Renal involvement in antiphospholipid syndrome.

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune disease defined by the presence of arterial or venous thrombotic events and/or pregnancy morbidity in patients who test positive for antiphospholipid antibodies (aPL). APS can be isolated (known as primary APS) or associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE; known as secondary APS). The kidney is a major target organ in APS and renal thrombosis can occur at any level within the vasculature of the kidney (renal arteries, intrarenal arteries, glomerular capillaries and renal veins);events reflect the site and size of the involved vessels. Histological findings vary widely, including ischaemic glomeruli and thrombotic lesions, without glomerular or arterial immune deposits on immunofluorescence. Renal prognosis is affected by the presence of aPL in patients with lupus nephritis and can be poor. In patients with SLE and aPL, biopsy should be performed because inflammatory and thrombotic lesions require different therapeutic approaches. Renal involvement in patients with definite APS is treated by anticoagulation with long-term warfarin. The range of renal manifestations associated with APS is broadening and, therefore, aPL has increasing relevance in end-stage renal disease, transplantation and pregnancy.

Key points

- Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by recurrent arterial or venous thrombosis and/or pregnancy morbidity and persistently elevated levels of antiphospholipid antibodies
- Renal involvement can be caused by thrombosis at any level within the vasculature of the kidney
- Clinical features include renal artery stenosis, renal infarction, renal vein thrombosis, thrombotic microangiopathy and hypertension
- Treatment of renal involvement in APS centres on anticoagulation with long-term warfarin
- Patients refractory to standard therapy with anticoagulation or who have catastrophic APS might benefit from targeted therapy, including the use of intravenous immunoglobulins, rituximab or eculizumab

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by recurrent arterial or venous thrombosis and/or pregnancy-related problems and persistently elevated levels of antiphospholipid antibodies (aPL). Since the first detailed description of APS by Graham Hughes in 1983,[1] this condition has become regarded as a crossroads of coagulation and the immune system. aPL comprise a heterogeneous group of antibodies that are directed against anionic phospholipids or protein–phospholipid complexes. Laboratory tests to identify aPL include solid-phase ELISA to detect antibodies against cardiolipin and β2-glycoprotein 1 (B2GPI) and functional assays, such as the lupus anticoagulant assay, that demonstrate the ability of aPL to prolong phospholipid-dependent clotting reactions.
An international consensus statement on definitive classification criteria for APS was published in 1998,[2] after a workshop in Sapporo, Japan, and was updated in 2006.[3] At least one clinical manifestation, such as vascular thrombosis or pregnancy morbidity, together with

two positive laboratory tests at least 12 weeks apart are required for diagnosis. APS alone is usually classified as primary APS; in the presence of other autoimmune disorders—especially systemic lupus erythematosus (SLE)—the condition is generally classified as secondary APS. (Figure 1)

Evidence suggests that the prevalence of aPL in the general population is low.[4,5] Standard techniques detect aPL in <1% of apparently healthy individuals and in up to 3% of the elderly population without clinical manifestations of APS.[4] However, the prevalence of aPL is notably high in patients with thrombotic manifestations, such as at first stroke in people <50 years (10–26%) and in women with recurrent pregnancy loss (10–40%).[6] In clinical practice, it is common to recognize patients with laboratory evidence of aPL **.** Among patients with SLE, 30–40% are positive for aPL.[5,6] Of patients with both SLE and aPL, around half develop APS within 10–20 years.[5]

Thrombotic events in patients with APS are most frequently observed in the deep veins of the lower limbs and the cerebral arterial circulation,[7] but the kidney is also a major target organ (Box 1). Thrombosis can occur at any level within the vasculature of the kidney and the manifestations of thrombotic events reflect the sites and dimensions of involved vessels. Thus, aPL-related nephropathy warrants inclusion in the diagnosis of APS.[8] In this Review, we describe the role of aPL antibodies in inducing renal disease and the clinical and histological features of APS involving the kidney. We also review the management of patients with renal involvement, including discussions of available and upcoming therapies.

aPL and thrombosis

In patients with circulating aPL, thrombotic events might but do not always occur, which suggests that the presence of aPL is necessary but not sufficient for thrombus formation *in vivo*. Rather, the theory that aPL creates a prothrombotic state that increases the risk of thrombotic events in the presence of another prothrombotic factor has been purported.[9] The aPL-related prothrombotic state could be induced by many different pathophysiological mechanisms, such as cellular effects (on platelet membranes, endothelial cells and monocytes), increases in expression of plasma coagulation regulatory proteins (clotting components, such as antithrombin, protein C and protein S) and fibrinolysis.[10]

The proposed pathophysiological mechanisms can be categorized into two types. Firstly, aPL might act *in vivo* by disrupting pro-coagulant and anticoagulant reactions occurring on cell membranes. Secondly, aPL might interact with specific cell-surface receptors (proteins, lipids or both) and induce signals downstream that will ultimately result in upregulation of cell-surface proteins.[10] We and others have suggested that expression of tissue factor, the major coagulation initiator *in vivo*, by endothelial cells and monocytes is a leading mechanism contributing to thrombosis in APS.[11] Several other processes have been related to aPLinduced thrombosis, such as conformational and post-translational redox modifications of B2GPI, decreased activity of endothelial nitric oxide synthase and complement activation. aPL can also cause direct or indirect cellular effects on endothelial cells, monocytes and platelets, mainly through binding to B2GPI expressed on cell membranes.[10] Additionally, interaction of aPL with proteins implicated in clotting regulation—such as prothrombin, factor X, protein C and plasmin—might interfere with the inactivation of pro-coagulant factors and fibrinolysis. These interactions induce a prothrombotic and proinflammatory phenotype (Figure 2).

