

Cutting-Edge Issues in Coronary Disease and the Primary Antiphospholipid Syndrome

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Abstract Antiphospholipid syndrome (APS) is the most frequent cause of venous and arterial thrombotic events in young patients. The brain arterial tree is primarily affected, but coronary ischemic manifestations are also relatively frequent. Coronary involvement was suggested to be closely related to the accelerated atherosclerosis linked to the underlying disease in APS associated to systemic autoimmune diseases, in particular, systemic lupus erythematosus. However, arterial ischemic events can occur in primary APS—with no other systemic disorders—even in the absence of traditional cardiovascular risk factors and overt atherosclerosis. From a biological point of view, this finding speaks in favor for a pro-coagulant activity of anti-phospholipid antibodies rather than for their role in atherosclerotic plaque formation. On the other hand, the clinical challenge is to avoid the risk to misdiagnose young patients with potentially life-threatening symptoms, such as myocardial infarction (MI). In fact, the occurrence of nonspecific symptoms related to coronary ischemic events is frequently misdiagnosed because of its rarity in young patients. This issue is well illuminated by two cases of MI in young patients reported in the manuscript together with a systematic review of the associations and implications of coronary ischemic events in APS.

Keywords Antiphospholipid syndrome · Arterial thrombosis · Myocardial infarction · Atherosclerosis

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Introduction and Case Reports

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the persistent presence of antiphospholipid antibodies (aPL) and at least one of the following clinical manifestations: venous or arterial thrombosis and recurrent fetal loss. The syndrome occurs in the absence (primary APS (PAPS)) or in association with another systemic autoimmune disease (secondary APS), particularly systemic lupus erythematosus (SLE) [1, 2].

aPL are widely accepted to be responsible for a pro-coagulant condition ending into thrombotic episodes that may be often multiple and recurrent. Arterial thromboses are less frequent than the venous ones and are mainly affecting the vessels in the central nervous system (CNS). However, coronary artery events have been reported in a consistent manner. For example, myocardial infarction (MI) occurs in APS young patients, and it has been also reported as the first manifestation of the syndrome, although such a possibility is not very common. The overall frequency of MI in a cohort of 1,000 European APS patients was found to be 2.8% [3]. The arterial recurrences reported in the recent 5-year follow-up of the same series still showed that CNS events were more frequent but 9 out of the 1,000 patients (0.9%) displayed coronary manifestations [4].

We report and discuss two typical cases and a review of the recent literature on this issue.

Case Report 1

The first case is a 28-year-old man in whom a diagnosis of deep venous thrombosis (DVT) of the superficial femoral and popliteal vessels and symptomatic pulmonary embolisms (PE) was made in the absence of known thrombotic risk factors in 2005. A therapy was started with low

molecular weight heparin (LMWH) followed by warfarin for 6 months. Laboratory tests showed positivity for lupus anticoagulant (LAC) and anti-cardiolipin antibodies (aCL) IgG at medium titer. After an asymptomatic period, oral anticoagulation therapy (OAT) was suspended for unknown reasons. Three years later, he presented a recurrent PE as a consequence of DVT of the left popliteal vein, and OAT was started again. The diagnosis of PAPS was eventually made on the basis of the positivity at medium/high titer for aCL and for anti-beta2-glycoprotein I (β 2GPI) IgG antibodies confirmed 12 weeks after. Because of the onset of tonsillitis and local mucosal bleeding, the patient spontaneously suspended OAT in December 2009. Some days after stopping the therapy, he suffered from chest pain and was referred to the Emergency Department of another Center. Due to a normal physical evaluation and an overt anxious state, he was discharged with the prescription for non steroidal anti-inflammatory drugs and anti-anxiety drugs, and no further clinical and instrumental investigations were made. The following day, the patient was referred again to the Emergency Department because of the symptom persistence; electrocardiography (ECG) showed an evolved ST elevation myocardial infarction (STEMI) of the inferior cardiac wall that was confirmed by elevated creatine phosphokinase MB (CK-MB) plasma levels. Echocardiography showed inferior dyskinesia with unmodified ejection fraction (EF). An emergency percutaneous coronary arteriography was performed, that showed a thrombotic occlusion of the medium trait of the right coronary artery although no signs of atherosclerosis were evident. He was treated with thromboaspiration, coronary angioplasty, and implantation of a metallic stent with contemporary infusion of an anti-platelet monoclonal antibody (abciximab). OAT was restarted. A concomitant *Staphylococcus aureus* mucosal infection was found and treated with an antibiotic therapy based on the antibiogram results. The patient was dismissed on OAT with a PT-international normalized ratio (INR) ranging from 2.5 to 3.5, plus clopidogrel and statin. The recent follow-up showed a well-controlled disease.

