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CASE REPORT

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Treatment of thrombotic microangiopathy associated with systemic lupus erythematosus with low-dose rituximab as an induction agent and belimumab as a maintenance agent

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Abstract

Introduction Thrombotic microangiopathy (TMA) is a serious complication that can occur in patients with systemic lupus erythematosus (SLE), and TMA adversely affects prognosis and increases mortality. The treatment of TMA often requires immunosuppressive agents, high-dose corticosteroids and plasma exchange (PEX). Both rituximab (RTX) and belimumab (BEL) target B cells. The combination of RTX and BEL has recently been used for refractory and severe organ involvement in systemic lupus erythematosus. However, the clinical outcome of patients with TMA and SLE treated with sequential therapy between RTX and BEL remains elusive.

Case reports.

We reported 2 patients who were diagnosed with SLE with TMA and were administered a combination treatment of high-dose corticosteroids, immunoglobulin, and PEX at the initial stage. No improvements in microangiopathic anaemia, thrombocytopenia, or renal failure were observed. Low-dose RTX was administered in both patients, and both patients responded well. BEL was utilized to rapidly reduce the reliance on these agents and prevent the relapse of SLE at the maintenance stage. Ultimately, 2 patients fully recovered with an SLE Disease Activity Index score of 0, and prednisolone was stopped without relapse.

Conclusion Sequential treatment with low-dose RTX and BEL could be an encouraging approach for the treatment of TMA in patients with SLE and rapid glucocorticoid reduction.

Keywords Thrombotic microangiopathy, Systemic lupus erythematosus, Rituximab, Belimumab

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the involvement of various organs and tissues due to the binding of self-antibodies and immune complex formation [1]. The pathological manifestations of SLE include the deposition of immune complexes and vasculitis. Clinically, multiple organs are often affected, and the levels of specific antibodies in the serum are elevated. Thrombotic microangiopathy (TMA) syndrome is a potentially life-threatening complication and is defined as an integrated syndrome of

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microangiopathic haemolytic anaemia, thrombocytopenia, and organ injury [2]. SLE is a major underlying cause of secondary TMA. According to reports, the incidence of SLE complicated with TMA ranges from 1 to 4% [3–5], with a mortality rate as high as 33.3% to 62.5% [2–9]. Currently, there is no standardized treatment protocol available for the management of SLE complicated with TMA [10]. We reported two patients with TMA with SLE who showed good efficacy and prognosis with sequential treatment with rituximab (RTX) and belimumab (BEL).

Patient 1: A 12-year-old girl presented with a 7-day history of gradually progressive bilateral lower extremity weakness, a sallow complexion and a 5-day history of fever in December 2020. The laboratory data revealed proteinuria, haematuria, pancytopenia, acute kidney injury, hypoproteinaemia, and decreased C3 and C4 levels. High titres of antinuclear antibody (ANA) and positive anti-double-stranded DNA and anti-Smith antibodies were detected. Lactic dehydrogenase (LDH) was also elevated. Lupus anticoagulant, ACL antibody, and anti-b2GP1 antibody levels and Coombs test results were all negative (Table 1). She was diagnosed with SLE. Her SLE Disease Activity Index (SLEDAI) was 24, indicating high disease activity; therefore, she was initially treated with 3 pulses of 1000 mg (20 mg/kg) intravenous methylprednisolone per day followed by intravenous methylprednisolone 48 mg per day, 20 g/day (total of 3 doses, 1 g/kg) intravenous immunoglobulin infusions and 100 mg oral hydroxychloroquine (HCQ) twice a day (3.4 mg/kg). The platelet concentration increased from 30×10^9/L to 208×10^9/L and then quickly decreased to 42×10^9/L. Her creatinine increased from 124 μmol/L to 208 μmol/L and then decreased to 166 μmol/L, the percentage of schistocytes in the patient's peripheral blood smear was 2.6%, and the level of lactate dehydrogenase (LDH) was 1020 U/L. Due to the patient's severe condition and low platelet count, a renal biopsy was not performed. The patient had no history of diarrhoea, bloody stools, neuropsychiatric symptoms, hypertension,or organ transplantation. Stool routine tests, coagulation function tests, pneumococcal antigen tests and magnetic resonance imaging of the brain were all negative. Based on these findings, refractory SLE and lupus nephritis with TMA were diagnosed. Despite the initial improvement, her anaemia, thrombocytopenia and renal failure recurred. PEX was performed once daily for 3 days, fresh frozen plasma was used as the replacement fluid during the PEX procedure. However, the patient's condition failed to improve. RTX (100 mg) was administered intravenously (1 dose every 2 weeks; a total of 2 doses), along with cyclophosphamide (800 mg/m^2, a total of 8 doses). After 2 doses of RTX, PLT and serum creatinine levels returned to normal. Despite follow-up laboratory examinations, which showed that her PLT and serum creatinine levels remained normalized and that her Hb gradually increased to normal levels, the patient still had proteinuria. Therefore, intravenous BEL (10 mg/kg) and oral mycophenolate mofetil (MMF, 1 g/day) were prescribed. She was maintained on BEL, MMF (1 g per day) and HCQ (0.2 g per day), and her prednisolone treatment was stopped in April 2023, with an SLEDAI score of 0. She developed upper respiratory syndrome twice during the follow-up, and these conditions were cured by symptomatic treatment. At the last visit, the patient was maintained with BEL, HCQ and MMF and had no relapse (Table 2).

