

Do Serological Findings Correlate with Cardiovascular Manifestations of Systemic Lupus Erythematosus Patients in India?

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ABSTRACT

Introduction: Cardiovascular (CV) manifestations are common causes of morbidity and mortality in systemic lupus erythematosus (SLE). Auto-antibodies anti-dsDNA and Antiphospholipids antibodies (APLA) are both pathogenic and diagnostic. Only few reports exist of correlation of serological positivity with CV manifestations in SLE, especially in Indian subjects.

Aims and Methods: The study aimed to characterize the CV manifestations of SLE and correlate them with anti-dsDNA and APLA positivity. Anti-dsDNA was assayed by immunofluorescence staining on Hep-2 cells and APLA was measured by both liquid phase (lupus anticoagulant) and solid phase (anti cardiolipin) ELISA.

Results: All the study subjects (n=30) were females with a mean age of 23.07 years. The most frequent CV manifestation was that of pericardial involvement occurring in 63.3% (n=19) patients. Valvular heart disease [VHD (46.6%)], myocarditis (13.3%) and pulmonary artery hypertension [PAH(20%)] were the other major CV involvements. Serological assay revealed 83.3% (n=25) positivity for anti-dsDNA, while APLA was positive in 36.7% (n=11) of the patients. APLA was significantly associated with VHD (p=0.0295), and also with increased pulmonary artery systolic pressure (p<0.001) and myocarditis (p=0.005). No significant association of anti-dsDNA was found with either VHD (p=0.102), myocarditis or PAH, but it was significantly associated with pericarditis (p=0.028).

Conclusion: As observed in western series, APLA were significantly associated with VHD in SLE in our series; although in contrast, pericarditis was more prevalent in anti dsDNA positive than negative patients. These results could prompt early echocardiography in patients with SLE and APLA positivity, and invite larger studies to establish pathogenic role of these antibodies.

Caveat: This study was accepted for presentation at the Cardiological Society of India annual conference 2015 and abstracted in the Indian Heart Journal 67(2015):s125.

Key words: Cardiovascular (CV) involvement, systemic lupus erythematosus, anti-dsDNA, and Antiphospholipids antibodies.

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INTRODUCTION

Cardiovascular diseases are fairly common in systemic lupus erythematosus.¹ Auto-antibodies anti-dsDNA and Antiphospholipids antibodies (APLA) are both pathogenic as well as serve a role as biomarker for diagnosis and severity.² There are only very few reports of correlation of anti-dsDNA and / or APLA positivity with cardiovascular manifestations in SLE, especially in Indian subjects.

MATERIAL AND METHODS

Patient population: This study included 30 patients admitted with SLE and cardiovascular disease, defined by American College of Rheumatology criteria, in whom systematic transthoracic and/or transesophageal echocardiography were performed, with descriptions of the exposure to anti-dsDNA and APLA and of the outcome (cardiac manifestation) in the Department of Medicine, Calcutta National Medical College and Hospital, Kolkata.

Study design: It was a cross-sectional case control study. Among the selected cases, the test group of patients with antibody positivity were labelled as “anti-dsDNA positive / APLA positive” group and those with antibody negative were labelled as “anti-dsDNA negative/APLA

negative” group. All patients were subjected to detailed clinical examination, ECG, levels of cardiac biomarkers of necrosis and systematic echocardiography and the following cardiovascular manifestations were grouped.

Pericarditis – characterised by either asymptomatic or symptomatic pericardial effusion or pericardial rub or ECG changes suggestive of pericarditis.

Myocarditis – Characterised by decreased LV ejection fraction, arrhythmia, unexplained tachycardia, cardiomegaly and positive biomarkers of necrosis.

Valvular abnormalities – Characterised by valve thickening, regurgitation (symptomatic or asymptomatic), vegetation or rarely valve stenosis.

Pulmonary artery hypertension - characterised by pulmonary artery systolic pressure >40 mm of Hg.

Serological assay

APLA was measured by both liquid phase (lupus anticoagulant) ELISA and solid phase (anti cardiolipin) ELISA assays. Anti-dsDNA assay was performed by immunofluorescence staining on Hep-2 cells.

Statistical Analyses

Normally distributed variables were summarized using the mean \pm standard deviation (SD) and nonnormally distributed variables were by the median and range. Percentages were used when appropriate. Mann-Whitney test was performed accordingly. For example, for a given cardiac condition like pericarditis, comparison was made between two groups – anti-dsDNA positive and anti-dsDNA negative groups. Univariate comparisons between nominal variables were calculated using chi-square test or Fisher's test where appropriate. Two-tailed *P* values were reported; *P* values less than 0.05 were considered significant.

