J Am Soc Nephrol 10: 507–518, 1999

The Intrarenal Vascular Lesions Associated with Primary Antiphospholipid Syndrome

DOMINIQUE NOCHY,* ERIC DAUGAS,* DOMINIQUE DROZ,†
HELENE BEAUFILS,‡ JEAN-PIERRE GRÜNFELD,† JEAN-CHARLES PIETTE,‡
JEAN BARIETY,* and GARY HILL*

**Service d'Anatomie Pathologique et Service de Néphrologie et Institut National de la Santé et de la Recherche Médicale (INSERM) U430, Hôpital Broussais; †Laboratoire de Pathologie Rénale et Service de Néphrologie, Hôpital Necker; and ‡INSERM U423 et Service de Médecine Interne, Groupe Hospitalier Pitié-Salpétrière, Paris, France.*

Abstract. Even 10 yr after the identification of the antiphospholipid syndrome (APS), renal involvement in the course of APS is still relatively unrecognized, and is probably underestimated. The association of anticardiolipin antibodies and/or lupus anticoagulant with the development of a vaso-occlusive process involving numerous organs is now confirmed. In a multicenter study, 16 cases of "primary" APS (PAPS) were found and followed for 5 yr or more, all with renal biopsy. In all 16 cases of PAPS, there was a vascular nephropathy characterized by small vessel vaso-occlusive lesions associated with fibrous intimal hyperplasia of interlobular arteries (12 patients), recanalizing thrombi in arteries and arterioles (six patients), and focal cortical atrophy (10 patients). In combination, these led to progressive destruction of the kidney, accelerated by acute glomerular and arteriolar microangiopathy in five patients. Focal cortical atrophy is a distinctive lesion, present in 10 biopsies, and likely represents the histologic and functional renal analogue to the multiple cerebral infarcts detected on imaging studies. The clinical hallmark of this vascular nephropathy in PAPS is systemic hypertension, only variably associated with renal insufficiency, proteinuria, or hematuria. The ensemble of histologic renal lesions defined in this study should aid in the separation of the lesions found in cases of secondary APS, especially systemic lupus erythematosus, into those lesions related to APS and those related to the underlying disease.

The anticardiolipin syndrome was described in 1986 (1,2). It was defined by the presence of antiphospholipid antibodies, recognized as anticardiolipin antibodies (aCL) and/or circulating lupus anticoagulant (LA) associated with thrombosis, particularly of the large arteries or veins and/or repeated spontaneous abortions. The term antiphospholipid syndrome (APS) is now used to describe this entity (3). It was in systemic lupus erythematosus (SLE) that the frequency of thrombotic complications and the presence of antiphospholipid antibodies was first well described (4–7). Love and Santoro (8) determined on the basis of a compilation of several series, including more than 1000 lupus patients, a prevalence of 34% for LA and 44% for aCL in this setting. Thrombotic events occur in nearly 30% of lupus patients demonstrating these antibodies (8). Although the renal lesions in APS have been described as intrarenal thromboses (7), there remains a lack of knowledge concerning the renal manifestations in the APS: their frequency, their severity, their symptomatology, and even the basic histology of these lesions (9,10). Piette *et al.* (11) have described and gathered the data from the literature on the renal manifestations of APS, occurring in the course of nephropathies as diverse as pregnancy, renal transplants, and particularly SLE. There is a strong association between the existence of LA and presence of thrombotic microangiopathy in biopsies from lupus patients (4,5), regardless of the subtype of lupus nephritis (7).

The primary antiphospholipid syndrome (PAPS) has been defined basically as APS in the absence of associated autoimmune disease (12–15). As opposed to SLE with APS, the intrarenal lesions of PAPS are poorly described, being derived either from isolated cases in the literature (16–22) or from cases included in small series of SLE with APS (23–30). Our study reports 16 cases of PAPS with renal manifestations, with the goal of describing the clinical and histopathologic lesions on renal biopsy, and of attempting to define a morphologic picture that should suggest the diagnosis of APS. In such cases of PAPS, it should be possible to observe the lesions due to APS in relatively pure form, without possible superadded vascular lesions due to the underlying disease associated with APS, as in the SLE-APS overlap syndrome. And conversely, this sort of analysis may be useful in the interpretation of renal biopsies from SLE or other conditions with associated APS.

Materials and Methods

Patients

We studied retrospectively 16 patients with PAPS and renal manifestations, gathered from three different University Hospitals in Paris

Received June 8, 1998. Accepted September 13, 1998.
Correspondence to Dr. Dominique Nochy, Service d'Anatomie Pathologique, 96 Rue Didot, Hôpital Broussais, 75014 Paris, France. Phone: +33 1 43 95 92 10; Fax: +33 1 43 95 92 12; E-mail: edaugas@infobiogen.fr
1046-6673/1003-0507$03.00/0
Journal of the American Society of Nephrology

(Hôpital Broussais, Hôpital Pitié-Salpétrière, and Hôpital Necker) from 1989 to 1996. All had a history of thrombotic events, recurrent fetal loss, livedo, seizures, thrombocytopenia, or other features suggestive of APS.

The diagnosis of PAPS was made according to established criteria (12–15). All patients had positive tests for LA or aCL or both. The current definition adopted for PAPS requires the exclusion of SLE (31), hence the lack of sufficient modified 1997 American Rheumatism Association (ARA) criteria (32), specifically the absence of anti-native (double-stranded [ds])-DNA and anti-extractable nuclear antibodies (ENA), and negative or weakly positive antinuclear antibodies. A follow-up longer than 5 yr after the first clinical manifestations is believed necessary to rule out the subsequent emergence of SLE (33,34). All 16 patients had renal insufficiency and/or proteinuria, and/or hematuria, and/or systemic hypertension.

Exclusions

The following patients were excluded from the study population:

1. Patients with established SLE, according to the ARA criteria, or "lupus-like "disease with elevated antibody titers to dsDNA or to ENA. Particular emphasis was placed on the absence of elevated dsDNA or ENA because the modified 1997 ARA criteria include elevated titers to antiphospholipid antibodies (32), thereby reducing to three the number of other criteria necessary for diagnosis of SLE.
2. Patients with diabetes or other well identified glomerulopathies such as IgA mesangial glomerulonephritis, membranous glomerulopathy, or transplant recipients.
3. Patients with biopsies showing glomerular Ig deposits by immunofluorescence (IF) to avoid the "overlapping influences of silent SLE or other autoimmune diseases." Thus, we excluded from the study three patients with suspected PAPS whose biopsies were not evaluated by IF and five other patients whose IF specimens showed, surprisingly, IgG mesangial deposits, since it was believed that lupus or other immune complex disease could not be ruled out. This left a total of 16 patients for study.

Detection of Antiphospholipid Antibodies

aCL (IgG isotype) were determined in all 16 patients with enzyme-linked immunosorbent assay standardized by the International Study Group, using commercial kits. The results were expressed in IgG phospholipid (GPL) units, with results below 15 units GPL considered negative. LA were sought in all 16 patients, using different procedures such as dilute activated partial prothromplastin time, kaolin clotting time, or diluted prothrombin time, or a combination of these tests. LA and aCL positivity were confirmed on a second sample collected 4 wk or later.

Other Laboratory Studies

Each serum specimen studied for aCL was tested for antinuclear antibodies, anti-dsDNA antibodies, serum immunoglobulins (IgA, IgG, IgM), complement levels (C3, C4), Coomb's test, cryoglobulins, antinuclear cytoplasmic antibodies, and for rheumatoid factor (latex and Waaler–Rose tests). When thrombocytopenia was present, microangiopathic hemolytic anemia was sought by the presence of schizocytes and nucleated red cells on peripheral smear. The sera of the 11 patients studied were found negative for hepatitis C, B, and HIV infections.

Most patients required imaging evaluation using angiography, ultrasonography, and/or computed tomographic (CT) scanning, and/or magnetic resonance imaging for the diagnosis of definite or suspected thrombosis or complications, such as deep venous or arterial abdominal and aortic thrombosis, for the diagnosis of pulmonary embolism, for the search for cardiac valve thickening or vegetations, cerebral vascular problems, and for visualizing possible renal cortical necrosis and stenosis or thrombosis of the trunk of renal arteries.

