primary APS and treatment, primary APS nephropathy treatment, rituximab and APS, in the literature published until 2015.

We performed an electronic search, piloted in PubMed and Embase. We supplemented electronic searches by checking references cited in published papers and in the articles extracted from the electronic searches. Unpublished studies were not searched. The following limits were applied: studies written in English, Spanish or French; and studies performed in humans.

Studies were screened for inclusion in different phases: duplicated articles were deleted; we first screened by title and then by abstract. When a title seemed relevant, the abstract was reviewed for eligibility; if any doubt remained, the full text of the article was retrieved and discussed (Fig. 1).

After the selection, a total of 114 articles were selected. To facilitate the analysis, articles were classified according to the following categories: pathophysiology, renal artery lesions, renal vein thrombosis, APS nephropathy and treatment.

Pathophysiology

A two-hit model of thrombosis in APS has been hypothesized in which a first hit creates a pro-thrombotic state followed by a second hit, possibly inflammatory, that perturbs the endothelium and initiates thrombosis [5].

The pathophysiologic mechanisms that contribute to the prothrombotic phenotype (first hit) include aPL-mediated activation of monocytes, endothelial cells and/or platelets, and/or inhibition of natural anticoagulant and fibrinolytic systems by aPL [6].

The various factors potentially involved in the pathogenesis of the prothrombotic phenotype are shown in Fig. 2.

aPLs

aPLs are directed principally against phospholipid binding proteins, likely to be the main factor in the pathogenesis of APS, by binding to the surface of endothelial cells, monocytes and platelets.

The loss of immune tolerance is thought to be responsible for the origin of pathogenic aPLs, which appears to be predominantly antigen driven. Bacterial and viral infections have been implicated in the development of aPL and shown to induce pathogenic antibodies against b2GPI. aPL develop in mice immunized with a cytomegalovirus-derived peptide, and a recent study demonstrated that protein H of *Streptococcus pyogenes* can bind b2GPI and expose neoepitopes that induce production of anti-b2GPI antibodies [7, 8].

It is probable that at least part of the injury observed in renal biopsies is related to the pathogenic action of aPL, which may be linked to prolonged immunological damage mediated by anti-DNA/nucleosome antibodies [9].

APLN is particularly associated with triple aPL positivity [10]. Gerhardsson and coworkers found that APLN was associated with aCL, but a strong trend between APLN and anti-β_2GP1 or LA was also detected. However, in other studies [11] focusing on glomerular microthrombi, a strong association with LA and anti-β_2GP1, but not with aCL was noted. Alternatively, it has been proposed that both LA and aCL are associated with an increased risk of vascular thrombosis [12, 13], while other reports have verified this relationship only with LA [14–16].

Finally, a study of 51 patients [17], suggested that the presence of aCL and/or glomerular thrombi predicts a worse renal outcome, as patients with aPL positivity had significantly more crescents, sclerosis and glomerular necrosis. These patients tend to develop hypertension and raised serum creatinine levels, in addition to other manifestations of APS, especially arterial thromboses, during the course of the disease.

It has been further demonstrated that aPL-associated vascular lesions have an ominous effect on long-term renal function, arterial hypertension and absence of response to immunosuppressive agents [9, 14, 18].

In contrast, others have shown no significant differences between patients with or without aPL-associated nephropathy in complete or partial remission, non-response to treatment or at end-stage renal disease [19].

The divergent aPL associations previously reported are likely to be due to methodological issues, as different assays for aPL and LA detection have been used, and cut-off values have varied between studies.

Cellular activation

aPL have been reported to bind to and activate vascular endothelial cells, monocytes and platelets in a b2GPI-dependent manner [20–23].

Endothelial cells, through the expression of anticoagulant proteins and the elaboration of antithrombotic substances such as prostacyclin, glycosaminoglycans and nitric oxide, play an important role in maintaining blood fluidity. Endothelial cell activation via aPL–b2GPI interactions leads to loss of these anticoagulant properties, with transformation to a pro-adhesive, procoagulant phenotype, characterized by increased expression of adhesion molecules and tissue factor, enhanced secretion of pro-inflammatory cytokines and chemokines, and the release of procoagulant and proinflammatory microparticles [24].

The vascular endothelium of proliferating intrarenal vessels, from patients with APLN, showed indications of the mechanistic target of rapamycin complex (mTORC) pathway activation. This phenomenon was also found in the vessels of autopsy specimens from patients with the sinister catastrophic APS. Patients with APLN who required transplantation and were receiving sirolimus, had no recurrence of vascular lesions and had decreased vascular proliferation on biopsy, compared with patients with aPL not on the drug. These results suggest that mTORC pathway is involved in the vascular lesions associated with the APS [25].

In contrast, Rauch *et al.* [26] showed TLR4 involvement in inducing a break in immune tolerance and production of aPL. Dysregulation of other TLRs, including TLR7, TLR8 and TLR9, may also contribute to the development

FIG. 1 Methodology of literature search
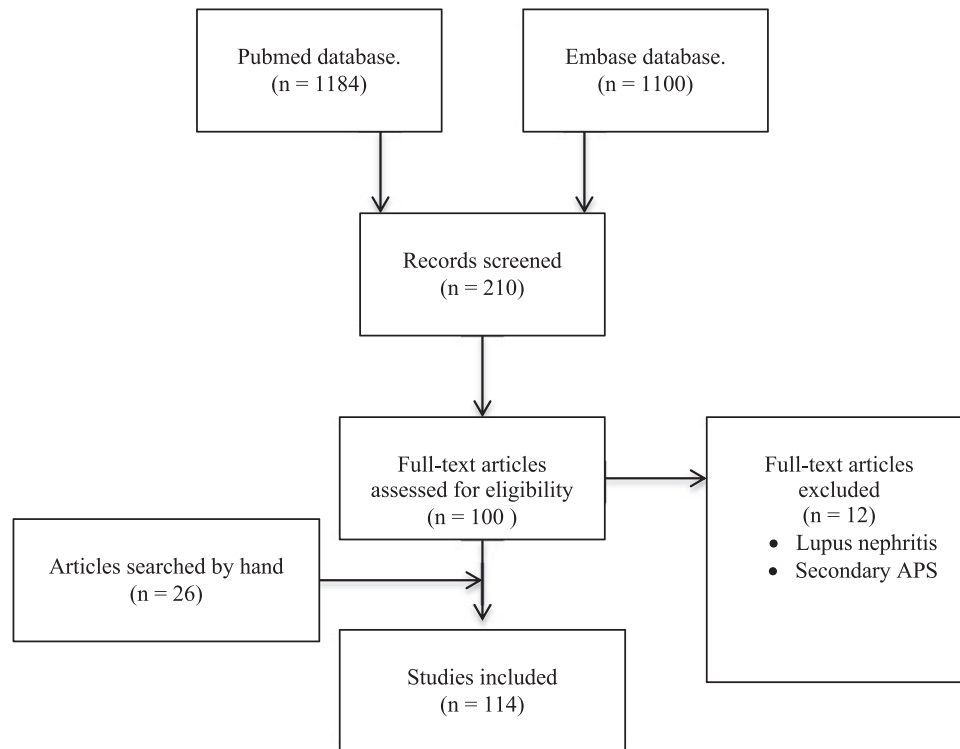
of aPL [27]. HCQ inhibits TLR7 and is associated with reduced persistence of aPL in patients with SLE [28].