RESULTS

All the study subjects ($n=30$) were females with a mean age of 23.07 years. The most frequent cardiac manifestation was that of pericardial involvement occurring in 63.3% ($n=19$) patients. Valve thickening or regurgitation was seen in 46.6% ($n=14$) patients in echocardiography. Myocarditis was suspected on basis of clinical, echo and cardiac enzyme studies to be in 13.3% ($n=4$). The incidence of pulmonary artery hypertension was found to be 20% ($n=6$).

Serological assay revealed that 83.3% ($n=25$) of the patients were positive for anti-ds DNA, while APLA was found to be positive in 36.7% ($n=11$) of the patients having cardiac disease. APLA was found to be significantly associated with valvular heart disease ($p=0.0295$). APLA was also found to have significant associations with pulmonary artery systolic pressure ($p<0.001$) and myocarditis ($p=0.005$). Anti ds DNA was not found to have any significant association with either valvular heart disease ($p=0.102$), myocarditis or pulmonary artery hypertension. However, a significant association between anti dsDNA and pericarditis was found ($p=0.028$). Mean SLEDAI (SLE Disease Activity Index), which is a measure of disease severity, was not found to be associated with anti ds DNA ($p=0.79$) or APLA positivity ($p=0.113$).

DISCUSSION

Systemic lupus erythematosus (SLE) is an inflammatory multisystem disease associated with immune complex deposition, various laboratory abnormalities and clinical features. Virtually any organ-system can involve, including arthritis, glomerulonephritis, skin rashes, serositis, and neurological symptoms.³

The disease prevalence is 15 to 50/100 000 worldwide and 90% of the patients are women. All the patients in our study of SLE with cardiac diseases were females. It is more common in blacks and younger patients, but can occur at any age. The diagnosis of SLE is based on clinical and laboratory features. Over 95% of patients with SLE have a positive antinuclear antibody (ANA); however, an isolated finding of a positive ANA is not diagnostic of SLE. Anti-double-stranded DNA is more specific for SLE but with lower sensitivity, occurring in only 50% to 70% of patients.⁴

Cardiac involvement is common and a significant cause of morbidity and mortality in SLE patients with prevalence estimated to be as high as 50%.¹ However, prevalence varies significantly depending on disease definitions and whether subclinical disease is included or not. SLE may involve any structure of the heart.¹

Pericarditis – It is the most common cardiovascular (CV) manifestation in SLE. Clinical or echocardiographic features of pericarditis may be seen in 20% to 50% of patients in various series, and autopsy reports have demonstrated pericardial involvement in more than 60% of patients.⁵ Pericarditis is commonly associated with chest pain; however, patients may present with asymptomatic pericardial effusions. Effusions are usually mild, and cardiac tamponade are rare in patients without

renal failure. As expected, our series also showed pericarditis as the most common CV manifestation involving 63.3% of all patients.

Valvular heart disease (VHD) – defined by vegetation, valve thickening, and dysfunction, including Libman-Sacks (LS) endocarditis, is frequent in SLE.⁶ Studies using transesophageal echocardiogram have shown valvular abnormalities in over 50% of patients, varying from non-specific mild valvular thickening to nodules and large vegetations that may cause serious valvular dysfunction. Valve thickening or regurgitation was seen in 46.6% of patients in our study, majority of whom underwent transesophageal echocardiography.⁷

Myocarditis – Myocarditis is infrequent in SLE, including in autopsy series. In the present study, myocarditis was suspected on basis of clinical, echo and cardiac enzyme studies to be in only 13.3% of patients.⁸

Pulmonary hypertension – Pulmonary artery hypertension (PAH) is common, but usually mild, in SLE and its manifestations are similar to idiopathic pulmonary hypertension.⁹ Clinically significant PAH is less common and patients may be asymptomatic at the time of diagnosis by echocardiography. A pulmonary artery systolic pressure >40 mm Hg by echocardiography was observed in 20% of patients in our study.

Serological correlation – Anti ds-DNA is usually positive in 50–70% of SLE patients. Anti dsDNA which serve as a disease marker has also been proposed to play a role in disease pathogenesis.¹⁰ This hypothesis may partly explain the high prevalence (83.3%) of anti ds-DNA positivity in our series of cardiac SLE patients. Anti ds-DNA was not found to have any significant association with either valvular heart disease ($p=0.102$), myocarditis or pulmonary artery hypertension. However, a significant association between anti dsDNA and pericarditis was found ($p=0.028$). In contrast, Fabrizio *et al.* showed the frequency of serositis in persistently anti-dsDNA negative patients to be higher than 80%.² A small sample size could account for this difference.