Renal Biopsy Processing

Standard percutaneous biopsies were performed in five patients, surgical in five other patients, and transjugular in the six thrombopenic or severely hypertensive patients. Specimens were fixed in alcoholic Bouin's fixative with standard embedding and stains for light microscopy. All biopsies had IF studies using anti-IgA, IgG, IgM, fibrinogen, C3, C4, C1q antibodies (Behringwerke, Marburg, Germany), and anti-κ and anti-λ light chain antibodies (Dakopatts A/S, Glostrup, Denmark). We estimated the renin content of five surgical renal biopsies from patients in whom occlusion of the main renal artery was ruled out. We used a semiquantitative assessment that we have reported previously (35) with a polyclonal antihuman renin antibody (gift from Pierre Corvol, Collège de France, Paris). To identify the nature of the vascular intimal proliferation, we used a monoclonal mouse antihuman muscle actin antibody, HHF35, which recognizes α and γ smooth muscle actin (Dakopatts) at a dilution of 1:50 in the labeled streptavidin-biotin (LSAB) method on paraffin sections of five biopsies.

Results

Of the 16 patients reported, 10 (62%) were male and six (37%) female, all Caucasians. Their ages ranged from 24 to 60 yr (average 37. 8 yr). All patients had been followed for more than 5 yr. There were three deaths, the youngest patient of pulmonary hypertension 2 yr after the biopsy (patient 1), and two others of cerebral accidents (patients 3 and 6). All of the clinical findings and biologic data are summarized in Tables 1 through 3.

Clinical Findings

Systemic arterial or venous thrombosis was present in 15 of 16 patients (93%). Deep venous thrombosis (DVT) took the form of thrombophlebitis of the legs, with repeated episodes in three patients. Two patients presented with pulmonary embolism and thromboembolic pulmonary hypertension. In our series, most often arterial thrombosis involved the cerebrovascular circulation (68%) (see below), but also other sites, including the trunk of renal arteries and suprarenal aortic occlusion associated with multiple visceral arterial thromboses, including the mesenteric and renal arteries. One patient (patient 5) suffered thrombosis of his vascular access for dialysis, followed 5 yr later by the thrombosis of the arterial anastomosis of a renal transplant at 13 d posttransplantation. Five patients presented both arterial and deep venous occlusions.

Fifteen of 16 patients (93%) had *systemic hypertension*, defined as BP $\geq$140/90 mmHg. Hypertension was thus as common as chronic renal insufficiency (87%), and its severity varied from mild in approximately half of patients to severe hypertension in the remainder. One patient (patient 5) with malignant hypertension developed acute renal failure with microangiopathic hemolytic anemia leading rapidly to end-stage

Table 1. Renal and clinical features in 16 patients with PAPS[a]

Patient	Age (yr)	Gender	Creatinine (mg/dl)	Proteinuria (g/d)	Hematuria	BP (mmHg)	Platelets/mm^3	LA	aCL (UGPL)	Thrombosis/Abortions	Other Clinical Features
1	24	M	1.23	−	−	180/110	100,000	+	5	Pulmonary, cerebral	CNS manifestations (stroke), livedo reticularis, leg ulcers, pulmonary HT
2	33	M	1.59	0.4	+	160/95	85,000	+	>860	DVT	Leg ulcers, cardiac valve lesions, alveolar hemorrhage
3	34	M	1.36	3	−	260/120	110,000	+	60	Cerebral, DVT	CNS manifestations (stroke), livedo reticularis
4	36	M	2.5	2	+	140/95	130,000	+	600	Cerebral	CNS manifestations (seizures, chorea, stroke), cardiac valve lesions, alveolar hemorrhage
5	38	M	2.27	2	+	250/140	100,000	+	17	Hemodialysis vascular access, renal graft artery	Microangiopathic hemolytic anemia
6	47	M	1.59	1.5	−	160/100	80,000	+	280	Cerebral, DVT	CNS manifestations (stroke), livedo reticularis, cardiac valve lesions, alveolar hemorrhage, pulmonary HT, immune hemolytic anemia
7	49	M	1.7	0.5	+	210/120	179,000	+	>45	Cerebral	CNS manifestations (multi-infarcts)
8	50	M	2.04	3	−	150/95	95,000	+	100	Suprarenal aorta, mesenteric, axillary, renal arteries, pulmonary and DVT	CNS manifestations (seizures), livedo reticularis, adrenal failure
9	52	M	1.59	0.2	−	150/100	159,000	+	20	Cerebral, DVT	CNS manifestations (multi-infarcts)
10	60	M	1.3	−	−	150/100	176,000	+	9	Cerebral	CNS manifestations (stroke), cardiac valve lesions
11	24	F	1.17	0.46	+	160/120	147,000	+	20	DVT	CNS manifestations (chorea), cardiac valve lesions
12	28	F	1.36	0.4	−	132/84	180,000	+	42	Cerebral, DVT, abortions	CNS manifestations (multi-infarcts), livedo, preeclampsia
13	32	F	1.02	−	+	170/120	107,000	+	>45	Abortions	Livedo reticularis, preeclampsia, cardiac valve lesions
14	35	F	2.5	7	+	180/110	100,000	+	46	Cerebral, abortions	CNS manifestations (multi-infarcts), livedo reticularis, cardiac valve lesions, immune hemolytic anemia
15	45	F	1.7	0.6	+	140/95	100,000	+	10	Cerebral	CNS manifestations (multi-infarcts)
16	59	F	1.36	−	+	190/100	168,000	+	160	Cerebral, renal artery	CNS manifestations (seizures, multi-infarcts), immune hemolytic anemia

[a] PAPS, primary antiphospholipid syndrome; LA, lupus anticoagulant; aCL, anticardiolipin antibodies; UGPL, IgG phospholipid units; CNS, central nervous system; DVT, deep venous thrombosis; HT, hypertension.

Table 2. Frequency of clinical manifestations in PAPS patients[a]

Clinical Manifestation	No. (%)
Arterial/venous thrombosis	15 (93%)
Systemic hypertension	15 (93%)
Renal insufficiency	14 (87%)
CNS manifestations (stroke, seizures, chorea, infarcts)	13 (81%)
Cutaneous manifestations (livedo, leg ulcers)	9 (56%)
Pregnancy complications (recurrent fetal loss)	3/6 (50%)
Cardiac manifestations (mitral valve thickening, vegetations)	5 (31%)
Pulmonary manifestations (embolism, pulmonary HT, alveolar hemorrhage)	4 (25%)
Nasal septum perforation	1 (6%)
Adrenal failure	1 (6%)
Thrombocytopenia	9 (56%)

[a] Abbreviations as in Table 1.

Table 3. Frequency of renal manifestations

Clinical Manifestation	No. (%)
Systemic hypertension	15 (93%)
Renal insufficiency	14 (87%)
Proteinuria (0.2 to 7 g/d)	12 (75%)
Hematuria	9 (56%)
Microangiopathic anemia	1 (6%)
Nephrotic syndrome	1 (6%)

renal failure and dialysis. Only this one patient progressed to end-stage renal failure.

All 16 patients had *renal symptoms* (Tables 1 and 3), with renal insufficiency in 14 (87%), mild in most patients (serum creatinine, mean 1.64 mg/dl, ranging from 1.02 to 2.50 mg/dl at the time of renal biopsy), with subsequent end-stage renal failure in patient 5 (see above). The occurrence of renal infarcts or cortical ischemia was revealed by abdominal CT scan in two women.

Neurologic manifestations were frequent, occurring in 13 of 16 patients (81%) with a first ischemic stroke or other event, recognized on neuroimaging as cerebral infarcts in 11 patients (68%). Eight of these patients with thrombotic episodes were between 24 and 50 yr old, and only three were older. The associated cerebral manifestations were distributed as follows: focal neurologic signs such as strokes, sometimes as transient ischemic attacks and often recurrent, were present in five patients; seizures in three patients; chorea in two patients. One patient developed all of the manifestations of cerebral APS-related disorders: strokes, seizures, chorea.

