Renal Involvement in Primary Antiphospholipid Syndrome: Retrospective Analysis of 160 Patients

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Background and objectives: The objective of this study was to evaluate the prevalence, clinicopathologic features, and outcome of renal involvement in a large cohort of patients with primary antiphospholipid syndrome (PAPS).

Design, setting, participants, & measurements: We retrospectively examined medical records of 160 patients with a diagnosis of PAPS of two general hospitals of northern Italy between 1985 and 2008.

Results: There were 140 women and 20 men. Mean age was 35 ± 12 yr. PAPS was characterized by thrombotic events in 41.2%, fetal loss in 39.4%, and both in 19.4%. Signs of renal abnormalities were present in 14 (8.7%) patients. All patients had proteinuria, in the nephrotic range in five; four patients had moderate chronic renal insufficiency, and one had end-stage kidney disease (ESKD). Two patients presented with acute renal failure and one with nephritic syndrome. Ten patients underwent a renal biopsy, which showed a membranous glomerulonephritis in four, proliferative glomerulonephritis in two, thrombotic microangiopathy in two, and vascular lesions consistent with chronic antiphospholipid antibodies nephropathy in two. Patients with renal involvement were older (41.8 *versus* 34.3 years; $P = 0.0269$), more frequently lupus anticoagulant positive (92.3 *versus* 48.9%; $P = 0.0068$), and had hypocomplementemia ($P < 0.05$).

Conclusions: Renal abnormalities are present in approximately 9% of patients with PAPS. In addition to APS nephropathy, the prevailing picture is membranous nephropathy. Outcome and long-term follow-up usually are good. Not all of the clinical manifestations of PAPS can be ascribed to thrombotic mechanisms. The heterogeneity of renal involvement confirms the presence of a continuum between systemic lupus erythematosus and PAPS.

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Antiphospholipid syndrome (APS) is defined by the presence of antiphospholipid antibodies, recognized as anticardiolipin antibodies and/or anti-β2 glycoprotein I and/or lupus anticoagulant, associated with thrombotic events (venous or arterial) and/or fetal loss (1,2).

Although APS was first described in patients with systemic lupus erythematosus (SLE) (3), >50% of patients with APS do not have clinical or laboratory evidence of another autoimmune disease and are classified as having primary antiphospholipid syndrome (PAPS) (4,5). Whereas the majority of visceral manifestations in the course of PAPS outside of the kidney has been well recognized since its description, renal involvement was underestimated and not well characterized until recently (6–13).

A large spectrum of renal thrombotic manifestations have been described in association with antiphospholipid antibodies, such as renal artery stenosis, renal infarction, renal vein thrombosis, acute or chronic thrombotic microangiopathy (7,8), and, more recently, the so-called "antiphospholipid antibodies nephropathy" (9,10). Indeed, thrombosis can occur at any level of the renal vascular tree: Renal and intrarenal arteries, glomerular capillaries, and renal vein. Histologic findings show ischemic glomeruli and thrombotic lesions, without glomerular or arterial immune deposits on immunofluorescence. In 1999, Nochy *et al.* (8) described 16 cases of primary APS with vascular nephropathy. They could distinguish two forms of vascular nephropathy: (*1*) An acute form clinically resembling other thrombotic microangiopathy, such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura, and (*2*) a chronic form of renal involvement, often clinically silent, consisting of the development of a vaso-occlusive process at all levels of the renal vasculature, from the main renal artery and its branches to arterioles to glomerular capillary and renal veins.

In addition to thrombosis, other kinds of renal lesions (*e.g.*, glomerulonephritis) have been anecdotally reported in primary APS (PAPS) (14–18). More recently, an expanding spectrum of renal diseases associated with APS have been described, identifying among 29 kidney biopsies, performed in patients with primary APS, nine (31%) cases with predominant pathologic features distinct from vascular APS nephropathy (19). In particular, membranous nephropathy (MN; three cases), minimal

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change disease/focal segmental sclerosis (three cases), mesangial C3 nephropathy (two cases), and pauci-immune crescentic glomerulonephritis (one case) were noted (19).