Case Report 2

The second case is a female with the diagnosis of antero-lateral MI in 2007, at the age of 28, while taking estrogenic oral pill in the absence of traditional cardiovascular risk factors. She experienced chest pain, irradiated to left shoulder and superior left limb, and was referred to Emergency Department. ECG showed ST elevation in aVL and V4 derivations. Echocardiography showed a limited area of dyskinesia of septum and antero-lateral region of heart, with a normal EF. Thrombolysis was immediately performed, and the patient was treated with LMWH, ticlopidine (because of aspirin allergy), and statin. Coronarography was performed, showing normal coronary arteries and no signs of atherosclerosis.

Laboratory tests showed elevated CK-MB, CPK, LDH; normal PT and aPTT, positive LAC, elevated factor VIII (252% activity), heterozygous MTHFR C677T and factor V G1691A Leiden mutations, normal homocysteinemia and low resistance to active protein C. IgG aCL resulted low positive in repeated tests. No signs or symptoms for systemic autoimmune disease were reported. The diagnosis of PAPS with coronary ischemic manifestation was made, and she is now doing well under OAT with a 2.5 INR target, anti-platelet and statin therapy.

Coronary Ischemic Events and aPL

The occurrence of MI in APS has been known since the description of the syndrome (reviewed in [5]).

A study published more than 15 years ago reported a low prevalence of acute MI in APS, ranging from 4% to 7%, and usually in association with SLE [6]. As stated before, this finding was confirmed in large epidemiological studies more recently [3, 4].

Evidence for a strong relationship between thrombophilic disorders and MI or stroke exists for APS only. For all the other thrombophilic conditions, none or only weak associations have been reported [7]. In contrast, high levels of aCL were found to represent an independent risk factor for MI in a prospective cohort of middle-aged men [8]. Beta2 glycoprotein I (β 2GPI)-dependent aPL IgG was also a risk factor for stroke and MI in men [9]. There is a correlation between serum levels of aCL and anti- β 2GPI antibodies and the incidence and severity of acute coronary syndrome, MI, and stroke [10]. In addition, the prevalence of aCL in patients with MI was found to be around 10%. This value increased up to 21% in patients with MI younger than 45 years and with persistent aCL titers [11, 12].

Coexisting inherited or acquired factors for thrombosis are not exclusion criteria for APS classification. However, APS patients should be recognized and stratified according to the presence or the absence of additional risk factors for thrombosis, such as age (>55 in men and >65 in women), presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index $\geq 30 \text{ kg m}^{-2}$, microalbuminuria, estimated GFR $< 60 \text{ mL min}^{-1}$, inherited thrombophilias, oral contraceptives, nephritic syndrome, malignancy, immobilization, and surgery) [1]. The lack of such a stratification would explain the discrepant results published in the literature regarding the association between aPL and MI when unselected patient populations were investigated [5].

The confounding effect of atherosclerosis is strong in middle-aged and elderly patients, but not in MI occurring in

the young. In fact, MI in young patients is usually associated with less coronary atherosclerosis and normal or nearly normal coronary angiograms as in the cases we reported [13–19]. In addition, MI is rare in men younger than 40–45 years accounting for only 2–6% of all incident cases and very rare in young women [13–19]. In this regard, case 1 is quite representative since the young age of the patient and the characteristic of the symptoms led to a delay in the diagnosis with risk for complications.

Young males are less frequently affected by APS than young women. This finding may explain why there are more reports on the association between aPL and MI in young women. For example, the presence of high levels of IgG aCL and anti- β 2GPI antibodies was significantly higher in young premenopausal women with MI independently of other risk factors, including the degree of coronary artery stenosis [20]. Moreover, in a study performed in a cohort of young women aged 18–49 years with a first MI or ischemic stroke, LAC was associated with an increased risk of MI (odds ratio (OR), 5.3) and ischemic stroke (OR, 43.1). Increased concentrations of anti- β 2GPI antibodies were also associated with an increased risk of ischemic stroke (OR, 2.3), but neither aCL nor anti-prothrombin antibodies alone increased the risk of MI or ischemic stroke. Finally, there were no indications that the presence of more than one positive result in aPL assays could affect the risk of MI or ischemic stroke [21].