Cutaneous manifestations, limited to frequent livedo reticularis and leg ulcers (two cases) were present in nine patients (56%), and in six this was associated with strokes or chorea.

Pregnancy complications were present in three of the six women (50%), with a total of seven repeated fetal losses followed by eclampsia in one patient.

Pulmonary manifestations: Four patients (25%) suffered from pulmonary manifestations. Two patients had pulmonary hypertension, followed by repeated episodes of thromboembolism in one. Alveolar hemorrhage was observed in three patients, as has previously been reported (22).

Cardiac manifestations were present in five patients (31%), with mitral valve thickening in all and valve vegetations in one patient

Nasal septum perforation was present in one patient, an observation also reported by others (22).

Adrenal failure occurred in the patient who had suffered widespread arterial and venous occlusions with massive involvement of the aorta and most of its abdominal visceral branches.

Serologic Results

Lupus anticoagulant was present and its positivity was confirmed in multiple samples in all 16 patients. aCL was considered positive (>15 GPL units) in 12 patients and negative in four patients at time of biopsy. In 10 patients, GPL values were highly positive (>40 units). Highest values of aCL (GPL units) are reported in Table 1.

Thrombocytopenia: Nine of 16 patients (56%) had documented thrombocytopenia of <110, 000 platelets/mm^3 on at least two occasions. Two patients had both thrombocytopenia and autoimmune hemolytic anemia, associated with agglutinins and Coomb's positivity in both. In a third patient, there was thrombocytopenia with microangiopathic hemolytic anemia with schizocytes in the peripheral smear and malignant hypertension (patient 5).

Antinuclear antibodies were present in six patients, in low titers ranging from 1:40 to 1:80.

Tissue-specific antibodies, anti-DNA antibodies, antinuclear cytoplasmic antibodies, and cryoglobulins were uniformly negative, as were antibodies to hepatitis C, B, and HIV in the 11 patients studied.

Spectrum of Renal Histopathologic Lesions

The frequency of the various histologic lesions is outlined in Tables 4 and 5. We describe here primarily the vascular lesions found in these biopsies, with emphasis on one particular lesion, focal cortical atrophy, involving the superficial cortex, which was present in 62% of cases. It is best understood, however, in the context of the vascular lesions, which are therefore described first.

Vascular Lesions. *Arteriosclerosis*, characterized by fibrous intimal thickening with luminal reduction in the arcuate and interlobular arteries, associated with arteriolar hyaline and arteriolosclerosis, was present in 75% of biopsies in PAPS (Figure 1).

Fibrous intimal hyperplasia (FIH) was present in 75%. The interlobular arteries and their branches were tortuous, with their intima thickened, primarily by an intense myofibroblastic intimal cellular proliferation (Figures 2 through 5), the cells being positive for α and γ smooth muscle actin in the cases

Table 4. Renal biopsy findings in 16 patients with PAPS[a]

Patient	Glomeruli			Interstitium			Vessels Involved							FCA
							Interlobular Arteries			Arteriolar Lesions				
	n	Global Sclerosis	Lesions	Fibrosis	Tubular Atrophy	Thyroidization	Arteriosclerosis	Fibrointimal Hyperplasia	Organizing Thrombosis	Hyalinosis	Sclerosis	TMA	Occlusions	
1	20	4	Double contour	10%	+	−	+	++	+	++	−	++	+	−
2	40	12 (FCA)		10%	+	+	−	++	++	−	+	−	+	+
3	12	0		40%	+	+	+	+	−	−	+	−	−	+
4	30	5	TMA, FSGS	40%	+	−	−	++	++	+	++	++	++	−
5	20	0	TMA, FSGS	20%	+	−	+	++	−	+	+	++	−	−
6	10	9 (FCA)		75%	++	++	−	+	−	−	+	−	+	+
7	12	6 (FCA)		10%	+	+	−	+	−	−	+	−	+	+
8	7	4	Double contour	70%	++	++	+	+	+	−	+	+	+	+
9	15	5		30%	+	+	+	−	−	+	+	−	−	−
10	102	10	FSGS (FCA)	10%	+	+	+	−	−	−	+	−	+	+
11	20	10 (FCA)		30%	+	+	+	+	+	−	+	−	+	+
12	13	1	Collapsed glom.	10%	+	+	+	−	−	+	+	−	−	−
13	12	1		10%	+	+	+	−	−	−	+	−	−	−
14	22	12 (FCA)	Collapsed glom.	40%	++	+	++	++	+	−	++	−	+	+
15	10	0		50%	+	−	+	+	−	−	+	−	+	+
16	20	10 (FCA)	Double contour	10%	+	+	+	+	−	+	−	+	−	+

[a] FCA, focal cortical atrophy; TMA, thrombotic microangiopathy with fibrin occlusion; FSGS, focal segmental glomerulosclerosis. +, focal lesions; ++, diffuse lesions.

Table 5. Frequency of histopathologic renovascular lesions in PAPS

Clinical Manifestation	No. (%)
Arteriosclerosis	12 (75%)
Fibrous intimal hyperplasia	12 (75%)
Tubular thyroidization	12 (75%)
Arteriolar occlusions	11 (68%)
Focal cortical atrophy	10 (62%)
Thrombotic microangiopathy (fibrin)	5 (31%)
Organizing thrombosis	6 (37%)
Vasculitis	0

studied (Figure 6), and also by extracellular matrix, often mucoid in character. The intima tended to be much more cellular than that seen in typical arteriosclerosis of aging. In one case, the thickened intima contained thrombi composed of fibrin and leukocytes. The media was either proliferative, with hypertrophic myocytes, or alternatively, atrophic and fibrous. Cross sections often revealed that the lumen was, to be sure, reduced, but primarily by fibrous intimal projections or "cushions " that bulged into the lumen. An onion-skin arrangement of intimal fibrosis was frequent. In five patients, the lumina were obstructed by fibrous tissue, sometimes permeated with endothelialized channels indicative of recanalizing thromboses (Figures 2 through 5). The organizing thrombi were always observed in biopsies with extensive FIH, except in one case in which the lesions were focal.

Arterial and arteriolar fibrous and fibrocellular occlusions were present in 68% of biopsies, involving small interstitial arteries (Figure 7).

Thrombotic microangiopathy (TMA) with fibrin thrombi in arterioles and glomeruli was found in five (31%) biopsies, all showing FIH as well. TMA most commonly affected the preglomerular arterioles, small interlobular arteries, as well as the glomerular capillaries. There was total noninflammatory occlusion of the vessels by intraluminal, subendothelial, or medial accumulation of fragmented red blood cells, leukocytes, and eosinophilic fibrinoid material. In three cases, glomeruli showed associated mesangiolysis and diffuse mesangial interposition with numerous double contours. By IF, fibrin was the sole element of the thrombi, with immunoglobulins being absent. In one biopsy, there were myriads of microthrombi occupying the hilus and capillaries of approximately 10 glomeruli (Figure 8). The glomerular capillaries were blocked by fibrin and hyperplastic endothelial cells bulging into the lumina.

Vasculitis, such as found in microscopic and macroscopic polyarteritis, was absent in this series.

Other Lesions. *Focal cortical atrophy (FCA)* was present in 62% of biopsies. It involved the superficial cortex under the renal capsule, as foci or triangles, and was seen to pass deeper into the cortex on surgical biopsies, where it was accompanied uniformly by a depression of the contour of the renal capsule. It was irregularly distributed and led to retraction of the tissue, with a sharp border with the rest of the normal cortex (Figures 6 and 9 through 11). All of the elements of the parenchyma were altered, creating an ensemble of lesions that are highly suggestive of the diagnosis of PAPS. There was dense interstitial fibrosis, with massive tubular atrophy and thyroidization, associated with the vascular lesions of FIH with recanalizing thrombi (Figures 2 through 6). The arterioles were occluded either by fibrin microthrombi or often by fibrous tissue. The glomeruli were often small and sclerotic, often in groups of five or six globally sclerotic glomeruli tightly clustered together. Alternatively, they could be voluminous, almost cystic, tending also to occur in groups. According to the plane of section, these latter were either completely devoid of glomerular tuft, or contained only a few residual retracted capillaries and a few vacuolated podocytes. These two basically different glomerular appearances, sclerotic and pseudocystic glomeruli, were often observed in the same biopsy. The more ordinary lesions of arteriosclerosis were primarily found at some distance in the internal cortex.

