ORIGINAL ARTICLE

Difference in thrombotic microangiopathy between concurrently and previously diagnosed systemic lupus erythematosus

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Abstract

Background: Thrombotic microangiopathy (TMA) syndromes are potentially life-threatening complications and are defined as integrated syndromes of microangiopathic hemolytic anemia, thrombocytopenia, and organ injury. Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect various organs, including the hematopoietic system. SLE can complicate with TMA and can be categorized into two distinct groups by chronological association: TMA occurring as the initial presentation and leading to a diagnosis of SLE concurrently (TMA-cSLE) or TMA developing in patients previously diagnosed as having SLE (TMA-pSLE). We examined the differences in clinical characteristics, treatment responses, and clinical outcomes between these groups.

Methods: We reviewed data of patients diagnosed as having TMA and SLE at Taipei Veterans General Hospital between 2002 and 2013. We included 29 patients: 8 and 21 in TMA-cSLE and TMA-pSLE groups, respectively. All underwent plasma exchange. Patients' demographic and clinical characteristics, disease activity, and treatment modality were summarized.

Results: Overall survival (OS) from SLE or TMA diagnosis was poor for the TMA-cSLE group. Median OS from SLE diagnosis was 2.9 months in the TMA-cSLE group and 103.5 months in the TMA-pSLE group ($p < 0.001$). Median OS from TMA diagnosis was 2.9 months in the TMA-cSLE group and 10.7 months in the TMA-pSLE group ($p = 0.58$). Time to TMA remission after treatment appeared longer in the TMA-cSLE group (38.00 vs 10.76 days). Multivariate Cox analysis revealed TMA-cSLE and anti-RNP positivity were independent risk factors for mortality in SLE patients with TMA.

Conclusion: The occurrence of TMA with SLE is rare, and its vigorous course results in high mortality and morbidity rates. In patients without a history of autoimmune disease, early suspicion of TMA and working-up for SLE under this condition are vital. Early recognition of TMA-cSLE and prompt plasma exchange with upfront immunosuppressive therapies for TMA-cSLE patients or anti-RNP-positive patients may improve their prognosis.

Keywords: Lupus erythematosus, systemic; Thrombotic microangiopathies; Plasma exchange

1. INTRODUCTION

Thrombotic microangiopathy (TMA) syndromes, defined as integrated syndromes of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia associated with platelet aggregation in the microcirculation, are potentially life-threatening complications responsible for ischemic manifestations, including organ injury and vascular damage.[1,2] The benchmark criterion for TMA diagnosis is tissue-biopsy-derived pathological proof of thrombosis in the arterioles and capillaries. However, tissue biopsy entails risk, particularly in TMA with thrombocytopenia. Schistocytes are predominant in peripheral blood smears; such predominance can thus be an essential rule for TMA diagnosis. Determining the level of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity is also essential in differentiating thrombotic thrombocytopenic purpura (TTP) from non-TTP.

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting every organ. Its clinical manifestations vary. The pathogenesis of SLE is multifactorial and includes genetic susceptibility, environmental effects, and disturbances in both innate and adaptive immunity.[3] SLE can mimic other autoimmune syndromes through various immune mechanisms, resulting in different presentations of SLE-associated symptoms.[4,5] Constitutional symptoms typically involve the skin and musculoskeletal systems. However, some patients may predominantly exhibit hematologic, renal, or central nervous system manifestations.[6] TMA can be a complication of a previously diagnosed SLE and, in rare cases, may occur as an initial presentation leading to the diagnosis of SLE.[7] The chronological association between TMA and SLE is recognized but has rarely been described in histological reports. TMA was observed in 0.5% to 10% of patients with SLE, with such patients presenting poorer outcomes than did other patients.[8–10] Considering the lack of

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comparative data on the presentation and outcome of therapy between TMA concurrently leading to SLE diagnosis (TMA-cSLE) and TMA in previously diagnosed SLE (TMA-pSLE), we conducted our study with the objective of identifying differences in clinical characteristics, therapeutic responses, and clinical outcomes between these groups. By comparing the therapeutic responses of these patients, we expected to provide information on treatment responses.

