Association between Cardiac Manifestations and Antiphospholipid Antibody Type and Level in a Cohort of Serbian Patients with Primary and Secondary Antiphospholipid Syndrome

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ABSTRACT: **Background:** Antiphospholipid syndrome (APS, also known as Hughes syndrome) may manifest itself as a primary or secondary disease, most commonly with systemic lupus erythemathosus (SLE) and various cardiac manifestations.
Objectives: To report the first results from the Serbian National Cohort study, which was started in January 2000.
Methods: Our study included 374 patients: 260 primary APS patients and 114 SLE patients with secondary APS. Antiphospholipid antibody (aPL) analysis included detection of anticardiolipin antibodies (aCL) (immunoglobulin G and M), β2-glycoprotein 1, and lupus anticoagulant. Echocardiography was performed in all patients, and data on myocardial infarction, unstable angina, chronic cardiomyopathy and acute heart failure were collected.
Results: There were 30.7% secondary APS patients and 9.2% primary APS patients with pseudo-infective endocarditis ($P = 0.0001$). Cardiac manifestations were observed in 28.7% of patients who had more than one type of antibody (category I), in 24.1% with category IIa, in 23.1% with category IIb, and in 27.8% with category IIc ($P = 0.78$). Age was confirmed as a significant factor for cardiac manifestations in APS patients (52.3 and 43.3 years, respectively, $P = 0.001$). aCL IgG and IgM positivity was related to valvular changes in all APS patients and high levels of those antibodies increased the risk of these manifestations.
Conclusions: Patients with secondary APS had a higher prevalence of valvular lesions, and some aPL types and high levels of aPL were risk factors for specific cardiac manifestations in APS patients.

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KEY WORDS: antiphospholipid antibodies (aPL), systemic lupus erythematosus (SLE), cardiac manifestations, national cohort study

Antiphospholipid antibodies are a family of autoantibodies that recognize various combinations of phospholipids and phospholipid-binding proteins [1]. These antibodies are present in a small percentage of the population, occurring more commonly in patients with connective tissue disorders such as systemic lupus erythematosus [2]. In the absence of an underlying connective tissue disorder, persistent presence of these antibodies is strongly associated with recurrent fetal losses and arterial or venous thrombosis (primary antiphospholipid syndrome), whereas their presence in another connective tissue disease is defined as secondary APS.

APS is associated with a variety of cardiac abnormalities. Indeed, in the most recent consensus conference in Sydney, Australia, valvular heart disease was recognized as an integral part of the syndrome [3]. Additionally, some small studies have suggested an association with carotid artery intima-media thickness, a manifestation of early atherosclerosis [4], and abnormal left ventricular diastolic filling [5]. Other recent studies also discussed autonomic dysfunction as a manifestation of autoimmune diseases [6]. In patients with SLE, aPL are associated with arterial and venous thrombosis and recurrent fetal loss; however, the extent to which they influence valvular [7], atherosclerotic [8] and myocardial [9] disease is either controversial or uncertain.

The objective of the present study was to analyze and report the incidence of the various cardiac manifestations in patients with APS recruited from the Serbian National Cohort study as well as investigate their possible relationship with certain type or level of aPL. Differences between patients with primary and secondary APS were also analyzed.

PATIENTS AND METHODS

This study includes 374 (Caucasian) APS patients; 260 were primary APS patients (198 females and 62 males, average age

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APS = antiphospholipid syndrome
SLE = systemic lupus erythematosus
aPL = antiphospholipid antibodies

45.60 ± 13.33 years), and 114 had APS associated with SLE (100 females and 14 males, average age 46.29 ± 15.01 years). Patients with APS were included consecutively from the year 2000 in a prospective manner and enrolled into the Serbian National Cohort Study. We investigated the association between cardiac manifestations and aPL type and level. All patients with SLE met the American College of Rheumatology classification criteria [10]. Disease activity was assessed at the time of enrollment in the study using the SLEDAI score [11]. All patients met the 2006 revised Sydney criteria for APS, i.e., 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 fetal losses). Although we perform aPL analysis routinely in SLE patients, these patients were not included in the study if they did not meet the 2006 revised Sydney criteria for APS, even if they had a positive aPL finding.

