Antiphospholipid Antibodies and Renal Involvement

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Key Words

Antiphospholipid antibodies • Antiphospholipid syndrome • Systemic lupus erythematosus nephritis • Antiphospholipid syndrome nephropathy

Abstract

Antiphospholipid antibodies are a heterogeneous group of autoantibodies associated with the hypercoagulable state affecting all vascular districts with thrombosis named antiphospholipid syndrome (APS). APS is an autoimmune disease with multifactorial etiology that includes cellular, molecular, genetic and pathogenic mechanisms. The APS clinical features are a combination of arterial and/or venous thrombosis, hematological events, recurrent fetal losses, neurological disorders and intra-abdominal manifestations. The renal involvement is associated with both primary and secondary APS. Clinical features include hypertension, renal artery stenosis, thrombotic microangiopathy and other histological manifestations of the nephropathy (APSN), venous renal thrombosis, APSN in the course of systemic lupus erythematosus and renal failure. APSN is an independent risk factor that should be included in the classification criteria for definite APS with characteristic clinical and histological features.

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Introduction

Antiphospholipid antibodies (aPL) are a heterogeneous group of autoantibodies associated with the hypercoagulable state affecting all segments of the vascular bed with thrombosis named antiphospholipid syndrome (APS) [1, 2].

The clinical features found in the course of APS include a combination of arterial and/or venous thrombosis, hematological events, recurrent fetal losses or other obstetric manifestations, neurological disorders and intra-abdominal manifestations [3].

The types of aPL that cross-react with anionic phospholipids are anticardiolipin (aCL), antiphosphatidic acid, antiphosphatidylserine, antiphosphatidylinositol and antiphosphatidylglycerol antibodies, while antibodies directed against neutral phospholipids are antiphosphatidylcholine and antiphosphatidylethanolamine [4].

Furthermore, these antibodies use β_2 -glycoprotein-I-like cofactor, having an important role in the thrombotic events, especially in arterial thrombosis in patients with systemic lupus erythematosus (SLE) and APS [5].

APS is considered an autoimmune disease with multifactorial etiology that includes cellular, molecular, genetic and pathogenic mechanisms [3, 6, 7], and the most important are:

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- (1) pathogenetic pathway and activation of the endothelium by aPL associated with a higher secretion of cytokines and activated prostacyclin metabolism;
- (2) an oxidant-mediated injury by low-density lipoproteins and macrophages on the vascular endothelium and the possible cross-reaction with aCL;
- (3) aPL interference with coagulation state: role of β_2 -glycoprotein I as a natural anticoagulant [8];
- (4) 'triggering' hypothesis: some infections, through molecular mimicry, may induce an increase in the clinical manifestations of aPL and APS [9].

Classification

The APS (Hughes's syndrome) is classified as primary APS without other autoimmune disease [10], secondary APS when other autoimmunity disorders occur, like SLE and other connective-tissue diseases, and catastrophic APS (Asherson's syndrome) characterized by rapid chronological occlusive events, shock, respiratory distress syndrome and multiorgan failure [11].

Primary APS may have a heterogeneous clinical presentation such as recurrent thrombosis, obstetric and fetal manifestations, central nervous system, hematological, osteoarticular, cardiopulmonary, adrenal, dermatological, ophthalmological, ear, nose and throat and intra-abdominal involvement (table 1).

The most frequent clinical features in the course of APS are deep venous thrombosis, stroke, pulmonary embolism, superficial thrombophlebitis, transient ischemic attacks and obstetric manifestations.

However, other clinical manifestations, considered minor criteria in the latest classifications, are moderate thrombocytopenia, livedo reticularis, migraine, heart valve thickening or dysfunction, epilepsy, myocardial infarction and amaurosis fugax [2, 12].

During APS some symptoms that reflect central nervous system involvement, such as myelitis and sensory disorders, may be mistaken for multiple sclerosis [13].

To define APS, at least 1 clinical and 1 laboratory criterion are necessary [14] (table 2).

Renal Manifestations

The renal manifestations are associated with both primary and secondary APS [15], and the clinical features include: hypertension, renal artery stenosis (RAS), thrombotic microangiopathy (TMA) and other histological

