Evaluation of Clinical Outcomes and Renal Vascular Pathology among Patients with Lupus

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Summary

Background and objectives The objective of this study was to determine the clinical significance of renal vascular lesions in lupus nephritis.

Design, setting, participants, & measurements Renal vascular lesions defined as thrombotic microangiopathy, lupus vasculopathy, uncomplicated vascular immune deposits, and arterial sclerosis were evaluated in relation to renal and vascular morbidity and overall mortality.

Results Biopsies from 161 patients revealed thrombotic microangiopathy (13), lupus vasculopathy (5), and arterial sclerosis (93). No renal vascular lesions were found in 24.8% of patients. At the time of biopsy, arterial sclerosis or lupus vasculopathy patients were older (arterial sclerosis=37.9±13.0 and lupus vasculopathy=44.4±8.9 versus controls=33.1±8.9 years, $P<0.05$), and the mean arterial pressure was higher in all groups compared with controls. Nephritis subtype, activity indices, and proteinuria were similar between groups, estimated GFR was lower in arterial sclerosis (70.5±33.3 versus 84.5±26.6 ml/min per 1.73 m^2, $P=0.03$), and chronicity index (thrombotic microangiopathy=3.5, lupus vasculopathy=4.5, and arterial sclerosis=2.5) was higher in all renal vascular lesions subgroups versus controls (1.0, $P<0.05$). In 133 patients with similar follow-up, the association between renal vascular lesions and vascular events was significant (Fisher exact test, $P=0.002$) and remained so after multivariate analysis (exact conditional scores test, $P=0.04$), where the difference between arterial sclerosis and uncomplicated vascular immune deposits was most noticeable (odds ratio [95% confidence interval]=8.35[0.98, 83.12], $P=0.05$). The associations between renal vascular lesions, renal outcomes, and death were not significant, likely because of insufficient power.

Conclusions Renal vascular lesions are common in SLE patients with nephritis and may be associated with arterial vascular events.

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Introduction

Renal pathology in SLE is characterized by mesangial cell proliferation, inflammation, necrosis, basement membrane abnormalities, immune complex deposition, and vascular abnormalities (1,2). Renal vascular lesions (RVLs) have been classified in a number of studies (3–5); however, they are not included in the International Society of Nephrology/Renal Pathology Society (ISN/RPS) revised 2004 criteria for lupus nephritis (LN) (6). Although associations between RVLs and renal outcomes have been proposed (3,4,7), the literature is hampered by its largely retrospective nature, and it has been argued that, because no clear definitions exist for many of the described lesions, their prognostic significance is not well understood (3,5).

Our study describes the clinical characteristics at time of renal biopsy of patients with RVLs and elucidates the following information: are vascular lesions found on renal biopsy in patients with SLE associated with (*1*) increased mortality, (2) increased risk of extrarenal vascular events, or (*3*) poor renal outcomes?

Materials and Methods

Patients with renal biopsy data were selected from the database registry of the University of Toronto Lupus Clinic (UTLC). Since 1970, the UTLC has prospectively followed patients who fulfilled at least four of the 1971 or 1982 American College of Rheumatology classification criteria (8) or three criteria and had positive histology. All patients gave their informed consent and were followed according to a standard protocol, which has had continuous approval from the University Health Network Research Ethics Board.

Renal biopsies (207), performed as clinically indicated, from 164 patients with SLE were identified from 1970 to 2007, reviewed by two independent pathologists, and scored based on the ISN/RPS revised 2004 criteria for LN (6); a third pathologist was used for consensus scoring if disagreement occurred. Only one biopsy per patient was included in the study. Three patients with overlapping lupus vasculopathy (LV) and thrombotic microangiopathy (TMA) were excluded to avoid confounding, leaving 161 patients

