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CASE BASED REVIEW

Clinical features and prognostic factors of thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus: a literature review of 105 cases from 1999 to 2011

Honghao Jiang · Xiangjie An · Ya Li · Yi Sun · Guanxin Shen · Yating Tu · Juan Tao

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Abstract This study aims to review clinical features, treatments, and prognostic factors of thrombotic thrombocytopenic purpura (TTP) associated with systemic lupus erythematosus patients (sTTP). The case reports of sTTP published in world literature from 1999 to 2011 were collected, and 105 cases were divided into death group and survival group. The epidemiologic characteristics, clinical manifestations, laboratory examinations, treatments, and prognostic factors were analyzed. We found that coexistence of renal and neurological impairments were significantly frequent in the death group (100 %) than in the survival group (56.5 %) (P=0.002). Type IV was predominant in 57.7 % of renal pathological damage, followed by type V (11.5 %), type II (5.8 %), and thrombotic microangiopathy (TMA) (5.8 %). TMA appeared more frequently (50 %) in the death group than in the survival group (6.25 %) (P=0.042). End-stage renal disease occurred in nine cases with type IV in five (55.6 %), type TMA in one (11.1 %), and unspecified in three cases (33.3 %). Of 32 cases, 40.6 % showed severe ADAMTS13 deficiency and returned to normal or mildly deficient after remission. The total mortality rate of sTTP was 12.4 % and the mortality rate of patients with infection (27.3 %) was significantly higher than those without infection (8.4 %) (P=0.028). Plasma exchange and glucocorticoids were administrated in over 80 % of cases with 65.7 % remission rate, while additional cytotoxics or rituximab was mostly used in refractory sTTP and achieved over 90 % of remission rate. Above all, coexistence of renal and neurological impairments, infection, and renal damage with type IV or TMA might denote a poor prognosis of sTTP.

Keywords ADAMTS13 · Infection · Prognostic factors · Systemic lupus erythematosus · Thrombotic thrombocytopenic purpura

Introduction

Thrombotic thrombocytopenic purpura (TTP) is an uncommon thrombotic microangiopathy (TMA) characterized with a clinical pentad: thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fever, neurological deficits, and renal dysfunction. Apart from some idiopathic cases, TTP may occur secondary to infections, malignancy, drugs, pregnancy, and autoimmune diseases such as systemic lupus erythematosus (SLE) [1]. Although plasma exchange dramatically improved the prognosis of TTP with over 80 % of survival rate [2], the episode will be severe and lethal (from 34.1 to 62.5 % morality rate) when TTP occurs in patients with SLE (referred as sTTP) [3, 4]. In addition, the diagnosis of TTP in the setting of SLE may be challenging because both of them share some or all elements of the classic pentad mentioned above [5], which in turn will delay the initialization of effective treatment. Moreover,

Honghao Jiang, Xiangjie An, and Ya Li equally contributed to this study.

H. Jiang · X. An · Y. Li · Y. Tu (✉) · J. Tao (✉)
Department of Dermatology, Affiliated Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No.1277 Jiefang Road, Wuhan 430030, China
e-mail: yatingtu@yahoo.com.cn
e-mail: tjhappy@126.com

Y. Sun
Department of Social Medicine, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

G. Shen
Department of Immunology, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

the response to therapy appeared to be poorer in sTTP than idiopathic TTP (iTTP) patients [3]. Furthermore, how sTTP occurs and how to improve its prognosis remain unclear until now.