Table 1. Clinical presentation of APS

<i>Thrombosis</i>	<i>Obstetric and fetal manifestations</i>
Deep-vein thrombosis	Pre-eclampsia
Superficial thrombophlebitis	Eclampsia
Arterial thrombosis	Early fetal losses (<10 weeks)
	Late fetal losses (>10 weeks)
<i>Cardiopulmonary</i>	<i>Neurological/psychiatric</i>
Pulmonary embolism	Strokes and transient ischemic attack
Pulmonary hypertension	Migraine and headache
Pulmonary microthrombosis	Memory loss
Myocardial infarction	Epilepsy
Angina	Chorea
Valve thickening/dysfunction, vegetations	Cerebellar ataxia
Myocardiopathy	Transverse myelopathy
	Multi-infarct dementia
	Depression
	Psychosis
<i>Osteoarticular</i>	<i>Ophthalmological</i>
Arthralgia	Amaurosis fugax
Arthritis	Retinal artery thrombosis
Avascular necrosis of bone	Optic neuropathy
Bone fractures	
<i>Renal</i>	<i>Intra-abdominal</i>
Hypertension	Mesenteric ischemia
Renal artery stenosis	Budd-Chiari syndrome
APS nephropathy	Splenic infarction
Renal venous thrombosis	
<i>Dermatological</i>	<i>Ear, nose and throat</i>
Livedo reticularis	Ménière's disease
Ulcers/gangrene	Vertigo
Pseudovasculitic lesions	Nasal septum perforation
Splinter hemorrhage	
<i>Hematological</i>	<i>Adrenal</i>
Thrombocytopenia	Acute insufficiency
Hemolytic anemia	

manifestations of the APS nephropathy (APSN), venous renal thrombosis, APSN in the course of SLE and renal failure [16].

Hypertension

Hypertension is the most frequent clinical feature described in the course of APS and often appears in association with livedo reticularis, especially when blood pressure is difficult to control suggesting a renovascular mechanism [17].

Because laboratory findings like urinalysis, serum urea and creatinine are normal, a glomerular filtration

Table 2. Diagnostic criteria for APS

APS is present if at least 1 of the clinical criteria and 1 of the laboratory criteria that follow are met

Clinical

- (1) Vascular thrombosis¹
One or more clinical episodes of arterial, venous or small-vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall
- (2) Pregnancy morbidity²
 - (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or defined according to standard definitions
 - (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of:
 - (i) eclampsia or severe preeclampsia or (ii) recognized features of placental insufficiency
 - (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory criteria³

- (1) Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on lupus anticoagulants/phospholipid-dependent antibodies)
- (2) aCL antibody of IgG and/or IgM isotype in serum or plasma, present in medium or at high titer (i.e. >40 GPL or MPL, or above the 99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA
- (3) Anti- β_2 -glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (at titers above the 99th percentile), present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures

GPL = Units for IgG; MPL = units for IgM.

¹ Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.

² Two subgroups of APS patients should be recognized, according to (a) the presence and (b) the absence of additional risk factors for thrombosis. Such indicative (but not exhaustive) factors include: age (>55 in men and >65 in women), the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated low-density lipoprotein or low high-density lipoprotein cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index >30, microalbuminuria, estimated glomerular filtration rate <60 ml min⁻¹), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization and surgery. Thus, patients who fulfil criteria should be stratified according to contributing causes of thrombosis. A thrombotic episode in the past could be considered as a clinical criterion, provided that

thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found. Superficial venous thrombosis is not included in the clinical criteria. Generally accepted features of placental insufficiency include: (i) abnormal or nonreassuring fetal surveillance test(s), e.g. a nonre-active nonstress test, suggestive of fetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.

³ In studies of populations of patients who have more than 1 type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to the following categories: I = more than 1 laboratory criterion present (any combination); IIa = lupus anticoagulant present alone; IIb = aCL antibody present alone; IIc = anti- β_2 -glycoprotein-I antibody present alone.

rate, urine sediment, 24-hour urinary protein excretion, renal ultrasound and scintigraphy are more sensitive to diagnose early APSN [16].

Nochy et al. [18] documented systemic hypertension as the main clinical sign of nephropathy in 93% of patients with primary APS, often secondary to vascular lesions (arteriosclerosis, fibrous intimal hyperplasia, arterial and arteriolar fibrous and fibrocellular occlusions, TMA).

High blood pressure and renal failure were described by Kleinknecht et al. [19] in all SLE patients with APS. It is well established that hypertension is a common complication of APS and it could be difficult to treat; in the presence of microthrombi, blood pressure control and anticoagulant therapy may improve renal function [20].

Fig. 1. The proximal tubules contain protein resorption droplets; there is a moderate dilatation of the tubules containing hyaline casts. PAS. $\times 100$.

Fig. 2. TMA in a patient with lupus nephritis WHO class IV. A section of an arteriole with fibrinoid necrosis, thrombosis and intramural entrapment of whole and fragmented erythrocytes. HE. $\times 200$.

Renal Artery Stenosis

RAS is one of the first manifestations of APS with important clinical consequences [21]. Sangle et al. [22] demonstrated the presence of RAS in 26% of 77 patients with aPL and uncontrolled blood pressure (60 with SLE and APS, 11 with primary APS, 6 with aPL only). They observed two possible *patterns* regarding stenotic artery lesions. The most represented pattern was smooth, well-defined and noncritical stenosis distal to the renal artery ostium; these findings are different from atherosclerotic and fibromuscular dysplasia-related lesions. Indeed, the other described pattern seems to be similar to atherosclerotic lesions and founded in the proximal region to the ostium of the renal artery, sometimes involving the aorta [22].

