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ORIGINAL ARTICLE

Echocardiographic findings in asymptomatic systemic lupus erythematosus patients

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Abstract The aim of this study is to use transthoracic echocardiographic (TTE) imaging methods to identify cardiac dysfunction in asymptomatic systemic lupus erythematosus (SLE) patients and to determine the association between echocardiographic findings and serology. This is a prospective cross-sectional study where 50 patients with confirmed diagnoses of SLE were recruited from rheumatology outpatient clinics. Clinical and serological evaluation to confirm the diagnosis of lupus was done in all patients. Fifty SLE patients, 46 (92%) females and 4 (8%) males, were recruited. Anti-double-stranded DNA (Anti-dsDNA), anticardiolipin, lupus anticoagulant, and anti-β2-glycoproteins were positive in 52.1, 32.6, 13.3, and 15.6%, respectively. Transthoracic echocardiogram revealed mitral regurgitation in 16 patients (32%), pericardial effusion in16 patients (32%), aortic regurgitation in five patients (10%), and tricuspid regurgitation in 10 patients (20%). Eleven patients had left ventricular hypertrophy (22%), and eight patients had ventricular systolic dysfunction (16%). Only four patients had ventricular diastolic dysfunction (8%). A significant association between mitral and tricuspid valve regurgitation and positive anti-dsDNA ($p < 0.018$, $p < 0.006$, respectively) was found. Positive anticardiolipin antibodies, lupus anticoagulant, and anti-β 2 glycoprotein antibodies were also associated with mitral valve regurgitation (p values 0.044, 0.006, and 0.023), respectively. Active disease assessed by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was found to be associated with increased risk of mitral valvular leaflet thickening (p value 0.028). Performing regular transthoracic echocardiogram in asymptomatic SLE patients is important for early detection and appropriate treatment of cardiac lesions. Clinically quiescent but serologically active disease and presence of antiphospholipid antibodies were associated with structural heart abnormalities.

Keywords Antiphospholipid syndrome (APS); anti-double-stranded DNA (dsDNA) · Echocardiogram · Systemic lupus erythematosus (SLE); valve

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by presence of autoantibodies directed against different structures; therefore, tissue damage may result from deposition of immune complexes and antigens in various organs including the heart, lungs, kidneys, brain, skin, serous membrane, peripheral nerves, and blood components. SLE is a worldwide disease, with prevalence of 15 to 50/100,000 individuals, while in Saudi Arabia, prevalence was estimated to be 19.28 per 100,000 population [1] and symptoms usually appear between the second and third decades [2]. Autoimmune process in SLE can cause myocarditis, pericarditis, endocarditis, valvular lesions, and defect in the conduction system. The most frequent valvular lesions reported in SLE patients were valve regurgitations with predilection to involve mitral and aortic valves [3]. Indeed, adverse effect of corticosteroid was also found to be another cause for cardiac disease in SLE. Cardiovascular system involvement in SLE might be associated with disease severity and activity [4]. Cardiac involvement as an initial manifestation of SLE is rare;

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however, in more than 50%of cases, the cardiac involvement is associated with significant morbidity and mortality rates [5].

Antiphospholipid syndrome (APS) also can affect the cardiovascular system and many of the cardiopulmonary manifestations of SLE are recognized in APS [4, 6, 7].Valvular lesions were the most common reported cardiac manifestations in APS [8]. Some studies showed that high levels of anticardiolipin antibodies were strongly associated with cardiac abnormalities in SLE and other lupus-like syndromes [9]. Hypertension (HTN), diabetes mellitus (DM), lipid disorders, corticosteroid therapy, and coronary vasculitis are considered risk factors for atherosclerosis and vessel wall damage [10].

The aim of this study is to detect cardiac structural abnormalities by transthoracic echocardiography (TTE) and determine the association between these abnormalities and serological markers among clinically asymptomatic patients with SLE.