The study fulfills the ethical guidelines of the most recent declaration of Helsinki (Edinburgh, 2000) and received approval from the local ethics committee. All patients were examined by a team comprising a rheumatologist, neurologist, neuro-ophthalmologist, psychiatrist, pulmonologist, cardiologist, radiologist, and hematologist.

DIAGNOSIS OF CARDIAC MANIFESTATIONS

Transthoracic echocardiography was performed using a standardized protocol that included M-mode, two-dimensional, and Doppler recordings. Valvular lesions were classified by valvular thickness and/or dysfunction (without presence of vegetations) and pseudo-infective endocarditis. Pseudo-infective (Libman-Sacks) endocarditis was defined as the precipitation of thrombus, not containing bacteria, on the valve cusps. The modified Duke criteria utilizing pathologic and clinical criteria differentiated between true infective endocarditis and Libman-Sacks endocarditis [12]. Transesophageal echocardiographic 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 the presence of a progressive disorder that impairs the structure and/or function of the muscles in the ventricles of the heart. Data on the history of previous myocardial infarction, episodes of acute heart failure and unstable angina were collected from patients' medical records. The diagnoses of myocardial infarction and unstable angina were made by integrating the typical symptoms with electrocardiogram ST-T changes and with the crucial differentiation rendered by troponin I levels: elevated suggested myocardial necrosis, i.e., establishment of a myocardial infarction diagnosis whereas normal levels classified patients as unstable angina. Acute decompensated heart failure was defined as a worsening of symptoms – typically shortness of breath (dyspnea), edema and fatigue – in a patient with existing heart disease.

PATIENT SELECTION

All diagnostic procedures were carried out at the time APS was diagnosed. Patients are assessed at 2 to 6 monthly intervals according to standard protocol, which includes a complete history, physical examination and laboratory tests. Exceptional diagnostic methods and additional tests were performed on the advice of relevant specialists.

LABORATORY TESTS

All patients were evaluated for the presence of antiphospholipid antibodies, accompanied by routine biochemistry and complete blood cell counts. Lupus anticoagulant was based on the initial use of phospholipid-depleted or platelet-depleted coagulation tests, such as kaolin clotting time, diluted Russell's venom viper time, the tissue thromboplastin inhibition test, and diluted activated partial thromboplastin time [13]. The LA tests were not performed while the patients were receiving anticoagulant therapy. Anticardiolipin (IgG/IgM) and anti-β2 glycoprotein I (IgG/IgM) antibodies were measured by an enzyme-linked immunosorbent assay and expressed in GPL or phospholipid (MPL) units. For better standardization, frozen samples were sent to the Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel. The level range was considered as low (11–40 PLU/ml), medium (41–99 PLU/ml), or high (> 100 PLU/ml). Also, we followed revised laboratory criteria for APS on two or more occasions at least 12 weeks apart [14].

APS patients were classified into the following categories: category I, the presence of two or more laboratory criteria in combination; category IIa, where lupus anticoagulant is present alone; category IIb, where anticardiolipin antibodies are present alone; and category IIc, where anti-β2GPI are present alone [15].

STATISTICAL ANALYSIS

The chi-square and Fisher's exact test were applied as appropriate to analyze statistically significant differences between categorical variables. Two-sided P values < 0.05 were considered significant. All analyses were performed with the SPSS statistical package Version 15.0 (SPSS, Chicago, IL, USA).

