A Cross-sectional Study of Cardiovascular Involvement in Systemic Lupus Erythematosus in an Urban Indian Tertiary Care Centre with Emphasis on 2-D Echocardiography

Seema Kini1, Chetan Vekhande2, Vikram Londhey3

Abstract

Background: Cardiovascular manifestations are responsible for considerable morbidity and mortality in patients with SLE. A wide range of manifestations due to active lupus, like pericarditis, valvular affection, myocarditis, and less commonly pulmonary hypertension, are described. This study was undertaken to study cardiovascular manifestations in SLE, with a focus on echocardiography findings, in an urban Indian setting.

Methodology: Fifty consecutive cases of SLE following up in the Rheumatology Clinic of TNMC and BYL Nair Charitable hospital, an Indian tertiary care hospital were studied. They were subjected to an echocardiographic examination if not already done. Detailed history, examination, study of past medical records and investigations were carried out, especially related to cardiovascular system. Treatment details, flares, other systemic involvement were noted. Serial echocardiography if done previously were noted down. The data was analysed using descriptive statistics.

Results: An echocardiographic abnormality was noted in 25 (50%) of the 50 subjects. Pulmonary hypertension in 21(42%); valvular abnormalities in 16 (32 %); pericardial effusion in 9 (18%) and diastolic dysfunction in 6(12%) were the echocardiography findings. Six out of the 7 cases with moderately to severe pulmonary hypertension seemed to be responding to immunosuppressive therapy clinically as well as on echocardiography; 1 did not respond. At least 1 traditional risk factor for atherosclerosis was present in 58% of cases.

Conclusions: Screening echocardiography may be recommended, especially at presentation, during SLE flare, or in the presence of cardiac symptoms. Moderate to severe pulmonary hypertension can develop any time in the course of the disease. It may be responsive to immunosuppression. Further detailed studies including multiple echocardiographic parameters and right heart catheterisation need to be undertaken to study the responsiveness of pulmonary hypertension to immunosuppresssive therapy.

Editorial Viewpoint

• SLE can affect the heart in numerous ways.
• 2D Echo is a good screening tool to pick up the same.
• Pulmonary hypertension (PH) may occur anytime during the course of SLE.
• PH with SLE may be responsive to immunosuppression.

Introduction

Systemic lupus erythematosus (SLE) is a chronic multi-systemic autoimmune disease that predominantly affects young females of the child-bearing age group. The disease has a wide spectrum of presentations and manifestations. From an involvement of a single system, to permutations and combinations of multiple system affection, remissions of unpredictable durations and relapses, the management of SLE remains a great challenge for the clinician.

Butterfly rash, discoid rash, photosensitivity, oral ulcers, polyarthritis, polyserositis,
nephrotic syndrome, seizures, psychosis, hemolysis and cytopenias are the well known manifestations of SLE. Besides the well known cardiac manifestation of pericarditis, we do come across valvular abnormalities, myocarditis, conduction abnormalities, impairment of systolic and diastolic function, pulmonary or peripheral arterial hypertension and microcirculatory problems.1

Cardiovascular disease has been recognised as an important cause of morbidity and mortality in SLE.

Methodology

We conducted a cross-sectional, observational study of 50 consecutive cases of SLE following up in the Rheumatology OPD of BYL Nair Charitable Hospital between June 2012 to June 2013, after ethics committee approval. All the cases, diagnosed as per the American College of Rheumatology Criteria for SLE, were included after a written, informed consent. The clinical history, examination and investigations were recorded. The past medical records were reviewed for any cardiovascular abnormalities, electrocardiograms, chest radiographs, 2D-echocardiography reports, flares, and treatment administered. Besides the routine investigations, 2-D echocardiography was done in all patients who had not done it before. Serial echocardiographic findings were noted if available. Those with other associated rheumatologic diseases, rheumatic heart disease or congenital heart disease were excluded. We noted the presence of traditional risk factors for atherosclerosis in our subjects, but did not perform carotid intima/media thickness due to financial constraint. Descriptive statistics and Chi square test were applied to get the results.

Results

A total of 50 patients of SLE were studied. Table 1 gives some characteristics of the study population. The immunologic profile of the study population is reflected in Table 2. Other systemic involvement besides cardiovascular is mentioned in Table 3. Single system involvement was seen in only 10 cases. Of the remaining forty, 25 were having two systems involved, 11 had 3 systems involved and 4 had 4 systems involved. Thus 40 (80%) patients had multi-system involvement.