for analysis. RVLs were defined according to the classification described in the work by Appel *et al.* (1,5). (*1*) LV: necrotizing changes in the vessel wall associated with abundant immune deposits causing luminal narrowing or occlusion that are often positive for fibrin, immunoglobulin, and complement with absence of inflammatory cells. (*2*) TMA: a luminal narrowing and occlusion by accumulation of eosinophilic and fuchsinophilic material with staining for fibrin with absence of discrete immune, histologically identical to hemolytic uremic syndrome–thrombotic thrombocytopenic purpura (TTP/HUS) lesions. (*3*) Arterial Fibrinoid Necrosis (lupus vasculitis): the small- and medium-sized arteries are affected; there is a prominent inflammatory cell infiltrate with mural inflammation and fibrinoid necrosis resembling microscopic polyangiitis. (*4*) Uncomplicated vascular immune deposits (UVIDs): lesions with vascular immune deposits that, when visualized by light microscopy, reveal that, despite the vessels appearing normal, immune complex deposits are present in the walls of arterioles and to a lesser extent, in the veins; no thrombosis or inflammatory infiltrate is present, and immunofluorescence is positive for immunoglobulins and complement. (*5*) Arterial sclerosis (AS) and arteriolar hyalinosis: control patients were selected who had renal biopsies without evidence of RVL.

SLE Disease Activity and Damage

Disease activity was determined using the SLE disease activity index 2000 (SLEDAI-2K) within 3 months of renal biopsy (9). The Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (10) was used to assess cumulative damage at the time of the relevant biopsy or within 6 months.

Renal Variables

Estimated GFR (eGFR) was calculated using the Modification of Diet in Renal Disease Study Group equation (11). ESRD was defined as serum creatinine of $\geq$200 μmol/L and/or eGFR $\leq$15 ml/min per 1.73 m^2 and/or dialysis for >6 months or having a kidney transplant (12). A secondary renal outcome was CKD as defined according to Kidney Disease: Improving Global Outcomes guidelines (12,13) as a sustained eGFR <60 ml/min per 1.73 m^2.

Vascular Risk Factors

Age, mean arterial pressure (MAP), smoking history, body mass index, blood lipids, history of diabetes, and use and cumulative dose of steroids were recorded at the time of biopsy. Arterial vascular events (composite variable) included myocardial infarction, angina, cerebrovascular accident, and transient ischemic attacks.

Outcomes Analyses

To explore associations between renal vascular findings and clinical manifestations of disease, a subset of the cohort of the 161 patients was selected if they had a period of observation in the UTLC database covering 8 years pre-biopsy and 7 years post-biopsy. This 15-year time window was chosen to maximize our use of the registry data, and it allowed a sufficient pre- and post-biopsy time period for events to occur and have biologic plausibility. Methodologically, it anchored the period of observation to a comparable period within an individual patient's time frame and between patients. This subset included 133 patients with a renal biopsy before December 31, 2003.

Demographic information, including ethnicity, and medication profile were also retrieved. Presence of antiphospholipid antibody syndrome was recorded according to Sydney criteria but without the test for the anti–β2-glycoprotein 1 antibody assay, because it is not available (14).

Statistical analysis was performed using SAS (version 9.2; SAS institute, Cary, NC) statistical software. When comparing two groups for demographics and baseline characteristics, the *t* and the Wilcoxon rank sum tests were used for continuous variables, and the chi-squared and Fisher exact tests were used for categorical variables. Four series of univariate and multivariate models based on logistic regressions were constructed to evaluate associations between the variables assessed and clinical outcomes. Specifically, for each clinical outcome, its association with each of the variables, such as RVL, patient demographic features, and baseline renal characteristics, was first examined, and variables that were significant and clinically relevant were considered for inclusion in the multivariate models, which were then assessed according to goodness of fit criteria (15). Given the small number of events, the exact method was used (16), and continuous variables in the model were dichotomized using clinically relevant cutoffs. Both the exact and mid-*P* values were reported as recommended in the literature for analyzing data with small sample sizes; the mid-*P* value was provided as a sensible way to overcome the conservatism in the exact method because of discreteness (17,18). A sensitivity analysis was conducted for each model by considering four scenarios for those patients who died or were lost to follow-up: (*1*) both cases had no event; (*2*) the former (died) had no event, and the latter (lost to follow-up) had an event; (*3*) the former had an event, and the latter had no event; and (*4*) both cases had an event. In cases of death, sensitivity analyses were conducted only for scenarios *3* and *4*.

