Thrombotic microangiopathy in lupus nephritis patients

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Objective
The aim of the present study was to evaluate the impact of thrombotic microangiopathy (TMA) on renal involvement in patients with lupus nephritis (LN).

Patients and methods
This study included 50 systemic lupus erythematosus patients with LN who had been referred for renal biopsy. Patients underwent clinical and laboratory assessment for disease activity and damage. The biopsy specimens were classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification, activity and chronicity indices, and assessed for renal TMA lesions.

Results
TMA was found in 7/50 LN patients (14%). Patients with TMA lesions had significantly higher systolic and diastolic blood pressure (P = 0.018 and 0.019, respectively), higher serum creatinine (P = 0.031), lower estimated glomerular filtration rate (P = 0.023) and higher consumption of C3 (P = 0.002) than that of those without TMA lesions. Lupus anticoagulant positivity was significantly more frequent in patients with TMA (P = 0.001). There was a significant association between the detection of TMA and LN class IV. LN patients with TMA had significantly higher renal activity indices (P = 0.022). Chronicity index was higher in patients with TMA, but it did not reach a statistical significance.

Conclusion
TMA is not an uncommon vascular change in patients with LN, especially in those with diffuse proliferative glomerulonephritis (class IV LN). It is associated with lupus anticoagulant positivity, C3 hypocomplentemia and higher renal biopsy activity index. TMA was significantly associated with renal impairment and systemic hypertension. Thus, TMA may be an important cause of renal injury and renal dysfunction in a subset of patients with LN, a histological entity associated with worse renal prognosis.

Keywords:
antiphospholipid syndrome, lupus anticoagulant, lupus nephritis, systemic lupus erythematosus, thrombotic microangiopathy

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Introduction

Lupus nephritis (LN), the main cause of morbidity and mortality in systemic lupus erythematosus (SLE), is the most common secondary glomerular disease [1]. LN develops in up to 60% of SLE patients during the course of the disease [2].

Thrombotic microangiopathy (TMA) is a common vascular change in patients with LN [3]. TMA is the most frequently reported intrarenal vascular lesion of antiphospholipid nephropathy in patients with primary antiphospholipid syndrome (APS), SLE-APS, as well as SLE patients with positive antiphospholipid antibodies (aPLs) [4]. The presence of glomerular TMA has been first described in LN patients [5] and was accepted as the acute manifestation of antiphospholipid nephropathy. In renal biopsy specimens obtained from SLE patients, evidence of a TMA is occasionally detected. In its most fulminant form, TMA presents with multiple fibrin thrombi in glomeruli and/or arterioles and capillaries generally without inflammation or vascular immune deposits [3]. TMA lesions may be focal or diffuse, with fresh as well as old and recanalizing thrombi. Immunofluorescence reveals a predominance of fibrin-related antigens, in the absence of immunoglobulins. Immune complexes are not seen [6]. The appearance of TMA lesions is similar to the changes observed in thrombotic thrombocytopenic purpura and the haemolytic uremic syndrome, entities occasionally occurring in the context of SLE. When making a diagnosis of TMA, the clinical context must be considered rather than relying only on biopsy criteria [7].

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The mechanism of TMA is largely unknown. It has been reported that TMA in LN patients is typically associated with the presence of aPLs, such as anticardiolipin antibodies (aCL), lupus anticoagulant (LAC) and anti-β2 glycoprotein I (β2GPI) antibodies [8–10], but the mechanism of aPL-induced TMA is still a topic of controversy [7,11–14]. In their study, Pierangeli *et al.* [15,16] found that aPL-mediated thrombophilia involves activation of the complement cascade. Enhanced in-situ complement fixation was associated with the presence of aPLs, and this process may influence thrombosis risk in patients with SLE [17].

Microangiopathy in the renal microcirculation have been associated with aPLs in lupus patients in some series [3,10,12,18,19], whereas not in others [11,13,14,20]. In addition, controversy still remains as to their significance in the progression of renal disease in LN.

We designed this study to evaluate the clinical and histopathological impact of TMA on LN and the association between TMA and aPLs.

