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ORIGINAL ARTICLE

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# Cardiac involvement in patients with systemic lupus erythematosus and correlation of valvular lesions with anti-Ro/SS-A and anti-La/SS-B antibody levels

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**Abstract** The aim of this study was to evaluate the incidence of morphologic and functional cardiac abnormalities in patients with systemic lupus erythematosus (SLE) and to correlate the findings with levels of anti-Ro/SS-A, anti-La/SS-B, and anti-cardiolipin antibody (aCL). Sixty-two patients with SLE were enrolled in this study. All patients underwent complete history taking, clinical assessment, and standard two-dimensional and Doppler echocardiography. Anti-Ro/SS-A, anti-La/SS-B, and aCL levels were measured using a standardized ELISA test. The patients were subdivided into two subgroups based on the presence or absence of valvular involvement. The two subgroups were then compared. Valvular involvement was present in 19 patients (30.6%), pericardial effusion in 12 patients (19.4%), impaired left ventricular relaxation abnormalities in 2 patients (3.2%), and pulmonary hypertension in 3 patients (4.8%). More patients in the valvular involvement group had positive anti-Ro/SS-A antibodies than in the valvular noninvolvement group (7/19 vs. 4/43). The difference was significant, with $P < 0.01$. Serum levels of anti-Ro/SS-A levels were significantly higher in the valvular involvement group ($33.7 \pm 36.0$ vs. $13.7 \pm 25.1$; $P < 0.01$), as were the serum anti-La/SS-B levels ($21.9 \pm 23.5$ vs. $10.7 \pm 17.8$; $P < 0.05$). The results suggest a causative correlation between anti-Ro/SS-A and anti-La/SS-B antibodies and the pathogenesis of the valvular lesions in SLE patients.

**Key words** Systemic lupus erythematosus (SLE) · Valvular involvement · Pulmonary hypertension · Anti-Ro/SS-A antibodies · Anti-La/SS-B antibodies · Anti-cardiolipin antibodies (aCL) · Echocardiography

## Introduction

The cardiovascular system is frequently involved in patients with systemic lupus erythematosus (SLE), and many of these patients with SLE develop cardiac manifestations during the course of their disease. Pericarditis is most commonly seen, whereas myocardial involvement is present in only a small number of patients. In recent years, owing to better noninvasive diagnostic techniques, valvular abnormalities have been demonstrated in an increasing number of patients.[1] In addition to the endocardium, myocardium, and pericardium, coronary vessels are also commonly involved, as has been described in clinical and necropsy studies.[2–4]

Many studies have investigated the relationship between the presence of anti-phospholipid (aPL) antibodies and cardiac abnormalities. Some authors have supported this association,[5–9] whereas others did not find any correlation between cardiac abnormalities in SLE patients and the aPL antibodies.[10–15]

An SLE association with anti-Ro/SS-A and anti-La/SS-B antibodies is well established in neonates,[16] and an association between anti-Ro/SS-A and myocarditis or cardiac conduction defects has been described in adults with SLE.[17] Anti-Ro/SS-A and anti-La/SS-B antibodies have been implicated in the initiation of the autoimmune inflammatory process of congenital heart block; in fact, they were the main autoantibodies detected in infants with congenital heart block and their mothers.[18]

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The specific aim of our study was to evaluate the incidence of morphologic and functional cardiac abnormalities in our SLE patient population and to correlate these data with their autoantibody profiles.

## Patients and methods

### Patients

Sixty-two patients fulfilling the American College of Rheumatology (ACR) criteria for diagnosis of SLE[19] were enrolled in this study. Females comprised most of the patients ($n = 59$). The mean age was 25.8 ± 9.5 years (range 10–55 years), and the mean duration of the disease was 3.9 ± 3.7 years (range 0.5–15.0 years). All were being followed in the Department of Rheumatology and Rehabilitation, Cairo University Hospital. Patients were from an ethnically homogeneous population.

During the recruitment phase of the study, the following exclusion criteria were applied: patients older than 60 years, smokers, patients who had a history suggestive of cardiac disease prior to the development of the clinical manifestations of SLE, and patients with echocardiographic evidence of valvular rheumatic heart disease.

Twenty normal subjects served as controls for anti-Ro/SS-A and anti-La/SS-B measurements (mean age 25.8 ± 9.5 for the patients vs. 28.8 ± 11.4 years for the controls; $P =$ NS). Informed consent was obtained from all participants.

