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CASE BASED REVIEW

Response to belimumab in thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus: a case-based review

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Abstract

Thrombotic thrombocytopenic purpura (TTP), a life-threatening syndrome characterized by acute microangiopathic hemolytic anemia, thrombocytopenia, and visceral ischemia, can be classified as congenital TTP (inherited due to a mutation in *ADAMTS13*) and acquired TTP. The acquired TTP is further classified as idiopathic and secondary TTP. Systemic lupus erythematosus (SLE) is regarded as one of the most common causes of secondary TTP (SLE-TTP). In contrast to patients with idiopathic TTP, some patients with SLE-TTP, especially those diagnosed with refractory TTP, are resistant to plasma exchange and high-dose corticosteroids and usually require second-line drugs, including newly developed biologicals. Belimumab, a B-lymphocyte stimulator-specific inhibitor, was the first approved new therapy for SLE in the past 50 years. Only two cases of SLE-TTP using belimumab have been reported; however, detailed information has not been made available. Herein, we describe a 28-year-old female patient who presented with palm petechiae, strong tawny urine, and yellow stained skin and sclera, and was diagnosed with SLE-TTP supported by high anti-ANA titers; positive anti-SSA/SM; pleural effusion; decreased platelet count, hemoglobin, and complement C3/C4 counts; increased lactate dehydrogenase level, along with increased schistocytes; and a significant deficiency of ADAMTS13 activity. Belimumab (10 mg/kg) was administered after six plasma exchanges. Good efficiency and outcomes without any adverse events, SLE, or TTP relapse were observed during 12 months of follow-up. Therefore, belimumab is a promising choice for SLE-TTP management. In addition, we provide a focused review of the existing literature on the pathogenesis, diagnosis, and therapeutic strategies for SLE-TTP.

Keywords Belimumab · Diagnosis · Systemic lupus erythematosus · Thrombotic thrombocytopenic purpura · Treatment

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening condition characterized by clinical pentad, microangiopathic hemolytic anemia (MAHA), severe thrombocytopenia, fever, neurological impairments, and renal dysfunction [1, 2]. TTP can be classified as congenital TTP, occurring due to *ADAMTS13* gene mutation, and acquired TTP, which can further be classified as idiopathic and secondary TTP [2]. Secondary TTP often occurs secondary to neoplasms, some drugs (ticlopidine, mitomycin C, and cyclosporine), severe infections, pregnancy, and several autoimmune disorders, including systemic lupus erythematosus (SLE) [1, 3]. SLE, a heterogeneous systemic autoimmune disease characterized by multiple clinical manifestations and various severity levels, is deleterious to multiple critical organs and systems, including the hematological system [4]. Despite the extremely rare rate of TTP in patients with SLE (referred to as SLE-TTP), with an incidence of approximately 0.5 to 2%, TTP-SLE mortality still ranges from 34 to 62.5% [5–7].

The diagnosis of SLE-TTP may be challenging because of the similarities in clinical manifestations of both SLE and TTP, thus delaying prompt and proper therapy, especially plasma exchange (PEX) [8, 9]. PEX combined with high-dose corticosteroids is the standard

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first-line treatment for TTP, dramatically improving TTP prognosis, with a decreased mortality rate from 90 to 20% [10]. In contrast to idiopathic TTP, a few patients with SLE-TTP, especially those diagnosed with refractory TTP, are poorly benefitted by this first-line therapy and usually require second-line drugs such as immunosuppressive agents (CsA and bortezomib) and biologicals (caplacizumab and rituximab) [10–13]. Belimumab, a B-lymphocyte stimulator-specific inhibitor, inhibits B cell survival and differentiation [14]. It was the first approved new therapy for SLE treatment in the past 50 years [15, 16], owing to its excellent efficiency and safety. However, it remains unclear whether belimumab can be used to treat SLE-TTP. To date, only two cases of SLE-TTP treated with belimumab have been reported, without detailed information being provided.

