

REVIEW

Vascular disease in patients with antiphospholipid syndrome: what do the cardiologists need to know?

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Abstract: Antiphospholipid syndrome (APS) is a clinical and laboratory condition associating arterial or venous thrombosis, obstetrical morbidity and positive antiphospholipid antibodies (aPL). A broad spectrum of cardiovascular manifestations was reported in patients with APS, focused mainly on thrombotic events. Recently, the vascular disease per se was described and discussed in these patients. The aim of this article is to review the spectrum of clinical and subclinical vascular abnormalities, mainly related to atherosclerosis, in patients with APS. Along with epidemiological and physiological data, the current status of therapy of patients with APS and atherosclerosis is also reviewed. The article emphasized also the need for a correct diagnostic of vascular events in patients with APS.

Keywords: antiphospholipid syndrome, atherosclerosis, endothelial dysfunction, arterial stiffness

Rezumat: Sindromul antifosfolipidic (APS) este o condiție clinică și de laborator ce asociază tromboze arteriale sau venoase, morbiditate obstetricală și anticorpi antifosfolipidici pozitivi (APL). Un spectru larg de manifestări cardiovasculare a fost raportat la pacienții cu APS, axat în principal pe evenimente trombotice. Recent, boala vasculară per se a fost descrisă și discutată la acești pacienți. Scopul acestui articol este de a revizui spectrul de anomalii clinice și subclinice vasculare, în principal legate de ateroscleroză, la pacienții cu APS. Împreună cu datele epidemiologice și fiziologice, tratamentul actual al pacienților cu APS și ateroscleroză este, de asemenea, revizuit. Acest articol subliniază de asemenea nevoia unui diagnostic corect a evenimentelor vasculare la pacienții cu APS.

Cuvinte cheie: sindrom antifosfolipidic, ateroscleroză, disfuncție endotelială, rigiditate arterială

INTRODUCTION

Antiphospholipid syndrome (APS) is an acquired prothrombotic status in which recurrent arterial or venous thrombosis may coexist with obstetrical pathology and positive antiphospholipid antibodies (aPL)¹. The disease is rare, occurring especially secondary to other clinical conditions as systemic lupus erythematosus (SLE) – secondary APS (SAPS).

A broad spectrum of cardiovascular manifestations was reported in patients with APS, focused mainly on thrombotic events. Recently, the vascular disease per se was described and discussed in these patients (Table 1). The aim of this article is to review the spectrum of clinical and subclinical vascular abnormalities, mainly related to atherosclerosis, in patients with APS.

SUBCLINICAL ATHEROSCLEROTIC DISEASE IN APS

Endothelial dysfunction

Endothelial dysfunction, an abnormal response of the vascular wall to vasodilator stimuli, represents a very early functional abnormality in the pathogenesis of atherosclerosis. There are several methods to assess it, used more for research purposes than in daily clinical practice. The most used is the flow-mediated dilatation (FMD) measurement at the level of brachial artery, but several biomarkers linked to endothelial dysfunction (i.e. von Willebrand factor) can also be used. An abnormal endothelial function was described in patients with other inflammatory rheumatic diseases².

There are reported data showing an endothelial impaired function in patients with APS^{3,4}. Cugno et al.⁵ re-

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Table 1. Spectrum of vascular disease in patients with APS

Macrovascular disease
Atherosclerotic vascular disease
Subclinical
Endothelial dysfunction
Increased arterial stiffness
Increased arterial intima-media thickness
High prevalence of asymptomatic atherosclerotic plaques
Peripheral vascular disease (low ankle-brachial index)
Other (increased risk for coronary calcifications)
Overt clinical disease (coronary heart disease, stroke, peripheral artery disease)
Revascularization conditions
By-pass occlusion
Restenosis after angioplasty
Non-atherosclerotic disease
Inflammatory changes (vasculitis-type lesions)
Microvascular disease (APS vasculopathy)
Renal, pulmonary, myocardial, cerebral etc.

cently reported higher levels of von Willebrand factor levels and an impaired response at FMD test in patients with APS compared to controls. Moreover, in this study the circulating endothelial cells were increased in patients with APS, with a significant reduction after antithrombotic treatment. A reduced FMD in patients with PAPS was reported by Bilora et al.⁶. Also, the impaired FMD in patients with PAPS was linked with the duration of the disease⁷, adhesion molecule levels (vascular-cell adhesion molecule-1 and intracellular adhesion molecule-1)⁷, with a significant reduction in patients with arterial disease comparing with those with venous disease⁸. Injection of antiphospholipid antibodies in mice was associated with an impaired relaxation

response to acetylcholine of the mesenteric arteries⁹. However, there are other authors that reported similar values for endothelial function markers (FMD, von Willebrand factor, CD40L, soluble P-selectin, circulating endothelial cells) in patients with PAPS without other cardiovascular factors and controls, emphasizing the pure thrombotic mechanisms in APS¹⁰.