Patients and methods

The study group comprised 50 SLE patients with LN who had been referred for renal biopsy from the inpatient section of the Rheumatology and Rehabilitation Department, School of Medicine, Kasr Al-Ainy Hospitals from May 2012 to April 2014. All patients fulfilled the American College of Rheumatology revised classification criteria for the diagnosis of SLE [21]. The patients were informed of the purpose of the study and gave their informed consent. The institutional review board of Kasr Al-Ainy School of Medicine approved this study.

Patients with pregnancy and/or vascular lesions, possibly due to other causes of renal microangiopathy, malignant hypertension, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, postpartum renal failure, diabetic nephropathy, HIV infection, chemotherapy or cyclosporine therapy, were excluded from the study.

At the time of renal biopsy, demographic and clinical data were recorded for each patient. Disease activity was assessed using the SLE Disease Activity Index (SLEDAI) [22] and disease damage by Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus [23].

Serum samples collected on the day of the biopsy were studied for antinuclear and anti-double stranded (ds) DNA antibodies, complement levels (C3, C4), complete blood count, erythrocyte sedimentation rate, serum creatinine and estimated glomerular filtration rate (eGFR). A urine analysis for haematuria, urinary casts and a 24 h urinary proteins were also carried out.

Detection of antiphospholipid antibodies

Anticardiolipin IgG/IgM antibodies and anti-β2GPI IgG/IgM antibodies were determined using IgG/IgM aCL and IgG/IgM anti-β2GPI enzyme-linked immunosorbent assays (Orgentec Diagnostika GmbH, Mainz, Germany), respectively, according to the manufacturer's instructions. The test was considered significantly positive if G phospholipid (a measurement unit) was greater than 20 for aCL IgG and if M phospholipid (a measurement unit) was greater than 20 for aCL IgM. LAC was determined using activated partial thromboplastin time, diluted Russell's viper venom time and tissue thromboplastin inhibition test.

Renal pathology

Biopsy samples

The renal tissues obtained by using ultrasound-guided needle biopsy were fixed in 10% neutral buffered formalin and embedded in paraffin. Paraffin sections of 2–3 mm were stained with haematoxylin and eosin (H&E), periodic acid-Schiff, silver methenamine and Masson's trichrome. Immunofluorescence studies of IgG, IgA, IgM, C1q, C3, C4 and fibrinogen were carried out in separate snap-frozen tissue.

A renal pathologist who had no prior knowledge of the clinical and laboratory findings in the patients evaluated and classified the biopsy specimens using the following:

(1) LN classification, which was carried out according to the most recent modification of the WHO classification from the International Society of Nephrology/Renal Pathology Society (ISN/RPS), 2003 [24].
(2) Activity and chronicity scores, which was carried out according to the activity and chronicity indices of LN [25].
(3) TMA, which was carried out when histologic lesions suggestive of TMA, consisting of the presence of fibrin thrombi in arteries, arterioles and/or glomeruli, were found [6].

Statistical analysis

Data were analysed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, Illinois, USA). Numerical data were expressed as mean and

SD or median and range, as appropriate. Qualitative data were expressed as frequency and percentage. The χ^2-test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between the two groups was carried out using the independent sample *t*-test or the Mann–Whitney test. A *P* value of less than 0.05 was considered significant.

Results

In this prospective study, 50 LN patients were included; out of them, 44 (88%) were females. At the time of kidney biopsy, the mean ± SD age was 25.9 ± 7.9 years (range 12–51), and disease duration was 5.14 ± 5.32 years (range 0.25–33). All studied patients were antinuclear antibodies positive and had proteinuria greater than 0.5 g/day. A total of 40 patients (80%) were anti-dsDNA positive. The mean SLEDAI score was 17 ± 5 (range 5–26) and the mean SLICC/ACR score was 1 ± 1 (range 0–6).