This study describes a previously healthy 28-year-old female patient diagnosed with SLE-TTP, who achieved a favorable response and sustained remission after six PEXs followed by belimumab. In addition, we provide a focused review of the existing literature on the pathogenesis, diagnosis, and therapeutic strategies of SLE-TTP.

Case details

In July 2020, a previously healthy 28-year-old woman presented to another hospital with a 10-day history of bilateral lower extremity petechiae, nausea and vomiting, weakness, and polypnea after activity. The patient had no significant medical or surgical history. Her menstrual cycle was regular, and she denied any pregnancies or abortions. Initial laboratory tests revealed thrombocytopenia (platelet (PLT) count, 13×10^9/L) and hemolytic anemia (hemoglobin (Hb), 57 g/L; lactate dehydrogenase (LDH), 1676 U/L; total bilirubin (TBil) 40.9 μmol/L, and indirect bilirubin (IBiL) 31.7 μmol/L). Apart from the elevated antinuclear antibody (ANA) titer (1:1000, normal: < 1:80), her serological examinations were positive for anti-Sjögren's syndrome-related antigen A autoantibodies (anti-SSA), anti-Smith antibody (anti-SM), and herpes simplex virus (HSV) IgM. A bone marrow biopsy obtained by aspiration revealed a significant decrease in megakaryocytes, thrombocytogenic megakaryocytes, and PLT counts. Based on the symptoms and laboratory findings, SLE and HSV infection was confirmed, and therapy with methylprednisolone (0.5 g for 3 days), blood transfusion (RBC and PLT), and acyclovir (0.25 g/d) was initiated. However, the patient's condition worsened. Because of palm petechiae, strong tawny urine, and yellow staining of the skin and sclera, the patient was transferred to our department for further treatment on July 20, 2020.

On admission, she was alert and oriented, and her vital signs were normal. In addition to systemic skin and scleral jaundice, scattered petechiae and ecchymoses were found in the bilateral lower limbs, palms, and neck. No lymphadenopathy or lower-extremity edema was observed. The cardiovascular, lung, abdominal, and neurological examinations yielded insignificant results. Routine laboratory investigations and radiographic examinations were immediately performed. As shown in Table 1, remarkably decreased PLT count (6×10^9/L) and Hb (42 g/L) level were detected, while LDH level increased to 3363 U/L, along with elevated TBil, direct bilirubin (DBil), and IBiL. Biochemical analysis revealed impaired liver and renal function, as evidenced by increased aspartate transaminase (AST), alanine transaminase (ALT), and creatinine levels and reduced estimated glomerular filtration rate. The D-dimer level increased, and the remaining coagulation profiles were normal. Despite the negative Coombs test results, the lupus anticoagulant test result was positive. In contrast to the decreased complement C3 and C4 levels, erythrocyte sedimentation rate and interleukin-6 levels were significantly elevated. High titers of anti-ANA (1:3200, normal: < 1:80) and anti-SSA/SM were detected (Table 1). The percentage of B cells increased, but the count was normal. A peripheral blood smear showed increased schistocytes and downregulated ADAMTS13 activity (0, normal: 70–120%), while positive ADAMTS13 inhibitors were also detected on July 23, 2020. Urine examination revealed proteinuria, hematuria, and bilirubinuria, but the urine culture was negative. Despite positive results for HSV IgM, the T-cell spot of tuberculosis assay, treponemiapallidum, Epstein-Barr virus, hepatitis virus, human immunodeficiency virus, and blood culture were negative. Computed tomography of the thorax and abdomen revealed few pleural effusions on the left side, enlargement of the spleen, and chronic cholecystitis (Fig. 1). The patient was diagnosed with SLE accompanied by TTP [8, 17]. Her SLE disease score was 21 (pleural 5', thrombocytopenia 4', low C3 and C4 4', lupus anticoagulant 2', and anti-SM antibodies 6') and was rated severe according to the SLE Disease Activity Index (SLEDAI) score.