Traditional cardiovascular risk factors, which are present in >50% of patients with APS,[7] also frequently play an important part. For example, we have reported that arterial hypertension and hyperlipidaemia are independent risk factors for thrombotic events in patients with APS and aPL.[12]

Clinical manifestations

Any organ can be affected in patients with APS and, therefore, the range of clinical features is extremely wide. Vessels of all sizes can be affected by thrombus formation. The vascular pathological appearance is bland occlusion without inflammatory infiltrates in the wall of the vessels.[13]

A wide spectrum of renal thrombotic effects have been described in association with aPL, such as renal artery stenosis, renal infarction, renal vein thrombosis and thrombotic microangiopathy (TMA).[14,15] Besides TMA, various intrarenal vascular lesions have been described in primary APS,[16] including APS nephropathy (also called aPL-associated nephropathy).[17,18] The variety in clinical manifestations is reflected in the range of histological findings, and include ischaemic glomeruli and thrombotic lesions, without glomerular or arterial immune deposits on immunofluorescence.[19]

APS nephropathy

APS nephropathy is clinically characterized by a syndrome of vascular nephropathy associated with hypertension, acute or chronic renal insufficiency, proteinuria and inconstant haematuria that can present differently depending on the rapidity of onset. Acute presentation features TMA, whereas the chronic course favours histopathologically characterized arterial fibrous intimal hyperplasia, tubular thyroid-like appearance, arteriosclerosis, arteriolar occlusions and focal cortical atrophy.[20]

Peculiar patterns of microscopic and ultrastructural findings are usually associated with TMA[19] and manifest clinically as proteinuria, hypertension and renal impairment.[15] Proteinuria is generally mild, but might be in the nephrotic range).[16–18] Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, along with other disorders that feature TMA, should be ruled out,[21] although differentiation can be challenging. Severe thrombocytopenia and microangiopathic anaemia are more commonly observed in thrombocytopenic purpura and haemolytic uraemic syndrome than in APS,[15] whereas the presence of schistiocytes on blood smear is rarely observed in APS. A negative aPL test is also a valid tool to distinguish between APS and other possible causes of TMA.[21] Catastrophic should be ruled out, especially in patients who have thrombosis in multiple organs that develops over a short period of time.[22]

Histological findings in APS neurophathy include distinctive microangiopathic features (focal and diffuse) that might affect any of the vessels within the intrarenal vasculature, including the glomeruli (Figure 3).[1,15,16] In studies of kidney biopsy samples from patients with primary APS, Nochy and co-workers[18] showed that all vaso-occlusive lesions were characterized by acute thrombosis (TMA) and chronic vascular lesions, such as fibrous intimal hyperplasia of interlobular arteries, recanalizing thrombi in arteries and arterioles, fibrous occlusions and focal cortical atrophy.[18] Ultrastructural findings might include glomerular basement membrane reduplication associated with glomerular basement membrane wrinkling.[15,16] Fakhouri and co-workers[23] found evidence of glomerulonephritis in 29 biopsy samples obtained from patients with primary APS without.[23] Characteristic features of APS nephropathy were observed in 20 (69%) of specimens. Nevertheless, about one-third of the cases showed some pathological changes other than vascular APS nephropathy, such as minimal change disease, focal segmental glomerulosclerosis, membranous glomerulonephritis, mesangial C3 nephropathy and pauci-immune crescentic glomerulonephritis.[23] In seven patients, the onset of the renal involvement was chronic or subacute.[23]

Sinico and co-workers[24] retrospectively studied 160 patients with primary APS and renal involvement was seen in 14 (9%). Renal biopsy samples were available for 10 patients. Histopathological changes included membranous glomerulonephritis in four, proliferative

glomerulonephritis in two, TMA in two and vascular involvement as observed in chronic APS nephropathy in the remaining two cases. Membranous glomerulonephritis was characterized by immune deposits in the subepithelial area, mesangium and subendothelial space; C1q deposits, immunoglobulins and C3 were positive on testing. Two of four patients with membranous glomerulonephritis had low complement levels and one of these two was also positive for antinuclear antibodies. Moreover, two patients had diffuse proliferative glomerulonephritis resembling class IV lupus nephritis. The main histological picture, therefore, was membranous glomerulonephritis, whereas only four patients had histological lesions consistent with acute or chronic APS nephropathy. The association between aPL and membranous glomerulonephritis (class V) seems unclear, as it has been reported in some studies and anecdotal case reports,[24–26] but not confirmed in others.[17,27]

In 2002, Daugas *et al*.[14] performed a retrospective study of 114 patients with lupus who had undergone renal biopsy. APS nephropathy was observed in 32% of patients with SLE, irrespective of lupus nephritis. APS nephropathy was significantly associated with lupus anticoagulant and extrarenal manifestations of APS (most frequently with arterial thrombosis and fetal loss). No association was found between APS nephropathy and venous thrombosis. Daugas and colleagues concluded that APS nephropathy was an independent risk factor for hypertension, elevated serum creatinine concentrations and increased interstitial fibrosis in SLE.