Results

In this study, 207 biopsies from 164 patients were examined. Three patients who had both TMA and LV on renal biopsy were excluded to avoid confusion. The present analysis is based on 161 patients: 13 (8.1%) patients had TMA, 5 (3.1%) patients had LV, 10 (6.2%) patients had UVID, and 0 patients had lupus vasculitis. AS alone was frequent, occurring in 93 patients (57.8%). Lesions of mild to moderate AS were seen in 27 (96.4%) patients with TMA, LV, or UVID (only one case of TMA had concomitant severe AS); 40 patients (24.8%) had no RVL and therefore, were used as controls (Figure 1).

Demographic Characteristics

The characteristics of subjects at the time of renal biopsy are reported in Table 1. There was no difference between TMA and control subjects with respect to gender distribution, but AS and LV patients were older. Lupus disease activity at time of biopsy was higher in the LV group compared with controls. All subgroups of patients with RVLs had higher percentages of people with damage (Systemic

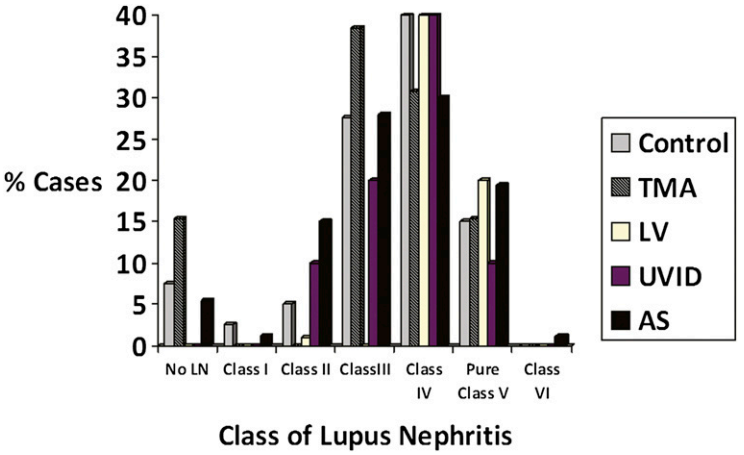

Figure 1. | **Proportion of cases of renal vascular lesions distributed among the renal biopsies based on the class of lupus nephritis.** There was no significant difference between classes of nephritis with respect to the relative distribution of renal vascular lesions. AS, arterial sclerosis; LV, lupus vasculopathy; TMA, thrombotic microangiopathy; UVID, uncomplicated vascular immune deposits.

Lupus International Collaborating Clinics/American College of Rheumatology damage index score ≥1) than controls, except the UVID group (Table 1); 0 of 13 patients with TMA had a diagnosis of TTP/HUS at the time of renal biopsy or during the course of follow-up.

Renal Variables

Renal variables are reported in Table 2. At the time of renal biopsy, the eGFR was lower in patients with AS and LV compared with controls. The majority of the patients had proliferative LN in proportions that were similar among all groups; 10 patients had no evidence of LN on biopsy (5 patients had only AS lesions, and 2 patients had only TMA) (Table 2). The chronicity score was higher in patients with all RVLs groups compared with controls, except the UVID group.

Cardiovascular Risk Factors

The presence of cardiovascular disease risk factors is reported in Table 2. The MAP was significantly higher in all patient groups with RVLs. The remainder of the risk factors was not different between groups. In total, 140 patients (86.9%) had at least one available anticardiolipin antibody or lupus anticoagulant test on record ever. There were no significant differences in the number of patients who met criteria for the antiphospholipid antibody syndrome (2 control [5.0%], 2 TMA [15.4%], 0 LV, 0 UVID, and 4 AS [4.3%] patients).