The patient was initially administered intravenous methylprednisolone (200 mg), immunoglobulin (20 g per day), oral hydroxychloroquine (HCQ, 200 mg twice per day), and other supporting therapies for 3 days before the ADAMTS13 result was confirmed. Her PLT count and Hb level decreased to 3×10^9/L and 56 g/L, respectively. Considering her serious condition and positive ADAMTS13 findings, on July 23, 2020, full plasma exchange was immediately applied daily for 2 days, followed by every other day (Fig. 2A).

Table 1 Laboratory examinations of the patient

Value	Normal range	Results	Value	Normal range	Results
RBC	3.8-5.1 (×10^12/L)	1.9	Anti-ANA		1:3200
HB	115-150 (g/L)	42	Anti-SSA		++
PLT	94-268 (×10^9/L)	6	Anti-SM		++
LDH	120.00-250.00 (U/L)	3363	Anti-cardiolipin		Negative
RBC-1	4.2-4.6 g/L	4.8	Anti-β2GP1		Negative
RBC-2	4.2-4.6 g/L	4.0	LA1	31.0-42.0 (s)	55.5
TBiL	1.7-23.0（μmol/L）	366	LA2	30.0-37.0 (s)	36.0
DBiL	0.00-6.80（μmol/L）	206.7	LA1/LA2	0.80-1.20	1.47
IBiL	0.00-16.20（μmol/L）	159.3	B cells (%)	4.50-18.10 (%)	37.84
D-dimer	0-232 (μg/L)	2837.98	B cells	0.07-0.41 (×10^9/L)	0.269
AST	13.0-35.0 (U/L)	759.8	CD4+ T cells	0.409-1.11 (×10^9/L)	0.179
ALT	7.0-40.0 (U/L)	402.4	CD8+ T cells	0.20-0.867 (×10^9/L)	0.198
ALB	40.0-55.0 (g/L)	37.8	HSV IgM		+
Urea nitrogen	2.6-7.5 (mmol/L)	10.71	T-SPOT		Negative
Crea	41.0-97.0 (μmol/L)	134.2	Hepatitis virus		Negative
eGFR	>90 ml/min/1.73m^2	53.5	EB virus		Negative
ADAMST-13 activity	70-120 (%)	0	TP		Negative
ADAMST-13 inhibitors	0-0.6 (BU)	3.59	HIV		Negative
Schistoyotes	0 (%)	12	***Urianalysis***		
Coomb's		Negative	Protein		++
Complement C3	0.79-1.52 (g/L)	0.48	RBC		+++
Complement C4	0.16-0.38 (g/L)	0.06	Bilirubin		+
ESR	0.0-20 (mm/h)	40	Bilinogen		+
IL-6	0-7 (pg/ml)	38.25	Urine culture		Negative

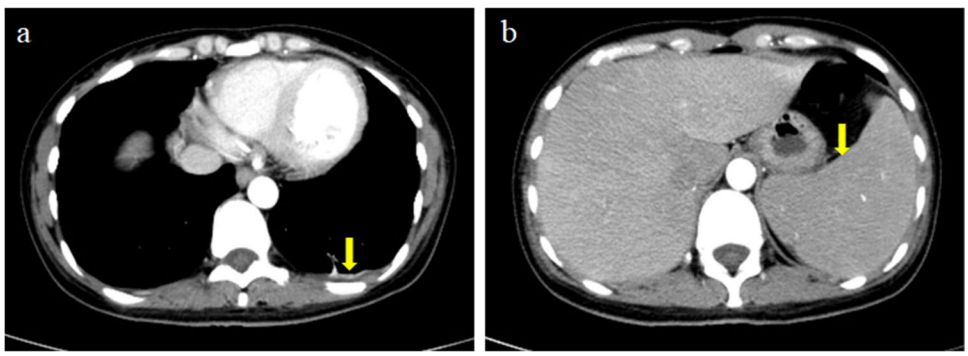

Fig. 1 Computerized tomography scan showing left pleural effusion (**a**), and the enlargement of spleen (**b**)