In a large cohort of patient with SLE, Tektonidou *et al*.[17] investigated prevalence, clinical associations and long-term outcomes of APS nephropathy. They diagnosed APS nephropathy in 32 (40%) of 81 patients with aPL, compared with only three (4%) of 70 without aPL. APS nephropathy was documented independently of lupus nephritis in approximately two-thirds of the patients with SLE with secondary APS. APS nephropathy was associated with the presence of lupus anticoagulant, antibodies against cardiolipin or both, but not with lupus nephritis. The authors concluded that among patients with SLE, APS nephropathy occurred almost exclusively in those with aPL. Patients with APS nephropathy developed hypertension, raised serum creatinine levels and histological progression of lesions, all of which are associated with poor renal outcomes. However, the frequency of renal insufficiency did not differ between patients with or those without APS nephropathy after 7 years of follow-up monitoring.[17]

Renal artery stenosis and thrombosis

APS has been suggested as a rare cause of renal artery stenosis, which has important acute (renal infarction leading to ischaemic acute renal failure) and chronic (such as slowly progressive ischaemic renal failure) clinical consequences. Renovascular disease is also observed in some patients.[20]

In 1990, Ostuni and colleagues[28] reported a case of renal artery thrombosis in a patient with aPL. This association between aPL, arterial hypertension and renal artery stenosis was confirmed by other groups.[29,30] Sangle *et al*.[31] studied magnetic resonance angiography findings from patients with APS and resistant hypertension. Of 77 patients with APS and uncontrolled hypertension, 20 (28%) had imaging features consistent with renal artery lesions, which was notably higher than the rates in young hypertensive controls (8%) and healthy controls (3%). The most frequently reported pattern was smooth, delineated, generally noncritical stenosis distal to the ostium of the renal artery, although in some patients features consistent with atherosclerotic changes were noted.

The most commonly observed clinical sign associated with renal artery thrombosis is newonset, often severe, hypertension or worsening of known systemic hypertension. Pain in the renal area, haematuria, or renal failure might be associated. The pathogenesis varies, ranging from *in situ* thrombosis of the renal arteries to embolization deriving from verrucous heart valve lesions.[32] The diagnostic approach might differ depending on the severity of clinical

presentation, but renal ultrasonography, abdominal CT, renal angiography, renal scintigraphy and gadolinium-enhanced magnetic resonance angiography have proved useful for diagnostic and prognostic purposes.

Renal vein thrombosis

Thrombosis of the renal vein has been observed in patients with different types of APS, such as aPL-positive patients with lupus nephritis and those with primary APS.[20] Renal vein thrombosis might present with proteinuria, often in the nephrotic range, and this symptom can sometimes be the first clinical manifestation of the syndrome.[1,33] Gluek and colleagues[34] reported in a large series of patients with SLE that the presence of lupus anticoagulant was strongly associated with renal thrombosis. Similarly, Asherson *et al*.[35] showed an association between aPL and renal vein thrombosis in two patients with SLE who were positive for lupus anticoagulant and had proliferative lupus nephirits.[35]

Nephrotic syndrome is rare in patients with primary APS but is more frequent in patients who have secondary APS concomitant with SLE. The renal vasculature should, therefore, be assessed with Doppler imaging to rule out renal vein thrombosis in aPL-positive patients who develop sudden severe proteinuria or acute impairment of renal function. Other conditions associated with the development of renal vein thrombosis should also be investigated, such as pregnancy and use of oral contraception. Renal vein thrombosis can complicate renal transplantation and affect outcomes, and these patients should receive special attention due to the increased risk of vaso-occlusive events.[36] Contrast-enhanced CT and magnetic resonance angiography are valid tools to confirm renal vein thrombosis.

Renal infarction

Renal infarction might be associated with APS. *In situ* thrombosis, emboli from an upstream arterial lesion or a heart valve lesion can result in thrombotic events occurring in smalldiameter intraparenchymal vessels leading to renal infarction.[2,18]

Symptoms at presentation of renal infarction include pain, hypertension (often severe) and impairment of renal function, and it might be one of the first features of APS. Multiple, often serious, thrombotic episodes have been described in some patients, mostly localized in the renal cortex.[37,38] The most frequently observed histological findings are ischaemic features at the level of the glomerulus, tubular atrophy and interstitial fibrosis.[20] Notably, Poux and coworkers [39] reported that in five of eight patients with APS who underwent biopsy, no histological changes consistent with TMA were observed. Subclinical cases might be revealed by abdominal CT performed for other reasons[32] but this can reveal scarring from an old silent infarct. Although renal infarction is not a classic clinical manifestation of APS, aPL testing should be performed in young people who present with this disorder[39] to tailor treatment if necessary. Withdrawal of drugs, such as hydroxychloroquine, is potentially related to this rare complication.[40]