Complement activation

Recent studies have shown that complement activation (induced by or coordinated with aPL), and the complement-induced tissue factor activation, may play a significant role in renal tissue injury [29].

Activation of the complement system is implicated in the development of thrombosis and fetal loss in APS [30]. Activated complement fragments bind to and activate cells through the C5b-9 membrane attack complex or through the C5a-receptor–mediated effects. aPLs, which activate complement, may generate the potent inflammatory mediator C5a, which recruits neutrophils and monocytes, and leads to tissue factor exposure by endothelial cells and neutrophils [31].

Recently, several case reports have documented the successful use of eculizumab (humanized anti-C5a mAb) in patients with complicating renal transplantation APS [32].

HLA

A link between certain HLA haplotypes and ALPN has been described. Thus, Gerhardsson and co-workers [10] found a significantly higher frequency of HLA-DRB1*13 and concluded that a genetic predisposition may contribute to APLN.

The activation of the mTORC pathway in endothelial cells during humoral rejection by anti-HLA antibodies (particularly anti-HLA class I antibodies) of primary APS. However, a recent study has shown that anti-HLA antibodies did not account for mTORC activation in microvascular endothelial cells; therefore, more studies are necessary to correlate this association [25].

Clinical manifestations

APS nephropathy is clinically characterized by a vascular nephropathy syndrome associated with hypertension, acute or chronic renal failure and proteinuria [33]. Proteinuria is generally mild (range between 0.5 and 3.0 g/day), but is occasionally nephrotic (>3.5 g/day) [9, 34, 35].

The presence of newly developed hypertension in a patient with positive aPL, in combination with proteinuria, haematuria and/or renal insufficiency should raise a suspicion of APLN, and kidney biopsy should be performed. When APLN lesions are detected in kidney biopsies, other causes associated with similar histological lesions should be excluded, including malignant hypertension, thrombotic thrombocytopenic purpura or haemolytic uremic syndrome, scleroderma, ciclosporin use or HIV infection [29].

When APLN is a result of renal artery thrombosis, different clinical features may be observed, most commonly, pain in the renal area or renal failure associated with severe hypertension or worsening of known systemic hypertension. Renal ultrasonography, abdominal CT,

Fɪɢ. 2 Potential mechanisms involved in the pathogenesis of thrombosis in the APS
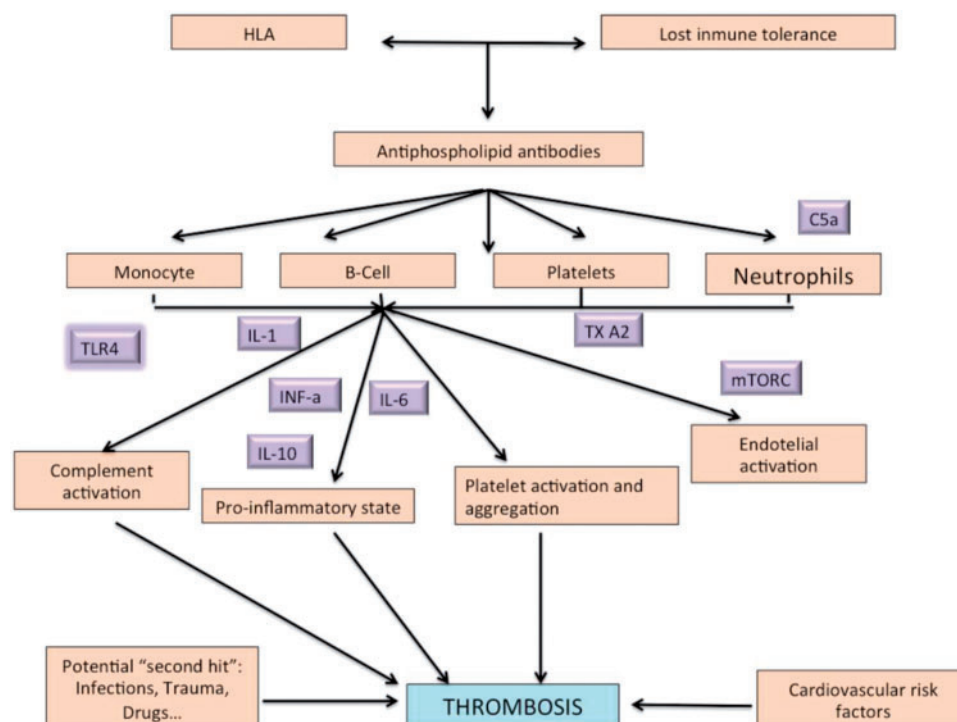
Modified from Chaturvedi S, McCrae KR. Recent advances in the antiphospholipid antibody syndrome. Curr Opin Hematol 2014;21:371–9.

renal angiography, renal scintigraphy and gadolinium-enhanced magnetic resonance angiography (MRA) have proved useful for diagnostic and prognostic purposes. MRA and renal ultrasonography with colour Doppler sonography are comparable methods for the detection of renal artery stenosis with lumen diameter narrowing of ⩾60%. However, renal ultrasonography with colour Doppler sonography is preferred as a screening method that helps to exclude renal vein thrombosis [36–38].

Nephrotic syndrome is uncommon among patients with primary APS, being more frequent in patients with secondary APS concomitant with SLE [39]. In the large patient cohort described by Tektonidou and co-workers, patients with APLN developed hypertension, raised serum creatinine levels and histological progression of lesions, all of which are associated with poor renal function. However, the frequency of renal insufficiency did not differ between patients with or without APLN during 7-years follow-up [9].

Usually APLN progresses slowly, only rarely leading to end-stage renal failure [40]. Primary APS is not usually considered in children with unexplained acute renal failure, nor is it considered to be a cause of end-stage renal disease, in adults or children [41]. However, there is a case report about a 53-year-old lady with end-stage renal failure in primary APS [42, 43].

Macro-anatomic and microscopic findings

There are numerous classifications for renal manifestations of APLN, based on their location [44]. They can be divided in three main groups, each having its own pathogenic, clinical and diagnostic characteristics: renal artery lesions, secondary to thrombosis, stenosis or occlusion of the main artery (uni- or bilateral); intrarenal vascular lesions (require biopsy confirmation); and renal vein thrombosis (Fig. 3).

Renal artery

Renal artery involvement is a relatively common manifestation in patients with APS. In 2003, MRA was performed in 88 APS patients with poor control of their blood pressure and compared with MRA of two control groups, one of young patients with hypertension and the other of potential kidney donors. A total of 20 patients (28%) affected by APS had lesions in the renal artery—significantly higher than in the other groups [45, 46].

