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Cardiac manifestations in antiphospholipid syndrome

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Abstract

Antiphospholipid syndrome (APS) is a systemic autoimmune disease associated with arterial and venous thrombotic events and recurrent fetal loss. Cardiac manifestations in APS primarily include accelerated atherosclerosis leading to cardiovascular disease. There is increased cardiovascular mortality in APS. Cardiovascular risk is even higher in secondary APS in lupus patients. Several traditional and disease-related, autoimmune-inflammatory risk factors are involved in APS-associated atherosclerosis and its clinical manifestations. Antiphospholipid antibodies (APA), lupus anticoagulant, anti-oxLDL and other antibodies have been implicated in vascular events underlying APS. The primary and secondary prevention of atherosclerosis and CAD in these diseases includes drug treatment, such as the use of statins and aspirin, as well as lifestyle modifications. Apart from atherosclerosis and CVD, other cardiac manifestations may also be present in these patients. Among these conditions, valvular disease including thickening and vegetations is the most common. APA are involved in the pathogenesis of Libman–Sacks endocarditis usually associated with SLE. In addition, ventricular dysfunction, intracardiac thrombi and myxomas, pulmonary hypertension may also exist in APS patients. Early diagnosis of APS, thorough examination of the heart, control of traditional risk factors by lifestyle modifications and pharmacotherapy, probably anti-inflammatory treatment close follow-up of APS patients may help to minimize cardiovascular risk in these individuals.

Keywords: Antiphospholipid syndrome; Atherosclerosis; Cardiovascular disease; Cardiac manifestations

Contents

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1. Introduction

Antiphospholipid syndrome (APS) is a prothrombotic state characterized by recurrent venous thrombotic events including deep venous thrombosis, as well as pulmonary embolism, arterial thrombosis, recurrent fetal loss due to placental thrombosis and the presence of circulating antiphospholipid antibodies (APA) [1]. Thrombophilia present in APS may be associated with premature and accelerated atherosclerosis [2,3]. Atherosclerosis in APS is mediated directly by the proinflammatory and procoagulant activity exerted by APA on vascular endothelial cells (EC), or indirectly via immuno-inflammatory mechanisms underlying autoantibody-mediated thrombosis [2,4,5]. Cardiovascular disease (CVD) has been associated with morbidity and mortality in APS, as well as in other autoimmune disorders including systemic lupus erythematosus (SLE), rheumatoid arthritis and systemic sclerosis [2,3].

In this review, we describe cardiac manifestations in APS. We will focus on the two major manifestations: CVD and valvular disease. Major traditional and non-traditional risk factors for APS-associated atherosclerosis will be discussed followed by diagnostic and therapeutic tools used during the management of CVD. Other cardiac manifestations, such as valvular disease, Libman–Sacks endocarditis, intracardiac thrombi and myxomas, diastolic dysfunction and pulmonary hypertension, will also be briefly described (reviewed in [1,6–12]).

2. Cardiovascular manifestations and accelerated atherosclerosis in APS

2.1. Epidemiology

In 1993, it was suggested for the first time that APA may be involved in atherosclerosis [13]. In this study, possible cross-reactivity between APA and antioxidized LDL (anti-oxLDL) antibody was also suggested [13].

APA and APS have been associated with atherosclerosis, as well as CVD, cerebrovascular and peripheral arterial diseases [3,14–20]. Premature atherosclerosis may first occur in the lower limbs [21]. In a preliminary report of three patients, severe systemic atherosclerosis including aortic occlusion was associated with high serum levels of anticardiolipin (aCL) autoantibodies and homocysteine [22]. A prospective study of 116 consecutive patients with recent onset intermittent claudication revealed, that some kind of thrombophilia occurred in about 25% of patients. In addition, more than half of the patients had elevated serum APA concentrations [21]. APA has been associated with mortality in CAD [18]. These results suggested that APA may be involved in the evolution of progressive atherosclerosis.

