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**Cardiovascular involvement in systemic lupus erythematosus: An autopsy study of 27 patients in India**

Panchal L, Divate S, Vaideeswar P, Pandit SP

**ABSTRACT**

Background: Although cardiovascular disease (CVD) is recognized as a leading cause of death in patients with systemic lupus erythematosus (SLE) in western countries, there is hardly any data regarding Indian subjects with SLE.

Aims: To determine the incidence of cardiac abnormalities and vascular lesions at autopsy and to assess their contribution to the mortality in patients with SLE.

Settings and Design: Retrospective retrieval of reports of autopsies performed on 35 patients with SLE over a 11 year period and analysis of 27 cases with cardiac and/or vascular lesions.

Materials and Methods: Gross and microscopic features in 27 autopsies were analyzed with special attention to the heart and the vasculature of all organs. Findings were correlated with clinical features and ante-mortem investigations. Their contribution towards mortality was assessed.

Results: Valvar lesions were the commonest cardiac lesions noted with non-bacterial thrombotic endocarditis in nine (33.33%), valvar thickening in two (7.41%), Libman-Sacks endocarditis and infective endocarditis in one (3.70%) each. Myocarditis and myocardial scarring were seen in 10 (37.03%) and seven (25.92%) cases, respectively. Fibinous pericarditis was noted in seven (25.92%). Thromboses/embolism, vasculitis and severe coronary atherosclerosis were seen in nine (33.33%), five (18.52%) and one (3.70%) subjects, respectively. Renal disease [13, 48.14%] and cardiovascular manifestations [8, 29.62%] were the leading causes of death in our patient population.

Conclusion: CVD contributes significantly to the mortality in patients with SLE in India. It is second only to renal disease in this regard.

**KEY WORDS:** Systemic lupus erythematosus, cardiovascular, autopsy, mortality

Recently published studies from the western countries indicate that cardiovascular disease (CVD) is a major cause of death in patients with systemic lupus erythematosus (SLE). However, the data in different Indian studies is conflicting and the importance of CVD in SLE is not clear. This striking contrast prompted us to review autopsy reports of patients with SLE who were admitted in our hospital to assess the incidence of cardiovascular lesions and their contribution to mortality.

**Materials and Methods**

At our center, autopsies are routinely performed to ascertain the cause of death. We retrospectively reviewed the autopsy findings of all cases of SLE who had died over a 11 year period (1991-2001). The diagnosis of SLE was made on the basis of clinical features and laboratory data in accordance with the revised criteria for the classification of SLE. Thirty five autopsies [28 females, 7 males; patient age range: 10-69 years, Mean age 24.14 years, SEM 1.64] were performed in subjects with SLE accounting for 0.20% of 17741 autopsies performed during the period. Amongst these, 27 patients (77.14%) who showed cardiovascular lesions at autopsy, were selected for the present study.

Patients’ medical records maintained by the hospital were retrieved. The documented clinical data, including details of the complete haemogram and biochemical and serological tests [including tests for antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid (anti-ds-DNA), antcardiolipin antibody (ACLA) and other prothrombotic markers] were reviewed. In addition, findings noted in autopsy reports were also reviewed and recorded. At the autopsy, the heart chambers were regularly examined for pathological changes in the pericardium, atria, ventricles, valves, ostia and all branches of coronary arteries, aorta and its branches, pulmonary artery and its branches. The chambers were studied with respect to chamber size and appearance of the endocardium and myocardium.
All parts of the valvar apparatus of the atrio-ventricular and semilunar valves were carefully inspected. Paraffin sections of the myocardium, valves and coronary arteries were stained with haematoxylin-eosin (HE) and elastic van Gieson (EVG). In addition, the vasculature of all organs was examined for atherosclerosis, thrombosis, vasculitis or any other change. The primary cause of death was attributed, with appropriate clinical and laboratory correlation, to the organ/system showing the most florid pathological lesions.