In this study 2D echo was done in each of 50 SLE patients at some point of time during the

Table 1: Certain characteristics of our study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
<th>Std. deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.9</td>
<td>26</td>
<td>9.3</td>
<td>14</td>
<td>59</td>
</tr>
<tr>
<td>Duration of disease (months)</td>
<td>71.7</td>
<td>36</td>
<td>86.2</td>
<td>2</td>
<td>360</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>23.8</td>
<td>23.5</td>
<td>7.0</td>
<td>12</td>
<td>41</td>
</tr>
<tr>
<td>Flare in last 5 years (n=43)</td>
<td>2.35</td>
<td>2.00</td>
<td>1.69</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>BMI</td>
<td>21.5</td>
<td>21.35</td>
<td>3.4</td>
<td>16</td>
<td>33.08</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.85</td>
<td>0.85</td>
<td>0.04</td>
<td>0.75</td>
<td>1.01</td>
</tr>
<tr>
<td>ESR</td>
<td>83.3</td>
<td>85</td>
<td>36.1</td>
<td>15</td>
<td>165</td>
</tr>
</tbody>
</table>

Table 2: Immunologic profile of the study population

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>Pos</td>
<td>50 (100)</td>
</tr>
<tr>
<td>ANA titers</td>
<td>1+</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>19 (38)</td>
</tr>
<tr>
<td></td>
<td>3+</td>
<td>12 (24)</td>
</tr>
<tr>
<td></td>
<td>4+</td>
<td>17 (34)</td>
</tr>
<tr>
<td>ANA pattern</td>
<td>Homogenous</td>
<td>26 (52)</td>
</tr>
<tr>
<td></td>
<td>Speckled</td>
<td>16 (32)</td>
</tr>
<tr>
<td></td>
<td>Nucleolar</td>
<td>5 (10)</td>
</tr>
<tr>
<td></td>
<td>Centromere</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Anti Ds DNA</td>
<td>Negative</td>
<td>22 (44)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>28 (56)</td>
</tr>
</tbody>
</table>

Table 3: Clinical profile of the study population: Involvement of systems other than CVS

<table>
<thead>
<tr>
<th>Systemic involvement</th>
<th>N=50 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatological</td>
<td>44 (88)</td>
</tr>
<tr>
<td>Renal</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>26 (52)</td>
</tr>
<tr>
<td>CNS</td>
<td>4 (8)</td>
</tr>
<tr>
<td>GIT</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Hematological</td>
<td>16 (32)</td>
</tr>
<tr>
<td>Thyroid abnormalities</td>
<td>11 (22)</td>
</tr>
</tbody>
</table>

The affection may be due to disease activity as well as accelerated atherosclerosis. The later is being increasingly recognised in the West,2-4 as well as Asian countries.5 This is perhaps due to longer survival due to better control of disease activity and infection in the recent years.

We conducted this study of cardiovascular disease in SLE patients at BYL Nair charitable hospital with emphasis on the echocardiographic findings and made interesting observations, in those found to have pulmonary hypertension, during their course of lupus.

Fig. 1: 2D, echo findings of 50 cases of SLE

![2D, echo findings of 50 cases of SLE](image-url)
course of the disease. Abnormal echocardiography was found in 25 (50%). The remaining had a normal echo. The most common echocardiographic finding was pulmonary hypertension (PH) [cases with Pulmonary arterial systolic pressure (PASP)>35 mm Hg were considered to have PH] found in 21 (42%) of the patients; followed by valvular abnormalities in 16 (32%); pericardial effusion in 9 (18%) and diastolic dysfunction in 6 (12%) (Figure 1).

![Fig. 2: Details of pulmonary hypertension in the study population](image)

**Fig. 2: Details of pulmonary hypertension in the study population**

Twelve patients had pulmonary hypertension (Figure 2); 17 of these were detected at the initial presentation, when the SLE was active. Out of 21 patients with pulmonary hypertension, 11 were found to be asymptomatic. They all had mild PH (PASP 36-50 mmHg). The 10 with symptomatic PH had moderate to severe (PASP >50 mmHg) PH. Of these 10, one had severe ILD and 2 had renal failure when PH was detected. Both these conditions would have significantly contributed to the PH. Of the remaining 7 with moderate to severe PH, without any other significant contributing factor, during the period of documentation of PH, 1 case of lupus nephritis (LN) was on MMF and 6 received cyclophosphamide either for LN, CNS lupus or symptomatic PH itself. At the time of analysis of this study, 4 had received greater than 1.5 years of MMF/Cyclophosphamide; their PH had normalised in 3 of the 4; and not responded in 1. The remaining 3 had completed 6-8 months of Pulse cyclophosphamide; their PH had reduced and they became asymptomatic. Thus 6 of 7 cases with moderately severe symptomatic PH seemed to be responsive to immunosuppression. All those with mild PH, remained clinically stable and asymptomatic for PH at the time of the analysis, since the time of detection of PH.