Routine laboratory examinations included a complete blood count, erythrocyte sedimentation rate, liver and kidney function assessment, and creatinine phosphokinase assay. Autoimmune profiles were performed by detecting antinuclear antibody using an immunofluorescence technique with HEp-2 cells, in addition to anti-DNA and complements 3 (C3) and 4 (C4) for all patients.

Anti-Ro/SS-A and anti-La/SS-B antibodies were measured using a standardized enzyme-linked immunosorbent assay (ELISA) technique using QUANTA Lite SS-A and QUANTA Lite SS-B kits (Inova Diagnostics, San Diego, CA, USA) for semiquantitative detection of anti-Ro/SS-A and anti-La/SS-B antibodies in human serum. The antigen used in the ELISA technique to detect the anti-Ro/SS-A antibodies was the isolated recombinant Ro 52 and 60 antigen.

The cutoff value at and above which the level was considered positive (2 SD above the mean in the control subjects) for the anti-Ro/SS-A antibodies was 25.9 (mean serum level in the controls was 11.5 ± 7.2). For the anti-La/SS-B antibodies, it was 23.3 (mean serum level in the controls was 10.9 ± 6.2).

ACL antibodies were assessed by ELISA technique using chromogenix AB (Sweden).

All patients were submitted to standard two-dimensional and Doppler echocardiographic evaluation of cardiac function and morphology. Guided with color-flow imaging, pulsed-wave Doppler was used to detect and quantitate the magnitude of mitral regurgitation according to the extent of the regurgitation jet in the left atrium as follows: grade 1+, regurgitant jet extends up to the proximal one-quarter of the left atrium; grade 2+, regurgitant jet is detected half way up the left atrium; grade 3+, regurgitant jet extends up to three-quarters of the left atrium; grade 4+, regurgitant jet extends beyond three-quarters of the left atrium.[20] Trivial regurgitation, which could be observed by color Doppler studies in healthy subjects, was not considered significant. Two physicians performed the echocardiographic examinations (M.H., M.A.).

### Statistical analysis

Data were reported as the mean ± standard deviation (median). The Mann-Whitney, chi-square, and Fisher's exact tests were used when appropriate.

## Results

Cardiac abnormalities that are likely to be associated with the underlying SLE disease process were detected in 28 patients (45.2%), with 14 of them having evidence of more than one abnormality. Valvular lesions were detected in 19 (30.6%) patients, and mitral regurgitation was detected in 18 (94.7%) of the patients with valvular lesions: grade 1+ in 14 (77.8%) patients and grade 2+ in 4 patients (22.2%). No patients were found to have grade 3+ or 4+ lesions. Among the 19 patients with valvular lesions, mitral stenosis was detected in 2 (10.5%), tricuspid regurgitation in 2 (10.5%), aortic regurgitation in 6 (31.6%), and aortic stenosis in 6 (31.6%). Various cardiac abnormalities detected in all patients are listed in Table 1.

The prevalence of various cardiac abnormalities in patients with positive anti-Ro/SS-A, anti-La/SS-B, and aCL antibodies is shown in Table 1. When patients were divided into two subgroups – those with and those without positive anti-Ro/SS-A antibodies – sicca manifestations were reported in seven patients (four in the former group and three in the latter group; $P = 0.04$).

Patients were also divided into two subgroups based on the presence or absence of echocardiographic evidence of valvular lesions. More patients in the valvular involvement subgroup had elevated anti-Ro/SS-A antibodies than did those in the valvular noninvolvement group (7/19 vs. 4/43); the difference was significant ($P < 0.01$).

The difference between the serum anti-Ro/SS-A antibody levels of the two subgroups was also significant (33.7 ± 36.0 vs. 13.7 ± 25.1 in the valvular involvement subgroup and valvular noninvolvement subgroup respectively; $P <$ 0.01).

Serum levels of anti-La/SS-B levels also were significantly more elevated in the valvular involvement subgroup (21.9 ± 23.5 vs. 10.7 ± 17.8; $P < 0.05$). The differences between the two subgroups are shown in Tables 2 and 3.