RESULTS

PREVALENCE AND TYPE OF CARDIAC MANIFESTATIONS

Several kinds of cardiac manifestations were diagnosed in 101 patients (27.0%) in both groups and were statistically more frequent in the secondary APS group (P = 0.002, odds ratio 2.11, 95% confidence interval 1.308–3.403). The most frequent manifestations were unstable angina pectoris (9.6%) in the primary APS group and valvular manifestations in the secondary

LA = lupus anticoagulant
β2GPI = β2-glycoprotein 1

Table 1. Prevalence of cardiac manifestations in patients with primary and secondary APS

Cardiac manifestation	Patients with primary APS (n=260)	Patients with secondary APS (n=114)	*P* value
Intracardiac thrombus	5 (1.9)	0 (0.0)	0.160
Valve thickening and dysfunction	9 (3.5)	7 (6.1)	0.182 OR 1.83, CI 0.662–5.026
Pseudo-infective endocarditis	24 (9.2)	35 (30.7)	0.0001 OR 4.36, CI 2.443–7.770
Myocardial infarction	15 (5.8)	5 (4.4)	0.394 OR 0.75, CI 0.266–2.113
Unstable angina pectoris	25 (9.6)	11 (9.6)	0.564 OR 1.00, CI 0.476–2.117
Chronic cardiomyopathy	17 (6.5)	7 (6.1)	0.544 OR 0.94, CI 0.377-2.321
Acute decompensated heart failure	5 (1.9)	4 (3.5)	0.280 OR 1.86, CI 0.489-7.038
Overall cardiac manifestations	58 (22.3)	43(37.7%)	0.002 OR 2.11, CI 1.308-3.403

Values are presented as number (%)

Table 2. Distribution of aPL in PAPS and SLE groups

	Patients with primary APS (n=260)	Patients with secondary APS (n=114)	*P* value
aPL			
aCL IgG	93 (35.8)	67 (58.8)	0.0001
aCL IgM	140 (53.8)	72 (63.2)	0.059
β2GPI IgG	83 (31.9)	48 (42.1)	0.038
β2GPI IgM	97 (37.3)	50 (43.9)	0.140
LA	133 (51.2)	56 (49.1)	0.402
Categories			
I	157 (60.4)	80 (70.2)	
IIa	47 (18.1)	7 (6.1)	0.024
IIb	43 (16.5)	22 (19.3)	
IIc	13 (5.0)	5 (4.4)	

Values are presented as number (%)

LA = lupus anticoagulant, aCL = anticardiolipin antibody, β2GPI = anti-β2 glycoprotein I antibody

Category I = more than one laboratory criterion is present (any combination), category IIa = LA present alone, category IIb = aCL present alone, category IIc = anti-β2GPI present alone

APS group, especially PIE (30.7%) which was observed significantly more often in secondary than primary APS patients (*P* = 0.0001, OR 4.36, 95%CI 2.44–7.77) [Table 1].

DISTRIBUTION OF PATIENTS ACCORDING TO ANTIBODY CATEGORIES

The distribution of aPL in the primary APS and SLE groups revealed a highly significant difference in the presence of aCL IgG and IgM, and β2GPI IgG antibodies, as presented in Table 2. More than one type of antibody (category I) was present in 237 patients (64.5%) (category I), of whom 157 (60.4%) were primary APS patients and 80 (70.2%) were SLE patients. Lupus anticoagulant was present alone (category IIa) in 47 patients (18.1%) with primary APS and only 7 (6.1%) with SLE. aCL antibodies were present alone in 43 (16.5%) with primary APS and 22 (19.3%) with SLE (category IIb). Anti-β2GPI antibodies were present alone in 13 (5.0%) with primary APS and 5 (4.4%) with SLE (category IIc). The difference between groups regarding aPL categories was statistically significant (*P* = 0.024) [Table 2].