Although early studies focused on cases of APS associated with SLE, there is an increasing number of reports that focus on the presence of renal artery impairment in patients with primary APS [47].

In 1992, Rossi et al. [48] reported two cases of renovascular hypertension with renal artery stenosis, and suggested a possible relationship between renal stenosis, thrombosis, aPL and fibromuscular dysplasia. This idea was supported by Mandreoli and colleagues [49]. Other studies described many cases of renal artery occlusion as a manifestation of APS, and related them to severe hypertension as the prime clinical manifestation [48, 50–59].

Fɪɢ. 3 Renal vascular involvement and renal manifestation in APS

| | Renal artery | Intra-renal vascular lesions | | | Renal vein |
	Renal artery lesions: Thrombosis/ occlusion/stenosis	Renal microangiopathy	Glomerulus disease	Cortical renal ischaemia	Renal vein: Thrombosis
Clinical features	Hypertension, decreased GRF, Renal infarcts	Hypertension, proteinuria, renal insufficiency.	Renal insufficency, proteinuria	Silent, painful, hematuria, oligoanuria	Proteinuria, Hematuria, Renal failure
Pathologic features	Proximal stenosis, distal stenosis, arteriosclerosis, FIH	Thrombotic microangioathy, Fiborus intimal hyperplasia, Focal cortical atrophy.	Glomerular thrombi, mesangiolysis, glomerular basement membrane wrinkling and reduplication, subendothelial deposits	Diffuse interstitial fibrosis, mononuclear infiltration, scleroti and ishemic glomeruli.	Thrombosis
Diagnostic evaluation	Ultrasound, MRA	Kidney biopsy	Kidney biopsy	Kidney biopsy	Doppler ultrasounds, CT scan, renal venography ultrasound, MRA, Kidney biopsy

Modified from Amigo MC. Kidney disease in antiphospholipid syndrome. Rheum Dis Clin North Am 2006;32:509–22 and Uthman I, Khamashta M. Antiphospholipid syndrome and the kidneys. Semin Arthritis Rheum 2006;35:360–67.

In general, two patterns of renal artery stenotic lesions, with some unique features, have been documented in APS patients. The more frequent pattern is characterized by smooth, well-delineated and often non-critical stenosis, distal to the ostium of the renal artery. Less frequently a pattern similar to atherosclerotic lesions, proximal and occasionally involving the aorta has been reported [46, 60, 61].

Thus renal artery occlusion may be due to two different mechanisms; the renal disease may be related to an *in situ* stenosis or thrombosis, or be due to an embolic event (such as a heart valve vegetation). However, some reports were not able to find a definitive cause for the renal infarction [51].

Occasionally hypertension may not be present in early stages of the disease, which may complicate the differential diagnosis and lead to delayed diagnosis [62].

Therefore, in all cases of unknown cause of renal artery stenosis, a diagnosis of APS should be considered. In addition to laboratory tests, renal scintigraphy and selective renal angiography facilitates the confirmation of the diagnosis and the extent of the lesions [44].

Intrarenal vascular lesions

Glomerular thrombosis

Unlike LN, where there are studies suggesting that patients with proliferative glomerulonephritis have a capillary thrombosis rate of up to 50% and whose presence implies a stronger prognostic marker [63], in primary APS, this finding is not specific. Amigo *et al.* described vascular lesions (both in arterioles and glomerular capillaries) often presenting with mesangiolysis, mesangial interposition, electron-lucent subendothelial material and ischaemic obsolescence of glomeruli. Renal biopsies also showed arterial luminal narrowing due to medial hypertrophy, amorphous mucoid deposits within the intima, thrombosis and general fibrosis [34, 64].

Nochy and colleagues [65] studied kidney biopsy specimens from 16 patients with APS, in which a combination of glomerular basement membrane wrinkling and reduplication were seen ultra-structurally.

Other histopathologic findings have been described, but these are not specific for APLN [44] (Table 1).

Intrarenal vascular lesions

Several reviews considered the involvement of the renal microvasculature to be the most frequent biopsy finding [35, 66, 67]. Gerhandsson *et al.* [10] described 236 renal biopsies from 112 SLE patients concluding that, in comparison to patients with pure LN, the presence of APLN was associated with intimal changes, inflammatory infiltrates, interstitial fibrosis and tubular atrophy.

The most commonly reported and characteristic intrarenal vascular lesion, in patients with APS [34, 44, 68–71] is TMA, characterized by the presence of distinctive microscopic and ultrastructural changes [72]. The most common clinical features of TMA include: hypertension,

TABLE 1 Main histologic features in glomerular affectation

Acute lesions	Chronic lesions
Mesangial expansion	Glomerular basement membrane thickening
Mesangiolysis	Cellular vanishing
Glomerular capillary collapse	Glomerular tuft retraction
Basement membrane wrinkling	Bowman's space widening
Double contours with mesangial interposition	Ischaemic obsolescence
Translucent subendothelial deposits	Segmental or global glomerular sclerosis
Intracapillary thrombi	
Thrombotic/haemorrhagic infarction	

Modified from Amigo MC. Kidney disease in antiphospholipid syndrome. Rheum Dis Clin North Am 2006;32:509–22.

proteinuria and renal impairment. Proteinuria is often mild but can be within nephrotic range [34, 73]. Histologically, focal or diffuse microangiopathic changes, affecting the whole intrarenal vascular tree and the glomerular tufts, have been observed [34, 65].

TMA is characterized by the presence of fibrin thrombi in glomeruli and/or renal arterioles and an absence of immune complexes and inflammatory cells. It lacks an association with any specific histologic class of LN [29]. Rarely, TMA can be associated to diffuse mesangial interposition with numerous double contours. By IF, the immunoglobulins are absent and the thrombi contain fibrin.

Intrarenal TMA may be the first manifestation that leads to a diagnosis of primary APS [74]. It has been emphasized that APS should be considered in the differential diagnosis of systemic hypertension and, that APS-related TMA may cause isolated hypertension without significant renal impairment.

Histologically, the morphological features of TMA are specific to a pathophysiology associated with thromboses, but they do not show any etiologic specificity. Other conditions including thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, post-partum renal failure, pre-eclampsia/eclampsia, scleroderma, malignant arterial hypertension or drugs (ciclosporin, chemotherapy, contraceptives), can produce similar lesions. The morphologic lesions are insufficient to make an aetiologic diagnosis, and require additional clinical and laboratory data, including aCL and LA determination, as well as exclusion of colibacillary infections, chronic hypertension, systemic sclerosis among others [44, 75].

A recent study [76] found that the inclusion of renal vascular lesions in the 2003 International Society of Nephrology/Renal Pathology Society histological classification system of LN, improves renal outcome prediction. TMA was associated with the poorest renal outcome among the other renal vascular lesions.

