Antiphospholipid Syndrome (APS) Nephropathy in Catastrophic, Primary, and Systemic Lupus Erythematosus-related APS

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ABSTRACT. ***Objective***. Renal involvement in antiphospholipid syndrome (APS) has been poorly recognized. A renal small-vessel vasculopathy, defined as APS nephropathy, has recently been observed in small series of patients with primary APS (PAPS) and systemic lupus erythematosus (SLE)-APS. We examined the renal histologic, clinical, and laboratory characteristics of different groups of patients with APS including catastrophic APS (CAPS).

Methods. Our study included all CAPS (n = 6), PAPS (n = 8), and SLE-APS (n = 23) patients with biopsy-proven renal involvement who were referred to our departments. The kidney biopsy specimens were retrospectively examined by the same renal pathologist. APS nephropathy was diagnosed as previously described. Demographic, clinical, and laboratory data were recorded.

Results. All patients with CAPS had acute and chronic renal vascular lesions compatible with diagnosis of APS nephropathy. Thrombotic microangiopathy (TMA), the acute lesion, was observed in all CAPS patients. Fibrous intimal hyperplasia of interlobular arteries (FIH) and focal cortical atrophy (FCA) were the most common chronic vascular lesions, occurring in 4 of 6 (66.7%) and 3 of 6 (50%) patients with CAPS, respectively. TMA was detected in 3 of 8 (37.5%) patients with PAPS and in 8 of 23 (35%) patients with SLE-APS, while FIH and FCA were found with similar frequencies in all 3 groups. Hypertension, proteinuria, hematuria, and renal insufficiency were the most common renal manifestations of all APS groups.

Conclusion. Acute and chronic APS nephropathy lesions were detected in all 3 APS groups. Acute lesions were more prominent in CAPS, while chronic lesions were found with similar frequencies in all groups. Hypertension, proteinuria, hematuria, and renal insufficiency were the most common renal manifestations of all APS groups. (First Release Aug 1 2008; J Rheumatol 2008;35:1983–8)

Key Indexing Terms:
ANTIPHOSPHOLIPID SYNDROME KIDNEY BIOPSY RENAL

Antiphospholipid syndrome (APS) is a multisystem disorder characterized by arterial and/or venous thromboses, pregnancy morbidity, and the persistent presence of antiphospholipid antibodies (aPL), namely anticardiolipin antibodies (aCL), lupus anticoagulant (LAC), and anti-ß$_2$-glycoprotein I (anti-ß$_2$-GPI)[1,2]. APS may be primary (PAPS) or can be associated with other underlying disorders, especially systemic lupus erythematosus (SLE-APS). Less than 1% of APS patients develop catastrophic APS (CAPS), which is characterized by multiple small-vessel thrombosis over a short period of time that may lead to multiple organ involvement. CAPS has been associated with fatal outcome in almost half of patients[3,4].

Renal involvement in APS has been poorly recognized until recently[5,6]. Kidney biopsies are rarely performed in PAPS because several manifestations associated with renal involvement, such as hypertension or proteinuria, are often ignored in this group of patients. On the other hand, the majority of studies in patients with SLE-APS are focused on immune complex glomerulonephritis rather than renal vascular disease. Additionally, since most patients with APS receive anticoagulant treatment or frequently present with thrombocytopenia, renal biopsy in APS is often considered a high-risk procedure.

Renal small-vessel vasculopathy, defined as APS nephropathy, has been recently described in small series of patients with PAPS and SLE-APS[7-9]. This nephropathy was characterized by the presence of acute thrombotic lesions [thrombotic microangiopathy (TMA)] and chronic vasoocclusive lesions such as fibrous intimal hyperplasia (FIH), arterial or arteriolar occlusions, and focal cortical atrophy (FCA)[7-9]. At the 11th International Congress on aPL, APS

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nephropathy was considered as a feature associated with APS, not included in the revised classification criteria for definite APS[2].