Pericardial effusion was detected in 12 patients (19.4%), and in one patient it was severe enough to require

**Table 1.** Various cardiac abnormalities detected by echocardiography of all patients, patients with positive anti-Ro/SS-A, anti-La/SS-B, and aCL autoantibodies

| Cardiac abnormality | All patients ($n = 62$) | Anti-Ro/SS-A-positive ($n = 11$) | Anti-La/SS-B-positive ($n = 11$) | ACL-positive ($n = 14$) |
|---|---|---|---|---|
| Valvular lesion (no.) | 19 (30.6%) | 7 (63.6%)** | 5 (45.5%) | 4 (28.6%) |
| MR | 18 (29%) | 7 (63.6%)** | 5 (45.5%) | 3 (21.4%) |
| MS | 2 (3.2%) | 0 | 1 (9.1%) | 2 (14.3%)** |
| TR | 2 (3.2%) | 1 (9.1%) | 1 (9.1%) | 0 |
| AR | 6 (9.7%) | 2 (18.2%) | 2 (18.2%) | 2 (14.3%)* |
| AS | 6 (9.7%) | 2 (18.2%) | 2 (18.2%) | 2 (14.3%)* |
| Pericardial effusion (no.) | 12 (19.4%) | 2 (18.2%) | 0 | 3 (21.4%) |
| Myocarditis (no.) | 2 (3.2%) | 0 | 1 (9.1%) | 0 |
| PH (no.) | 3 (4.8%) | 2 (18.2%)* | 1 (9.1%) | 1 (7.1%) |

ACL, anticardiolipin; AR, aortic regurgitation; AS, aortic stenosis; PH, pulmonary hypertension; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation

* $P < 0.05$, ** $P < 0.01$ when comparing patients with and without a specific cardiac abnormality. The chi-square test with Fisher's exact test was used

**Table 2.** Clinical and laboratory data for all patients and patients with and without valvular involvement

| Parameter | All patients ($n = 62$) | Patients with valvular lesion ($n = 19$) | Patients without valvular lesion ($n = 43$) | *P* |
|---|---|---|---|---|
| Age (years), mean ± SD | 25.8 ± 9.5 | 25.9 ± 8.8 | 25.8 ± 9.8 | NS |
| Duration (days), mean ± SD | 3.9 ± 3.7 | 4.1 ± 3.7 | 3.9 ± 3.8 | NS |
| Malar rash (no.) | 51 (82.3%) | 15 (78.9%) | 36 (83.7%) | NS |
| Discoid rash (no.) | 5 (8.1%) | 3 (15.8%) | 2 (4.7%) | NS |
| Photosensitivity (no.) | 45 (72.6%) | 14 (73.7%) | 31 (72.1%) | NS |
| Oral ulcers (no.) | 36 (58.1%) | 12 (63.2%) | 24 (55.8%) | NS |
| Arthritis (no.) | 26 (41.9%) | 9 (47.4%) | 17 (39.5%) | NS |
| Renal disorders (no.) | 25 (40.3%) | 8 (42.1%) | 17 (39.5%) | NS |
| Hypertension (no.) | 25 (58.1%) | 12 (63.2%) | 13 (30.2%) | 0.02 |
| Neurologic disorders (no.) | 35 (56.5%) | 15 (78.9%) | 20 (46.5%) | NS |
| Serositis (no.) | 29 (46.8%) | 10 (52.6%) | 19 (44.2%) | NS |
| Hematologic disorders (no.) | 17 (27.4%) | 5 (26.3%) | 12 (27.9%) | NS |
| Antinuclear antibodies (no.) | 61 (98.4%) | 18 (94.7%) | 43 (100%) | NS |
| C4 consumption (no.) | 24 (38.7%) | 13 (68.4%) | 11 (25.6%) | 0.002 |
| Hypercholesterolemia (no.) | 8 (12.9%) | 2 (10.5%) | 6 (13.9%) | NS |
| SLAM | 5–23 | 7–23 | 5–22 | NS |