Patient 2: A 12-year-old girl with a 1-week history of fever, a 5-day history of polyarthritis and a 4-day history of haematuria and oedema was admitted to our centre in December 2021. Routine blood tests revealed thrombocytopaenia, anaemia and an elevated reticulocyte count. Urine tests revealed albuminuria and haematuria, with an elevated 24-h urine protein level (24hUPro). Peripheral blood and bone marrow smears showed numerous schistocytes. ANA and anti-double-stranded DNA were positive, and decreased C3 and C4 levels were observed. Lupus anticoagulant, ACL antibodies, anti-b2GP1 antibodies and Coombs tests were all negative (Table 1). The patient had no history of diarrhoea, bloody stools, neuropsychiatric symptoms, or organ transplantation. Stool routine tests, coagulation function tests, pneumococcal antigen tests and magnetic resonance imaging of the brain were all normal. She was treated with intravenous methylprednisolone 48 mg per day. Oral HCQ (100 mg) was prescribed twice per day. The PLT initially improved from 80×10^9/L to 122×10^9/L. Renal biopsy was performed to evaluate her renal dysfunction. We detected IgA(++), IgG(+++), C3(+++), Fib(+), IgM(+), and C1q(+++) using immunofluorescence. Under light microscopy, a total of 13 glomeruli were observed, and the findings were as follows: moderate-severe diffuse proliferation of the mesangial matrix, diffuse endocapillary hypercellularity composed of swollen endothelial cells, leukocytes, irregularly thickened glomerular capillary wall segments, double track changes, capillary lumen stenosis, and scattered thrombosis. ADAMTS13 inhibitor and anti-factor H autoantibodies were negative. The patient also underwent whole-exon gene sequencing, which revealed that the proband had heterozygous mutations in DNASE1 (c.653 T > A, p.I218N, Chr16:3,707,291). The DNASE1 gene is associated with susceptibility to systemic lupus erythematosus (SLE), and it is inherited in an autosomal dominant manner, with heterozygous variations potentially causing the disease.We did not find any gene markers related

