Thrombotic microangiopathy and poor renal outcome in lupus patients with or without antiphospholipid syndrome

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Abstract

Objective

To assess the presence of acute thrombotic microangiopathy (aTMA) and chronic vascular lesions (cTMA) in lupus nephropathy, and to evaluate their association with extrarrenal lupus features, aPL positivity, antiphospholipid syndrome (APS) and renal survival.

Methods

We studied lupus patients with renal biopsy, ≥1 year of post-biopsy follow-up and at least two aCL (IgG-IgM), anti-β_2GP-I (IgG-IgM) and/or lupus anticoagulant (LAC) determinations. A blinded nephropathologist evaluated all biopsies. We retrospectively collected clinical, serological, treatment and renal survival data. We plotted survival curves and used Cox regression analysis.

Results

A total of 90 biopsies were included with a median disease duration 5.9 years and median follow-up 2.4 years. Eleven patients (12.2%) had cTMA and 3 (3%) aTMA. There was no difference in age, lupus duration, hypertension, drugs, APS, non-renal lupus features, low C3 or C4 aCL IgG, anti-β_2GP1-IgG or IgM and LAC between cTMA and non-cTMA groups. The cTMA group had aCL-IgM less frequently (27% vs. 66%, p=0.02), more class IV nephropathy (100% vs. 40%, p=0.01), higher activity index scores (7.5 vs. 2, p=0.03) and a tendency to need chronic dialysis (54.5% vs. 24% p=0.06). At four years of follow-up, 28% of the cTMA group and 62% of the non-cTMA group were free of dialysis (log rank p=0.03). cTMA was associated with chronic dialysis (RR 2.9, CI 95% 1.1-8.1, p=0.03).

Conclusion

cTMA conferred a poor renal outcome. We found a low frequency of TMA that was not associated with with APL positivity or APS, suggesting that other factors hitherto not studied are involved in its pathogenesis.

Key words

thrombotic microangiopathy, lupus nephropathy, antiphospholipid syndrome

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Introduction

Thrombotic microangiopathy (TMA) is characterised by fibrin thrombi in glomeruli and/or arterioles in the absence of immune deposits or inflammatory inflitrations (1). Its histopatological spectrum encompasses acute or chronic thrombotic lesions such as fibrous intimal hyperplasia of arterioles and interlobular arteries, organised thrombi with or without recanalisation, fibrous arterial and arteriolar occlusions, and focal cortical atrophy (1). The reported prevalence of this condition in systemic lupus erythematosus (SLE) is between 23–32% in biopsy-proven renal patients (2, 3). TMA may be present in all lupus classes of lupus nephritis, however classes III and IV have higher rates (4, 5). Clinically, TMA has been associated with hypertension, low-grade proteinuria (2, 5) and recently with severe post-renal biopsy bleeding (6).

In renal lupus TMA lesions, have been mostly attributed to the presence of clinical or serological (specifically LAC) antiphospholipid syndrome (APS) (2, 3, 6-8) (2, 5-7, 9). Furthermore, TMA is the best recognised and most characteristic lesion of APS nephropathy, and is included as a non-criteria APS manifestation in the revised Sydney classification criteria (10). TMA has also been associated with livedo (2), arterial thrombosis and fetal loss (2, 3). Other studies, however, have not confirmed this link. For instance, in a Thai population, TMA was not associated with APS (5). In another study of 38 lupus patients with TMA, the aPL status did not correlate with renal microthrombi, suggesting that other factors may be required for the development of TMA (11). In this regard, evidence indicates that activation of both classic and alternative complement pathways may play a role in the pathogenesis of TMA lupus associated nephropathy (11).

In addition, it is still controversial whether or not TMA influences poorly the renal prognosis. For instance, three studies demonstrated poor renal survival (4, 5, 12) whereas two reported no difference in the frequency of ESRD between TMA and non-TMA groups (2, 8). Finally, with the exception of microangiopatic haemolytic anaemia (4), it is unknown if there is an association of TMA with other extra-renal lupus features.