ASSOCIATION OF CARDIAC MANIFESTATIONS WITH APL TYPE AND LEVEL

The prevalence of various cardiac manifestations was similar in all antibody category groups. Overall, cardiac manifestations were observed in 41 patients (17.3%) with category I, in 5 (9.3%) with category IIa, in 10 (15.4%) with category IIb, and in only 3 (16.72%) with category IIc (*P* = 0.540). A significant association was observed between the presence of aCL IgG and the presence of PIE (*P* = 0.009, OR 2.04, CI 1.161–3.584) and valve thickening and dysfunction (*P* = 0.030, OR 3.09, CI 1.050–9.067) as well as overall cardiac manifestations (*P* = 0.026, OR 1.62, CI 1.024–2.567). LA positivity was significantly associated with the presence of myocardial infarction (*P* = 0.010, OR 3.96, CI 0.523–2.072). Regarding the levels of various types of antibodies, a statistically significant correlation was observed between episodes of acute heart failure and aCL IgG levels, since the highest prevalence of this cardiac manifestation was related to high levels of this aPL type (*P* = 0.001). A similar observation was made regarding aCL IgG levels, PIE presence (*P* = 0.027) and valve thickening and dysfunction (*P* = 0.019). Patients in our study group with high levels of anti-β2GPI IgM were prone to PIE (*P* = 0.044) [Tables 3 and 4].

AGE AS A RISK FACTOR FOR CARDIAC MANIFESTATIONS

Older age was a significant risk factor for the development of cardiac manifestations in patients with APS. The median age of patients with all types of cardiac manifestations was 52.3 years, compared to 43.3 years in patients without cardiac events (*P* = 0.0001). Similarly, the median age of patients with a history of myocardial infarction was 55.6 years, compared to 45.3 years for patients without this manifestation (*P* = 0.001). Age was a significant risk factor for unstable angina episodes (58.8 and 44.4 years, respectively, *P* = 0.0001), chronic cardiomyopathy (57.4 and 45.0 years, respectively, *P* = 0.0001), heart failure episodes (58.9 and 45.5 years, respectively, *P* = 0.004), PIE (50.1 and 45.0 years, respectively, *P* = 0.009), and valvular thickening and dysfunction (52.3 and 45.5 years, respectively, *P* = 0.035).

CARDIAC MANIFESTATIONS IN PRIMARY APS

Cardiac manifestations were observed in 58 primary APS patients (22.3%). The prevalence of different types of cardiac manifestations was similar in primary APS patients [Table 1],

PIE = pseudo-infective endocarditis
OR = odds ratio
CI = confidence interval

Table 3. Distribution of aCL IgG/IgM levels in PAPS and SLE patients with cardiac manifestations

	Level of aCL IgG				Level of aCL IgM			
	Low	Medium	High		Low	Medium	High	
	N (%)	N (%)	N (%)	*P*	N (%)	N (%)	N (%)	*P*
PAPS								
Overall cardiac manifestations	14 (22.6)	5 (29.4)	4 (28.6)	0.804	20 (19.4)	2 (8.0)	5 (38.5)	0.095
Intracardiac thrombus	1 (1.6)	0 (0.0)	2 (14.3)	0.007	4 (3.9)	0 (0.0)	0 (0.0)	0.310
Valve thickening and dysfunction	4 (6.5)	0 (0.0)	1 (7.1)	0.333	5 (4.9)	1 (4.0)	1 (7.7)	0.485
Pseudo-infective endocarditis	5 (8.1)	3 (17.6)	2 (14.3)	0.550	9 (8.7)	1 (4.0)	3 (23.1)	0.281
Myocardial infarction	4 (6.5)	1 (5.9)	2 (14.3)	0.529	5 (4.9)	0 (0.0)	1 (7.7)	0.479
Unstable angina pectoris	6 (9.7)	3 (17.6)	1 (7.1)	0.697	11 (10.7)	1 (4.0)	1 (7.7)	0.771
Chronic cardiomyopathy	6 (9.7)	1 (5.9)	2 (14.3)	0.359	9 (8.7)	1 (4.0)	0 (0.0)	0.558
Acute decompensated heart failure	0 (0.0)	0 (0.0)	2 (14.3)	0.005	2 (1.9)	0 (0.0)	0 (0.0)	0.808
Secondary APS								
Overall cardiac manifestations	17 (41.5)	2 (18.2)	7 (53.8)	0.300	18 (39.1)	8 (44.4)	4 (50.0)	0.633
Valve thickening and dysfunction	2 (4.9)	1 (9.1)	3 (23.1)	0.042	2 (4.3)	1 (5.6)	0 (0.0)	0.654
Pseudo-infective endocarditis	14 (34.1)	2 (18.2)	7 (53.8)	0.158	15 (32.6)	6 (33.3)	4 (50.0)	0.480
Myocardial infarction	2 (4.9)	1 (9.1)	1 (7.7)	0.553	2 (4.3)	1 (5.6)	0 (0.0)	0.932
Unstable angina pectoris	6 (9.7)	3 (17.6)	1 (7.1)	0.697	4 (8.7)	2 (11.1)	0 (0.0)	0.755
Chronic cardiomyopathy	4 (9.8)	0 (0.0)	1 (7.7)	0.559	1 (2.2)	2 (11.1)	0 (0.0)	0.336
Acute decompensated heart failure	1 (2.4)	0 (0.0)	2 (15.4)	0.099	0 (0.0)	1 (5.6)	0 (0.0)	0.281

