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Cardiac Involvement in Systemic Lupus Erythematosus Patients: Imaging Approach

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ABSTRACT

***Background**: Lupus myocarditis is a potentially life-threatening condition. It can be oligosymptomatic or even silent. Lupus myocarditis necessitates a reliable imaging tool for early detection. **Objective:** This study aimed to assess myocardial edema in active Systemic Lupus Erythematosus (SLE) patients with T2 weighted dual inversion recovery black blood sequence. **Methods:** Cardiac MRI was performed on 20 active SLE patients (17 females and 3 males) with no history of previous cardiovascular diseases. Transthoracic echocardiography was performed for all patients. **Results:** Functional MRI analysis revealed preserved EF% (n=12) and reduced EF% (n=8). A highly statistically significant correlation between EF measured by ECHO and CMR was detected. The analysis revealed an excellent agreement between the two measures, ICC=0.753. Myocardial edema was noticed in 5 patients. One case showed delayed enhancement in LGE images and 7 patients (7/20) had pericardial effusion successfully diagnosed by both echocardiography and CMR. **Conclusion:** T2-double IR black blood imaging identified the worthy percentage of myocardial edema in active SLE patients, even in absence of clinical symptoms, denoting early myocardial involvement. Thus, cardiac MRI is a potential non-invasive diagnostic tool for cardiac surveillance in SLE patients.*

Keywords: Cardiac MRI, Systemic lupus erythematosus, Echocardiography

INTRODUCTION

Myocardial involvement in the course of systemic lupus erythematosus (SLE) is not uncommon. Assessment of cardiac functions should be carried out in lupus patients who clinically present with arrhythmias, tachycardia, and dyspnea which considered a life-threatening manifestation of SLE [1].

In the past, cardiac manifestations were profound leading to death and they were frequently discovered on post-mortem examination. Recently, cardiac manifestations are often mild and are easily early recognized by echocardiography and non-invasive tests [2-6].

The pathogenesis of myocardial necrosis and tissue destruction is attributed to inflammatory and immune-mediated pathways [7,8]. Non-specific clinical symptoms, invasive endomyocardial biopsy together with non-conclusive echocardiographic finding hinder myocardial tissue characterization [2-6].

In 1996, a new T2 based-MRI pulse sequence has been established for the detection of myocardial edema [9]. Edema imaging sequence has been utilized to differentiate acute versus chronic myocardial infarction, transplant rejection, myocarditis and stress-induced cardiomyopathy [10-15]. MRI is used for diagnosing myocardial involvement in SLE as a T2 value sensitively indicated myocardial relaxation abnormalities, even at the preclinical stage [16].

This study was conducted to assess myocardial edema in active SLE patients with T2 weighted dual inversion recovery black blood sequence.

PATIENTS AND METHODS

Patients

This prospective study was approved by IRB of Mansoura University and written informed consent was taken from all participants. Total 20 SLE patients were recruited from the Rheumatology and Immunology unit in the period from March 2017 to January 2018.

Inclusion Criteria

Active SLE patients based on SLEDAI (systemic lupus disease activity index) with no history of previous cardiovascular diseases were included in the study.

Exclusion Criteria

Patients with congestive heart failure, GFR <30 ml/min and known contraindications to MRI examination were excluded.

Methods

Echocardiography: A two-dimensional echocardiogram was done to help in the detection of pericardial effusion, cardiac valves affection and cardiac muscle affection. Patients were subjected to detailed Trans-thoracic echo (TTE) using: MEDISON (Medison CO-LTD), model-Sonoace X6 power 100-120/200-240 V-0.8/5A, 50/60 HZ equipped with 2.5-5 MHZ transducer.

M mode echocardiography: Left ventricular parameters, End-diastolic diameter (EDD), End-systolic dimensions (ESD), Ejection fraction (EF), left ventricular Posterior wall thickness (PWT) and Interventricular septal thickness (IVST). LV EFs of <52% for men and <54% for women are suggestive of abnormal LV systolic function [17].

Anteroposterior left atrial diameter; normal references for men 3.0 to 4.0 cm and for women 2.7 to 3.8 cm [17]. Pericardial effusion by the presence of persistence of an echo-free space between the epicardium and parietal pericardium throughout the cardiac cycle was present.