Renal involvement represents one of the most common manifestations of CAPS; however, renal histopathology in CAPS remains unidentified. A possible explanation is that CAPS is a very rare disease, and further kidney biopsies are only rarely performed because of the catastrophic consequences of the syndrome. In isolated cases where a kidney biopsy was performed, TMA was the most frequently described histologic lesion, characterized by the presence of fibrin thrombi in glomeruli and/or arterioles[10,11]. The existence of other APS nephropathy lesions has not been previously examined in this group of patients.

We examined the renal histologic, clinical, and laboratory characteristics of 3 different groups of APS patients with biopsy-proven renal involvement and compared pertinent data.

MATERIALS AND METHODS

Our study included all patients with CAPS (n = 6), PAPS (n = 8), and SLE-APS (n = 23) and biopsy-proven renal involvement who were referred to or had regular followup in the Department of Pathophysiology, the largest referral center for autoimmune diseases in Greece, and the Rheumatology Department of the Euroclinic Hospital. Eighteen of the 23 patients with SLE-APS had also been included in our previous study examining APS nephropathy in SLE patients with positive aPL[9]. All the present patients were diagnosed between 1994 and 2006. CAPS was diagnosed according to the preliminary criteria for the classification of CAPS, established by the 10th International Congress on aPL[12]. APS was diagnosed according to the Sapporo criteria[13]; however, all patients also fulfilled classification criteria for definite APS suggested by the 11th International Congress on aPL[2]. The patients with SLE-APS fulfilled the above criteria for APS and at least 4 of the American College of Rheumatology criteria for the classification of SLE[14]. Patients with other diseases associated with renal microangiopathy such as malignant hypertension, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, paroxysmal nocturnal hemoglobinuria, HELLP syndrome, and systemic sclerosis were excluded from the study. The protocol was approved by the regional ethics committee, and informed written consent was obtained from the participants.

Renal biopsies were performed in patients who had proteinuria, abnormal urinary sediment, or elevated serum creatinine level. In patients with CAPS, all kidney biopsies were performed at the time of the acute CAPS events. Renal biopsy specimens were retrospectively examined, using light microscopy, by the same renal pathologist, who had no knowledge of the patient's medical status. The World Health Organization (WHO) class of lupus glomerulonephritis was reevaluated in cases with coexistent features of SLE[15]. The immunofluorescence microscopy findings were as described in the initial reports of the kidney biopsies. APS nephropathy was diagnosed when at least one of the following acute or chronic intrarenal vascular lesions was detected, according to previous publications: TMA characterized by fibrin thrombi in arterioles and/or glomeruli in the absence of immune deposits or inflammatory cells (acute lesion), or fibrous arterial and arteriolar occlusions, FIH, organized thrombi with or without recanalization, and FCA (chronic lesions)[2,7-9].

Demographic, clinical, and laboratory data of all patients were recorded: sex, age at renal biopsy, SLE duration (time from SLE diagnosis to biopsy), APS duration (time from APS diagnosis to biopsy), arterial or venous thrombosis and pregnancy morbidity according to the Sapporo criteria, pulmonary embolism, livedo reticularis, systemic hypertension (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg), increased serum creatinine (> 1.4 mg/dl), proteinuria (≥ 0.5 g/24 h), nephrotic syndrome (urinary protein concentration > 3.5 g/24 h), hematuria (> 10 red blood cells/high power field), renal insufficiency (creatinine clearance < 75 ml/min), thrombocytopenia (platelets < 100,000/mm^3), microangiopathic hemolytic anemia (schistocytes and nucleated red cells on peripheral smear), LAC, anti-ß$_2$-GPI, and IgG and IgM aCL. Anticoagulant therapy and treatment with corticosteroids, cyclophosphamide, intravenous immunoglobulin, or plasmapheresis during the acute CAPS events were also recorded. During the followup period (time from renal biopsy to the last visit), serum creatinine levels, renal insufficiency, endstage renal disease requiring dialysis or transplantation, and death were recorded.

Renal biopsy processing. Renal tissues obtained by needle biopsy were fixed in Bouin's fluid or in 10% neutral buffered formalin, gradually dehydrated, and embedded in paraffin. Paraffin sections 2–3 μm were stained with eosin and hematoxylin, periodic-acid Schiff reaction (PAS), silver-methenamine, Masson's trichrome, and elastica-Van Gieson stain. Small portions of fresh renal tissue were snap-frozen and stored at –80°C. Cryostat sections 4 μm were incubated with fluorescein-conjugated rabbit antisera against human IgG, IgA, IgM, C1q, C3, C4, κ and λ light chains, and fibrinogen and were examined by direct immunofluorescence. All antisera were purchased from Dako (Glostrup, Denmark).