Outcomes: Univariate and Multivariate Analyses

Four models were generated to determine if RVLs were predictive of death, arterial vascular events, or renal outcomes on a subset of 133 patients with available follow-up. For the models studying arterial vascular events, the association was tested over a period of 15 years (8 years before and 7 years after the biopsy). A sensitivity analysis was conducted for each model by considering four scenarios, as described above, for those patients who died or were lost to follow-up for each outcome.

A total of 20 patients died within 7 years of follow-up: 2 patients in the control group (2/34, 5.9%), 11 patients in the AS group (11/76, 14.5%), 3 patients with TMA (3/10, 30.0%), 2 patients with LV (2/4, 50.0%), and 2 patients with UVID (2/9, 22.2%). A total of 16 patients were lost to follow-up during this period of time. On univariate regression analysis, RVLs were not associated with increased mortality, and this finding did not change with sensitivity analysis. On multivariate analysis, higher SLEDAI-2K at the time of renal biopsy was associated with mortality, and the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers was protective (Table 3).

A total of 14 patients had systemic arterial vascular events within this 15-year period: 2 patients in our control group (2/34, 5.9%), 4 patients in the AS group (4/76, 5.3%), 3 patients in the TMA group (3/10, 30.0%), 2 patients in the LV group (2/4, 50.0%), and 3 patients in the UVID group (3/9, 33.3%). On sensitivity analysis, considering scenario *1*, we assumed that, if a patient died or was lost to follow-up within 7 years of renal biopsy, then the patient had no thromboembolic event. On univariate analysis, the association between RVL groups (for RVL types and control) and thrombotic events was significant (Fisher exact test, P=0.002; exact conditional scores test, P=0.006), with the greatest group difference occurring between AS and UVID (odds ratio [OR; 95% confidence interval (CI)=8.57 [1.02, 65.71], P=0.047 and 8.57 [1.33, 51.87], mid-P=0.03); none of the individual lesions (RVL types) were marked differently from the controls for thrombosis. On sensitivity analysis, the results from scenario *2* were similar to the results from scenario *1*; the results from scenario *3* were similar to the results from scenario *4*. When patients who died during follow-up were all assumed to have had an arterial vascular event (scenario *3*), the presence of TMA was associated with arterial vascular events (OR [95% CI]=5.5 [1.0, 34.9]). On multivariate analysis under scenario *1*, the association between RVL groups and arterial vascular events was significant (exact conditional scores test, P=0.04), and the difference between AS and UVID was most noticeable (OR [95% CI]=8.35 [0.98, 83.12], P=0.05); compared with the

Table 1. Demographic features of SLE patients with renal vascular lesions compared with controls (*n*=161)