The aim of this study was to assess the presence of acute thrombotic microangiopathy (aTMA) and chronic vascular renal lesions (cTMA) in lupus nephropathy and to evaluate their association with extrarenal lupus features, hypocomplementaemia, aPL positivity, presence of APS and renal survival.

Methods

Patients

We studied consecutive patients with SLE and biopsy-proven nephropathy attending the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary referral care centre, from 2008-2012. We studied patients with the following inclusion criteria: diagnosis of SLE according the ACR criteria (12), available renal biopsy, ≥1 year of post-biopsy follow-up and at least two aCL (IgG-IgM), anti-β_2GP-I (IgG-IgM) and/or lupus anticoagulant (LAC) determinations 12 weeks apart. If patients had more than one renal biopsy, only the first one was analysed. We excluded patients with other causes of renal microangiopathy, such as systemic sclerosis, malignant hypertension, thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome, postpartum renal failure, preeclampsia and diabetic nephropathy.

Patients' clinical records were carefully reviewed according to a pre-established protocol. We collected information regarding demographic data, extra-renal lupus manifestations (vasculitis, serositis, arthritis, Raynaud's, haematologic, neurologic and cutaneous involvement), clinical and serological antiphospholipid status according to the updated classification criteria for APS (10), C3 and C4 serum levels at the time of the biopsy or the closest available one, use of immunosuppresors, anticoagulants and aspirin at the last medical appointment as well as renal failure assessed as the need for chronic dialysis (more than 3 months). We defined hypertension as a systolic blood pressure of 140 mm Hg or greater and/or a diastolic blood pressure of 90 mm Hg or greater in the absence/presence of anti-hypertensive agents at least in two determinations.

Overall, as induction treatment, patients with proliferative lupus nephropathy were treated with oral prednisone (initially 1 mg/kg tapered as physician criteria)and monthly pulse of intravenous cyclophosphamide (0.75–1g/m^2) or mofetil micophenolate 2–3 gr/day. For maintenance therapy, patients who were under cyclophosphamide switched to azathioprine and those on mofetil micophenolate continued a lower dose of 1.5–2 g/day.

Biopsy assessment

An expert nephropathologist, blinded to the serological and clinical data re-evaluated all biopsies by light microscopy. All cases were classified according with the ISN/RPS lupus nephritis classification (13), activity and chronicity indices were also evaluated. Histological criteria for acute TMA (aTMA) as well as chronic TMA (cTMA) were based on those described by Kambham (1).

Antiphospholipid assays

aCL (IgG and IgM) were determined by ELISA according to published methods (14). IgG and IgM antibodies to phospholipid-free human β_2GP-I were determined by ELISA according to Cabiedes *et al*. (14). Lupus anticoagulant was determined by LAC/1 screening reactant and a confirmatory test LAC/2 according to published guidelines (15). Cut-off points for aCL or anti-β_2GP-I at time of study were considered positive according to reference values of the Immunology and Rheumatology Laboratory of our Institution. These correspond to values above the 99th percentile of 100 normal controls.

Statistical analysis

Categorical variables were compared using either χ^2 or Fisher's exact test when appropriate, continuous variables were compared using Student's *t*-test and Mann Whitney U-test when non-normally distributed. We plotted survival curves for renal survival and use Cox regression analysis. A two-tailed $p<0.05$ was considered significant. All analyses were performed using SPSS for Windows 20.0.