In the last two decades, autoimmunity or vasculopathy with endothelial damage and platelet aggregation was considered as the pathogenesis of TTP in the setting of SLE [4, 6]. In 1998, Musio et al. [4] demonstrated that endothelial damage related to autoantibodies, platelet abnormalities, and disorders of fibrinolysis shared by both SLE and TTP might partially explain the generation and development of TMA according to 40 reports of sTTP from world literatures. In addition, excess of hemoglobin and increase of thrombin and D-dimer may also offer insights into the microangiopathic process of TTP [6, 7]. In recent years, an autoimmunity mechanism was proposed to be more important to the onset of TTP in the context of SLE, which was supported by the presence of various antibodies such as anti-endothelial cell antibody, antiplatelets antibody [3, 8], and anti-ADAMTS13 (von Willebrand factor cleaving metalloprotease) antibody [6]; this was further supported by the successful treatment of sTTP with cytotoxics and rituximab [9, 10]. Although the deficiency of ADAMTS13 activity related to its inhibitory IgG antibodies plays an important role in idiopathic TTP patients [1], it is still unclear whether both of them take part in the pathogenesis of sTTP and affects the treatment and prognosis of sTTP due to its rare incidence and limited reports.

In this study, we reviewed the worldwide literatures over more than 10 years (from January 1999 to December 2011), systematically analyzed epidemiologic characteristics, clinical manifestations, laboratory examinations, and treatments of 105 sTTP cases. Moreover, we divided the total cases into two groups (death group and survival group) and tried to find some factors characteristically involved in the prognosis of sTTP.

Patients and methods

Data collection

We searched Medline, Embase, Elsevier, and China National Knowledge Infrastructure Database for articles to identify all reported cases of sTTP published from January 1999 to December 2011 with the following terms: "systemic lupus erythematosus" or "SLE" and "thrombotic thrombocytopenic purpura" or "TTP." Articles published in English and other languages were all included. Our initial search revealed 81 references. We excluded 16 studies in which TTP cases were not associated with SLE. Because Musio et al. [4] systemically reviewed 40 cases of sTTP reported in world literatures before 1998, the cases documented before 1998 or studies without detailed records in five references were also excluded. Finally, we collected 105 cases in 60 references from January 1999 to December 2011 (*the 60 references were not presented for request of reference numbers in instructions for authors*).

Definition

Diagnosis definition Selected cases were identified with sTTP according to both SLE and TTP diagnosis criteria. All selected cases met the 1982 revised criteria for the classification of SLE [11]. Because no clinical symptom or biological criterion available is specific for TTP until now, the diagnosis of TTP in the selected cases was determined by the association of MAHA and unexplained thrombocytopenia as two major criteria, along with at least one of three minor criteria including fever, neurological deficits, and renal impairment, followed by exclusion of other causes for thrombocytopenia such as autoimmune hemolytic anemia, disseminated intravascular coagulation, cancer, eclampsia, drug toxicity, stem cell transplantation, or malignant hypertension [1, 2, 6]. SLE may occur before, simultaneously, or after the diagnosis of TTP. The simultaneous diagnosis of TTP and SLE was considered if both disorders were diagnosed during the same admission within a 14-day period [12].

Outcome definition sTTP remission is defined as laboratory and clinical abnormalities typically resolved with normal neurological status and platelet count [3, 13]. Refractory disease or resistance is defined as persistent thrombocytopenia (platelet <150,000 μL) or LDH elevation or organ involvement after a total of seven daily plasma exchanges and (or) intensive immunosuppressive therapy [3, 14]. Survival is defined as achievement of remission [13]. Death from TTP is defined as occurring within 30 days of stopping plasma exchange in two studies [13, 15]. After reviewing the literature concerning the 105 cases, we found that the follow-up data in most reports were not presented in detail. Therefore, we define death from sTTP as occurring within the hospitalization period with a clearly diagnosis of sTTP, and deaths beyond the hospitalization period was not taken into account. Relapse is defined as the recurrence of thrombocytopenia and MAHA after remission is achieved [13, 15].

Data synthesis and analysis

All data including gender, age, sequence of disease onset (SLE preceding TTP or SLE following TTP or SLE concomitant with TTP), major clinical features, laboratory examination, treatment, and prognosis in each case were entered and analyzed with SPSS version 19.0. Laboratory data recorded gave the most abnormal values when sTTP was diagnosed. According to the outcome during hospitalization period, all 105 cases were divided into the death group (13 cases) and the survival group (92 cases). Numerical data were compared by the independent-samples *t* test or Welch's *t* test. The qualitative differences were performed using

chi-square test or Fisher's exact test. $P<0.05$ was considered to be a significant difference between the groups.

