What nephrologists need to know about antiphospholipid syndrome

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Abstract
Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by recurrent arterial or venous thrombosis and/or pregnancy losses, in the presence of persistently elevated levels of anticardiolipin antibodies (aCL) and/or evidence of circulating lupus anticoagulant (LA). The kidney is a major target organ in both primary and secondary APS. With the expanding spectrum of renal diseases associated with APS, and the impact of APS in ESRD care, this subject is of increasing relevance to nephrologists. This review describes the various clinical manifestations and histological features of this syndrome, with reference to the kidney.

Keywords: anticardiolipin antibodies; antiphospholipid syndrome; lupus anticoagulants; nephropathy

Introduction
The antiphospholipid syndrome (APS) was first described by Hughes in the mid-1980s as a disorder of hypercoagulability in association with antiphospholipid antibodies (aPL), namely anticardiolipin antibodies (aCL) and/or circulating lupus anticoagulants (LA) [1]. It was in systemic lupus erythematosus (SLE) that this syndrome was first reported [2]; however, APS may occur, though less frequently, in the absence of associated autoimmune disease, the so-called primary APS [3]. In the past two decades, a variety of immunologically mediated thrombotic events related to almost every organ system has been identified as features of this syndrome. The diagnosis of definite APS is made when the patient fulfils one clinical (vascular thrombosis or pregnancy morbidity) and at least one laboratory [LA, aCL and/or anti-β2-glycoprotein-1 (anti-β2GP1) antibodies] criterion [4]. As the kidney represents a major target organ in both primary and secondary APS, some nephrologists are now challenging to include the nephropathy of APS in the classification criteria of definite APS [5–7].

Renal involvement in primary APS is typically caused by thrombosis occurring at any location within the renal vasculature, leading to diverse effects, depending on the size, type and site of the vessel involved. The renal manifestations of APS thus may include renal artery stenosis (RAS) and/or renovascular hypertension, renal infarction, APS nephropathy (APSN), renal vein thrombosis, and increased allograft vascular thrombosis [8–12]. The spectrum of renal lesions associated with primary APS has been more recently expanded to involve non-thrombotic conditions, such as glomerulonephritis [13]. It is unclear whether, in addition to thrombosis, other mechanisms could also contribute to the pathogenesis of APS-associated nephropathy. Furthermore, renal manifestations of APS may co-exist with other pathologies, especially proliferative lupus nephritis.

The true incidence of renal involvement in primary APS has not been well determined, in part because of the frequent occurrence of thrombocytopenia and systemic hypertension, discouraging renal biopsy. It has also been suggested that patients with APS may have a higher risk of developing biopsy-related complications, which could be challenging to manage.

Although the kidney represents a major target organ in APS, renal involvement in this syndrome was poorly recognized until recently. The objective of this review is to present the best available information related to the renal manifestations of APS. A summary of the treatment options will also be presented.
The role of aPL antibodies

APS is considered an autoimmune disorder with multifactorial aetiology that includes cellular, molecular, genetic and pathogenic mechanisms, as reported in detail elsewhere [11,14,15]. Antiphospholipid antibodies are a heterogeneous group of antibodies observed in a range of pathological conditions as well as in healthy populations [16]. They play a crucial role in the pathogenesis of APS (Table 1); however, not all patients with these antibodies develop clinical features of APS, suggesting that additional factors are also involved. Antibodies to cardiolipin and β2GP1 of IgG and IgM isotype are routinely measured in serum by solid-phase ELISA, or similar, assays. Lupus anticoagulant is suggested by a prolonged activated partial thromboplastin time (APTT) and confirmed by prolongation of the diluted Russell viper venom test (DRVVT) indicating the presence of a transferable inhibitor of coagulation. Lupus anticoagulant cannot be readily measured in patients receiving anticoagulants.

It is unclear which patients with aPL will develop thrombosis. In general, LA are more specific for APS, whereas aCL are more sensitive. The association between aPL and thrombosis is stronger with LA than with aCL. In a recent meta-analysis of 25 studies involving >7000 patients, the odds ratio for thrombosis was 11.0 for LA and 1.6 for aCL [17]. Moreover, LA for which the prolongation of clotting times is dependent on the presence of β2GP1 show a much stronger association with thrombosis (odds ratio, 42.3) than do LA that are independent of β2GP1 (odds ratio, 1.6) [18]. Again, which particular subset of aPL is associated with renal involvement is yet to be defined. Antiphospholipid antibodies can be detected in lupus nephritis patients without evidence of APS-related renal disease. Both antiplatelet agents and warfarin have been considered in this context, but there is no clear evidence that they are beneficial.