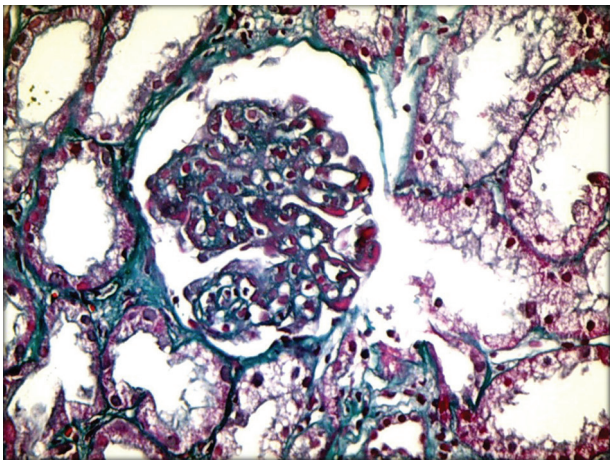
APS manifestations of arterial or venous (A/V) thrombosis were found in 10 patients (20%) and nine out of the 44 studied females (20.5%) had a history of obstetric complications.

Renal biopsy showed histologic lesions suggestive of TMA in 7/50 patients (14%) (Fig. 1), of whom five were females. There were 43 patients without TMA, of whom 39 were females.

Patients with TMA had a mean ± SD age of 28.1 ± 12.8 years and a mean ± SD disease duration of 9.1 ± 11.03 years. Patients without TMA had a mean ± SD age of 25.6 ± 6.9 years and a mean ± SD disease duration of 4.5 ± 3.6 years. There was no statistical significant difference between patients with and without TMA in age, sex and disease duration ($P > 0.05$ for all). Table 1 shows the clinical, laboratory and renal manifestations of the LN patients with and without TMA.

Patients with TMA had statistically significant higher systolic and diastolic blood pressure ($P = 0.018$ and

Figure 1



The glomerulus shows intracapillary thrombi (Masson trichrome's stain).

Table 1 Clinical and laboratory features of the lupus nephritis patients with and without thrombotic microangiopathy

Item	Overall series (*n* = 50)	With TMA (*n* = 7)	Without TMA (*n* = 43)	*P* value
SLEDAI (mean ± SD)	17 ± 5	18.57 ± 4.65	16.21 ± 5.12	0.250
SLICC/ACR (mean ± SD)	1 ± 1	2.57 ± 2.23	1.33 ± 1.06	0.180
Renal manifestations				
Proteinuria (g/day) (mean ± SD)	3.08 ± 2.26	3.97 ± 2.48	2.93 ± 2.22	0.166
Serum creatinine (mg/dl) (mean ± SD)	0.9 ± 0.6	1.6 ± 1.1	0.8 ± 0.4	0.031*
eGFR (ml/min/1.73 m²) (mean ± SD)	113.4 ± 58.8	67.8 ± 58.3	120.9 ± 56.1	0.023*
Systemic hypertension [*n* (%)]	26 (52)	5 (71.4)	21 (48.8)	
Systolic pressure (mmHg) (mean ± SD)	135 ± 26	157 ± 25	132 ± 24	0.018*
Diastolic pressure (mmHg) (mean ± SD)	88 ± 16	100 ± 14	86 ± 16	0.019*
APS manifestations [*n* (%)]				
Arterial/venous thrombosis	10 (20)	1 (14.3)	9 (20.9)	1
Obstetric events	9/44 (20.5)	0/5 (0)	9/39 (23.1)	0.566
aPL profile [*n* (%)]				
aCL IgG positivity	5 (10)	0 (0)	5 (11.6)	1
aCL IgM positivity	4 (8)	0 (0)	4 (9.3)	1
LAC positivity	20 (40)	7 (100)	13 (30.2)	0.001*
Anti-β2GPI IgG positivity	7 (14)	1 (14.3)	6 (14)	1
Anti-β2GPI IgM positivity	3 (6)	0 (0)	3 (7)	1
Complement consumption [*n* (%)]				
Low complement C3	35 (70)	7 (100)	28 (65.1)	0.002*
Low complement C4	19 (38)	2 (28.6)	17 (39.5)	0.582

aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; eGFR, estimated glomerular filtration rate; LAC, lupus anticoagulant; β2GPI, β2-glycoprotein I; SLEDAI, SLE Disease Activity Index; TMA, thrombotic microangiopathy; *Significant *P* value.

