Renal histopathological changes and clinical characteristics of antiphospholipid nephropathy in lupus nephritis patients

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Objective
The aim of the present study was to evaluate the renal histopathological changes and clinical characteristics associated with antiphospholipid nephropathy (APSN) in lupus nephritis (LN) patients.

Patients and methods
This study included 50 LN patients referred for renal biopsy. Patients underwent clinical and laboratory assessments 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 vascular lesions of APSN – acute (thrombotic microangiopathy) and chronic (fibrous intimal hyperplasia, fibrous arterial/arteriolar occlusion and focal cortical atrophy).

Results
APSN lesions were found in 17/50 patients (34%); furthermore, 7/50 patients (14%) had thrombotic microangiopathy lesions, whereas chronic APSN lesions were detected in 15/50 patients (30%). LN patients with APSN had significantly higher age and Systemic Lupus International Collaborating Clinics scores ($P = 0.032$ and 0.004, respectively), but there were no differences in renal and antiphospholipid syndrome manifestations. Lupus anticoagulant positivity was significantly more frequent in patients with APSN ($P = 0.002$). LN patients with APSN had significantly higher renal chronicity scores ($P = 0.033$) with more frequent interstitial fibrosis and tubular atrophy ($P = 0.006$ for each). There was no significant difference in the distribution of LN classes in patients with and without APSN.

Conclusion
APSN is frequently found in LN patients irrespective of the LN class and antiphospholipid syndrome manifestations. It is associated with lupus anticoagulant positivity, higher disease damage, and renal biopsy chronicity indices, particularly interstitial fibrosis and tubular atrophy. Only the identification of intrarenal vascular lesions could characterize these patients, thus is it not time to revisit the ISN/RPS classification of LN to include renal vascular lesions of APSN.

Keywords:
antiphospholipid nephropathy, antiphospholipid syndrome, lupus anticoagulant, lupus nephritis, systemic lupus erythematosus

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Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by arterial/venous thrombosis and recurrent pregnancy loss in association with persistently positive antiphospholipid antibodies (aPLs), mainly lupus anticoagulant (LAC), anticardiolipin antibodies (aCL) and anti-β2-glycoprotein-I antibodies (anti-β2-GPI) [1]. aPLs are detected in about 30–40% of patients with systemic lupus erythematosus (SLE), whereas arterial or venous thrombosis develop in nearly one-third of these patients [2].

In both primary and secondary APS the kidney is a major target organ. Antiphospholipid nephropathy (APSN) is a vaso-occlusive nephropathy characterized by vascular lesions in the glomeruli, arterioles and/or interlobular arteries in patients with aPLs. APSN vascular lesions may be acute, also known as thrombotic microangiopathy (TMA), and/or chronic, such as arteriosclerosis, fibrous intimal hyperplasia (FIH), fibrous arterial/arteriolar occlusion (FAO), tubular thyroidization and focal cortical atrophy (FCA) [3–5].

APSN has been described in patients with primary APS, SLE-related APS and SLE/non-APS patients with aPLs [6]. Lupus nephritis (LN) is responsible for the major share of morbidity and mortality in SLE patients and available evidence seems to indicate

a poorer prognosis for LN with superimposed APSN [7–10]. In LN, renal lesions related to APSN may be overshadowed by those related to the LN itself [11]. Therefore, whether APSN is an entity with clinical characteristic and histological features completely distinct from LN [12] or whether there is a clinicopathological continuum between LN and APSN [13,14] remains a key area of debate, and is it possible to identify distinct clinical and histological features characteristic of APSN? [11].

Accordingly, we aimed to evaluate the renal histopathological changes and clinical characteristics of APSN in LN patients.

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, Faculty of Medicine, Kasr Al-Ainy Hospital from May 2012 to April 2014. All patients fulfilled the American College of Rheumatology revised classification criteria for the diagnosis of SLE [15]. 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.