**Results**

All the 27 SLE patients [22 females, 5 males] with cardiovascular involvement at autopsy were young [Age range: 10-38 years, mean 23.29, S.E.M. 1.50]. All patients were on treatment with corticosteroids, however details of duration of therapy or dosages were not available. Sixteen (59.26%) patients had clinical records of ANA and/or anti-ds-DNA with ANA titers ranging from 1:40 to 1:160. ACLA was tested for in patients who had clinical records of ANA and/or anti-ds-DNA with or without effusion. Thirteen (48.15%) patients were ANA positive. Coronary lesions were seen in 13 (48.15%) patients. Thrombosis in the intra-myocardial coronary arteries in a 24 years old male subject, presented with mild, acute pericarditis with or without effusion was seen in seven (25.92%) patients. Pericardial effusion alone was seen in three (11.11%) other patients.

Valvar lesions were seen at autopsy in 13 (48.15%) patients [Table 1]. Multiple, tiny, tan-colored, warty vegetations of nonbacterial thrombotic endocarditis (NBTE) were seen along the lines of closure of the mitral valve [Figure 1] in eight (29.62%) patients and on the mitral and aortic valves in one (3.70%). Three (11.11%) patients of NBTE of the mitral valve had other associated valvar abnormalities. These comprised mitral and tricuspid regurgitation, mitral valve thickening and mitral regurgitation (MR) with a small vegetation in one patient (3.70%) each respectively.

As shown in Table 1, the spectrum of myocardial lesions included myocarditis, scarring and hypertrophy. Myocardial scarring [7 patients, 25.92%] was thought to be possibly ischemic in origin as six (22.22%) of them had a variety of coronary lesions. Multiple thrombi in the coronary arteries were seen in one (3.70%) 14 years old female patient; she had presented with acute respiratory distress. Coronary lesions seen in the other five included critical, greater than 90%, atherosclerotic narrowing of the left anterior descending coronary artery [Figure 2] in an 18 years old female, thrombosis of the intra-myocardial coronary arteries in a 24 years old male subject, moderate fibro-cellular intimal thickening with medial hypertrophy of the intra-myocardial coronaries in a 24 years old female, coronary arteritis in a female aged 35 years and emboli in the intra-myocardial coronaries in a 29 years female with bi-ventricular mural thrombi [Figure 3]. The myocardial fibrosis was streaky and interstitial in these five patients. Two of them had come with acute respiratory distress and died soon thereafter. The seventh, a 22 years old male, who had streaky myocardial scarring showed normal coronary arteries. But, thrombotic micro-angiopathy (TMA) seen in the kidneys suggested a probable thrombotic cause for the fibrosis. Myocardial hypertrophy was seen in five cases [Table 1]. Left ventricular hypertrophy that could be attributed to systemic hypertension was seen in four cases with hearts weighing 240-600 gm, The right ventricular hypertrophy noted in one of the hearts was probably due to diffuse interstitial lung disease with resultant pulmonary hypertension. A patchy mild to moderate, lymphocytic myocarditis was seen in nine (33.33%) patients and the patient with infective endocarditis of the aortic valve had a neutrophilic myocarditis (3.70%).

Fibrinous pericarditis with or without effusion was seen in seven (25.92%) patients. Pericardial effusion alone was seen in three (11.11%) other patients.

Vasculitides were seen in five (18.52%) patients [Table 1]. Pulmonary vasculitis was seen in one (3.7%) patient while systemic vasculitides were seen in another four (14.81%). The latter involved the intra-renal vessels [Figure 4], coronary, mesenteric and ovarian vessels. Venous or arterial thromboses were seen in nine (33.33%) patients [Table 1]; tests for ACLA were done in only three (11.11%) of these patients. Thrombosis involved the intra-pulmonary vessels [Figure 5] in six (22.2%) patients. Of these, one (3.70%) each, had thrombosis of the coronary artery and cerebral vein. A patchy mild to moderate, lymphocytic myocarditis was seen in nine (33.33%) patients and the patient with infective endocarditis of the aortic valve had a neutrophilic myocarditis (3.70%).

