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Review

Antiphospholipid syndrome and the heart: A case series and literature review

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ABSTRACT

Antiphospholipid syndrome is a rare autoimmune disease characterized by a high tendency of developing thrombotic events. It is diagnosed in the presence of specific laboratory criteria (positivity for lupus anticoagulant, and the presence of anticardiolipin and aβ2GPI antibodies) and clinical criteria such as thrombosis in any district (arterial or venous) and pregnancy morbidity. Being a multisystem disease, the heart is commonly affected by direct (autoimmune mediated action) or indirect (thrombosis) pathological mechanisms. Heart valve lesions are the most frequent manifestations; however, the haemodynamic significance is quite uncommon but when it occurs it may require surgery that further complicates the picture due to the high risk of thrombosis. Coronary arteries and myocardium are also affected leading to ischaemic heart disease and left ventricular dysfunction. Other findings include chronic thromboembolic pulmonary hypertension and accelerated atherosclerosis. The consequences of heart involvement may be significant in overt disease. The treatment of cardiac complications is challenging and requires an in-depth knowledge of the disease.

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1. Introduction

The antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPLs)

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leading to a hypercoagulable state associated with vascular thrombosis and pregnancy loss [1]. Thrombosis mainly occurs in the venous district but arterial thrombosis is also common. Due to the vascular nature, a number of organs are affected, and among these, the cardiovascular system (Table 1).

The term antiphospholipid is a misnomer, because the antibodies itself are directed against plasma proteins, specifically the domain I (DmI) of the β2GPI molecule [2]. The mechanisms by which this interaction causes the cardiac involvement are multiple and not fully understood. Not only are they related to thrombosis [3], but also to immune mediated injury [4]. Valve involvement is the typical example immune mediated damage; however, cardiovascular involvement is multifactorial and thrombosis plays an important part. Both valve abnormalities and coronary artery disease account for more than two-thirds of the cardiac manifestations in APS. This review will deal with a brief excursus on the APS in general, followed by a detailed coverage of cardiovascular presentations of the disease.

2. APS — a brief walk through pathophysiology and laboratory diagnosis

According to the revised classification criteria, APS is diagnosed in the presence of clinical and laboratory criteria [1]. Clinical criteria comprise objectively proven venous or arterial thrombosis and pregnancy morbidity. Laboratory criteria include coagulation tests to detect the presence of Lupus Anticoagulant (LA) and two enzyme-linked immunosorbent assays (ELISA) to measure autoantibodies directed against cardiolipin (aCL ELISA) and β2-Glycoprotein I (aβ2GPI ELISA). To ensure the pathologic antibodies are persistent, positive laboratory tests must be confirmed on two or more occasions at least 12 weeks apart [5].

Pathogenic antibodies are those directed against β2GPI, a plasma protein the physiologic role of which is unknown. Moreover, antibodies against the DmI of the β2GPI molecule have LA activity and are significantly related to thrombosis [2]. The mechanism by which autoantibodies cause thrombosis is not yet clear, but the most accredited theory, the two-hit hypothesis, puts in the centre of the pathogenic mechanism the β2GPI molecule and the antibodies directed against it [6].

Because the laboratory diagnosis is based on three tests, different combinations of these are possible with a different weight on the risk of thrombosis [7]. The association with thrombosis is strong with full positive aPL profile (triple positivity) and weak or absent when a single test is positive [8,9]. A cumulative analysis assessing the prevalence of, and association with thrombosis of aPL profiles, found that triple positivity was associated with thrombosis in 87% of cases while in the other profiles the association was below 50% [10]. Triple positivity confers a higher risk factor for occurrence of events in aPL carriers (i.e. patients with only positive laboratory tests and without clinical manifestations) than does double or single positivity, with an incidence rate of 5.3% per year [11]. These recent findings, should lead the way of simplification and the increase of the diagnostic accuracy in APS thus defining patients at high risk of thrombosis.

Table 1
Cardiovascular manifestations in primary and secondary APS.