2. METHODS

2.1. Patients

We retrospectively reviewed the data of patients diagnosed as having TMA and SLE at Taipei Veterans General Hospital between January 2002 and December 2013. All patients met the 1997 American College of Rheumatology revised criteria for SLE or the SLICC classification criteria if diagnosed after August 2012. TMA diagnosis was based on the presentation of MAHA and thrombocytopenia, demonstration of a negative Coombs' test at presentation, and presentation of organ damage.[11] Peripheral blood smears were reviewed by an expert hematologist at the hospital. TMA-cSLE was defined as TMA presenting at the initial diagnosis of SLE; accordingly, patients diagnosed as having SLE and TMA within a time frame of <4 weeks were assigned to the TMA-cSLE group. TMA-pSLE was defined as TMA occurring in patients previously diagnosed as having SLE, and the diagnoses were at least 4 weeks apart. To safeguard against the inclusion of patients with preexisting SLE in the TMA-cSLE group, we reviewed all medical records carefully, including detailed medical histories. We uncovered no suspected histories or clinical presentations possibly related to SLE or other autoimmune diseases in the TMA-cSLE group. Patients with TMA clinically related to a drug, hypertension crisis, infection, or cancers were excluded. Demographic characteristics, including age, sex, SLE disease activities, various clinical and immunological features of SLE, therapeutic strategies, and complications, were collected from the medical records and reviewed. Our institute measured the SLE disease activities of all patients using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).[12] SLE autoantibodies were also assessed when available, including antinuclear antibodies (ANA), anti-SSA/SSB, anti-dsDNA antibodies, anti-Sm antibodies, anti-RNP antibodies, and antiphospholipid antibodies (including anticardiolipin antibodies, anti-b2 glycoprotein-1 antibodies, and lupus anticoagulant). Hematology profiles, including the white blood cell count, hemoglobin levels, and platelet count, were evaluated. Serum complement levels (C3 and C4), albumin levels, and proteinuria severity were also assessed for univariate and multivariate analyses of prognostic factors. The expert hematologist verified evidence of MAHA and thrombocytopenia by reviewing patients' peripheral blood smears.

We compared the TMA-cSLE and TMA-pSLE groups in terms of the collected data. All patients were followed up until death or the last follow-up. The study was approved by Taipei Veterans General Hospital's Institutional Review Board.

2.2. TMA treatment

All patients received plasma exchange (PEX) therapy when TMA was confirmed. Some patients received immunosuppressive agents such as corticosteroid, cyclophosphamide, mycophenolate mofetil, azathioprine, rituximab, or intravenous immunoglobulin (IVIG). The dosage of corticosteroid was tailored to each patient's SLE disease activity or presence of TMA features. Empiric antibiotics were used in accordance with the clinical manifestations and pathogen culture reports if an infection episode was highly suspected or diagnosed.

2.3. Response evaluation

Therapeutic responses were identified as complete remission (CR), partial remission, or treatment failure. The definitions of CR and refractory TMA followed the British Society of Hematology guidelines.[13] CR was defined as a normal neurological status, platelet count, and lactate dehydrogenase (LDH) level along with a rising hemoglobin level. We defined the time to TMA remission as the period between the plasmapheresis initiation date and CR.[13] CR in terms of hematological responses was defined as a return of serum platelet levels to >150 000/μL and hemoglobin levels to the normal range (men: 14-18 g/dL; women: 12-16 g/dL). Refractory TMA was defined as the progression of clinical symptoms or persistent thrombocytopenia despite the administration of PEX therapy.

2.4. Study endpoints and statistical analysis

Descriptive statistics were used to summarize patients' demographic and clinical characteristics, disease activity, and treatment modality. Two survival periods were calculated: one was calculated from the date of initial SLE diagnosis to the date of death or last follow-up visit and the other was calculated from the date of TMA diagnosis to the date of death or last follow-up visit. Quantitative results are expressed as means with standard deviations and as percentages. Survival time was analyzed using Kaplan-Meier analysis. Prognostic factors were analyzed using Cox proportional hazard models compared with negative controls. Factors with statistical significance ($p < 0.1$) in the univariate analysis were included in the multivariate analysis. A p value of <0.05 was considered statistically significant. The results are expressed as hazard ratios (HR) and their corresponding 95% CIs. We used SPSS (version 22) for data analysis.