Atherosclerosis, among the fibrous lesions, present in 75% of biopsies in some reports [34], is not specific. In contrast, fibrous intimal hyperplasia (FIH) (described in 75% of the specimens), arteriolar occlusions (68%) and focal cortical atrophy (FCA) (62%) are only seen infrequently in other vascular nephropathies, and are highly suggestive of APLN when they are observed in the same biopsy with interstitial fibrosis and foci of tubular atrophy with pseudothyroidization (75%).

FIH of arterioles and interlobular arteries show a plexiform pattern of tortuous vessels with a cellular proliferation of actin-positive myofibroblastic cells in the intima, associated with an increased extracellular matrix. Most of these vessels have a reduced lumen obstructed by fibrous projections, cushions or organizing thrombi with recanalization [35].

FIH with organized thrombi was the second vascular lesion observed [77] in renal biopsies from a group of pregnant women with APS and LA. These lesions were also described by others in patients with primary APS, not only in intrarenal arteries, but also in other organs like: brain, lung, heart or skin [70, 78–81].

The fibrotic vascular lesions of typical nephroangiosclerosis (NAS) are relatively acellular, with diffuse arteriosclerosis and exceptional FIH. Arteriosclerosis is more fibrous, often characterized by an atrophic media with, on occasions, an onion-skin arrangement of the intima of the blood vessels.

Tubular atrophy with pseudothyroidization and interstitial fibrosis are frequently observed, but tend to be more diffusely distributed without the isolated subcapsular foci, typical of FCA. This appearance is likely to be because the lesions of typical NAS are more uniformly distributed than is the case for FCA in APLN. Furthermore, the organized thrombi, responsible for vascular occlusion in APLN, are absent in NAS [4].

Among the chronic pathological aspects, atherosclerosis is typically associated with intimal fibrous hyperplasia, thickening of arteries due to fibrosis and proliferation of myofibroblastic cells; with the consequent lumen restriction and ischaemia, which is common in APLN and rarely seen in other nephropathies [35, 82].

Redundant and wrinkled segments of basal membrane accompanied by a duplicate straighter thin membrane adjacent to the endothelium have been reported as a pathognomonic feature of the syndrome. In addition, some authors suggest an association between minimal change nephropathy and focal segmental glomerulosclerosis, both as independent clinical-pathological presentations of APLN [38, 72, 83].

Fakhouri and co-workers [84] reported some new aspects of the renal involvement in APS, in a study of 29 biopsies from patients with GN associated with APS in the absence of underlying autoimmune disorders. Twenty biopsies showed characteristic APLN features. However, predominant pathological features, distinct from vascular APS nephropathy, were noted in nine biopsies, including: membranous nephropathy (MN) (three cases), minimal change disease/focal segmental glomerulosclerosis (three cases), mesangial C3 nephropathy (two cases) and pauci-immune crescentic GN (one case).

Other cases of MN in association with APS have been reported [70, 84–86]. Moreover, in a series reported by Quereda and colleagues [87], aPL were detected in 3 out of 15 patients with MN (20%), 2 of whom fulfilled APS diagnostic criteria.

Cortical renal ischaemia

Occlusion of small isolated parenchymatous renal vessels causes small foci of cortical necrosis. These are generally asymptomatic. However, if they are multiple or generalized they may lead to patchy or diffuse cortical necrosis as described in the catastrophic APS [88].

One of the first reported cases was a 27-year-old man with coronary occlusion, arterial hypertension, thrombophlebitis, atrial thrombus and positive aPL. An abdominal CT scan revealed cortex hypodensity in both kidneys. Renal biopsy showed diffuse interstitial fibrosis, mononuclear infiltration, sclerotic and ischaemic glomeruli with negative immunofluorescence studies. These findings suggest cortical sclerosis and atrophy as sequelae from old cortical necrosis [89].

Pérez et al. [81] reported a man with APS and multiorgan arterial and venous thrombosis, seemingly a catastrophic syndrome. This patient had a 2-cm renal cortical infarction and multiple petechiae in the renal cortex. At autopsy, an organizing interlobular vein thrombus plus microthrombi in the microvasculature of the medulla were found. This case illustrated medium- and small-vessel thrombosis affecting the intra- and extrarenal vasculature.

The FCA, located in the subcapsular renal cortex, is associated with dense interstitial fibrosis leading to tissue retraction and kidney contour depression, giving it a scar-like appearance with sharp borders surrounded by areas of normal parenchyma, which is considered to be very typical of APLN [22, 82].

The fibrotic lesions of FIH and FCA are observed in surgical nephrectomies performed to reduce hypertension in cases of unilateral renal artery stenosis. In these surgical samples, zones of subcapsular depression representing foci of FCA with ischemic and cystic changes can be found with vascular lesions of FIH, often quite proliferative, with zones of tubular pseudothyroidization.

The great similarities of these lesions with those of APLN suggest they have the same pathophysiology. This could be the consequence of parenchymal ischaemia and activation of the renin–angiotensin system. In contrast, vascular occlusions by thrombi with recanalization are not seen in these kidneys downstream; nor is arterial stenosis [4].

Amigo and García-Torres suggested that cortical renal ischaemia is a well-defined clinicopathologic entity in patients with APS. The lesion may leave a variable impairment of renal function [44]. The additional presentation of renal cortical ischaemia was described by Leaker et al. [73]. This is an insidious, slowly progressive nephropathy that, in the long term, leads to renal failure. Clinically, patients have arterial hypertension, mild proteinuria and a slowly progressive renal failure.

Renal vein thrombosis

Surprisingly, renal vein thrombosis is a rare complication of primary APS, whereas peripheral vein thrombosis is a common feature. In contrast, renal vein thrombosis is a well-known complication of MN with nephrotic syndrome, either idiopathic or associated with SLE [90–94]. Isolated cases of renal vein thrombosis have been reported in patients with primary APS, including one case of bilateral renal vein thrombosis in the postpartum period [94].

Treatment

Control of hypertension, associated with various other drugs (anti-platelet drugs, anti-coagulants, steroids or rarely plasma exchange) may lead to remarkable improvement in renal function [1, 67, 74, 95, 96].

Heparin anti-coagulation, followed by long-term vitamin K antagonist anticoagulation is the mainstay of thrombotic APS therapy. However, a significant proportion of patients have recurrent thrombosis, despite anti-thrombotic therapy [97]. Vitamin K antagonists are also problematic due to food or drug interactions, bleeding complications and the need for frequent monitoring. Furthermore, aPLs interact variably with different thromboplastin reagents, affecting the prothrombin time monitoring and international normalized ratio (INR) [98].

Sangle et al. reported the effect of anticoagulation on blood pressure (BP) control and renal function in hypertensive APS patients. Fourteen such APS patients with renal artery stenosis, who received oral anti-coagulation for >1 year, were studied retrospectively. Patients were divided into two groups based on their INR (<3.0 and ⩾3.0). The results suggested that patients whose INR was maintained ⩾3.0 did well, their BP was better controlled (BP was 120/80 mmHg), renal function remained stable or improved and renal artery stenosis was reversed in some patients. In contrast, patients with a median INR <3.0 had poorly controlled BP and a significant deterioration in mean serum creatinine values [99].

