Original article

Clinical features and outcomes of thrombotic thrombocytopenic purpura with severe ADAMTS13 deficiency at Maharat Nakhon Ratchasima Hospital

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Abstract:

Introduction: *Thrombotic thrombocytopenia purpura (TTP) is a rare but serious disease that is characterized by the microangiopathic hemolytic anemia (MAHA), thrombocytopenia, neurological abnormalities, renal impairment and fever, the so-called pentad. However identifying cases who completely fulfill the pentad is unusual and its various clinical presentations cause difficult diagnosis and high mortality rate.* ***Objective:*** *The study aimed to review clinical data, laboratory data, therapeutic interventions and treatment outcomes of patients with a diagnosis of TTP at Maharat Nakhon Ratchasima Hospital (MNRH) between January 2007 and June 2017.* ***Result:*** *In all, 22 TTP patients received a definite diagnosis with severe ADAMTS13 deficiency. Their mean age was 59.8 years. Twenty were classified as idiopathic (91.0%) while two were SLE-associated TTP (9.0%). All patients had MAHA and thrombocytopenia, 93% had neurological presentations, and 45.4% had bleeding disorder. Their mean laboratory data included hemoglobin concentration, platelet, and creatinine level of 7.1 g/dL, 11.4 x10^9 /L and 1.7 mg/dL, respectively. Only 36.3% of patients had the full pentad of TTP. Their treatments at the time of diagnosis consisted of plasma exchange in 11, plasma infusion in 10 and only immunosuppressants in 1 patient. The mean interval between symptom onset and plasma exchange was 6.6 days. The complete remission rate was 50%. Two patients relapsed only within the first year, one could achieve complete remission again by plasma exchange with immunosuppressants but the other patient passed away. The overall mortality rate was 50.0%.* ***Conclusion:*** *Almost all patients with TTP in our series had neurological symptoms clinically mimicking ischemic stroke, so the diagnosis could be delayed and might be the cause of the high mortality rate.*

Keywords : ● *Thrombotic thrombocytopenic purpura* ● *Severe ADAMTS13 deficiency* ● *Plasma exchange*

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นิพนธ์ต้นฉบับ

ลักษณะทางคลินิกของ thrombotic thrombocytopenic purpura ในผู้ป่วยที่มี ADAMTS13 ต่ำมาก ในโรงพยาบาลมหาราชนครราชสีมา

