Antiphospholipid-mediated thrombosis: interplay between type of antibodies and localisation of lung, and cardiovascular incidences in primary antiphospholipid syndrome

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Abstract

Objective

The aim of this study was to analyse prevalence and type of pulmonary manifestations in patients with primary antiphospholipid syndrome (PAPS), their association to antiphospholipid antibody (aPL) type and localisation of peripheral vascular thrombosis, and possible relationship to existing cardiac manifestations.

Methods

Our cross-sectional study comprised 318 PAPS patients, enrolled in the study as the Serbian APS Registry. aPL analysis included detection of aCL (IgG/IgM), β_2GPI (IgG/IgM) and LA, served to evaluate associations with cardiac and pulmonary manifestations.

Results

In patients with pulmonary embolism and infarction, we observed significant prevalence of myocardial infarction (p=0.044), unstable angina pectoris (p=0.001), venous thrombosis (p=0.007) arterial thrombosis (p=0.0001), deep venous thrombosis of the low extremities (p=0.008), and superficial thrombophlebitis of the low extremities (p=0.023). Patients with primary pulmonary hypertension were more prone to unstable angina pectoris (p=0.009), while patients with secondary pulmonary hypertension were more prone to venous thrombosis (p=0.04) and deep venous thrombosis of the inferior extremities (p=0.04). Patients with pulmonary microthrombosis were more prone to unstable angina pectoris (p=0.026), arterial thrombosis (p=0.002), venous thrombosis (p=0.001), deep venous thrombosis of the inferior extremities (p=0.001), and superficial thrombophlebitis of the inferior extremities (p=0.001). The presence of LA was significantly higher in patients with pulmonary embolism and infarction (p=0.001), secondary pulmonary hypertension (p=0.032), and pulmonary microthrombosis (p=0.001).

Conclusion

Presence of LA was associated with distinct pulmonary manifestations in the Serbian APS cohort. There is a strong link between some cardiovascular and pulmonary manifestations in PAPS patients, suggesting complexity and evolutionary nature of PAPS.

Key words

antiphospholipid syndrome, antiphospholipid antibody type, cardiovascular and pulmonary manifestations

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Introduction

Antiphospholipid syndrome (APS), or Hughes syndrome, represents a systemic autoimmune disorder characterised by arterial and/or venous thrombosis, multiple and recurrent foetal losses, accompanied by elevated levels of antiphospholipid antibodies (aPL), such as lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and aß$_2$GPI antibodies (1-3). This syndrome is considered primary (PAPS) if unassociated with any other connective tissue disease or secondary (SAPS) if it appears in association with other autoimmune disorders, mainly systemic lupus erythematosus (SLE) (4-13). An unusual variant of APS, termed catastrophic antiphospholipid syndrome (CAPS), is marked by a high mortality rate of approximately 50%, despite seemingly adequate therapy (14-16).

A variety of pulmonary manifestations, including pulmonary embolism/infarction, pulmonary hypertension, adult respiratory distress syndrome (ARDS), fibrosing alveolitis, intra-alveolar haemorrhage, primary thrombosis of lung vessels, both major and minor, and pulmonary capillaritis may be associated with this syndrome in both primary and secondary forms (17, 18). Furthermore, postpartum syndrome and fibrosing alveolitis can also be associated with APS, although less commonly (18). Many of these manifestations may occur simultaneously in the same patient. This spectrum of pulmonary disorders in patients with antiphospholipid antibodies is referred to as the *antiphospholipid lung syndrome* (19).

APS is also associated with a variety of cardiac abnormalities. In the most recent consensus conference in Sydney, Australia, valvular heart disease was accepted as an integral part of the antiphospholipid syndrome, although not considered as a diagnostic criterion (20). However, the extent to which they influence valvular, atherosclerotic and myocardial disease is uncertain.

The aim of our cross-sectional study of PAPS patients was to investigate associations between pulmonary and cardiac features observed at the time of diagnosis. The results presented here are derived from the Serbian APS Registry.