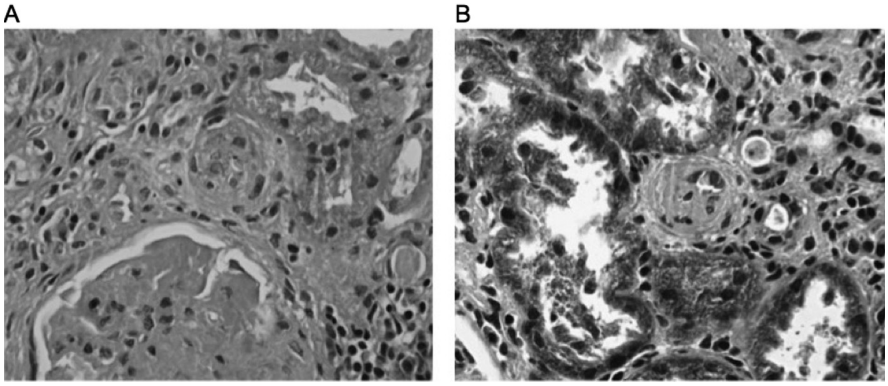

Fig. 1. A. Thrombotic microangiopathy affecting an interlobular artery surrounded by interstitial fibrosis and tubular atrophy. There is a bloodless glomerulus nearby (HE 600x).
B. Interlobular artery showing prominent circumferential intimal expansion, with fragmented erythrocytes (Trichrome stain 600x).

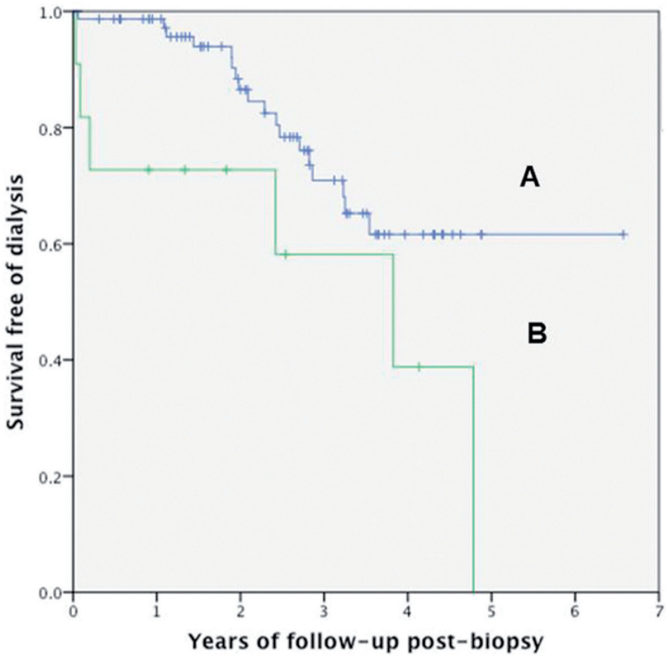

Fig. 2. Kaplan-Meier curves of the probability of being free of chronic dialysis in the two study groups:
A. without cTMA or
B. with cTMA.

Results

We identified 255 renal biopsies with lupus nephritis diagnosis and available material at the Surgical Pathology file. We excluded 165 biopsies for the following reasons: patients who lacked two determinations of antiphospholipid serology (n=131), not enough follow-up (n=19), diabetes mellitus (n=2), PTT (n=3) and more than one biopsy of the same patient (n=10).

Thus, for the present study we included 90 patients with SLE each with a kidney biopsy. Seventy-nine (87.7%) patients were females, with mean age at the time of the renal biopsy 31.2±9.5 years, a median lupus duration of 5.9 years (range: 0–49.3) and a median post-biopsy follow-up of 2.4 years (range: 1–6.5). We did not find any difference in the median time of follow-up between patients who needed or not dialysis (2.1 *vs*. 2.5 years, p=0.42).

The overall antiphospholipid serology was: aCL-IgG 30.3% (27/89), aCL-IgM 61.3% (54/88), anti-β_2GP-I IgG 45.5%, anti-β_2GP-I IgM 38.6% (34/88) and LAC 13.9% (12/86). In addition, 32 patients (35.5%) had a diagnosis of APS according to the Sydney criteria (10). Most of them had only thrombotic events (n=24), eleven had a pure obstetric syndrome and three patients had both thrombotic and obstetric events.

We demonstrated the presence of cTMA in eleven patients and aTMA in

Table I. Demographic and clinical variables.