Arterial hypertension

Hypertension is associated with aPL and frequently presents with coexisting livedo reticularis.[1] Arterial hypertension affects many patients with primary and secondary APS, and has been proposed as a sensitive sign of potential renal involvement. In a study of 16 patients with primary APS, Nochy *et al*.[18] reported hypertension in 93% of 16 cases and noted that, in most, the condition was the only manifestation of possible kidney involvement. The high rate of hypertension is suggested to be due to severe vascular lesions, including fibrous intimal hyperplasia (in most of the cases), arteriosclerosis, arterial and arteriolar fibrous and fibrocellular occlusions and TMA.[15,18] An analysis of 73 patients with borderline hypertension by Frostegard and co-workers[41] showed higher titres of antibodies against B2GP1 in patients than in age-matched controls. The presence of IgG isotype antibodies

correlated with plasma levels of insulin, insulin-like growth factor binding protein-1 and calculated insulin resistance, which suggests roles in both atherosclerosis and hypertension from the early stages onwards. Rollino and colleagues[42] studied 26 patients with renal artery stenosis and 25 patients with severe essential hypertension (diastolic blood pressure >110 mmHg or taking three or more hypertensive drugs) and compared them with 61 healthy controls matched for age and sex. Two (8%) of the 25 patients with severe essential hypertension had aPL compared with none of the controls. Several cases of malignant hypertension associated with aPL or in the context of APS have been described.[43–45] Of note, systemic hypertension has been reported as a strong risk factor for thrombosis in patients with aPL, which suggests that careful blood pressure control is warranted in these patients.[12,46] Taken together, the evidence suggests that hypertension is a frequent manifestation of APS, but optimum management might be difficult to achieve. Control of arterial hypertension and anticoagulation when necessary (for example, in patients with histologically proven microthrombi) are thought to prevent progression to end-stage renal disease and future thrombosis.[15]

Effects on lupus nephritis APS can affect the prognosis and renal outcomes in patients with lupus nephritis. Pérez Velásquez and colleagues[47] reviewed a large cohort of patients with SLE (n = 600) and reported that among those with secondary APS, 56% had renal disease and, of those, 43% had typical features of APS on biopsy. Lupus anticoagulant and IgG antibodies against cardiolipin were more prevalent in these patients than in those without APS and they correlated with mortality.[47]

Moroni and co-workers[48] undertook a prospective study of 111 patients with lupus nephritis who were followed up for a mean of 14 years. 26% of the patients were positive for aPL, which was associated with increased incidence of thrombosis and pregnancy morbidity. A strong association between aPL and poor prognosis was also observed. Even after multivariate adjustment, the aPL remained associated with poor renal outcomes, high plasma creatinine levels at presentation and high chronicity index scores. These findings seem to support the role of aPL as an independent risk factor of chronic impairment of renal function in patients with SLE, but in other studies no such association has been found.[49,50]

Tektonidou *et al*.[17] evaluated the frequency of APS nephropathy in 151 patients with SLE who had undergone renal biopsy. APS nephropathy was independently related to lupus nephritis in about two-thirds of patients who had SLE and APS and in one-third of patients with SLE and aPL but not APS. By contrast, <5% of patients with SLE but without aPL had any histological signs of APS nephropathy. Indeed, APS nephropathy was associated with positive tests for lupus anticoagulant and antibodies against cardiolipin.[17] The same study evaluated the progression of APS nephropathy through analysis of serial kidney biopsy findings. Evolution from acute thrombotic features to chronic thrombotic disease characterized by proliferative, obstructive and fibrotic lesions was found. If the first biopsy sample showed findings suggestive of TMA, chronic forms were frequently observed in the second or third biopsy specimens, for example, fibrous intimal hyperplasia, arteriolar occlusions, focal cortical atrophy or sclerotic features.[17] Another study showed two distinct sets of findings for acute and chronic disease in biopsy specimens.[51] Fibrin thrombi in interlobular arteries and involving glomerular arterioles were frequently found in samples from patients with acute renal episodes. In samples taken months or years later, chronic disease was characterized by arteries narrowed by recanalizing thrombi, ischaemic glomeruli with double contours and cellular or fibroelastic intimal proliferation.

Coexisting APS nephropathy and lupus nephritis have been associated with poor renal outcome in some studies[29,35] but not in others.[52,53] In a cohort of 51 patients with SLE, the prevalence of crescents, sclerosis and glomerular necrosis was higher in patients with than in those without APS nephropathy which supports the concept that aPL and glomerular

thrombosis are associated with poor renal outcomes.[54] More patients with aPL had hypertension and raised creatinine levels than those without aPL, and were often associated with thrombosis (mainly arterial) during follow-up monitoring.[17] In SLE patients with renal involvement, therefore, distinguishing between patients who have lupus nephritis (immunecomplex disease) and those who have impaired kidney function related to aPL (thrombotic events) is crucial to guide treatment.[15] Immunosuppressive therapy is useful to treat lupus nephritis, whereas in patients with APS who have APS nephropathy lesions on renal biopsy, additional anticoagulation might be required.[55] Patients with co-existing lupus nephritis and APS who test positive for lupus anticoagulant and have histological evidence of TMA, fibrous intimal hyperplasia or both are at increased risk of bleeding after renal biopsy.[56] These observations need confirmation, but they support testing for aPL in all patients with lupus nephritis before renal biopsy is performed.

In summary, the prompt recognition of clinical and serological findings suggestive of renal involvement in patients with APS is crucial, and treating physicians should avoid postponing renal biopsy to ensure appropriate treatment is started early.[32]

End-stage disease and transplantation Positive tests for aPL are more frequent among patients with end-stage renal disease than in the general population.[57–59] aPL does not seem to be related to demographic features, such as age or sex, or to dialysis factors, including the duration of dialysis or the type of membrane used.[55] Treatments or chronic viral hepatitis seem not to influence whether patients with end-stage renal disease have aPL.[57,60,61] The mechanism underlying the association between aPL and end-stage renal disease remains unclear, although several have been proposed, including dialysis membranes,[61] blood-cell activation during the haemodialysis circuit[62] and the presence of microbial agents or their products (for example, endotoxins) in the dialysate.[63]