Systemic hypertension

Hypertension is one of the first major features described in association with livedo reticularis and aPL [19]. It is exceedingly common in both primary and secondary APS, and is considered to be a sensitive marker of nephropathy in this syndrome. In the series of primary APS reported by Nochy et al., hypertension was present in 93% of their 16 patients and was sometimes the only clinical sign suggestive of nephropathy [20]. Consequently, it was recommended to investigate patients with APS complicated by hypertension for an underlying renal lesion. Imaging the renal arteries should be considered as RAS/thrombosis has been shown to respond well to anticoagulation with or without percutaneous balloon angioplasty, leading to recovery of renal function and return to normal blood pressure [21,22]. Hypertension in APS may often be severe, with some patients presenting with hypertensive emergencies [23,24]. Malignant hypertension in APS may often be severe, with some patients presenting with hypertensive emergencies [23,24]. Malignant hypertension in APS may often be severe, with some patients presenting with hypertensive emergencies [23,24]. Malignant hypertension in APS may often be severe, with some patients presenting with hypertensive emergencies [23,24]. Malignant hypertension in APS may often be severe, with some patients presenting with hypertensive emergencies [23,24].

Renal artery lesions

APS has been well documented as a unique, non-traditional cause of RAS with important clinical consequences. It may manifest in multiple ways ranging from renal infarction to ischaemic acute renal failure to slowly progressive ischaemic chronic renal failure to renovascular disease. Using magnetic resonance angiography, 26% of aPL-positive patients with poorly controlled hypertension were found to have RAS, significantly higher compared with 8% of relatively young (≤50 years) hypertensive controls and 3% of healthy potential kidney donors [25]. Two patterns of stenotic lesions have been described in APS. The more common pattern is characterized by smooth, well-delineated and often non-critical stenoses in the mid-portion of the renal artery, quite distinct from either fibromuscular dysplasia or atherosclerosis (Figure 1). The less common pattern is similar to atherosclerotic lesions situated proximally and occasionally involving the aorta [25].
Although the nature of the RAS in APS remains unclear, the response to anticoagulation does suggest a thrombotic process. Previous reports have shown that anticoagulation treatment with international normalized ratio (INR) >3 may reverse RAS and achieve subsequent clinical improvement [26,27]. Remondino et al. [28] reported a case of bilateral RAS associated with APS in which complete recanalization of both renal arteries was observed on a repeat renal spiral CT scan after 5 months of treatment with anticoagulation. Besides thrombosis, other potential aetiologic factors for RAS in APS include accelerated atherosclerosis [29] as well as increased endothelin levels resulting in vasoconstriction [29,30].

Renal infarction

Renal infarction results from occlusive lesions in smaller diameter intraparenchymal vessels, which are caused by either in situ thrombosis or emboli from a pre-existing upstream arterial lesion or a cardiac valvular lesion [20]. Clinically, patients with renal infarction, which could be the first manifestation of APS, may present with flank pain, severe hypertension and/or renal dysfunction. Some of these patients may have multiple, often serious, thrombotic episodes, and many have multiple infarctions in the renal cortex [31]. Histologically, glomerular ischaemia, tubular atrophy and interstitial fibrosis may be seen in patients with renal infarction due to primary APS. Interestingly, in five out of eight such patients in whom biopsies were performed, no histological evidence of associated thrombotic microangiopathy (TMA) was found, as summarized in the report by Poux et al. [32]. Although renal infarction is a rare complication of APS, this diagnosis should be considered in any young subject who presents with renal infarction.

APSN

APSN refers to the kidney damage caused by vascular lesions in the glomeruli, arterioles and/or interlobular arteries in patients with aPL. APSN vascular lesions may be acute, the so-called TMA, and/or chronic, such as arteriosclerosis, fibrous intimal hyperplasia, tubular thyroidization and focal cortical atrophy [7,20]. APSN has been described in patients with primary APS, SLE-related APS and SLE/non-APS patients with aPL. The same histologic lesions, especially TMA, are also observed in patients with catastrophic APS [33]. Generally, APSN manifests with hypertension, acute and/or chronic renal failure, and often a low-grade proteinuria. Multiple cortical infarctions can result in a ‘moth-eaten’ appearance on renal imaging.