By IF, fibrin was sometimes seen persisting in the thickened cellular intima associated with C3 and IgM. Renin was observed in the juxtaglomerular apparatus (Figure 11) and in the wall of the interlobular arteries. In all of the FCA areas studied with antirenin antibody, more than 30% of juxtaglomerular apparatus were positive with similar high ratios of renin-containing cells to those we have found in thrombotic microangiopathy in other human glomerular and vascular renal diseases (35).

Other glomerular lesions were sometimes present in addition to TMA. Three biopsies showed lesions of focal segmental glomerulosclerosis, with two of these showing retracted tuft with detached podocytes (outside the areas of FCA).

Tubular thyroidization was present in 75% of biopsies, characterized by large zones of atrophic tubules containing eosinophilic casts, resembling thyroid tissue. It occurred mainly in the deep cortex or medulla. It primarily formed a part of the ensemble of lesions comprising FCA (Figure 1).

Discussion

All of the patients in this series showed a clear-cut PAPS. They all meet the established definition (1,2,9) of APS (association of arterial or venous thromboses and/or repeated abortions with antiphospholipid antibodies) and the definition of PAPS (12–15), notably the absence of the appearance, over 5 yr follow-up of any diseases, such as SLE, which might cause APS (33).

The abundance of extrarenal clinical manifestations described here (Table 1), likely related to the high levels of aCL (62% of patients >40 GPL units) (36), are a testimony to the severity of the thrombotic process. Moreover, the extrarenal clinical involvement in our patients corresponds to that described in the course of PAPS (12–15), thereby offering reassurance that the renal lesions in our series are representative of those seen in the course of PAPS.

Hypertension was present in nearly all of the patients and was sometimes the only clinical sign suggestive of nephropathy. It was often severe with diastolic pressure ≥ 110 mmHg in

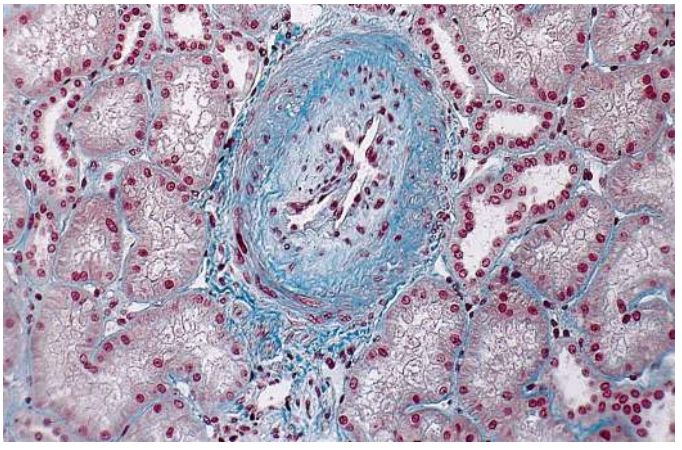

Figure 1. Arteriosclerosis of an interlobular artery in an otherwise normal cortical section from patient 14. It differs from typical arteriosclerosis by the "cellular" nature of the fibrous intima and the irregular contours of the markedly retracted lumen. Masson's trichrome stain. Magnification, ×160.

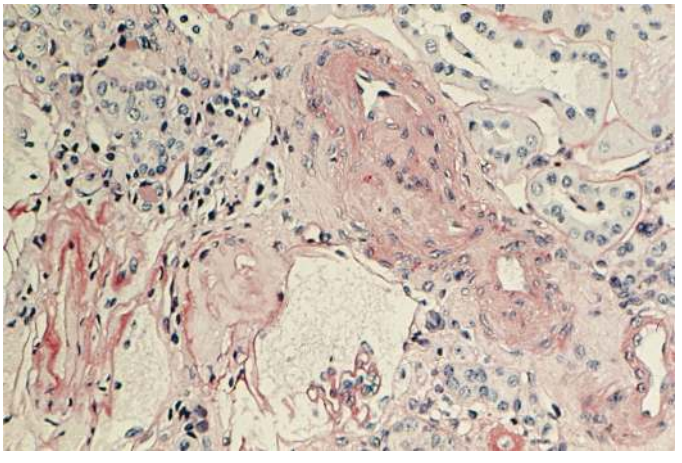

Figure 2. Fibrous intimal hyperplasia. Interlobular artery and intracortical arterioles show striking cellular and fibroelastic intimal thickening with a fibrous intimal projection or cushion bulging into the lumen. Periodic acid-Schiff (PAS) stain. Magnification, ×200.

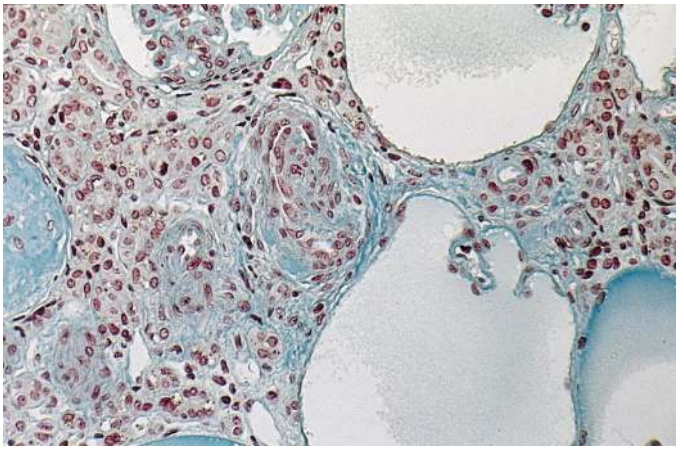

Figure 3. Fibrous intimal hyperplasia. Intrarenal artery showing obstructive and proliferative vaso-occlusive modifications. Glomeruli are cystic with severely retracted tufts. Masson's trichrome stain. Magnification, ×200.

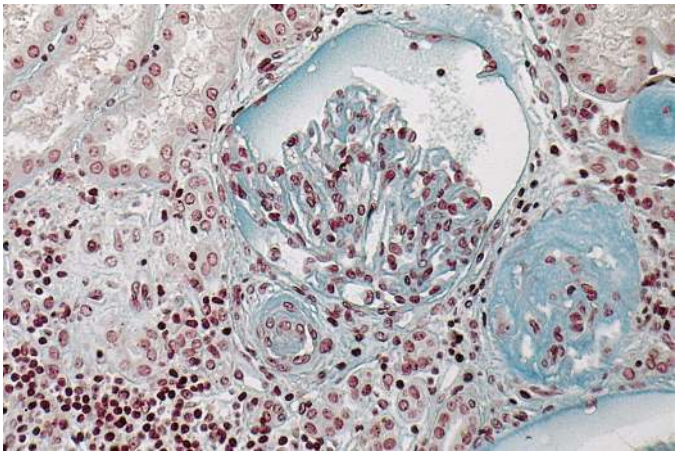

Figure 4. Fibrous intimal hyperplasia with organizing thrombi occluding the lumen of a preglomerular arteriole. Glomerulus shows ischemic atrophy with enlargement of Bowman's space. Masson's trichrome stain. Magnification, ×200.