SLAM, systemic lupus activity measure

Chi-square test and Fisher's exact test were used

**Table 3.** Prevalence of anti-Ro/SS-A, anti-La/SS-B, and aCL antibodies in addition to steroid intake in all patients and patients with and without valvular involvement

| Parameter | All patients ($n = 62$) | Patients with valvular lesion ($n = 19$) | Patients without valvular lesion ($n = 43$) | *P* |
|---|---|---|---|---|
| Anti-Ro/SS-A[a] | 11 (17.7%) | 7 (36.8%) | 4 (9.3%) | < 0.01 |
| | 19.9 ± 30.1 (9) | 33.7 ± 36.0 (12) | 13.7 ± 25.1 (6) | < 0.01 |
| Anti-La/SS-B[a] | 11 (17.7%) | 6 (31.6%) | 5 (11.6%) | NS |
| | 14.6 ± 20.4 (7) | 21.9 ± 23.5 (11) | 10.7 ± 17.8 (6) | 0.05 |
| ACL-positive[b] | 14 (22.6%) | 4 (21.1%) | 10 (23.3%) | NS |
| Steroid intake[a] | 55 (88.7%) | 16 (84.2%) | 39 (90.7%) | NS |
| Daily dose (mg) | 22.3 ± 11.3 (20) | 24.7 ± 11.9 (30) | 21.3 ± 11.1 (20) | NS |
| Duration (weeks) | 20.1 ± 25 (12) | 24.1 ± 22.4 (18) | 18.4 ± 26 (9) | NS |
| Total dose (mg) | 2484.4 ± 2534.3 (1680) | 3850 ± 3135.8 (2940) | 1924.1 ± 2034.1 (1260) | NS |

[a] Results are expressed as the number and percent of patients, followed by the mean ± SD, with the median in parentheses

[b] Number of patients

ACL, anticardiolipin antibodies

Mann-Whitney test, chi-square, and Fisher's exact tests were used

pericardiocentesis. No difference has been observed in the antibody profiles between patients with and without pericardial effusion.

Myocarditis was diagnosed in two patients (3.2%), both of whom had active disease and negative aCL antibodies. Impaired left ventricular relaxation (diastolic dysfunction) was detected in two patients (3.2%), left ventricular dilatation in three (4.8%), and right ventricular dilatation in two (3.2%).

Pulmonary hypertension was detected in three patients, in two of whom it was associated with severe valvular disease.

## Discussion

The aim of this study was to evaluate the incidence of valvular, pericardial, and myocardial abnormalities as well as pulmonary hypertension in patients with SLE using echocardiography. We also aimed to detect any possible correlation with elevated anti-Ro/SS-A, anti-La/SS-B, and aCL antibody levels.

Valvular lesions were detected in 30.6% of all patients. The prevalence of rheumatic valvular disease in Egypt was estimated in a previous study to be 1/5000.[21] No studies were done to estimate the incidence of other cardiac abnormalities in the general population in Egypt.

The pathogenic mechanisms underlying valve dysfunction in SLE patients include acute valvular endothelium inflammation, necrotizing vasculitis with infiltration of valvular tissue, nodular and mass calcifications, and valvular fibrosis possibly complicating corticosteroid therapy.[22–26] By dividing the patients into two subgroups – patients with and those without valvular lesions – the difference between the two groups in terms of the percentage of those with elevated levels as well as the serum anti-Ro/SS-A antibody level was significant ($P < 0.01$). This was also true for the difference in serum anti-La/SS-B levels for the two subgroups ($P < 0.05$).

Anti-Ro/SS-A antibodies present in the serum of individual patients are directed against a small cytoplasmic RNA protein complex. In SLE patients anti-Ro/SS-A is known to be associated with photosensitive rash, subacute cutaneous lupus, pulmonary disease, lymphopenia, and neonatal lupus syndrome. Less discussed anti-Ro/SS-A associations include the presence of rheumatoid factor, nephritis, thrombocytopenia, anti-La/SS-B antibody, complement (especially C4) deficiency, and HLA-DQ1, HLA-DQ2, HLA-DQ3, and DR2, particular proteasome alleles.[27]

In this study, C4 consumption was detected significantly more often in patients with a positive anti-Ro/SSA assay ($P = 0.002$), which supports the findings of previous studies.[27]

Permanent cardiac disease is the most common manifestation of the neonatal lupus syndromes. The neonatal disease is presumed to be due to transplacental passage of these immunoglobulin G (IgG) autoantibodies from the mother with SLE.[28] Anti-Ro/SS-A and anti-La/SS-B antibodies are also the main autoantibodies detected in infants with congenital heart block and their mothers,[18] where it is found that anti-Ro/SS-A antibodies bind to the fetal cardiac epitopes.[29] Epitopes recognized by anti-Ro/SS-A are located on two proteins (60 and 52 kDa) that are bound intracellularly as a complex to small ribonucleic acids called hY1, hY3, hY4, and hY5.[30] The binding of the antibodies to the cardiac epitopes results in heart block after maturation of the fetal heart at approximately 16 weeks of age. The atrioventricular node is severely damaged and replaced by fibrous tissue and areas of calcification.[29]