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บทคัดย่อ

บทนำ *Thrombotic thrombocytopenic purpura (TTP) เป็นโรคที่พบได้น้อยแต่มีความรุนแรง ลักษณะประกอบด้วย โลหิตจางแบบ microangiopathic hemolytic anemia (MAHA) เกล็ดเลือดต่ำ มีความผิดปกติทางระบบประสาท การทำงานของไตเสื่อมลง และ มีไข้ รวมเรียกว่า ปัญจลักษณ์ อย่างไรก็ตามการที่ผู้ป่วยจะมีครบปัญจลักษณ์พบได้น้อย ประกอบกับมีอาการแสดงหลากหลาย ทำให้การวินิจฉัยค่อนข้างยากและมีอัตราการตายสูง* ***วัตถุประสงค์*** *เพื่อศึกษาอาการและอาการแสดงทางคลินิก การตรวจทางห้องปฏิบัติการ การรักษา และผลการรักษา ในผู้ป่วยที่ได้รับการวินิจฉัย TTP ที่มี ระดับ ADAMTS13 ต่ำมาก ในโรงพยาบาลมหาราชนครราชสีมาที่ได้รับการวินิจฉัยระหว่าง เดือนมกราคม พ.ศ. 2550 ถึงเดือนมิถุนายน พ.ศ. 2560* ***ผลการศึกษา*** *มีผู้ป่วยที่ได้รับการวินิจฉัย TTP ที่มี ระดับ ADAMTS13 ต่ำมาก จำนวน 22 ราย อายุเฉลี่ย 59.8 ปี ผู้ป่วย 20 รายเป็นชนิดไม่ทราบสาเหตุ (ร้อยละ 91.0) อีก 2 รายเป็นชนิดที่เกี่ยวกับโรค เอส แอลอี (ร้อยละ 9.0) ผู้ป่วยทุกคนมีภาวะซีดแบบ MAHA และ เกล็ดเลือดต่ำ ร้อยละ 93 มีความผิดปกติทางระบบประสาท ร้อยละ 45.4 มีภาวะเลือดออกผิดปกติ ค่าเฉลี่ยผลการตรวจทางห้องปฏิบัติการของผู้ป่วย ระดับฮีโมโกลบิน ระดับเกล็ดเลือด และ ค่าการทำงานของไต ได้แก่ 7.1 กรัม/ดล., 11.4 x10^9 ตัว/ล. และ 1.7 มก/ดล. ตามลำดับ โดยพบผู้ป่วยที่มีอาการครบปัญจลักษณ์ เพียงร้อยละ 36.3 เท่านั้น การรักษาประกอบด้วย การแลกเปลี่ยน พลาสมา 11 ราย เพิ่ม พลาสมา 10 ราย และ ได้ยากดภูมิต้านทาน 1 ราย ระยะเวลาเฉลี่ยตั้งแต่เกิดอาการจนได้รับการแลกเปลี่ยน พลาสมา คือ 6.6 วัน ผู้ป่วยหายดีร้อยละ 50 มี 2 รายอาการกำเริบในขวบปีแรกและ 1 รายในจำนวนนี้สามารถหายได้อีกหลังจากได้รับการแลกเปลี่ยน พลาสมาร่วมกับยากดภูมิส่วนอีกรายเสียชีวิต อัตราการตายของผู้ป่วยโดยรวม ร้อยละ 50.0* ***สรุป*** *ผู้ป่วยเกือบทั้งหมดในการศึกษามีความผิดปกติทางระบบประสาท ซึ่งในบางรายมีอาการคล้ายกับผู้ป่วยที่เป็นเส้นเลือดสมองอุดตัน เป็นสาเหตุให้การวินิจฉัยล่าช้า และอาจมีส่วนในการเพิ่มขึ้นของอัตราการตาย*

คำสำคัญ : ● *Thrombotic thrombocytopenic purpura* ● *การขาด ADAMTS13* ● *การแลกเปลี่ยนพลาสมา*
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Introduction

Thrombotic thrombocytopenic purpura (TTP), firstly described by Moscowitz in 1924, is a rare but potentially fatal hematologic disorder characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, neurological involvement, fever and renal impairment, the so-called pentad. TTP basically results from the deficiency of a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13) enzyme, which normally cleaves large von Willebrand's factor (vWF) multimers into smaller appropriate sizes. Lack of ADAMTS13 causes a large vWF and activates platelet aggregation and the MAHA blood picture. Its delayed diagnosis increases the mortality rate.

TTP is divided in congenital and acquired TTP that may be idiopathic and secondary to autoimmune disease, pregnancy, bone marrow transplant, drugs (ticlopidine, cyclosporin), malignancy, HIV and other infectious diseases. In idiopathic TTP, most patients present alterations of consciousness and some present neurological deficit that can mimic stroke. When some patients present bleeding and fever, it can cause misdiagnosis as sepsis with DIC or severe infection. In the settings of reviewed studies, less than10% of patients with TTP clinically presented the pentad. Because of this, ADAMTS13 activity is used to guide the diagnosis of TTP when its level is < 10%. Although the diagnostic value of ADAMTS13 activity for TTP has been well established, its clinical significance for response, mortality, recurrence and prognosis remains unclear and requires further investigations. Therefore we analyzed clinical characteristics and laboratory data to assess prognostic factors that relate to the severity or recurrence of TTP.

Patients and Methods

The descriptive study was approved by the ethics committee of Maharat Nakhon Ratchasima Hospital. Patients with TTP diagnosed between January 2007 and June 2017 at the Department of Medicine, Maharat Nakhon Ratchasima Hospital were retrospectively reviewed.