Two-dimensional Doppler echocardiography: Assessment of regional LV function and wall motion abnormalities in the 17-segment model in the apical 2 chambers, 4 chambers, apical long axis, and short axis views. Visual assessment was used for regional myocardial function evaluation based on the observed wall thickening and endocardial motion of each myocardial segment. A semi-quantitative wall motion was either:

- Normal or hyperkinetic
- Hypokinetic (reduced thickening)
- Akinetic (absent thickening, or scar)
- Dyskinetic (systolic thinning or stretching, e.g., aneurysm)

Assessment of valvular lesions was performed by assessment of valve morphology, thickening or masses, and color flow mapping for assessment of mitral or aortic regurgitation.

Assessment of pericardial was involved in all standard echocardiographic views and subcostal views. For the presence of pericardial effusion or other findings like increased pericardial brightness, pericardial thickening, and abnormal septal bounce. Semi-quantitative assessment of the size and of the effusion on the basis of the size of the echo-free space was seen between the parietal and visceral pericardium at end-diastole; trivial (seen only in systole), small (<10 mm), moderate (10 to 20 mm), large (>20 mm), or very large (>25 mm) [18].

Cardiac MRI: All cases were examined using (1.5 T Ingenia Philips Medical Systems, Best the Netherlands) equipped with dedicated cardiac MR software. All patients were in sinus rhythm during the examination, no sedation was used. Imaging was performed supine with the patient positioned in a 6-element phased array surface coil. All images were ECG gated and were performed with breath hold.

CMR protocol: The scan protocol was carried out in the following order: after a survey and reference scan, steady states free precession sequence with parallel imaging (balanced Fast Field Echo (b-FFE) was acquired in 2-chamber, 4-chamber and multi-slice short axis during single breath-holds (end-expiratory of about 9-13 sec) in 25 cardiac phases. TR/TE=3.2/1.7, 215-256 × 256 matrices and 60 flip angles with 320 mm FOV were performed for all patients. In the short axis views, we used 8 mm slice thickness and 10-12 slice numbers encompassing the ventricles. For tissue characterization T2- double inversion recovery black blood imaging was performed. Delayed myocardial enhancement scans were carried out in short axis, 2-chamber and 4-chamber orientations 10 to 15 min after IV injection of gadolinium (0.2 mm/kg). IR TFE breath holds with TR/TE=6.1/3; flip angle 25 and 8 mm slice thickness was used. The inversion time was chosen by performing a T1 mapping using a look-locker sequence in each patient to estimate the proper inversion time which ranged from 200 to 320 ms. The evidence of delayed myocardial enhancement was confirmed by imaging different views of the myocardium.

Image Interpretation: Cardiac MRI images were evaluated by a concurrence of two radiologists who were blinded to the echocardiographic data, using cardiac analysis tool pack on Philips extended workstation (EWS) View Forum.

Myocardial edema assessment: Myocardial edema is identified on T2-double IR black blood imaging as areas of high signal intensities. Assessment of location of edema was according to 17 segment model. Distribution of myocardial edema is assessed (subendocardial, transmural, subepicardial) and morphology of edema (mural, linear, patchy) for the comparison to delay the enhancement images [19,20]. Wall motion abnormality of the same regions was assessed on the cine images [16].

LV functional analysis: LV global function was calculated, after manual tracing of the endocardial and epicardial contours of the left ventricular wall at end diastole and end systole on the short axis cine images. Wall thickness, wall motion abnormality, EDV, ESV, CO, SV, and EF were calculated [21]. Pericardial thickness and presence of pericardial effusion were assessed in T2WI as well as extracardiac findings. Enhancement of pericardium and myocardium was assessed in LGE images with a full description of the pattern, distribution, and burden of enhanced areas.

Ethical Standards and Patient Consent

We declare that all human studies have been approved by the Institutional Review Board of Faculty of Medicine, Mansoura University (MFM-IRB) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave written informed consent from parents of enrolled patients and control group prior to inclusion in this study. We declare that this manuscript does not contain experimental or animal studies.

Statistical Methods

The mean and standard deviation have been used for quantitative variables and frequency and rate have been used for qualitative variables. Chi-square test and t-test were used for comparison of frequencies and means as well. Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. McNemar's test was used for determination of differences on a dichotomous dependent variable between two related groups. The intraclass correlation coefficient was analyzed for agreement between diagnostic methods. Paired sample t-test was used for concordance of both methods. A $p \leq 0.05$ was considered statistically significant at CI 95%. SPSS statistical software version 20.0 was used for data analysis.