Variable	cTMA n=11	Without cTMA n=79	*p*
Age in years	31.0 ± 8.8	31.6 ± 13.1	1
Follow-up in years	1.83 (1-4.78)	2.4 (1-6.58)	0.54
SLE duration in years	5.3 (1.3-5.9)	3.6 (0-49.3)	0.19
Proteinuria, n (%)	11 (100)	76 (96)	1
Nephrotic syndrome, n (%)	6 (54)	45 (56)	0.86
Haematuria, n (%)	9 (81)	70 (88)	0.68
Cilindruria, n (%)	5 (45)	41 (51)	0.79
Hypertension, n(%)	6 (54)	42 (53)	1
Serum creatinine at time of biopsy (mg/dl)	3.5 ± 1.1	3.9 ± 2.9	0.44
24 hr. creatinine clearance at time of biopsy (ml/min)	28.7 ± 23.9	32 ± 24	0.93
ISN/RPS Nephropathy class, n (%)			0.01
III	0	15 (18.9)	
IV	11 (100)	32 (40.5)	
V	0	2 (2.5)	
VI	0	3 (3.7)	
III+V or IV+V	0	27 (34.1)	
Median activity index	7.5 (1-9)	2 (0-13)	0.03
Median chronicity index	8 (3-10)	3.5 (0-10)	0.75

Table II. APS clinical and serological status.

Variable	cTMA n=11	Without cTMA n=79	*p*
Obstetric APS, n (%)	3 (27)	8 (10)	0.31
Thrombotic APS, n (%)	3 (27)	21 (26)	1
APS, n (%)	4 (36)	28 (35)	1
APL positivity, n (%)	6/10 (60)	56 (70)	0.48
aCL-IgG, n (%)	3 (27)	24/78 (30)	1
aCL- IgM, n (%)	3 (27)	51/77 (66)	0.02
anti-β_2GP-I IgG, n (%)	4 (36)	37 (46)	0.78
anti-β_2GP-I IgM, n (%)	2/9 (22)	32 (40)	0.47
Lupus anticoagulant (LAC), n (%)	2/10 (20)	10/76 (13)	0.62
Triple marker (aCL+β_2GP-I+LAC), n (%)	1/10 (10)	7/76 (9)	1

three patients, leading a prevalence of 12.2% (95% CI 6–20) and 3% (95% CI 1-9), respectively. All patients from the aTMA group also had cTMA lesions. A typical TMA lesion is shown in Figures 1 A-B. We therefore focused the analysis on cTMA findings. We did not find any difference regarding the follow-up, age at biopsy, lupus duration, hypertension, serum creatinine, 24 hr. creatinine clearance, cilindruria, haematuria and proteinuria at time of the biopsy when we compared patients with or without cTMA (Table I). The histological features of all renal biopsies are also depicted in Table I. All patients in the cTMA group had class IV lupus nephropathy and had higher activity indices. Although these patients also had higher chronicity indexes, the difference was not statistically significant.

The presence of APS or aPL positivity was similar among groups, with the exception of aCL-IgM that was less frequent (27% *vs*. 66%, *p*=0.02) in the cTMA group (Table II). The cTMA and non-cTMA groups were similar with respect to C3 serum levels (65.4 mg/dl (17.2–105) *vs*. 41.2 mg/dl (23–65.5), *p*=0.49) and C4 (14.8 mg/dl (4.8–37) *vs*. 9.2 mg/dl (2–19.8), *p*=0.96).

Table III shows the extra-renal lupus features and the treatment modalities utilised between groups. The distribution of all the evaluated extra-renal lupus features was similar in cTMA and non-cTMA groups. Moreover there was no difference in the use of immunosuppresors, aspirin and anticoagulant therapy at the last medical appointment among cTMA and non-cTMA patients. Overall 13 patients were under anticoagulation, and in all the cases, the indication was a previous thrombotic event. Furthermore, patients with cTMA had a tendency to require more chronic dialysis (54.5% *vs*. 24%, *p*=0.06).