Pregnant patients and/or those with vascular lesions, possibly due to other causes of renal microangiopathy, malignant hypertension, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, postpartum renal failure, diabetic nephropathy, human immunodeficiency virus 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) [16] and disease damage by Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for SLE [17].

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). 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-β2-GPI IgG/IgM antibodies were determined using IgG/IgM aCL and IgG/IgM anti-β2-GPI enzyme-linked immunosorbent assays (Orgentec Diagnostika GmbH, Mainz, Germany), respectively, according to the manufacturer's instructions. Each 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) greater than 20 for aCL IgM. LAC using activated partial thromboplastin time, diluted Russell's viper venom time and tissue thromboplastin inhibition test were also carried out.

Renal biopsies

The renal tissues were obtained by using the ultrasound-guided needle biopsy; specimens were fixed in 10% neutral buffered formalin and embedded in paraffin. Paraffin sections of 2–3 mm were stained with haematoxylin and eosin, 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 of the patients evaluated and classified the biopsy specimens according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis [18]. Activity and chronicity scores were classified according to the Activity and Chronicity Indices of Lupus Nephritis [19].

The diagnosis of APSN was made when at least one of the lesions suggestive of APSN was found. Lesions identified on biopsy were classified into acute or chronic according to the following:

(1) *Acute APSN*: presence of TMA, consisting of fibrin thrombi in arteries, arterioles and/or glomeruli [20].
(2) *Chronic APSN*: presence of FIH, consisting of myofibroblastic cellular proliferation in the intima with luminal narrowing of small arteries, FAO consisting of arterial fibrous occlusion and FCA with or without tubular thyroidization [21].

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 done using the independent sample *t*-test or Mann–Whitney test. A *P* value of less than 0.05 was considered significant.

Results

In this prospective study, 50 LN patients were included; 44 (88%) were females. At the time of kidney biopsy, the mean ± SD age was 25.9 ± 7.9 (range 12–51) years, and the disease duration was 5.14 ± 5.32 (range 0.25–33) years. The mean SLEDAI score was 17 ± 5 (range 5–26) and the mean SLICC/ACR score was 1 ± 1 (range 0–6).

All the studied patients had proteinuria greater than 0.5 g/day. All were antinuclear antibodies positive and 40 patients (80%) were anti-dsDNA positive.

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 of APSN in 17/50 patients (34%), acute APSN lesions (TMA) in seven (14%) (Fig. 1), chronic APSN lesions (FIH, FAO and/or FCA) in 15 (30%) (Fig. 2) and five had simultaneous acute and chronic lesions.

The mean ± SD age in the patients with and those without APSN was 29.6 ± 8.9 years and 24 ± 6.7 SD years, respectively ($P = 0.032$). Patients with APSN had longer mean ± SD disease duration (7.41 ± 7.73 years) than that of those without APSN (3.96 ± 3.04 years); however, the difference was not statistically significant ($P = 0.064$). Table 1 shows the clinical, laboratory and renal manifestations of the LN patients with and without APSN.

LN patients with APSN had significantly higher disease damage index (SLICC/ACR) scores than did the patients without APSN (2 ± 1 vs. 1 ± 1 SD, $P = 0.004$). However, no statistical significant difference was found between the patients with and those without APSN regarding disease activity by SLEDAI.

No statistical significant differences in APS manifestations were found between patients with and without APSN for either arterial/venous (A/V) thrombotic events or obstetric complications as seen in Table 1.

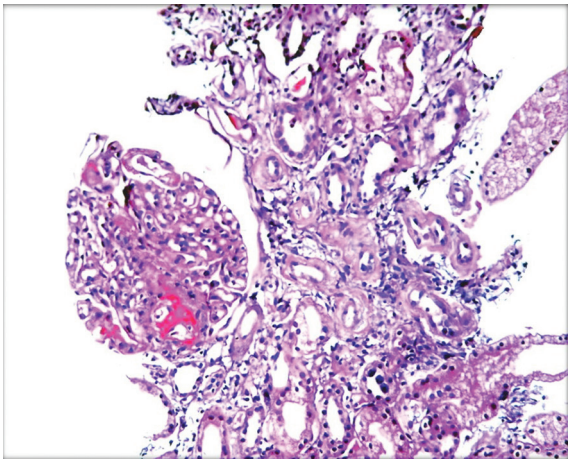
Renal manifestations to determine the degree of renal involvement, proteinuria, serum creatinine, eGFR, nephrotic syndrome and systemic hypertension (both systolic and diastolic blood pressure) were not significantly different between patients with and without APSN ($P > 0.05$ for all) (Table 1).