Arterial and venous thrombosis are well documented in the kidney, and a high prevalence of RAS in the course of APS suggests a physiopathological relation with the prothrombotic state. Furthermore, aPL plays an important role in accelerated atherosclerosis, as a severe risk factor [23, 24]; moreover, aCL may cross-react with oxidized low-density lipoprotein [25, 26].

Atsumi et al. [27] have also described, in many APS patients with arteriolar lesions, the pathogenic role of high levels of endothelin 1 in a vasoconstrictive mechanism.

In the literature many data suggest that oral anticoagulation may strengthen the treatment, especially in patients developing intrastent restenosis. Anticoagulant therapy may play a role to stabilize or improve the steno-

sis, to prevent the presence of restenosis after angioplasty and as prophylaxis against thrombotic events in other vascular districts.

In conclusion, thrombosis may be the starting point for the development of RAS in hypertensive and uncontrolled blood pressure patients with APS.

Renal outcome may improve targeting an international normalized ratio (INR) of 3–4.5 and tightly monitoring anticoagulation therapy [28].

APS Nephropathy

APSN is characterized by vascular involvement associated with hypertension, acute and/or chronic renal failure and low-grade proteinuria (fig. 1).

Biopsy-proven renal lesions are statistically related to lupus anticoagulant (LAC), but not with aCL, and their presence and severity represent independent risk factors to develop hypertension, elevated serum creatinine and increased interstitial fibrosis [29]. Furthermore, in the course of APSN, extrarenal signs such as renal arterial (but not venous) thrombosis are associated with APS [30].

APSN vascular lesions may be acute (TMA) and/or chronic (arteriosclerosis, arterial fibrous intimal hyperplasia, tubular thyroidization, arteriolar occlusions and focal cortical atrophy) [18].

TMA is determined by fibrin thrombi in glomeruli and in the whole intrarenal vascular tree, without inflammatory cells or vascular immune deposits. In fact, by immunofluorescence study, fibrin is the main constitu-

Color version available online

Fig. 3. Variable intimal fibrosis of the arteries, arteriolar hyalinosis. There is also interstitial fibrosis, tubular atrophy and dilatation. PAS. $\times 100$.

Color version available online

Fig. 4. Complete arteriolar occlusion due to severe intimal hyalinosis (arrow). PAS. $\times 200$.

ent of thrombi, in the absence of immunoglobulins (fig. 2).

Arteriosclerosis and arteriolosclerosis are characterized by fibrous intimal thickening associated with arteriolar hyalinosis that reduces the vascular lumen of arcuate and interlobular arteries.

Fibrous intimal hyperplasia is different from that observed as a consequence of aging arteriosclerosis, because cellular proliferation is more intense. The myofibroblastic intimal cellular proliferation leads to intima thickening, with tortuosity of interlobular arteries and their branches.

The media shows two different patterns: proliferative with hypertrophic myocytes or, alternatively, atrophic and fibrous. The lumen is often reduced by areas of fibrous thickening of intima or recanalizing thrombosis (fig. 3).

Fibrocellular and fibrous arterial and arteriolar occlusions are often present in small interstitial arteries (fig. 4).

Focal cortical atrophy involves superficial zones of the subcapsular cortex, associated with a depression of the contour of the renal capsule. In the regions involved by focal cortical atrophy, the glomeruli can appear small and sclerotic or, in contrast, pseudocystic and voluminous, often clustered in groups, sometimes in the same biopsy. Focal cortical atrophy is considered to be very typical of APSN and leads to dense interstitial fibrosis, with thyroidization and tubular atrophy. It can often be seen associated with the vascular lesions of fibrous intimal hyperplasia. Immunofluorescence can reveal fibrin and more inconstantly C3 and IgM deposits in the vessels

Color version available online

Fig. 5. Focal atrophic area: there is global wrinkling and thickening of glomerular basement membranes. Bowman's capsule is thickened. There is interstitial fibrosis and tubular atrophy. Fibrinoid change in the arteriolar wall (arrow). PAS. $\times 100$.

showing thickening; sometimes, renin deposits may be observed in the juxtaglomerular apparatus (fig. 5).

Tubular thyroidization is characterized by tubular atrophy, with eosinophilic casts, resembling thyroid tissue, often in the deep cortex or medulla.

However, in a few cases it is possible to distinguish other pathological variants of APSN, resembling membranous nephropathy, minimal-change disease, focal segmental glomerulosclerosis, segmental glomerulosclerosis, mesangial C3 nephropathy and pauci immune crescentic glomerulonephritis [15].