Materials and methods

Patients

This study included 318 patients (Caucasians) with primary APS, 184 female and 134 male, mean age 47.9±10.4 years (Table I). Patients were included consecutively from the year 2000, and enrolled in the study as the Serbian APS Registry. All analysed patients met the 2006 revised Sydney criteria for APS, meaning that all patients were diagnosed with APS not only by the presence of antiphospholipid antibodies but also according to other diagnostic criteria (arterial and/or venous thrombosis, multiple and recurrent foetal losses) (20). All patients were under treatment according to accepted international protocols (21).

The study fulfills the ethical guidelines of the most recent declaration of Helsinki (Edinburgh, 2000) and has received approval from the local ethics committee.

Diagnosis of cardiac manifestations

Transthoracic echocardiography was performed using a standardised protocol that included M-mode, 2-dimensional (2-D) and Doppler recordings. Valvular lesions were classified using valvular thickness and/or dysfunction (without presence of vegetations) and pseudoinfective endocarditis. Pseudoinfective (Libman Sacks) endocarditis (PIE) was defined as precipitation of thrombus, not containing bacteria, on the valve cusps. The modified Duke criteria utilising pathologic and clinical criteria were used to differentiate between true infective endocarditis and Libman-Sacks endocarditis (22). Transesophageal echocardiographic (TEE) study was performed in all patients with vegetations in order to confirm the diagnosis and establish the severity of disease. Chronic cardiomyopathy, primary or secondary, was defined as presence of a progressive disorder that impairs the structure and/or function of the muscles in the ventricles of the heart. Data regarding history of previous myocardial infarction, episodes of acute heart failure and unstable angina were collected from patients' medical records. Myocardial infarction (MI) and unstable angina (UA) were diagnosed by integrating typical

symptoms with electrocardiogram ST-T changes, and with the crucial differentiation made by Troponin I levels. Elevated levels suggested myocardial necrosis (MI), whereas normal levels corresponded to unstable angina (UA). Acute decompensated heart failure was defined as a worsening of the symptoms, typically shortness of breath (dyspnea), oedema and fatigue, in a patient with existing heart disease.

Diagnosis of pulmonary manifestations

Diagnosis of pulmonary manifestations was established by clinical findings (chest pain, dyspnea, tachypnea, cough, haemoptysis, and others), followed by chest radiography, echocardiography, radionuclide lung scanning, laboratory analysis (D-dimer test), multislice computed tomography, ventilation perfusion scintigraphy, and MDCT pulmonary angiography. All tests were performed in patients with suspected pulmonary thrombosis or embolism as the first presentation of PAPS.

Diagnosis of peripheral thrombosis was established by Doppler ultrasound.

Laboratory tests

All patients were evaluated for the presence of antiphospholipid antibodies with routine biochemistry tests and by complete blood cell counts. Lupus anticoagulant (LA) was based on the initial use of phospholipid-depleted or platelet-depleted coagulation tests, such as kaolin clotting time (KCT), dilute Russell's venom viper time (DRVVT), tissue thromboplastin inhibition test, and diluted activated partial thromboplastin time. LA tests were not performed while patients were receiving anticoagulant therapy. Anti-cardiolipin (aCL: IgG/IgM) and anti-$\beta_2$glycoprotein I (aβ_2GPI: IgG/IgM) antibodies were measured by an enzyme-linked immunosorbent assay (ELISA, Binding Site) and expressed in GPL or phospholipids (MPL) units (GPL-U and MPL-U). Also, we followed revised laboratory criteria for APS on two or more occasions at least 12 weeks apart (20).

Statistics

All statistics were calculated using the SPSS 16.0 statistical package. Results are presented as the mean standard deviation (SD), except for frequencies that are expressed as percentages. Comparisons between groups were made by means of Mann-Whitney U-tests for continuous variables, and by chi-square analysis for categorical variables. *p*-values less than 0.05 (2-tailed) were considered significant.

Table I. Demographic and clinical characteristics of the patient group.