	Controls (*n*=40)	TMA (*n*=13)	*P*	LV (*n*=5)	*P*	UVID (*n*=10)	*P*	AS (*n*=93)	*P*
Age at time of renal biopsy (year)	33.1±8.9	35.1±12.2	0.50	44.4±8.9	0.01	39.1±10.5	0.07	37.9±13.0	0.02
Female (*n*; %)	35 (87.5)	11 (84.6)	1.00	5 (100.0)	0.40	9 (90.0)	0.83	74 (79.6)	0.28
Ethnicity (*n*; %)									
Caucasians	22 (55.0)	10 (76.9)	—	3 (60.0)	—	5 (50.0)	—	59 (63.4)	—
African Americans	4 (10.0)	2 (15.4)	—	1 (20.0)	—	2 (20.0)	—	15 (16.1)	—
SLEDAI at time of biopsy	10.5±6.2	11.8±8.0	0.57	20.8±7.7	0.001	15.3±9.2	0.06	9.9±5.5	0.59
SDI score ≥1 (*n*; %)	5 (14.3)	4 (57.1)	0.03	4 (80.0)	0.001	2 (22.2)	0.56	35 (45.4)	0.001
Medications in the year post biopsy									
cumulative steroid dose (g) median [IQR]	7.6 [5.7, 42.9]	23.2 [5.1, 66.1]	0.39	5.0 [3.2, 7.2]	0.19	10.1 [6.0, 64.5]	0.71	9.7 [4.4, 25.2]	0.77
immunosuppressive drugs[a] (*n*; %)	23 (60.5)	11(84.6)	0.11	2 (50.0)	0.68	4 (40.0)	0.24	52 (59.1)	0.88
antimalarial (*n*; %)	21 (55.3)	2(15.4)	0.01	1 (25.0)	0.25	6 (60.0)	0.79	45 (51.1)	0.70
ACE inhibitor or ARB (*n*; %)	9 (23.7)	7(53.8)	0.08	2 (50.0)	0.25	5 (50.0)	0.10	38 (43.2)	0.04
statins (*n*; %)	2 (5.3)	2 (15.4)	0.27	0 (0.0)	1.00	2 (20.0)	0.13	17 (19.3)	0.04
ASA (*n*; %)	2 (5.3)	1 (7.7)	0.25	0 (0.0)	1.00	2 (20.0)	0.13	10 (11.4)	0.03
coumadin (*n*; %)	1 (2.6)	2 (15.4)	0.16	0 (0.0)	1.00	0 (0.0)	1.00	1 (1.1)	0.51

Results are reported as mean (SD) or percentage or median and interquartile range. $P<0.05$ is considered a statistically significant difference. TMA, thrombotic microangiopathy on renal biopsy; LV, lupus vasculopathy on renal biopsy; UVID, uncomplicated vascular immune deposits on renal biopsy; AS, arterial sclerosis on renal biopsy; SLEDAI, SLE Disease Activity Index within 3 months of renal biopsy; SDI, Systemic Lupus International Collaborating Clinics Damage Index within 6 months of renal biopsy; IQR, interquartile range; ACE or ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; ASA, acetylsalicylic acid.

[a]Immunosuppressive drug use within 1 year of renal biopsy: azathioprine, mycophenolate mofetil, mycophenolate sodium, and cyclophosphamide (intravenous or oral).

Table 2. Baseline renal and cardiovascular characteristics in patients with and without renal vascular lesions on renal biopsy

	Controls (n=40)	TMA (n=13)	P	LV (n=5)	P	UVID (n=10)	P	AS (n=93)	P
Renal characteristics									
serum creatinine μmol/L median (IQR)	76.0 (66.0–92.0)	95.0 (72.0–172.0)	0.14	124.0 (56.0–215.0)	0.42	100.5 (74.0–119.5)	0.07	92.5 (71.0–136.0)	0.01
baseline eGFR (ml/min per 1.73 m^2)	84.5±26.6	76.0±43.7	0.57	67.9±38.5	0.05	75.2±20.6	0.36	70.5±33.3	0.03
baseline proteinuria (g/d) median (IQR)	1.6 (0.6–3.5)	2.2 (1.7–5.1)	0.27	2.5 (0.6–5.2)	0.61	2.9 (1.1–4.9)	0.38	1.6 (0.3–3.6)	0.91
ISN/RPS classification (n, %)									
No lupus nephritis	3	2	—	0	—	0	—	5	—
I	1 (2.5)	0 (0.0)	1.00	0 (0.0)	1.00	0 (0.0)	1.00	1 (1.1)	0.51
II	2 (5.0)	0 (0.0)	1.00	0 (0.0)	1.00	1(10.0)	0.49	14 (15.0)	0.15
III	11 (27.5)	5 (38.5)	0.50	0 (0.0)	0.31	2(20.0)	1.00	26 (28.0)	0.96
IV	17 (42.5)	4(30.8)	0.45	4(80.0)	0.17	6 (60.0)	0.48	28 (30.1)	0.17
V	6 (15.0)	2(15.4)	0.97	1(20.0)	1.00	1 (10.0)	1.00	18 (19.4)	0.55
VI	0 (0.0)	0 (0.0)	/	0 (0.0)	/	0 (0.0)	/	1 (1.1)	1.00
Renal activity index median (IQR)	4.3 (0.8–8.0)	5.0 (3.0–7.0)	0.64	8.0 (8.0–8.5)	0.20	7.3 (4.0–9.0)	0.22	1.5 (0.5–5.0)	0.10
Renal chronicity index median (IQR)	1.0 (0.0–3.0)	3.5 (0.5– 4.5)	0.05	4.5 (3.0–7.5)	0.01	3.0 (1.0–3.0)	0.13	2.5 (1.0–3.5)	0.01
Body mass index (kg/m^2) median (IQR)	24.0 (21.9–28.3)	21.1 (20.2–26.5)	0.21	18.2 (18.2–21.9)	0.14	21.5 (21.0–21.9)	0.06	24.9 (20.6–28.6)	0.95
Total cholesterol (mmol/L) at time of renal biopsy	6.3±1.8	6.5±1.4	0.69	6.8±1.9	0.55	7.7±1.9	0.06	6.3±2.2	0.97
MAP at time of renal biopsy (mmHg)	91.6±10.9	108.9±21.4	0.01	114.9±11.3	<0.001	102.2±12.2	0.01	101.9±13.9	<0.001
Smoker ever (%)	4 (10.0)	1 (8.3)	0.86	0 (0.0)	1.00	1 (10.0)	1.00	17 (18.5)	0.22
Diabetes ever (%)	2 (5.1)	0 (0.0)	1.00	0 (0.0)	1.00	1 (10.0)	0.56	7 (7.8)	0.72

