

# Antiphospholipid syndrome-associated nephropathy in systemic lupus erythematosus

*“Renal pathologists should be aware of the histologic characteristics of antiphospholipid syndrome-associated nephropathy when they examine kidney biopsies of systemic lupus erythematosus patients, especially those with positive antiphospholipid antibodies.”*

**KEYWORDS:** antiphospholipid antibodies ■ antiphospholipid syndrome-associated nephropathy ■ renal involvement ■ systemic lupus erythematosus ■ thrombotic microangiopathy

Renal involvement in antiphospholipid syndrome (APS) is characterized by a noninflammatory occlusion of renal vessels, ranging in size from large vessels to intrarenal microvasculature. APS is characterized by recurrent arterial or venous thromboses and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL) and it can be classified as primary or associated with other autoimmune disorders, mainly systemic lupus erythematosus (SLE). Despite thrombosis in APS being able to take place at any vascular site, the intrarenal vascular involvement has been poorly recognized until recently, probably as a result of kidney biopsies rarely being performed in patients with primary APS, and the majority of studies in SLE have focused on the glomerular disease rather than renal microangiopathy.

## APS-associated nephropathy lesions in primary APS & SLE

Thrombotic microangiopathy was the most frequently reported intrarenal vascular lesion in early studies of patients with primary APS, SLE-related APS, and SLE patients with positive aPL not fulfilling the clinical criteria for APS. Thrombotic microangiopathy is characterized by fibrin thrombi in glomeruli and/or arterioles in the absence of immune deposits or inflammatory cells. In 1990, D'Agati *et al.* [1] and Becquemont *et al.* [2] first described cases with primary APS and renal involvement with histologic lesions of thrombotic microangiopathy in their kidney biopsies. The presence of glomerular capillary thrombosis in SLE was first reported by Kant *et al.* [3] and Glueck *et al.* [4] and was associated with the presence of aPL, especially lupus anticoagulant. Besides

thrombotic microangiopathy, chronic intrarenal vascular lesions were further reported by a few case reports and case series with primary APS [5]. In 1999, Nochy *et al.* examined in a multicenter retrospective study the kidney biopsies of 16 primary APS patients with renal involvement [6]. All of the patients had a small-vessel vaso-occlusive nephropathy, defined as APS-associated nephropathy, including the acute thrombotic lesions (thrombotic microangiopathy) and chronic vascular lesions such as fibrous intimal hyperplasia of interlobular arteries, recanalizing thrombi in arteries and arterioles, fibrous occlusions, or focal cortical atrophy.

A few years later, the same French group evaluated the presence of APS-associated nephropathy in patients with SLE; 24 patients with SLE-related APS, 52 SLE/non-APS patients with positive aPL and 20 SLE patients without aPL were examined [7]. APS-associated nephropathy was diagnosed in 63, 22 and 15% of the above patient groups, respectively, in addition to, and independently of, lupus nephritis. An association of APS-associated nephropathy with extrarenal APS (mainly with arterial thrombosis and pregnancy morbidity) and positive lupus anticoagulant test was observed. Hypertension was the predominant clinical manifestation of this nephropathy.

Tektonidou *et al.* examined the prevalence, clinical associations and long-term outcome of APS-associated nephropathy in 151 patients with SLE with or without aPL [8]. APS-associated nephropathy lesions were detected in two-thirds of patients with SLE-related APS, a third of SLE/non-APS patients with positive aPL, and in only 4% of SLE patients without aPL, independently of lupus nephritis lesions. The most frequently



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detected histologic lesions were thrombotic microangiopathy, fibrous intimal hyperplasia and focal cortical atrophy. Other medical conditions associated with thrombotic microangiopathy in the kidney were excluded from these studies, such as malignant hypertension, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, toxemia of pregnancy or disseminated intravascular coagulation. A strong association between APS-associated nephropathy lesions and the presence of APS, arterial thromboses (especially stroke), pulmonary embolism, livedo reticularis and a positive lupus anticoagulant test was noted. During the follow-up period, thrombosis developed in seven (35%) of 20 patients with APS nephropathy, compared with four (9%) of 43 patients without APS nephropathy ( $p = 0.04$ ) [8]. We also recently investigated the APS-associated nephropathy lesions in three different groups of APS; primary APS, SLE-related APS and, for the first time, catastrophic APS [9]. The same histologic and clinical characteristics were detected among all the three APS groups [9].

APS-associated nephropathy lesions have been further investigated by other studies of SLE patients with biopsy-proven renal involvement. The prevalence of APS-associated nephropathy ranged from 11 to 34% and was associated with mild-to-severe hypertension, acute renal failure, proteinuria and hematuria, and in some studies, with high activity and chronicity indices and a tendency to progress to end-stage renal disease [10].