2.2. Traditional and autoimmune-inflammatory risk factors for atherosclerosis in APS

A number of traditional cardiovascular risk factors, such as hyperlipidemia, diabetes mellitus, smoking, obesity, arterial hypertension and sedentary lifestyle were assessed in APS patients (Table 1). None of these Framingham risk factors showed any difference between APS patients and the general population [5]. Therefore, APS-associated atherosclerosis may rather be explained by inflammatory and immunopathological factors, primarily APA.

APA including aCL and anti-β2GPI antibodies, as well as lupus anticoagulant (LA) exert direct pro-inflammatory and procoagulant activity on the endothelial surface. APA also trigger an inflammatory cascade [2,23]. Others and we showed correlation between serum levels of aCL and anti-β2GPI antibodies and the incidence and severity of acute coronary syndrome, myocardial infarction and stroke [14–16]. APA-induced arterial events are the most pronounced in SLE-associated secondary APS, where traditional and non-traditional risk factors are multiplied and atherosclerosis occurs more prematurely [2,14,15,24,25].

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Table 1
Traditional and non-traditional risk factors for atherosclerosis and cardiovascular disease in antiphospholipid syndrome

1. Traditional (Framingham) factors	Age
	Postmenopausal status
	Hyperlipidemia
	Hypertension
	Diabetes mellitus
	Obesity
	Sedentary lifestyle
2. Inflammatory-immunological factors	Acute phase reactants (CRP, fibrinogen)
	Antiphospholipid antibodies
	Anti-oxLDL, anti-hsp
	Lupus anticoagulant
	Hyperhomocysteinemia
	Increased vessel wall angiogenesis
	Defective apoptosis

In a recent retrospective analysis of 1519 APA-positive patients, among them 637 with clinical APS, we detected venous thrombotic events more frequently in patients having circulating lupus anticoagulant (LA) in comparison to patients with other types of APA. In contrast, coronary, carotid and peripheral arterial thrombosis occurred more often in patients with elevated serum levels of IgG or IgM APA, including aCL or anti-β2 glycoprotein I (β2GPI) antibodies. Our results suggest that mainly APA are involved in arterial thrombotic events underlying APS [26].

We and others have suggested the involvement of APA in acute coronary syndrome (ACS) [16,20,27]. We found an increased frequency of anti-β2GPI antibodies in ACS compared to controls. Anti-β2GPI antibodies of the IgA isotype seemed to be the most relevant for the onset and outcome of ACS. Anti-β2GPI antibodies were also associated with previous stroke in ACS patients [16]. There is evidence that increases in serum APA levels precede the clinical manifestation of ACS [16,20]. Coronary restenosis occurred more frequently in APA positive ACS patients [27].

There is a cross-reactivity between aCL and other antibodies, such as anti-oxLDL, anti-HDL or anti-apolipoprotein A-I IgG [2,3,14,23,28]. Both APA and anti-oxLDL are atherogenic and they can bind to neoepitopes of oxLDL, as well as to oxLDL–β2GPI complexes [2,28]. Autoantibodies against these complexes have been detected in APS, as well as SLE patients [2,29]. Serum levels of autoantibodies to the oxLDL ligand-β2GPI complexes were significantly higher in APS patients in comparison to SLE patients without APS or healthy subjects [2,29]. Both APA and anti-oxLDL may account for increased mortality in CVD [18].

Heat-shock proteins (hsp), oxLDL and β2GPI are present within atherosclerotic lesions [14,30]. Others and we detected the β2GPI cofactor in the wall of large arteries in the vicinity of $CD4^+$ T cell infiltrates. Macrophages and endothelial cells bind to β2GPI during the atherosclerotic process [14–16,30]. Furthermore, immunization with these autoantigens triggers an immune response leading to the progression of atherosclerosis [2,14,28,31]. A humoral response to β2GPI and hsp in the atherosclerotic plaque may play a role in the pathogenesis of stroke. The production of IgA anti-β2GPI and IgG anti-hsp60/65 antibodies is independently associated with increased risk for stroke [32].