Patients and methods

This is a prospective cross-sectional study in which we included a total 50 SLE patients, age more than 12 years with a confirmed diagnosis of SLE based on the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for diagnosis of SLE [11] who are clinically inactive (asymptomatic) after obtaining a detailed history. Patients with clinically active lupus (symptomatic) and patients with rheumatic or congenital heart diseases were excluded. Data on clinical manifestations and laboratory findings at the time of presentation were obtained from the medical records of outpatient clinics at the King Fahad Medical City, Riyadh, Saudi Arabia, between October 2015 and April 2016.

Demographic data were analyzed along with history of comorbidities, drugs history including prednisolone, mycophenolate mofetil, cyclophosphamide, hydroxychloroquine, azathioprine, and other agents such as rituximab. Laboratory evaluations included complete blood counts (CBC), urinalysis, anti nuclear antibodies (ANA) detected by indirect immunofluorescence, anti-dsDNA antibodies measured by a standardized enzyme-linked immunosorbent assay (ELISA), and serum complement (C3 and C4) levels were done. Antiphospholipid antibodies (aPL) (lupus anticoagulant, positive screening and confirmation to document the phospholipid dependence of the inhibitor) (IgG&IgM anticardiolipins, anti–β2-glycoprotein I measured by ELISA) were reviewed in all patients to evaluate its associations with TTE findings. TTE was performed during the same time by an experienced echocardiographer, who had no knowledge about the patients' status.

The following parameters were assessed by TTE: left ventricle diastolic and systolic functions, ejection fraction, myocardial regional wall motion abnormalities, pulmonary arterial pressure, pericardial effusion, and cardiac valve status. Ethical approval for the current study was obtained from the ethics committee at King Fahad Medical City. All participants were enrolled in the study after signing a written informed consent.

Statistical analysis

All data was entered and analyzed through statistical package SPSS version 22. Categorical variables were presented as numbers and percentages whereas continuous variables were expressed as median, range, and Mean ± S.D. Chi-square/ Fisher's exact test was conducted according to whether the cell-expected frequency is smaller than 5 and it was used to determine the significant relationship among categorical variables. p value of less than 0.05 was considered as statistically significant.

Results

Fifty patients with SLE, 46 (92%) females and 4 (8%) males, were recruited. The mean duration of the disease at the time of examination ranged from 4 to 120 months (53.6 ± 35.9). In terms of comorbidities, nine patients had HTN and three patients had DM but none of them had ischemic heart disease. Forty-eight patients (96%) were on hydroxychloroquine, and 46 patients (92%) were on prednisolone. Immunosuppressive treatments included azathioprine in 20 (40%) patients, mycophenolate mofetil in 20 (40%), cyclophosphamide in 11 (22%), rituximab in seven (14%), methotrexate in four (8%), belimumab in one (2%), cyclosporine in one (2%), and tacrolimus in one (2%). Based on SLEDAI score, 44% of patients have inactive disease and 56% have mild-moderate disease activity (≥1 but ≤10).

The presence of autoantibodies (ANA, anti-dsDNA, anticardiolipin, lupus anticoagulant, and anti-β2-glycoprotein) and the low concentrations of complement C3 and C4 components are shown in Table 1.

Echocardiographic examinations revealed mitral valve regurgitation in 16 patients (32%), mitral leaflet thickness in four patients (8%), and mitral calcification nodule in three patients (6%). Pericardial effusion was present in 16 patients (32%). Eleven (68.75%) had mild and five (31.25%) moderate effusion. None of our patients with pericardial effusion had clinical features of pericarditis. Increased anti-dsDNA, low C3 levels, and thrombocytopenia are the main abnormalities detected in this group (SLEDAI 4-10).

