Case Report

Extensive Bilateral Ischemic Stroke after Platelet Transfusion in Thrombotic Thrombocytopenic Purpura (TTP): A Case Report

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A 36-year-old woman presented with abdominal pain followed by fever, confusion, right sided weakness and nuchal rigidity. The investigation showed severe anemia, thrombocytopenia and left middle cerebral artery (MCA) territory infarction. The platelet was given before the lumbar puncture. After that, the patient's clinical was deteriorating to quadriplegia and stuporous. Then the patient was referred to Siriraj Hospital. The patient was diagnosed thrombotic thrombocytopenic purpura (TTP) following pentad of clinical features: microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic, and renal abnormalities. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of brain showed extensive bilateral MCA and mid basilar artery stenosis. That was uncommon findings in TTP. The authors believed that platelet transfusion made the clinical deterioration and develop extensive intracranial vessels stenosis. Even the plasma exchange was performed but the neurological symptoms did not improved. Finally, the patient succumbed from ventilator associated pneumonia at 2 months after diagnosis.

***Keyword**: Middle cerebral artery infarction, Thrombotic thrombocytopenic purpura, TTP, Platelet transfusion*

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Thrombotic thrombocytopenic purpura (TTP) is a rare and life threatening disease, with the annual incidence in the United States at 4 to 11 cases per million people[1] and an affected female predominance to male of approximately 10 to 1, has been noted[2]. TTP is important because the disease responds well to plasma exchange treatment[3] and is associated with a high mortality rate when untreated. Before the era of effective treatment with plasma exchange, 90 percent of patients with TTP died from systemic microvascular thrombosis that caused cerebral and myocardial infarctions and renal failure[4]. The diagnosis of TTP is based on the progressive appearance of the following pentad of clinical features: microangiopathic hemolytic anemia, thrombocytopenia, fever, neurological and renal abnormalities[4].

Pathophysiology of TTP is based on deficiency of or an autoantibody to a von Willebrand factor-cleaving protease, ADAMTS 13. These findings result in abnormally large von Willebrand factor multimers in plasma causing a greater ability to react with platelets and producing the disseminated platelet thrombi which are the characteristic features of TTP[5].

The current therapeutic mainstay is therapeutic plasma exchange[3]. Immunomodulatory agents (such as, corticosteroids, vincristine, cyclophosphamide, azathioprine, cyclosporins and high-dose immunoglobulins) have been reported for refractory TTP with variable effectiveness[6-8].

Although full recovery after TTP with neurological dysfunction such as convulsions has been reported in literature, outcome of the central nervous system involvement mimicking acute ischemic stroke is not clear[9-11].

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Case Report

A 36-year-old Thai woman was admitted to Siriraj Hospital due to right sided weakness 6 days prior to referral. She had a history of generalized abdominal pain and nausea 2 weeks prior. These

symptoms persisted for 2 days, then she developed headache, fatigue and dyspnea on exertion. She was admitted to a local hospital, then she developed fever, confusion, right sided weakness and nuchal rigidity one day after admission. Investigations showed marked anemia (hemoglobin 4 g/dL, hematocrit 14%), with normal white blood cell count and low platelet count (9,000/mm^3). Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were normal. Non-contrast computed tomography (CT) of the brain revealed hypodensity lesion from left frontal area to left external capsule compatible to left middle cerebral artery territory. Packed red cell and platelet transfusion were given prior to lumbar puncture. Cerebrospinal fluid (CSF) profile showed white cell count (WBC) 15 cell/mm^3 (mononucleated cell 100%), red cell count (RBC) 45 cell/mm^3, protein 54 mg/dL and normal glucose level. Her clinical condition then gradually worsened.