Despite the increasing knowledge of kidney as target organ in APS, little is known about the prevalence and clinicopathologic features of renal involvement in PAPS. Most of the data derive, indeed, from case reports and small series or from selected biopsy series (6–8,14–21). In a large series of patients with APS, renal complications occurred in 2.7% of cases (5); however, this prevalence is probably underestimated because only thrombotic lesions were considered and patients with APS rarely undergo a kidney biopsy because of the frequent presence of thrombocytopenia and/or anticoagulant treatment.

The aim of our work was to examine the prevalence and clinical features of renal involvement in a large cohort of consecutive unselected patients with PAPS. Moreover, we reviewed the renal histologic findings when available.

Materials and Methods

Patients

We examined retrospectively the medical records of all patients who had a diagnosis of PAPS and attended the Clinical Immunology/Rheumatology and Nephrology Units of Spedali Civili, Brescia, and Ospedale San Carlo Borromeo, Milano, Italy. All patients who were registered between 1985 and 2008 were included in the study. The diagnosis of PAPS was made according to the Sapporo classification criteria (1) and the absence of secondary APS.

Definitions

Renal involvement was defined as the presence of renal insufficiency (serum creatinine >1.4 mg/dl) and/or of urinary abnormalities (proteinuria >0.3 g/d with or without microscopic hematuria on two separate occasions, in the absence of urinary infection). A renal biopsy was performed whenever judged necessary by the physicians who were taking care of the patients. Light microscopy slides were prepared and stained according to standard methods for light and immunofluorescence microscopy. All patients were screened for signs of renal involvement at least once a year in the follow-up. Long-term follow-up and outcome were established after the patient's last visit or death.

Autoantibody Testing

Autoantibodies were determined at diagnosis and at follow-up. Antinuclear antibodies (ANAs) were detected by indirect immunofluorescence on HEp-2 cells (Kallestad, Chaska, MN); a titer of 1:80 or higher was considered positive. Anti–double-stranded DNA (anti-dsDNA) was detected by Farr assay (Kodak Clinical Diagnostics Ltd., Amersham, UK); a value of ≥4.2 IU/ml of dsDNA binding is considered positive in our laboratory. Anticardiolipin antibodies (enzyme immunoassay) were measured following the method suggested by the International Standardization Workshop (22). Antibodies to extractable nuclear antigen were determined by counter immunoelectrophoresis, according to Bernstein *et al.* (23), using a rabbit thymus extract (Peel-Freeze, Rogers, AR, USA); antibodies to Ro/Sjögren syndrome serum A were determined by counter immunoelectrophoresis, using human spleen extract as substrate. Human spleen extract was prepared according to Clark *et al.* (24) and Venables *et al.* (25). The detection of anti–β2-glycoprotein I antibodies was performed by ELISA according to Balestrieri *et al.* (26). Lupus anticoagulant was detected in blood by using at least two phospholipid-dependent tests (kaolin clotting time, activated thromboplastin time, and prothrombin time), as previously recommended (27).

Statistical Analysis

All of the parameters were evaluated by χ^2 test with Yates or Pearson correction, when indicated. Statistical significance was accepted at $P < 0.05$.

Results

A total of 160 patients were identified as having PAPS. There were 140 women and 20 men. Mean age was 35.0 ± 12.0 years. PAPS was characterized by thrombotic events in 66 (41.2%), fetal loss in 63 (39.4%), and both thrombotic events and fetal loss in 31 (19.4%). Patients were followed for a mean of 8.3 years (SD 7.1 years).

Renal involvement, as previously defined, was present in 14 (8.7%) patients. Table 1 shows the main demographic and clinical features of these patients. There were 11 women and three men with a mean age of 41.8 years (range 28.0 to 76.0 years).