Vaidya[66] reported that 27 (3%) of 802 patients awaiting renal transplantation had APS. In two patients, post-transplant renal thrombosis was observed within 24 h despite warfarin therapy, which supports a potential pathogenic role for aPL in end-stage renal disease.[66] Matsuda and co-workers[64] demonstrated that antibodies against cardiolipin detected in patients undergoing dialysis seemed mostly to be B2GPI-independent.[64] This finding suggests that the clinical value of measuring B2GPI-independent antibodies against cardiolipin is uncertain, as the precise risks for thrombosis associated with the presence of these antibodies in end-stage renal disease patients are not known.[63,65]

Overall, however, the evidence is inconclusive with regards to pathogenic roles of aPL and antibodies against cardiolipin.[66–71] In some studies, the presence of aPL was associated with an increased rate of haemodialysis-associated vascular access thrombosis.[72–74] Whether measurement of antibodies against cardiolipin and of lupus anticoagulant should be considered separately remains uncertain, as whether they are equally associated with recurrent access thrombosis is unclear. Some studies report that both lupus anticoagulant and antibodies against cardiolipin increase the risk of vascular access thrombosis,[74,75] but this association has been confirmed only for lupus anticoagulant.[73,76]

End-stage renal disease is a rare complication of primary APS and only a few studies have investigated this relationship.[24,40,77–79] The complication is particularly rare in paediatric patients.[80] In a large retrospective study of 160 patients with primary APS, only one developed end-stage renal disease.[24] Similarly, only one patient with end-stage renal disease was noted in a prospective study of 39 patients with primary APS.[78] IgA antibodies against B2GPI in patients receiving haemodialysis have been suggested as an independent risk factor for mortality.[81] The pathogenic role of the IgA isotype, however, remains unclear and studies are needed to investigate the clinical relevance of these antibodies.[82]

Several studies investigating the clinical relevance of aPL in patients who underwent renal transplantation increased the risk of graft failure and thrombosis at any site within the renal vasculature.[83–85] McIntyre and Wagenknecht[86] reported that among 110 transplant recipients,

those with aPL at the time of transplantation had a higher rate of early renal allograft failure than those without aPL. In patients who undergo renal transplantation, the frequency of aPL seems to be increased independently of the presence of SLE.[87] 57% of 56 patients who had early kidney allograft failure had aPL, compared with 35% of matched patients with functioning grafts.[85] Biopsy samples from the aPL-positive patients with graft failure showed thrombotic features in nine and infarction in five.[85] Indeed, anticoagulation does not completely abolish the risk of graft loss or thrombosis.[88] Canaud *et al*.[89] reviewed 1,359 kidney transplantations performed in a single centre and found that at the time of transplantation, 37 (3%) patients had aPL. A notably high incidence of APS nephropathy was also observed in recipients positive for lupus anticoagulant. Furthermore, the presence of lupus anticoagulant was associated with accelerated progression of chronic vascular changes within the first year after transplantation. Biopsy analysis at 3 months and 12 months showed that progression of tubule-interstitial chronic lesions was delayed in relation to vascular lumen narrowing, which suggests a causal link between vascular damage and graft scars.[89] Other studies, however, have found no evidence of aPL as an independent risk factor for thrombosis after kidney transplantation. Fernández-Fresnedo and colleagues[90] studied 197 kidney grafts in cadavers of patients who had had functioning grafts for >1 year. Of these, 27% had aPL before transplantation and 16% developed aPL after transplantation. The presence of aPL in the serum before transplantation was not associated with increased risk of post-transplant thrombosis. Furthermore, the development of aPL after transplantation was associated with acute rejection.

Overall, the role of aPL in transplant recipients is still a matter of debate. However, the control of cardiovascular risk factors should be intensified in these patients if aPL are detected to reduce the risks of morbidity and transplant failure.

Pregnancy

Careful management of pregnancy in women with SLE and aPL is crucial from a nephrological standpoint. Pregnancy can influence SLE activity and lead to adverse effects on the kidneys in the short-term and long-term[91] that might accelerate evolution to end-stage renal disease.[92] Moreover, aPL-positive status is a well-documented risk factor for pregnancy morbidity, including recurrent miscarriage, premature delivery, intrauterine growth restriction and pre-eclampsia.[3]

A possible link between hypertension and postpartum renal failure in pregnant women with SLE and aPL was purported by Kincaid-Smith and colleagues.[51] Findings on renal biopsy were compatible with TMA, with fibrin thrombi present in glomeruli and arterioles, and were similar to those seen in thrombocytopenic purpura and haemolytic uraemic syndrome. Of note, these findings are also common in patients who present with malignant hypertension during treatment with oral contraceptives.[32] A case of postpartum bilateral renal cortical necrosis in a woman with APS and SLE has also been reported.[93]

The associations between aPL, renal involvement and pregnancy outcomes, however, remain poorly understood. A meta-analysis showed an association between aPL and hypertension in pregnant women, preterm delivery and recurrent miscarriages.[91] The increased frequency of hypertension in women with APS might increase the risk of pre-eclampsia, which has a welldocumented
association with APS.[91] aPL is frequently found in patients with hypertension, independently of active lupus nephritis.[91]

Women with aPL or SLE and aPL, irrespective of the presence of lupus nephritis, should be counselled before becoming pregnant about the impact of these antibodies on maternal and pregnancy outcomes.