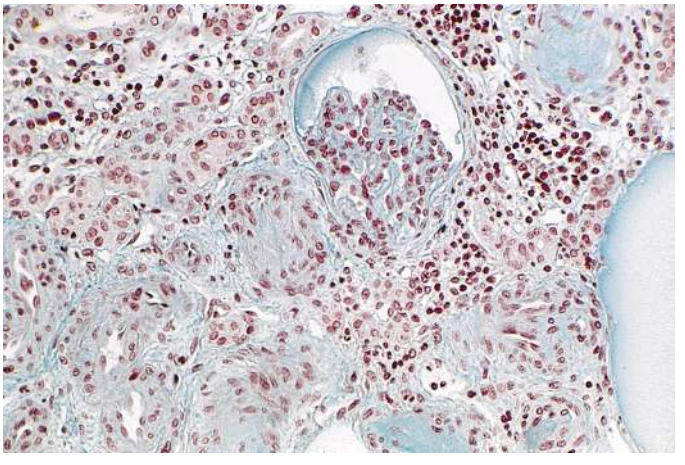

Figure 5. Fibrous intimal hyperplasia of interlobular arteries and intrarenal arterioles showing a plexiform vascular pattern with tortuous thickened vessels with vascular occlusions, organizing thrombi, and endothelialized channels. Masson's trichrome stain. Magnification, ×200.

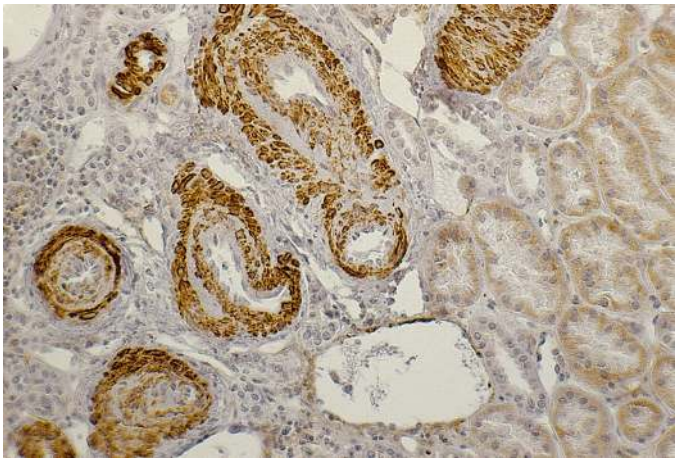

Figure 6. Fibrous intimal hyperplasia in a "focal cortical atrophy" under the renal capsule showing a strong staining for α and γ smooth muscle actin confined to intracortical vasculature in the media and in the myofibroblastic intimal proliferation, using the antihuman muscle actin antibody HHF35. LSAB method. Magnification, ×200.

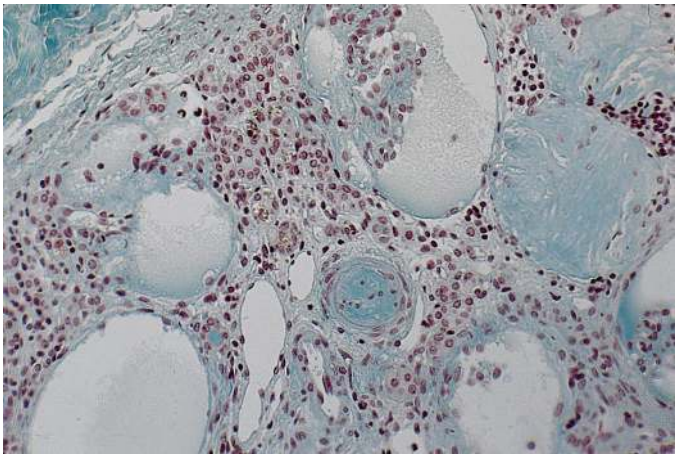

Figure 7. Arterial and arteriolar fibrous occlusions. In the center of the photomicrograph there is an intrarenal interstitial artery showing fibrous occlusion and glomeruli with severe retracted tuft. Masson's trichrome stain. Magnification, ×160.

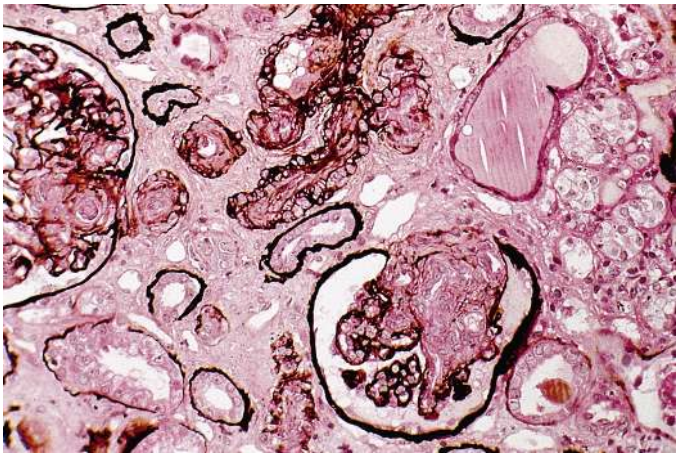

Figure 8. Thrombotic microangiopathy (TMA). Two glomerular hilar regions are occluded by fibrin microthrombi and proliferative endothelial cells bulging in the arteriolar lumen. Silver methenamine (Jone's) stain. Magnification, ×200.

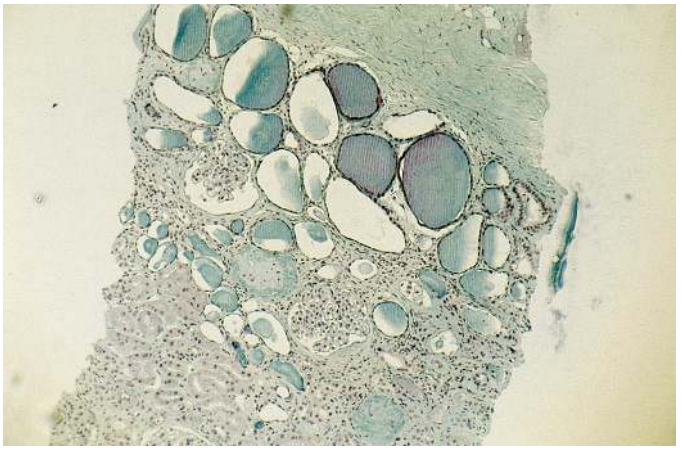

Figure 9. Focal cortical atrophy (FCA) from patients 2 and 10 involves the superficial cortex under the renal capsule. There is dense interstitial fibrosis, with numerous microcystic dilations of tubular or glomerular origin. Also shown are predominantly abnormal tubular dilations with a pattern of tubular thyroidization at the border with normal cortical area.

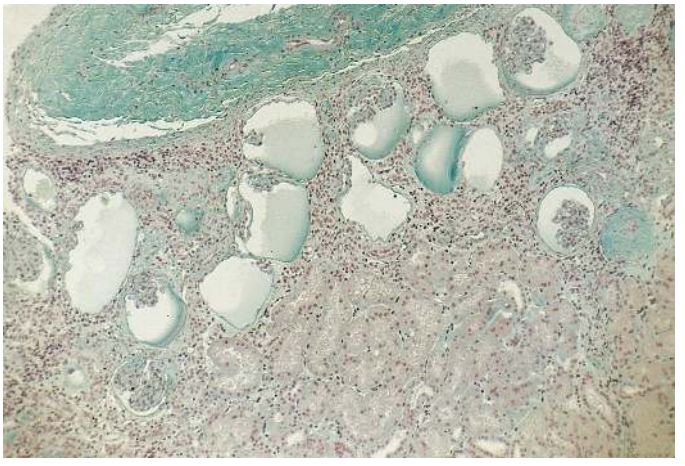

Figure 10. In an FCA area, numerous pseudocystic glomeruli are totally devoid of visible tuft or contain only a small residual retracted tuft. Interstitial fibrosis and vessels with fibrous intimal hyperplasia are observed. Masson's trichrome stain. Magnification, ×60.