The next day she developed left-sided weakness, then she was referred to a provincial hospital. Physical examination demonstrated stuporous, global aphasia, bilateral weakness (right more than left side), with Babinski's sign on the right. Repeated complete blood count showed hemoglobin of 9.4 g/dL, hematocrit of 28%, normal WBC, platelet count of 10,000/mm^3. Peripheral blood smear revealed many schistocytes, polychromasia, few nucleated RBC, and thrombocytopenia. Brain magnetic resonance imaging (MRI) revealed acute infarction over the left middle cerebral artery territory and right lentiform nucleus. Brain magnetic resonance angiography (MRA) showed diffuse moderate to severe degree, irregular surface of intracranial vessels stenosis of both middle cerebral arteries and stenosis of mid basilar artery (Fig. 1). Patient was given fresh-frozen plasma and platelet transfusion. She was deteriorating and had respiratory arrest, then requiring mechanical ventilation. She was then referred to Siriraj Hospital.

Upon admission to Siriraj Hospital, her vital signs were temperature 39°C, blood pressure 140/90 mmHg, pulse rate of 90 per minute and respiratory rate of 18 per minute. She was stuporous, with acutely ill. There was no rash, no edema. Heart, lungs and abdomen were unremarkable. Neurological examination revealed a Glasgow coma score of $E_2V_TM_4$, with intermittent eye opening and gaze deviation to the right. Her pupillary reflex was symmetric and reactive. There was no facial asymmetry. Motor system demonstrated spastic tone on right side more than left, the motor power of proximal muscle was grade 0/V, the distal muscle grade II/V bilaterally. Deep tendon reflexes

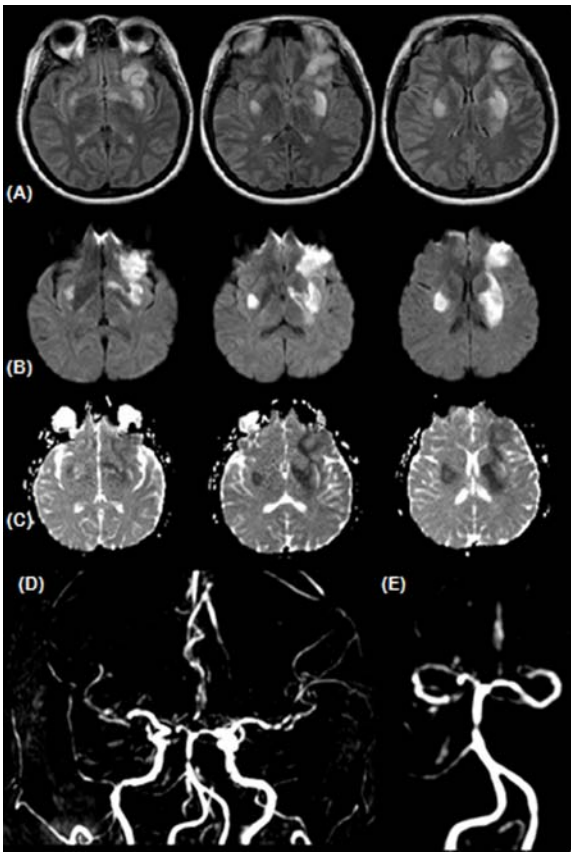

Fig. 1 Brain magnetic resonance imaging (MRI) was performed after she developed left-sided weakness; Panel A (T2W FLAIR) showed hypersignal at right lentiform nucleus , left basal ganglion and left basal frontal. Panel B (DWI) and panel C (ADC) showed restricted pattern in these area, compatible with acute infarction. MRA brain panel D and E showed intracranial vessels with moderate to severe degree with irregular surface and stenosis of both middle cerebral arteries, and stenosis of mid basilar artery

revealed hyperreflexia on the right with Babinski sign. National Institute of Health Stroke Score (NIHSS) was 25 points.