In cases in which TMA was detected on light microscopy, additional paraffin sections were studied for fibrinogen deposits by immunohistochemistry. After dewaxing and dehydration, paraffin sections were transferred to Tris buffered saline (TBS) and subjected to antigen retrieval in a microwave oven for 15 min. After rinsing in distilled water for 5 min, the sections were incubated with peroxidase-blocking solution (3% H_2O_2) for 10 min, rinsed in distilled water for 5 min, and washed in TBS for 10 min. Further, they were incubated with polyclonal anti-human fibrinogen serum for 30 min at room temperature (1:1500, Dako) and washed in TBS for 10 min. EnVision/horseradish peroxidase was then applied for 30 min followed by TBS bath for 10 min. Sections were incubated with diaminobenzidine-^{3}HCl for 10 min and rinsed in distilled water for 5 min. PAS was used as counterstain. Control sections were treated with non-immune γ-globulin.

Laboratory examinations. IgG and IgM aCL and anti-ß$_2$-GPI antibodies were determined by enzyme-linked immunosorbent assay[16]. Cardiolipin 50 μg/ml in ethanol (Sigma Chemical, St. Louis, MO, USA) was used as antigen on polystyrene microtiter plates (Nunc, Naperville, IL, USA), which were left to dry overnight at 4°C. After washing with PBS, nonspecific binding sites were blocked by 10% bovine serum in PBS. LAC was assayed by activated thromboplastin time, kaolin clotting time, or dilute Russell's viper venom time and confirmed by mixture tests and correction by phospholipid excess according to the guidelines of the International Society on Thrombosis and Hemostasis[17].

Statistical analysis. Demographic, clinical, laboratory, and histological characteristics are presented as median (interquartile range) or n (%), as appropriate. Renal biopsy findings were compared between CAPS and PAPS or SLE-APS using the Z-test or Fisher's exact test for the categorical variables and the Kruskal–Wallis test for the continuous variables. The inflation of type I error due to multiple comparisons was corrected using the Bonferroni rule. A p value < 0.05 was considered significant. Statistical analysis was performed using the SPSS v. 13 statistical package (SPSS, Chicago, IL, USA).

RESULTS

All patients with CAPS (3 female, 3 male) were Caucasian. Four patients (Table 1, Patients 1, 3, 4, 5) had evidence of acute involvement of 3 or more organs at the same time, and 2 had acute involvement of 2 organs at the same time, according to the preliminary criteria for the classification of CAPS[12]. Renal biopsies were performed at the time of the