At the time of renal biopsy, LAC positivity was significantly more frequent in APSN patients ($P = 0.002$). However, no statistical significant differences were found regarding aCL IgG/IgM and anti-β2-GPI IgG/IgM ($P > 0.05$) (Table 1).

Distribution of LN class was as follows: class II seven (14%) patients, class III 14 (28%) patients, class IV 16 (32%) patients, class V four (8%) patients, class II+III seven (14%) patients and class II+V two (4%) patients. There was no statistical significant difference between patients with and without APSN ($P > 0.05$) in the ISN/RPS classes. However, the chronicity index score was statistically significantly higher in patients with APSN compared with patients without APSN (4 ± 3 vs. 2 ± 2 SD, $P = 0.033$), whereas the activity index showed no statistical significant difference ($P = 0.2$) (Table 2).

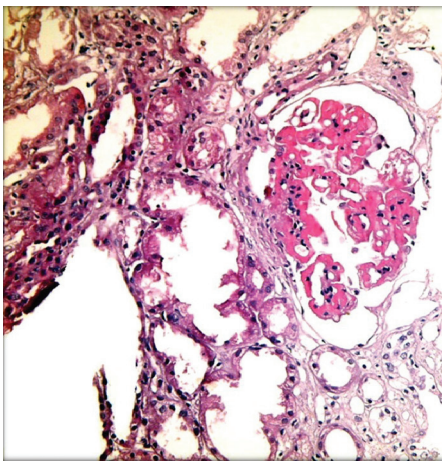
The presence of hyaline thrombi was the only activity lesion that was significantly higher in patients

Figure 1



The glomerulus shows evidence of thrombotic microangiopathy (TMA) (bloodless glomeruli and intracapillary thrombus) (haematoxylin-eosin stain).

Figure 2



Intimal thickening with cellular hyperplasia [fibrous intimal hyperplasia (FIH)] (Masson's trichrome stain).

Table 1 Clinical and laboratory features of the lupus nephritis patients with and without antiphospholipid nephropathy

Item	LN overall series (*n* = 50)	With APSN (*n* = 17)	Without APSN (*n* = 33)	*P* value
SLEDAI (mean ± SD)	17 ± 5	18 ± 5	16 ± 5	0.3
SLICC/ACR (mean ± SD)	1 ± 1	2 ± 1	1 ± 1	0.004*
Renal manifestations				
Increased creatinine [*n* (%)]	6 (12)	3 (17.6)	3 (9.1)	0.375
Nephrotic syndrome [*n* (%)]	14 (28)	6 (35.3)	8 (24.2)	0.511
Proteinuria (g/day) (mean ± SD)	3.08 ± 2.26	3.61 ± 2.04	2.8 ± 2.35	0.073
Serum creatinine (mg/dl) (mean ± SD)	0.9 ± 0.6	1 ± 0.7	0.8 ± 0.6	0.161
eGFR (ml/min/1.73 m²) (mean ± SD)	113.4 ± 58.8	93.7 ± 45.4	123.6 ± 62.9	0.122
Systemic hypertension [*n* (%)]	26 (52)	11 (64.7)	15 (45.5)	
Systolic pressure (mmHg) (mean ± SD)	135 ± 26	142 ± 2	132 ± 24	0.186
Diastolic pressure (mmHg) (mean ± SD)	88 ± 16	91 ± 16	87 ± 16	0.32
APS manifestations [*n* (%)]				
A/V thrombosis	10 (20)	4 (23.5)	6 (18.2)	0.717
Obstetric events	9/44 (20.5)	2/14 (14.3)	7/30 (23.3)	0.47
aPLs profile [*n* (%)]				
aCL IgG positivity	5 (10)	1 (5.9)	4 (12.1)	0.65
aCL IgM positivity	4 (8)	0 (0)	4 (12.1)	0.285
LAC positivity	20 (40)	12 (70.6)	8 (24.2)	0.002*
Anti-β2-GPI IgG positivity	7 (14)	3 (17.6)	4 (12.1)	0.667
Anti-β2-GPI IgM positivity	3 (6)	1 (5.9)	2 (6.1)	1