Table 4. Distribution of anti-β2GPI-IgG/IgM levels in PAPS and SLE patients with cardiac manifestations

	β2GPI-IgG				β2GPI-IgGM			
	Low	Medium	High		Low	Medium	High	
	N (%)	N (%)	N (%)	*P*	N (%)	N (%)	N (%)	*P*
Primary APS								
Overall cardiac manifestations	18 (25.0)	5 (45.5)	3 (25.0)	0.207	16 (23.9)	2 (28.6)	4 (36.4)	0.612
Intracardiac thrombus	2 (2.8)	0 (0.0)	0 (0.0)	0.864	2 (3.0)	0 (0.0)	1 (9.1)	0.251
Valve thickening and dysfunction	3 (4.3)	1 (9.1)	0 (0.0)	0.662	2 (3.0)	0 (0.0)	2 (18.2)	0.055
Pseudo-infective endocarditis	7 (9.7)	2 (18.2)	2 (16.7)	0.527	5 (7.5)	1 (14.3)	4 (36.4)	0.015
Myocardial infarction	3 (4.3)	3 (27.3)	1 (8.3)	0.018	3 (4.5)	1 (14.3)	0 (0.0)	0.594
Unstable angina pectoris	9 (12.5)	3 (27.3)	0 (0.0)	0.090	6 (9.0)	1 (14.3)	1 (9.1)	0.975
Chronic cardiomyopathy	7 (9.7)	1 (9.1)	0 (0.0)	0.481	5 (7.5)	0 (0.0)	1 (9.1)	0.869
Acute decompensated heart failure	2 (2.8)	0 (0.0)	0 (0.0)	0.864	1 (1.5)	0 (0.0)	0 (0.0)	0.910
Secondary APS								
Overall cardiac manifestations	13 (36.1)	2 (50.0)	4 (57.1)	0.677	14 (48.3)	2 (25.0)	2 (33.3)	0.539
Valve thickening and dysfunction	2 (5.6)	0 (0.0)	2 (28.6)	0.082	4 (13.8)	1 (12.5)	0 (0.0)	0.154
Pseudo-infective endocarditis	11 (30.6)	2 (50.0)	4 (57.1)	0.325	14 (48.3)	2 (25.0)	2 (33.3)	0.118
Myocardial infarction	2 (5.6)	0 (0.0)	1 (14.3)	0.522	2 (6.9)	0 (0.0)	0 (0.0)	0.781
Unstable angina pectoris	1 (2.8)	0 (0.0)	0 (0.0)	0.153	5 (17.2)	0 (0.0)	0 (0.0)	0.317
Chronic cardiomyopathy	2 (5.6)	0 (0.0)	0 (0.0)	0.815	4 (13.8)	0 (0.0)	0 (0.0)	0.229
Acute decompensated heart failure	1 (2.8)	0 (0.0)	0 (0.0)	0.887	1 (3.4)	0 (0.0)	0 (0.0)	0.893