Aortic valves regurgitations were detected in five patients (10%) while aortic leaflet thickness in five (10%) and aortic valve calcification nodule in three (6%) patients. Tricuspid valve regurgitations were observed in10 patients (20%). Stenotic lesions were not found in our population. Left ventricular hypertrophy was found in 11 patients (22%). Eight

Table 1 Basic characteristics of SLE patients ($n = 50$)

Sociodemographic characteristics			serology	
		n (%)		*n* (%)
Age (year)	12–20	8 (16.0)	ANA	40 (81.0)
	21–30	21 (42.0)	Anti-dsDNA (at the time of echo)	25 (52.0)
	31–40	9 (18.0)	Anti-SM	9 (18.0)
	41–50	8 (16.0)	Anti-RO (SSA)	6 (12.0)
	51–60	3 (6.0)	Anti-LA (SSB)	2 (4.0)
	>60	1 (2.0)	Antiphospholipid antibodies	15 (30.0)
Gender	Female	46 (92.0)		
	Male	4 (8.0)	Anticardiolipin	15 (30.0)
Duration of the disease (month)	Mean ± SD (min, max)	53.6 ± 35.9 (4, 120)	Lupus anticoagulants	6 (12.0)
			Anti-β2-glycoprotein	7 (14.0)
Associated comorbidity	No any	37 (74.0)	C3 (low)	30 (60.0)
	One	10 (20.0)		
	Two	3 (6.0)		
	More than two	0 (.0)	C4 (low)	13 (26.0)
Comorbidity type	DM	3 (6.0)		
	HTN	9 (18.0)		
	IHD	0 (.0)		

patients (16%) found to have ventricular systolic dysfunction while only four patients (8%) had left ventricular diastolic dysfunction. TTE showed wall motion abnormality in six patients (12%) (Table 2).

Significant association between mitral and tricuspid valve regurgitations and positive anti-dsDNA ($p < 0.018$, $p < 0.006$, respectively), were found (Table 3). Our study also revealed significant association between mitral valve regurgitation and anticardiolipin antibodies, lupus anticoagulant, and anti-β2-glycoprotein (p values 0.044, 0.006, and 0.023, respectively) (Table 4). However, no association was found between aortic valves abnormalities (regurgitation/nodules/leaflet thickness) and anti-dsDNA or aPL positivity. A significant association between SLEDAI scores and mitral valve leaflet thickening (p value 0.028) was found. There was no association between SLEDAI scores and mitral valve nodules (p value 0.658) as well as with aortic valve leaflet thickness and nodules (p value 0.603, p 0.131, respectively).

In this study, anti-β2-glycoprotein antibodies were found to be associated with elevated pulmonary arterial systolic pressure (p value 0.034) (Table 4). Moreover, lupus anticoagulant was associated with low ejection fraction (p value 0.029) (Table 4). Furthermore, no association was encountered between heart valves abnormalities and other parameters such as age, gender, immunosuppressive medications, C3 and C4 levels, HTN, and DM (Table 3).

Among the 15 patients who had positive aPL, four were diagnosed with APS. Mitral, tricuspid, and aortic valve regurgitations were detected in four (36.4%), one (9.1%), and two (18.2%), respectively, of patients with aPL. Of patients with APS, three (75%) had mitral regurgitation and two (50%) had tricuspid valve regurgitations but none with aortic valve abnormalities. Pericardial effusions were detected in three (27.3%) patients with aPL and three (75%) patients with APS. Data analysis did not reveal any statistical significance between this subgroup of SLE patients which is likely due to small numbers of patients with APS.

Discussion

SLE is an autoimmune disease with genetic and environmental background, characterized by multi-organ involvement. Early mortality occurs because of infections and disease activity, whereas late mortality is mostly associated with cardiovascular involvement [12].

Anti-double-stranded DNA antibodies (anti-dsDNA) are present in almost half of our SLE patients, but none has any clinical activities which indicate a serologically active, but clinically quiescent disease is not uncommon. Our current study revealed significant association between mitral and tricuspid valves regurgitation and positive anti-dsDNA antibodies ($p < 0.018$, $p < 0.006$), respectively, which is similar to what was described before by the SPECT study [13, 14]. In this study, mitral valve regurgitation was found in 32% of patients which is almost consistent with De Godoy et al. study who found mitral valve regurgitation in 34.6% of patients [15]. During SLE