TMA is the best known and most characteristic lesion of APSN, with distinctive microscopic and ultrastructural changes [7,20,34]. The pathological changes of TMA, however, are not exclusive for APS, as they can occur in many other conditions caused by coagulation disturbances or endothelial cell injury, such as thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, scleroderma renal crisis, malignant hypertension, pre-eclampsia, cyclosporine toxicity, chemotherapy and renal transplant rejection [6]. The pathological features of TMA are characterized by fibrin thrombi in glomeruli and in the

Fig. 1. Right renal artery stenosis associated with hypertension in antiphospholipid syndrome. The aorta is smooth, suggesting that the stenosis is not related to atherosclerosis. Reprinted from reference [9] with permission.

Fig. 2. Glomerulus showing reduplication of the capillary basement membrane (arrows) (hexamine silver stain ×400).

Fig. 3. Glomerulus showing extensive mesangiolysis (arrowhead) and intracapillary fibrin thrombi (arrows) (haematoxylin and eosin stain ×400).
whole intrarenal vascular tree, without inflammatory cells or vascular immune deposits. During the acute phase, fibrin thrombi containing fragmented blood cells, along with oedema of endothelial cells, narrow or occlude the vascular lumen. Thrombi eventually organize into fibrocellular and fibrous vascular occlusions, which can be recannulated by endothelialized channels resulting in onion-skin arrangement of intimal fibrosis [20]. Similarly, as a consequence of repeated thrombosis/recanalization, splitting and multilayering of the glomerular basement membrane (GBM) develop [34]. On light microscopy, the silver stains show a combination of GBM wrinkling and duplication (Figure 2). Other light microscopic features include fibrin microthrombi in the glomerular capillary lumen and mesangiolysis (Figure 3). Neither necrotizing vasculitis nor fibrinoid necrosis are seen in primary APS. By immunofluorescence study, fibrin is the sole element of the thrombi, with immunoglobulins being absent. Electron microscopy (Figure 4) shows widening of the GBM, with areas of mesangial interposition accounting in part for the double contours on light microscopy. No electron-dense deposits are seen [34].

Among the chronic pathological aspects, arteriosclerosis is typically seen associated with fibrous intimal hyperplasia, intimal thickening of the arteries and arterioles primarily by myofibroblastic cellular proliferation, with consequent lumen restriction and ischaemia (Figure 5). Focal cortical atrophy involves the superficial cortex under the renal capsule, as foci or triangles with sharp borders with the rest of the normal cortex, accompanied by depression of the contour of the renal capsule. In these atrophic areas, all elements of the renal parenchyma were altered in a pattern considered to be very typical of APSN. The glomeruli appear either small and sclerotic or voluminous, but almost devoid of glomerular tuft 'glomerular ballooning'. The tubules are atrophic packed with eosinophilic casts, resembling thyroid tissue 'tubular thyroidization'. The arterioles are occluded by fibrin microthrombi or often by fibrous tissue [20].

**Renal vein thrombosis**

Thrombosis of the renal veins classically presents with nephrotic-range proteinuria and has been described in aPL-positive patients with lupus nephritis, as well as in primary APS, and it can be the first clinical manifestation of APS [35,36]. Nephrotic syndrome, a common finding in APS associated with SLE, is unusual in patients with primary APS. Thus, careful Doppler studies of the renal vasculature should be considered in any patient with persistently positive aPL who develops sudden heavy proteinuria or acute deterioration of renal function to rule out renal vein thrombosis. Alternatively, contrast-enhanced computed tomography and magnetic resonance angiography can be used to provide the diagnosis.

**The significance of aPL and glomerular microthrombosis in lupus-associated nephritis**

There is sound evidence that APS contributes to the renal morbidity in patients with lupus nephritis [5,37,38]. Moroni and co-workers [39] prospectively followed up 111 patients with lupus nephritis (LN) for a mean of 173 ± 100 months. The overall prevalence of aPL in their cohort was 26%. Interestingly, they reported not only an increased risk of vascular and obstetric complications in lupus patients with aPL but also a strong association between aPL antibodies and prognosis in LN. With multivariate analysis, aPL antibody positivity, high plasma creatinine level at presentation and chronicity index were independent predictors of chronic renal function deterioration [39]. Tektonidou and colleagues [6] examined the prevalence and long-term...
outcome of APSN in 151 SLE patients with or without aPL as well as the histologic evolution of APSN lesions on serial kidney biopsies. APSN was documented, in addition to and independently from lupus nephritis, in almost 40% of patients with aPL compared with only 3 out of 70 patients without aPL, suggesting a critical role of aPL in the pathogenesis of APSN. Compared with patients without APSN, those with APSN had a higher frequency of hypertension and raised serum creatinine levels at the time of kidney biopsy, and developed progression of histologic lesions, all of which are associated with a poor renal outcome [6].