and the most frequent manifestations in these patients were ischemic disease (history of myocardial infarction or unstable angina). The prevalence of most cardiac manifestations was not significantly associated with aPL type and level, except in the LA-positive primary APS patients where prevalence of myocardial infarction was highly statistically related to this type of aPL ($P = 0.004$, OR 6.78, CI 1.50–30.64). There was no association between the number of aPL present and cardiac manifestations in this group of patients. Regarding aPL levels, an association was found between high levels of anti-β2GPI IgG and myocardial infarction ($P = 0.018$) as well as between high levels of anti-β2GPI IgM and PIE ($P = 0.015$). High levels of aCL IgM were related to heart failure ($P = 0.005$), whereas high levels of aCL IgG were related to intracardiac thrombus ($P = 0.007$). Age was a significant risk factor for occurrence of overall cardiac manifestations in primary APS patients (median age 53.7 years and 43.3 years respectively, $P = 0.0001$). Unstable angina pectoris was found more often in patients older than 55 years (22.4% compared to 8.4% in the age category 35–55 years, $P = 0.0001$). Similar findings were established regarding chronic cardiomyopathy ($P = 0.005$), heart failure episodes ($P = 0.007$), and valve thickening and dysfunction ($P = 0.031$).

CARDIAC MANIFESTATIONS IN SLE

Cardiac manifestations were observed in 43 SLE patients (37.7%). The most frequent manifestations were valvular

abnormalities. PIE was present in 35 SLE patients (30.7%) and was observed more often in patients with positive aCL IgM antibodies ($P = 0.036$, OR 4.41, CI 0.94–20.60), whereas valve thickening and dysfunction was related to anti-β2GPI IgM positivity in SLE patients ($P = 0.027$, OR 8.60, CI 1.0–73.9). The relationship between the number of aPL present and cardiac manifestations in different categories of SLE patients was not established. Valve thickening and dysfunction were related to high levels of aCL IgG ($P = 0.042$).

All types of cardiac manifestations were observed more often in older SLE patients (median age 51.0 and 43.4 years respectively, $P = 0.008$), but only regarding chronic cardiomyopathy was a relationship with different age groups established ($P = 0.008$). The activity of SLE (SLEDAI) was significantly associated with the prevalence of cardiac manifestations. The median SLEDAI score was 8.5 in patients without cardiac manifestations and 12.5 in patients with ($P = 0.03$).

DISCUSSION

The prevalence and type of cardiac manifestations in association with aPL type and level were analyzed in 374 patients with primary and secondary antiphospholipid syndrome. All patients were enrolled in the Serbian National Cohort Study and we report here some of the first results of this project. The present study indicates that certain types and levels of aPL are associated with increased probability of specific cardiac manifestations. The observation that IgG anticardiolipin levels are significantly higher in patients with valvular dysfunction supports the notion of a causative relationship between circulating antibodies and such lesions. Although valvulopathies [9,16] have been described in the majority of patients with SLE at autopsy, clinically significant valvular heart disease is much less common, 1% to 18% [17]. Similar valvular lesions are seen in patients with primary APS, suggesting that aPL plays a role in the pathogenesis of valvular heart disease in SLE [18].