Table 2 Echocardiographic findings of SLE patient

Echocardiography		
		n (%)
Mitral valve abnormalities		16 (32.0)
Mitral valve stenosis		0 (.0)
Mitral leaflet thickness	Normal	46 (92.0%)
	Abnormal	4 (8.0%)
Mitral calcification nodule	Normal	47 (94.0%)
	Abnormal	3 (6.0%)
Mitral valve regurgitation	Mild	6 (37.5)
	Moderate	5 (31.3)
	Severe	5 (31.3)
Pericardial effusion	Mild	11(68.75)
	Moderate	5 (31.25)
Aortic valve abnormalities		5 (10.2)
Aortic valve stenosis		0 (.0)
Aortic leaflet thickness	Normal	45 (90.0%)
	Abnormal	4 (8.0%)
Aortic valve calcification nodule	Normal	47 (94.0%)
	Abnormal	3 (6.0%)
Aortic valve regurgitation	Mild	4 (80.0)
	Moderate	1 (20.0)
	Severe	0 (.0)
Tricuspid valve abnormalities		10 (20.4)
Tricuspid valve stenosis		0 (.0)
Tricuspid valve regurgitation	Mild	4 (44.4)
	Moderate	5 (55.6)
	Severe	0 (.0)
Left ventricular hypertrophy		11 (22.4)
Ventricular systolic dysfunction		8 (16.3)
Ejection fraction	<30	3 (6.1)
	31–40	2 (4.1)
	41–50	3 (6.1)
	51–60	21 (42.9)
	>60	20 (40.8)
Ventricular diastolic dysfunction		4 (8.2)
SPAP		7 (14.3)
SPAP (mmHg)	31–40	5 (71.4)
	41–50	1 (14.3)
	>50	1 (14.3)

activity, patients may have experienced subclinical myocarditis which may result in a slight enlargement of the heart chambers. Indeed, left ventricular hypertrophy (LVH) in patients with SLE might be due to arterial hypertension (HTN) or the effects of corticosteroids [16].

In our study, 22% patients had LVH. Similarly, Ong et al. reported 20% of SLE patients were found to have LVH [17]. In the present study, systolic and diastolic left ventricular (LV) dysfunction was found in 16 and 8% of patients, respectively. On the other hand, De Godoy et al., reported that LV diastolic dysfunction in 11.5% and LV systolic dysfunction in 3.8% of patients [15]. These discrepancies could be explained by small number of patient in their study in comparison to our study.

Our study showed that regional LV hypokinesia occurs in 3% and global LV hypokinesia in 3% which are almost similar to what was reported previously. De Godoy et al. reported regional LV hypokinesia in 3.8% and global hypokinesia in 3.8% of patients [15]. Similarly, Leung et al. reported LV wall motion abnormality in 4% [18]. Pericardial effusion was found to be one of the commonest cardiac abnormalities in SLE. In this study, pericardial effusion was found in 32% of patients. Previously, Hameed et al. reported pericardial effusion in 57% of patients [19]. This difference can be explained by the protective effects of corticosteroids, as most of our patients were on prednisolone as well as our inclusion criteria where we excluded symptomatic individuals. Our study revealed significant association between mitral valve regurgitation and anticardiolipin antibodies, lupus anticoagulant, and anti-β2-glycoprotein (p values 0.044, 0.006, and 0.023), respectively. Our findings were in line with a study conducted by a Spanish group which revealed that severe valvular regurgitations were significantly associated with the presence of high levels of IgG anticardiolipin antibodies [20]. Of note, both primary and secondary APS were associated with valvular lesions [8].Valvular lesions in patients with positive aPL are defined by the presence of valve lesions with/without moderate to severe valve dysfunction discovered by transthoracic (TTE) or transesophageal (TEE) echocardiography which include localized leaflet thickening in the proximal or middle portions, irregular nodules on the mitral valve and/or the aortic valve, and valve thickness of more than 3 mm [21]. Recently, a meta-analysis showed a threefold increased risk for valvular lesions in SLE patients with aPL compared with those without aPL [3].The possible pathogenic role of aPL for valvular lesions could be explained by promoting thrombus formation causing valve thickening and fibrosis. Moreover, aPL and complements may form immune complexes that deposited in subendothelial valve areas resulting in overexpression of endothelial activation markers and subsequent valvular damage [22].