Remondino and coworkers [100] described recanalization of bilateral renal artery stenosis and BP normalization in a young hypertensive woman with APS. These findings support the idea that anti-coagulation with INR maintained ⩾3.0 may have an important role in preventing the progression of these renal artery lesions.

However, the role of anti-coagulation therapy in the evolution of renal function is uncertain, due to the limited number of patients and follow−up period in the majority of

cases [29]. Even when full anti-coagulation is administered following renal allografting, the risks of graft loss and systemic thrombosis were not completely eliminated [101]. Unfortunately, there are no available recommendations about the optimal anti-coagulation regimen to be used during renal transplantation.

The risk of systemic or renal vasculature thrombosis is high in aPL−positive patients. However, the risk of graft failure due to major bleeding should be considered. In addition, the anti-coagulation therapy efficacy in preventing thrombotic microangiopathy is uncertain [102, 103].

The oral direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban and apixaban) overcome some of these disadvantages. They are prescribed at a fixed dose, do not need routine monitoring and have few drug or food interactions. However, they are irreversible and there is limited experience in patients with APS. There are no data recommending their use in APS patients with APLN, though results of the rivaroxaban in aPL syndrome (RAPS) study comparing warfarin and rivaroxaban in APS patients with history of venous thrombosis are expected shortly. Good control of systemic hypertension may be hard to achieve, but is vital to prevent the progression to end-stage renal disease [42].

Biologic therapy

Other therapeutic approaches have been attempted in refractory cases, including the use of IVIG, plasmapheresis and rituximab [104, 105]. Rituximab has been shown to decrease the titres of aPLs and, therefore, should decrease the thrombotic risk of patients with APS [106]. Thus, Ioannou and colleagues [107] reported a major fall in IgG aCL titres in seven SLE patients who had received treatment with rituximab and CYC. Moreover, 8 out of 12 APS patients treated with rituximab due to recurrent thrombosis or refractory thrombocytopenia showed normalization or a reduction in aPL titres [108]. The Rituximab in APS trial, a prospective, open-label, phase II trial of rituximab in primary APS patients, reported that rituximab is also effective in controlling some non-criteria manifestations of APS, such as thrombocytopenia, haemolytic anaemia, skin ulcers, and nephropathy [109]. The authors suggested that improvement might be due to the blockade of B cell effector functions independent of antibody production.

Two APLN patients were included in the open−label phase II trial of rituximab for non−criteria manifestations of APS; one patient withdrew early due to an infusion reaction, and the other had a partial response to treatment with rituximab [110].

Given this evidence, rituximab is an attractive alternative in the treatment of APLN. Reducing the number of B cells, rituximab may decrease both the aPL titres and also the production of ferritin and cytokines such as TNF-α, IL-1, IL-2 and IL-6, that may be responsible for some of the clinical features of APS [110]. Abatacept, a CTLA4 blocker, and belimumab, a BAFF antagonist, are approved for the treatment of RA and SLE, respectively,

but to our knowledge have not yet been used in patients with APS.

Complement inhibition with the C5a inhibitor eculizumab has been successfully used in isolated kidney post-transplant TMA cases [111]. Eculizumab carries a risk of infection with encapsulated organisms and patients should be immunized against meningococcus before starting treatment [112]. The therapeutic effects on the complement inhibition, tissue factor inhibition and anti-CD20, need to be investigated in prospective long-term studies. Further research on APS pathogenesis may identify new potential targets for its treatment. Multicentre, prospective studies are also needed for the validation of APLN histological criteria and the identification of histological, clinical and laboratory characteristics of this worse-renal-prognosis nephropathy.

References

1 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 2006;4:295–306.

2 Sinico RA1, Cavazzana I, Nuzzo M *et al*. Renal involvement in primary antiphospholipid syndrome: retrospective analysis of 160 patients. Clin J Am Soc Nephrol 2010;5:1211–7.

3 Jordan N, Chaib A, Sangle S *et al*. Association of thrombotic microangiopathy and intimal hyperplasia with bleeding post-renal biopsy in antiphospholipid antibody–positive patients. Arthritis Care Res 2014;66:725–31.

4 Nochy D, Daugas E, Hill G, Grünfeld JP. Antiphospholipid syndrome nephropathy. J Nephrol 2002;15:446–61.

5 Meroni PL, Borghi MO, Raschi E, Tedesco F. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. Nat Rev Rheumatol 2011;7:330–9.

6 Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. N Engl J Med 2013;11:1033–44.

7 Uthman IW, Gharavi AE. Viral infection and antiphospholipid antibodies. Semin Arthritis Rheum 2002;31:256–63.

8 Van Os GM, Meijers JC, Agar Ç *et al*. Induction of anti-β2 glycoprotein I autoantibodies in mice by protein H of *Streptococcus pyogenes*. J Thromb Haemost 2011;9:2447–56.

9 Tektonidou MG, Sotsiou F, Nakopoulou L *et al*. Antiphospholipid syndrome nephropathy in patients with systemic lupus erythematosus and antiphospholipid antibodies. Arthritis Rheum 2004;50:2569–79.

10 Gerhardsson J, Sundelin B, Zickert A *et al*. Histological antiphospholipid-associated nephropathy versus lupus nephritis in patients with systemic lupus erythematosus:

an observational cross-sectional study with longitudinal follow-up. Arthritis Res Ther 2015;17:109.

11 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 2009;11:R93.

12 Prieto LN, Suki WN. Frequent hemodialysis graft thrombosis: association with antiphospholipid antibodies. Am J Kidney Dis 1994;23: 587–90.

13 Prakash R, Miller CC, Suki WN. Anticardiolipin antibody in patients on maintenance hemodialysis and its association with recurrent arteriovenous graft thrombosis. Am J Kidney Dis 1995;26:347–52.

14 Daugas E, Nochy D, Huong DL *et al*. Antiphospholipid syndrome nephropathy in systemic lupus erythematosus. J Am Soc Nephrol 2002;13:42–52.

15 Chew SL, Lins RL, Daelemans R *et al*. Are antiphospholipid antibodies clinically relevant in dialysis patients? Nephrol Dial Transplant 1992;7:1194–8.

16 Haviv YS. Association of anticardiolipin antibodies with vascular access occlusion in hemodialysis patients: cause or effect? Nephron 2000;86:447–54.

17 Bhandari S, Harnden P, Brownjohn AM, Turney JH. Association of anticardiolipin antibodies with intraglomerular thrombi and renal dysfunction in lupus nephritis. QJM 1998;91:401–9.

18 Cheunsuchon B, Rungkaew P, Chawanasuntorapoj R *et al*. Prevalence and clinicopathologic findings of antiphospholipid syndrome nephropathy in Thai systemic lupus erythematosus patients who underwent renal biopsies. Nephrology 2007;12:474–80.

19 Silvariño R, Sant F, Espinosa G *et al*. Nephropathy associated with antiphospholipid antibodies in patients with systemic lupus erythematosus. Lupus 2011;20:721–9.