	Features
Accelerated atherosclerosis	Atherosclerosis of aorta, carotid, iliofemoral, coronary arteries. Thrombosis of the aorta or axillary, carotid, hepatic, iliofemoral, mesenteric, pancreatic, popliteal, splenic, or subclavian artery
Valve involvement	Mitral valve incompetence (frequent) and stenosis (rare). Valve abnormalities including leaflet thickening, vegetations, nonbacterial thrombotic endocarditis
Myocardial involvement	Ventricular hypertrophy, diastolic and systolic dysfunction, myocarditis, heart failure
Coronary artery disease	Embolization or atherosclerosis, angina, myocardial infarction, microvascular damage
Pulmonary thromboembolism	Pulmonary emboli, pulmonary arterial in situ thrombosis, chronic thromboembolic pulmonary hypertension (CTPH).

3. Valve involvement in APS

3.1. Case presentation 1

A 35-year-old Caucasian female presented to our ambulatory for recurrent episodes of transitory ischaemic attacks (TIAs). Her relevant past medical history included a suspected diagnosis of thrombotic thrombocytopenic purpura (TTP) at the age of nine. APS was diagnosed at the age of 24 after an episode of TIA with facial and right hand paraesthesia, dysphasia, dysarthria, diplopia and visual field defects. Cerebral magnetic resonance revealed several small infarcts in the white matter of the left hemisphere. Three years later she experienced another episode of TIA and laboratory criteria for APS were confirmed (LA, aCL, aβ2GPI positivity). She started anticoagulation therapy. An echocardiogram showed nodularities on the mitral valve. At the age of 32, she had two further recurrences of cerebral ischaemia presenting with amaurosis fugax and dizziness. Laboratory findings revealed a high titre of aβ2GPI IgGs. A transesophageal echocardiogram was performed showing mitral valve involvement and mild mitral regurgitation (Fig. 1).

3.1.1. Valve involvement in APS

APS-related valvulopathy is defined as the echocardiographic detection of valvular regurgitation or stenosis in patients with aPLs in the presence of valvular apparatus involvement. Valvular alterations include valve thickness of more than 3 mm involving the leaflet's proximal or middle portion and/or irregular nodules on the atrial face of the edge of the mitral valve and/or the vascular face of the aortic valve [1]. Almost one third of the patients with primary APS present valve abnormalities [12–14] that are best detected and followed up with imaging techniques like transthoracic and transesophageal echocardiography [15]. In a review [16] of the largest echocardiographic studies, the prevalence of valve involvement as assessed with transthoracic echocardiogram was 32–38% as compared to 0–5% in the controls.

One possible pathologic mechanism is related to micro-injuries in haemodynamically vulnerable sites, such as valves, that expose negative phospholipids on the surface of valve structures or on endothelial cells of intra-valve capillaries [17]. β2GPI adheres to the negative phospholipid surface changing conformation and exposing the DmI to the immune system; the resulting complexes causes cell activation subendocardial inflammatory infiltration and tiny spots of coagulation, valve thickening and rigidity. The histological analysis on valve specimens in patients with APS, revealed that the non-inflammatory lesions were characterized by superficial or intra-valve fibrin deposits, vascular proliferation, laminar or verrucous superficial thrombosis, intra-valve capillary thrombosis, and calcification [18–20]. Microscopy, revealed positive staining for aCL (mainly IgG), immunoglobulin and for complement (C1q, C3c, and C4) all appearing along the surface of the leaflets and cusps as a continuous ribbon-like layer with complement deposits being more granular [21]. On the other hand, control valves from aPL-negative patients and control tissue specimens from APS patients without valve involvement did not demonstrate such deposits [21]. The inflammatory process might be initiated by the deposition of aPL antibodies in the subendothelial layer of the valve [22] leading to valve thickening, and, with time, to valve deformation [23].

Left sided valves are more frequently affected, probably due to higher shear from jet effect and turbulence, with a predilection for mitral with respect to the aortic valve [24–26] especially in secondary APS [27]. Tricuspid valve seems to be seldom affected [12]. Peculiarities of the nodular abnormalities at the coapting site of the leaflets are the focal localization and symmetry [28]. Vegetations may be present in up to 40% of the patients [12], are usually solitary but may be multiple. They are irregular, predominantly thrombotic, but can be inflammatory or mixed, may be mobile or not, and change in appearance, resolve, or