Of note, our study has some limitations. Firstly, the possibility of the selection bias affecting the results cannot be ruled out. Secondly, majority of our patients (43%) were young which might have affected the results as well. Finally, a relatively small sample size, therefore; it should be interpreted with caution. To confirm these findings, a large sample size study should be conducted. To our knowledge, this is the first study evaluating the finding of TTE in asymptomatic Saudi patients with SLE.

Table 3 Association between mitral and tricuspid valve abnormalities and study parameters

		Mitral valve abnormalities		*p* value			Tricuspid Valve abnormalities		*p* value
		No	Yes				No	Yes	
Age	12–20	3 (9.4%)	4 (25.0%)	0.121	Age	12–20	4 (10.5%)	3 (30.0%)	0.575
	21–30	12 (37.5%)	9 (56.3%)			21–30	18 (47.4%)	3 (30.0%)	
	31–40	5 (15.6%)	3 (18.8%)			31–40	6 (15.8%)	2 (20.0%)	
	41–50	8 (25.0%)	0 (0.0%)			41–50	6 (15.8%)	2 (20.0%)	
	51–60	3 (9.4%)	0 (0.0%)			51–60	3 (7.9%)	0 (0.0%)	
	>60	1 (3.1%)	0 (0.0%)			> 60	1 (2.6%)	0 (0.0%)	
Gender	Female	30 (90.9%)	15 (93.8%)	0.733	Gender	Female	35 (89.7%)	10 (100.0%)	0.291
	Male	3 (9.1%)	1 (6.3%)			Male	4 (10.3%)	0 (0.0%)	
HTN	No	28 (84.8%)	12 (75.0%)	0.404	HTN	No	32 (82.1%)	8 (80.0%)	0.881
	Yes	5 (15.2%)	4 (25.0%)			Yes	7 (17.9%)	2 (20.0%)	
DM	No	31 (93.9%)	15 (93.8%)	0.979	DM	No	37 (94.9%)	9 (90.0%)	0.566
	Yes	2 (6.1%)	1 (6.3%)			Yes	2 (5.1%)	1 (10.0%)	
Hydroxychloroquine	No	1 (3.0%)	1 (6.3%)	0.593	Hydroxychloroquine	No	2 (5.1%)	0 (0.0%)	0.465
	Yes	32 (97.0%)	15 (93.8%)			Yes	37 (94.9%)	10 (100.0%)	
Azathioprine	No	18 (54.5%)	11 (68.8%)	0.343	Azathioprine	No	25 (64.1%)	4 (40.0%)	0.167
	Yes	15 (45.5%)	5 (31.3%)			Yes	14 (35.9%)	6 (60.0%)	
Mycophenolate mofetil	No	20 (60.6%)	9 (56.3%)	0.771	Mycophenolate mofetil	No	24 (61.5%)	5 (50.0%)	0.508
	Yes	13 (39.4%)	7 (43.8%)			Yes	15 (38.5%)	5 (50.0%)	
Cyclophosphamide	No	26 (78.8%)	12 (75.0%)	0.766	Cyclophosphamide	No	31 (79.5%)	7 (70.0%)	0.521
	Yes	7 (21.2%)	4 (25.0%)			Yes	8 (20.5%)	3 (30.0%)	
Prednisolone	No	4 (12.1%)	2 (12.5%)	0.97	Prednisolone	No	6 (15.4%)	0 (0.0%)	0.185
	Yes	29 (87.9%)	14 (87.5%)			Yes	33 (84.6%)	10 (100.0%)	
C3	Normal	14 (42.4%)	5 (31.3%)	0.452	C3	Normal	15 (38.5%)	4 (40.0%)	0.929
	Low	19 (57.6%)	11 (68.8%)			Low	24 (61.5%)	6 (60.0%)	
C4	Normal	25 (75.8%)	11 (68.8%)	0.602	C4	Normal	29 (74.4%)	7 (70.0%)	0.781
	Low	8 (24.2%)	5 (31.3%)			Low	10 (25.6%)	3 (30.0%)	
ANA	Negative	4 (12.5%)	5 (31.3%)	0.117	ANA	Negative	8 (21.1%)	1 (10.0%)	0.426
	Positive	28 (87.5%)	11 (68.8%)			Positive	30 (78.9%)	9 (90.0%)	
Anti-dsDNA (at the time of echo)	Negative	19 (61.3%)	4 (25.0%)	*0.018	Anti-dsDNA (at the time of echo)	Negative	22 (59.5%)	1 (10.0%)	*0.006
	Positive	12 (38.7%)	12 (75.0%)			Positive	15 (40.5%)	9 (90.0%)	