20 Simantov R, LaSala JM, Lo SK *et al*. Activation of cultured vascular endothelial cells by antiphospholipid antibodies. J Clin Invest 1995;96:2211–9.

21 Zhang J, McCrae KR. Annexin A2 mediates endothelial cell activation by antiphospholipid/anti-beta2 glycoprotein I antibodies. Blood 2005;105:1964–9.

22 Nojima J, Masuda Y, Iwatani Y *et al*. Tissue factor expression on monocytes induced by anti-phospholipid antibodies as a strong risk factor for thromboembolic complications in SLE patients. Biochem Biophys Res Commun 2008;365:195–200.

23 Martinuzzo ME, Maclouf J, Carreras LO, Levy-Toledano S. Antiphospholipid antibodies enhance thrombin-induced platelet activation and thromboxane formation. Thromb Haemost 1993;70:667–71.

24 Williams FM, Parmar K, Hughes GR, Hunt BJ. Systemic endothelial cell markers in primary antiphospholipid syndrome. Thromb Haemost 2000;84:742–6.

25 Canaud G, Bienaimé F, Tabarin F *et al*. Inhibition of the mTORC pathway in the antiphospholipid syndrome. New Engl J Med 2014;371:303–12.

26 Rauch J, Dieudé M, Subang R, Levine JS. The dual role of innate immunity in the antiphospholipid syndrome. Lupus 2010;19:347–53.

27 Aguilar-Valenzuela R, Nickerson K, Romay-Penabad Z *et al*. Involvement of TLR7 and TLR9 in the production of antiphospholipid antibodies. Arthritis Rheum 2011; 63:s281.

28 Broder A, Putterman C. Hydroxychloroquine use is associated with lower odds of persistently positive antiphospholipid antibodies and/or lupus anticoagulant in systemic lupus erythematosus. J Rheumatol 2013; 40:30–3.

29 Tektonidou MG. Identification and treatment of APS renal involvement. Lupus 2014;23:1276–8.

30 Fischetti F, Durigutto P, Pellis V *et al*. Thrombus formation induced by antibodies to beta 2-glycoprotein I is complement dependent and requires a priming factor. Blood 2005;106:2340–6.

31 Ritis K, Doumas M, Mastellos D *et al*. A novel C5a receptor-tissue factor cross-talk in neutrophils links innate immunity to coagulation pathways. J Immunol 2006;177:4794–802.

32 Lonze BE, Zachary AA, Magro CM *et al*. Eculizumab prevents recurrent antiphospholipid antibody syndrome and enables successful renal transplantation. Am J Transplant 2014;14:459–65.

33 Sciascia S, Cuadrado MJ, Khamashta M, Roccatello D. Renal involvement in antiphospholipid syndrome. Nat Rev Nephrol 2014;10:279–89.

34 Amigo MC, Garcia-Torres R, Robles M, Bochicchio T, Reyes PA. Renal involvement in primary antiphospholipid syndrome. J Rheumatol 1992;19:118–25.

35 Nochy D, Daugas E, Droz D *et al*. The intrarenal vascular lesions associated with primary antiphospholipid syndrome. J Am Soc Nephrol 1999;10:507–18.

36 Voiculescu A, Hofer M, Hetzel GR *et al*. Noninvasive investigation for renal artery stenosis: contrast-enhanced magnetic resonance angiography and color Doppler sonography as compared to digital subtraction angiography. Clin Exp Hypertens 2011;23:521–31.

37 Rountas C, Vlychou M, Vassiou K *et al*. Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, GD-enhanced MR angiography, and digital substraction angiography. Ren Fail 2007;29:295–302.

38 D'Cruz DP. Renal manifestations of the antiphospholipid syndrome. Lupus 2005;14:45–8.

39 Moss KE, Isenberg DA. Comparison of renal disease severity and outcome in patients with primary antiphospholipid syndrome, antiphospholipid syndrome secondary to systemic lupus erythematosus (SLE) and SLE alone. Rheumatology 2001;40:863–7.

40 Saracino A, Ramunni A, Pannarale G, Coratelli P. Kidney disease associated with primary antiphospholipid syndrome: clinical signs and histopathological features in an case experience of five cases. Clin Nephrol 2005;63:471–6.

41 Butani L. End-stage renal disease from glomerulonephritis associated with anti-phospholipid syndrome. Pediatric Nephrol 2004;19:812–4.

42 Dayal NA, Isenberg DA. Endstage renal failure in primary antiphospholipid syndrome—case report and review of literature. Rheumatology 2003;42:1128–9.

43 Sciascia S, Lopez-Pedrera C, Roccatello D, Cuadrado MJ. Catastrophic antiphospholipid syndrome (CAPS). Best Pract Res Clin Rheumatol 2012;26:535–41.

44 Amigo MC. Kidney disease in antiphospholipid syndrome. Rheum Dis Clin North Am 2006;32:509–22.

45 Sangle SR, D'Cruz DP, Jan W et al. Renal artery stenosis in the antiphospholipid (Hughes) syndrome and hypertension. Ann Rheum Dis 2003;62:999–1002.

46 Harris EN, Boey ML, Mackworth-Young CG et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet 1983;322:1211–4.

47 Alarcón-Segovia D, Cardiel MH, Reyes E. Antiphospholipid arterial vasculopathy. J Rheumatol 1989;16:762–7.

48 Rossi E, Sani C, Zini M, Casoli MC, Restori G. Anticardiolipin antibodies and renovascular hypertension. Ann Rheum Dis 1992;51:1180–1.

49 Mandreoli M, Zucchelli P. Renal vascular disease in patients with primary antiphospholipid antibodies. Nephrol Dial Transplant 1993;8:1277–80.

50 Asherson RA, Noble GE, Hughes GR. Hypertension, renal artery stenosis and the ''primary'' antiphospholipid syndrome. J Rheumatol 1991;18:1413–5.

51 Cacoub P, Wechsler B, Piette JC et al. Malignant hypertension in antiphospholipid syndrome without overt lupus nephritis. Clin Exp Rheumatol 1993;11:479–85.

52 Riccialdelli L, Arnaldi G, Giacchetti G, Pantanetti P, Mantero F. Hypertension due to renal artery occlusion in a patient with antiphospholipid syndrome. Am J Hypertens 2001;14:62–5.

53 Sirvent AE, Enriquez R, Antolin A et al. Malignant hypertension and antiphospholipid syndrome. Nephron 1996;73:368–9.

54 Serino R, Osajima A Hiroshige K et al. Renovascular hypertension associated with antiphospholipid antibodies in a woman with systemic lupus erythematosus. Nippon Jinzo Gakkai Shi 1996;38:417–22.

55 Ames PR, Cianciaruso B, Bellizzi V et al. Bilateral renal artery occlusion in a patient with primary antiphospholipid antibody syndrome: thrombosis, vasculitis or both? J Rheumatol 1992;19:1802–6.

56 Mandreoli M, Zuccalà A, Zucchelli P. Fibromuscular dysplasia of the renal arteries associated with antiphospholipid auotantibodies: two case reports. Am J Kidney Dis 1992;20:500–3.