3. RESULTS

3.1. Patient characteristics

We identified an inception cohort of 29 patients with TMA and SLE; of these patients, 8 were assigned to the TMA-cSLE group and 21 were assigned to the TMA-pSLE group (Table 1). All patients met the diagnostic criteria for TMA and received PEX therapy. The two groups did not differ significantly in terms of demographic and laboratory characteristics, including hemograms; serum complement levels (C3 and C4); proteinuria severity; ANA levels; anti-dsDNA levels; SLEDAI score; and anti-Sm, anti-SSA/Ro, anti-SSB/La, anti-RNP, anticardiolipin IgG, anticardiolipin IgM, and antiphospholipid Ab-IgG positivity (Table 1). However, the median age at SLE diagnosis in the TMA-cSLE group was 41 years, whereas that in the TMA-pSLE group was 24 years ($p = 0.027$). No patient in the TMA-cSLE group had a history of antiphospholipid syndrome (APS), but 28.57% (6/21) of patients in the TMA-pSLE group were diagnosed as having APS ($p = 0.129$). Additionally, for the TMA-cSLE and TMA-pSLE groups, we noted significant trends in the positive rate of lupus anticoagulant (37.5% vs 76.2%; $p = 0.054$) and in median serum albumin levels (3.25 vs 2.80 mg; $p = 0.053$). The positive rate of anti-RNP was 62.5% (5/8) in the TMA-cSLE group and 33.3% (7/21) in the TMA-pSLE group ($p = 0.161$; Table 4). In addition, the mortality rates for positive anti-RNP cases were similar between the groups: 80.0% (4/5) in the TMA-cSLE group and 85.7% (6/7) in the TMA-pSLE group. The presence of anti-RNP antibodies tended to indicate a lower remission rate in the TMA-cSLE group (3/5 in anti-RNP-positive patients vs 2/3 in anti-RNP-negative patients, $p = 0.85$), TMA-pSLE group (3/7 in anti-RNP-positive patients vs 12/14 in anti-RNP-negative patients, $p = 0.04$), and entire population (6/12 in anti-RNP-positive patients vs 14/17 in anti-RNP-negative patients, $p = 0.064$). We also observed a longer median

Table 1

Demographic and laboratory characteristics of the study patients (n = 29)

Characteristics	TMA with cSLE (n = 8)	TMA with pSLE (n = 21)	*p*
Age (median), y	41	24	0.027
Gender (male/female)	1/7	4/17	0.682
WBC (median), /mm^3	7185	6320	0.403
Hemoglobin (median), g/dL	7.75	7.5	0.502
Platelet (median), /mm^3	59000	56000	0.660
Albumin (median), g/dL	3.25	2.80	0.089
C3 (median), mg/dL	47.9	52.5	0.976
C4 (median), mg/dL	11.80	10.6012.24±1.85	0.956
Proteinuria (median), g/24 h	2.79	1.81	0.329
SLEDAI (median, scores)	15	14	0.920
ANA (median)	1:240	1:640	0.413
Anti-dsDNA (median), WHO units/mL	125.5	174	0.496
Lupus nephritis (positive/all)	3/8	16/21	0.054
Lupus anticoagulant (positive/all)	1/8	3/21	0.903
Anti-Sm (positive/all)	1/8	3/21	0.903
Anti-SSA/Ro (positive/all)	5/8	6/21	0.098
Anti-SSB/La (positive/all)	1/8	1/21	0.470
Anti-RNP (positive/all)	5/8	7/21	0.161
Anticardiolipin IgG (positive/all)	0/8	6/21	0.095
Anticardiolipin IgM (positive/all)	0/8	6/21	0.095
Antiphospholipid Ab-IgG (positive/all)	0/8	1/21	0.537
History of APS (positive/all)	0/8	6/21	0.095
Hematological remission (positive/all)	5/8	15/21	0.648
Time of TMA remission (median), d	19.0	8.0	0.071

cSLE = concurrent systemic lupus erythematosus; pSLE = prior systemic lupus erythematosus; TMA = thrombotic microangiopathy; WBC = white blood cell; C = complement; SLEDAI = SLE Disease Activity Index; RNP = ribonucleoprotein; ANA = antinuclear antibody; dsDNA = double-stranded DNA; WHO = World Health Organization. APS = antiphospholipid syndrome.

time to hematological remission of TMA in anti-RNP-positive patients compared with anti-RNP-negative patients (7 ± 0.9 vs 19 ± 13.8 days; $p = 0.037$).

3.2. Clinical outcome

The median overall survival (OS) time from the date of SLE diagnosis to the date of death or last follow-up visit was 2.9 months in the TMA-cSLE group (95% CI: 1.79-4.01) and 103.5 months in the TMA-pSLE group (95% CI: 63.53-143.41; Fig. 1; log-rank $p < 0.001$). Moreover, the median survival time from the date of TMA diagnosis to the date of death or last follow-up visit was 2.9 months in the TMA-cSLE group (95% CI: 1.79-4.01) and 10.7 months in the TMA-pSLE group (95% CI: 0.00-37.3; Fig. 2; log-rank $p = 0.58$).