Variable		Frequency (%)
Age	<45	52 (16.35)
	45-50	179 (56.29)
	50-55	49 (15.40)
	>55	38 (11.96)
Sex	Female	184 (57.86)
	Male	134 (42.14)
Pulmonary manifestations	Pulmonary embolism and infarction	47 (14.78)
	Primary pulmonary hypertension	5 (1.58)
	Secondary pulmonary hypertension	19 (5.98)
	Major pulmonary arterial thrombosis	8 (2.52)
	Pulmonary microthrombosis	47 (14.78)
	Acute respiratory distress syndrome	6 (1.89)
Cardiac manifestations	Intracardiac thrombus	5 (1.57)
	Valve thickening and dysfunction	10 (3.14)
	Pseudoinfective endocarditis	23 (7.23)
	Myocardial infarction	18 (5.67)
	Unstable angina pectoris	43 (13.52)
	Chronic cardiomyopathy	21 (6.60)
	Acute heart failure	3 (0.94)

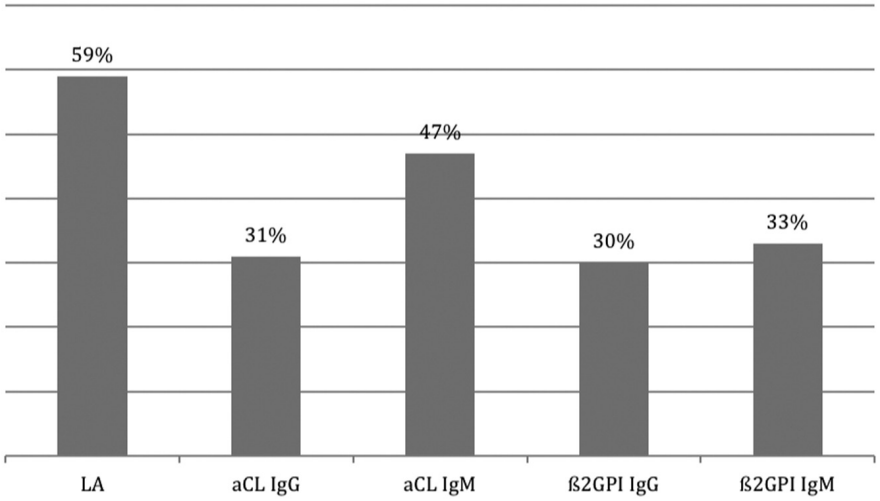

Fig. 1. Distribution of aPL in PAPS patients.
aCL: anticardiolipin antibodies; β_2GPI: anti- β_2 glycoprotein I antibodies; LA: lupus anticoagulant; aPL: antiphospholipid antibodies.

Results

Distribution of aPL in PAPS patients is presented in Figure 1. The presence of LA was significantly higher in patients with pulmonary embolism and infarction (p=0.001), in secondary pulmonary hypertension (p=0.032), and in patients with pulmonary microthrombosis (p=0.001) (Table II).

Significant correlations between several pulmonary manifestations and laboratory findings have been obsserved. Increased levels of CRP was significantly more frequent in patients with pulmonary embolism and infarction (p=0.01), in patients with pulmonary microthrombosis (p=0.004),) and in patients with ARDS (p=0.015). Increased levels of CH50 and major pulmonary arterial thrombosis were also detected (p=0.015) (Table II).

We also analysed the relationship be-

Table II. Correlations between several pulmonary manifestations and aPL, CRP and CH50 in PAPS patients.