In contrast with the previous findings, anti- β 2GPI IgA antibodies were found elevated in unstable angina and MI with STEMI in young men [22]. Moreover, anti- β 2GPI IgA antibodies have been also reported to be associated with an increased risk of thromboembolic events in SLE [23].

Despite therapy, patients with APS have a significant burden of morbidity and mortality [24]. MI was found to account for 19% of all causes of death according to a recent European epidemiologic study performed in 1,000 APS patients during a 5-year follow-up period [4].

Patients with primary APS were reported to display the so-called syndrome X, a condition characterized by angina-like chest pain with positive response to stress testing and normal coronary angiograms in the absence of traditional risk factors for heart disease [25].

Coronary Artery Disease: aPL Pathogenic Role

aPL are not only diagnostic but also pathogenic autoantibodies [26]. There is evidence from epidemiological studies as well as from in vitro and in vivo experimental models that aPL may be responsible for venous and arterial thrombosis. Different, and not necessarily alternative, pathogenic mechanisms have been reported. Among them, the interaction between aPL and their antigenic target (mainly β 2GPI) on

the surface membranes of cells involved in the coagulation cascade—namely, platelets, monocytes, and endothelial cells—is nowadays largely accepted [27, 28].

However, aPL are necessary but not sufficient by themselves to trigger clotting, and an additional second hit has been suggested. In this regard, inflammatory innate immunity responses play a major role, and inflammation secondary to infectious agents has been suggested to be the most frequent second hit [29]. Case 1 is illuminating in this aspect since the acute coronary event was consequent to the combination of an infectious episode of the upper airways and the spontaneous OAT stopping by the patient, making his whole thrombotic risk profile quite high. In the same way, we can speculate that in case 2 the patient developed the arterial thrombotic event because of the concomitant contraceptive estrogen therapy in association with other risk factors (i.e., factor V G1691A Leiden mutation).

CNS and/or coronary artery disease are hallmarks of atherosclerosis. On the other hand, aPL are associated with both CNS and coronary thromboses [10, 30, 31]. The consequent question is whether or not aPL are also responsible for an increased atherosclerosis.

There is large evidence that aPL may display pro-atherogenic effects in several in vitro and in vivo experimental models (reviewed in [32]). However, studies carried out in PAPS patients in order to confirm the presence of an accelerated atherosclerosis did not draw definite conclusions. In fact, there are discrepant results regarding the number of atherosclerotic plaques in the carotid arteries as well as in the intima media thickness, while most of the authors found an abnormal arterial stiffness [33–44]. In addition, large studies in SLE patients found no association between aPL and the accelerated atherosclerotic process that is characteristic of this disease [45–49]. A comparable lack of association between aCL and anti- β 2GPI antibodies and coronary atherosclerosis was recently reported in a cohort of patients suffering from rheumatic diseases who underwent coronary bypass [50].

Our case reports and others published in the literature [13–19] support the fact that no coronary atherosclerotic lesions are usually found in young APS patients with MI. Accordingly, the association between aPL and MI in young premenopausal women was independent on coronary atherosclerosis [20].

It is difficult to explain this discrepancy. In the absence of atherosclerotic lesions or in the presence of mild vessel lesions, the thrombogenic potential of aPL may contribute to the acute coronary artery occlusion. In addition, β 2GPI-dependent aPL may activate endothelium and monocytes by favoring a more inflammatory local environment that may increase the instability of the plaques, their rupture, and eventually atherothrombosis (Fig. 1).