Results

Epidemiologic characteristics

There were 18 males (17.1 %) and 87 females (82.9 %) in 105 cases. The mean age was 32.3±13.4 years ranging from 8 to 74 years (median age, 30 years). The onset of SLE preceded, coincided, or followed the onset of TTP in 53 cases (50.5 %), 48 cases (45.7 %), and 4 cases (3.8 %), respectively. Detailed epidemiologic data were presented in supplementary material.

Main clinical features

Initial clinical manifestations

In our study, 17 initial clinical manifestations involving over seven systems and organs were described in detail in 68 patients (Table 1). The most common complaints were recurrent fever (19.1 %), followed by fatigue (16.2 %) and headache (14.7 %).

Neurological deficits

Neurological symptoms occurred in 80 (76.2 %) of 105 sTTP cases. Among the 80 cases, neurological symptoms were described clearly in 69, with single neurological symptom in 31 (44.9 %) and more than one symptom in 38 (55.1 %). Eight types of neurological symptoms were presented, including disturbance of consciousness (41 cases, 59.4 %), seizures (33 cases, 47.8 %), headache (19 cases, 27.5 %), mental confusion (13 cases, 18.8 %), optic nerve damage (7 cases, 10.1 %), hemiparesis (6 cases, 8.7 %), peripheral nerve palsy (4 cases, 5.8 %), and language disorder (4 cases, 5.8 %). In the death group, all 13 patients (100 %) had neurological symptoms, which were significantly frequent than in the survival group (67 of 92 cases, 72.8 %) ($\chi^2=4.637$, $P=0.035$). Among the 80 cases with neurological symptoms, 44 underwent head imaging tests (CT or MRI) and 22 cases (50 %) presented positive results including cerebral infarction and (or) ischemic lesions in 17

Table 1 Initial clinical manifestations in 105 sTTP patients

Initial clinical manifestations	Total cases ($n=68$)	Death group ($n=11$)	Survival group ($n=57$)
General manifestation			
Recurrent fever	13	3	10
Fatigue	11	1	10
Rash			
Ecchymosis	4	0	4
Gastrointestinal system			
Abdominal pain	6	2	4
Jaundice	2	0	2
Vomit	1	1	0
Respiratory system			
Dyspnea	5	1	4
Chest pain	2	0	2
Urinary system			
Edema	3	0	3
Dark urine	3	2	1
Neurologic system			
Headache	10	1	9
Conscious disturbance	2	0	2
Seizures	2	0	2
Language disorder	1	0	1
Paresthesia	1	0	1
Motor system			
Arthralgia	1	0	1
Gynecologic system			
Hypermenorrhea	1	0	1

cases (77.3 %), leukodystrophy in 3 (13.6 %), and cerebral hemorrhage in 4 (18.1 %).

Renal impairment

Among 105 patients, 88 (83.8 %) cases showed renal impairment such as proteinuria, hematuria, increase of plasma urea nitrogen and creatinine, and renal failure, including all 13 cases (100 %) in the death group and 75 of 92 cases (81.5 %) in the survival group. Fifty-two of 88 cases (59.1 %) took a kidney biopsy and revealed 11 types of renal pathological damage. Type IV was predominant in 57.7 % of renal pathological damage, followed by type V (11.5 %), type II (5.8 %), and TMA (5.8 %) (Table 2). TMA appeared more frequently (2 of 4 cases, 50 %) in the death group than in the survival group (3 of 48 cases, 6.25 %) (χ^2=8.132, P=0.042). The end-stage renal disease occurred in 9 of 88 (10.2 %) cases with type IV kidney damage in five (55.6 %), type TMA in one (11.1 %), and unspecified in three cases (33.3 %).