Autoantibodies against malondialdehyde-modified lipoprotein(a) [Lp(a)] were detected in 104 APS patients. This supports the potential role of oxidative processes in atherogenesis [2,33]. APA also induce nitric oxide and superoxide production. Furthermore, direct interference of APA with the antioxidant enzyme paraoxonase also contributes to accelerated atherosclerosis [2,34].

All the above described data support the pathogenic role of APA and other autoantibodies in the development of APS-associated atherogenesis. In contrast, the passive administration of monoclonal antibodies against some phospholipids and LDL antigens protected against atherosclerosis in LDL receptor-deficient mice [2,3,34,35]. This controversy may arise from the fact that different types of autoantibodies, such as "pathogenic" and "protective" may exist, and in some studies these two types of antibodies are assessed together [34]. Therefore, antibodies with different pathogenic roles should be dissected.

2.3. Overlapping patterns in the pathogenesis of APS and atherosclerosis

Endothelial injury caused by several factors including shear stress, viruses, homocysteine, autoantibodies, immune complexes, complement activation, oxidative stress is a key event in atherogenesis [36–39]. As described above, APA can bind to neoepitopes of oxLDL, as well as to oxLDL-β2GPI complexes [28,36]. This promotes enhanced uptake of oxLDL by macrophages via scavenger receptors and the transition of macrophages to foam cells [36].

Endothelial injury then results in endothelial dysfunction and a perpetuating inflammatory response, which leads to the progression of atherosclerosis. This inflammatory response includes increased production of pro-inflammatory cytokines, chemokines and other mediators. There is an increased expression of cell

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adhesion molecules on leukocytes and endothelial cells. The enhanced production of these mediators then stimulate further leukocyte adhesion and recruitment to the vessel wall, as well as the proliferation of monocyte/macrophages, vascular endothelial and smooth muscle cells. Macrophages turn into foam cells leading to the formation of fatty streaks and atheromatous plaques. The production of matrix-degrading proteases and tissue factor by macrophages eventually lead to plaque rupture and thrombus formation [2,3,12,36,40].

2.4. Diagnostic aspects of APS-associated CVD: Imaging and laboratory

Imaging techniques allow the detection of subclinical atherosclerosis by revealing early endothelial dysfunction, abnormalities of circulation or atherosclerotic plaques [2,19]. Common carotid B-mode ultrasound is suitable for the detection of atherosclerotic plaques and for the assessment of common carotid intimal-medial thickness (ccIMT) [2,41]. ccIMT is regarded as an early, sensitive marker for atherosclerosis, whereas endothelial dysfunction precedes manifest atherosclerosis [2,19]. Coronary artery calcification can be assessed by using electron beam computed tomography [42]. Early endothelial dysfunction in APS can be assessed by flow-mediated (FMD) and nitroglycerine-mediated (NMD) vasodilatation of the brachial artery using high-resolution ultrasound [2,19,43].

Unfortunately, only very few such studies have been performed with respect to APS. Early endothelial dysfunction and increased common carotid intimal-medial thickness (ccIMT) have been observed in APS [2]. We reported abnormal FMD and increased ccIMT in 46 patients with primary APS. The FMD in patients (3.4%) was significantly lower than that in sex- and age-matched controls (8%). ccIMT was significantly higher in APS (0.71 mm) in comparison to controls (0.58 mm). This was associated with increased production of von Willebrand antigen in APS [19]. Others found a correlation between aCL IgG antibody levels and ccIMT. These data support the atherogenic role for APA [2,3,44]. Premenopausal women with APS had an increased prevalence of carotid and femoral plaques using ultrasound. This was not associated with APA or any other predictors of atherosclerosis tested including age, lipid levels or cumulative corticosteroid use [2].