Interestingly, one patient (3.70%) who died following acute pancreatitis showed thrombosis of bilateral renal veins, inferior vena cava and superior pulmonary vein. and another, a 19 years old, female, who had presented with breathlessness and edema feet but subsequently developed altered sensorium with cortical venous thrombosis showed multiple cerebral and cerebellar infarcts. This latter patient was ACLA positive. Coronary atherosclerosis was uncommon (3.70%); only one 18 years, female, had significant, greater than 90%, atherosclerotic narrowing of the left anterior descending artery. The right coronary artery in this patient showed only mild concentric fibrous intimal thickening.

All the 27 patients with cardiovascular lesions at autopsy showed concomitant lesions in the renal and/or pulmonary parenchyma [Table 1]. Multi-organ involvement with disor-
Table 1: Clinical and pathological features in SLE patients with cardiovascular lesions.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Cardiovascular lesions</th>
<th>Other systems involved</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Myocarditis*, NBTE (MV and AV)</td>
<td>K</td>
<td>ARF</td>
</tr>
<tr>
<td>2</td>
<td>Myocarditis*, Libman-Sacks endocarditis, pericarditis, LVH</td>
<td>K</td>
<td>ARF</td>
</tr>
<tr>
<td>3</td>
<td>Myocarditis*</td>
<td>K</td>
<td>CRF</td>
</tr>
<tr>
<td>4</td>
<td>PTE - occasional*</td>
<td>K, L</td>
<td>CRF</td>
</tr>
<tr>
<td>5</td>
<td>Fibrinous pericarditis, right ventricular hypertrophy</td>
<td>K, L</td>
<td>ARF</td>
</tr>
<tr>
<td>6</td>
<td>IE of AV, Neutrophilic myocarditis, pulmonary vasculitis</td>
<td>K, L</td>
<td>IE†</td>
</tr>
<tr>
<td>7</td>
<td>Pericardial effusion†</td>
<td>K</td>
<td>ARF</td>
</tr>
<tr>
<td>8</td>
<td>Coronary arteritis, myocardial fibrosis, LVH, renal vasculitis</td>
<td>K</td>
<td>M Isch†</td>
</tr>
<tr>
<td>9</td>
<td>Thrombi – Co A, PTE*, myocardial scars, pericarditis, LVH</td>
<td>K, L</td>
<td>M Isch†</td>
</tr>
<tr>
<td>10</td>
<td>Myocarditis*, NBTE, pericarditis, renal vasculitis*</td>
<td>K</td>
<td>ARF</td>
</tr>
<tr>
<td>11</td>
<td>Pericardial effusion*, LVH, renal vasculitis*</td>
<td>K, L</td>
<td>ARF</td>
</tr>
<tr>
<td>12</td>
<td>PTE, pericarditis</td>
<td>K</td>
<td>PTE†</td>
</tr>
<tr>
<td>13</td>
<td>Myocardial scars, Hyperplastic myocardial coronaries</td>
<td>K, L</td>
<td>BrPneu</td>
</tr>
<tr>
<td>14</td>
<td>Pericarditis</td>
<td>K, L</td>
<td>TB</td>
</tr>
<tr>
<td>15</td>
<td>Pericarditis†, myocarditis*</td>
<td>K, L</td>
<td>BrPneu</td>
</tr>
</tbody>
</table>

Chief clinical manifestations: Acute respiratory distress

| 1      | CAS*, myocardial scars, bicuspid AV, VSD, MV thickening | K | CRF |
| 2      | PTE | K, L | PTE† |
| 3      | Thrombi – Co A, healed myocardial infarct, NBTE†, stenosis -MV (thickening†) and AV, myocarditis*, multi-site vasculitis | K, L | M Isch† |
| 4      | NBTE, MV thickening, LVH | K | ARF |

Chief clinical manifestations: Altered sensorium with or without seizures

| 1      | Myocarditis*, NBTE, (MR and TR†) | L, K | AIP |
| 2      | NBTE | K | ARF |
| 3      | NBTE, myocardial scars, renal thrombotic microangiopathy* | K, L | ARF |
| 4      | Myocarditis*, NBTE, brain infarcts (ACLA positive) | K, L | CVA† |

Chief clinical manifestations: Neuropsychiatric manifestations, progressive azotemia

| 1      | MV thickening†, pericardial effusion† | K, L | CRF |

Chief clinical manifestations: Lower limb gangrene and acute respiratory distress

| 1      | Intracardiac thrombi, coronary embolism, PTE*, myocardial fibrosis, NBTE | K, L | M Isch† |