Table 1 Clinical and laboratory baseline data of the 2 patients

Item	Patient 1	Patient 2	Reference range
Race/Ethnicity	Yellow race/The Han nationality	Yellow race/The Han nationality	-
Age/Gender	12/F	12/F	-
Weight (kg)	59	62	
Body surface are (m^2)	1.63	1.69	
Fever	-	-	-
Rash	-	-	-
Oral ulcers	-	-	-
Nonscarring alopecia	-	+	-
Arthritis	-	+	-
Serositis	+	+	-
Neurologic	-	-	-
ESR (mm/h)	2	22	0–20
CRP (mg/L)	0.9	0.5	0–8
White blood cells ($\times 10^9$/L)	3.44	3.94	4–10
Haemoglobin (g/L)	62	80	115–150
Platelets ($\times 10^9$/L)	30	108	100–300
Reticulocyte proportion (%)	8.4	3.5	0.5–2.2
TBil (mmol/L)	12.15	5.06	3.5–23.5
DBil (mmol/L)	1.65	0.83	0.5–6.5
ALT (U/L)	19	43	7–40
AST (U/L)	25	28	13–35
Albumin (g/L)	29	23.2	40–55
Serum creatinine (umol/L)	124	97	40–105
Lactate dehydrogenase (U/L)	633.1	516	120–250
24hUPro (g)	4.68	9.8	< 0.15
Urine erythrocytes (/HPF)	23.8	1769.3	0–3
D-Dimer (mg/L)	1.5	2.07	0–0.5
PT (seconds)	11.4	7.12	9.2–12.5
APTT (seconds)	23.9	29.8	25.1–36.5
Fibrinogen (g/L)	1.63	2.61	2.0–4.0
ANA	1:1000	1:1000	< 1:100
Anti-dsDNA antibody (IU/ml)	204.3	302.89	0–100
Anti-Smith antibody (IU/ml)	40	7.7	0–20
Anti-SSA antibody (IU/ml)	10.3	5.54	0–20
Anti-SSB antibody (IU/ml)	8.45	5.1	0–20
LA	0.95	1.06	0.92–1.20
ACL antibodies (CU)	1.7	2,7	0–20
Anti-b2GPI antibodies IgG (CU)	13	8.9	0–20
C3 (g/L)	0.2	0.2	0.79–1.17
C4 (g/L)	0.02	0.06	0.1–0.4
Blood smear	Schistocytes and reduced platelets	Schistocytes and reduced platelets	-
Bone marrow biopsy	Schistocytes and reduced platelets	Schistocytes and reduced platelets	-

ESR erythrocyte sedimentation rate; *CRP* C-reactive protein; *TBil* total bilirubin; *DBil* direct bilirubin; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *24hUPro* 24-h urine protein; *PT* prothrombin time; *APTT* activated partial thromboplastin time; *ANA* anti-nuclear antibody; *Anti-SSA* anti-Sjögren's syndrome A; *Anti-SSB* anti-Sjögren's syndrome B; *LA* lupus anticoagulant; *ACL* anticardiolipin; *Anti-b2GP1* anti-β2-glycoprotoein 1; *C3* complement 3; *C4* complement 4; *IgG* immunoglobin G

Table 2 The result of laboratory tests of patient 1 in different time points

Item Time points	Hemoglobin (g/L)	Platelets (×109 /L)	Serum creatinine (umol/L)	24hUPro (g)	Lactate dehydrogenase (U/L)	C3 (g/L)	C4 (g/L)	Anti-dsDNA antibody (IU/ml)	Treatment
Baseline	62	30	124	4.68	936	0.2	0.02	204.3	
Day 10 of treatment	99	208	-	-	633.1	0.44	0.07	65.54	GC high-dose corticosteroids HCQ
Day 20 of treantment	90	63	184	6.45	467.9	-	-	-	GC high-dose corticosteroids HCQ
Day30 of treatment	71	67	161		549.5	1.02	0.14	101.8	GC high-dose corticosteroids IVIG HCQ
Day after 3 PEX	78	68	138.8	7.24	680.1				GC HCQ PEX
Day of 1 week after first dose of RTX	108	131	91	5.59	594.9	1.03	0.14	20.21	GC HCQ RTX
Day of 1 week after second dose of RTX	106	177	85.7	-	527.8,	1.18	0.18	< 10	GC HCQ CTX RTX
Day before the first dose of BEL	108	215	70.9	1.01	-	1.29	0.25	< 10	GC MMF HCQ
1 year follow-up	126	227	75.4	0.81	394.3	1.25	0.28	< 10	GC MMF HCQ BLE
2 year follow-up	132	224	69.7	0.15	-	1.11	0.29	< 10	GC MMF HCQ BLE
3 year follow-up	136	221	68.6	0.14	-	1.15	0.35	< 10	MMF HCQ BLE