0.019, respectively), higher serum creatinine ($P = 0.031$) and lower eGFR ($P = 0.023$). LAC positivity and C3 consumption were significantly higher ($P = 0.001$ and 0.002, respectively) in patients with TMA than in those without TMA. However, SLEDAI, SLICC/ACR disease damage score, the severity of proteinuria, APS manifestations, aCL (IgG and IgM), anti-β2GPI (IgG and IgM) positivity and titre of C4 were not significantly different (Table 1).

Distribution of LN class was as follows: class II with seven patients (14%), class III with 14 patients (28%), class IV with 16 patients (32%), class V with four patients (8%), class II+III with seven patients (14%) and class II + V with two patients (4%). Class IV LN was the most frequently observed class in patients with TMA. Patients with TMA had significantly more frequent class IV LN than those without TMA ($P = 0.027$). No TMA was detected in patients with class II and V. The activity index score was statistically significantly higher in patients with TMA compared with patients without TMA ($P = 0.022$). The chronicity index score was observed to be higher in patients with TMA; however, it did not reach statistical significance ($P = 0.063$) (Table 2).

Discussion

The potential role of aPLs in the pathogenesis of TMA was already suggested in the 1980s by Kant *et al.* [5] and Kincaid-Smith *et al.* [26] Later, TMA has been recognized both in primary APS and LN and has been related to aPLs positivity [9,27]. TMA is accompanied by severe hypertension, proteinuria and/or severe decline in renal function in LN patients and also associated with aPLs, particularly LAC [19].

Table 2 Renal histopathological characteristics of the lupus nephritis patients with and without antiphospholipid nephropathy

Item	Overall series ($n = 50$)	With TMA ($n = 7$)	Without TMA ($n = 43$)	*P* value
ISN/RPS classification for LN [*n* (%)]				
Class II	7 (14)	0 (0)	7 (16.3)	0.573
Class II + III	7 (14)	0 (0)	7 (16.1)	0.573
Class II + V	2 (4)	0 (0)	2 (4.7)	1
Class III	14 (28)	2 (28.6)	12 (27.9)	1
Class IV	16 (32)	5 (71.4)	11 (25.6)	0.027*
Class V	4 (8)	0 (0)	4 (9.3)	1
Activity index (mean ± SD)	2 ± 2	4 ± 1.73	2.1 ± 2.26	0.022*
Chronicity index (mean ± SD)	3 ± 2	4.29 ± 2.22	2.6 ± 1.45	0.063

LN, lupus nephritis; TMA, thrombotic microangiopathy; *Significant *P* value.

TMA is not an uncommon vascular change in patients with LN, especially in those with severe diffuse proliferative glomerulonephritis. In this prospective study, TMA was found in 14% of LN patients, and 71.4% of the patients with class IV LN had TMA. Previous studies found TMA in 14–18% among LN patients [7,10,19,28]. TMA was significantly associated with class IV LN (i.e. diffuse proliferative glomerulonephritis), a finding previously reported by other studies [3,11,19]. Moreover, biopsy specimens of LN patients with TMA had significantly higher LN activity indices than of those without TMA. Similarly, in their respective studies, Shen *et al.* [3] and Zheng *et al.* [19] found a significant association between the existence of TMA and higher activity and chronicity indices.

TMA could incite and amplify local inflammation and injury in the diseased kidney and perpetuate the lupus-induced renal destruction [13]. Recent studies demonstrated that thrombosis interacts and intertwines with inflammation at multiple points. An increasing number of haemostasis factors have been found to reside at the nexus between thrombosis and inflammation processes, expressing multiple functions at the interface of these two pathophysiologic events [29,30]. However, Gong *et al.* [13] reported in their study that there was no significant association between the detection of TMA and LN classification.

In this study, patients with TMA had significantly higher serum creatinine levels, lower eGFR and higher systolic and diastolic blood pressure measurements. Microthrombi could mechanically obstruct glomerular capillaries, diminishing blood supply to glomeruli and renal tubules, thereby causing hypoxic/ischaemic injuries to the affected glomeruli and tubules. This would, in turn, decrease the GFR leading to the loss of nephrons and impair renal function, suggesting that this histological entity may be associated with a worse renal prognosis.