Results are reported as mean (SD) or percentage or median and interquartile range. $P<0.05$ is considered a statistically significant difference. For conversion of serum creatinine from SI units to conventional units, divide by 88.4; for conversion of cholesterol from SI units to conventional, divide by 0.0259. TMA, thrombotic microangiopathy on renal biopsy; LV, lupus vasculopathy on renal biopsy; UVID, uncomplicated vascular immune deposits on renal biopsy; AS, arterial sclerosis on renal biopsy; IQR, interquartile range; eGFR, estimated GFR; ISN/RPS, International Society of Nephrology/Renal Pathology Society; MAP, mean arterial pressure.

Table 3. Associations between clinical features and death, CKD, and arterial vascular events

Variable	OR (95% CI)	*P* Value	95% Mid-*P* CI	Mid-*P* Value
Model 1 outcome: death				
RVL[a]		0.21		0.21
AS versus control	3.65 (0.66, 38.78)	0.19	(0.77, 27.39)	0.11
TMA versus control	12.18 (0.59, 268.30)	0.12	(0.88, 178.73)	0.06
LV versus control	3.21 (0.03, 222.9)	1.00	(0.06, 131.87)	0.55
UVID versus control	4.08 (0.20, 81.4)	0.50	(0.30, 54.86)	0.28
age at the time of biopsy (>35 versus ≤35 yr)	3.31 (0.84, 16.64)	0.10	(0.95, 13.74)	0.06
ACE inhibitor or ARB use within 1 year postrenal biopsy	0.09 (0.01, 0.61)	0.006	(0.01, 0.52)	0.003
SLEDAI (>12 versus ≤12)	5.39 (1.17, 30. 22)	0.03	(1.36, 24.64)	0.02
Model 2 outcome: vascular events				
RVL		0.04		0.04
AS versus control	0.76 (0.07, 10.98)	1.00	(0.10, 7.57)	0.78
TMA versus control	5.62 (0.24, 149.8)	0.40	(0.36, 97.85)	0.21
LV versus control	11.73 (0.12, 768.28)	0.37	(0.24, 444.04)	0.19
UVID versus control	6.24 (0.42, 141.20)	0.25	(0.57, 93.07)	0.14
age at time of biopsy (>35 versus ≤35 yr)	1.55 (0.32, 8.94)	0.79	(0.37, 7.27)	0.56
smoker	5.69 (0.95, 42.24)	0.06	(1.15, 32.79)	0.03
24-hour proteinuria (≥4.4 versus <4.4 g/d)	5.62 (1.06, 34.49)	0.04	(1.26, 27.87)	0.02
class V lupus nephritis	0.18 (0.01, 1.25)	0.10	(0.02, 1.04)	0.05
Model 3 outcome: CKD[b]				
RVL		0.49		0.49
AS versus control	0.48 (0.14, 1.54)	0.26	(0.16, 1.39)	0.18
TMA versus control	0.27 (0.02, 2.84)	0.38	(0.03, 2.16)	0.22
LV versus control	0.19 (0.01, 4.37)	0.42	(0.01, 2.91)	0.23
UVID versus control	0.65 (0.07, 7.49)	1.00	(0.09, 5.54)	0.68
age at time of biopsy (>35 versus ≤35 yr)	0.93 (0.33, 2.49)	1.00	(0.36, 2.30)	0.88
eGFR (≥90 versus <90 ml/min per 1.73 m^2)	0.15 (0.05, 0.43)	<0.001	(0.05, 0.40)	<0.001
MAP (>100 versus ≤100 mmHg)	3.56 (1.28, 10.57)	0.01	(1.39, 9.56)	0.01