RESULTS

In this study, 20 active SLE patients were included and their demographic data and clinical features were presented in Table 1. Their age ranged between 18 to 55 years with mean age of 30.1 years. There were 3 males and 17 females. Median disease duration was 3 years. Patients were clinically presented with chest pain (n=14), shortness of breath (n=11) and hypertension (n=6) with overlapping symptoms. Two patients were free of cardiac symptoms and agreed to participate in the study. According to SLEDAI, there was mild activity (n=5), moderate (n=7), high (n=6) and very high disease activity (n=2) (Figure1).

Table 1 SLE demographic and clinical data of participants

Criteria		Value
Age (years)		30.1 ± 2.2
Sex	Female	17
	Male	3
Duration of SLE year (range)		3 (1-10%)
Clinical symptoms	Chest pain n (%)	14 (70%)
	Shortness of breath n (%)	11 (55%)
	Hypertension n (%)	6 (30%)
	Asymptomatic n (%)	2 (10%)
SLEDAI	Mild (1-5) n (%)	5 (25%)
	Moderate (6-10) n (%)	7 (35%)
	High (11-19) n (%)	6 (30%)
	Very high (>20) n (%)	2 (10%)

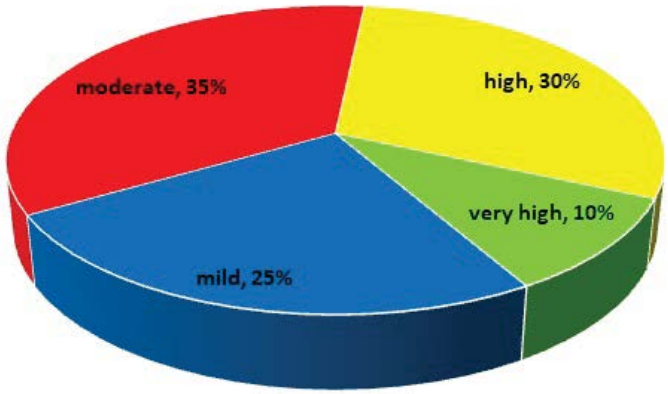

Figure 1 Disease activities of SLE according to the SLEDAI score of all studied patients

Transthoracic Echocardiographic findings

ECHO findings in studied SLE patients are presented in Table 2. EF% was preserved in 13 patients (65%) and reduced EF % in 7 patients (35%). In total, 15 patients (75%) had free wall motion, while 3 (15%) had regional hypokinesia and 2 (10%) had global hypokinesia. Pericardial effusion was found in seven cases (35%).

Table 2 ECHO findings in SLE patients

Criteria		Value
EF (%)	Preserved n (%)	13 (65%)
	Reduced n (%)	7 (35%)
Wall motion	Free wall motion n (%)	15 (75%)
	Regional hypokinesia n (%)	3 (15%)
	Global hypokinesia n (%)	2 (10%)
Pericardial effusion	Absent n (%)	13 (65%)
	Present n (%)	7 (35%)

Functional MRI analysis revealed preserved EF% (n=12) and reduced EF% (n=8) (Table 3). The EF % results by echo and Cardiac MRI were presented in Table 4. A highly statistically significant correlation was found between EF measured by ECHO and CMR. The analysis revealed an excellent agreement between the two measures, ICC = 0.753.

Table 3 Cardiac MRI findings and results of functional evaluation of 20 SLE cases

Criteria		Value
EF	Normal EF n (%)	12 (60%)
	Reduced EF n (%)	8 (40%)
Cardiac MRI findings	Myocardial edema n (%)	5 (25%)
	Pericardial effusion n (%)	13 (65%)
	Pleural effusion n (%)	5 (25%)
	Bilateral pleural effusion + ascites n (%)	3 (15%)
Correlation	r	0.725
	p	<0.001
ICC	estimate	0.753
	95% CI	0.222-0.911
ICC: intra class correlation coefficient; CI: confidence interval		