3.3. Prognostic factor assessment

As presented in Table 2, the prognostic factors for mortality, as identified through multivariate analysis, for all patients were TMA-cSLE (HR = 17.05; 95% CI: 2.31-125.83; $p = 0.005$) and positive anti-RNP (HR = 3.49; 95% CI: 1.22-9.97; $p = 0.020$). Furthermore, patients who did not achieve remission (HR = 5.9; 95% CI: 1.64-21.19; $p = 0.006$) also tended to have inferior prognoses compared with other patients. Our data did not demonstrate a significant relationship of age, gender, lupus nephritis, ANA titer, positive rate autoantibodies (including dsDNA, anti-Sm, anti-SSA, anti-SSB, antiphospholipid antibodies, and lupus anticoagulants), C3/C4 level, hemograms, proteinuria presence, or SLEDAI score with the survival of patients with SLE and TMA (Table 3).

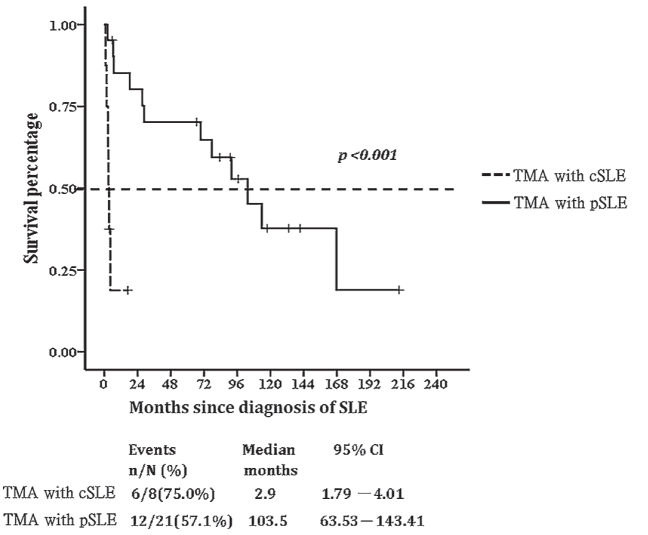

Fig. 1 Survival time after the diagnosis of systemic lupus erythematosus (SLE). Compared with that in the thrombotic microangiopathy (TMA)-cSLE group, the median overall survival time from the diagnosis of SLE was longer in the TMA-pSLE group (2.9 vs 103.5 months; $p < 0.001$). cSLE = concurrent systemic lupus erythematosus; pSLE = prior systemic lupus erythematosus.

4. DISCUSSION

Although TMA syndromes are remarkably diverse, they are united by common, defining clinical and pathological features. Such syndromes often present suddenly and result in severe illness in patients. Their clinical features include MAHA, thrombocytopenia, and organ injury. TMA is commonly suspected upon observation of MAHA and thrombocytopenia in an appropriate setting, and definite pathological proof may not be mandatory. In our study, all patients presented the three clinical features of TMA. Supplementary Table 1 (http://links.lww.com/JCMA/A52)

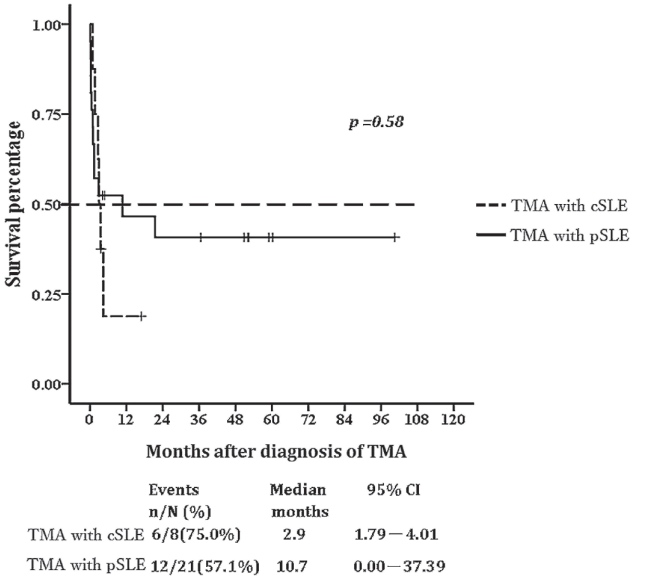

Fig. 2 Survival time after diagnosis of thrombotic microangiopathy (TMA). Compared with that in the TMA-cSLE group, the median overall survival time from the diagnosis of TMA was longer in the TMA-pSLE group (2.9 vs 10.7 months; $p = 0.58$). SLE = systemic lupus erythematosus; cSLE = concurrent systemic lupus erythematosus; pSLE = prior systemic lupus erythematosus.