Increased arterial stiffness

Arterial stiffness is regarded now as an important cardiovascular risk marker^{11,12}. However, the assessment of arterial stiffness in daily clinical practice, using techniques mainly based on pulse wave analysis, is not widely available. Data regarding the arterial stiffness in patients with PAPS are very limited. In patients with PAPS, arterial stiffness parameters correlate with decreased FMD, demonstrating the link between these functional abnormalities¹³. There are no differences regarding arterial stiffness between PAPS and SAPS patients¹⁴. In patients with lupus, carotid artery stiffness was not associated with the presence of the antiphospholipid antibodies¹⁵.

Intima-media thickness

Intima-media thickness (IMT), measured most frequently at the level of carotid artery, correlates with cardiovascular and cerebrovascular diseases¹⁶⁻¹⁹. There are several reports showing that IMT values are higher in patients with PAPS than controls²⁰, linked to the age of patients²¹, memory T CD45RO+ cells²², factor XIII activity²³, paraoxonase activity, as a marker of oxidative imbalance, and with IgG anti-β2 GPI-ox Lig-1 (7-ket-

Table 2. Therapeutic recommendations for patients with APS and vascular lesions

Pathologic target	Treatment option
Atherosclerotic lesions with chronic symptoms (angina, claudication)	Treatment according to existing national or international guidelines Tight control of traditional cardiovascular risk factors Statins in the context of high cholesterol levels (until now, statins are not indicated per se in APS) Aspirin if not previous thrombotic events Oral anticoagulants and aspirin if previous thrombotic events Hydroxichloroquine (possible)
Acute events – pure “thrombotic”	Oral anticoagulants (eventually with aspirin)
Acute events – “mixed” mechanism (atherosclerosis and thrombosis)	Treatment according to existing national or international guidelines Tight control of traditional cardiovascular risk factors Statins in the context of high cholesterol levels (until now, statins are not indicated per se in APS) Oral anticoagulants and aspirin Hydroxichloroquine (possible)
Restenosis after angioplasty and by-pass occlusion	Aspirin Oral anticoagulants if thrombotic mechanism supposed
High values of intima-media thickness, asymptomatic plaques and low ABI	Tight control of traditional cardiovascular risk factors Statins in the context of high cholesterol levels (until now, statins are not indicated per se in APS) Aspirin if no previous thrombotic events
High-calcium coronary score	Similar to general population
Vasculitis-type lesions	Glucocorticoids (?) Immunosuppressant (?)

cholesteryl-9-carboxynonanoate moiety of oxLDL) complex²⁴. In a study that included both patients with PAPS and subjects with persistent titer of aCL without any underlying disease, Ames et al showed that IgG aCL independently predicted increased IMT at all carotid segments²⁵.

Asymptomatic atherosclerotic plaques

Belizna et al showed the increased prevalence for subclinical atherosclerotic carotid and femoral plaques (21%), independently predicted by the aCL titre¹⁵. Vlachoyiannopoulos reported an increased prevalence of carotid and femoral plaques in premenopausal women with APS compared to healthy controls or patients with rheumatoid arthritis²⁶ without association with the levels of antiphospholipid antibodies. In the study of Jimenez et al.²⁷, the prevalence of carotid plaques was not increased in patients with PAPS comparing with controls, but was higher in patients with SAPS with SLE than in patients with PAPS.

Ankle-brachial index

Ankle-brachial index (ABI) identifies peripheral arterial disease of the lower limbs in asymptomatic individuals²⁸. Baron et al. reported an increased prevalence for an abnormal ABI in patients with PAPS than controls, without any correlation with traditional cardiovascular risk factors²⁹. A significant prevalence of an abnormal ABI was reported also in women with APS with pregnancy loss without thrombotic events³⁰.

Other asymptomatic vascular manifestations

Few reports are published regarding the presence of coronary calcifications in patients with PAPS. The risk for coronary calcifications, assessed by computed tomography was found to be increased in patients with SLE and positivity for aPL³¹. Typical signs of silent ischemic heart disease and myocardial infarction were reported with an increased prevalence in patients with APS using the cardiac magnetic resonance imaging³².

Cardiovascular risk – focus on coronary artery disease

The association between APS and coronary artery disease has been the subject of many controversies over the last years.

Several important points have to be considered when discussing this association. Thrombus formation, *in situ* or embolic thrombus, with the occlusion of the artery and subsequent ischemia is considered to be the main mechanism involved in acute vascular events in patients with APS (“thrombotic risk”). From this point of view, there are a large number of studies

regarding the risk for acute thrombotic events in these patients. However, more recently, the “atherosclerotic risk” in APS patients, leading to atherosclerosis plaque generation, became more and more discussed in the medical literature. As the plaque progresses, the specific symptoms may be present (i.e. stable angina, lower limbs claudication). According to this point of view, several case-reports and very few studies investigating the chronic atherosclerotic vascular diseases in patients with APS were published.