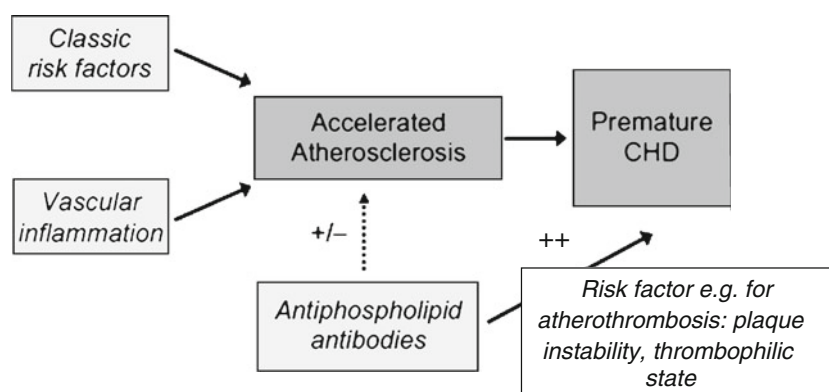


Fig. 1 Role of anti-phospholipid antibodies in coronary heart disease (CHD). There is no sound evidence from epidemiological studies that aPL are associated to an accelerated atherosclerosis. On the other hand, the experimental findings support a role for aPL in inducing endothelial perturbation and monocyte activation in the atherosclerotic

plaque, favoring its instability and rupture. In addition, aPL are responsible for a thrombophilic state that eventually favors atherothrombosis. Altogether, these mechanisms contribute to the increased risk for premature CHD in aPL-positive patients

Alternatively, aPL may be produced as a consequence of the vascular insult, being just an epiphenomenon. However, this does not seem to be the case since aPL were undetectable in unselected males and females of older age who were investigated close to the acute event, and blood samples from premenopausal women with MI and aPL were collected during a period of time spanning 3 to 12 months after acute MI [20].

Therapy

There is consensus in treating patients with APS and first venous thrombosis with oral anticoagulation to a target INR of 2.0–3.0. A recent systematic review recommended a target INR >3.0 also in the group of patients with APS and arterial thrombosis [51].

Successful thrombolysis in hypercoagulable states has been reported in the literature [52]. In spasm-induced MI such as by cocaine, thrombolysis should be given if there is no prompt resolution in symptoms and ST segment changes

after adequate doses of vasodilators (nitrates and calcium channel blockers). There are also reports of successful percutaneous transluminal coronary angioplasty with or without coronary artery stenting in APS [53].

Ideally, young patients with MI should undergo primary angioplasty as thrombolysis is likely harmful if the patient has a coronary artery dissection [54]. Nevertheless, thrombolysis has been reported to be effective in stabilizing coronary artery blood flow in a series of patients, and large clots were also successfully aspirated as in our case [55].

As far as other therapeutic interventions are concerned, there are currently no data supporting the concomitant use of additional therapies such as aspirin for patients on OAT with an INR >3.0 [56]. Specific studies regarding the additional use of hydroxychloroquine are still lacking in patients with primary APS who have experienced at least an arterial thrombotic event [57]. Similarly, the ability of statins to counteract the aPL effects in experimental models suggested their use in APS, but specific clinical trials are still lacking [57]. In conclusion, there is no evidence to recommend other treatments in addition to appropriate OAT

Table 1 Cornerstones for APS diagnosis and treatment in patients with acute coronary syndrome

- The diagnosis of APS should be taken into consideration in patients with acute coronary syndrome when:
 - the patient's age is young (<55 in men and <65 in women),
 - coronary arteries display normal angiography,
 - there are no other traditional cardiovascular risk factors,
 - there is no history of drug abuse,
 - there are no other causes of heart diseases (i.e., congenital abnormalities).
- Treatment of acute coronary thrombosis is not different in aPL-positive and aPL-negative patients.
- Anticoagulation with a target INR >3.0 has been recently suggested in APS patients and arterial thrombosis.
- The persistent presence of medium-high aPL titers is a risk for arterial recurrences, and anticoagulation should be continued.
- The elimination or reduction of other cardiovascular risk factors is mandatory.
- There are no data to recommend additional treatments (i.e., aspirin, hydroxychloroquine, or statins).

for secondary prevention of arterial thrombotic events in patients with primary APS.

Conclusions

The involvement of the coronary arterial vessels in APS is not frequent, and it occurs usually in young patients with no traditional risk factors for cardiovascular disease. aPL-associated acute coronary disease is closely related to the thrombogenic effect of the autoantibodies. A prompt diagnosis is mandatory to avoid complication. Although no large clinical studies are published in the literature, there is a general agreement on some guideline points (Table 1).

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