Concomitantly, the patient was treated with intravenous methylprednisolone (120 mg daily) and oral HCQ (200 mg twice daily). The patient's condition improved after six plasma exchanges. Hematological examination revealed that the PLT count improved from 3×10^9/L to 93×10^9/L (Fig. 2B), along with decreased LDH level, improved liver function (ALT and AST, Fig. 4), and reduced serum bilirubin (TBiL, IBiL, and DBiL, Fig. 3). However, her PLT count rapidly dropped again (27×10^9/L) 5 days after the last plasma exchange therapy (Fig. 2B), despite continuous treatment with methylprednisolone and HCQ.

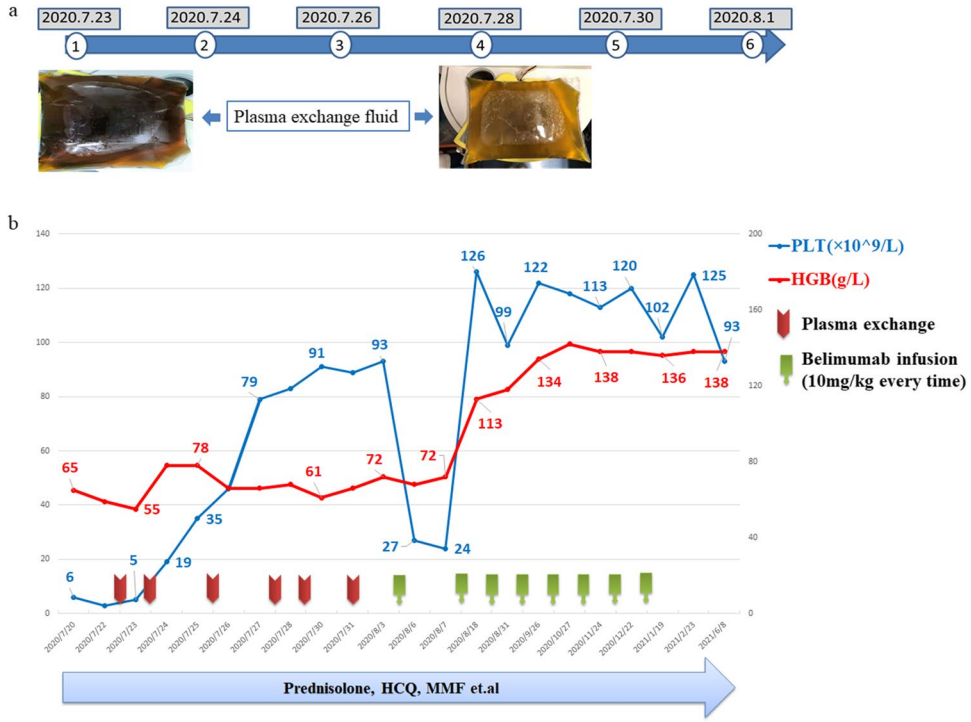

Fig. 2 **a** Scheme of plasma exchange therapy. (**b**) Platelet counts and HGB response to treatment. MMF was added 2 days after the first belimumab administration

Because of her poor economic condition, she planned to give up after TTP relapse and refused to receive continuous PEX or rituximab. To date, caplacizumab has not been authorized for the treatment of TTP in China. Fortunately, supported by a free assistance program (Belle New-Systemic lupus Erythematosus assistance Program, GlaxoSmithKline) for SLE for low-income families, she received eight sessions of belimumab treatment. She was intravenously administered belimumab (10 mg/kg) biweekly for the first three times, followed by 10 mg/kg monthly for the remaining five times. The patient was discharged from our department 2 days after the first belimumab administration and was continually treated with oral prednisolone (60 mg, 1 mg/kg) daily, HCQ (200 mg), and mycophenolate mofetil (MMF, 1 g) twice per day. As shown in Fig. 2B, PLT count and Hb level normalized 12 days after the first treatment. Follow-up examination results over time are shown in Fig. 2B, Fig. 3, and Fig. 4. Additionally, her current therapy was tapered to prednisolone (5 mg/day), HCQ (200 mg/day), and MMF (0.5 g) twice per day. Belimumab treatment was well tolerated without any