Chief clinical manifestations: Bleeding disorder (thrombotic thrombocytopenic purpura)

| 1      | Thrombi* – brain, PTE | L, B | DAH |

Chief clinical manifestations: Tuberculous pleural effusion, abdominal pain and collapse

| 1      | PTE, Thrombi* – IVC, renal veins, SPV, Myocarditis* | K, L, P | Ac Panc |

Symbols: *Cardiac or vascular lesions that could have contributed to mortality as a secondary factor; †cardiac or vascular causes of death; †feature noted on ante-mortem investigations.


Involvement of other systems was the main cause of death in 19 (70.37%) patients, however, as seen in Table 1, cardiovascular...
Figure 1: Multiple warty lesions of NBTE seen along the line of closure of the mitral valve in a 22 years old, male who had presented with seizures. Other autopsy findings were lupus nephritis, thrombotic microangiopathy and streaky myocardial fibrosis.

Figure 2: Left anterior descending coronary artery with severe atherosclerotic narrowing and a tiny lumen (indicated by an asterisk) in a 18 years old, female who had streaky myocardial fibrosis. She had died of chronic renal failure. (HE, 160x)

Figure 3: Fresh mural thrombus adherent to right ventricular endocardium in a 19 years old, female with biventricular thrombi, coronary and pulmonary thromboembolism, and lupus nephritis. She had presented with lower limb gangrene and acute respiratory distress. (HE, 160x)

Figure 4: Intra-renal artery showing fibrinoid necrosis. Polyarteritis-like picture in a 14 years old, female SLE patient with multi-vessel vasculitis and coronary artery thrombosis. She had presented with severe respiratory distress and died due to myocardial ischaemia. (HE, 250x)

Figure 5: Large intrapulmonary artery with occlusive fresh thrombus in a 11 years old, male who presented with dyspnoea and pedal edema and died due to pulmonary thromboembolism with multiple lung infarcts. (HE, 63x)

lar lesions were significant enough to be the primary cause of death in eight of the 27 patients (29.62%). Majority, i.e. six (22.22%) were thrombotic manifestations that had resulted in myocardial ischemia in three (11.11%), pulmonary thromboembolism (PTE) in two (7.41%) and multiple brain infarcts in one (3.70%). In another 14 (51.85%) patients cardiovascular lesions like myocarditis, PTE, coronary artery disease (CAD), renal vasculitis and TMA could have contributed towards mortality, albeit as secondary factors.

Discussion

Although CVD is the third leading cause of death in SLE in western countries, its contribution to mortality in Indian subjects with the same disease has not been uniformly highlighted in various clinical studies. However, autopsy analyses have been more successful in this respect. The importance of CVD as a primary cause of death has been noted in two clinical reports where autopsies were performed in a propor-
tation of the cases.\cite{5,11} Our autopsy study observed CVD to be important factors contributing to mortality. Nevertheless, renal disease is the leading cause of death in SLE patients in India; as seen in our and other studies.\cite{6,7}

Thrombotic and atherosclerotic diseases are the commonest cardiovascular causes of mortality in SLE in western countries.\cite{2,3,8,12} The incidence of thromboses in our study is comparable with observations by Cervera et al.\cite{2} Thromboembolism was also seen in a similar proportion of cases in the only other autopsy series in Indian patients with SLE.\cite{4} However this study does not explain why thromboembolism was not considered to be a cause of death. SLE patients in western countries are noted to have a high risk for atherosclerotic CVD.\cite{13} However, coronary atherosclerosis was strikingly uncommon in our study, possibly due to the younger ages of our patients. Coronary atherosclerosis was also not noted in the other autopsy study of Indian patients with SLE.\cite{14} Nevertheless, CAD has been reported in young SLE patients.\cite{11,13} Our patient with coronary atherosclerosis was a young 18 years old, female. Between 14-69\% of SLE patients may have hypertension; renal failure and steroid therapy are proposed as the precipitating factors.\cite{16} In our study, all patients with hypertension had renal disease and were on steroid therapy.