Anti-phospholipid antibodies (APLA) are frequently associated with SLE. In one meta analysis, APLA was prevalent in 40% of SLE patients.¹¹ Because APLA are associated with a hypercoagulable state, thrombosis at the valvular surface could be a possible mechanism of increased HVD in SLE and of Libman Sachs endocarditis in particular.¹² A 3- to 5.5- fold higher risk for HVD has been reported in APLA-positive compared with APLA -negative SLE patients in western series.¹¹ In our series of Indian subjects, APLA was likewise found to be significantly associated with valvular heart disease ($p=0.0295$). These results should lead clinicians to perform systematic echocardiographic examinations in patients with SLE and APLA, even without a history of valve dysfunction, to detect patients with HVD or LS endocarditis who are at higher risk for arterial thrombosis. Further more in our study, APLA was also found to have significant associations with increased pulmonary artery systolic pressure ($p<0.001$) and myocarditis ($p=0.005$).

Although this study aims to highlight the cardiac manifestations and serological correlations in Indian SLE subjects in whom previous data is sparse, the present study may be limited by its sample size and referral bias.

CONCLUSION

Cardiac manifestations are fairly common in SLE and may lead to increased morbidity and mortality. Pericarditis is the most common cardiac involvement but valvular heart diseases (VHD) are fairly common in SLE. Serological positivity (anti ds-DNA and APLA) in cardiac patients of SLE may indicate a diagnostic as well as a pathogenic role of these antibodies. As observed in western series, APLA were significantly associated with VHD in SLE in our series; although in contrast, pericarditis was more prevalent in anti dsDNA positive than negative patients. This study results could prompt early echocardiographic examinations

in patients with SLE and APLA positivity, and invite larger studies to establish pathogenic role of these antibodies.

REFERENCES

- Moder KG, Miller TD, Tazelaar HD. Cardiac involvement in systemic lupus erythematosus. *Mayo Clin Proc.* 1999;74(3):275-84.
- Fabrizio C, Fulvia C, Carlo P, Laura M, Elisa M, Francesca M. Systemic Lupus Erythematosus with and without Anti-dsDNA Antibodies: Analysis from a Large Monocentric Cohort. *Mediators Inflamm* 2015 6;2015:328078. Epub 2015 May 6.
- Alexandra Villa-Forte, Brian F. Mandell. Cardiovascular Disorders and Rheumatic Disease. *Revista Española de Cardiología (English Edition)*. 2011;64(9):809-17.
- Isenberg DA, Manson JJ, Ehrenstein MR, Rahman A. Fifty years of anti-ds DNA antibodies: are we approaching journey's end? *Rheumatology*. 2007;46(7):1052-6.
- Crozier IG, Li E, Milne MJ, Nicholls MG. Cardiac involvement in systemic lupus erythematosus detected by echocardiography. *Am J Cardiol.* 1990;65(16):1145-8.
- Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006;4(2):295-306.
- Roldan CA, Shively BK, Crawford MH. An echocardiographic study of valvular heart disease associated with systemic lupus erythematosus. *NEJM.* 1996;335(19):1424-30.
- Doria A, Iaccarino L, Sarzi-Puttini P, Atzeni F, Turriel M, Petri M. Cardiac involvement in systemic lupus erythematosus. *Lupus.* 2005;14:683-6.
- Johnson SR, Gladman DD, Urowitz MB, Ibanez D, Granton JT. Pulmonary hypertension in systemic lupus. *Lupus.* 2004;13(7):506-9.
- Foster MH, Cizman B, Madaio MP. Nephritogenic autoantibodies in systemic lupus erythematosus: immunochemical properties, mechanisms of immune deposition, and genetic origins. *Laboratory Investigation.* 1993;69(5):494-507.
- Zuily S, Regnault V, Selton-Suty C, Eschwège V, Bruntz J-F, Bode-Dotot E. Increased Risk for Heart Valve Disease Associated With Antiphospholipid Antibodies in Patients With Systemic Lupus Erythematosus: Meta-Analysis of Echocardiographic Studies. *Circulation.* 2011;124(2):215-24.
- Ford SE, Lillicrap D, Brunet D, Ford P. Thrombotic endocarditis and lupus anticoagulant: a pathogenetic possibility for idiopathic 'rheumatic type' valvular heart disease. *Arch Pathol Lab Med.* 1989;113(4):350-3.

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