### APS-associated nephropathy & classification criteria for APS

The strong association of APS-associated nephropathy with the presence of aPL and especially with APS manifestations, as well as the tendency of the patients with APS-associated nephropathy to develop thrombotic events demonstrated by some studies, has been discussed in the 11th International Congress on aPL [11]. It was decided that APS nephropathy was to be included among the manifestations associated with APS (noncriteria APS manifestations), but not in the revised criteria for APS [11]. In the recent 13th International Congress on aPL, one of the objectives of a task force on noncriteria APS manifestations was the identification and grading (according to evidence-based medicine criteria) of the studies that analyze the relationship between aPL and APS nephropathy [12]. Summary data from all of the studies that examined APS-associated nephropathy in SLE showed a higher frequency of APS-associated nephropathy among the patients with positive aPL (with or without APS)

in comparison to those without aPL ( $p < 0.001$ ). The aPL were correlated with both the acute (thrombotic microangiopathy) and the chronic lesions of APS-associated nephropathy (evidence level II–III). APS-associated nephropathy lesions were more frequently detected among APS patients (primary or SLE-related) than among SLE/aPL/non-APS patients (evidence level II).

### Full spectrum of renal pathology in APS-associated nephropathy

An expanding spectrum of kidney pathology has recently been described in association with APS. Fakhouri *et al.* identified 29 renal biopsies performed in patients with primary APS and they observed features distinct from vascular APS nephropathy in nine of them: membranous nephropathy ( $n = 3$ ); minimal change disease/focal segmental glomerulosclerosis ( $n = 3$ ); mesangial C3 nephropathy ( $n = 2$ ); and pauci-immune crescentic glomerulonephritis ( $n = 1$ ) [13]. Sinico and coworkers also examined the renal biopsies of ten patients with primary APS and they detected membranous glomerulonephritis in four patients, proliferative glomerulonephritis in two, thrombotic microangiopathy in two, and chronic APS-associated nephropathy lesions in the remaining patients [14].

The renal outcome of patients with APS-associated nephropathy remains uncertain. Moroni *et al.* [15] and a recent retrospective study of children with lupus nephritis [16] showed that aPL positivity was an independent predictor of chronic renal function deterioration; however, other studies did not confirm this association. In regards to the presence of intrarenal vascular lesions, Zheng *et al.* found that patients with lupus nephritis and lesions of thrombotic microangiopathy had higher disease activity, activity and chronicity indices, serum creatinine and proteinuria levels, and a higher frequency of hypertension than those with lupus nephritis but without thrombotic microangiopathy ( $p < 0.05$  for all) [17]. Daugas *et al.* [7] and Tektonidou *et al.* [8] observed that SLE patients with APS-associated nephropathy had higher frequency of hypertension and raised serum creatinine at the time of renal biopsy; however, the prevalence of renal insufficiency, ESRD or death at the end of follow-up was similar among the patients with and without APS nephropathy.

The management of APS-associated nephropathy is also partially elucidated [18]. Currently, there is no consensus on the treatment of APS-associated nephropathy and the other noncriteria APS manifestations including heart valve disease,

cognitive impairment, livedo reticularis and thrombocytopenia [19]. Empirical therapeutic approaches have been reported in patients with renal involvement and primary or SLE-related APS. Anticoagulation treatment and/or anti-platelet agents in combination with the immunosuppressive treatment of lupus nephritis have been effectively used in cases or studies including patients with this nephropathy [20,21]. The appropriate management of hypertension, especially with angiotensin-converting enzyme inhibitors, was emphasized by most studies.

Current evidence suggests that besides from their prothrombotic role, aPL can also induce complement activation, thereby leading to tissue damage [22]. Recent studies showed a strong relationship between the intensity of glomerular C4d staining and the presence of fibrin microthrombi in renal biopsies from patients with lupus nephritis [23]. A new animal model of renal injury that shares many features with thrombotic microangiopathy was also recently developed [24]. Genetic deletion of C5aR and low tissue factor expression prevented glomerular injury and renal failure in aPL-treated mice, suggesting that complement inhibition or tissue factor inhibition might represent potential therapeutic interventions in renal microangiopathy [24]. Therapeutic management of inflammation in addition to that of thrombosis might be proven to be beneficial in APS-associated nephropathy and should be investigated in large multicenter studies.

## Conclusion

A small-vessel vaso-occlusive nephropathy defined as APS-associated nephropathy has recently been recognized, first among patients with primary APS and subsequently among patients with SLE-related APS and SLE/non-APS patients with positive aPL in addition to, and independently of, lupus nephritis lesions.

Renal pathologists should be aware of the histologic characteristics of APS-associated nephropathy when they examine kidney biopsies of SLE patients, especially those with positive aPL. In patients with APS-associated nephropathy lesions and persistently positive aPL, the diagnosis of APS should be considered, provided that other conditions resulting in similar renal biopsy lesions are excluded. Prospective large-scale studies are warranted to examine the full spectrum of the clinical and histological characteristics of APS-associated nephropathy, the significance of this nephropathy in the long-term outcome of SLE patients and its appropriate therapeutic management.

