

Antiphospholipid Syndrome Nephropathy in Different Scenarios



There have been several reviews on antiphospholipid (aPL) antibodies and the kidneys (antiphospholipid syndrome nephropathy, APSN)^{1,2}. The second review, appearing some 13 years after the first, was timely and stressed the existence of underlying renal artery stenosis and hypertension, which had been pointed out in an early case study³.

In this issue of *The Journal* the article by Tektonidou, *et al* is more than timely⁴, and compares renal biopsies of patients with catastrophic, primary, and systemic lupus erythematosus-related antiphospholipid syndrome for the first time. Although the presence of renal failure in patients with catastrophic APS (CAPS, Asherson's syndrome)⁵ has been noted from the CAPS registry in 70% of these difficult patients, biopsies have not been routinely performed, and there may be several reasons for the onset of non-fatal renal failure in patients with CAPS including thrombotic microangiopathy shown so clearly in that article. Hypertension, hematuria, proteinuria, and renal insufficiency were the commonest clinical and laboratory findings, and were acute in the CAPS patients with nephrotic syndrome and more frequent, without being statistically significant. Thrombotic microangiopathy was the most frequent histopathological finding in the patients with CAPS, but chronic vascular lesions were also detected, presumably on the basis of previous renal disease.

The first identification of intrarenal vascular lesions and aPL antibodies, characterized by the presence of lupus anticoagulant (LAC), began as early as 1959, when a lupus patient's renal biopsy showed what has been called an "atypical vascular lesion."⁶ The next decades witnessed a full range of multiple clinical expressions and detailed descriptions of pathologic features of this complex form of APS. Renal vascular lesions associated with classical histological aspects of lupus nephritis (LN) have been recognized sporadically but were not included as SLE lesions⁷, and were probably those now recognized as secondary to APSN.

It has become confirmed by different studies that among lupus patients, APSN may be found associated with glomerulonephritis in around one-third of the biopsies reviewed⁸. These studies clearly established a positive correlation of APSN with LAC⁹ or anticardiolipin antibodies (aCL)¹⁰. It has been further demonstrated that aPL-associated vascular lesions have an ominous effect on longterm renal function, arterial hypertension, and absence of response to immunosuppressive agents. Despite general acceptance of these clinico-pathological aspects and their prognostic importance, the recently proposed and widely accepted classification of LN (International Society of Nephrology/Renal Pathology Society 2003)¹¹ merely suggests its description as complementary findings. We should keep in mind, however, that in clinical practice, in a subset of patients with SLE, these alterations may be present not only as additional lesions, but may represent the true pathological mechanism for moderate/severe hypertension, hematuria, proteinuria, and reduced glomerular filtration rate, all signs that could easily be attributed to LN itself.

On the other hand, APSN was also found to be associated with the primary subset of antiphospholipid syndrome (PAPS) first described by Asherson, *et al* in 1989¹². Amigo, *et al*¹³ identified in 1992 that 25% of PAPS cases studied presented clinical kidney disease with proteinuria, hypertension, renal failure and variable degrees of severity, extension and chronic microangiopathy. Vascular lesions were found both in arterioles and glomerular capillaries, which presented many times with mesangiolytic, mesangial interposition, electron-lucent subendothelial material, and ischemic obsolescence of glomeruli. Renal biopsies also disclosed arterial luminal narrowing due to medial hypertrophy, amorphous mucoid deposits within the intima, thrombosis, and general fibrosis^{13,14}.

Among chronic pathological aspects, atherosclerosis is typically seen associated with intimal fibrous hyperplasia,

See Obituary: Ronald Asherson, page 2066

See APS nephropathy in catastrophic, primary, and SLE-related APS, page 1983

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thickening of arteries due to fibrosis, and proliferation of myofibroblastic cells, with the consequent lumen restriction and ischemia, which is rarely seen in other nephropathies, making it very suggestive of APSN¹⁵. The focal cortical atrophy (FCA), located in the subcapsular renal cortex, associated with dense interstitial fibrosis leading to tissue retraction and kidney contour depression, gives a scar aspect with a sharp border among areas of normal parenchyma, which is considered to be very typical of APSN¹⁶.

Some recent reports have emphasized the less frequent but possibly very specific renal lesions found in patients with APSN. Redundant and wrinkled segments of basal membrane accompanied by a duplicate straighter thin membrane adjacent to the endothelium have been reported as a pathognomonic finding of the syndrome^{17,18}. Additionally, some authors suggested an association between minimal-change nephropathy and focal segmental glomerulosclerosis, both as independent clinico-pathological presentations of APSN^{19,20}.

The currently accepted frequent association of APSN to LN, and its related clinical manifestations and prognosis, makes renal biopsy a mandatory procedure for most SLE patients who develop renal disease, besides the search for aCL antibodies and mainly LAC. It is probable that at least part of the classical chronicity index on renal biopsies as much as refractoriness to the immunosuppressive regimen is related to the pathogenic action of aPL antibodies⁹, associated or not with prolonged immunological damage mediated by anti-DNA/nucleosome antibodies. These same statements in reference to renal biopsy are probably also true for all patients who develop any clinical and/or laboratory sign suggestive of APS and hypertension, proteinuria, renal insufficiency, or hematuria.

The APSN article by Tektonidou, *et al* in this issue⁴ sheds light on some very important aspects regarding undiagnosed longterm renal damage in patients with aPL antibodies. The chronic renal vascular lesions, not previously reported, that were present in two-thirds of patients with CAPS suggest that even the catastrophic presentation of this syndrome may be secondary to progressive ongoing vascular damage as reported in heart valve lesions and limb amputation cases²¹. It also shows that despite the general acceptance that severe hypertension is always present in these patients, some of them may have diffuse catastrophic vascular disease without it.

The authors also call attention to the importance of current accumulated evidence of specific epidemiological, clinical, and histopathological features of APSN in different scenarios, findings that certainly strengthen their reliability as specific APS diagnostic criteria after exclusion of other causes for these vascular lesions (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, scleroderma renal crisis, malignant hypertension, preeclampsia, and use of cyclosporine). Meanwhile, according to the current APS classification criteria, APSN should not be accepted as clin-

ical criteria, but as an “associated feature.”²² In clinical practice, however, the prompt recognition of early signs of ischemic nephropathy in a patient who is aPL-positive may stimulate full anticoagulation, which sometimes promotes partial or complete control of proteinuria and arterial hypertension^{14,23}. In fact, biopsy-proven acute and/or chronic ischemic renal lesions, in any patient with some other APS clinical feature, even without aPL antibody, may also indicate full anticoagulation, since in some few cases aPL positivity may not occur until antibody consumption decreases²⁴.

One of the major aspects also highlighted by Tektonidou, *et al*⁴, and despite the small number of cases included, is the better longterm survival of patients with CAPS. It seems probable that as much as we keep in mind the possibility of CAPS, the higher our chances of making early diagnosis and beginning effective anticoagulation.

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