Catastrophic APS

Catastrophic APS is a very severe variant of classic APS, and is characterized by acute clinically apparent multiple organ involvement, evidence of multiple small vessel occlusions on histopathology and usually a high titre of aPL. Although catastrophic APS is seen in <1% of all patients with APS, the condition is generally life threatening.[22,94] Renal involvement is a common clinical feature of catastrophic APS.[95]

Ischaemia of the bowels, lungs, heart and brain are most frequent, but rarely has adrenal, testicular, splenic, pancreatic or skin involvement been described. TMA is characteristic and leads to symptoms related to dysfunction of the affected organs. Precipitating factors of catastrophic APS include infections, surgical procedures, withdrawal of anticoagulant therapy and the use of oral contraceptives.[96,97]

Tektonidou *et al*.[98] compared histological renal biopsy findings for patients with catastrophic APS ($n = 6$), primary APS ($n = 8$) and secondary APS (with SLE; $n = 23$). Acute vascular lesions were documented in all patients with catastrophic APS and around one-third of patients with primary APS and secondary APS. Chronic changes were seen in two-thirds of patients in all APS groups. This study supports the observation that the main distinguishing feature between catastrophic and noncatastrophic APS is the higher frequency of the acute changes in the former.

Treatment

The treatment of patients with aPL without previous thrombotic events remains controversial. The current consensus is not to treat patients with low titres of aPL or with intermittent positivity of aPL.[99] In patients with persistently medium to high titres of aPL, strict control of conventional risk factors for cardiovascular disease is essential Patients positive for multiple factors (lupus anticoagulant, as well as antibodies against cardiolipin and B2GPI) are at increased risk of thrombosis[12,100,101] and might benefit from antiaggregation therapy.

All patients with aPL should receive primary thromboprophylaxis with low-molecular-weight heparin in prothrombotic situations, such as surgery or immobilization. Some studies suggest use of hydroxychloroquine[102,103] and statins[101] in patients with persistently high titres of aPL. Treatment of APS with long-term warfarin for arterial or venous thrombosis is recommended (Box 2).[99,104] Treatment with intermediate intensity warfarin (international normalized ratio 2.0–3.0) is usually effective in patients after the first episode of venous thrombosis. Patients with arterial thrombosis or recurrent thrombotic events despite ongoing treatment might require higher intensity warfarin treatment (international normalized ratio 3.0–4.0). The use of an additional antiplatelet agent could be considered.[99,104]

Renal artery stenosis can be managed with antihypertensive agents, antiplatelet drugs or anticoagulants.[32] We analysed 14 hypertensive patients with APS and renal artery stenosis who received oral anticoagulation for >1 year. All patients benefited in terms of blood pressure and renal outcomes,[32] which confirmed the finding of by Remondino and coworkers,[105] who reported the recanalization of bilateral renal artery stenosis after anticoagulation treatment in a young woman with previously documented hypertension and APS. These observations support a role for anticoagulation in preventing the progression of these renal artery lesions.[106]

A history of renal disease related to APS (especially renal impairment) is associated with complications during pregnancy and the puerperium. For these reasons, close multidisciplinary management, including obstetricians and nephrologists, is crucial to improve pregnancy outcomes.[20]

Although corticosteroids, hydroxycloroquine[107] and some immunosuppressive agents have occasionally been reported to reduce aPL titres,[108] whether they have a role in reducing the risk of thrombosis is not proven. A few studies have been assessed the role of immunosuppressant agents in primary APS nephropathy and have reported favourable

effects.[109,110] Korkmaz *et al*.[109] described four patients with primary APS with renal involvement who responded to steroids plus azathioprine or cyclophosphomide added to anticoagulation. Corticosteroids and other immunosuppressants, however, are not generally recommended for the treatment of APS.

Patients with catastrophic APS are frequently treated with a combination of anticoagulants and corticosteroids plus intravenous immunoglobulin, and/or plasma exchange as first-line therapy.[20] The use of cyclophosphamide, therefore, might be useful to treat catastrophic APS in patients with co-existing SLE .[22]

Long-term intravenous immunoglobulin has been reported in a few cases of primary APS in which patients have relapsed despite standard treatment.[111] New oral anticoagulants, such as dabigatran and rivaroxaban, are available. They have been efficacious in the management of venous thromboembolism and do not require laboratory monitoring. A trial of efficacy and safety of rivaroxaban in APS is under way.[112]

B-cell depletion by treatment with rituximab has been suggested for use in selected cases of APS, mainly in those patients with severe thrombocytopenia.[108] Erkan and co-workers[113] conducted a 12-month, phase II pilot study of rituximab, including adult patients with aPL and non-criteria APS manifestations. One patient was diagnosed as having nephropathy and achieved partial remission with no recurrence after two doses of 1,000 mg rituximab on day 1 and day 15. Other targeted therapies have been efficacious in experimental models of APS.[114] For example, acute recurrence of TMA after renal transplantation was successfully treated with eculizumab and antibodies against C5, which suggests that such therapy could be beneficial in patients with fulminant recurrence of TMA after kidney transplantation resistant to classical therapy.[115]

Future studies exploring the mechanisms of aPL in inducing the clinical manifestations associated with APS will be useful in the design of further tailored approaches.