Table 2

Prognostic factors for the survival of SLE patients with TMA (n = 29)

	Univariate Cox regression			Multivariate Cox regression		
Factors	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Mean age, y						
≤31 (n = 22)	1	...	...	1	...	...
>31 (n = 7)	3.67	1.32-10.21	0.013	0.83	0.23-2.95	0.772
Gender						
Female (n = 24)	1	...	...			
Male (n = 5)	1.40	0.38-5.11	0.613			
Combined SLE						
pSLE (n = 21)	1	...	...	1	...	...
cSLE (n = 8)	12.24	2.80-53.54	0.001	17.05	5.83-277.51	<0.001
Lupus nephritis						
No (n = 10)	1	...	...			
Yes (n = 19)	0.78	0.30-2.01	0.602			
ANA ratio						
≤1:160 (n = 10)	1	...	...			
>1:160 (n = 19)	1.07	0.37-3.05	0.906			
Positive dsDNA						
No (n = 14)	1	...	...			
Yes (n = 15)	0.51	0.20-1.31	0.161			
Positive anti-Sm						
No (n = 25)	1	...	...			
Yes (n = 4)	1.05	0.30-3.65	0.944			
Positive anti-SSA						
No (n = 18)	1	...	...			
Yes (n = 11)	1.23	0.45-3.38	0.683			
Positive anti-SSB						
No (n = 27)	1	...	...			
Yes (n = 2)	1.11	0.14-8.49	0.922			
Positive RNP						
No (n = 17)	1	...	...	1	...	...
Yes (n = 12)	3.61	1.35-9.69	0.011	3.54	1.11-11.30	0.033
Antiphospholipid antibody						
Negative (n = 28)	1	...	...			
Positive (n = 1)	2.12	0.27-16.61	0.475			
Lupus anticoagulant						
Negative (n = 25)	1	...	...			
Positive (n = 4)	0.73	0.17-3.21	0.679			
Low C3						
No (n = 2)	1	...	...	1	...	...
Yes (n = 27)	0.21	0.04-1.03	0.265	0.19	0.03-1.32	0.052
Low C4						
No (n = 2)	1	...	...			
Yes (n = 27)	0.56	0.21-1.54	0.265			
WBC, /mm^3						
<3000 (n = 24)	1	–	–			
≥3000 (n = 5)	0.88	0.20-3.91	0.866			
Hemoglobin, g/dL						
>7 (n = 20)	1	...	...			
≤7 (n = 9)	0.82	0.31-2.21	0.695			
Platelet, /mm^3						
<100 000 (n = 22)	1	...	...			
≥100 000 (n = 7)	2.32	0.53-10.17	0.265			
Proteinuria, g/24 h						
<0.5 (n = 8)	1	...	...			
≥0.5 (n = 21)	1.33	0.47-3.80	0.592			
SLEDAI (scores)						
≤12 (n = 8)	1	...	...			
>12 (n = 21)	0.82	0.29-2.35	0.709			
Remission						
Yes	1	...	...	1	...	...
No	3.76	1.44-9.83	0.07	5.9	1.64-21.19	0.006
Days of remission						
≤18 (n = 23)	1	...	...	1	...	...
>18 (n = 6)	3.47	1.19-10.10	0.023	0.257	0.05-1.25	0.093

HR = hazard ratio; cSLE = concurrent systemic lupus erythematosus; pSLE = prior systemic lupus erythematosus; TMA = thrombotic microangiopathy; WBC = white blood cell; C = complement; SLEDAI = SLE disease activity index; ANA = antinuclear antibody; dsDNA = double-stranded DNA; RNP = ribonucleoprotein.

Table 3

Baseline characteristics of patients with TMA with concurrent SLE (n = 8)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
ANA	1/40	1/640	1/160	1/640	–	1/160	1/2560	1/320
Anti-dsDNA, U/mL	21	219	207	438	43.4	309.2	44	12
Anti-SSA/SSB	+/–	+/–	+/–	+/+	+/–	–/–	–/–	–/–
Anti-Sm	–	+	–	–	–	–	–	–
Anti-RNP	–	+	+	–	+	+	+	–
C3/C4, mg/dL	40.6/10.6	77.8/13	18.9/3.84	23.1/3.41	32.5/8.34	68/14.1	64.4/23.1	91.3/20.1
UTP, g/24 h	<0.15	4.158	3.546	10.29	15.47	0.647	1.38	2.024
SLEDAI	20	13	13	21	16	20	14	11
Initial treatment of disease	PP + MTP	PP + MTP + rituximab	PP + MTP + Aza.	CYC + MMF + PP + MTP	PP + MTP + CYC	PP + MTP + rituximab	PP + MTP	PP
Time of TMA remission	6 d	41 d	19 d	5 d	No	6 d	No	No
Cause of death (day after TMA)	Alive	Sepsis (day 131)	Alive	Sepsis (day 87)	Pul. bleed Sepsis/TMA (day 49)	Sepsis (day 104)	SLE/TMA (day 26)	SLE/TMA Sepsis (day 80)