24hUPro 24-h urine protein; *C3* complement 3; *C4* complement 4; *PEX* plasma exchange, *RTX* rituximab; *BEL* belimumab; *GC* glucocorticoid; *HCQ* hydroxychloroquine; *IVIG* intravenous immunoglobulin; *CTX* cyclophosphamide; *MMF* mycophenolate mofetil;—not performed

to TMA recurrence. SLE with TMA was diagnosed, and haematological recovery was observed after she was treated with 2 pulses of 500 mg methylprednisolone (10 mg/kg) per day for 3 days followed by 60 mg/day oral prednisolone (1 mg/kg). Despite the initial improvement, thrombocytopenia, anaemia, and increased LDH and serum creatinine levels recurred. Treatment with high-dose corticosteroids was interrupted because of CMV infection. Intravenous immunoglobulin infusions of 20 g/day (total of 3 doses, 1 g/kg) along with PEX were performed once daily for 5 days and then every two days 5 times. However, the patient's condition failed to improve. A total of 100 mg RTX per 2 weeks with 800 mg cyclophosphamide (500 mg/m^2) was administered to this patient when the CMV infection was cured. PLT and serum creatinine levels returned to normal after 3 doses of RTX and 1 dose of cyclophosphamide. Treatment with cyclophosphamide was interrupted because of a gastrointestinal reaction. Intravenous BEL (10 mg/kg) and oral MMF (1 g/day) were administered because of persistent gross haematuria and moderate levels of proteinuria. She developed upper respiratory syndrome once during the follow-up, which was resolved by symptomatic treatment. At the last visit, the patient had been maintained with BEL, HCQ and MMF (Table 3).

Discussion

TMA is less common but is a potentially lethal disease affecting small vessels. Classically, TMA presents with a triad of haemolytic anaemia, thrombocytopaenia, and ischaemic end-organ failure (most commonly, the kidneys). More commonly, TMA manifests as a secondary complication of other systemic diseases, often autoimmune diseases, including SLE [2, 11]. The differential diagnosis of TMA in patients with SLE includes antiphospholipid antibody syndrome, thrombocytopenic purpura, complement-mediated and infection-associated haemolytic uraemic syndrome, drug-mediated TMA, and malignant hypertension [12]. Previous studies have reported that TMA is an independent risk factor for poor renal outcomes in patients with lupus nephritis, and patients with this condition may have an inadequate response to conventional therapy compared to those with lupus nephritis but without TMA, leading to a higher mortality rate [10, 13, 14]. Clinically, it can be challenging to differentiate TMA from fever, thrombocytopenia, and renal function

Table 3 Laboratory test results for Patient 2 at different time points

Item Time point	Haemoglobin (g/L)	Platelets (×109/L)	Serum creatinine (umol/L)	24hUPro (g)	Lactate dehydrogenase (U/L)	C3 (g/L)	C4 (g/L)	Anti-dsDNA antibody(IU/ml)	Treatment
Baseline	80	108	97	9.8	526	0.2	0.06	302.89	
Day 10 of treatment	79	122	79.6	-	414.7	-	-	-	GC high-dose corticosteroids HCQ
Day 20 of treatment	80	162	114.2	-	679.8	-	-	-	GC high-dose corticosteroids HCQ
Day 30 of treatment	74	39	98.5	-	-	-	-	-	GC high-dose corticosteroids IVIG HCQ
Day after 5 PEX	64	76	82.6	-	416.2	-	-	-	GC PEX HCQ
Day of 1 week after first dose of RTX	79	87	81.4	-	344.8	0.61	0.13	-	GC PEX RTX HCQ
Day of 1 week after second dose of RTX	83	162	79.9	-	480.3	0.85	0.18	38.5	GC HCQ CTX RTX
Day of 1 week after third dose of RTX	100	129	63.4	2.87	-	1.15	0.25	-	GC MMF HCQ CTX RTX
Day before the first dose of BLM	123	235	53.3	1.18	-	1,18	0.24	< 10	GC MMF HCQ
1 year follow-up	126	319	61.8	0.11	-	1.23	0.29	11.48	GC MMF HCQ BLE
2 year follow-up	125	324	56.3	0.08	-	1.17	0.3	< 10	MMF HCQ BLE