Multivariate analysis was used to determine associations, and $P<0.05$ was considered statistically significant. Variables for the model were selected according to clinical relevance and statistical significance as well as goodness of fit criteria for model assessment. OR, odds ratio; CI, confidence interval; RVL, renal vascular lesion; AS, arterial sclerosis on renal biopsy; TMA, thrombotic microangiopathy on renal biopsy; LV, lupus vasculopathy on renal biopsy; UVID, uncomplicated vascular immune deposits on renal biopsy; ACE or ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; SLEDAI, SLE Disease Activity Index within 3 months of renal biopsy; eGFR, estimated GFR; MAP, mean arterial pressure.

[a]Global significance of RVL in the model.

[b]CKD defined as estimated creatinine clearance calculated by Modification of Diet in Renal Disease Study Group equation ≤60 ml/min per 1.73 m^2 on two or more occasions.

control group, there is no significant association for individual lesion type (Table 3). Additionally, patients with ≥4.4 g/d proteinuria at the time of renal biopsy, which represents the upper third quartile in our cohort, were more likely to have a systemic arterial vascular event (Table 3).

A total of 71 patients had CKD within 7 years postrenal biopsy, including 17 patients in the control group (17/34, 50.0%), 42 patients with AS (42/76, 55.3%), 5 patients with TMA (5/10, 50.0%), 2 patients with LV (2/4, 50.0%), and 5 patients with UVID (5/9, 55.6%). On univariate analysis, none of the RVLs were associated with CKD on sensitivity analysis (data not shown). In multivariate analysis, at the time of renal biopsy, an MAP >100 was associated with CKD, and a higher eGFR was protective. None of the RVLs were independently associated with CKD. Our sensitivity analysis did not alter these findings.

A total of five patients had ESRD within 7 years after renal biopsy, including one patient in the AS group (1/76, 1.3%), three patients in the TMA group (3/10, 30.0%), one patient in the LV group (1/4, 25.0%), and zero patients in the UVID or control groups. We could not perform additional analysis, because the number of outcomes was too small.

Discussion

To our knowledge, this study is the first to link RVLs to prospectively followed and recorded clinical outcomes in a cohort of patients with SLE. This study shows that RVLs, especially AS, are prevalent in patients with nephritis. Although RVLs may not be independently associated with renal outcomes or mortality, they are associated with an increased risk of systemic arterial vascular events. Interestingly, two variables unrelated to RVLs were significant in our multivariate model on mortality: use of an ACE inhibitor within 1 year of biopsy was associated with a strong protective effect, whereas a higher disease activity measured by SLEDAI at the time of biopsy was a predictor of increased mortality at 7 years.