All patients were required to have MAHA (as characterized by schistocytes on the peripheral blood smear and elevated serum LDH), thrombocytopenia with or without bleeding symptom and severe deficiency of ADAMTS13 activity (10%) with or without sign of renal dysfunction, neurological abnormality and fever. The information including demographic data, underlying diseases, clinical presentation, relevant laboratory profiles such as complete blood count, peripheral blood smear, ADAMTS13 activity, serum creatinine, serum lactate dehydrogenase (LDH), antinuclear antibodies, HIV serology and coagulation studies was extracted from medical records. Treatments including plasma exchange, plasma transfusion, immunosuppressive drugs and treatment outcomes were also collected from medical records.

Statistical analysis

All data were analyzed using SPSS for Windows, Version 13.0 (SPSS Inc., Chicago, IL, USA) and presented as frequency, mean, median, standard deviation (SD), percentage, and maximal and minimal values as appropriate.

Result

Baseline characteristic data: All 22 patients received a diagnosis of TTP with severe deficiency of ADAMTS13 activity (< 10 %). Their mean age was 59.8 ± 18.2 (31-90) years, and one half were males (50.0%). The mean time interval from onset of symptoms to plasma exchange was 6.6 ± 4.2 days. Among them, 20 of 22 were found idiopathic (90.9%) but 2 of 22 patients were found to have SLE (9.1%), as shown in Table 1.

Laboratory data: The laboratory data were presented as mean ± SD (range). On admission, the blood tests included hemoglobin 7.1 ± 1.4 g/dL (5.0-11.0), white blood cell 11 ± 6 $x10^9$ cells/L (1.7-30.8 $x10^9$ cells/L), platelet 17.3 ± 14.66 $x10^9$/L (6.0-64.0 $x10^9$/L), LDH 2.4 ± 1.9 $x10^3$ U/L (0.4-8.4 $x10^3$) and creatinine 1.7 ± 1.6 mg/dL (0.6-4.5), as shown in Table 1.

Table 1 Clinical features and treatment outcomes of patients with TTP

	Number (%) or mean ± SD (range)
Age (years)	59.8 ± 18.2 (31-90)
Female	11 (50)
Symptoms	
Fever	18 (81.8)
Neurologic involvement	20 (90.9)
Bleeding	10 (45.4)
Laboratory features	
WBC	11 ± 6 $x10^9$ cells/L (1.7-30.8 $x10^9$)
Hemoglobin	7.1 ± 1.4 g/dL (5.0-11.0)
Platelet count	17.3 ± 14.6 $x10^9$ /L (6.0-64.0 $x10^9$)
Serum LDH	2.4 ± 1.9 $x10^3$ U/L (0.4-8.4 $x10^3$)
Serum creatinine	1.7 ± 1.6 mg/dL (0.6-4.5)
ADAMTS13 activity	3.5 ± 0.7% (< 3-5)

Table 2 Neurological manifestations among patients with TTP

Clinical	Number of patients
Consciousness change GCS <15	8
Generalized tonic seizure	7
Hemiparesis	1
Hemiparesthesia	1
Headache	1
Blurred vision	1

Table 3 Bleeding disorders among patients with TTP

Clinical	Number of patients
Ecchymosis	3
Gum bleeding	2
Abnormal uterine bleeding	2
Petechiae	1
Intracerebral hemorrhage	1
Hematuria	1

Symptoms: Almost all patients presented neurological involvement (90.9%), the most common symptom was alteration of consciousness (8 patients), followed by seizure (7 patients), hemiparesis (1 patient), hemiparesthesia (1 patient) and headache (1 patient). All patients presenting focal neurologic deficit (hemiparesis and hemiparesthesia) were investigated using computer tomography of the brain and all results were normal (Table 2). Bleeding was the second most common presentation (45.5%), ecchymosis (3 patients), gum bleeding (2 patients), bleeding per vagina (2 patients) and petechiae, hematuria and intracerebral hemorrhage (1 patient presented with status epilepticus) as shown in Table 3. Fever was found among 18 patients (81.8%), while renal abnormality (impair renal function) was documented among 11 patients (50 %). The pentad

of TTP: Among patients, only 8 of 22 patients (36.4%) presented the complete pentad; the rest were found to have only three symptoms.