Table 4 Reliability measurement of EF by ECHO and CMR

Cases ID		7	8	17	18	19
SLEDAI		18 (high)	6 (moderate	14 (high)	16 (high)	2 (mild)
ECHO	EF (%)	45 (reduced)	73 (normal)	54 (reduced)	50 (reduced)	70 (normal)
	Wall motion	Regional hypokinesia	free wall motion	free wall motion	free wall motion	Regional hypokinesia
	Effusion	Present	Present	Present	Present	Absent
CMRI	EF (%)	35 (reduced)	56.3 (reduced)	42 (reduced)	58 (reduced)	65.8 (normal)
	EDV (ml)	133.6	104	78	150	186
	ESV (ml)	87	45.5	45.4	63	63.4
	SV (ml)	46.7	59	32.4	87	122
	Pericardial effusion	Minimal	No	Minimal	Moderate	No
	Associated findings	No	No	bilateral pleural effusion and ascites	Right-sided pleural effusion	No
	Wall motion	hypokinesia	Free wall motion	Free wall motion	hypokinesia	hypokinesia
Myocardial segment		Mid-wall anterior and anteroseptal apical segments.	Mid-wall Septal	Mid-wall Lateral apical segment.	Epicardial distribution, mid-lateral segment of myocardium	Epicardial and mid wall distribution (basal, mid and apical inferior, inferolateral and lateral segments)
LGE		Negative	Negative	Negative	Negative	Positive

Myocardial edema (Figures 2 and 3) showed tissue characterization sequences which revealed abnormal high signal intensity areas within the myocardium in 5 patients. One case showed delayed enhancement in LGE images (Figure 2). Total 7 patients (7/20) had pericardial effusion successfully diagnosed by both echocardiography and CMR (Figure 3).

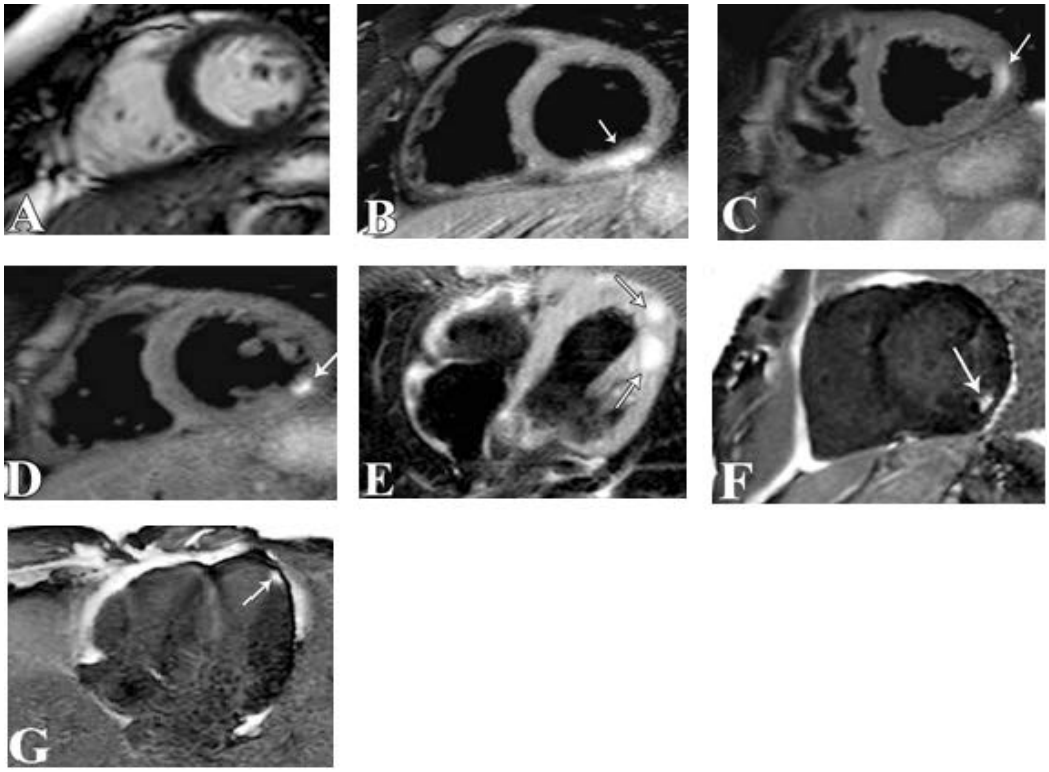

Figure 2 Active SLE Male patient 19 years old; A: T2 weighted bright blood, short axis view shows no pericardial effusion; B, C, and D: T2 weighted dual inversion dark blood images, short axis; and E: 4 chamber views show abnormal high signal intensity in the myocardium (myocardial edema). Subepicardial and mid wall distribution (basal, mid and apical inferior, inferolateral and lateral segments); F and G. Dynamic MRI short axis and 4 chamber views show delayed enhancement of apical inferolateral segment of myocardium on the postcontrast study