Neurological deficits together with renal impairment

Among 105 cases, both neurological deficits and renal impairment were seen in 65 (61.9 %) cases including all 13 cases (100 %) in the death group and 52 cases (56.5 %) in the survival group. Coexistence of renal and neurological impairments were significantly frequent in the death group than in the survival group (χ^2=9.130, P=0.002).

Laboratory examinations

Thrombocytopenia, anemia, and elevated LDH were shown in 105 (100 %), 97 (92.4 %), and 86 (81.9 %) cases, and the levels of PLT, Hb, and LDH were 39.3±31.1×10^9/L, 71.1±22.1 g/L, and 1,304±1,575 IU/L, respectively. A peripheral blood smear test was elaborately described in 99 cases, and all showed schistocytes (usually >1 % of total erythrocytes).

Coombs' tests were detailed in 80 of 105 patients with a negative rate of 77.5 % (62 cases). ADAMTS13 activities were tested before treatment in 32 patients, with severe deficiency (<5 % of normal) in 13 cases (40.6 %), moderate deficiency (10–25 %) in 2 cases (6.3 %), mild deficiency (26–50 %) in 12 cases (37.5 %), and normal (>50 %) in 5 cases (15.6 %) [10]. ADAMTS13 activities were re-examined in 14 cases after remission. The levels of ADAMTS13 activities were elevated in all 14 cases, with normal levels in 10 cases, and mild deficiency in 4 cases. Anti-ADAMTS13 antibody was tested in 24 patients with positive rates of 91.7 % in 22 cases. Positive rates of main immunological parameters were summarized in detail in Table 3. All abnormal values mentioned above were not significantly different between the death group and the survival group (P>0.05).

Treatment and prognosis

Combination therapies were widely used in sTTP patients, and the most common therapeutic modalities were plasma exchange combined with glucocorticoids pulse therapy and cytotoxic agents (in 52 cases, 49.5 %), followed by plasma exchange combined with glucocorticoids pulse therapy (in 35 cases, 33.3 %) (Table 4). Among the combination therapies, glucocorticoids were administrated in 99 cases (94.3 %). Plasma exchange and (or) hematodialysis and (or) plasma infusion were used in 95 cases (90.5 %). When plasma exchange was absent in 10 cases, the refractory and mortality rates were as high as 60 and 30 %, respectively (Table 4). Several cases were refractory to one therapy (e.g., plasma exchange with glucocorticoids pulse therapy) but responded to additional cytotoxics or rituximab. Combination therapies with cytotoxics could significantly improve the remission rate when compared with therapies without cytotoxics (P<0.05, Table 4).

Table 2 Renal pathological damages in 105 sTTP patients

Renal pathological damages	Total cases (n=52)	Death group (n=4)	Survival group (n=48)
IV	30	1	29
V	6	0	6
TMA[a]	3	2	1
II	3	1	2
III	2	0	2
VI	2	0	2
III and V	1	0	1
IV and V	1	0	1
V and TMA[a]	1	0	1
VI and TMA[a]	1	0	1
II and III	1	0	1
Normal	1	0	1

TMA thrombotic microangiopathy

[a] TMA appeared more frequently (50 %) in the death group than in the survival group (3 of 48 cases, 6.25 %) (χ^2=8.132, P=0.042) by using Fisher's exact test

Table 3 Positive rates of main immunological parameters in 105 sTTP patients

Antibodies	Total *n* (%)	Death group *n* (%)	Survival group *n* (%)
Anti-ANA	94/97 (96.9)	12/12 (100)	82/85 (96.5)
Anti-dsDNA	56/97 (57.7)	5/12 (41.7)	51/85 (60)
Anti-Sm	20/97 (20.6)	2/12 (16.7)	18/85 (21.2)
Anti-phospholipid antibody	19/64 (29.7)	2/6 (33.3)	17/58 (29.3)
ADAMTS13 activities (<5 %)	13/32 (40.6)	2/3 (66.7)	11/29 (37.9)
anti-ADAMTS13 antibody	22/24 (91.7)	2/2 (100)	20/22 (90.9)