Treatment: Only one half of 22 patients received treatment with plasma exchange, 10 of 22 patients received treatment with FFP infusion and one received only immunosuppressive drugs. Mean time interval from symptom onset to plasma exchange was 6.6 ± 4.2 days. (Table 4)

Result of treatment: Complete remission (CR) was achieved among 11 patients (50%). Two of 11 patients had relapse within the first year and the mean time to relapse was 77 days (34-120). One relapsed patient could achieve CR again by plasma exchange with immunosuppressive drugs but the other passed away. The overall mortality was 11 of 22 (50%); 2 of 11 of plasma exchange group (18.1%) and 8 in 10 (80%) of the plasma fusion group. The causes of death are summarized in Table 5.

Discussion

This study described the characteristics of patients with TTP with severe ADAMTS13 deficiency and the prognostic significance of ADAMTS13 in TTP. We found no significant difference in sex but the age of onset appeared older as compared with those in other studies[2,3]. Most cases were idiopathic TTP. We found high mortality rates among patients that presented focal neurological deficit because the clinical features mimicked ischemic stroke, so causing delay for diagnosis. Other presentations included bleeding and fever that did not differ from other studies[2-4] but the pentad of symptoms was presented only in 36%.

The laboratory data, mean hemoglobin level (7.1 g/dL) and platelet count of 17.3 x10^9/L were approximately similar to those in other studies.[2-4] Importantly, all patients presented mean creatinine level less than 2.0 mg/dL (1.7 ± 1.6 mg/dL) that was comparable to the studies of Jang et al.[1] (creatinine level 1.6 ± 2.3 mg/dL) and Bendapudi et al.,[15]who proposed a cut off creatinine level less than 2.0 mg/dL for the diagnosis of renal involvement of TTP.

In the present study, the survival was predominantly seen in the plasma exchange group (82%), opposed to the plasma infusion group (20%). The group with acquired TTP secondary to systemic lupus erythematosus had the best prognosis because the survival rate was 100%.

Table 4 Treatments of 22 TTP patients

Treatment	Number (%) or mean ± SD (range)
Plasma exchange	11 (50)
Plasma infusion	10 (45.4)
Corticosteroid alone	1 (0.04)
Plasma exchange with corticosteroid	11 (50%)
Mean onset symptoms to plasma exchange	6.6 ± 4.2 (2-14)

Table 5 Outcomes of treatment of 22 patients with TTP

Outcomes	Number (percent)
Complete remission	11 (50%)
Death	11 (50%)
Relapse	2 (18.1%)
Cause of death (n = 11)	
Hospital acquired pneumonia	6 (54.5)
Urinary tract infection	4 (36.3)
Catheter related infection	1 (0.1)

The time from symptom onset to plasma exchange was about 6.6 days and crucial factors decreasing the mortality rate were rapid diagnosis and treatment. Other studies[1-3] have indicated the longer the time interval is, the higher the mortality rate. In our study, one half of the patients received plasma exchange using varying doses of FFP until complete remission and 40% of this group were also concurrently treated with corticosteroid. We found corticosteroid produced benefits in the relapsed group and in the acquired TTP group due to SLE in aspects of complete remission and survival rate.

One study on TTP involving severe ADAMPTS13 deficiency among Thai patients was conducted in King Chulalongkorn Memorial Hospital in 2014. It recruited all 16 patients with TTP whose baseline characteristic data were approximately similar to those in our study except the mean time interval of symptom onset to plasma exchange was 9.5 days, longer than the 6.6 days of our study. We found immunosuppressants might be beneficial only when they were combined with plasma exchange and among patients in relapse or SLE groups.

As in any retrospective study, some data were missing. Additionally, the small sample size was a limitation of this study.

Conclusion

Almost all patients with TTP with severe ADAMTS13 deficiency had neurological abnormalities and some had focal neurological deficit that might have led to misdiagnosis as stroke. The combination of neurological abnormalities, thrombocytopenia and MAHA should promptly remind a physician to diagnose and treat TTP, and not wait for ADAMTS13 activity.

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