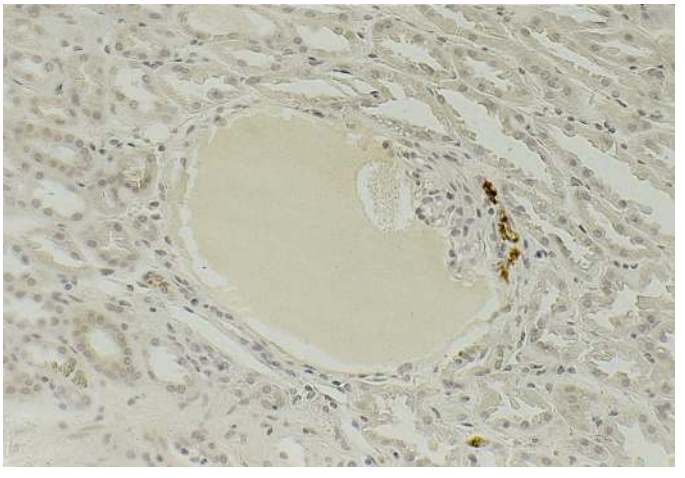

Figure 11. Focal cortical atrophy. Renin is observed in the juxtaglomerular apparatus of one glomerulus. This glomerulus has only a markedly retracted tuft in a cystically dilated Bowman's space. Immunoperoxidase with antihuman renin antibody. Magnification, ×200.

five patients (31%) and even malignant in two patients (12%). This observation raises the issue of the pathophysiology of hypertension in the course of PAPS. In all patients the renal biopsies revealed significant vascular renal lesions. In two patients (patients 1 and 9), there was thrombosis of a trunk of the renal artery, possibly leading to renovascular hypertension (37–39). In the remaining 14 patients, the intrarenal vascular lesions seemed to be playing this role. Given the severity of the vascular lesions, the first hypothesis that one might propose is that the hypertension was caused by the vascular lesions via stimulation of the renin-angiotensin-aldosterone system. Our results indicate that renin-containing cells were increased in the five surgical biopsies studied, which is in favor of strong stimulation of intrarenal renin (35). The reverse explanation is also plausible, that the vascular lesions observed were secondary to the hypertension as during the course of nephroangiosclerosis. However, the severity of the vascular lesions in five

patients (patients 4, 9, 10, 12, and 15) who were normotensive or mildly hypertensive would seem to favor the first hypothesis. We propose, therefore, that at least initially, the intrarenal vascular lesions related to the PAPS cause the hypertension, which may secondarily worsen and extend the lesions.

Renal insufficiency was frequent (87% of patients) and sometimes severe, often associated with proteinuria and hematuria (Table 2). Three patients had heavy proteinuria of glomerular origin (>3 g/d), one of whom had a nephrotic syndrome, without however any specific glomerular lesion being recognized. Twelve patients (75%) presented with chronic renal insufficiency, underlining the chronic nature of the nephropathy with underlying irreversible lesions. Acute renal failure was present exclusively in the two patients presenting with malignant hypertension (in the absence of abnormality of the main renal artery), with a clinical course in one resembling that seen in other thrombotic microangiopathies. Because all of the patients of the series demonstrated severe vascular intrarenal lesions (Table 4), it seems likely that the loss of renal function is the consequence of the vascular lesions. Patients have been reported with SLE and LA or APS who developed malignant hypertension and acute renal failure related to intrarenal vascular lesions in absence of overt lupus glomerulonephritis (40,41). In the study of Kleinknecht *et al.* (23), all patients with SLE and APS had severe hypertension with renal insufficiency. Kincaid-Smith *et al.* (42) described acute renal failure and severe hypertension in pregnant patients with LA. In PAPS, most authors (16–22) have described systemic hypertension as a very common symptom of renal involvement.

Therefore, it appears that hypertension is the most prominent abnormality in patients with PAPS-associated nephropathy. Thus, this diagnosis should be considered in any patient suffering from APS and hypertension, regardless of whether it is accompanied by renal insufficiency, proteinuria, or hematuria. By contrast, microangiopathic hemolytic anemia is an uncommon mode of presentation. In fact, of five patients showing a histologic picture of microangiopathy, only one had the customary clinical picture of microangiopathic hemolytic anemia with thrombocytopenia.

The major contribution of this study is the histologic characterization of the PAPS-related nephropathy: a vaso-occlusive lesion of the intrarenal vessels associating, side by side, acute thromboses and fibrotic vascular occlusions. Such thrombotic lesions of the arteries and arterioles have previously been described in the brain, the lungs, and the skin, as well as the kidney in PAPS (43–46). In our series, FIH was the most frequent lesion (75%) (see below). However, it was TMA, observed in 31% of our patients, that has attracted the most attention in prior reports in PAPS (16–21,42), so it is best discussed first.

SLE was the first condition in which the association of TMA with LA, then aCL, was first recognized over the course of several studies (4,5,8), leading eventually to a new classification of vascular lesions in SLE (47–50). It was found that in some patients, the lesions of TMA with arteriolar and capillary microthrombi can develop with a clinical picture of thrombocytopenic purpura or hemolytic uremic syndrome associated with APS, regardless of the underlying type of lupus glomerulopathy that exists (7,51). On histology, the principal vaso-occlusive lesion observed is that of fibrinous obstruction without IgG deposits (28). This latter lesion should not be confused with the glomerular intracapillary coagula of immunoglobulins, which may occur as well in SLE (50). Moreover, the study of Banfi *et al.* (52) comprising 285 lupus patients showed that TMA was the most important of the renal vascular lesions threatening the renal prognosis. More recently, it has been shown (26,40,41) that terminal renal insufficiency can occur in SLE as the result of intrarenal vascular lesions only and not of glomerulonephritis. It seems probable that the significance of the vascular lesions is similar in the course of PAPS. Interestingly, however, the incidence of TMA in SLE with LA is much lower than in PAPS. In one series of 33 such patients, only five had evidence of TMA (50). In another clinical setting, Kincaid-Smith and coworkers (42), in a series of 12 pregnant women with LA, reported acute arteriolar and glomerular thrombotic lesions in the course of PAPS (eight of these women *a posteriori* could be placed in the category of PAPS, the other four having SLE).

Subsequently, the intrarenal lesions of TMA were sought for and identified in the course of PAPS (16–21). TMA is sometimes the very first manifestation leading to the diagnosis of PAPS (patient 5) (18). The functional prognosis of this lesion has not been established. Nonetheless, it may be ominous, as in the series of Amigo *et al.* (17), in which five of 20 patients with PAPS had renal symptomatology attributable to TMA, with evolution in two patients to terminal renal insufficiency.

In our series, 75% of renal biopsies showed FIH of arterioles and interlobular arteries, with narrowing of the vascular lumen. Interlobular arteries predominantly had a cellular proliferation of actin-positive cells in the intima, while others showed more advanced collagen and elastic fiber deposition with less cellularity. Finally, 68% of biopsies showed numerous fibrous and fibrocellular vascular occlusions, the final stage of the small-vessel vaso-occlusive renal disease of PAPS, resembling lesions of the diffuse vaso-occlusive disease of other organs described by Lie (46) in APS. FIH was the second vascular lesion observed by Kincaid-Smith and colleagues (42) in renal biopsies of the group of pregnant women with PAPS. Other authors (24,28,29) have described in small numbers of PAPS cases intimal hyperplasia with organized thrombi in not only the intrarenal arteries, but also in other organs: lung, meninges, and brain (43–46). Our study is in accord with that of Kincaid-Smith *et al.* (42), who clarified the pathophysiology of APS, particularly the outcome of the intrarenal vascular lesions. With follow-up and rebiopsy several years after the initial episode (up to 10 yr in one patient), they have shown the progression of the proliferative and obstructive intimal lesions of the interlobular arteries and arterioles with progressive destruction of the kidney, sometimes accelerated by acute thrombotic events.

The same lesions of FIH in intrarenal arteries with marked narrowing of the lumen are observed in surgical nephrectomies performed for renal artery stenosis (seeking to reduce hypertension secondary to unilateral stenosis) (53, personal obser-

vations). In this form of renal ischemia, in addition to hypoperfusion, the intervention of the renin-angiotensin system, particularly angiotensin II, seems to cause the lesions of FIH. Furthermore, these nephrectomy specimens frequently show lesions of tubular thyroidization, present in 75% of our cases, suggesting a similar pathophysiology. FIH and tubular thyroidization in PAPS are likely the consequences of tissue ischemia and of the activation of the renin-angiotensin system.