The most common cytotoxic agents for treatment was cyclophosphamide (52 cases, 49.5 %), mycophenolate mofetil (16 cases, 15.2 %), and vincristine (8 cases, 7.6 %). Furthermore, plasma exchange combined with glucocorticoids pulse therapy were seemed to be widely used in cases with normal or slightly deficiency of ADAMTS13 activity, while combination with additional cytotoxics or rituximab were frequently used to treat cases with severely or moderately deficient ADAMTS13 activity (Table 5). Besides therapies mentioned above, intravenous immunoglobin, anticoagulant drugs, erythropoietin, and erythrocyte or platelet transfusion were also chosen in several cases.

The total mortality rate was 12.4 % and the main causes of death included sTTP itself (single or multiple organ failure) and (or) in combination with overwhelming infection (Table 4). Twenty-two (21 %) patients suffered from an infection in which pneumonia was predominant in 17 cases (77.3 %). The pathogenic microorganisms included *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas*, *Pneumocystis carinii*, *Aspergillus*, and *Cytomegalovirus*. The mortality of patients with an infection (6 of 22 cases, 27.3 %) was significantly higher than patients without an infection (7 of 83 cases, 8.4 %) (χ^2=5.690, P=0.028). Forty-six patients were followed up for a mean time of 25.3±26.5 months (ranging from 2 to 96 months). Seven patients (15.2 %) had relapse records of TTP (mean 2.43 times, ranging from one to nine times) during follow-up.

Comparison with cases before 1998 [4]

The incidence of patients with SLE concomitant with TTP (48 cases, 45.7 %) in our study was significantly more than before 1998 (5 cases, 12.2 %), while the cases with SLE preceding (53 cases, 50.5 %) or following (4 cases, 3.8 %) TTP were both less

Table 4 Various therapies and their recorded outcome in 105 sTTP cases

Various therapies	Total utilization rate (N=105) *n* (%)	Remission rate *n* (%)	Refractory rate *n* (%)	Gain remission by additional therapy[a] *n* (%)	Total per mortality *n* (%)	Cause of death
PE alone[b]	6 (6.7)	3/6 (50)	3/6 (50)	2/6 (33.3)	1/6 (16.7)	sTTP
ST and (or) cytotoxics without PE[c]	10 (9.5)	4/10 (40)	6/10 (60)	3/10 (30)	3/10 (30)	sTTP (single organ failure)
PE + ST[d]	35(33.3)	23/35 (65.7)	12/35 (34.3)	8/35 (22.9)	4/35 (11.4)	Overwhelming infection/sTTP (multiple organ failure)
PE + cytotoxics	3 (2.9)	3/3 (100)	0	0	0	No
PE + ST + cytotoxics[e]	52 (49.5)	47/52 (90.4)	5/52 (9.6)	0	5/52 (9.6)	Refractory sTTP/ overwhelming infection
Rituximab + PE with or without ST (or cytotoxics)	11 (10.5)	10/11 (90.9)	1/11 (9.1)	1/11 (9.1)	0	No
Others	2 (2.9)	2/2 (100)	0	0	0	No

PE plasma exchange and(or) hematodialysis and(or) plasma infusion, *ST* steroids (glucocorticoids), mostly pulse methylprednisolone therapy, *cytotoxics* including cyclophosphamide, mycophenolate mofetil, vincristine, cyclosporine A, and methotrexate, *others* including rTM (recombinant human soluble thrombomodulin) in one and bilateral nephrectomy in the other

[a] The patient was refractory to one therapy, but achieved remission by additional therapy such as cytotoxics or rituximab