A “combined” mechanism might involve thrombus generation on a pre-existent plaque, leading to acute events. We should note than studies regarding the aPL in patients with acute events, very rarely made the distinction between the “thrombotic risk” and “atherosclerotic risk”, as this is difficult, needing invasive intravascular imaging techniques (i.e. angiography or intravascular ultrasound).

Otherwise, most of the studies used a single positivity for aPL, patients not having all criteria for APS, making the interpretation of the data more difficult.

There are few cohorts of APS, mainly secondary to SLE, evaluating this risk. One of the largest cohorts is the Euro-Phospholipid cohort that includes 1000 patients with PAPS and SAPS. During the follow-up, the cumulative frequency of myocardial infarction was 5.5% and of angina was 2.7% and the cumulative frequency of stroke was 19.8%³³. In this cohort 5.3% of the patients died during the follow-up; myocardial infarction (19%) and stroke (13%) were among the most common causes of death. The authors reported no clinical or immunological predictor for thrombotic events and death in patients with APS³⁴. Farsi et al. reported an increased prevalence of anti- β 2-GPI in patients with ischemic heart disease comparing to healthy controls (29.7% vs 2.5%; $p < 0.005$), with a significant difference between patients with unstable versus effort angina (45% vs 11.8%, $p = 0.03$)³⁵. In the same study the level of anti- β 2-GPI was increase in patients with unstable angina versus stable angina and versus healthy controls.

Vaarala et al demonstrated in a prospective cohort of healthy middle-aged men the value of high titer of aCL antibody as independent risk factor for myocardial infarction or cardiac death³⁶. Similar data comes from the cohort of Honolulu Heart Program showing that aCL IgG, especially the β 2-GPI-dependent, was an important predictor for stroke and myocardial infarction in men in a 20 years follow-up³⁷. However, until now, these antibodies are not currently recommended in daily clinical practice for cardiovascular risk stratification.

The positivity for aPL was associated with an unfavorable prognostic after coronary events^{38,39}. However, the association between aCL and the risk of recurrent cardiovascular events in acute myocardial infarction survivors is controversial⁴⁰⁻⁴³. Zuckerman et al reported a high prevalence for aCL in young patients with acute myocardial infarction, high titers of these antibodies being predictive for recurrent myocardial infarction⁴⁴.

Other reports linked aCL with an increased risk for restenosis after angioplasty⁴⁵⁻⁴⁹ and with an earlier development of restenosis⁵⁰. However, there are studies reporting no association between aCL and restenosis⁵¹. Morton et al reported an association between preoperative aCL level and the incidence of late graft occlusion in patients with coronary artery by-pass graft surgery⁵².

VASCULITIS IN APS

Even if the absence of significant inflammatory lesions is mandatory for the diagnostic of APS, histological signs of vasculitis were reported in some patients with APS needing amputation⁵³. The relevance of these lesions is not clear but inflammatory changes are in any case unspecific and discrete in patients with APS.

PHYSIOPATHOLOGICAL HYPOTHESES

The traditional cardiovascular risk factors failed to explain the cardiovascular excess morbidity in patients with APS⁵⁴. Metabolic syndrome, as a cluster of cardiovascular risk factors, was found to have a similar prevalence in patients with APS and controls⁵⁵. Taking into account the immune theory of atherosclerosis⁵⁶, these mechanisms were studied in order to explain atherosclerotic lesions in APS, similarly to other inflammatory diseases⁵⁷. The clear mechanisms by which the aPL are involved in the process of atherosclerosis are incompletely understood until now.

One of the first steps in the pathogenesis of atherosclerosis is an abnormal endothelial function. Antiphospholipid antibodies were studied in this setting and several mechanisms were described linking them to endothelial dysfunction. The molecular structure of β 2-GPI with a large positively charged domain is the key element in the interaction with negatively charged phospholipids from the endothelial cells membranes⁵⁸. Another way to bind the β 2-GPI to the endothelium is the annexin II, an endothelial cells receptor for tissue plasminogen activator (t-PA), which exhibits high affinity for β 2-GPI (59). The anti β 2-GPI antibodies recognize this β 2-GPI attached on the surface of the endothelium shifting the function of endothelial to a

pro-adhesive and pro-inflammatory phenotype⁶⁰⁻⁶⁵. An imbalance between prostacyclin and thromboxane A₂, leading to a local prothrombotic status, was also reported as a consequence of direct APA binding to endothelial cells⁶⁶. Apoptosis of the endothelial cells triggered by APA and the synthesis of vasoconstrictors as endothelin I are other mechanisms proposed to promote endothelial dysfunction in APS⁶⁷.