Anti-La/SS-B antibodies are directed against an auxiliary protein (48 kDa) of the RNA-polymerase III. The cross-reactivity of laminin with anti-La antibodies could be an important factor in the initiation of the autoimmune process.[18] The Ro proteins and the La protein are probably intracellular components of identical or partially identical ribonucleoprotien particles.[30]

Isolated endocardial fibroelastosis (EFE) associated with maternal anti-Ro and anti-La antibodies in the absence of complete atrioventricular block has been reported.[31] The diffuse deposition of IgG and the presence of a T-cell infiltrate throughout the myocardium suggest that the transplacental passage of maternal autoantibodies induces an immune reaction in the myocardium, leading to isolated EFE.

Although the precise pathogenetic mechanism of autoantibody-mediated tissue injury is not defined, it has been demonstrated in adult rabbit and human fetal hearts that sera containing anti-Ro/SS-A antibodies induce atrioventricular block and inhibit L-type calcium currents in isolated ventricular myocytes.[28] Experimental evidence in a rabbit model supports a direct role for anti-Ro/SS-A and anti-La/SS-B antibodies in cardiac involvement.[32]

The fetal heart appears to be uniquely vulnerable, as complete block has never been described in their mothers despite exposure to similar circulating autoantibody levels. Extensive work from several laboratories has resulted in molecular characterization of the maternal autoantibody responses and the cloning of genes expressing the cognate antigens whose structural features suggest a role in transcriptional regulation.[28] Oshiro et al.[33] reported a significant relation between cardiac involvement in a pediatric SLE population (including pericarditis and myocarditis) and the presence of anti-Ro/SS-A and anti-La/SS-B antibodies.

Primary Sjögren syndrome is an autoimmune disorder characterized by the presence of high levels of anti-Ro/SS-A antibodies. Valvular disease associated with this syndrome has been described in isolated cases.[34] In a study done by Espinola et al.,[35] 23 patients with primary Sjögren syndrome were studied by transthoracic echocardiography, which found that the main alterations were at the valvular level. The abnormal valves were the mitral, aortic, and tricuspid, but none showed evidence of significant dysfunction. The authors concluded that the development of morphologic abnormalities at the valvular level in some cases depends on the immunopathologic features of the disease.

Corticosteroids are known to have an overall deleterious effect on the heart. Systemic hypertension and left ventricular hypertrophy appear; or if they are already present, they get worse. Then congestive cardiac failure increases. On the other hand, corticosteroids in patients with SLE were suggested to cause smaller, fewer, univalvular Libman-Sacks-type endocardial lesions and healed, calcified verrucae.[22] In our study, the mean duration and the mean total dose of glucocorticoids were higher in patients with valvular lesions than in those without such lesions. Although the difference was not significant, it does not exclude the possible role of glucocorticoids in accelerating fibrosis of the inflamed valvular lesions.

Previous studies regarding the relation between the presence of aPL antibodies and a valvular lesion in SLE patients have reported conflicting results.[5–15] Gentile et al.[9] reported a relation between high aPL antibody levels and the severity of valvular lesions. We did not detect this relation. All our patients with mitral regurgitation had grade 1+ or 2+ regurgitation; grades 3+ and 4+ were not seen. The number of patients with grade 2+ regurgitation in the recent study was too small for statistical evaluation and might not even allow investigation for the relation between autoantibodies and the degree of severity of a valvular lesion.

Pericardial effusion was detected in 19.4% of SLE patients. There were no differences in antibody profiles between the patients with and those without pericardial effusion.

Gentile et al.[9] found regional wall motion abnormalities in 8.8% of their patients. They considered myocarditis as a possible cause of the wall motion abnormality and suggested that the aPL antibody plays a role in the pathogenesis of regional myocardial dysfunction. In our study, myocarditis was diagnosed in 3.2% of the SLE patients with active disease and with a negative aPL antibody assay. Regional wall abnormalities were not detected in our study.

## Conclusions

Cardiac abnormalities are frequently detected in SLE patients. Our study suggests that anti-Ro/SS-A and anti-La/SS-B antibodies play a role in the pathogenesis of valvular lesions in SLE patients.

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