Conclusions

The kidney is a major target organ in primary and secondary APS. Renal involvement is a well-recognized manifestation of the syndrome and is characterised by thrombosis that can affect any vascular site in the kidneys. Treatment of renal involvement in patients with definite APS involves long-term anticoagulation with warfarin. New oral anticoagulants have been developed for clinical use and a trial to assess the efficacy and safety of rivaroxaban in APS is ongoing. Other therapeutic approaches might be useful in refractory cases, including the use of intravenous immunoglobulins, rituximab or eculizumab. Future studies need to focus on the pathogenesis of APS, which might yield potential targets for treatment, such as tissue factor pathway and complement factor inhibitors. A compelling need exists for trials aimed at improving clinical outcomes in APS and attempting to solve the crucial issues, such as reducing the thrombotic risk in patients with aPL or tailored approaches in refractory cases.

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Author contributions

S. S. and D. R. researched data for the article. S. S. and M. J. C. wrote the article and made substantial contribution to discussion of the content. M. K. made substantial contribution to discussion of the content. S. S., M. K. and D. R. reviewed and edited the manuscript before submission.

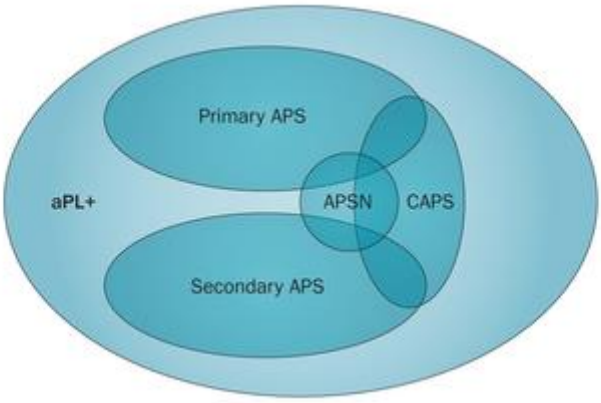

Figure 1 Venn diagram of the clinical presentation of APS. APS alone is usually classified as primary APS and, in the presence of SLE or another autoimmune disorder, is classified as secondary APS. This distinction is mainly for research and classification purposes, although there seem to be few differences in complications and antibody specificity. Most patients with primary APS do not progress to SLE. Abbreviations: aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; APSN, APS-associated nephropathy; CAPS, catastrophic APS.

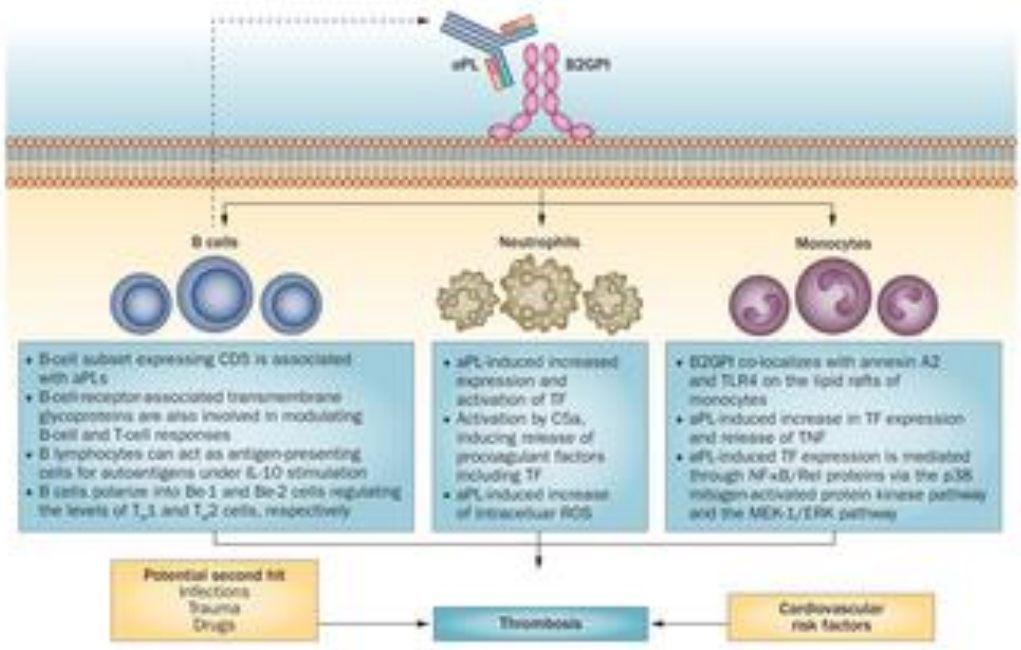

Figure 2 Pathophysiological mechanisms of thrombogenesis induced by antiphospholipid antibodies. A two-stage process is purported whereby aPL creates a prothrombotic state that increases the risk of thrombotic events in the presence of another prothrombotic factor Abbreviations: aPL, antiphospholipid antibodies; ROS, reactive oxygen species; TF, tissue factor; TH, T-helper cell; TNF, tumour necrosis factor.