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Table 1. Clinical and laboratory characteristics of 6 CAPS patients with biopsy-proven renal involvement.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
History of APS	—	Stroke, transverse myelitis	Epilepsy, stroke	Epilepsy	Epilepsy, DVT, leg ulcer	Migraine, amaurosis fugax
Manifestations						
Skin	—	—	—	Livedo reticularis	Livedo reticularis, leg ulcer	—
CNS	—	Stroke	Epilepsy	Stroke	Stroke	Stroke
Heart	Myocardial infarction	—	Libman-Sacks	—	Libman–Sacks, heart failure	—
Abdominal	Gallbladder necrosis, ↑ liver enzymes	—	—	—	↑ Liver enzymes	—
Pulmonary		—	Alveolar hemorrhage	—	Pulmonary embolism	—
Renal						
Blood pressure, mm Hg	130/80	125/75	120/70	160/100	170/90	150/95
Serum creatinine, mg/dl	1.8	1.3	1.4	1.5	2	1.7
Proteinuria, g/day	1.1	0.9	6.1	0.6	3.9	4.1
Hematuria	+	–	–	+	+	+
WHO class	—	V	IV	—	—	—
Laboratory						
Platelets/mm^3	105,000	340,000	98,000	185,000	116,000	92,000
Microangiopathic anemia	+	–	–	–	+	+
aCL IgG*	250	590	1000	580	920	350
aCL IgM*	0	230	0	390	370	190
LAC	+	+	–	–	+	+
Treatment	CG, AC, IVIG	GC, AC, CPM	GC, AC, CPM	AC CPM, IVIG	GC, AC, CPM	GC, AC,
CAPS-related death	–	–	+	–	+	–
Histologic lesions						
No. of glomeruli	37	30	30	50	9	14
Global glomerular sclerosis, no.	14	0	0	15	3	4
TMA	+	+	+	+	–	–
Interstitium						
Tubular atrophy, %	40	0	20	30	0	45
Fibrosis, %	30	0	—	40	0	0
Inflammation, %	0	0	10	—	0	10
Thyroidization	–	–	–	+	–	–
Interlobular arteries						
FIH	+	+	–	+	–	+
Arteriosclerosis	–	–	+	–	+	–
Organizing thrombosis	–	–	–	+	–	–
Interlobular arterioles						
TMA†	++	–	–	++	++	+
Hyalinosis	–	–	–	+	+	–
Onion skin-like lesions	+	–	–	+	–	–
Occlusions	–	-	–	–	+	–
FCA, %	30	0	0	30	20	0

* Normal range 0–100 IU. † Thrombotic microangiopathy of interlobular arterioles: +: focal lesions; ++: diffuse lesions. CAPS: catastrophic antiphospholipid syndrome; PAPS: primary antiphospholipid syndrome; SLE-APS: systemic lupus erythematosus-related antiphospholipid syndrome; CNS: central nervous system; Libman-Sacks: Libman-Sacks vegetations; DVT: deep venous thrombosis; blood pressure: blood pressure at the time of renal biopsy; WHO class: WHO class of lupus nephritis in patients with coexistent features of lupus nephritis; aCL: anticardiolipin antibodies; LAC: lupus anticoagulant; GC: steroids; AC: anticoagulant treatment; CPM: cyclophosphamide; IVIG: intravenous immunoglobulin; TMA: thrombotic microangiopathy; FIH: fibrous intimal hyperplasia; FCA: focal cortical atrophy.

acute CAPS events. All patients had persistently positive aPL. In one patient, CAPS manifestations were the first manifestations associated with APS (Patient 1). Another patient (Patient 5) was previously diagnosed with PAPS and received anticoagulant treatment, but he discontinued his treatment 1 month before the onset of CAPS manifestations. The other 4 patients had previous manifestations of APS that had remained unrecognized, and never received anticoagulant therapy. Two of the above 4 patients had underlying SLE (Patients 2 and 3).

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Demographic, clinical, and laboratory characteristics of the patients with CAPS, PAPS, and SLE-APS are described in Tables 1 and 2. The characteristics of CAPS patients are additionally presented in Table 2 for direct comparison with the other 2 groups. Regarding renal involvement, the most common clinical and laboratory findings of all the groups were hypertension, hematuria, proteinuria, and renal insufficiency. The renal insufficiency was acute in patients with CAPS, developing at the time of CAPS events. Increased serum creatinine levels, proteinuria, and nephrotic syndrome were found more frequently in CAPS patients than in the other 2 APS groups, without reaching statistical significance (Table 2).

The renal biopsy findings of the 6 patients with CAPS are shown in Table 1. The frequencies of renal histopathologic lesions in CAPS, PAPS, and SLE-APS are shown in Table 3. In CAPS patients, the most frequently detected histologic lesion was TMA: all 6 patients had fresh or partially recanalized thrombi either in glomeruli or arterioles (Figure 1A). In addition, chronic lesions were also detected (Figure 1B and 1C). FIH and FCA were the most common chronic vascular lesions, occurring in 4 of 6 (66.7%) and 3 of 6 (50%) patients with CAPS, respectively. Regarding PAPS and SLE-APS patients, TMA was detected in 37.5% and 35% of patients, respectively, while the frequencies of FIH and FCA were similar to those observed in CAPS patients ($p > 0.99$; Table 3).