PAPS was characterized by only fetal loss in two patients (patients 2 and 4), and thrombocytopenia was present in four cases (patients 3, 7, 11, and 12). Renal involvement was present at diagnosis in all of the patients except two (data not shown). All patients had proteinuria, in the nephrotic range (>3.5 g/d) in five; four patients had moderate (stage 3) chronic renal insufficiency (patients 1, 5, 6, and 11) with estimated GFR between 41 and 59 ml/min per 1.73 m^2 (28). Two patients presented with acute renal failure (patients 7 and 10) and one (patient 8) with nephritic syndrome. One patient (patient 13) came to our attention with ESKD characterized by a history of bilateral renal artery stenosis and nephrotic-range proteinuria. Eight patients had high BP at diagnosis.

Lupus anticoagulant was positive in 12 (92.3%) of 13 of the patients, whereas anticardiolipin antibodies (IgG and/or IgM isotype) were positive (at medium-high titer) in 12 of 14. Anti–β2-glycoprotein I antibodies were positive in 10 of 13 (Table 1).

ANAs were positive, usually at low titer, in nine (64.3%) patients, whereas anti-dsDNA was found at borderline titer in four (28.6%) cases. Anti-Sjögren syndrome serum A antibodies were present in two patients (Table 1). Eight patients had some degree of hypocomplementemia (Table 1).

Comparing the 14 patients with nephropathy and the 146 patients without, we found a more frequent positivity of lupus anticoagulant (92.3 *versus* 48.9%; $P = 0.0068$) in the first group. No significant difference was found concerning distribution of other autoantibodies between the two groups, although anti-dsDNA and anti-extractable nuclear antigen antibodies were more frequently detected in cases with nephropathy (28.6 *versus* 8.9 and 14.3 *versus* 2.3%, respectively).

Moreover, patients with renal involvement more frequently showed complement activation, in terms of low C3 (35.7 *versus* 9.7%; $P = 0.017$), low C4 (42.8 *versus* 5.2%; $P < 0.001$; Table 2), and low CH50 (50 *versus* 10%; $P = 0.002$; data not shown). Noteworthy, patients with kidney disease were older than the whole population (41.8 *versus* 34.3 years; $P = 0.0269$).

Ten patients underwent a renal biopsy, which showed a membranous glomerulonephritis in four, proliferative glomer-

Table 1. Main clinical, laboratory, and histologic data of patients with renal involvement

Patient	Age/ Gender	Extrarenal Symptoms	sCreat (mg/dl)	Hematuria	Proteinuria (g/d)	High BP	LA	aCL	aβ2	ANA	Anti-dsDNA	Anti-ENA	C3/C4	Histology	Therapy	Follow-up (years)
1	39/F	Retinal thrombosis, preeclampsia	1.5	±	0.5	No	+	+	+	+ (speckled)	−	−	↓	MN	PD, C	6.9 stable
2	36/F	Fetal loss	0.9	−	2.5	No	ND	+	ND	−	−	−	↓	MN	PD	Lost
3	30/F	Venous thrombosis, fetal loss, thrombocytopenia	0.9	−	1.5	No	−	+	−	−	−	−	–	MN	PD	14.1 remission
4	34/F	Fetal loss	0.6	+	10.0	Yes	+	−	−	−	−	−	–	MN	PD, C	10.0 remission
5	40/M	Skin ulcer	1.8	+	0.6	Yes	+	+	+	−	−	−	–	cAPSN	–	1.6 stable
6	39/M	Myocardial infarction	1.6	−	0.8	Yes	+	+	+	+ (speckled)	−	−	–	cAPSN	–	1.0 stable
7	76/F	Cerebral ischemia, hemolytic anemia, thrombocytopenia	12.0	+	1.1	Yes	+	+	+	+ (speckled)	−	−	↓	TMA	HD, FFP	4.2 remission
8	46/F	Venous thrombosis, fetal loss	2.1	+	6.0	Yes	+	+	+	+ (homog)	±	SSA	↓	DPGN	PD, C	1.0 remission
9	43/F	Venous thrombosis, fetal loss	0.8	+	4.5	No	+	−	+	+ (homog)	+	−	↓	DPGN	PD, C	1.0 remission
10	38/F	CAPS	5.0	+	0.5	No	+	+	−	−	−	−	–	TMA	HD, PD, PE, IVIg	5.0 remission
11[a]	44/M	Venous thrombosis, pulmonary embolism, thrombocytopenia	1.5	−	1.6	Yes	+	+	+	+ (nucleolar)	±	−	↓	ND	PD, AZA	9.2 stable
12[a]	33/F	Fetal loss, preeclampsia, thrombocytopenia	1.2	±	3.2	No	+	+	+	+ (speckled)	−	−	–	ND	PD	5.0 remission
13[a]	59/F	Cerebral ischemia, bilateral renal arterial stenosis	5.7	+	3.7	Yes	+	+	+	+ (homog)	−	−	↓	ND	–	ESKD
14[a]	28/F	HELLP, fetal loss, cerebral ischemia	1.2	+	5.3	Yes	+	+	+	+ (homog)	±	SSA	↓	ND	PD	2.0 remission