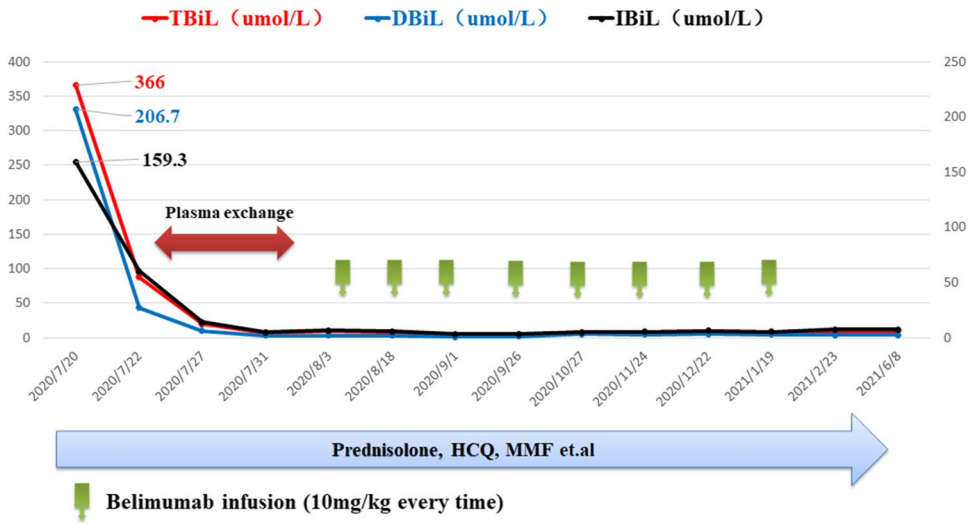

Fig. 3 The changes of TBiL, DbiL and IbiL during the belimumab therapy. MMF was administration 2 days after the first belimumab intravenous injection

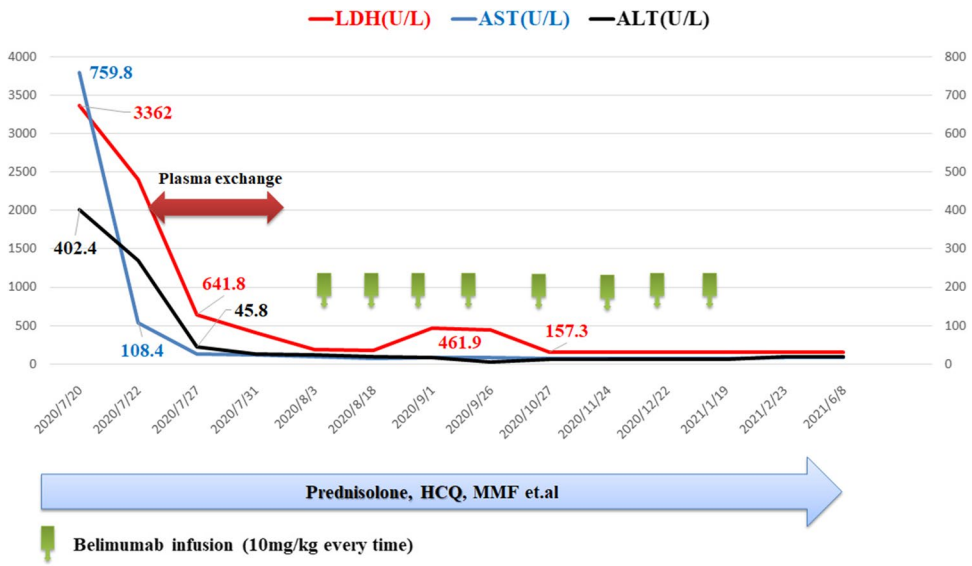

Fig. 4 LDH, AST, and ALT response in relation to the serial treament. MMF was added 2 days after the first belimumab administration

adverse events and SLE or TTP relapse during the 12 months of follow-up.