The hematologic profiles showed hemoglobin 6.8 g/dL, hematocrit 21%, mean corpuscular volume 89.7 fl, white blood cell count 12,130/mm^3 with neutrophil predominated (79%), platelet count 27,000/mm^3, PT 12.9 sec, aPTT 31.5 sec and D-dimer 8,027 ug/dL (normal < 500 ug/dL). Peripheral blood smear demonstrated fragmented erythrocyte, schistocyte, polychromasia, many nucleated red blood cells and thrombocytopenia. Biochemistry results were reported as albumin (4.2 g/dL), globulin (3.1 g/dL), total bilirubin (2.8 mg/dl), direct bilirubin (0.6 mg/dL), alanine aminotransferase (59 U/

L), aspartate aminotransferase (186 U/L), alkaline phosphatase 102 U/L, lactate dehydrogenase (7,803 IU/L: normal < 450 IU/L), creatinine (1.5 mg/dL) and blood urea nitrogen (38.4 mg/dL).

Evidence of microangiopathic hemolytic anemia in association with thrombocytopenia, neurological deficits and fever, led to a diagnosis of TTP. Patient was treated with daily therapeutic plasma exchange using fresh-frozen plasma for replacement fluid as first-line treatment in combination with intravenous steroid. She was transferred to ICU because of the worsening of her condition on the next day. Daily plasma exchange for 5 cycles in 8 days was performed. By day 9, her mental status had not improved and her hematologic profile was as follows: hemoglobin 10 g/dL, hematocrit 30.9%, mean corpuscular volume 91.2 fl, WBC count 17,860/mm^3 and platelet count 222,000/mm^3. Blood chemistry profile was reported as follows: creatinine 2.1 mg/dL, blood urea nitrogen 55.4 mg/dL and lactate dehydrogenase 1,023 IU/L. Plasma exchange was discontinued, but high dose steroid was prescribed throughout the course of treatment. Neurological examination revealed drowsiness, spontaneous eye opening but not following command, with assisted ventilation. Motor system demonstrated spastic tone of all extremities, with power grade 2/5 equally. Deep tendon reflexes were hyperreflexia, symmetric and bilateral Babinski's signs. After 2 months of assisted ventilation, she had sepsis due to ventilator associated pneumonia and succumbed.

Discussion

The authors described a patient with idiopathic TTP who presented with abdominal pain, fatigue, generalized weakness, and prior to developed acute bilateral middle cerebral artery infarction in a 36-year-old woman. Diagnosis TTP in this patient depends on clinical symptoms and laboratory results. She had 4 out of 5 of the clinical pentad: namely fever, microangiopathic hemolytic anemia, thrombocytopenia, and neurological disturbances. While the full classic pentad of clinical features of TTP is seen in only 40% of cases[16]. Increased lactate dehydrogenase (LDH) level is common. In our patient, LDH level was high (7,803 IU/mL). The result of coagulation appeared normal which support the diagnosis TTP. Neurological symptoms in the presented patient were very interesting. Half of patients with TTP have severe neurological abnormalities at presentation or fluctuating symptoms during the course of the illness, such as seizure, or hemiparesis[12]. Multiple territory ischemic strokes can be considered as a consequence of TTP, with atypical presentation. The usual presentation of TTP was due to microangiopathic thrombi, occluded small vessel disease[13]. In the presented patient, extensive ischemic strokes were found in bilateral middle cerebral arteries and mid basilar artery. Special attention must be emphasized in the issue of platelet transfusion in patients with TTP. In this patient, she had severe neurological deficit of left middle cerebral artery infarction, confusion and nuchal rigidity, prior to platelet transfusion. After that her condition was progressively worsened due to sepsis. Finally she succumbed in spite of proper management. In 1981, Harkness[14] and Bynrnes[15], reported patients with rapid neurological deterioration followed by death in a neurologically normal patient with TTP who was given 7 units of platelets as preparation before endoscopy. Since then, it has been recommended that platelet transfusion should not be given in patients with TTP except for life-threatening hemorrhage. In 2009, a systematic review of 34 publications describing outcomes of patients with TTP after platelet transfusion found that 9 attributed complications to platelet transfusions, 4 suggested that they may be safe and 21 did not comment on a relationship between platelet transfusions and outcomes[17]. The Oklahama TTP-HUS Registry was prospectively analyzed and found that mortality rate and severe neurological events were not different whether or not platelet transfusions were prescribed. So the harmful effects of platelet transfusion in patients with TTP is uncertain[17]. Then the presented patient developed left sided weakness with progressive aphasia after platelet transfusion. So the authors proposed that the worsened clinical outcome in the presented patient was due to platelet transfusion.