aβ2, anti–β-2 glycoprotein I antibodies; aCL, anticardiolipin antibodies; anti-ENA, anti–extractable nuclear antigen antibodies; AZA, azathioprine; C, cyclophosphamide; CAPS, catastrophic anti-hospholipid syndrome; cAPSN, chronic antiphospholipid syndrome; DPGN, diffuse proliferative glomerulonephritis; FFP, fresh-frozen plasma; HD, hemodialysis; HELLP, hemolysis, elevated liver enzymes, and low platelet count syndrome; homog, homogeneous; IVIg, intravenous immunoglobulins; LA, lupus anticoagulant; ND, not done; PD, prednisone; PE, plasma exchange; sCreat, serum creatinine; SSA, Sjögren syndrome serum A; TMA, thrombotic microangiopathy.

[a]Patients who did not undergo renal biopsy.

Table 2. Main clinical and immunologic features in patients with or without renal involvement

Feature	Patients without Renal Involvement ($n = 146$)	Patients with Renal Involvement ($n = 14$)	P
Age (years; mean ± SD)	34.3 ± 11.8	41.8 ± 12.5	0.0269
Male/female	17/129	3/11	NS
Follow-up (years; mean ± SD)	8.4 ± 6.5	5.1 ± 4.2	NS
Arterial hypertension (%)	22.6	57.1	0.0122
Thrombotic events (%)	41.1	42.9	NS
Fetal loss (%)	41.8	14.3	NS
Thrombotic events + fetal loss (%)	17.1	42.9	NS
LA positive (%)	48.9	92.3	0.0068
Anticardiolipin antibodies positive (%)	69.9	85.7	NS
Anti–β2-glycoprotein I antibodies (%)	75.3	76.9	NS
ANA positive (%)	47.9	64.3	NS
Anti-dsDNA positive (%)	8.9	28.6[a]	NS
HypoC3 (%)	9.7	35.7	0.017
HypoC4 (%)	5.2	42.8	<0.001

LA, lupus anticoagulant.
[a]Borderline value.

Table 3. Main histologic and immunohistologic features of four cases of MN and two cases of diffuse proliferative glomerulonephritis in patients with PAPS

Patient	Stage of MN	Mesangial Proliferation	Mesangial Deposits	Subendothelial Deposits	IgG Deposits	IgA Deposits	IgM Deposits	C3 Deposits	C1q Deposits
1	I to II	−	++	−	+++	+++	+++	+++	++
2	III	−	+	+	++	−	+	+	+
3	II to III	−	+	+	ND	ND	ND	ND	ND
4	II	−	−	−	+++	−	+	++	++
8	–	+++[a]	++	+++	+++	++	+++	+++	+++
9	–	+++	++	+++	+++	+++	+++	+++	+++