Previous echocardiography studies have shown conflicting results regarding the role of aPL in valvular disease in SLE. Nihoyannopoulos et al. [19] showed that 50% of SLE patients with very high levels of aCL (> 100 IU) had valvular disease, compared with 37% with lower aCL levels (9–100 IU) and 14% without aCL. In their study of 132 lupus patients, Khamashta et al. [20] reported that of those with LA or aCL positivity at any level, 16% had mitral vegetations and 38% had mitral regurgitation, as compared to 1.2% and 12%, respectively, in patients without aPL. Roldan and colleagues [21] used TEE to diagnose valvular abnormalities in 22 SLE patients with aPL and 32 patients without aPL. They established a high prevalence of aCL IgG and aCL IgM in these patients, using much lower levels of aCL than in the present study.

TEE = transesophageal echocardiography

In our study the prevalence of valvular lesions was observed in APS patients with higher levels of aPL, especially in those with high levels of aCL IgG. Differences among these studies probably relate to variably small sample sizes, different definitions of valvular disease and aCL positivity, and selection and ascertainment biases. In particular, the use of TEE may result in a greater detection of minor non-specific valvular thickening, compared to transthoracic echocardiography used in our study. Therefore, although SLE patients with aPL and patients without aPL had a similar prevalence of any valvular abnormality detected by TEE, discrete valvular masses, probably comparable with nodules or Libman-Sacks lesions described in other studies [22], were seen in 41% of patients with aPL and in 25% of those without.

Some previous studies also found a close association between clinical manifestations of APS and β2GPI antibodies. Moreover, Cabiedes et al. [23] showed that clinical manifestations of APS in patients with SLE associate more strongly with β2GPI antibodies than with other aPL. In our study the presence of valve thickening and dysfunction was related to anti-β2GPI IgM positivity in SLE patients.

Our study confirmed that older age is an important risk factor for cardiac events. The median age of patients with cardiac manifestations was 52.3 years, compared to 43.3 years in patients without cardiac involvement. Patients over 55 years old were at a higher risk for the majority of cardiac manifestations except for pseudo-infective endocarditis and intracardiac thrombus. A similar observation was confirmed in primary APS and SLE patients separately.

In our study we confirm prior results that valvular lesions occur more commonly in patients with SLE-associated secondary APS, compared to primary APS patients. Interestingly, an association between aPL and rheumatic heart disease has been suggested by some studies but was not subsequently confirmed by others [24].

Therefore, there appears to be a poorly understood predisposition for mitral valve damage involving aPL in a number of immune-mediated conditions. It is possible that the increase in valvular abnormalities in aPL-positive patients is at least partly due to lesser use of steroids in this group, which is consistent with autopsy findings. The use of transthoracic rather than transesophageal echocardiography to detect valvular lesions probably attenuated their real frequency; however, the use of transthoracic echocardiography in our study allowed the inclusion of a large study population without the selection bias inherent in patients agreeing to an invasive procedure.

Recent studies have confirmed that SLE is independently associated with accelerated atherosclerosis [25]. In our study, patients with primary APS more often presented with coronary artery disease, although without statistical significance, possibly related to the very small sample size analyzed.

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Capsule

RNA viruses can hijack vertebrate microRNAs to suppress innate immunity

Currently, there is little evidence for a notable role of the vertebrate microRNA (miRNA) system in the pathogenesis of RNA viruses. This is primarily attributed to the ease with which these viruses mutate to disrupt recognition and growth suppression by host miRNAs. Trobaugh et al. report that the hematopoietic cell-specific miRNA miR-142-3p potently restricts the replication of the mosquito-borne North American eastern equine encephalitis virus in myeloid-lineage cells by binding to sites in the 3' non-translated region of its RNA genome. However, by limiting myeloid cell tropism and consequent innate immunity induction, this restriction directly promotes neurologic disease manifestations characteristic of eastern equine encephalitis virus infection in humans. Furthermore, the region containing the miR-142-3p binding sites is essential for efficient virus infection of mosquito vectors. We propose that RNA viruses can adapt to use antiviral properties of vertebrate miRNAs to limit replication in particular cell types and that this restriction can lead to exacerbation of disease severity.

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"He who asks is a fool for five minutes, but he who does not ask remains a fool forever"

Chinese proverb