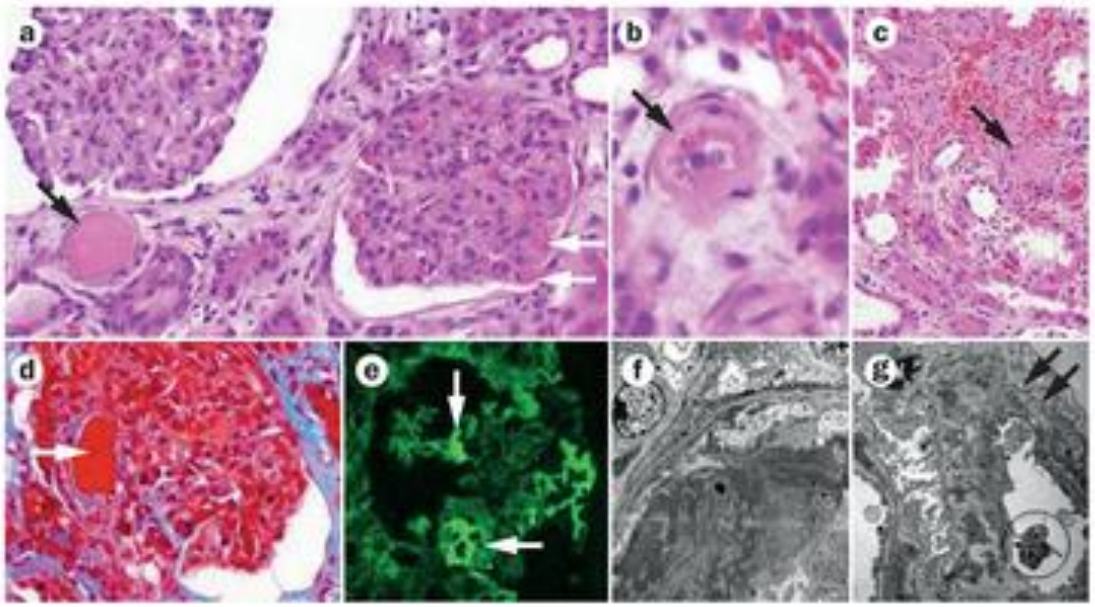

Figure 3 Histological characterization of APS-associated nephropathy. **a** | Haematoxylin and eosin stain showing two glomeruli, one of which (right) contains intracapillary thrombi (white arrows). The afferent arteriole of the glomerulus on the left is entirely occluded by a fibrin thrombus (black arrow). **b** | Haematoxylin and eosin stain showing fibrinoid necrosis and mucoid intimal oedema in the intima of an arteriole (red arrow) with fragmented red blood cells. The interstitium around the arteriole is oedematous. **c** | Haematoxylin and eosin stain showing thrombi occluding peritubular capillaries (black arrow). Interstitial oedema, haemorrhage and acute tubular injury might be present dependent on the severity of acute ischemic injury. **d** | A large intravascular thrombus at the vascular pole of a glomerulus stained red with trichrome staining (black arrow). **e** | Direct immunofluorescence also shows positive staining for fibrinogen in glomerular capillary lumina and at the vascular pole (white arrows). **f** | On ultrastructural analysis fibrin can be seen occluding the capillary lumen. Endothelial cells have lost fenestration and podocytes reveal extensive foot process effacement. **g** | In chronic disease, double contours without interposition of electron dense immune-complexes can be seen (white arrows). Platelets are seen in capillary lumina in both acute and chronic phases (black circle). Podocytes are often injured and reveal foot process effacement (black arrows). Permission to reproduce obtained from L. Barisoni, Department of Pathology, Division of renal pathology, University of Miami, Miller School of Medicine, Miami, FL, USA

Box 1 | Renal involvement in antiphospholipid syndrome
Antiphospholipid syndrome nephropathy
Renal artery stenosis and thrombosis
Renal vein thrombosis
Renal infarction
Systemic hypertension
Glomerular microthrombosis in lupus-associated nephritis related to antiphospholipid antibodies
Catastrophic antiphospholipid syndrome

Box 2 | Primary and secondary thromboprophylaxis in patients with aPL*

Primary thromboprophylaxis

Patients with primary APS and aPL

- Control of cardiovascular risk factors, especially in patients with high-risk aPL profiles (for example, positive for aCL, aB2GPI and LA)
- Long-term prophylaxis with low-dose aspirin is suggested in patients with a high-risk aPL profiles, especially in the presence of other cardiovascular risk factors
- Prophylaxis with LMWH in high-risk prothrombotic situations (for example, surgery, long-term immobilization and puerperium)

Patients with aPL and concomitant autoimmune disease (for example, SLE)

- Hydroxychloroquine, with or without low-dose aspirin

Secondary thromboprophylaxis

Definite APS and a first venous event

- Warfarin to a target INR of 2.0–3.0

Definite APS and arterial thrombosis

- Warfarin to a target INR of 3.0–4.0

Kidney involvement

Renal artery stenosis

- Antihypertensive agents, antiplatelet drugs, or anticoagulants have been reported to be efficacious

APS patients with APS nephropathy lesions on renal biopsy

- Anticoagulants Catastrophic APS
- combined anticoagulants and corticosteroids plus intravenous immunoglobulin, plasma exchange or both
- The use of cyclophosphamide might be considered in patients with co-existing SLE

Therapy duration

Patients with definite APS and thrombosis

- Indefinite therapy with warfarin

Cases of first venous event, non-high-risk aPL profile and a known precipitating factor (for example, oral contraceptive pill)

- Anticoagulants for a maximum of 6 months

Refractory or difficult cases (difficult INR control, bleeding or major bleeding risk)

Alternative therapies could be explored, including long-term LMWH, hydroxychloroquine, statins or biological therapy (for example, rituximab), but no data from clinical trials prove the efficacy of these drugs

*Recommendations based on Ruiz-Irastorza *et al*.[99] Abbreviations: aBGPI, antibodies against β2-glycoprotein I; aCL, antibodies against cardiolipin; AL; aPL, antibodies against phospholipid; APS, antiphospholipid syndrome; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SLE, systemic lupus erythematosus