The mean followup period for the 3 APS groups was 4.5 ± 0.5, 6.7 ± 2.7, and 7.2 ± 3.1 years, respectively. At the end of followup, no difference was detected among the 3 groups in the frequency of renal insufficiency (33.3% vs 25% vs 21.7%; $p = 0.53$). No patient in the above 3 groups had end-stage renal disease. Two patients with CAPS died during acute catastrophic events, and 2 patients with SLE-APS died during the followup period. During the followup period, all APS patients were undergoing anticoagulant therapy.

DISCUSSION

We examined, for the first time to our knowledge, the renal histologic, clinical, and laboratory characteristics of 3 different groups of APS patients with biopsy-proven renal involvement and compared the pertinent data.

APS nephropathy was first described in a multicenter study examining the renal biopsy specimens from 16 patients with PAPS[7]. Some years later, the above group as well as our group examined the presence of APS nephropathy in 24 and 18 patients with SLE-APS, respectively[8,9]. APS nephropathy was detected in about two-thirds of SLE-APS patients, and its inclusion in the classification criteria for definite APS was suggested[8,9].

Table 2. Demographic, clinical, and laboratory characteristics of CAPS, PAPS, and SLE-APS patients with biopsy-proven renal involvement. Data are presented as median (interquartile range) or absolute (relative) frequencies.

Characteristics	CAPS, n = 6	PAPS, n = 8	SLE-APS, n = 23
Female, n (%)	3 (50)	5 (62.5)	18 (78.2)
Age at biopsy, yrs	36 (34.2–42.2)	37 (24–42)	28 (21.2–36.5)
SLE duration, yrs	8.2 (7.1–9.3)	—	11 (6.5–19)
APS duration, yrs	2.5 (0.47–4.1)	6 (4–7.5)	7 (4–9)*
Arterial thrombosis, n (%)	3 (50.0)	3 (37.5)	8 (34.8)
Venous thrombosis, n (%)	1 (16.6)	2 (25.0)	4 (17.4)
Pulmonary embolism, n (%)	1 (16.6)	2 (25.0)	4 (17.4)
Pregnancy morbidity, n (%)	0	1 (12.5)	4 (17.4)
Stroke, n (%)	4 (66.7)	3 (37.5)	6 (26.1)
Livedo reticularis, n (%)	2 (33.3)	4 (50.0)	12 (52.2)
Hypertension, n (%)	3 (50.0)	6 (75.0)	16 (69.6)
Increased serum creatinine, n (%)	4 (66.7)	4 (50.0)	10 (43.5)
Serum creatinine, mg/dl	1.62 ± 0.26	1.67 ± 0.81	1.39 ± 0.62
Proteinuria, n (%)	6 (100)	6 (75.0)	17 (73.9)
Nephrotic syndrome, n (%)	3 (50.0)	3 (37.5)	8 (34.8)
Hematuria, n (%)	4 (66.7)	5 (62.5)	15 (65.2)
Death	2 (33.3)	0	2 (8.6)
aCL, n (%)	6 (100)	7 (87.5)	22 (95.6)
LAC, n (%)	4 (66.7)	5 (62.5)	12 (52.2)
Anti-ß$_2$-GPI antibodies	1 (16.6)	2 (25.0)	6 (26.1)

* $p < 0.05$ for comparisons between PAPS, SLE-APS vs CAPS. p values from the post-hoc comparisons are corrected using the Bonferroni rule. CAPS: catastrophic antiphospholipid syndrome; PAPS: primary APS; SLE-APS: systemic lupus erythematosus-related APS; SLE duration in CAPS: SLE duration for the 2 CAPS patients with lupus; aCL: anticardiolipin antibodies (IgG or IgM isotype); LAC: lupus anticoagulant; ß$_2$-GPI: ß$_2$-glycoprotein I.