ND, not done.
[a]Plus segmental extracapillary proliferation.

ulonephritis in two, thrombotic microangiopathy in two, and vascular lesions consistent with chronic antiphospholipid antibody nephropathy in two. Patients with MN usually had immune deposits confined not only in the subepithelial area but also in the mesangium (three patients) and in the subendothelial space (two patients; Table 3). C1q deposits (not prominent), in addition to Igs and C3, were present in all three cases tested for (Table 3). Two of four patients with MN had low complement levels and one of the two was also ANA positive (Table 1). Two patients had diffuse proliferative glomerulonephritis resembling class IV lupus nephritis.

Two patients had renal histologic lesions consistent with chronic antiphospholipid antibody nephropathy (Table 1). Both patients had mild chronic renal impairment, high BP, and proteinuria <1 g/d. Two patients had thrombotic microangiopathy; both of them presented with acute renal failure that required hemodialysis (Table 1).

All patients were treated with anticoagulation. Patients with MN were treated with steroids with addition of cyclophosphamide in two. Remission was achieved in two patients with MN; one was stable with mild proteinuria (0.5 g/d), and one patient was lost to follow-up. Both patients with diffuse proliferative glomerulonephritis were treated with corticosteroids plus cyclophosphamide with remission of nephrotic-range proteinuria (Table 1).

At the end of a follow-up of 5.1 ± 4.2 years, none of the patients (with the exception of the patient who came to our attention with advanced chronic renal insufficiency) reached ESKD or doubling of serum creatinine. Six patients were in complete remission (proteinuria <0.30 g/d). Urinary abnormalities (non–nephrotic-range proteinuria) were still present in six. Two of the patients (both with diffuse proliferative glomerulonephritis) developed full-blown SLE 13 and 18 years after the diagnosis of PAPS, respectively.

Discussion

This is one of the first studies to investigate systematically, even if in a retrospective way, the prevalence, presentation, and

clinical course of renal involvement in a large cohort of patients with PAPS. We tried to minimize selection bias of patients in our study by enrolling patients from both renal and rheumatology/clinical immunology units of two large general hospitals from northern Italy.

Renal disease was present in 8.7% of our patients with PAPS. All patients had significant proteinuria, in the nephrotic range (>3.5 g/d) in five; four patients had mild chronic renal impairment, and one had ESKD. Two patients presented with acute renal failure, and one presented with nephritic syndrome.

It is possible that the prevalence of renal involvement might have been underestimated in our series. Indeed, a cutoff serum creatinine level >1.4 mg/dl could be considered too high to define renal insufficiency in a population of mainly young women. Moreover, a significant percentage (up to 25%) of patients with APS nephropathy may not have proteinuria (8); however, none of our patients without renal involvement, as previously defined, developed signs of kidney disease in the follow-up.

Patients with kidney disease were older than the whole population, suggesting that renal involvement is a complication that develops during the course of the disease. Noteworthy, the main histologic picture was MN or proliferative glomerulonephritis, and only four patients had histologic lesions consistent with acute or chronic APS nephropathy.

The prevalence of renal disease in primary APS is unclear. Most of the data derive, indeed, from case reports and small series or from selected biopsy series (14–21). In a large series of patients with APS, renal complications occurred in 2.7% of cases (5); however, this prevalence is probably underestimated, because only thrombotic lesions were considered and patients with APS rarely undergo a kidney biopsy because of the frequent presence of thrombocytopenia and/or anticoagulant treatment. Another group found, in a series of 78 patients with PAPS, signs of renal involvement in eight (10%) (29). APS nephropathy–compatible features, in the absence of other characteristics of lupus nephritis, occurred in only one biopsy from patients with PAPS. On the contrary, the other four kidney biopsies showed immune complex glomerulonephritis, with features of MN in two (29). Our findings are, in some way, in agreement with this study and with a previous one on 29 kidney biopsies from patients with PAPS that reported a high frequency of glomerulonephritis (almost one third) and especially MN (19).