In our series, 61% of the cases showed the lesions of FCA. This histologic lesion seems to have been described in earlier publications under different names such as "ischemic cortical necrosis," "cortical infarcts," or "cortical scars" (24,42,54–57). This fibrous subcapsular cortical lesion includes in association with different vaso-occlusive lesions, retraction of tuft with sclerotic and pseudocystic glomeruli occurring in groups, as well as destructive fibrosis with areas of tubular atrophy and loss with thyroidization. This picture is also present in the subcapsular cortex of ischemic kidneys distal to a renal artery stenosis, suggesting once again that the lesions of FCA may be the consequence of tissue ischemia and activation of the renin-angiotensin system. These lesions of FCA are likely the histologic equivalent of the subcapsular images recognized by renal imaging (angiography and CT scan). The lesions of TMA may also be present with fibrin thrombi and fragmented red cells in the small arterioles and glomeruli, with the latter sometimes showing mesangiolysis and double contours such as are seen in the hemolytic uremic syndrome.

The overall ensemble of cellular FIH with partial or complete vascular occlusion and FCA, together with variable TMA, represents a constellation more or less characteristic of PAPS. The combination of any two of these three elements should alert the pathologist to the possibility of PAPS, to be confirmed clinically. However, because each of these elements may occur in other conditions, a word should be said about the distinction of these conditions from PAPS.

The vascular lesions of PAPS differ in several ways from those of the typical nephroangiosclerosis (NAS) of aging and essential hypertension. First, the thickened arterial intima in PAPS tends to be cellular, sometimes markedly so, in contrast to the relatively acellular, densely collagenous intima of NAS. Second, there tends to be less arterial medial fibrosis than in the lesions of NAS, which are more degenerative in nature. Third, fresh and organized arterial thrombi and TMA are not seen, of course, in NAS. Conversely, in conditions associated with TMA, such as hemolytic uremic syndrome, predominantly small vessels and glomeruli are affected, cellular FIH in larger arteries is not prominent, and lesions affect the parenchyma more uniformly so that FCA is uncommon. A possible exception is malignant hypertension, in which the same constellation of lesions might appear, so that here the distinction would have to be made on clinical grounds.

Conclusion

This study allows us to approach the nephropathy of PAPS as an entity in its own right, characterized by small-vessel vaso-occlusive intrarenal pathology that likely evolves by repeated flares leading to a morphologic picture suggestive of its diagnosis even in the absence of history. This picture combines the lesions of TMA, FIH of the arteries and arterioles, and FCA. The clinical hallmark of this nephropathy is hypertension, only variably associated with renal insufficiency, proteinuria, or hematuria. Conversely, the recognition of such lesions on a biopsy performed for diagnostic purposes should lead to work-up for possible PAPS. However, we need to understand better the morbidity associated with this nephropathy to be able to define the indications for and modalities of treatment.

Acknowledgments

We thank Drs. B. Canaud (Department of Nephrology, Montpellier, France) and D. Chauveau (Hôpital Necker, Paris) for giving us clinical information concerning their patients. We are also most appreciative of the technical assistance of Chantal Jouanneau (Institut National de la Santé et de la Recherche Médicale U423, Paris), Nicole Pfister, and Annette Rakotosalama (Pathology Department, Hôpital Broussais, Paris).

References

1. Hughes GRV: The anticardiolipin syndrome. *J Rheumatol* 13: 486–489, 1986
2. Harris EN, Phil M, Chan JKH, Asherson RA, Gharavi AE, Hughes GRV: Thrombosis, recurrent fetal loss and thrombocytopenia: Predictive value of the anticardiolipin antibody test. *Arch Intern Med* 146: 2153–2156, 1986
3. Asherson RA, Cervera R: The antiphospholipid syndrome: A syndrome in evolution. *Ann Rheum Dis* 51: 147–150, 1992
4. Kant KS, Pollack VE, Weiss MA, Glueck HI, Miller MA, Hess EV: Glomerular thrombosis in systemic lupus erythematosus: Prevalence and significance. *Medicine* 60: 71–80, 1981
5. Glueck HI, Kant KS, Weiss MA, Pollak VE, Miller MA, Coots M: Thrombosis in systemic lupus erythematosus: Relation to the presence of circulating anticoagulants. *Arch Intern Med* 145: 1389–1395, 1985
6. Alarcón-Segovia D, Delezé M, Oria CV, Sánchez- Guerrero J, Gómez-Pacheco L, Cabiedes J, Fernández L, Ponce de León S: Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus: A prospective analysis of 500 consecutive patients. *Medicine* 68: 353–365, 1989
7. Frampton G, Hicks J, Cameron JS: Significance of anti-phospholipid antibodies in patients with lupus nephritis. *Kidney Int* 39: 1225–1231, 1991
8. Love PE, Santoro SA: Antiphospholipid antibodies: Anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. *Ann Intern Med* 112: 682–698, 1990
9. Asherson RA, Kant KS: Antiphospholipid antibodies and the kidney. *J Rheumatol* 20: 1268–1272, 1993
10. Piette JC, Cacoub P, Weschler R: Renal manifestations of the antiphospholipid syndrome. *Semin Arthritis Rheum* 23: 357–366, 1994
11. Piette JC, Kleinknecht D, Bach JF: Renal manifestations in the antiphospholipid syndrome. In: *The Antiphospholipid Syndrome*, edited by Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Boca Raton, FL, CRC Press, 1996, pp 169–181
12. Asherson RA, Kant KS: A "primary " antiphospholipid syndrome? *J Rheumatol* 15: 1742–1746, 1988