Glomerular microthrombosis (GMT) is seen in ~20–30% of patients with lupus nephritis, especially in those with severe diffuse proliferative glomerulonephritis, and has been shown to be a strong predictor of glomerular sclerosis and poor renal outcome [40,41]. The mechanism underlying the formation of GMT is largely unknown. Although several studies have reported the association of aPL with GMT [6,41,42], the relation between GMT and aPL remains controversial. Zheng et al. [41] compared the clinical and serological profile of 124 LN patients with and without GMT. The authors showed higher rates of LA and antibodies against β2GP1 and thrombin in lupus patients with GMT, who also had a lower serum C3 level and more intense glomerular C3 and C1q staining than those without GMT [41]. Their findings imply that complement activation, induced by or coordinated with aPL, may play a pathogenic role in the development of renal tissue injury leading to thrombosis. However, not all patients with SLE and aPL develop GMT. According to Harris and Pierangeli [43], a ‘second hit’, e.g. infection or trauma, is necessary to trigger thrombosis at the vessel site where aPL have deposited. On the other hand, Cohen et al. [44] demonstrated a strong relationship between the intensity of glomerular C4d staining and the presence of GMT, irrespective of the type of circulating antibodies present. Taking into account the impact of GMT on the prognosis of LN, whether those patients with renal biopsy-proven GMT should be treated with anticoagulants in the absence of other thrombotic processes remains unclear and warrants further study.

It is also worth mentioning that patients with primary APS and SLE share some common clinical and serological manifestations [45,46]. Primary APS may evolve into full-blown SLE suggesting that these apparently different diseases are related [45,47]. It is not known to what extent these two conditions share a common genetic background.

**Catastrophic antiphospholipid syndrome (CAPS)**

CAPS (also known as Asherson’s syndrome) is an accelerated variant of APS resulting in multi-organ failure [48]. A definitive diagnosis of CAPS requires (i) clinical evidence of involvement of three or more organ systems in a period of less than a week, (ii) histopathological evidence of small vessel occlusion in at least one organ system, and (iii) laboratory confirmation of the presence of aPL, usually in high titre [49]. Approximately 60% of the catastrophic episodes are preceded by a precipitating event, mainly infections.

The kidney is the organ most commonly affected by CAPS. According to the CAPS registry data [50], no fewer than 71% of patients had renal involvement, usually resulting in acute renal failure, severe hypertension and laboratory evidence of glomerular damage (proteinuria and haematuria). Renal biopsy, in the vast majority of cases, revealed the typical frank microangiopathy. Immune complex nephritis was seldom encountered. Renal infarctions were also present in some patients.

Although patients with CAPS represent <1% of all patients with APS, the condition is life threatening, with a 50% mortality rate. The presence of SLE is the only identified poor prognostic factor for a higher mortality rate in patients with CAPS. Causes of death include major organ involvement (other than the kidney) as well as infection [51].

### The significance of aPL in haemodialysis patients

A few studies have reported an unexpectedly high prevalence of aPL in ESRD patients undergoing haemodialysis [52,53]. These antibodies were independent of age, length of time on dialysis, sex, type of dialysis membrane, drugs, and chronic B and C hepatitis [53]. Although the precise mechanisms involved in the genesis of aPL in ESRD are unknown, they appear to be mostly β2GP1-independent [54]. Possible causes include dialysis membranes, trauma to blood passing through the haemodialysis circuit, and induction by microbial agents or their products, such as endotoxins present in the dialysate. The precise risk associated with the presence of aPL in ESRD is also uncertain. While some studies suggest that these antibodies are not pathogenic [55,56], others have reported that aPL are associated with haemodialysis vascular access thrombosis [57,58].