Again, there is difference between primary and secondary APS in this context, as higher number and earlier development of carotid plaques were observed in SLE-associated APS in comparison to primary APS. Secondary APS patients also had a higher prevalence of traditional risk factors for CVD [2,25,45]. Therefore the role of APA and/or APS as independent risk factors for atherosclerosis and CVD is difficult to assess as the majority of studies include patients with APS secondary to SLE [2]. Among the few primary APS studies, the prevalence of ccIMT was investigated in 28 patients and 28 age- and sex-matched controls. Significantly increased ccIMT and decreased lumen diameter were found in primary APS compared to controls. APS patients with higher ccIMT exerted a 3-fold higher risk for stroke than those without increased ccIMT [46]. In another study, ccIMT was higher among 20 primary APS patients in comparison to 20 matched controls. Especially patients >40 years old had evidence for atherosclerosis [2].

Regarding *laboratory markers*, it is evident that the determination of APA and LA is necessary to diagnose APS. Furthermore, the assessment of anti-dsDNA and other autoantibodies may confirm an underlying lupus in secondary APS [1]. High sensitive CRP (hs-CRP) is a marker of inflammation and, as described above, the determination of hs-CRP independently predicts CVD, stroke and peripheral artery disease. In a recent cohort of 55 APA positive patients with recent stroke, elevated levels of hs-CRP were associated with an increased rate of recurrent or residual symptoms [47].

2.5. Management of atherosclerosis and CVD in APS

There has been a consensus report on the management of cardiac disease in APS [48]. Atherosclerosis treatment strategies in primary and secondary APS include an aggressive control of all traditional risk factors including hyperlipidemia, hypertension, smoking, obesity, diabetes mellitus should be performed by using both drug treatment and changes in lifestyle [2,48]. There is no solid evidence from randomized, controlled trials indicating the preventative action of any drugs in APS [2,23]. Medications used to prevent atherosclerosis and to treat CVD in APS include antiplatelet agents and anticoagulants, as well as statins, folic acid, B vitamins and, as described later, possibly antimalarial agents [2,48].

Statin therapy significantly reduces the risk of CVD [23,49]. Apart from their beneficial effects on lipid profile, statins reduce serum CRP levels, directly inhibit interferon-γ-induced MHC class II expression and thus suppress T cell-driven autoimmunity [23]. Statins also prevent endothelial dysfunction [49]. Statin therapy should be considered in APS patients, if LDL-C >3.4 mmol/l, or when LDL-C is persistently >2.6 mmol/l even after weight reduction and dietary modifications [48,50].

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Aspirin has been used for a long time to prevent CVD and reduce mortality in the general population [23]. Regarding APS, in a decision analysis model, aspirin intake in 40-year-old lupus patients was estimated to gain 3 months of quality-adjusted survival in APA negative, and 11 months in APA positive individuals [51]. APA positive SLE patients should be prescribed aspirin if there are no contraindications [48,50]. As aspirin treatment has not been shown to add any benefit over warfarin alone, the use of aspirin may not be necessary in warfarin-treated patients [52]. Folic acid and B vitamins may be used liberally [48]. Unfortunately, these data only suggest the potential benefit of the use of such agents in APS, but there is no high-quality clinical evidence in this context.

Anti-inflammatory treatment utilized in APS may be pro- or antiatherogenic [23,36,53]. *Corticosteroids* are atherogenic by unfavorably affecting body fat distribution, blood pressure and glucose metabolism leading to dyslipidemia, hypertension and diabetes mellitus [23,36]. However, other studies were unable to confirm an association between glucocorticoid use and atherosclerosis [23,36]. Controversy arises from the dual action of glucocorticoids, as they are atherogenic, but, on the other hand, also anti-inflammatory [23]. Thus, the patients' own anti-inflammatory and metabolic response to glucocorticoid therapy may influence the individual therapeutic strategy to be used in a single APS patient [2,3,23,36] (Table 1).

In contrast to corticosteroids, *antimalarial drugs*, such as chloroquine and HCQ, may exert evident antiatherogenic properties [23]. In vitro studies suggest that antimalarials may inhibit platelet aggregation and the thrombogenic effects of APA [54,55]. Despite these potential benefits, the antiatherogenic effects of antimalarial drugs need to be clinically confirmed.