NBTE was clinically significant in only few patients in our study, however steroid therapy implicated in healing of NBTE and the resultant fibrosis may have contributed to the observed mitral valve abnormalities.\cite{17} While NBTE was common in our study, classical LSE was rare and we wonder whether the former was due to SLE related hypercoagulability rather than immune complex deposition.\cite{18,19} Myocarditis is often subclinical in SLE but has a higher autopsy incidence.\cite{16} It was not diagnosed clinically in any of our patients. Lupus myocarditis is reported to be a poor prognostic factor.\cite{20} In our study it may have contributed as a secondary factor towards death. Pericarditis is common in SLE at autopsy.\cite{16,21} The incidence in our study is comparable to observations by Jindal et al.\cite{9} A necrotising vasculitis can affect various viscera in SLE.\cite{22} However a lower incidence of coronary arteritis was noted in our study and by Jindal et al as compared to the findings of Doherty et al.\cite{4,16} Vasculitis in SLE is associated with increased mortality.\cite{23} It was the cause of death in our patient with coronary arteritis. TTP usually presents with renal TMA in SLE.\cite{24} Our patient with TTP, interestingly, had no renal manifestations or lesions.

CVD may be subclinical in SLE.\cite{12,36} In our study only 22.22\% of patients had a clinically diagnosed cardiac abnormality. However the presence of lupus nephritis may mask involvement of other organ systems and the latter may thus remain undetected.

Only a proportion of SLE related deaths were autopsied in our study, thus selection bias could have influenced our findings and these may not accurately represent the picture in the general SLE population in India. Furthermore, while retrospec-

### References

**Histopathological study of the cardiac conduction system in systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory connective disease characterized by the production of auto-antibodies and immuno-complexes. SLE can affect all organs including heart.

Overall, the prevalence of cardiac involvement is estimated to affect more than 50% of SLE cases. All portions of the heart can be involved: pericardium, myocardium, cardiac conduction system, as well as coronary arteries. Pericarditis is the most common finding, while endocarditis is characterized by small nonbacterial vegetations along the valve leaflets known as Libman Sacks endocarditis. The involvement of the cardiac conduction system in SLE has been less commonly described but should always be taken into account.

SLE affects particularly young women and the passive acquisition of maternal IgG antibodies during pregnancy cause neonatal lupus, which is often related to congenital heart block.

Pre- or perinatal death from heart block due to severe autoimmune lesions of the atrioventricular junction has been reported with emphasis to the possible lethal association between maternal auto-antibodies and QT-prolongation.[1] Recently, we reported a case of sudden unexpected intrauterine death of a term fetus in a anti-cardiolipin positive mother.[2] The findings of the postmortem examination including the study of the cardiac conduction system and brainstem on serial sections ruled out the clinically suspected atrioventricular block due to the anti-cardiolipin antibodies, and disclosed severe bilateral hypoplasia of the arcuate nucleus which is an important chemoreceptor center for the control of breathing activity, located on the medullary ventral surface.[3,4]

As the volume of data on new morphological and functional alterations of the cardiac conduction system increases, it becomes worldwide essential that victims of SLE, especially in cases of sudden deaths in young age, be submitted to an in-depth necropsy examination, focusing particularly on the study of the cardiac conduction system on serial sections.[3,5] To examine the cardiac conduction system, two blocks of heart tissue should be obtained, for paraffin embedding. The first block contains the junction of superior vena cava and right atrium encompassing the entire area of the sino-atrial node. This sinoatrial block should be cut serially sectioned in a plane parallel to the crista terminalis. The second block contains the atrioventricular node (AV), His bundle down to bifurcation and bundle branches, with two centimeters of attached septum above and below. This AV junctional block is serially sectioned in a plane parallel to the two atrioventricular valve rings. All sections are to be cut serially at intervals of 40-mm (levels) and stained alternately with hematoxylin-eosin and trichromic Heidenhain. Should such an investigation not be feasible in the local facility, it is advisable that the hearts be preserved in buffered formalin and transported to a referral specialist center experienced in the study of cardiac conduction system.

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**References**


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**Expert’s Comments**