SLE = systemic lupus erythematosus; TMA = thrombotic microangiopathy; ANA = antinuclear antibody; C = complement; UTP = urine total protein; SLEDAI = SLE disease activity index; dsDNA = double-stranded DNA; RNP = ribonucleoprotein; PP = plasmapheresis; MTP = methylprednisolone; Aza = azathioprine; CYC = cyclosporine; MMF = mycophenolate mofetil; Pul = pulmonary; + = present; – = absent.

Table 4

Anti-RNP positive rate and death rate in anti-RNP-positive patients in TMA-SLE groups

	TMA-cSLE	TMA-pSLE
Positive rate of anti-RNP	62.5% (5/8)	33.3% (7/21)
Death rate in positive anti-RNP	80.0% (4/5)	85.7% (6/7)
Remission rate in positive anti-RNP	60.0% (3/5)	42.9% (3/7)
Remission rate in negative anti-RNP	66.7% (2/3)	85.7% (12/14)
Median time to remission in positive anti-RNP (95% CI)	41.0 (6.7-75.3)	10.0 (4.1-15.9)
Median time to remission in negative anti-RNP (95% CI), d	6.0 (4.4-7.6)	7.0 (3.5-10.5)

TMA = thrombotic microangiopathy; cSLE = concurrent systemic lupus erythematosus; pSLE = prior systemic lupus erythematosus; RNP = ribonucleoprotein.

presents each patient's laboratory examination results for LDH, hemoglobin, haptoglobin, bilirubin, reticulocyte count, and schistocyte presence. A tissue biopsy was not performed for most of our patients because of their difficulties in accessing the location, low platelet count, poor renal function with high hemorrhage risk, or poor consciousness status that prevented them from cooperating with the invasive procedure. The sensitivity of the TMA triad has not been adequately discussed in previous studies; nevertheless, the presence of two of the three clinical features indicates probable TMA, and a tentative diagnosis may help avoid delays in developing appropriate therapeutic approaches.

Despite its low incidence, concurrent TMA and SLE is a life-threatening condition with a high mortality rate, ranging from 33.9% to 62.5% in previous studies, even with widespread administration of PEX therapy.[11,14–16] Distinguishing between TMA and SLE as the cause of MAHA is challenging because they share similar clinical characteristics, such as neurological signs, renal insufficiency, and fever. The clinical benefit of PEX therapy for TMA syndromes other than TTP is unclear, and clinical trials have yet to provide recommendations for this therapy; nevertheless, PEX therapy plays a central clinical role in treating TMA syndromes with unclear mechanisms and is a valuable treatment strategy for refractory SLE patients.[5,17]

Autoantibodies may present many years before the diagnosis of SLE, and the literature suggests that their appearance in patients tends to follow a predictable clinical course. The development of clinically overt SLE involves at least three phases: a normal immunity stage, benign autoimmunity stage, and pathogenic autoimmunity stage. The culmination of clinical illness is preceded by the pathogenic autoimmunity stage, and patients in this stage may have trivial clinical presentations.[18–20]

Various pharmaceutical treatments were administered to our patients. The backbones of initial treatments were PEX and immunosuppressive agents, with steroids being used in the majority of treatments because of their low cost and high efficacy. Case reports and evidence-based studies for the management of organ-specific manifestations of SLE are limited, except for kidney and skin manifestations; in addition, treatment strategies have demonstrated conflicting results in terms of SLE prognosis.[21,22] Furthermore, due to heterogeneous presentations of SLE and unpredictable disease courses, therapeutic approaches are highly variable, and due to treatment variegations, prognosis cannot be adequately predicted in general. In this study, patients in the TMA-pSLE group were diagnosed as having SLE before the onset of TMA, and some patients maintained protracted use of immunosuppressive agents. In the TMA-cSLE group, two patients had used rituximab. One reached remission after 41 days of treatment, and the other reached remission for 6 days. Both patients passed away due to sepsis. Two other patients received cyclophosphamide; one reached remission after 5 days, but the other never remitted; both passed away due to sepsis and uncontrolled disease. Two other patients received azathioprine along with steroid and PEX. Of these two patients, one reached remission after 19 days and remained alive, but the other never reached remission and expired due to sepsis. On the basis of the limited number of cases in our study and high mortality rates associated with various treatment combinations, we can conclude that the influence of treatment diversity on prognosis is not evident, which is consistent with the literature.