Thus, TMA may be an important cause of renal injury and renal dysfunction in a subset of patients with LN and this agrees with the results of a study by Zheng *et al.* [19], who conducted a prospective study of 124 Chinese patients to evaluate the aPLs profiles in LN with glomerular microthrombosis (GMT); they found that serum creatinine and proteinuria levels were significantly greater in the LN-GMT group than in the LN-non-GMT group. In addition, patients in the LN-GMT group also had a higher frequency of systemic hypertension. Moreover, Shen *et al.* [3] reported that serum creatinine levels as well as frequency of systemic hypertension were significantly greater in the LN-GMT group than in the LN-non-GMT

group. However, proteinuria did not differ between the two groups. Other clinical studies have indicated that LN patients with TMA have more severe renal tissue injuries, poorer responses to general treatment and worse renal outcomes than do patients without TMA [7,10,12,13].

Although we did not find an association between SLE disease activity as measured by SLEDAI and the presence of TMA. In their respective studies, Shen *et al.* [3] and Zheng *et al.* [19] documented a significant association between TMA and higher SLEDAI.

Clinical manifestations of APS including A/V thrombosis and obstetric events were not associated with the presence of TMA lesions in kidney biopsies. Similarly, Shen *et al.* [3] and Gong *et al.* [13] could not find a relation between TMA and APS manifestations. However, Daugas *et al.* [10] reported a significant association between TMA and arterial thrombosis and obstetric events.

aPLs, including LAC, aCL and anti-β2GPI antibodies, are considered to be of pathogenic significance in thrombosis in APS and SLE patients, which makes them the most frequently examined factors in the investigation of the pathogenesis of TMA in LN. In the present study, there was a strong association between the existence of TMA and LAC positivity, but neither IgG/IgM aCL nor IgG/IgM anti-β2GPI. We also found that TMA was significantly associated with low complement C3 level, but not with C4.

Similarly, in their respective studies, Shen *et al.* [3] and Zheng *et al.* [19] reported that GMT was strongly associated with LAC, in addition to IgG anti-β2GPI and consumption of C3. There was no association between the presence of GMT and the existence of IgG/IgM aCL, IgM anti-β2GPI and the consumption of C4. This probably indicates that GMT may be associated with aPL that recognizes antigens such as β2GPI and some haemostatic and fibrinolytic proteases instead of cardiolipin [19]. Complement activation, induced by or coordinated with aPL, may play a pathogenic role in the development of renal tissue injury leading to thrombosis [3,19]. Many studies have shown that complement activation may play an important role in thrombotic events. aPLs may activate the complement pathway, generating split products that lead to thrombosis [15,31,32]. Furthermore, similar results were reported in a study by Daugas *et al.* [10].

These findings further strengthen the notion that LAC confers among aPLs the highest thrombotic risk. Indeed, as reported by a large meta-analysis (~7000 patients), LAC-positive patients appear to be significantly more prone to all vascular district thrombosis than do aCL-positive patients [33].

In contrast to previous results, Bhandari *et al.* [12], who conducted a study on 51 British patients to evaluate the association of aCL antibodies with intraglomerular thrombi and renal dysfunction in LN, reported a significant association between the presence of intraglomerular thrombi and aCL antibodies. There was no association between the presence of intraglomerular thrombi and consumption of C3 or C4. Similar results were reported in a study by Naiker *et al.* [18].

Although TMA was found to be associated with different aPLs in the previous studies, Moroni *et al.* [20] reported that there was no significant association between TMA and aPLs positivity, although the detection of TMA was greater in the aPLs-positive group than in the aPLs-negative group. Furthermore, Gong *et al.* [13] and Cohen *et al.* [14] found no significant difference between patients with and those without GMT in terms of aPLs.

Conclusion

LN patients with TMA have more active and severe kidney disease than do those without TMA, as evidenced by more active LN, impaired renal functions and association with LN class IV. Taken together, abundant evidence indicates that TMA plays an important role in the progression and exacerbation of LN. TMA is significantly associated with the presence of aPLs, particularly LAC. Nevertheless, the mechanism accounting for TMA in patients with LN remains largely unknown and needs further exploration.

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Conflicts of interest

There are no conflicts of interest.

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