[b] χ^2 =7.378, P=0.029

[c] χ^2 =14.589, P=0.001

[d] χ^2 =8.098, P=0.04

[e] The remission rate by using the therapy (PE + ST + cytotoxics) was significantly higher than the other three therapies (PE alone, ST and (or) cytotoxics without PE, and PE + ST)

Table 5 Various therapies and recorded outcome in 32 cases with different ADAMTS 13 activity

Various therapies	ADAMTS 13 activity (<5 % of normal) (*N*=13)	ADAMTS 13 activity (10–25 %) (*N*=2)	ADAMTS 13 activity (25–50 %) (*N*=12)	ADAMTS 13 activity (>50 %) (*N*=5)
PE alone	NR	NR	1 died	1 Rf[a]
ST and (or) cytotoxics	NR	1 Rm	1 Rm	1 Rf[a]
PE + ST pulse therapy	7 Rm, 2 Rf[a] 2 died	1 Rm	1 Rm	NR
PE + cytotoxics	1 Rm	NR	1 Rm	NR
PE + ST pulse therapy + cytotoxics	2 Rm	NR	6 Rm	1 Rm
Rituximab + PE with or without ST (or cytotoxics)	1 Rm	NR	2 Rm	3 Rm
rTM	NR	NR	NR	1 Rm

PE plasma exchange and (or) hematodialysis and (or) plasma infusion, *ST* steroids (glucocorticoids), mostly with pulse methylprednisolone therapy, *cytotoxics* including cyclophosphamide, mycophenolate mofetil, vincristine, cyclosporine A, and methotrexate, *rTM* recombinant human soluble thrombomodulin, *Rf* refractory, *Rm* remission, *NR* not reported

[a] The patient was refractory to one therapy but achieved remission by additional therapy such as cytotoxics or rituximab

than before 1998 (30 cases/73.2 % and 6 cases/14.6 %, respectively) ($P<0.05$, Table 6). The mortality rate (12.4 %) in our review from 1999 to 2011 was significantly lower than before 1998 (34.1 %) [4] ($\chi^2=9.267$, $P=0.004$).

Discussion

The initial clinical manifestations are easily ignored in sTTP patients due to non-specification, in which the most complaints are commonly related to the early TTP, such as neurological deficits (e.g., headache, conscious disturbance, ischemia associated), fatigue, and abdominal pain (bleeding associated) [1, 5]. Meanwhile, we found that neurological deficits and renal impairment occurred frequently in 76.2 and 83.8 % of cases, respectively. The occurrence of neurological deficits alone or accompanied by renal impairment was significantly higher in the death group than in the survival group, which suggested that neurological deficits especially together with renal impairments might be a possible prognostic factor for sTTP patients although the accuracy of using this tenuous relation is debatable. The poor eventual treatment outcome might be related to two factors. In the first place, acute ischemia related to thrombotic microangiopathy is common in TTP [1, 3, 16], which is also supported by the head imaging tests in this review with ischemic lesions occurring in 77.3 % of the cases. In the second place, the brain will be the most common target for ischemia [1]. In addition, Kwok et al. [17] also found that SLE patients with neurologic manifestations had a higher mortality rate.

Table 6 Epidemiologic characteristics and mortality rate of sTTP at different times

	Time	Total	Male	Female	SLE preceding TTP[a]	SLE following TTP[a]	SLE Concomitant with TTP[a]	<20 (year)	20–49 (year)	≥50 (year)
Cases	Before 1998, *n* (%)	41	5 (12.2)	36 (87.8)	30 (73.2)	6 (14.6)	5 (12.2)	6 (14.6)	29 (70.7)	6 (14.6)
	1999–2011, *n* (%)	105	18 (17.1)	87 (82.9)	53 (50.5)	4 (3.8)	48 (45.7)	21 (20)	70 (66.7)	14 (13.3)
Mortality[a]	Before 1998, *n* (%)	14/41 (34.1)	2/5 (40.0)	12/36 (33.3)	13/30 (43.3)	0	1/5 (20)	1/6 (16.7)	12/29 (41.4)	1/6 (16.7)
	1999–2011, *n* (%)	13/105 (12.4)	2/18 (11.1)	11/87 (12.6)	7/53 (13.2)	1/4 (25)	5/48 (10.4)	1/21 (4.8)	8/70 (11.4)	4/14 (28.6)