### The significance of aPL in renal transplantation

There is considerable evidence that aPL-positive patients undergoing renal transplantation are at significantly increased risk of renal vascular thrombosis with consequent graft loss. In a striking study, within a group of 78 patients who received renal transplant, six had APS. Each of these patients thrombosed their renal allografts within a week of transplantation. In contrast, the remaining 72 patients were all doing well 1 year after transplantation [59]. Wagenknecht and co-workers [60] reported significantly more aPL in patients with early renal allograft failure than in patients with functioning grafts. In that study, 57% of final crossmatched sera from patients with early allograft non-function were positive for IgG, IgM and IgA aPL. Biopsies of these failed allograft kidneys from aPL-positive patients showed thrombi in nine patients and infarction in five. In addition, aPL-positive patients who had no history of haemodialysis were at the greatest risk. Thus, it was suggested that aPL that develops during dialysis may be less pathogenic. Another possibility is a possible protective effect of residual heparin received at haemodialysis [60].
It has been reported that renal allograft recipients, even those without SLE, have an increased incidence of aPL. Among 178 non-SLE renal allograft recipients, 50 (28.1%) had positive aPL; a minority (15.7%) acquired these antibodies post-transplant [61]. How aPL may be acquired after transplantation is curious, but is as yet unexplained. It has been suggested that these aPL may be related to post-transplant infection or autoimmune reactions to infections. Patients with and without aPL did not differ for age, gender, underlying disease, immunosuppressive regimen, serum creatinine concentration and platelet count. Both pre-transplant and post-transplant aPL were associated with thrombosis; however, the risk was greater in the latter group [61]. Patients with SLE, who generally have similar cadaveric and living-related allograft survival to the general population undergoing renal transplantation when adjusted for multiple confounding variables, appear to be at considerable risk of graft thrombosis if they are positive for aPL, particularly when no anticoagulation is administered [62].

Although hepatitis C virus (HCV)-positive patients may have aPL, they do not usually manifest the APS. Preliminary data suggest that this may not be the case in post-renal transplantation, as these patients may be at increased risk for thrombotic complications after renal transplantation [63].

Given these risks, there are some who question whether aPL-positive patients should undergo transplantation at all, because even when full anticoagulation is administered following renal transplantation, the risks of graft loss and systemic thrombosis are not completely eliminated [64]. Identifying high-risk patients through pre-transplant screening for pro-thrombotic risk, including aPL, will reduce the morbidity and risk of failed transplantation.

**Treatment**

Treatment of APS remains centred on anticoagulation; however, it has also included the use of corticosteroids and other immunosuppressive therapy.

The current recommendations in a patient with arterial or venous thrombosis are treatment with heparin followed by long-term warfarin as long as the abnormal antibody persists. In general, intermediate-intensity treatment with warfarin (INR 2.0–3.0) is sufficiently effective in most patients with a first episode of venous thrombosis who do not have a major risk of bleeding. In patients with arterial events or with recurrent thrombotic events, however, a higher high-intensity treatment (INR 3.0–4.0) or an additional antiplatelet agent may be required [65].

In pregnancy, a prophylactic therapy with unfractionated heparin or low-molecular-weight heparin plus aspirin should be considered, particularly in the presence of prior pregnancy loss [66]. Women with previous renal disease from APS and renal impairment are at high risk of complications during pregnancy and in the puerperium. To improve the outcomes of pregnancies in such women, a closer obstetric surveillance and multidisciplinary clinics, including nephrologists, are essential. The prophylactic role of anticoagulation in non-pregnant patients who are aPL positive but have had no manifestations of APS remains unclear [65].

While corticosteroids and other immunosuppressive agents may alter the presence or the titre of aPL, they do not reduce the risk of thrombosis. A few reports have shown, however, beneficial effects of immunosuppression in primary APSN [67,68]. It has been suggested that corticosteroids and/or immunosuppressive agents may prevent target organs from further damage by decreasing inflammatory response likely to develop due to aPL.

Patients with catastrophic APS usually receive a combination of anticoagulants and corticosteroids plus intravenous immunoglobulin and/or plasma exchange, as the first-line therapy. Additionally, cyclophosphamide should be considered in SLE-associated CAPS patients but not in primary APS patients [51].

Other potential approaches for the management of persistently aPL-positive patients include hydroxychloroquine, statins, rituximab, anti-C5 antibodies and other targeted therapies that have been effective in experimental APS models [69]. A better understanding of the intracellular mechanisms of aPL-mediated thrombosis will help us design more targeted anti-inflammatory or immunomodulatory therapies.

**Conclusions**

APS is being increasingly recognized as an important cause of renal injury due to thrombosis at any location within the renal vasculature. Accordingly, the renal manifestations of APS may include systemic hypertension in association with livedo reticularis, RAS, renal infarction, APSN, renal vein thrombosis and increased allograft vascular thrombosis. Testing for aPL must therefore be considered in patients with any of these manifestations. Nephrologists are expected to be involved more frequently in managing patients with APS, whether it is primary, secondary or, most certainly, with CAPS. Renal pathologists should carefully examine renal biopsies obtained from SLE patients with positive aPL for the presence of APSN, as this may have significant implications on therapeutic decisions. Anticoagulation remains the mainstay treatment of patients with renal involvement due to APS. In addition, patients with catastrophic features often require immunosuppressive therapy. Future studies may help to identify more targeted therapeutic agents.

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