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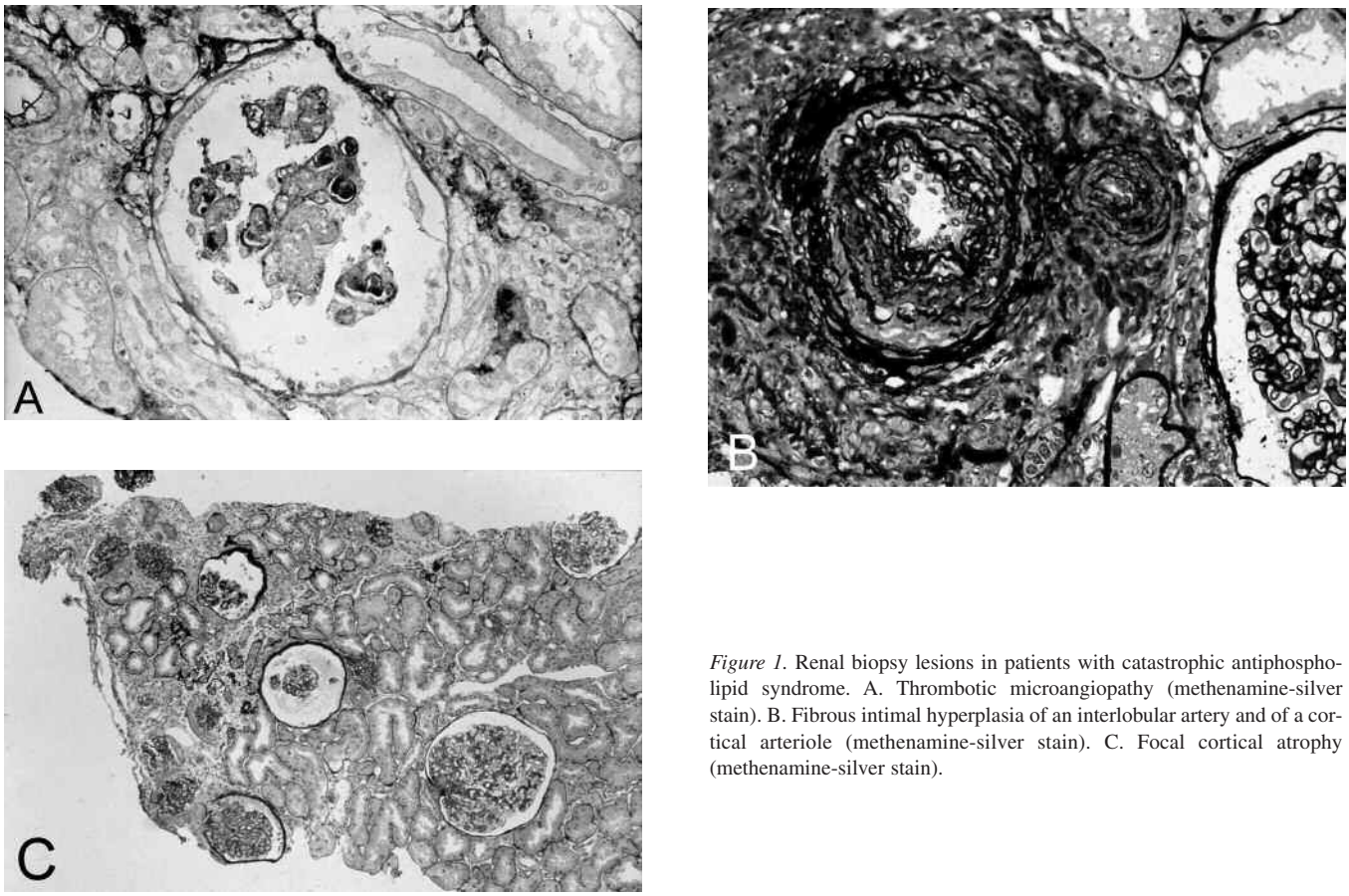

Figure 1. Renal biopsy lesions in patients with catastrophic antiphospholipid syndrome. A. Thrombotic microangiopathy (methenamine-silver stain). B. Fibrous intimal hyperplasia of an interlobular artery and of a cortical arteriole (methenamine-silver stain). C. Focal cortical atrophy (methenamine-silver stain).