Interestingly, a few studies but not all on antiphospholipid antibodies and lupus nephritis (30–32) reported a strong association between the presence of antiphospholipid antibodies and MN (class V). Moreover, anecdotal case reports showed that a number of patients with antiphospholipid antibodies and nephrotic syndrome displayed membranous nephritis at renal biopsy (15–18). Because membranous nephritis may precede the clinical and biologic manifestations of SLE, some of these patients could eventually develop SLE. Finally, immunodeficient mice that received transfusions of peripheral blood lymphocytes of a patient with antiphospholipid antibodies and membranous nephritis developed renal lesions that resembled human membranous nephritis (15).

Follow-up of our patients with MN was long (8.5 years; range 6.9 to 14.1 years); nevertheless, none of our patients developed full-blown SLE. It should be stressed, however, that these patients were treated with steroids (plus cyclophosphamide in two) because of glomerulonephritis, and this could have prevented other SLE clinical manifestations from occurring.

Patients with MN or proliferative glomerulonephritis, especially when C1q deposits and hypocomplementemia are present, should be considered at high risk for developing SLE. Careful monitoring is therefore necessary in these patients.

None of the patients (with the exception of the patient who came to our attention with advanced chronic renal insufficiency) reached ESKD or doubling of serum creatinine at the end of a mean follow-up of 5 years. This might suggest that kidney disease in PAPS is not associated with a high renal morbidity when adequately diagnosed and treated.

Recently, we reported an unexpectedly high frequency of antinucleosome (anti-NCS) antibodies, considered a marker of SLE, in patients with PAPS (33). Eighty-one (77%) of 105 patients with PAPS were positive for IgG and/or IgM anti-NCS antibodies. Moreover, medium-high titers of anti-NCS antibodies were present in 46% of cases. As expected, anti-NCS antibodies were more frequently detected in PAPS with lupus-like disease, and two patients, with high titers of anti-NCS antibodies many years before, developed full-blown SLE during the follow-up (33).

PAPS is considered a systemic autoimmune disease in which a number of different autoantibodies have been described (34,35). Thrombosis seems to be the most important pathogenetic mechanism playing a role in organ involvement and tissue damage (36); however, not all of the clinical manifestations can be ascribed to thrombosis (36). Among them, renal involvement seems to be targeted in PAPS by other mechanisms such as immune complex deposition. In this work, we found more frequently different circulating autoantibodies and complement reduction in patients who had PAPS with nephropathy. Moreover, the heterogeneity of renal involvement confirms the presence of a continuum between SLE and PAPS (19) and suggests that a complete nephrologic workup should be performed in patients with signs of renal disease (including kidney biopsy) to classify and treat patients correctly.

No studies have evaluated the efficacy of therapy (anticoagulation) on APS nephropathy. If the vaso-occlusive lesions that are characteristic of APS nephropathy are due to microvascular thrombosis as suspected, then long-term anticoagulation should be warranted, even in the absence of extrarenal thrombosis (*e.g.*, PAPS with only fetal loss). Unfortunately, it is not possible to draw conclusions on the effect of anticoagulation to prevent progression of renal disease in our cohort of patients because

1. All of the patients were treated with anticoagulants.
2. No repeat renal biopsies were performed.
3. The patient and kidney outcomes were usually favorable.
4. Renal involvement was heterogeneous.

Conclusions

- Renal disease is present in 8 to 10% of patients with PAPS.
- In addition to APS nephropathy, glomerular diseases, in particular MN, can occur.

- Kidney biopsy can have an important role in the treatment of these patients.
- Not all of the clinical manifestations of PAPS can be interpreted on the basis on thrombotic lesions.
- Our findings confirm that PAPS can be considered an autoimmune systemic disease.
- The heterogeneity of renal involvement confirms the presence of a continuum between SLE and PAPS.
- Renal prognosis seems to be good.

Disclosures

None.

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