24hUPro 24-h urine protein; *C3* complement 3; *C4* complement 4; *PEX* plasma exchange, *RTX* rituximab; *BEL* belimumab; *GC* glucocorticoid; *HCQ* hydroxychloroquine; *IVIG* intravenous immunoglobulin; *CTX* cyclophosphamide; *MMF* mycophenolate mofetil;—not performed

impairment caused by lupus activity itself, which can complicate diagnosis and treatment decisions. Kidney biopsy can confirm renal microangiopathy [15]. However, when a kidney biopsy cannot be performed due to special circumstances, TMA can be indicated by specific laboratory indicators, such as a decrease in haemoglobin levels, a decreased platelet count, elevated LDH levels, the presence of fragmented red blood cells in the peripheral blood, and a negative Coombs test [16]. The laboratory examination of our 2 patients revealed a decrease in haemoglobin levels; a decrease in platelet count; an increase in LDH levels; the presence of fragmented red blood cells in the peripheral blood; and decreases in the Coombs test, ACL antibodies, and anti-b2GP1 antibodies; and decreased C3 and C4 levels. ADAMTS13 inhibitor and anti-factor H autoantibodies were negative in Patient 2, and a renal biopsy was also performed in Patient 2, revealing histological findings of wire-loop lesions with double contours and the formation of microthrombi in glomerular capillaries. However, in Patient 1, kidney biopsy could not be performed initially due to the severity of the disease and the progressive decrease in PLT levels. Special medication, infection, organ transplantation and other medical history were excluded for the two patients presented in this study.

Treatment for SLE with TMA includes high-dose corticosteroids, PEX, intravenous immunoglobulin infusions and immunosuppression therapy.

Renal replacement therapy is needed for patients with progressive deterioration of kidney function or severe renal insufficiency [17, 18]. Immunosuppression therapy for SLE patients with TMA includes corticosteroids, cyclophosphamide, and MMF [19]. The present study reported 2 patients who received high-dose corticosteroids, intravenous immunoglobulin infusions, and PEX at the initial stage. Both patients had recurrent thrombocytopenia, anaemia and increased serum creatinine levels. RTX is a human-murine chimeric anti-CD20 antibody that cankill target cells through antibody-dependent cytotoxicity, complement-dependent cytotoxicity or direct effects, inhibit excessive cytokine release, and reduce endothelial cell damage. The European League Against Rheumatism stated that RTX should be considered for treating organ-threatening, refractory lupus [20, 21], and no guidelines for the treatment of TMA in patients with LN have been established. It has been reported that RTX is a standard treatment for relapsed

and refractory TMA based on the excellent outcomes observed in patients who respond poorly to PEX and high-dose corticosteroids [22]. The optimal dose and schedule of RTX for TMA are unclear, but the most common approach is 375 mg/m^2 RTX once or twice per week for 4 to 8 weeks. The satisfactory efficacy of reduced-dose regimens of 100 mg weekly for 4 weeks has been demonstrated in a previous study [22]. In our report, Patient 1 was prescribed low-dose RTX (100 mg weekly for 2 weeks), and Patient 2 was prescribed low-dose RTX (100 mg weekly for 3 weeks). We chose this dose in consideration of the high cost and infection risk of RTX. Both patients responded well to low-dose RTX.