A/V, arterial/venous; aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; APSN, antiphospholipid nephropathy; eGFR, estimated glomerular filtration rate; LAC, lupus anticoagulant; LN, lupus nephritis; SLEDAI, SLE Disease Activity Index; SLICC/ACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology; β2-GPI, β2-glycoprotein I; *Significant *P* value.

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

Item	LN overall series (*n* = 50)	With APSN (*n* = 17)	Without APSN (*n* = 33)	*P* value
ISN/RPS classification for LN [*n* (%)]				
Class II	7 (14)	0 (0)	7 (21.2)	0.08
Class II+III	7 (14)	4 (23.5)	3 (9.1)	0.209
Class II+V	2 (4)	0 (0)	2 (6.1)	0.542
Class III	14 (28)	4 (23.5)	10 (30.3)	0.746
Class IV	16 (32)	7 (41.2)	9 (27.3)	0.353
Class V	4 (8)	2 (11.8)	2 (6.1)	0.597
Activity index (mean ± SD)	2 ± 2	3 ± 3	2 ± 2	0.2
Active lesions [*n* (%)]				
Endocapillary proliferation	26 (52)	11 (73.3)	15 (65.2)	0.728
Wire loops	15 (30)	6 (35.3)	9 (27.3)	0.746
Hyaline thrombi	10 (20)	7 (41.2)	3 (9.1)	0.012*
Cellular crescents	4 (8)	3 (17.6)	1 (3)	0.108
Interstitial leukocytic infiltration	2 (4)	2 (11.8)	0 (0)	0.111
Fibrinoid necrosis	1 (2)	1 (5.9)	0 (0)	0.34
Chronicity index (mean ± SD)	3 ± 2	4 ± 3	2 ± 2	0.033*
Chronic lesions [*n* (%)]				
Sclerotic lesions	29 (58)	12 (70.6)	17 (51.5)	0.238
Interstitial fibrosis	21 (42)	12 (70.6)	9 (27.3)	0.006*
Tubular atrophy	2 (42)	12 (70.6)	9 (27.3)	0.006*
Fibrous crescents	8 (16)	5 (29.4)	3 (9.1)	0.102

APSN, antiphospholipid nephropathy; LN, lupus nephritis; *Significant *P* value.

with APSN compared with those without APSN ($P = 0.012$), as shown in Table 2.

Patients with APSN had statistically significantly more chronic lesions, interstitial fibrosis and tubular atrophy than did patients without APSN ($P = 0.006$ for each). Otherwise, no statistical significant difference was found between patients with and those without APSN (Table 2).

Discussion

Specific histological features of the intrarenal vasculature involvement due to the association of APSN with LN have been described [8,9,22–24]. There is growing evidence that seems to indicate a poorer prognosis and an ominous effect on long-term renal function, arterial hypertension and absence of response to immunosuppressive agents for LN patients with superimposed APSN [7–10,25].

In an attempt to identify these patients, this study was designed to evaluate the renal histopathological changes and clinical characteristics of APSN in lupus nephropathy patients.

In the present study, APSN was detected in 34% (17/50) of the studied LN patients, TMA was found in 14% of patients, whereas chronic APSN was found in 22%.