Search strategy

We searched the PubMed/MEDLINE, Web of Science, and Embase databases using the following keywords: systemic lupus erythematosus, thrombotic thrombocytopenic purpura, and belimumab, including their abbreviations. Only articles available in English were reviewed, and there were no time limitations regarding publication dates. To date, only two cases, published by the 10th European Lupus Meeting as an abstract and in February 2022 as a letter to the editor, have been found. Another meeting abstract was published regarding the successful treatment of refractory TTP with belimumab (Table 2).

Table 2 Reported cases of SLE-TTP or TTP patients treated with belimumab

Case	Author	Sex/ Age	Clinical manifestations	ADAMST13 activity and inhitiors	Peripheral blood smear	Clinical disgnosis	Treatment	Remission length	Compli cations
1	Gerosa. et al [37]	Unkn own	Anemia Thrombocytopenia Renal injury Neurological injury	14% and High positive	Unknown	SLE-TTP	PEX+IVIG+ high does CS+ belimumab	Not available	None
2	Tong. et al [38]	F/31	Anemia Thrombocytopenia Renal injury Neurological injury	5% and unknown	Positive	SLE-TTP	PEX+high does CS+ CyA+ belimumab	6 mo	None
3	Woods. et al [39]	M/14	Anemia Thrombocytopenia Neurological injury	0 and 26 BU	Positive	TTP	PEX+rituximab +high does CS+ CyA+ belimumab	31 mo	None
4	Present	F/28	Anemia Thrombocytopenia Renal injury	0 and 3.5 BU	Positive	SLE-TTP	PEX+IVIG+ high does CS+ belimumab	12 mo	None

M, male; *F*, female; *PEX*, plasma exchange; *IVIG*, intravenous immunoglobulin; *CS*, corticosteroid; *CyA*, cyclosporine A; *mo*, month

Discussion

TTP is a life-threatening syndrome characterized by manifestations of acute microangiopathic hemolytic anemia, thrombocytopenia, and visceral ischemia related to the formation of small blood clots in the microcirculation [2]. In addition, SLE is one of the most common causes of secondary TTP [5]. Herein, we describe the case of a previously healthy 28-year-old woman diagnosed with SLE complicated TTP, who showed a favorable response and sustained remission with belimumab after six rounds of plasma exchange.

SLE-TTP has been reported for several decades in the literature; however, the underlying pathogenic mechanisms remain unclear. Recent studies have revealed that the pathogenesis of SLE-TTP is related to endothelial injury or platelet aggregation caused by vasculopathy [18]. Abnormally large von Willebrand factor (vWF) multimers are hyperactive in platelet binding and aggregation, promoting the formation of intravascular microthrombosis in critical organ systems, ultimately leading to TTP development and progression [19]. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type I motif member 13) is a vWF cleaving metalloproteinase that cleaves vWF multimers into inactive smaller monomers [20]. Decreased activity of ADAMTS13, either hereditary or acquired, is associated with multiple diseases, such as SLE, infections, and neoplasms, whereas extremely reduced activity (less than 10%) is closely related to TTP [20]. Moreover, endothelial damage related to PLT abnormalities, autoantibodies, and dysfunction of fibrinolysis was found in both SLE and TTP, which might partially explain the vasculopathy in SLE-TTP [21].

Recently, autoimmune conditions have been considered to be more important in the pathogenesis of SLE-TTP, as evidenced by the massive presence of various autoantibodies such as anti-platelet, anti-ADAMTS13, and anti-endothelial cell antibodies [5]. Successful treatment of SLE-TTP with immunosuppressive agents (cytotoxics, rituximab, and caplacizumab) also supports the importance of disordered autoimmune conditions in the pathophysiology of SLE-TTP [11, 12, 22]. Consistent with this, the good effectiveness and sustained remission with belimumab in this case further confirmed this autoimmune mechanism. T-regulatory (Treg) cells play a critical role in maintaining immune balance and participate in several autoimmune disorders [23, 24]. It was found that lower Treg cell count in patients with SLE-TTP is closely correlated with its severity, supporting the hypothesis that Treg cells might be an important mediator in this condition [25]. Additionally, a previous study suggested that increased Hb, thrombin, and D-dimer levels may contribute to the development of SLE-TTP [26].