The cases before 1998 were presented in Musio's review[4], and the data from 1999 to 2011 was reviewed in this study

[a] They were significantly different between Musio's review and our study, including the total mortality ($\chi^2=9.267$, $P=0.004$), cases with SLE preceding TTP ($\chi^2=6.191$, $P=0.013$), SLE following TTP ($\chi^2=5.415$, $P=0.03$), and SLE concomitant with TTP ($\chi^2=14.327$, $P=0.00$)

Among the 105 sTTP cases, the most common renal pathological damage was type IV (57.7 %), followed by type V (11.5 %), type II (5.8 %), and TMA (5.8 %). The findings were supported by Mustafa et al. [18] who presented that type IV was predominant in 60 % SLE cases. In addition, renal TMA usually occurs in patients with severe lupus nephritis [8], and TMA also adversely affect the prognosis of the renal disease [19]. We found that type IV was not only the most common type in sTTP patients but also capable of evolving end-stage renal disease than other types, and TMA appeared more frequently in the death group. Thus, renal damage of type IV or TMA may be another risk factor related to poor prognosis of sTTP. Conducting a renal pathological biopsy at an early stage could be helpful for evaluating disease condition and prognosis.

Apart from thrombocytopenia, MAHA, and elevated LDH, negative Coombs test, dysfunction of ADAMTS13, and anti-ADAMTS13 antibody are also reported to be crucial for making an early diagnosis of TTP [2]. However, we found that 22.5 % of cases had a positive direct Coombs test along with clear features of TTP. Therefore, a Coombs test may be positive in sTTP as part of immune phenomena of SLE and is not necessarily against the diagnosis sTTP. ADAMTS 13, a vWF (Von Willebrand Factor) cleaving metalloprotease, which is caused by either an autoimmune inhibitor or genetic mutation, is referred as one of the causative factors of TTP [6]. ADAMTS 13 deficiency will result in formation of ultra-large vWF multimers and thrombosis in TTP. Although about two thirds to three quarters of patients with iTTP have been found to be severely deficient in ADAMTS13 activity [2, 20], only 40.6 % of sTTP cases were presented with severe deficiency in our study. Inconsistent with less than half of patients with severe ADAMTS13 deficiency, anti-ADAMTS13 antibody was found in 91.7 % of cases. These results might be associated with following factors. Firstly, severe deficiency of ADAMTS13 might be alleviated by immunosuppressive drugs by suppressing the formation or function of anti-ADAMTS13 antibody. Secondly, although most patients had anti-ADAMTS13 antibody, a few of them may have anti-ADAMTS13 antibody without neutralizing activity [6]. Thirdly, detection time also needs to be considered because the level of ADAMTS13 activity fluctuates during the process of disease. It has been reported that many iTTP patients usually have severe ADAMTS13 dysfunction or even lack ADAMTS13 activity only during an initial episode or later recurrence [2].

Meanwhile, we also found that severe or moderate deficiency of ADAMTS13 mostly (75 %) became normal after remission. More interestingly, sTTP with severe or moderate deficiency of ADAMTS13 were mostly treated with simple therapies (e.g., plasma exchange combined with glucocorticoids pulse therapy) [21–24], while cases with normal or slightly ADAMTS13 deficiency responded well to additional cytotoxics or rituximab [19, 25, 26]. From the above findings, monitoring the level of ADAMTS13 activity might be advantageous to determining the approach for treating sTTP patients and assessing the approach's efficacy, but more cases are needed to further evaluate its value for the diagnosis and treatment of sTTP. TTP with severe ADAMTS13 deficiency was also reported to have a higher likelihood of relapse [2, 27], but it was not shown in this review due to the lack of follow-up data.