3. Other cardiac manifestations in APS

3.1. Valvular disease

Apart from atherosclerosis-induced CVD, valvular involvement including thickening and vegetations is the most common cardiac manifestation in APS [1,6–12,56]. Valvular disease including thickening of the mitral valve cusps and valvular vegetations are more frequently seen in patients with primary APS than in non-APS SLE patients [57]. In SLE, 48% of APA positive patients but only 21% of APA negative patients had valvular involvement [6,8]. In some studies, valvular disease has been associated with higher serum APA levels [6–8] while others found no relationship [58,59]. *Valvular thickening* is the most common abnormality detected by echocardiography. The mitral valve is most commonly involved followed by the aortic valve. Hemodynamic changes may occur: mitral and aortic regurgitation have been observed in 22% and 6% of APS patients, respectively [6,8]. However, most cases are asymptomatic and can only detected by thorough chest auscultation, echocardiography or at autopsy. Altogether 4–6% of SLE and primary APS patients develop severe valvular regurgitation requiring valve replacement in about half of these patents [6–9].

Early reports of the link between APA and SLE-associated *valvular vegetations* date back to the mid 1980s [6,9]. This so-called "Libman–Sacks endocarditis" has been classically described in lupus patients as verrucous endocarditis of valve leaflets, papillary muscles and the mural endocardium [61]. Today the mitral valve is involved most often, followed by the aortic and tricuspid valves. Valvular disease is usually not clinically significant [6,8,62]. Some studies suggest that APA may play an important role in the development of vegetations in Libman–Sacks endocarditis [6,8,9,63]. Studies with two β2GPI-related peptides also mimicking common pathogens suggested that Libman–Sacks endocarditis may have infectious origin [63]. In addition, valvular disease is detected in about one-third of APS patients and valvular thrombus formation may exist in APS [58,59].

Regarding the *pathogenesis* of APA-associated valvular disease, when histological analysis of valve specimens was performed, non-inflammatory lesions were characterized by intravalvular capillary thrombosis, laminar or verrucous superficial thrombosis, vascular proliferation, fibrosis and calcification [6–9]. Positive staining for aCL, human immunoglobulins and for complement was observed in the subendothelial layer of the leaflets and cups [6,64]. Circulating APA may bind to the valvular endothelium leading to endocardial damage, resulting in superficial thrombosis and subendocardial inflammatory infiltration. These events eventually lead to fibrosis and calcification [6,8]. Valvular disease, especially Libman–Sacks endocarditis, may resemble rheumatic fever. Both APS and rheumatic fever include cardiac and central nervous system involvement. There may be a molecular mimicry between pathogens and autoantigens. APS may be associated with streptococcal infection. In addition, a cross-reactivity between antibodies to streptococcal M-protein and APA has been observed [6,65].

A consensus committee recommend anticoagulation in symptomatic valvular disease. Asymptomatic patients

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should be prophylactically treated with aspirin. The administration of corticosteroids in valvular disease is not recommended, however, if there is clinical evidence for inflammatory valvulitis, anti-inflammatory treatment may be introduced [48].

3.2. Other cardiac manifestations

In one study, 10 patients with primary APS and 10 controls underwent echocardiography I order to assess *systolic and diastolic function*. APS patients had decreases in the peak early filling velocity, in the ratio of peak early to peak atrial filling velocities and in the mean deceleration rate of early filling in comparison to healthy matched controls. The left ventricular systolic function appeared to be normal [66].

There have been scattered reports of intracardiac thrombi and myxomas, as well as pulmonary hypertension in APS [10,12,56]. Intensive anticoagulation should be introduced in intracardiac thrombi and pulmonary hypertension [48]. The management of pulmonary hypertension also includes prostaglandins or endothelin antagonists [48]. A case of interauricular communication detected by transesophageal echocardiography has been reported [56]. These rare manifestations could only be diagnosed if thorough examination and diagnostic tests are performed.

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