The pathology of TMA is characterized by microvascular occlusion by platelet-rich thrombi as well as erythrocyte damage. It represents a final pathological pathway that results from the disruption of the normal platelet/erythrocyte interphase. Previous studies have reported that most TMA syndromes developed after the occurrence of SLE.[15,16,23] In addition to SLE disease activity and low ADAMTS13 level, TMA may be caused by coexisting antiphospholipid antibodies, scleroderma, overlapping syndromes, malignant hypertension, infection, and calcineurin inhibitor toxicity in patients with SLE.[24,25] In our study, among the 21 patients in the TMA-pSLE group, 6 were previously diagnosed as having APS. APS is diagnosed

if the following clinical and laboratory criteria are met: confirmed venous thromboembolism; arterial thrombosis; small-vessel thrombosis; obstetric morbidities, including placenta insufficiency, placenta loss, or premature birth; and persistently positive levels of antiphospholipid antibodies measured on two separate occasions 12 weeks apart. Antiphospholipid antibodies may persist in patients previously diagnosed as having APS. By contrast, no patient in the TMA-cSLE group was diagnosed as having APS; this can be attributed to the low positive rate of APS antibodies and low probability of meeting the clinical criteria within the relatively short OS time. Antiphospholipid antibodies can damage vascular endothelial cells and initiate chain events that result in TMA; this thus implies that these antibodies were possibly related to the development of TMA in the TMA-pSLE group. In contrast to the high positive rate of antiphospholipid antibodies in the TMA-pSLE group, we can speculate a different mechanism underlying the pathogenesis of TMA in the TMA-cSLE group. A previous study[23] suggested that antiphospholipid antibodies are not related to disease severity or clinical outcome of TMA-SLE. We also demonstrated that antiphospholipid antibodies did not constitute a prognostic factor for OS in the two groups.

The clinical benefits of PEX therapy for the treatment of TTP are well documented. The assumed mechanism of PEX involves replacing ADAMTS13 as well as removing autoantibodies directed to ADAMTS13 activity and removing ultralarge von Willebrand factor (vWF) multimers.[26,27] However, because patients with TMA and SLE were reported to exhibit poor responses to PEX therapy,[28] the role of immunosuppressive agents may be prioritized over that of PEX. We observed no statistically significant difference between the two groups in terms of remission rate with PEX treatment; however, the median time to TMA remission tended to be longer in the TMA-cSLE group (19.0 vs 8.0 days; $p = 0.071$). On the basis of the trend of lower remission rate and longer period to remission in the TMA-cSLE group, we may speculate a different mechanism contributing to the pathogenesis of TMA in this group. In addition, the longer median time to TMA remission indicates longer use of immune suppressants and slower dose tapering in the TMA-cSLE group, resulting in prolonged immunocompromised status with the consequence of sepsis and even death.

To identify clinical prognostic factors among SLE patients with TMA, we also described the clinical characteristics and outcomes of TMA with cSLE and pSLE in our study. According to historical investigations, rituximab exposure may be an independent protective factor for the short-term survival of patients with TMA and SLE.[29] Active SLE disease activity, a diagnosis of lupus nephritis, an age of ≥40 years, the presence of acute renal failure or infection, two or more infection sites, four or more TMA features, the presence of acute pancreatitis, and C3 values of ≤60 mg/dL may be prognosis factors for relatively poor outcomes.[16] The association of TMA with lupus nephritis has been mentioned in several reports.[25,30] The reported prevalence of TMA-associated lupus nephritis has varied considerably, ranging from 0.5% to 24%.[31–33] However, lupus nephritis had no significant relationship with the survival of patients with SLE and TMA in our study. In addition, we observed that anti-RNP positivity was related to a poor prognosis in the two groups. Previous studies have discussed the possible mechanism of anti-RNP and SLE.[34,35] Anti-RNP antibodies may interact with proteins associated with U1 RNA and form U1snRNP anti-U1 RNP antibodies are present in a subset of patients with SLE, and the presence of high-titer anti-U1 RNP antibodies was observed inmixed connective tissue disease.[36] Anti-U1 RNP antibodies may also be present in other autoimmune diseases, including rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, and polymyositis.[34,35] Although research has yet to provide major evidence of the role of anti-U1 RNP in SLE-related TMA, some studies have suggested that anti-RNP antibodies are linked to the disease activity and severity of SLE and an increased risk of lupus nephritis.[37,38] Anti-RNP autoantibody positivity may be related to more severe SLE disease activity and renal involvement and lead to higher mortality and morbidity rates. Our chi-square test did not reveal a statistically significant difference in anti-RNP-positive rate between the two groups because of the limited number of cases in this study; however, the anti-RNP-positive rate was numerically higher in the TMA-cSLE group (Table 4). The mortality rates in anti-RNP-positive patients were similar between the groups. The presence of anti-RNP antibodies indicates a lower remission rate, and a longer median time to hematological remission of TMA was observed. This suggests that anti-RNP is a key prognostic factor in patients with SLE and TMA. Although a higher anti-RNP-positive rate may have been related to poorer prognosis in the TMA-cSLE group, we noted that the concurrence of SLE with TMA and anti-RNP positivity were two independent unfavorable risk factors for OS after adjustment by multivariate cox regression analysis. Prolonged administration of immune suppressants is expected in these patients, for whom infection and sepsis may be inevitable.