13. Alarcón-Segovia D, Sánchez-Guerrero J: Primary antiphospholipid syndrome. *J Rheumatol* 16: 482–488, 1989
14. Asherson RA, Khamashta MA, Ordi-Ros J, Derken RH, Machin SJ, Barquinero J, Outt HH, Harris EN, Vilardell-Torres M: The primary antiphospholipid syndrome: Major clinical and serological features. *Medicine* 68: 366–374, 1989
15. Asherson RA, Cervera R, Piette JC, Shoenfeld Y: The antiphospholipid syndrome: History, classification, and differential diagnosis. In: *The Antiphospholipid Syndrome*, edited by Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Boca Raton, FL, CRC Press, 1996, pp 3–12
16. Becquemont L, Thervet E, Rondeau E, Lacave, Mougenot B, Sraer JD: Systemic and renal fibrinolytic activity in a patient with anticardiolipin syndrome and renal thrombotic microangiopathy. *Am J Nephrol* 10: 254–258, 1990
17. Amigo MC, Garcia-Torrés R, Robles M, Biochicchio T, Reyes PA: Renal involvement in primary antiphospholipid syndrome. *J Rheumatol* 19: 1181–1185, 1992
18. Lacueva J, Enriquez R, Cabezuelo JB, Arenas MD, Teruel A, Gonzalez C: Acute renal failure as first clinical manifestation of the primary antiphospholipid syndrome. *Nephron* 64: 479–480, 1993
19. Sokunbi DOB, Miller F, Wadhwa NK, Nord EP: Reversible renal failure in the primary antiphospholipid syndrome: A report of two cases. *J Am Soc Nephrol* 3: 28–35, 1993
20. Domrongkitchaiporn S, Cameron EC, Jetha N, Kassen BO, Sutton RAL: Renal microangiopathy in the primary antiphospholipid syndrome: A case report with literature review. *Nephron* 68: 128–132, 1994
21. Hamidou MA, Moreau A, Jego P, Testa A, Banisadr F, Buzelin F, Grolleau JY: Captopril and aspirin in treatment in renal microangiopathy in primary antiphospholipid syndrome. *Am J Kidney Dis* 25: 486–488,1995
22. Callot V, Sirieix ME, Cohen P, Jouachem Y, Jacquot C, Nochy D, Capron L, Fiessinger JN: Ulcéres de jambe récidivants, hémorragie intra-alvéolaire, perforation de la cloison nasale: Syndrome primaire des anti-phospholipides? *Ann Méd Interne* 146: 366–369, 1995
23. Kleinknecht D, Bobrie G, Meyer O, Noel LH, Callard P, Ramdane M: Recurrent thrombosis and renal vascular disease in patients with a lupus anticoagulant. *Nephrol Dial Transplant* 4: 854–858, 1989
24. D'Agati V, Kunis C, Williams G, Appel GB: Anticardiolipin antibody and renal disease: A report of three cases. *J Am Soc Nephrol* 1: 777–784, 1990
25. Hughson MD, Nadasdy T, McCarty, Sholer C, Min KW, Silva F: Renal microangiopathy in patients with systemic lupus erythematosus and the antiphospholipid syndrome. *Am J Kidney Dis* 20: 150–158, 1992
26. Leaker B, McGregor A, Griffiths M, Snaiyh A, Neild GH, Isenberg D: Insidious loss of renal function in patients with anticardiolipin antibodies and absence of overt nephritis. *Br J Rheumatol* 30: 422–425, 1991
27. Scolari F, Savoldi S, Costantino E, Spitti C, Franceschini F, Taranico R, Morassi L, Maiorca R: Antiphospholipid syndrome and glomerular thrombosis in the absence of overt lupus nephritis. *Nephrol Dial Transplant* 8: 1274–1276, 1993
28. Isenberg DA, Griffiths M, Neild, GH: Woman with livedo reticularis, renal failure, and benign urinary sediment. *Nephrol Dial Transplant* 10: 295–297, 1995
29. Hughson MD, McCarty GA, Brumback RA: Spectrum of vascular pathology affecting patients with the antiphospholipid syndrome. *Hum Pathol* 26: 716–724, 1995
30. Sirvent AE, Enriquez R, Antolin A, Cabezuelo JB, Gonzalez C, Arenas MD: Malignant hypertension and antiphospholipid syndrome. *Nephron* 73: 368–369, 1996
31. Piette JC, Wechsler B, Frances C, Godeau P: Systemic lupus erythematosus and the antiphospholipid syndrome: Reflections about the relevance of ARA criteria [Editorial]. *J Rheumatol* 19:1835–1837, 1992
32. Hochberg MC: Updating the American College of Rheumatology revisited criteria for the classification of systemic lupus erythematosus [Letter]. *Arthritis Rheum* 40: 1725, 1997
33. Asherson RA, Bagueley E, Pal C, Hughes GRV: The antiphospholipid syndrome: 5 years followup. *Ann Rheum Dis* 50: 805–810, 1991
34. Piette JC, Wechsler B, Frances C, Papo T, Godeau P: Exclusion criteria for primary antiphospholipid syndrome. *J Rheumatol* 20: 1802–1824, 1993
35. Nochy D, Barres D, Camilleri JP, Bariéty J, Corvol P, Ménard J: Abnormalities of renin-containing cells in human glomerular and vascular renal diseases. *Kidney Int* 23: 375–379, 1983
36. Finazzi G, Brancaccio V, Moia M, Ciavarella N, Mazzucconi G, Shinco PC, Ruggeri M, *et al*: Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: A four- year prospective study from the Italian Registry. *Am J Med* 100: 530–536, 1996
37. Asherson RA, Noble GE, Hughes GRV: Hypertension, renal artery stenosis and the "primary " antiphospholipid syndrome. *J Rheumatol* 18: 1413–1415, 1991
38. Rossi E, Sani C, Zini M, Casoli MC, Restori G: Anticardiolipin antibodies and renovascular hypertension. *Ann Rheum Dis* 51: 1180–1181, 1992
39. Sonpal GM, Sharma A, Miller A: Primary antiphospholipid antibody syndrome, renal infarction and hypertension. *J Rheumatol* 20: 1221–1223, 1993
40. Jouquan J, Pennec Y, Mottier D, Youinou P, Cledes J, Leroy JP, Le Menn G: Accelerated hypertension associated with anticoagulant and false positive VDRL in systemic lupus erythematosus [Abstract]. *Arthritis Rheum* 29: 147, 1986
41. Cacoub P,Weschsler B, Piette JC, Beaufils H, Herreman G, Blétry O, Godeau P: Malignant hypertension in antiphospholipid syndrome without overt lupus nephritis. *Clin Exp Rheumatol* 11: 479–485, 1993
42. Kincaid-Smith P, Fairley KF, Kloss M: Lupus anticoagulant associated with renal thrombotic microangiopathy and pregnancy-related renal failure. *Q J Med* 69: 795–815, 1988
43. Harris EN, Bos K: An acute disseminated coagulopathy-vasculopathy associated with the antiphospholipid syndrome. *J Rheumatol* 19: 508–512, 1992
44. Perez RE, McClendon JR, Lie JT: Primary antiphospholipid syndrome with multiorgan arterial and venous thromboses. *J Rheumatol* 19: 1289–1292, 1992
45. Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A, Lim K, Munoz- Rodriguez FJ, Levy RA, Boué F, Rossert J, Ingelmo M: Catastrophic antiphospholipid syndrome: Clinical and laboratory features of 50 patients. *Medicine* 77: 195–207, 1998
46. Lie JT: Pathology of the antiphospholipid syndrome. In: *The Antiphospholipid Syndrome*, edited by Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Boca Raton, FL, CRC Press, 1996, pp 89–104

47. Bhatena DB, Sobel BJ, Migdal SD: Noninflammatory renal microangiopathy of systemic lupus erythematosus ("lupus vasculitis"). *Am J Nephrol* 1: 144–159, 1981
48. Schwartz MM: Lupus vasculitis. In: *Systemic Lupus Erythematosus: Renal Vasculitis*, edited by Sessa A, Meroni M, Battini G, Basel, Karger, 1992, pp 35–45
49. Appel GB, Pirani C, D'Agati V: Renal vascular complications of systemic lupus erythematosus. *J Am Soc Nephrol* 4: 1499–1515, 1994
50. Descombes E, Droz D, Drouet L, Grünfeld JP, Lesavre P: Renal vascular lesions in lupus nephritis. *Medicine* 76: 355–368, 1997
51. Farrugia E, Vicente ET, Gastineau D, Michet CJ, Holley KE: Lupus anticoagulant in systemic lupus erythematosus: A clinical and renal pathological study. *Am J Kidney Dis* 5: 463–471, 1992
52. Banfi G, Bertani T, Boeri V, Faraggiana T, Mazzucco G, Monga G, Sacchi G, for the Gruppo Italiano per lo Studio della Nefrite Lupica (GISNEL): Renal vascular lesions as a marker of poor prognosis in patients with lupus nephritis. *Am J Kidney Dis* 18: 240–248, 1991
53. Heptinstall RH: Hypertension II. In: *Pathology of the Kidney*, 4th Ed., edited by Heptinstall RH, Boston, Little, Brown, 1992, pp 1029–1095
54. Asherson RA, Hughes GRV, Derksen RHWM: Renal infarction associated with antiphospholipid antibodies in systemic lupus erythematosus and '"lupus-like" disease [Abstract]. *J Urol* 140: 1028, 1988
55. Ramdane M, Gryman R, Bacques O, Callard P, Kleinknecht D: Ischémie rénale corticale, thrombose auriculaire droite et occlusion coronaire au cours d'un syndrome des anticardiolipides. *Néphrologie* 10: 189–193, 1989
56. Mandreoli M, Zucchelli P: Renal vascular disease in patients with primary antiphospholipid antibodies. *Nephrol Dial Transplant* 8: 1277–1280, 1993
57. Poux JM, Boudet R, Lacroix P, Jauberteau MO, Plouin JF, Aldigier JC, Leroux-Robert C: Renal infarction and thrombosis of the infrarenal aorta in a 35-year-old man with primary antiphospholipid syndrome. *Am J Kidney Dis* 27: 721–725, 1996