BEL is a recombinant human IgG-1λ monoclonal antibody that inhibits the binding of B-cell activating factor (BAFF) to its receptor. Some studies have revealed that B-cell depletion with RTX leads BAFF overexpression [23]. An increase in BAFF levels after RTX may contribute to severe flares and could limit the effectiveness of RTX in some patients with SLE [21]. This finding provides a basis for the use of RTX sequentially with BEL therapy in SLE patients. The phase II SynBioSe study showed significant clinical and immunological improvements from baseline in patients with severe refractory SLE who received RTX followed by BEL and that patients maintained a response over two years [24]. The 2019 update of the EULAR recommendations for the management of SLE suggested that BEL is beneficial for tapering daily doses of glucocorticoids to acceptable levels (a maximum of 7.5 mg/d) [20]. S Hanai et al. reported the case of a young girl who was diagnosed with TMA with refractory LN and who received RTX combined with BEL, which gradually improved the patient's LN and TMA. Prednisone was tapered to 5 mg/day, and the patient experienced no recurrence for approximately 3 years [10]. Jun Liu et al. reported that patients who were all diagnosed with thrombotic thrombocytopenia purpura with SLE received sequential treatment with RTX and BEL. All 4 patients recovered with an SLE Disease Activity Index score of 0 and reached the prednisolone dose goal of < 7.5 mg/d without relapse [25]. We reported sequential therapy of BEL followed by RTX in patients with SLE with TMA who had good follow-up outcomes and no glucocorticoid doses.

The most common adverse reaction to RTX is an infusion reaction, and the most common adverse reaction to BEL is infection. In a randomized controlled trial (NCT02260934), researchers showed that a combination of RTX and cyclophosphamide followed by BEL was safe [26]. Another phase 2, randomized, double-blind trial (ISRCTN: 47,873,003) showed that BEL after RTX did not increase the incidence of serious adverse events in SLE patients [27]. In this report, the 2 patients both experienced upper respiratory syndrome during follow-up, and no infusion reactions or other serious adverse reactions occurred.

Eculizumab is a fully humanized IgG2/IgG4 monoclonal antibody directed at C5 that prevents the formation of the terminal complement complex. The alternative complement system can be pathogenically activated in SLE by the increased presence of immune complexes, leading to overactivation of the terminal complement complex (C5b-9) and tissue damage [28, 29]. Wright RD et al. systematically reviewed the efficacy of eculizumab in 30 SLE patients with TMA in 14 clinical studies and reported that 93.3% (28/30) of these patients responded well to treatment. Eculizumab is directly recommended for complement-mediated TMA patients who have a poor response to plasma exchange and immunosuppression therapy [30]. Complex (C5b-9) tests were not performed for these two patients because of limitations. Eculizumab entered the Chinese market in November 2022; therefore, ecaluzimab was not administered to our patients.

Conclusion

In conclusion, early low-dose rituximab was effective for refractory SLE patients with TMA. RTX kills target cells through antibody-dependent cytotoxicity, complement-dependent cytotoxicity or direct effects, inhibits excessive cytokine release, and reduces endothelial cell damage. Patients who respond poorly to PEX and high-dose corticosteroids respond well to low-dose RTX. B-cell depletion with RTX leads to BAFF overexpression, and an increase in BAFF levels after RTX may contribute to severe flares and could limit the effectiveness of RTX in some patients with SLE. BEL can inhibit the binding of BAFF to its receptor. BEL treatment could significantly reduce the dose of glucocorticoids needed in patients with SLE with TMA. Sequential treatment with low-dose RTX and BEL could be an encouraging choice for preventing the relapse of SLE patients with TMA and rapid glucocorticoid reduction.

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Authors' contributions

ZY and SL wrote the manuscript and contributed to patient management. ZZ, QL, LYu contributed to patient management. SS and LYu coordinated and supervised the data collection and critically reviewed the manuscript for important intellectual content. All the authors read and approved the final version of the manuscript.

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Data availability
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restriction.

Declarations

Ethics approval and consent to participate
This is not applicable, as this study is a case report.

Consent for publication
Written informed consent for publication was obtained from the patients' caregivers.

Competing interests
The authors declare no competing interests.

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