57 Poux JM, Boudet R, Lacroix P et al. Renal infarction and thrombosis of the infrarenal aorta in a 35-year-old man with primary antiphospholipid syndrome. Am J Kidney Dis 1996;27:721–5.

58 Godfrey T, Khamashta MA, Hughes GRV, Abbs I. Antiphospholipid syndrome and renal artery stenosis. Q J Med 2000;93:127–9.

59 Aizawa K, Nakamura T, Sumino H et al. Renovascular hypertension observed in a patient with antiphospholipid-antibody syndrome. Jpn Circ J 2000;64:541–3.

60 George J, Shoenfeld Y. The anti-phospholipid (Hughes) syndrome: a crossroads of autoimmunity and atherosclerosis. Lupus 1997;6:559–60.

61 Harats D, George J, Levy Y et al. Atheroma: links with antiphospholipid antibodies, Hughes syndrome and lupus. QJM 1999;92:57–9.

62 Hughes GRV, Harris EN, Gharavi AE. The anticardiolipin syndrome. J Rheumatol 1987;13:486–9.

63 Kant KS, Polla KVE, Weiss MA et al. Glomerular thrombosis in systemic lupus erythematosus: prevalence and significance. Medicine 1981;60:71–86.

64 Glueck HI, Kant KS, Weiss MA et al. Thrombosis in systemic lupus erythematosus. Relation to the presence of circulating anticoagulants. Arch Intern Med 1985; 145:1389–95.

65 Domrongkitchaiporns S, Cameron EC, Jetha N, Kassen BO, Sutton RA. Renal microangiopathy in the primary antiphospholipid syndrome: a case report with literature review. Nephron 1994;68:128–32.

66 Petras T, Rudolph B, Filler G et al. An adolescent with acute renal failure, thrombocytopenia and femoral vein thrombosis. Nephrol Dial Transplant 1998;13:480–3.

67 Hamidou MA, Moreau A, Jego P et al. Captopril and aspirin in treatment of renal microangiopathy in primary antiphospholipid syndrome. Am J Kidney Dis 1995;25: 486–8.

68 Piette JC, Cacoub P, Wechsler B. Renal manifestations of the antiphospholipid syndrome. Semin Arthritis Rheum 1994;23:357–66.

69 Kleinknecht D, Bobrie G, Meyer O et al. Recurrent thrombosis and renal vascular disease in patients with a lupus anticoagulant. Nephrol Dial Transplant 1989;4: 854–8.

70 D'Agati V, Kunis C, Williams G, Appel GB. Anti-cardiolipin antibody and renal disease: a report of three cases. J Am Soc Nephrol 1990;1:777–84.

71 Becquemont L, Thervet E, Rondeau E et al. Systemic and renal fibrinolytic activity in a patient with anticardiolipin syndrome and renal thrombotic microangiopathy. Am J Nephrol 1990;10:254–8.

72 Griffiths MH, Papadaki L, Neild GH. The renal pathology of primary antiphospholipid syndrome: a distinctive form of endothelial injury. QJM 2000;93:457–67.

73 Leaker B, McGregor A, Griffiths M et al. Insidious loss of renal function in patients with anticardiolipin antibodies and absence of overt nephritis. Br J Rheumatol 1991; 30:422–5.

74 Lacueva J, Enríquez R, Cabezuelo JB et al. Acute renal failure as first clinical manifestation of the primary antiphospholipid syndrome. Nephron 1993; 64:479–80.

75 Karim MY, Alba P, Tungekar MF et al. Hypertension as the presenting feature of the antiphospholipid syndrome. Lupus 2002;11:253–6.

76 Wu LH, Yu F, Tan Y et al. Inclusion of renal vascular lesions in the 2003 ISN/RPS system for classifying lupus nephritis improves renal outcome predictions. Kidney Int 2013;83:715–23.

77 Kincaid-Smith P, Fairley KF, Kloss M. Lupus anticoagulant associated with renal thrombotic microangiopathy and pregnancy-related renal failure. Q J Med 1988;68:795–815.

78 Asherson RA, Cervera R, Piette JC et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features in 50 patients. Medicine 1998;77:195–207.

79 Isenberg DA, Griffiths M, Neild GH. Woman with livedo reticularis, renal failure, and benign urinary sediment. Nephrol Dial Transplant 1995;10:295–7.

80 Hughson MD, McCarty GA, Brumback RA. Spectrum of vascular pathology affecting patients with the antiphospholipid syndrome. Hum Pathol 1995;26:716–24.

81 Pérez RE, McClendon JR, Lie JT. Primary antiphospholipid syndrome with multiorgan arterial and venous thromboses. J Rheumatol 1992;19:1289–92.

82 Nochy D. [Antiphospholipid syndrome nephropathy]. Ann Med Interne (Paris) 2003;154:51–8.

83 Rossiñol T, Cervera R, López C et al. Antiphospholipid syndrome and minimal change nephropathy. Lupus 2006;15:547–8.

84 Fakhouri F, Noël LH, Zuber J et al. The expanding spectrum of renal diseases associated with antiphospholipid syndrome. Am J Kidney Dis 2003;41:1205–11.

85 Levy Y, George J, Ziporen L et al. Massive proteinuria as a main manifestation of primary antiphospholipid syndrome. Pathobiology 1998;66:49–52.

86 Dorel M, Daniel L, Liprandi A, Lerda D, Pellissier JF. Idiopathic membranous glomerulonephritis associated with primary antiphospholipid syndrome. Nephron 2000;86:366–7.

87 Quereda C, Otero GG, Pardo A, Orte L et al. Prevalence of antiphospholipid antibodies in nephropathies not due to systemic lupus erythematosus. Am J Kidney Dis 1994;23:555–61.

88 Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992;19:508–12.

89 Ramdane M, Gryman R, Bacques P, Callard P, Kleinknecht D. Ischémie rénale corticale, thrombose auriculaire droite et occlusion coronaire au cours d'un syndrome des anticorps antiphospholipides. Néphrologie 1989;10:189–93.

90 Ko W, Lim PS, Sung YP. Renal vein thrombosis as first clinical manifestation of the primary antiphospholipid syndrome. Nephrol Dial Transplant 1995;10:1929–31.

91 La Milia V, Tentori F, Pozzi C, Taddei G, Locatelli F. Primary antiphospholipid antibody syndrome with membranous obstruction of the interior vena cava—successful PTA and thrombolytic therapy. Nephrol Dial Transplant 1998;13:2641–4.

92 Liano F, Mampaso F, Garcia Martin F et al. Allograft membranous glomerulonephritis and renal-vein thrombosis in a patient with a lupus anticoagulant factor. Nephrol Dial Transplant 1988;3:684–9.

93 Morgan RJ, Feneley CL. Renal vein thrombosis caused by primary antiphospholipid syndrome. Br J Urol 1994;74:807–8.

94 Asherson RA, Buchanan N, Baguley E, Hughes GRV. Postpartum bilateral renal vein thrombosis in the primary antiphospholipid syndrome. J Rheumatol 1993;20:874–6.