TTP is a rare but lethal complication of SLE [2, 9]. However, it is difficult to diagnose TTP in SLE for several reasons. First, the similarities between clinical symptoms and laboratory examinations in both patients with TTP and SLE, such as MAHA, thrombocytopenia, fever, and neurological dysfunction, cause a delay in correct diagnosis [8]. Second, similar to this case, some autoimmune diseases usually make it difficult to diagnose TTP, especially in patients with SLE with atypical clinical manifestations of TTP [3]. Moreover, distinguishing TTP from other types of thrombotic microangiopathy may be difficult [17]. Finally, the rate of diagnosis of TTP concomitant with SLE was significantly increased from 45.7 to 60%, reported in two recent studies, compared to 12.2%, reported two decades ago, occasionally leading to difficulty and delay in SLE-TTP diagnosis because of their overlapping manifestations [9, 27]. In this case, TTP might have occurred concomitantly with SLE, supported by hemolytic anemia, thrombocytopenia, and increased LDH level; however, its diagnosis and treatment were delayed. Thrombocytopenia, low complement levels, and pleural effusion could be more likely related to TTP. However, differentiating between the two conditions is not straightforward because of the similarities in clinical symptoms and laboratory examinations [8, 9]. Therefore, we suggest that TTP diagnosis should be immediately considered in SLE patients with skin petechiae, hemolytic anemia, thrombocytopenia, and increased LDH level.

In addition to MAHA, thrombocytopenia, elevated LDH level, negative Coombs test, peripheral blood smear with schistocytes, and reduced ADAMTS13 activity; the presence of ADAMTS13 inhibitors are considered to be essential for making a prompt diagnosis of TTP [20, 28]. It has been reported that a peripheral blood smear is a quick and effective test, and the presence of schistocytes strongly supports the diagnosis of TTP [9]. Moreover, repeated blood smears should be performed to increase the positive detection rate of schistocytes and exclude possible negative results [29]. Notably, a positive Coombs test could not completely exclude TTP diagnosis because of the positive Coombs test in a few SLE-TTP patients, possibly caused by autoimmune dysfunction in SLE [27]. ADAMTS13 deficiency, caused by either genetic mutations or acquired immune inhibitors, is considered one of the most important causative factors of TTP [20]. Therefore, ADAMTS13 dysfunction is an essential diagnostic parameter for TTP [28]. Consistent with this finding, ADAMTS13 activity and inhibitors were examined immediately after patient administration in our case. The extremely low ADAMTS13 activity (0) and presence of its inhibitors (3.57 BU) supported the diagnosis of TTP. SLE in patients with MAHA, thrombocytopenia, and elevated LDH level should help diagnose TTP, and the repeated peripheral blood smear and ADAMTS13 activity should be tested to allow the timely diagnosis and treatment of this life-threatening complication.

To date, therapeutic strategies for patients with SLE-TTP include plasma exchange, high-dose corticosteroids, and immunosuppressive medications. Although plasma exchange showed a favorable response for idiopathic TTP with more than 80% remission, this strategy alone is insufficient to control TTP in patients with SLE [6, 27]. High-dose corticosteroids and plasma exchange are the mainstay therapy (first-line therapy) with a 65.7% remission incidence, as described previously [27]. However, TTP secondary to SLE is more severe and lethal than idiopathic TTP, leading to a higher mortality rate [9]. Moreover, a few cases did not respond well and were refractory to this mainstay treatment, which is regarded as the major challenge for SLE-TTP therapy [5]. Therefore, additional cytotoxic medication is required [30]. A previous study revealed that the addition of cytotoxic drugs combined with plasma exchange and high-dose corticosteroids remarkably increased the remission rate to 90.4% compared to strategies without cytotoxic therapy [27].