Pulmonary manifestations	PAPS patients n. (%) positive	negative	*p*-value
		LA	
Pulmonary embolism and infarction	30 (76.9)	2 (15.4)	*p*=0.001
Secondary pulmonary hypertension	11 (84.6)	2 (16.7)	*p*=0.032
Pulmonary microthrombosis	11 (25)	33 (75)	*p*=0.001
		aCL-IgG	
Pulmonary embolism and infarction	14 (35.9)	25 (64.1)	*p*=0.650
Secondary pulmonary hypertension	3 (23.1)	10 (76.9)	*p*=0.450
Pulmonary microthrombosis	15 (34.1)	29 (65.9)	*p*=0.833
		aCL-IgM	
Pulmonary embolism and infarction	19 (48.7)	20 (51.3)	*p*=0.767
Secondary pulmonary hypertension	8 (61.5)	5 (38.5)	*p*=0.435
Pulmonary microthrombosis	20 (45.5)	24 (54.5)	*p*=0.433
		aβeta$_2$GPI-IgG	
Pulmonary embolism and infarction	12 (30.8)	27 (69.2)	*p*=0.783
Secondary pulmonary hypertension	3 (23.1)	10 (76.9)	*p*=0,450
Pulmonary microthrombosis	11 (25)	33 (75)	*p*=0,241
		aβeta$_2$GPI -IgM	
Pulmonary embolism and infarction	16 (41)	23 (59)	*p*=0.897
Secondary pulmonary hypertension	5 (38.5)	8 (61.5)	*p*=0.978
Pulmonary microthrombosis	18 (40.9)	26 (59.1)	*p*=0.887
		CRP	
Pulmonary embolism and infarction	25 (64.1)	14 (35.9)	*p*=0.01
Pulmonary microthrombosis	28 (63.6)	16 (36.4)	*p*=0.004
ARDS	4 (66.7)	2 (33.3)	*p*=0.015
		CH50	
Major pulmonary arterial thrombosis	1 (16.7)	5 (83.3)	*p*=0.015

tween pulmonary and cardiac manifestations, as well as localisation of peripheral thrombosis; results are presented in Table III. Patients who had pulmonary embolism and infarction also had significant prevalence of MI (*p*=0.044), UA (*p*=0.001), venous thrombosis (*p*=0.007), arterial thrombosis (*p*=0.0001), deep venous thrombosis of the low extremities (*p*=0.008), and superficial thrombophlebitis of the low extremities (*p*=0.023).

Patients with primary pulmonary hypertension were more prone to UA (*p*=0.009), whereas secondary pulmonary hypertension was significantly related to venous thrombosis (*p*=0.04) and deep venous thrombosis of the inferior extremities (*p*=0.04). On the other hand, patients with microthrombosis were more prone to UA (*p*=0.026), arterial thrombosis (*p*=0.002), venous thrombosis (*p*=0.001), deep venous thrombosis of the inferior extremities (*p*=0.001), and superficial thrombophlebitis of the inferior extremities (*p*=0.001) (Table III).

Discussion

Prevalence and type of pulmonary and cardiac manifestations, their mutual association, and their association with aPL type and with localisation of peripheral thrombosis were analysed in 318 PAPS patients.

The present study indicates that LA is associated with increased probability of specific pulmonary manifestations. The observation that LA presence is associated with pulmonary embolism and infarction (*p*=0.001), secondary pulmonary hypertension and pulmonary microthrombosis supports the notion of a causative relationship between circulating antibodies and such manifestations. This finding is in accordance with our study performed on a smaller cohort of 214 PAPS patients (18).

Chronic inflammation as a crucial part of antiphopholipid syndrome leads to established prothrombotic conditions (23). aPL activate endothelial cells and platelets, and contribute to thrombosis and tissue injury. Sciascia *et al*. recently demonstrated that APS patients had significantly higher levels of CRP, also related to triple postitivity of aPL (24). In our study, increased levels of CRP were significantly more frequent in patients with pulmonary embolism and infarction (*p*=0.01), with pulmonary microthrombosis (0.004), and with ARDS (0.015).

Activation of the complement cascade is an important mechanism for antiphospholipid antibody-mediated thrombosis (25). Increased levels of CH50 and major pulmonary arterial thrombosis were also detected in our PAPS patients.

In our study, patients who had pulmonary embolism and infarction were more likely to develop myocardial infarction (*p*=0.044) and unstable angina pectoris (*p*=0.001), whereas PAPS patients with primary pulmonary hypertension were more prone to unstable angina pectoris (*p*=0.009). Our study confirmed the expected relationship between pulmonary embolism and primary pulmonary hypertension with peripheral vascular thrombosis, both arterial and venous.