Early use of plasma exchange shows good efficacy for iTTP with over 80 % of survival rate [3, 13, 17]. This approach is also useful in treating sTTP. In 10 cases without receiving plasma exchange, the refractory and mortality rates of sTTP were as high as 60 and 30 %, respectively, in this review. However, plasma exchange alone is not enough to control TTP in the setting of SLE. Combined therapies with plasma exchange and immunosuppressor (including steroids and cytotoxic agents) were presented to be more appropriate than plasma exchange or immunosuppressor alone in treating sTTP patients and achieved a higher remission rate (65.7–90.4 % vs 40–50 %) in this review. This result was also supported by Letchumanan et al. who reported that TTP patients in the setting of SLE were more refractory to plasma exchange and had a poorer prognosis than iTTP [3]. In this review, plasma exchange combined with glucocorticoids remained the first-line treatment due to over 80 % utilization rate and 65.7 % remission rate. However, several cases were refractory to plasma exchange combined with glucocorticoids (34.3 % refractory rate). On this occasion, cytotoxics should be considered in several reports [10, 28]. Our review further confirmed this point, in which plasma exchange combined with glucocorticoids pulse therapy and cytotoxic drugs could significantly improve the remission rate (90.4 %, $P<0.05$) when compared with therapies without cytotoxics.

In addition, except cytotoxics, biological therapy such as rituximab (a chimeric monoclonal antibody against the protein CD20, which depletes B lymphocytes) was also recommended by successfully treating refractory sTTP patients (90.9 % remission rate) in several cases [9, 25, 26, 29] in this review. It has been shown that rituximab could remove ADAMTS13 inhibitor and improve clinical outcomes in TTP [9, 25]. In this review, rituximab was not only effective for sTTP cases with impaired ADAMTS13 activity [29] but also useful for cases with normal ADAMTS13 activity [25, 26]. However, owing to the small number of cases treated with rituximab in this review, the value of rituximab in treating refractory sTTP requires to be further evaluated.

The total mortality of 105 sTTP cases in this review was 12.4 %, which was significantly lower than 34.1 and 62.5 % in reported in two reviews [3, 4]. This may be attributed to following factors. Firstly, earlier diagnosis and more effective treatment (mentioned above) were realized compared with before. Secondly, deaths beyond the hospitalization period were not taken into account in this review due to lack of follow-up data. In addition, we also found that the mortality

rate in patients with infection (27.3 %) was significantly higher than those without infection (8.4 %), and overwhelming infection was also one of the main causes of death. Besides renal damage type (IVor TMA), and concomitant occurrence of renal and neurological impairments, infection might be considered as the third poor prognosis factor for sTTP. This result was consistent with Kwok' study [17] which showed that sTTP can be fatal especially in the presence of infection. Infection is obviously related to the use of immunosuppressant and biological therapy, so aseptic conditions for treatment and infection prevention would be helpful for a more favorable prognosis.

Although some findings mentioned above are both interesting and useful for a physician to engage a patient with sTTP, several limitations are obvious. Firstly, retrospective data collection from case reports will not be as rigorous as a prospective study. In addition, some laboratory evaluations were not completely consistent due to cases from different countries, which could influence the analysis of laboratory data. Finally, the data among three groups (SLE preceding TTP, SLE following TTP, and SLE concomitant with TTP) were not able to be presented and analyzed meaningfully due to the relatively fewer cases in SLE following TTP group (only four cases), which limited the statistical power for comparisons.

Conclusion

In conclusion, plasma exchange combined with glucocorticoids remains the first-line treatment for sTTP, while cytotoxic agents and biological therapy are recommended for refractory sTTP. Coexistence of neurologic and renal impairments, renal damage with type IV or TMA, and infection might be three risk factors for poor prognosis of sTTP.

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Disclosures None.

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