In addition to cytotoxic drugs, biologicals such as rituximab and caplacizumab have been reported to achieve favorable responses in immune-mediated TTP cases [11, 12, 22]. Additionally, belimumab, a recombinant human IgG1λ monoclonal antibody, could specifically target the Bcell activating factor (BAFF), blocking the interaction of BAFF with its three receptors on B lymphocytes, promoting apoptosis, and preventing the differentiation and survival of B cells [31, 32]. Belimumab can significantly reduce the levels of several types of B cells, including $CD20^{+}CD69^{+}$ activated B cells and $CD20^{+}CD138^{+}$ Ig-producing plasma B cells [33]. Auto-reactive B cells with massive autoantibodies have been shown to be essential mediators of SLE pathogenesis [16]. Autoantibodies against ADAMTS13 cause TTP development and progression [20]. Moreover, increased serum BAFF levels were found in patients with SLE and TTP [14, 34]. Therefore, targeting B cells with belimumab appears to be a novel and logical strategy for SLE-TTP treatment.

Accordingly, belimumab was administered after suspension of plasma exchange in this case. An excellent response was obtained after the first belimumab therapy, and sustained remission was observed in the 12 months of follow-up without SLE or TTP relapse. To date, only two cases of successful treatment of SLE-TTP with belimumab have been reported. A patient with a 14-year history of SLE was diagnosed with TTP supported by anemia, thrombocytopenia, kidney injury, neurological involvement, decreased ADAMTS13 activity (13%), and anti-ADAMTS13 antibody (highly positive). Because of the gastrointestinal side effects of full-dose MMF, belimumab was added, and a favorable response without TTP relapse was observed [35]. Moreover, a previously healthy 31-year-old female, diagnosed with SLE-TTP supported by decreased ADAMTS13 activity (4%) and increased schistocytes, responded well to belimumab [36]. Interestingly, a 14-year-old man diagnosed with refractory TTP without SLE also achieved successful treatment and durable remission with belimumab [37].

Collectively, belimumab sheds light on SLE-TTP treatment, especially in those who might be refractory to first-line (mainstay) therapies. However, comparative studies or randomized controlled trials of belimumab in SLE-TTP may not be possible because of its rarity. Reports regarding the application and outcomes of belimumab in treating SLE-TTP should be encouraged to define the critical role of this biological drug. Furthermore, the optimal dose and timing of belimumab administration for SLE-TTP require further investigation. MMF appeared to be safe for relapsed TTP [38]. However, whether MMF contributes to an excellent response or reduces the risk of relapse requires a longer formal study. Additional studies are needed to establish whether treatment influences long-term outcomes and to explore the combination of belimumab and rituximab in managing SLE-TTP.

Conclusions

In summary, SLE-TTP is extremely rare but life-threatening. Disordered autoimmune conditions play an essential role in the pathogenesis of this disease. SLE with MAHA, thrombocytopenia, and elevated LDH level should immediately indicate TTP diagnosis. Repeated peripheral blood smear and ADAMTS13 activity should be tested to allow the timely diagnosis of this serious and lethal complication. Plasma exchange with high-dose corticosteroids remains the mainstay treatment for SLE-TTP, with biological agents, including belimumab, rituximab, and caplacizumab offering promising therapeutic strategies.

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Author contribution Shen-ju Liang, Quan-you Zheng, and Yi Yang: case reporting, literature screening, manuscript preparation, and editing; Shen-ju Liang, Meng-shan Li, and Ming-ye Lv: patient follow-up and data acquisition; Wen-ting Chen and Yi Yang: conceptualization, review, support, and supervision. All the authors approved the final version of the manuscript.

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Data availability All data analyzed in this study are available from the first or corresponding authors upon reasonable request.

Written informed consent was obtained from the patient for the publication of this report and related clinical images.

Compliance with ethical standard

Disclosures None.

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