In 1992, Asherson, *et al* described the catastrophic variant of APS (CAPS-Asherson's syndrome)[3,10]. Renal involvement has been described as one of the most frequent manifestations of CAPS[3,4,12,18]; nevertheless, very little information has been published regarding renal histopathology. In isolated cases with CAPS where a kidney biopsy was performed[10,11,19-22], as well as in autopsy material[4], fibrin thrombi have been detected in arterioles and glomerular tufts (TMA). The presence of chronic vascular lesions such as FIH and FCA has been only sporadically described[11,22].

Our study included a significant number of CAPS patients with biopsy-proven renal involvement, given the

Table 3. Frequency of renal histopathological lesions in patients with CAPS, PAPS, and SLE-APS.

Histologic Lesions	CAPS, n = 6 no. (%)	PAPS, n = 8 no. (%)	SLE-APS, n = 23 no. (%)
TMA†	6 (100)	3 (37.5)*	8 (34.8)*
Interstitial fibrosis	2 (33.3)	3 (37.5)	8 (34.8)
Interstitial inflammation	2 (33.3)	3 (37.5)	8 (34.8)
Tubular atrophy	4 (66.7)	4 (50.0)	12 (52.2)
FIH†	4 (66.7)	5 (62.5)	15 (65.2)
Organizing thrombi with or without recanalization†	1 (16.7)	2 (25.0)	4 (17.4)
Hyalinosis	2 (33.3)	3 (37.5)	8 (34.8)
Concentric (onion skin-like) fibrosis of arterioles	2 (33.3)	2 (25.0)	4 (17.4)
Arterial or arteriolar occlusions†	1 (16.7)	3 (37.5)	7 (30.4)
FCA†	3 (50.0)	4 (50.0)	12 (52.2)

* $p < 0.01$ for comparisons between PAPS, SLE-APS vs CAPS. p values from the post-hoc comparisons are corrected using the Bonferroni rule. † APS nephropathy lesions. CAPS: catastrophic antiphospholipid syndrome; PAPS: primary antiphospholipid syndrome; SLE-APS: systemic lupus erythematosus-related APS; TMA: thrombotic microangiopathy; FIH: fibrous intimal hyperplasia; FCA: focal cortical atrophy.

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rarity of the syndrome and the difficulty to perform biopsies in these critical conditions. All the CAPS, PAPS, and SLE-APS patients with biopsy-proven renal involvement from our total APS population were included in the present analysis. The results of our study confirmed the results of the 3 previous series detecting APS nephropathy lesions in the majority of PAPS and SLE-APS patients with biopsy-proven renal involvement[7-9]. In our study, all 6 patients with CAPS and one-third of patients with PAPS and SLE-APS had acute vascular lesions, while chronic lesions occurred in about two-thirds of patients in all APS groups. Indeed, the only difference between patients with catastrophic and non-catastrophic APS was the predominance of the acute APS nephropathy lesions in CAPS patients, a finding that is not surprising and can be explained by the acute expression of this syndrome. APS nephropathy as well as the other thrombotic manifestations of CAPS patients (central nervous system, skin, heart, pulmonary, abdominal) originated mainly in small vessels, in keeping with the tendency of CAPS to manifest as widespread concurrent thrombotic events from the microvasculature.

Regarding the renal clinical and laboratory characteristics of APS patients in this study, the most frequent findings in all 3 APS groups were hypertension, proteinuria, hematuria, and renal insufficiency. The same characteristics have also been described in previous series examining APS nephropathy[7-9]. The presence of the same histologic, clinical, and laboratory characteristics of APS nephropathy among all 3 groups of APS patients suggests an association between this nephropathy and APS. APS nephropathy should be included in the classification criteria for definite APS, and the use of an appropriate anticoagulant treatment in patients with this nephropathy should be examined. Multicenter prospective studies are needed to examine this issue.

In conclusion, acute and chronic renal vascular lesions compatible with the diagnosis of APS nephropathy were detected in all 3 groups of patients with APS. The acute lesions were more prominent in CAPS, while the chronic lesions were found with similar frequencies in all groups. Hypertension, proteinuria, hematuria, and renal insufficiency were the most common renal manifestations of all APS groups. The clinical and laboratory findings that suggest renal involvement in APS patients should be recognized promptly. If findings cannot be explained otherwise, clinicians should order renal biopsy without delay so that this condition can be detected and treated early.

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