Treatment of TTP in this patient required combination of corticosteroids and plasmapheresis. Bell et al reported a 91% survival rate in a series of 108 patients with this regimen. Initial response rates were also higher with plasma exchange; within 7 days after randomization, 24 patients (47%) treated with plasma exchange had a normal platelet count and no new neurologic events[18]. In the present report, after complete course of plasma exchange, 5 cycles in 8 days, her hematologic profile was improved. However, severe neurological deficit persisted. The patient was continued high dose corticosteroid as a maintainance treatment.

Conclusion

TTP is a medical emergency, life threatening

but well response to plasma exchange. Rapid diagnosis and appropriate treatment are necessary for decreasing the risk of mortality in patients with TTP. General practitioner should be alert for clinical criteria and laboratory abnormalities of TTP. For the issue of platelet transfusion in patient with TTP, following this to prospective analysis revealed no difference in mortality and severe neurological events. But that our patient developed severe neurological deficit both prior to and after receiving platelet transfusion was obvious, resulting in respirator dependency and tetraplegia with aphasia. Finally she succumbed in spite of proper management.

Potential conflicts of interest

None.

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ภาวะหลอดเลือดสมองอุดตันเฉียบพลันในผู้ป่วยโรค Thrombotic Thrombocytopenic Purpura หลังได้รับเกล็ดเลือด: รายงานผู้ป่วย 1 ราย

ศรัทธาวุธ วงษ์เวียงจันทร์, นิพนธ์ พวงวรินทร์

ผู้ป่วยหญิงไทยอายุ 36 ปี อาการสำคัญมาด้วย ไข้ สับสน อ่อนแรงซีกขวา ตรวจร่างกายพบลักษณะอ่อนแรงซีกขวาร่วมกับคอแข็ง ผลตรวจค่าความสมบูรณ์ของเลือดเบื้องต้นพบ ภาวะซีดรุนแรงร่วมกับเกล็ดเลือดต่ำ จึงได้มีการให้เกล็ดเลือดเพื่อที่จะเจาะน้ำไขสันหลังมาตรวจเพิ่มเติม แต่หลังจากที่ได้รับเกล็ดเลือดไปนั้น อาการทางระบบประสาทของผู้ป่วยเลวลงจนเป็นอ่อนแรงร่างกายทั้ง 2 ซีกร่วมกับระดับความรู้สึกตัวลดลงมาก ต่อมาผู้ป่วยจึงถูกส่งตัวมารักษาต่อที่โรงพยาบาลศิริราช ขณะแรกรับได้รับการวินิจฉัยว่าเป็นภาวะ thrombotic thrombocytopenic purpura (TTP) ได้รับการตรวจเพิ่มเติมด้วยเครื่องเรโซแนนซ์แม่เหล็กสมอง (Magnetic Resonance Imaging) พบว่าหลอดเลือดแดงของสมองใหญ่ทั้ง 3 แขนง ได้แก่ หลอดเลือด Middle cerebral ทั้ง 2 ข้าง และหลอดเลือด Basilar มีลักษณะตีบตัน ซึ่งไม่ได้เป็นลักษณะทั่วไปที่พบได้ในภาวะนี้ แพทย์ผู้ให้การรักษาเชื่อว่าเกิดจากที่ผู้ป่วยได้รับเกล็ดเลือดมาก่อนหน้านี้ หลังจากที่ผู้ป่วยได้รับการรักษาด้วยการเปลี่ยนถ่ายน้ำหลือง (plasma exchange) อาการทางระบบประสาทไม่ดีขึ้น ผู้ป่วยไม่รู้สึกตัวและต้องใช้เครื่องช่วยหายใจ ในเวลาต่อมาผู้ป่วยเสียชีวิตลงเนื่องด้วยจากการติดเชื้อที่ปอดเหตุสัมพันธ์กับการใช้เครื่องช่วยหายใจ