Longitudinal observational studies such as our study are limited by attrition, and data in the study are dependent on capture, recording, and reviewer's biases if not blinded to the hypothesis. The work by Gladman *et al.* (19) has previously reported that 11% of the UTLC is lost to follow-up, which is similar to our findings (12%). Because renal biopsies were conducted as clinically necessary and not part of a standard protocol, the analyses may be biased by indication, and the renal outcome correlations may have been obscured by lesions other than vascular lesions. However, we believe that these limitations reflect real-life practice, and contrasting the presence or lack of presence of vascular lesions in nephritis remains an interesting comparison. Our observations are also limited by large CIs because of a small number of observations (20), and in general, our study has limited power to make conclusions about subjects with LV. Because the numbers of vascular events were small, we were not able to comment on any association between type of vascular event (*e.g.*, arterial or venous) and type of lesion, and we were unable to examine the association between RVLs and ISN/RPS subclasses of nephritis. AS lesions occurred on 96% of the biopsies that had other RVL lesions, and this finding may have confounded our results. The AS observed in all but one case with LV or TMA was of mild or moderate severity and could be compared with a group of patients with AS without TMA or LV. Lastly, other vascular and thrombophilic risk factors, such as clotting factor deficiencies, are not captured.

RVLs in SLE were first described in autopsy series (21,22). However, clinical outcomes were first described in the work by Banfi *et al.* (4), which retrospectively analyzed 285 renal biopsies; 27.7% had RVLs (9.5% with LV, 8.4% with TTP/HUS-like changes, 7.0% with AS, and 2.8% with vasculitis). The prevalence of RVLs and more specifically, AS in our study was much higher. However, in line with the findings of our present study, patients with RVLs had higher serum creatinine and were more likely to be hypertensive compared with controls, whereas degree of proteinuria was similar between the various groups.

In contrast to previous reports (3,4), we found no association between the proliferative subtypes of lupus nephritis and the type of RVLs. This finding may be partially explained by the introduction of the ISN/RPS (6) classification criteria for lupus nephritis and may have resulted in reclassification of some subjects. The chronicity and activity indices in our patients were also instructive. Unlike previously published data (3,4), we found that renal biopsies with RVLs did not differ from controls in their activity scores, although they did have higher chronicity scores in keeping with previous reports (3,4).

In our study, five patients in the RVL group and zero patients in the control or UVID groups developed ESRD over 7 years of follow-up. The work by Descombes *et al.* (3) reported that patients with arteriosclerotic changes or LV on biopsy had similar renal outcomes compared with those patients without RVLs; however, the latter group received more immunosuppressive medications, suggesting more aggressive disease. This finding was not felt to be the case in our cohort. In contrast, the work by Banfi *et al.* (4) reported that the probability of renal survival was decreased in patients with RVLs (hazard ratio=5.49 [95% CI=2.6, 11.3]); however, the cohort had more significant renal failure at the time of biopsy. All studies concluded that survival is not predicted by the presence of RVLs.

Another novel finding of our study was the demonstration of an increased risk of systemic arterial vascular events in patients with RVL. The precise magnitude of this effect is difficult to appreciate because of wide CIs. This is a finding that warrants exploration in future studies. The increased risk of vascular events may be partially explained by an increased prevalence of hypertension in patients with RVLs.

This study is the first of patients followed in a prospective cohort with RVLs on biopsy. The presence of any RVLs was not independently associated with renal outcomes or overall survival in our cohort, although we had limited power to examine LV outcomes. The mortality at 7 years post-biopsy was decreased in those patients prescribed an ACE inhibitor within 1 year of their biopsy and increased in those patients with a higher lupus disease activity at the time of biopsy. The presence of RVLs was found to be associated with hypertension and diminished renal function at time of renal biopsy, and these two variables were the only significant predictors of poor renal function in the multivariate analysis. We found an association between RVL and systemic arterial vascular events in the absence of other traditional risk factors for cardiovascular disease and independently of proteinuria.

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Disclosures

None.

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