The concept of enhanced atherosclerosis in antiphospholipid syndrome is well known (4, 9, 26, 27). Coronary heart disease is the leading cause for morbidity and mortality in patients with connective tissue diseases (28, 29). This condition has not been solely explained with higher incidence of traditional risk factors, but with chronic inflammation and its destructive impact on lipid particles. Moreover, in recent publications, aPL have been indicated to represent nontraditional risk factors for coronary and peripheral artery disease (30-31). This standpoint has been confirmed in our study.

Conclusion

The presence of lupus anticoagulant is associated with distinct pulmonary manifestations, suggesting its predictive role. The increased levels of CRP were significantly more frequent in patients with pulmonary embolism and infarction, with pulmonary microthrombosis and with ARDS.

There is a strong link between several cardiopulmonary and the peripheral thrombosis manifestations in APS patients, suggesting the evolutionary nature of APS.

Table III. Association between pulmonary and cardiac manifestations, and localisation of peripheral vascular thrombosis in PAPS

PAPS patients n=318		Myocardial infarction n. (%)			Unstable angina pectoris n. (%)			Venous thrombosis n. (%)		
		not present	present	*p*	not present	present	*p*	not present	present	*p*
Pulmonary embolism and infarction	not present	272 (84.47)	11 (3.42)	0.044	265 (82.30)	18 (5.59)	0.001	213 (66.15)	69 (21.43)	0.007
	present	34 (10.56)	5 (1.55)		30 (9.32)	9 (2.79)		20 (6.23)	19 (5.91)	
Primary pulmonary hypertension	not present	303 (94.10)	16 (4.97)	0.691	294 (91.30)	25 (7.76)	0.009	232 (72.72)	86 (26.71)	0.44
	present	3 (0.93)	0 (0)		1 (0.31)	2 (0.62)		1 (0.31)	2 (0.62)	
Secondary pulmonary hypertension	not present	294 (91.30)	15 (4.65)	0.645	285 (88.50)	24 (7.45)	0.06	228 (70.80)	80 (24.84)	0.04
	present	12 (3.73)	1 (0.31)		10 (3.10)	3 (0.93)		5 (1.55)	8 (2.48)	
Pulmonary microthrombosis	not present	267 (82.92)	11 (3.42)	0.03	25 (80.43)	19 (5.90)	0.026	211 (65.52)	66 (20.50)	0.001
	present	39 (12.11)	5 (1.55)		36 (11.18)	8 (2.48)		22 (6.83)	22 (6.83)	
PAPS patients		Arterial thrombosis (n, %)			Deep venous thrombosis of the low extremities (n, %)			Superficial thrombophlebitis of the low extremities (n, %)		
		not present	present	*p*	not present	present	*p*	not present	present	*p*
Pulmonary embolism and infarction	not present	179 (55.76)	103 (32.09)	0.0001	249 (77.33)	33 (10.25)	0.008	232 (72.05)	50 (15.53)	0.023
	present	11 (3.42)	28 (8.69)		28 (8.70)	11 (3.42)		25 (7.76)	14 (4.35)	
Primary pulmonary hypertension	not present	188 (58.38)	130 (40.49)	0.953	27 (85.40)	43 (13.35)	0.001	255 (79.19)	63 (19.57)	0.832
	present	2 (0.62)	1 (0.31)		2 (0.62)	1 (0.31)		2 (0.62)	1 (0.31)	
Secondary pulmonary hypertension	not present	182 (56.52)	126 (39.13)	0.911	271 (84.16)	37 (11.49)	0.04	249 (77.33)	59 (18.32)	0.215
	present	8 (2.48)	5 (1.55)		6 (1.86)	7 (2.17)		8 (2.48)	5 (1.55)	
Pulmonary microthrombosis	not present	174 (54.04)	103 (31.99)	0.002	247 (76.70)	30 (9.32)	0.001	231 (71.74)	46 (14.28)	0.001
	present	16 (4.97)	28 (8.70)		30 (9.32)	14 (4.35)		26 (8.07)	18 (5.59)	

PAPS: primary antiphospholipid syndrome; n: number of patients.

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