recognized phenomenon. Both these conditions can cause significant mortality and morbidity if there is a delay in initiation of treatment.

CASE ILLUSTRATION

A 29 year-old man with no past medical history was brought to the emergency department by family members with a one week history of altered behaviour and aggression on the day of admission. The family report he has been talking irrelevantly and having auditory hallucinations for one week. Furthermore, he had a five day history of fever associated with diarrhoea, loss of appetite, lethargy and one episode of haemoptysis. He did not have any vomiting or abdominal pain. Unfortunately, as patient was confused, we could not get much history from the patient and family members could only give a limited history. There was no history of foreign travel.

He is an active smoker of 13 pack years and consumed alcohol socially. He had history of cannabis use but last used nine years ago according to the family. He denied taking traditional medications. He was separated from his wife and worked as a computer analyst.

On admission, his Glasgow Coma Scale was 14/15 (E4, V4, M6). He was unkempt and confused. There was no jaundice and peripheries were warm with capillary refill time < 2 seconds with good pulse volume. His temperature was 37.6˚C, pulse rate 126 beats per minute, blood pressure was 157/106 mmHg, respiratory rate of 18 breaths per minute and oxygen saturation of 97% on room air. Blood glucometer was 6.1 mmol/l. Cardiovascular and respiratory system examinations were unremarkable. On abdominal examination there was splenomegaly of 2 finger breaths below the left costal margin. He had a petechial rash over bilateral lower limbs. Neurological examination revealed no neck stiffness and photophobia. He was confused but able to obey commands and power was 5/5 bilaterally with normal reflexes and down going plantar response.

A full blood count revealed:- haemoglobin was 12.5 g/dL (13.5-17.4), white cell count of 3.1 x 10^9/L (4.1-11.4), with neutrophils 0.8 x 10^9/L (3.9-7.1), lymphocytes 1.7 x 10^9/L (1.8-4.8) and platelet count was 20 x 10^9/L (142- 350). Renal function revealed sodium 125 mmol/L (136- 145), potassium 4.1 mmol/L (3.5-5.1), urea 23.3 mmol/L (3.2- 7.4) and, creatinine 740.8umol/L (63.6- 110.5). Liver function test revealed bilirubin level of 18.7 umol/l (3.4-20.5). His coagulation profile was within normal limits.

Dengue serology was performed as it is endemic in this part of the world and as patient had thrombocytopenia and leucopenia and dengue non structural protein 1 antigen test was positive. Dengue serology Ig G and Ig M were negative.

Arterial blood gas was done due to renal insufficiency and blood gas showed pH of 7.348 with serum bicarbonate level of 19.2 mmol/L (22- 28). Serum lactate level was 2.7 mmol/L (0.5- 1.6). Urine examination revealed proteinuria and microscopic haematuria.

Thrombotic thrombocytopenic purpura was entertained as a diagnosis and therefore secondary causes including infections and autoantibody diseases needed to be excluded.

Hepatitis B surface antigen, anti- hepatitis C antibody and human immunodeficiency virus (HIV) antigen and antibody were non reactive. C3 level was slightly low with level of 89.5 mg/ dL (90- 180) and C4 was normal at 26.4 mg/ dL (10- 40). Serum antinuclear antibody was negative.

In view of thrombocytopenia and confusion, an urgent Computed tomography scan of the brain was performed to exclude any intracerebral bleeding which was normal. Ultrasound of the hepatobiliary system and kidney was done in view of renal insufficiency and was normal except for splenomegaly at 13.5 cm.

Repeat full blood count 8 hours later demonstrated a drop in haemoglobin to 8.0 g/dL (13.5-17.4) and further drop in platelet count to 8 x 109/L (142- 350). In view of thrombocytopenia and diagnosis of thrombotic thrombocytopenic purpura was entertained, further investigations including coagulation and full blood picture was requested. The initial full blood picture showed hypochromic microcytic red blood cells with occasional fragmented red cells seen. Platelet count was markedly reduced (1-2/ hpf). Lactate dehydrogenase (LDH) level was 3036 U/L (125-220). Reticulocyte count was 0.3% (0.5- 2.5). Direct coombs test was negative. Diagnosis of thrombotic thrombocytopenic purpura secondary to severe dengue was made.

Patient was started on plasma exchange of approximately of 3L fresh frozen plasma daily. He was also transfused 2 pints of packed cells. He also underwent one session of haemodialysis on day 3 of admission as he was oliguric with worsening of his renal function. At the same time he received supportive treatment of blood transfusion with strict monitoring of input and output as part of fluid therapy in dengue management.

Follow up full blood picture on day 4 of admission showed there were spherocytes and microspherocytes seen with schistocytes, few target cells and blister cells seen. However, his clinical condition had improved by the second day and was fully alert, conscious and coherent. He was not confused at all. Infact the patient felt so well, that he wanted to be discharged even though his renal function had not normalized. After five plasma exchanges, his serum creatinine was 419.8umol/L (63.6- 110.5) and platelet count 123x 109/L (142- 350) with haemoglobin of 7.1 g/ dL (13.5-17.4) but stable.

He took discharge against medical advice after being counselled and assessed by a patient psychiatrist who deemed him competent. The patient subsequently did not turn up for follow up.