We also studied the probability of being free of chronic dialysis in patients with or without cTMA. The results of this analysis are shown in the Kaplan-Meier curve (Fig. 2), where after four years of follow-up only 28% of patients from the cTMA group were free of dialysis compared vs. 62% of the non-cTMA group (log Rank *p*=0.03). Finally the Cox regression analysis, which included all significant variables at the univariate analysis, showed that the cTMA lesion was significantly associated with the use of chronic dialysis (RR 2.9, CI 95% 1.1–8.1, *p*=0.03).

Discussion

Renal small-vessel vaso-occlusive vasculopathy has been described in APS and SLE-APS (2, 3, 7, 8). In lupus population, when this vasculopathy is present, 15–18% corresponds to acute cases and 22–24% to chronic cases (2, 3, 12). These figures are similar to those reported here. We also corroborated that class IV lupus nephropathy is the most frequent renal lesion associated with TMA (4, 5, 12). The renal outcome of TMA associated nephropathy, however, has been controversial. Herein, we found that TMA is a risk factor for chronic dialysis. This result is similar to Cheunsuchon's *et al*. who reported that Thai lupus patients with APS nephropathy and TMA had a worst outcome, with a tendency to develop ESRD requiring dialysis or transplantation (5). Recently, Song *et al*. reported that patients with TMA are younger, with higher activity scores, lower rates of partial remission and more treatment failures (12). These authors also reported an association between TMA and poor renal survival (12). Conversely two studies have not found any differences in the frequency of end stage renal disease (ESRD) between TMA and non-TMA groups (2, 8). One of them, however, found that TMA correlated with poor renal prognostic factors such as hypertension (2). This fact was also described by Daugas *et al*. who found an association of TMA with altered renal function and interstitial fibrosis (3). Moreover in lupus patients with renal biopsy-class IV+TMA, the renal survival rate at 1,

Table III. Extra-renal lupus features and treatment.

Variable	cTMA n=11	Without cTMA n=79	*p*
Arthritis, n (%)	11 (100)	72 (91.1)	0.59
Serositis, n (%)	11 (100)	72 (91.1)	0.59
Haematologic involvement, n (%)	5 (45.4)	24 (30.3)	0.32
Raynaud, n (%)	1 (9)	9 (11.3)	1
Mucocutaneous involvement, n (%)	11 (100)	65 (82.2)	0.20
Vasculitis, n (%)	1 (9)	18 (22.7)	0.44
Neurologic involvement, n (%)	4 (36.3)	15 (18.9)	0.23
Cyclophosphamide, n (%)	7 (63.6)	57 (72.1)	0.72
Azathioprine, n (%)	10 (90.9)	67 (84.8)	0.78
Mofetil micophenolate, n (%)	5 (45.4)	44 (55.6)	0.53
Antimalarials, n (%)	7 (63.6)	37 (46.8)	0.38
Tacrolimus, n (%)	1 (9)	3 (3.7)	0.41
Aspirin, n (%)	3 (27.2)	12 (15.1)	0.57
Anticoagulant, n (%)	2 (18.1)	11 (13.9)	0.65
Chronic dialysis, n (%)	6 (54.5)	19 (24)	0.06

3, and 5 years was 62.5%, 62.3% and 46.7%, respectively (4).

Thrombotic microangiopathy has been traditionally recognised as a lesion associated with aPL (16), particularly with LA (2, 3, 7), followed by double aPL positivity (LAC+aCL) (8) and aCL alone (2). Only one study so far has analysed the association of anti-β_2GP-I with TMA with negative results (12). Finally, TMA has been associated with livedo (2), arterial thrombosis (2, 3) and obstetric complications (3).