APSN in lupus patients was found to be associated with glomerulonephritis in around one-third of the biopsies reviewed as confirmed by different

studies [3,8,9,11,22,24,26]. These studies clearly established a positive association between APSN and LAC or aCLs. In our study, there was a significant association between APSN and LAC, but not with aCLs or anti-β2-GPI antibodies. Even though LAC is most strongly associated with the thrombotic complications associated with APS [27], there was no association between the histological features of APSN and clinical APS manifestations including arterial/venous thrombosis or obstetric events. Our results were similar to those reported by previous studies [22,24]. On the other hand, a strong association between APSN and APS-related manifestations, particularly arterial thrombosis and obstetric events, was reported in other studies [8,9,11].

At the time of the renal biopsy, LN patients with APSN were significantly older and had a higher disease damage index as measured by the SLICC/ACR damage index for SLE, but there was no relation to disease duration or disease activity by SLEDAI. In their study, Daugas *et al.* [8] reported a higher median age of patients with APSN than those with only LN. Furthermore, Cheunsuchon *et al.* [22] found that the prevalence of APSN was significantly much more in the adult than in the paediatric population. However, other studies could not find an association between APSN and older age or longer disease duration [9,11,24]. Other studies reported that APSN was significantly associated with high disease damage index (SLICC/ACR) [11,28].

We were not able to detect differences in serum creatinine level, eGFR, nephrotic syndrome, systemic hypertension and severity of proteinuria between patients with and without APSN. Of note, the impact of APSN on renal functions in LN patients is still controversial; renal function affection and arterial hypertension have been associated with APSN in some studies [8,9,22,23], whereas in their respective studies, Erre *et al.* [11] and Silvariño *et al.* [24] reported no differences in the frequency of systemic hypertension, nephrotic syndrome, severity of proteinuria and haematuria between patients with and without APSN, although they found that serum creatinine levels were significantly increased in patients with APSN compared with those without APSN.

In our series, APSN was independent of the ISN/RPS class of LN, as has been demonstrated in other studies [8,9,24]. An association between APS nephropathy and class IV LN was detected in the studies of Cheunsuchon *et al.* [22] and Miranda *et al.* [23]. However, further large prospective studies are required to prove or disprove an association between APSN and LN class.

Even though some studies reported no differences in renal activity or chronicity scores in LN patients with and without APSN at the time of renal biopsy [9,11], we found significantly higher chronicity indices on renal biopsy in APSN patients compared with LN patients without APSN, particularly interstitial fibrosis and tubular atrophy, although the results of this study showed no significant association between APSN and elevated serum creatinine or hypertension. However, Daugas *et al.* [8] in their study found interstitial fibrosis to be an independent risk factor for hypertension and elevated serum creatinine. There was no difference in the activity index. A finding was previously described by Cheunsuchon *et al.* [22] and Silvariño *et al.* [24], who found both activity and chronicity indices significantly higher in APSN patients compared with patients without APSN suggesting that the presence of an APSN may worsen the renal functional prognosis in SLE.

Despite reports that morphologic lesions of APSN aggravate kidney parenchymal damage in LN and that the progression of acute APSN to chronic lesions has been correlated with poor renal prognosis, we could not identify these patients clinically. The clinical characteristics of these patients were not related to the APS symptoms; the renal involvement was not specific and could be attributed to the LN. APSN still remains a pathologic diagnosis with specific vascular lesions that deserve to be included in the ISN/RPS 2003 classification of LN.

Conclusion

APSN is frequently found in LN patients irrespective of the LN class and APS manifestations. It is associated with LAC positivity, higher disease damage scores and renal biopsy chronicity indices, particularly interstitial fibrosis and tubular atrophy. Acute APSN was significantly associated with renal impairment and systemic hypertension. Only identification of intrarenal vascular lesions could characterize these patients; thus, is it not time to revisit the ISN/RPS 2003 classification of LN to include renal vascular lesions of APSN?

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Conflicts of interest

There are no conflicts of interest.

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