There was no significant association of pulmonary hypertension with disease duration of greater than or less than 5 years, presence or absence of Raynaud’s phenomenon, other systemic involvement. Antiphospholipid antibodies were not available in all the patients to study the association.

Valvular abnormalities were found in 16 (32%) patients. All of these were regurgitant lesions; none were stenotic. Valvular lesions were as follows: Only mitral regurgitation (MR): 4; Only Aortic regurgitation (AR): 2; Both MR and AR: 4; significant tricuspid regurgitation: 4; aortic sclerosis: 2 cases. Only half of the 16 with valvular affection were symptomatic.

The most common risk factor for atherosclerosis (Figure 3) found in this study was dyslipidemia found in 20 (40%) of the patients followed by hypertension found in 17 (34%). Longer duration of SLE was significantly associated with the presence of hypertension (Point Biserial coefficient $r_{PB}=-0.37$; $p$ value=0.007). Eleven
(22%) of the patients were found to be overweight. Diabetes was found in none. Family history for hypertension was found to be significant in only one patient. None of them were smokers. Twenty nine cases had either dyslipidemia, HT or they were overweight. Of these, 11 had 2 risk factors and 2 of them had 3 risk factors. Though all of the above are traditional risk factors for ischaemic heart disease (IHD), only one patient was documented to have IHD. She had unstable angina, with a normal 2D echo. Coronary angiography and cardiac stress test, could not be done due to lack of consent.

Pericardial effusion was found in 10 (20%) patients. Quantifying, 8 of them have mild effusion and 2 had moderate effusion. However all were asymptomatic with no evidence of chest pain, haemodynamic compromise or cardiac tamponade. A single case had pericarditis without effusion.

Diastolic dysfunction was found in 12% and systolic dysfunction in 8% of patients. None of the patients had regional wall motion abnormalities suggestive of IHD.

ECG abnormalities were seen in 11 (22%) of the patients of which ST-T changes and q waves in anterior leads were seen in 2 patients each. However all these patients were clinically asymptomatic. LVH was seen in 6 patients; all of them were hypertensive. P- pulmonale with or without RVH was seen in 8 patients, all of whom were having pulmonary hypertension.

The chest radiograph showed normal heart in 40 of the 50 cases. Of the remaining 10, four had cardiomegaly and 7 had a prominent pulmonary conus (One had cardiomegaly with prominent pulmonary conus).

Discussion

Many of the commonly described cardiovascular manifestations of SLE have been seen in our study. There was a high prevalence of echocardiographic abnormalities 25 cases (50%). Majority of the patients were asymptomatic. So screening 2D Echo in all cases of SLE seems necessary.

A striking finding was the detection of pulmonary hypertension during the course of SLE, in a large number of cases. There is a possibility of over-diagnosis by 2D echo as compared to the gold standard, right-heart catheterisation. We were unable to perform the same due to cost and invasiveness of the procedure. There are studies on the accuracy of echocardiography being used for the assessment of PH and the results are contradictory. There have been prior studies on PH in connective tissue disorders in which PH was based on echocardiographic features, mainly PASP to quantify PH; Western as well as Indian.11-13

In our study the PASP by TR jet seemed to correlate with the WHO class functional class of the patient and the ECG and X-ray Chest findings. The ones with moderate to severe PH (PASP>50mmHg) had functional class II, III or IV, but those with mild PH were asymptomatic. Of the 10 cases with moderate to severe PH, 8 had P-pulmonale with or without RVH on ECG and 7 had a prominent pulmonary conus on X-ray. Hence in our set-up where right heart catheterisation is not feasible, 2-D echocardiography, along with ECG and chest radiograph may be the best way to diagnose and monitor the level of PH. But the possibility remains that at least some of the asymptomatic ‘PH’ cases may have got excluded after a right heart catheterisation. So it remains a limitation of the study, that right heart catheterisation was not done to confirm the presence of pulmonary hypertension, as in most Indian studies on PH in connective tissue diseases.15

Our study did show a high number of cases with PH. This may be due to the fact that we considered them to have had PH any time during the course of the illness and not only at the time of the study assessment. So the figure does not indicate the prevalence in a cross-section of our SLE patients. Also there is a possibility of selection bias as a symptomatic individual would be more likely to have an echocardiography report than an SLE without cardiac symptoms. Various studies have reported highly variable rates of PH in SLE due to varying methods of assessing PH, varying cut-offs for PH or varying methodologies. As per a recently published review, the prevalence of PH in SLE is 8-17.2% in Caucasians and 35.3-49% in Asians. Thus Asians do have a higher prevalence of PH in SLE as compared to Caucasians.