In the study reported here, we found a low overall prevalence of cTMA in lupus kidney biopsies (12%) and that only 4/32 SLE patients with definite APS (13%) had this lesion. This is in contrast with previously reported figures (2, 3, 7). For instance, in a retrospective study of 151 lupus patients, TMA was diagnosed in 35 patients (23%) and in 12/18 patients (66%) with definite APS (2). In the same series, TMA was diagnosed in 40% of patients with aPL compared with 4.3% of aPL-negative patients (2). Similarly, in a cohort of 114 lupus patients Daugas *et al*. reported TMA in 63% patients with APS versus 22% in those without APS (3). Other reports are in agreement with these observations (6-8).

Other studies besides the current one have not found an association of TMA with APS and/or aPL. For instance, in a study of 38 kidney biopsies from lupus patients Cohen *et al*. detected aPL in twenty of them (53%) with glomerular microthrombi present only in 8 that were not related to the presence of aCL or LAC (11). More recently, in a study of a Thai population of 155 lupus patients, Cheunsuchon *et al*. found that only 10 of them (6.7%) had TMA and APS (5). Similarly, Hu *et al*. reported that among 33 renal biopsies with diffuse proliferative lupus glomerulonephritis and TMA, there was no significant correlation with their APL status (4).

All previous studies, including ours, have evaluated the antibody profile as a dichotomous variable and did not consider the title; weather this issue did have an impact in the development of TMA is unknown.

It therefore seems plausible that TMA in lupus nephropathy may not only be attributed to APS, but there are other factors involved in its pathogenesis. For example, intense glomerular C4d staining has been correlated with the presence of microthrombi in lupus biopsies with TMA and capillary C3 deposits (11). Moreover, Song *et al*. recently reported that patients with TMA and C4d deposition had higher urine protein excretion, higher serum creatinine, higher scores of total activity indices, endocapillary hypercellularity, subendothelial hyaline deposits and other histopathological features not described for APS nephropathy (12). In addition, these authors also found that a decreased serum complement factor H was associated with a poorer renal outcome among patients with TMA (12). Here, we were not able to find any differences in C3 and C4 levels among patients with and without TMA, however we only measured this variable in a single time period. It is therefore possible that the differences in the low frequency of the TMA lesion found in the studies reported to date, including the current one, compared to the high frequencies found in the aforementioned studies (2, 3, 7, 8) may account for the discrepancies of the results.

In a recent study, Canaud *et al*. demonstrated that the vascular endothelium of proliferating intrarenal vessels from 37 kidney-transplant recipient patients with APS had activation of the mammalian target of rapamycin complex (mTORC) pathway (17). Interestingly, 10 of these patients who were treated with mTOR inhibitors had better graft survival and no recurrence of vascular lesions (17).

Finally, the association of extra-renal lupus features with the presence of TMA has scarcely been evaluated. For instance Hu *et al*., reported in an uncontrolled study of lupus patients with class IV nephropathy and TMA, a higher prevalence of thrombocytopenia and microangiopathic haemolytic anaemia (4). Herein we did not find any extra-renal lupus feature associated with TMA, however we excluded patients with TTP. Similarly, just as Tektonidou and Daugas, we did not find any differences regarding the use of immunosupressors and prednisone (2, 3), nor in the use of aspirin or anticoagulation in groups with or without TMA (3).

We acknowledge the following limitations of our study. The main one is its retrospective design and the small number of patients with cTMA that may bias our conclusion. In addition, we were not able to analyse the totality of patients who underwent renal biopsy at our Institution during the study period due to the lack of data regarding their aPL status. Third, biopsies were performed in patients with suspected underlying nephritis, thus we might have missed patients with mild renal disease hampering the strength of our results. Finally in spite of the short follow up, we were able to identify a worst renal prognosis among patients with cTMA.

Based on our results and in light of recent aforementioned published reports, it appears clear that TMA confers a

poor renal outcome and is not associated with extra-renal lupus manifestations. We propose that cTMA should not only be pathogenetically attributed to the aPL positivity or the presence of APS, and there are other factors hitherto not described that are involved in its pathogenesis.

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