## Financial & competing interests disclosure

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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## References

- 1 D'Agati V, Kunis C, Williams G, Appel GB. Anticardiolipin antibody and renal disease: a report of three cases. *J. Am. Soc. Nephrol.* 1(5), 777–784 (1990).
- 2 Becquemont L, Thervent E, Rondeau E, Lacave R, Mougenot B, Sraer JD. Systemic and renal fibrinolytic activity in a patient with anticardiolipin syndrome and renal thrombotic microangiopathy. *Am. J. Nephrol.* 10(3), 254–258 (1990).
- 3 Kant KS, Pollak VE, Weiss MA, Glueck HI, Miller MA, Hess EV. Glomerular thrombosis in systemic lupus erythematosus. Prevalence and significance. *Medicine* 60(2), 71–86 (1981).
- 4 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(8), 1389–1395 (1985).
- 5 Amigo MC, Garcia-Torres R, Robles M, Biochicchio T, Reyes PA. Renal involvement in primary antiphospholipid syndrome. *J. Rheumatol.* 19(8), 1181–1185 (1992).
- 6 Nochy D, Dugas E, Droz D *et al.* The intrarenal vascular lesions associated with primary antiphospholipid syndrome. *J. Am. Soc. Nephrol.* 10, 507–518 (1999).
- 7 Dugas E, Nochy D, Huang DL *et al.* Antiphospholipid syndrome nephropathy in systemic lupus erythematosus. *J. Am. Soc. Nephrol.* 13, 42–52 (2002).
- 8 Tektonidou MG, Sotsiou F, Nakopoulou L *et al.* Antiphospholipid syndrome nephropathy in patients with systemic lupus erythematosus and antiphospholipid antibodies: prevalence, clinical associations, and long-term outcome. *Arthritis Rheum.* 50, 2569–2579 (2004).
- 9 Tektonidou MG, Sotsiou F, Moutsopoulos HM. Antiphospholipid syndrome (APS) nephropathy in catastrophic, primary and systemic lupus erythematosus-related APS. *J. Rheumatol.* 35, 1983–1988 (2008).
- 10 Cheunsuchon B, Rungkaew P, Chawanasantorapoj R, Pattagarn A, Parichatikanond P. Prevalence and clinicopathologic findings of antiphospholipid syndrome nephropathy in Thai systemic lupus erythematosus patients who underwent renal biopsies. *Nephrology (Carlton)* 12, 474–480 (2007).
- 11 Miyakis S, Lockshin MD, Atsumi T *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J. Thromb. Haemost.* 4(2), 295–306 (2006).
- 12 Cervera R, Tektonidou MG, Espinosa G *et al.* Task Force on Catastrophic Antiphospholipid Syndrome (APS) and Non-criteria APS Manifestations (I): catastrophic APS, APS nephropathy and heart valve lesions. *Lupus* 20(2), 165–173 (2011).
- 13 Fakhouri F, Noel LH, Zuber J *et al.* The expanding spectrum of renal diseases associated with antiphospholipid syndrome. *Am. J. Kidney Dis.* 41(6), 1205–1211 (2003).
- 14 Sinico RA, Cavazzana I, Nuzzo M *et al.* Renal involvement in primary antiphospholipid syndrome: retrospective analysis of 160 patients. *Clin. J. Am. Soc. Nephrol.* 5(7), 1211–1217 (2010).
- 15 Moroni G, Ventura D, Riva P *et al.* Antiphospholipid antibodies are associated

- with an increased risk for chronic renal insufficiency in patients with lupus nephritis. *Am. J. Kidney Dis.* 43(1), 28–36 (2004).
- 16 Lee BS, Cho HY, Kim EJ *et al.* Clinical outcomes of childhood lupus nephritis: a single center's experience. *Pediatr. Nephrol.* 22(2), 222–231 (2007).
  - 17 Zheng H, Chen Y, Ao W *et al.* Antiphospholipid antibody profiles in lupus nephritis with glomerular microthrombosis: a prospective study of 124 cases. *Arthritis Res. Ther.* 11, R93 (2009).
  - 18 Tektonidou MG. Renal involvement in the antiphospholipid syndrome (APS)-APS nephropathy. *Clin. Rev. Allergy Immunol.* 36(2–3), 131–140 (2009).
  - 19 Ruiz-Irastorza G, Cuadrado M, Ruiz-Arruza I *et al.* Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies. *Lupus* 20(2), 206–218 (2011).
  - 20 Korkmaz C, Kabukcuoglu S, Isiksoy S, Yalcin AU. Renal involvement in primary antiphospholipid syndrome and its response to immunosuppressive therapy. *Lupus* 12(10), 760–765 (2003).
  - 21 Klumb E. Primary antiphospholipid nephropathy beginning during pregnancy. *Rheumatol. Int.* 27(3), 289–293 (2007).
  - 22 Lim W. Complement and the antiphospholipid syndrome. *Curr. Opin. Hematol.* 18(5), 361–365 (2011).
  - 23 Cohen D, Koopmans M, Kremer Hovinga IC *et al.* Potential for glomerular C4d as an indicator of thrombotic microangiopathy in lupus nephritis. *Arthritis Rheum.* 58(8), 2460–2469 (2008).
  - 24 Seshan SV, Franzke CW, Redecha P, Monestier M, Mackman N, Girardi G. Role of tissue factor in a mouse model of thrombotic microangiopathy induced by antiphospholipid antibodies. *Blood* 114(8), 1675–1683 (2009).