An important step in the atherosclerosis pathways in APS is the interaction between oxidized low density lipoprotein (ox-LDL), β 2-GPI and anti- β 2-GPI antibodies. Oxidized low density lipoprotein, an important component of foam cells and atherosclerotic lesions⁶⁸, co-localizes with β 2-GPI and lymphocytes⁶⁹. β 2-GPI binds ox-LDL, preventing the uptake and degradation of ox-LDL by macrophages. The ox-LDL/ β 2-GPI complexes might have a protective effect on vascular wall. The anti- β 2-GPI antibodies bind the ox-LDL/ β 2-GPI complexes and facilitate the macrophage uptake of anti- β 2-GPI/ β 2-GPI/ox-LDL complex, promoting foam cells development⁷⁰.

OTHER MECHANISMS

The antiphospholipid antibodies may impair the para-oxonase (antioxidant enzyme) leading to the synthesis of a high-density lipoprotein (HDL) with abnormal activity⁷¹. There are also reports in which the anticardiolipin antibodies were related with oxidative stress⁷². Heat-shock proteins were found in the atherosclerotic plaques and there are published data suggesting the association of IgG anti-hsp and IgA anti β 2-GPI with an increased risk for stroke⁷³. A link between TNF-alpha, aPL (anticardiolipin, antibeta 2 GPI, anti-annexin A5) and anti-ox-LDL was found in patients with type 2 diabetes mellitus without vascular complications, characterizing a possible high atherogenic profile⁷⁴.

Until now, the clear mechanisms linking the aPL and APS to atherosclerosis are incomplete and controversial. There are some data from animal studies suggesting a protective effect on atherosclerosis of the aPL^{75,76}.

Vasculopathy or "thrombotic microangiopathy"

Vasculopathy is another name of so-called "thrombotic microangiopathy", one of the most intriguing features of the APS. Most authors consider APS vasculopathy as having a primordial thrombotic mechanism and, secondarily and not in all cases, vasculitis features⁷⁷, with a good clinical response to antithrombotic treatment. The clinical importance of APS vasculopathy is at the level of several organs (i.e. kidneys, lungs, heart, brain etc.), leading to specific manifestations.

TREATMENT OF VASCULAR DISEASE IN APS

The main treatment in patients with thrombotic events is oral anticoagulation with antivitamin K with a target INR according to each clinical condition: arterial or venous thrombosis, first or recurrent event, obstetrical manifestations⁷⁸.

In some conditions, the supplementation with aspirin is advisable. Beyond the classical antiaggregant effect, aspirin seems to have some other beneficial effects on endothelial cells in patients with APS⁷⁹.

Hydroxychloroquine was shown to have beneficial effects on cardiovascular risk profile in patients with rheumatoid arthritis^{80,81} and SLE⁸². Hydroxychloroquine have reported to have beneficial effects on thrombosis prophylaxis^{83,84} in patients with APS but consistent data concerning the positive effects on atherosclerosis are still lacking. However, the hydroxychloroquine may be used in patients with history of ischemic heart disease (angina, myocardial infarction) according to the recommendations of a consensus committee⁸⁵.

The use of statins in patients with APS might be attractive taking into account their reported pleiotropic effects⁸⁶. There are controversial data regarding the beneficial effects of statins in animal models receiving aPL⁸⁷⁻⁸⁹. Until now, the use of statins in patients with APS must follow the recommendations for general population. Studies with statins in patients with APS are needed in order to have valid conclusions.

There are no studies investigating the effects of different therapies on subclinical vascular function in patients with APS.

Regarding the corticosteroids and immunosuppressants, the data regarding the effects on atherosclerosis lesions in patients with APS are scarce.

Screening for subclinical vascular disease in APS

The screening for subclinical vascular disease in patients with APS should be driven according to recommendations existing for general population as there are not specific guidelines in patients with APS.

Taking into account the availability of the IMT measurements in daily clinical practice, its assessment in patients with APS might be done, especially in those with SAPS or in the context of the presence of other cardiovascular risk factors.

The individual assessment of cardiovascular risk must be done with cardiovascular risk scores, as SCORE chart proposed by European Society of Cardiology and other societies⁹⁰.

CONCLUSIONS

The data regarding the high risk for developing atherosclerosis lesions in patients with APS are still increasing. Along with the classical thrombotic risk, these patients may have atherosclerosis-related cardiovascular manifestations. Moreover, the entire spectrum of subclinical vascular disease was described in patients with APS.

Clinicians should be aware of these manifestations and perform a complete cardiovascular risk assessment in these patients. In high risk patients and in patients with cardiovascular manifestations, treatment according to existing guidelines is advisable. The beneficial role of hydroxychloroquine and statins in patients with APS and cardiovascular morbidity related to atherosclerosis is still a matter of debate.

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