DISCUSSION

Thrombotic thrombocytopenic purpura is rare condition but has a high morbidity and mortality and therefore treatment has to be instituted early.[1] However, the first priority is to recognize and diagnose thrombotic thrombocytopenic purpura. Diagnosis of thrombotic thrombocytopenic purpura is made when at least 2 of the major criteria for diagnosis (microangiopathic haemolytic anaemia - MAHA, neurologic signs and thrombocytopenia) are associated with at least 2 minor criteria (fever, renal changes, and presence of thrombi in the circulation).[2] However, thrombotic thrombocytopenic purpura is still a diagnosis according to clinical history, physical examination and blood film. Thrombotic thrombocytopenic purpura can present without the full pentad with up to 35% of patients at presentation do not have renal impairment, neurological signs and fever.[1]

Diagnosis of thrombotic thrombocytopenic purpura can be very difficult, as there is clinical overlap with other thrombotic microangiopathy and autoimmune diseases and can sometimes be similar to haemolytic uraemic syndrome (HUS). Secondary thrombotic thrombocytopenic purpura can occur following infections, malignancy, drug induced and pregnancy associated.

Recently the criteria for thrombotic thrombocytopenic purpura has been revised in view of highly preventable early death in this clinical condition should treatment been given early. However, this may lead to increasing referral of other thrombotic microangiopathy. According to the revised diagnostic criteria, with the presence of thrombocytopenia and MAHA alone, thrombotic thrombocytopenic purpura must be considered and plasma exchange should be initiated as soon as possible, preferably within

4-8 hours in the absence of other identifiable cause.[3]

In our patient the diagnosis of thrombotic thrombocytopenic purpura was made based on clinical presentation, and laboratory investigations and he fulfilled 4 criteria, ie. thrombocytopenia, neurologic signs, fever and renal impairment. However, all these could be due to purely dengue with dengue encephalopathy and acute kidney injury due to dengue. Acute kidney injury in dengue fever can be due to acute tubular necrosis, glomerulopathy, nephrotic syndrome or even haemolytic uraemic syndrome.[4,5] Dengue was confirmed on the laboratory investigations. We treated the patients as thrombotic thrombocytopenic purpura secondary to dengue fever based on the presence of few fragmented red blood cells on the full blood film and the rapid drop in the haemoglobin and elevated lactate dehydrogenase.

The treatment of dengue fever is supportive whereas if thrombotic thrombocytopenic purpura is suspected then plasma exchange needs to be initiated early. We initiated plasma exchange and there was a rapid improvement in the patients' neurological condition.

Our patient had secondary thrombotic thrombocytopenic purpura whereas in the cases of acquired thrombotic thrombocytopenic purpura, treatment not only involves plasma exchange but also steroids and immunosuppressive therapy.[1] In thrombotic thrombocytopenic purpura, inhibition of ADAMTS13 activity is by autoantibodies that appear transiently as a result of disturbances between normal platelet-endothelium interaction. Therefore in thrombotic thrombocytopenic purpura, ADAMTS13 assays would help to confirm the diagnosis however it takes time for the results to be available.[1] We did not perform ADAMTS13 as it is not readily available at our institution and would take a few days for the results to be available. Duration of treatment was made on patient's clinical presentation.

There has been a few reported case of dengue with haemolytic uraemic syndrome. Wan et al[5] reported haemolytic uraemic syndrome with dengue viral infection and their patient was dialysis dependent after recovery from dengue fever. This was one of our differential diagnosis but we felt the patient erred towards thrombotic thrombocytopenic purpura in view of the predominant of neurologic involvement whereas haemolytic uraemic syndrome kidney involvement is dominant.[6] Thrombotic thrombocytopenic purpura is also reportedly to have more severe thrombocytopenia (<30x109/L) compared to haemolytic uraemic syndrome.[6]

Plasma exchange removes ADAMTS13 autoantibodies and replaces ADAMTS13 in thrombotic thrombocytopenic purpura.[7] The exact incidence of thrombotic thrombocytopenic purpura in dengue fever is not documented but there are a few case reports in countries where it is pandemic such as India.[7,8] In some of these reports they did measure ADAMTS13 and reported the mechanism of reduction in ADAMTS13 level was caused by the anti-ADAMTS13 IgG from dengue fever has been potentially similar to idiopathic thrombotic thrombocytopenic purpura TTP.[7] Gavali et al.[8] described a case of thrombotic thrombocytopenic purpura in dengue viral infection who was treated with plasma exchange and rituximab injection. The patient recovered completely and there was no recurrence after 6 months of follow up. There is another case of dengue fever- induced thrombotic microangiopathy reported by Bhargava et al, of which this patient has kidney biopsy proven features of thrombotic microangiopathy.[9] However, this patient was treated with haemodialysis without plasma exchange and the patient was followed up for 9 months post- discharge, she recovered well with normal renal function.

The possible causes of development of ADAMTS13 inhibitor include endothelial cell damage or stimulation by dengue fever which remains undetermined and needs further study.[7] This may explain why Bhargava et al.[9] did not do plasma exchange and their patient recovered spontaneously. In our patient, in view of the neurological involvement, we opted to treat with plasma exchange.

CONCLUSION

TTP in dengue is becoming increasing recognised and clinicians need to have a high

index of suspicion as the clinical features may overlap.

CONFLICT OF INTEREST

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