TMA can occur subsequent to, before, or simultaneously with SLE and can have different clinical outcomes. However, few reports have described the clinical characteristics, prognostic factors, and outcomes associated with SLE and TMA sequentiality. SLE and TMA developed simultaneously in a minority of cases. In most cases, SLE developed before TMA.[23,39] The overall mortality rate is extremely high in SLE patients with TMA.[5,26,40] A case series reported that 33.3% patients with simultaneous SLE and TMA died, and the mortality rate was markedly higher (40.5%) in those with SLE preceded by TMA.[14] Another study revealed that the mortality rate of TMA-pSLE was 43% (13/30), whereas that of TMA-cSLE was 20% (1/5).[23] By contrast, we identified a high-mortality rate for patients with either TMA-pSLE (12/21 or 57.1%) or TMA-cSLE (6/8 or 75%). In addition, our multivariate analysis revealed the concurrence of SLE and TMA to be an unfavorable prognostic factor for survival, and a shorter survival time was observed (Fig. 1). The median OS time from the diagnosis of either SLE or TMA was longer in the TMA-pSLE group than in the TMA-cSLE group, but only the median OS time from the diagnosis of TMA was significantly longer in the TMA-pSLE group (2.9 vs 103.5 months; $p < 0.001$). A possible explanation is that TMA with a poor prognosis occurred in SLE patients regardless of whether SLE was active. In the TMA-cSLE group, the most common cause of mortality was sepsis. In addition to the clinical impact of advanced age, TMA syndromes are associated with increased SLE activity, exacerbated intercurrent infections, and reduced long-term renal function, and the concurrence of SLE and TMA indicates increased SLE activity. As mentioned, the role of immunosuppressive agents may be prioritized over that of PEX.[28] However, the groups' SLEDAI scores did not show significant discrepancies, implying that the disease activity in TMA-SLE patients may not be well translated by serological abnormalities.

Our study has several limitations. First, it was retrospective with a limited sample size due to the low prevalence of TMA in SLE patients. A multicenter prospective study may help address this limitation. Because the clinical course of TMA-SLE is aggressive and fulminant, the results of this study should be interpreted with caution regarding TMA-SLE treatment. Second, TMA comprises subcategories caused by differing mechanisms, and PEX is mostly evidenced in TTP. However, ADAMTS13 testing was not available in our hospital, and TTP could not be excluded from our study. We could not determine the number of TTP cases present in our cohort; nevertheless, this does not restrain our discussion of the general clinical presentations

of TMA in SLE patients or the prognosis in different temporal associations. Furthermore, steroid/immune suppressants and PEX are the mainstays of treatment and were administered in nearly all our patients. Third, patients with undiagnosed SLE or categorized as having preclinical SLE (or latent lupus) may have already developed autoantibodies without symptoms or had subclinical symptoms/signs. However, this group of patients fell outside the scope of the discussion, and including it would be a deviation of the original intention of our cohort, which was to study TMA occurring as an initial presentation that leads to the diagnosis of SLE.

The occurrence of TMA with SLE is rare. Its vigorous course results in high mortality and morbidity rates, highlighting the necessity of identifying the chronological association between TMA and SLE, early diagnosis, and aggressive treatment with PEX and immunosuppressive agents. TMA-cSLE and anti-RNP positivity are independent risk factors for relatively poor prognosis in SLE patients with TMA. For patients without a history of autoimmune disease, early suspicion of TMA upon observation of the three clinical features and work-up for SLE under this condition are vital. Early recognition of TMA-cSLE, prompt PEX, and upfront immunosuppressive therapies for patients with TMA-cSLE and those with positive anti-RNP antibody may be considered to improve patients' prognosis.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000344.

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