95 Sokunbi DO, Miller F, Wadhwa NK, Nord EP. Reversible renal failure in the primary antiphospholipid syndrome—a report of two cases. J Am Soc Nephrol 1993;4:28–35.

96 KDIGO GN Work Group. KDIGO clinical practice guideline for glomerulonephritis—chapter 12: lupus nephritis. Kidney Int Suppl 2012;2:S221–32.

97 Cervera R, Khamastha MA, Shoenfeld Y et al. Morbidity and mortality in the antiphospholipid syndrome during a 5 year period: a multicenter prospective study of 1000 patients. Ann Rheum Dis 2009;68: 1428–32.

98 Tripodi A, Chantarangkul V, Clerici M et al. Laboratory control of oral anticoagulant treatment by the INR system in patients with the antiphospholipid syndrome and lupus anticoagulant. Br J Haematol 2001;115:672–8.

99 Sangle SR, D'Cruz DP, Abbs IC, Khamashta MA, Hughes GR. Renal artery stenosis in hypertensive patients with antiphospholipid (Hughes) syndrome: outcome following anticoagulation. Rheumatology 2005;44:372–7.

100 Remondino GI, Mysler E, Pissano MN et al. A reversible bilateral renal artery stenosis in association with antiphospholipid syndrome. Lupus 2000;9: 65–7.

101 Amigo MC, García-Torres R. Morphology of vascular, renal, and heart lesions in the antiphospholipid syndrome: relationship to pathogenesis. Curr Rheumatol Rep 2000;2:262–70.

102 Barbour TD, Crosthwaite A, Chow K et al. Antiphospholipid syndrome in renal transplantation. Nephrology 2014;19:177–85.

103 Espinosa G, Cervera R. Current treatment of antiphospholipid syndrome: lights and shadows. Nat Rev Rheumatol 2015;11:586–96.

104 Chaturvedi S, McCrae KR. Recent advances in the antiphospholipid antibody syndrome. Curr Opin Hematol 2014;21:371–9.

105 Silverman G, Weisman S. Rituximab therapy and autoimmune disorders: prospects for anti–B cell therapy. Arthritis Rheum 2003;48:1484–92.

106 Youinou P, Renaudineau Y. The antiphospholipid syndrome as a model for B cell–induced autoimmune diseases. Thromb Res 2004;114:363–9.

107 Ioannou Y, Lambrianides A, Cambridge G et al. B cell depletion therapy for patients with systemic lupus erythematosus results in a significant drop in anticardiolipin antibody titres. Ann Rheum Dis 2008;67:425–6.

108 Erre G, Pardini S, Faedda R, Passiu G. Effect of rituximab on clinical and laboratory features of antiphospholipid syndrome: a case report and a review of literature. Lupus 2008;17:50–5.

109 Erkan D, Vega J, Ramón G, Kozora E, Lockshin MD. A pilot open-label phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. Arthritis Rheum 2013;65:464–71.

110 Rodríguez-Pintó I, Cervera R, Espinosa G. Rituximab and its therapeutic potential in catastrophic antiphospolipid syndrome. Ther Adv Musculoskelet Dis 2015;7:26–30.

111 Safa K, Logan MS, Batal I *et al*. Eculizumab for drug-induced de novo posttransplantation thrombotic microangiopathy: a case report. Clin Nephrol 2015; 83:125–9.

112 Erkan D, Aguiar CL, Andrade D *et al*. 14th International Congress on Antiphospholipid Antibodies: Task Force report on antiphospholipid syndrome treatment trends. Autoimmun Rev 2014;13:685–96.

Clinical vignette

Eosinophilic granulomatosis with polyangiitis presenting with a vesicovaginal fistula

A 55-year-old woman presented with pelvic pain, vaginal bleeding and an offensive discharge. The patient subsequently described late-onset asthma, chronic sinusitis, unexplained polyarthralgia and intermittent paraesthesia of both hands.

A necrotic, fungating mass causing a large vesicovaginal fistula was characterized clinically and radiologically (Fig. 1A). Malignancy was suspected, but histology demonstrated a florid acute and chronic inflammatory cell infiltrate, with focal microabscess formation and areas of granulomatous inflammation, consistent with eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–Strauss syndrome). Her blood workup demonstrated an eosinophilia and a positive cANCA (ELISA negative).

An attempt at surgical closure of the fistula failed and flare of the EGPA subsequent to surgical intervention resulted in rapid deterioration of her condition with acute renal failure and sepsis (*Pseudomonas aeruginosa*), which was treated with meropenem. Methyprednisolone resulted in a dramatic improvement in her pain and normalization of CRP, allowing sufficient conditions in which an ileal conduit diversion was possible. Treatment with CYC for 6 months led to resolution of the pelvic mass (Fig. 1B), although control of her systemic symptoms remains an issue. Despite the plethora of organ involvement described in EGPA, this is the first description of a patient presenting with a vaginal mass and fistula formation.

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FIG. 1 MRI of the pelvis (A) before and (B) after steroid therapy
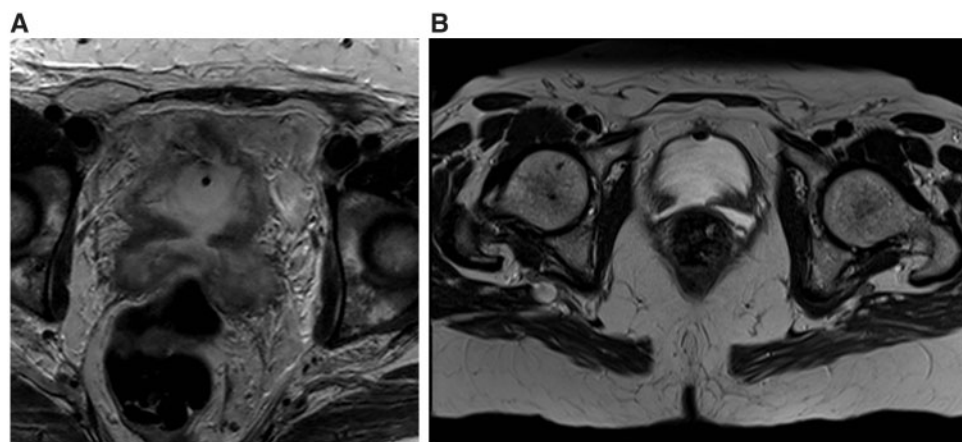
(**A**) Presenting MRI imaging: Markedly thick-walled vagina distended with non-enhancing material (slough and oedematous mucosa) and partly opacified from the vesicovaginal fistula. The thickening extends into the neck of the fistula and likely involves the bowel wall. A cystic node seen in the right groin has a thick-walled appearance and has likely ulcerated. (**B**) Marked resolution of the vaginal wall thickening following steroid treatment, although the large vesicovaginal fistula persists. The right groin lesion has also resolved.