Most of cases had mild PH that did not seem to progress, but even normalise with the control of SLE disease activity. Of the ones with moderate to severe PH, and without ILD or renal failure (both of which contribute to causing PH), immunosuppression with pulse cyclophosphamide or MMF seemed to show benefit, clinically as well as on echocardiographically. However we cannot make a definitive conclusion, as the number of cases of SLE with PH was small; their follow-up duration was short and confirmatory right heart catheterisation was not done. There are some previous studies that support the use of immunosuppression in the treatment of PH in SLE. All these studies have the limitation of having small numbers. A single Indian study by Kommireddy S, et al studied 24 cases of SLE with PH and observed their response to immunosuppression in the form of monthly cyclophosphamide pulses for 6 months. They found an improvement in a significant proportion of patients. However in this study too, right heart catheterisation to confirm PH, was not performed.

Further double blind, randomised
(pulmonary vasodilators vs immunosuppression) prospective studies with larger study group are needed to confirm the usefulness of immunosuppression in PH with SLE, based on our pilot findings. Also multiple parameters for assessment of PH on echocardiography, 6-minute walk test, BNP levels, and right heart catheterisation hemodynamic parameters should be serially assessed in a pre-planned manner.

Recent articles show a major concern about premature atherosclerosis in patients with SLE. In our study, peripheral vascular involvement seemed to be clinically due to vasculitis or antiphospholipid antibody syndrome; and not due to atherosclerosis. We did not evaluate the coronary status nor peripheral dopplers in all the patients. Only a single patient had documented IHD with unstable angina. This would make one think whether atherosclerosis is a theoretical concern in SLEs. However we cannot conclude thus as we have not evaluated the coronary status nor the intima-media thickness of carotids. Also, only 4 cases from our study population were above the age of 40. Survival from disease activity and opportunistic infections still may be a bigger concern in Indian SLEs than that of atherosclerosis.

Several studies including Asian studies have documented the concern for atherosclerosis to be true. In an Indian postmortem study by Panchal, et al, it was shown that death due to cardiovascular cause seen in 8 of 27 SLEs; this was second to death due to renal disease (13 of 27). Thromboses/embolism, vasculitis and severe coronary atherosclerosis were seen in nine, five and 1 of the 27 subjects, respectively. Thus we must make all efforts to monitor and aggressively treat the traditional risk factors of atherosclerosis. Dyslipidemia was the most common risk factor for atherosclerosis in our study. In another Indian study, Bhatt SP et al, have shown that dyslipidemia is a significant risk factor for peripheral vascular disease in SLE. In our study hypertension is the second commonest risk factor and was associated with longer disease duration, possibly due to steroids. However dyslipidemias did not show the same relationship. Inability to perform Carotid intima media thickness was also a limitation of this study.

The nontraditional factors for cardiovascular disease in SLE are disease-specific like renal disease manifestation as Lupus nephritis (LN), presence of pro-inflammatory cytokines, some of inflammatory mediators, antiphospholipid antibodies, anti-oxLDL (anti oxidised low density lipoprotein) antibodies, corticosteroid uses and cumulative dose of glucocorticoids. Svenungsson E, et al have proven the distinct influence of these factors by studying 3 age-matched groups: SLE with cardiovascular event, SLE controls and population controls. Hence disease activity control and at the same time early introduction of steroid-sparing regimens may need to be emphasised.

**Limitations of our Study**

- Possible selection bias enrolling cases of SLE who already had a 2DEcho report.
- Echocardiographies done by more than 1 operator.
- Lack of confirming the diagnosis of PH with a right heart catheterisation when PASP was found to be higher than 40.
- The number of those who had PH does not represent the prevalence as it was noted during the course of SLE and not at enrolment.
- Carotid intima-media thickness was not performed as a marker of atherosclerosis.
- Antiphospholipid antibodies were not evaluated for in all the cases.

**Conclusions**

- **Echocardiographic** abnormalities are common in SLE. They may be related to disease activity like, pericardial effusion, pulmonary hypertension, diastolic dysfunction. Majority were detected at initial presentation and most were asymptomatic.
- Screening of all cases of SLE with echocardiography is recommended, especially at presentation, during SLE flare, or in the presence of cardiac symptoms.
- Moderate to severe pulmonary hypertension can develop any time in the course of the disease. It may be responsive to immunosuppressive therapy if there are no other contributing causes. However these are just pilot observations. Further research is needed to prove the usefulness of immunosuppressives for pulmonary hypertension in SLE.
- **Traditional risk factors** for atherosclerosis like dyslipidemias, hypertension, diabetes and overweight are prevalent in over half of the cases of SLE. These need to be regularly monitored for and treated.
- Steroid therapy may increases the risk of atherosclerosis further as per literature. Hence steroid sparing therapies should be initiated early in the disease course.

**References**