Renal Venous Thrombosis

Both primary APS and aPL-positive patients with SLE nephritis are prone to develop thrombosis of the renal veins and inferior vena cava, associated with nephrotic-range proteinuria, especially in those with LAC positivity.

aPL Associated with SLE

In a large series, Tektonidou et al. [31] demonstrated that APSN occurs in 39.5% of SLE patients with aPL, whilst only in 4.3% of the SLE patients without aPL. APSN was strongly associated with LAC, aCL and livedo reticularis. In serial kidney biopsies, it was possible to find both acute and chronic lesions, such as fibrotic, proliferative and obstructive lesions due to thrombotic changes [31]. The renal prognosis in SLE patients worsens in the presence of APSN. The severity of renal SLE is related neither to APSN nor to the WHO classes of lupus glomerulopathy [30].

In SLE patients the presence of aCL is related to a greater degree of sclerosis, crescent formation and necrosis of glomeruli [32, 33].

The clinical presentation of SLE patients with aCL includes hypertension from mild to malignant, hematuria, proteinuria from mild to nephrotic range, and acute or chronic renal insufficiency.

The biptic distinction between APSN and SLE nephropathy is helpful to decide on the appropriate therapy, choosing only anticoagulants in APSN patients and cytotoxic agents in the course of lupus nephritis [34].

End-Stage Renal Disease and Renal Transplantation

End-stage renal disease is an uncommon feature in the course of primary APS [15].

It has been well documented that the frequency of aPL in patients undergoing hemodialysis for unknown causes of renal failure is higher as compared to the general population.

No correlation between these antibodies and age, length of time on dialysis, sex, infections, drugs or type of dialysis membrane was found [34, 35].

The exact role of aPL in end-stage renal disease is unknown, but some studies have reported associations between aPL and vascular access thrombosis [36].

Several investigations have reported that both aCL and LAC increase the risk of vascular access thrombosis; oth-

er studies suggest that thrombotic events are associated only with LAC [37].

There is evidence that in patients undergoing renal transplantation, aPL positivity correlates with a high frequency of vascular thrombosis, graft failure and systemic coagulation disorders, even if these patients were treated with anticoagulant therapy [15, 38].

Management

The APS management is based on four classes of drugs: aspirin, heparin, warfarin and immunosuppressive drugs.

In a meta-analysis, Lim et al. [39] proposed an algorithm for antithrombotic treatment of patients with antiphospholipid antibodies, in relation to the presence or absence of prior thrombosis and fetal loss, balancing the bleeding risk against antithrombotic effects.

In nonpregnant patients without prior thrombosis, no treatment or low-dose aspirin is required; otherwise, pregnancy suggests a prophylactic therapy with unfractionated heparin or low-molecular-weight heparin plus aspirin, particularly in the presence of prior pregnancy loss.

Venous thromboembolism is the most frequent clinical feature, and treatment consists of initial unfractionated or low-molecular-weight heparin for at least 5 days.

The first thrombotic episode or thrombosis recurrences (both venous and arterial) need a long-term anticoagulant therapy, targeting an INR of 2.0–3.0. Instead, cerebral artery thrombosis requires long-term anticoagulant therapy with a lower INR (1.4–2.8) or long-term aspirin treatment.

Furthermore, the association of APS with SLE justifies an immunosuppressive therapy such as cyclophosphamide.

In the presence of catastrophic APS, immunosuppressants, intravenous immunoglobulins or plasma exchange may offer help as rescue therapy.

In the literature the use of rituximab, an anti-CD20 monoclonal antibody, is reported in selected patients. However, clinical trials are needed to evaluate the clinical indication of rituximab in APS patients [13, 40].

Conclusion

APSN should be included in the classification criteria for defining APS.

The more frequent manifestations of APS are renal artery thrombosis or RAS, renal infarction, renal vein thrombosis and end-stage renal disease.

Clinically, APSN is characterized by a vascular nephropathy characterized by hypertension, low-grade proteinuria, and acute and/or chronic renal insufficiency.

Furthermore, aPL testing should be considered in nonaged patients with RAS, high blood pressure and unexplainable deterioration of renal function. In these patients renal outcome may improve with anticoagulant therapy targeted to keep an INR between 3 and 4.5.

Histological findings are TMA as acute thrombosis and fibrous intimal hyperplasia, arteriosclerosis and fo-

cal cortical atrophy, arterial and arteriolar fibrous and fibrocellular occlusions, and tubular thyroidization as chronic vascular lesions. Biopsy-proven renal lesions are statistically related to LAC, but not with aCL, and are helpful to predict the development of hypertension, renal insufficiency and progressive interstitial fibrosis.

In conclusion, in SLE patients with positivity for aPL, renal involvement may be due to connective tissue diseases or APS, the correct diagnosis of which can be very important to establish a correct therapeutic approach and improve the outcome.

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