The asterisks mean a statistical significance

Table 4 Association between antiphospholipid antibodies (aPL) and valve abnormalities

aPL		Anticardiolipin		*p* value	Lupus anticoagulant		*p* value	β2-glycoprotein		*p* value
Valve abnormality		Negative	Positive		Negative	Positive		Negative	Positive	
Mitral valve abnormalities	No	23 (76.7%)	7 (46.7%)	*0.044	28 (73.7%)	1 (16.7%)	*0.006	27 (73.0%)	2 (28.6%)	*0.023
	Yes	7 (23.3%)	8 (53.3%)		10 (26.3%)	5 (83.3%)		10 (27.0%)	5 (71.4%)	
Aortic Valve abnormalities	No	27 (90.0%)	13 (86.7%)	0.737	34 (89.5%)	6 (100.0%)	0.405	32 (86.5%)	7 (100.0%)	0.302
	Yes	3 (10.0%)	2 (13.3%)		4 (10.5%)	0 (0.0%)		5 (13.5%)	0 (0.0%)	
Tricuspid valve abnormalities	No	26 (86.7%)	10 (66.7%)	0.114	31 (81.6%)	4 (66.7%)	0.400	31 (83.8%)	4 (57.1%)	0.109
	Yes	4 (13.3%)	5 (33.3%)		7 (18.4%)	2 (33.3%)		6 (16.2%)	3 (42.9%)	
Ejection fraction	<30	1 (3.3%)	1 (6.7%)	0.577	1 (2.6%)	1 (16.7%)	*0.029	2 (5.4%)	0 (0.0%)	0.060
	31–40	1 (3.3%)	1 (6.7%)		2 (5.3%)	0 (0.0%)		1 (2.7%)	1 (14.3%)	
	41–50	1 (3.3%)	2 (13.3%)		1 (2.6%)	2 (33.3%)		1 (2.7%)	2 (28.6%)	
	51–60	16 (53.3%)	5 (33.3%)		18 (47.4%)	2 (33.3%)		18 (48.6%)	3 (42.9%)	
	>60	11 (36.7%)	6 (40.0%)		16 (42.1%)	1 (16.7%)		15 (40.5%)	1 (14.3%)	
SPAP	Normal	27 (90.0%)	11 (73.3%)	0.146	32 (84.2%)	5 (83.3%)	0.956	33 (89.2%)	4 (57.1%)	*0.034
	Abnormal	3 (10.0%)	4 (26.7%)		6 (15.8%)	1 (16.7%)		4 (10.8%)	3 (42.9%)	

The asterisks mean a statistical significance

Conclusions

Asymptomatic SLE patients who have clinically inactive but serologically active disease or positive antiphospholipid antibodies should be screened for the presence of structural cardiac abnormalities. TTE can be helpful as a noninvasive diagnostic tool for early detection of the abnormalities, resulting in earlier treatment and reduction in mortality and morbidity rates.

Compliance with ethical standards

Disclosures None.

Ethical approval for the current study was obtained from the ethics committee at King Fahad Medical City.

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