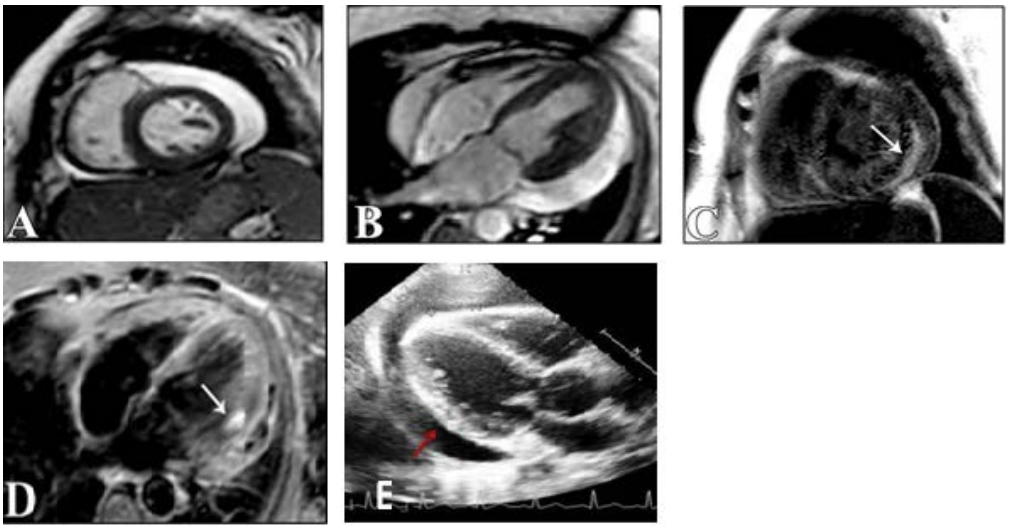

Figure 3 Female patient 50 years old with a history of systemic lupus for 10 years with no cardiac symptoms. EF was 50% by echocardiography with no regional wall motion abnormalities and by MRI was 58%. SLEDAI was high (score=16); A and B: T2 bright blood, short axis, and 4 chamber views show moderate pericardial effusion; C and D: T2 weighted dual inversion dark blood images, short axis, and 4 chamber views show abnormal high signal intensity in the myocardium (myocardial edema). Subepicardial in a mid-lateral segment of the myocardium of the left ventricle; E: Parasternal 4 chamber (two dimensional) echocardiographic view shows pericardial effusion

DISCUSSION

In the current study, tissue characterization performed by T2 double inversion recovery technique (edema sequence) revealed myocardial edema in 25% of tested cases with one clinically silent case denoting subclinical myocarditis. Only one case of them showed enhancement pattern of myocarditis on LGE having epicardial and midwall distribution. In agreement with previous reports that showed that myocardial edema can be detected even in those who do not meet clinical criteria for acute myocarditis [22,23].

Subclinical myocarditis is common in SLE patients. In a study of active SLE patients, cardiac MRI diagnosed myocarditis is more frequent than clinical diagnosis. Also even in inactive SLE patients and normal cardiac function, low-grade myocardial inflammation already existed on cardiac MRI [3]. Myocardial edema can be detected even in those who do not meet clinical criteria for acute myocarditis [24,25].

These findings were in agreement with Mavrogeni, et al., in 2013, using cardiac MRI has suggested that subclinical myocarditis is common in SLE patients [26]. Also even in SLE patients with inactive disease and normal cardiac function, low-grade myocardial inflammation is already present [27].

The associations of myocarditis or fibrosis with SLEDAI scores and anti-ds DNA antibodies may indicate a mechanistic link between SLE activity, autoimmunity, and subclinical myocardial pathology. Although the exact pathophysiological mechanisms underlying the development of myocardial abnormalities are not clear, global diseases activity may be accompanied by subclinical end-organ injury [28,29].

Thus, much more attention should be addressed to patients with no cardiac manifestations or apparent clinical activity before drug dose modulation in the state of remission of the disease which could be harmful if silent myocardial edema was existent. Lupus myocarditis necessitates prompt medical attention because of the potential of arrhythmias, conduction defects, dilated cardiomyopathy and finally HF [8]. It can be rather oligosymptomatic, so more advanced imaging modalities, as Cardiovascular Magnetic Resonance (CMR) is required to ascertain early diagnosis [26].

Previous studies of myocardial inflammation by MRI in SLE applied the edema ratio (dividing myocardial signal by the signal of skeletal muscle on fast spin-echo based dark blood T2 WI), this is uncertain because of variability of T2 signal with heart rates, blood flow, coil inhomogeneity, and cardiac motion, also it postulates normal skeletal muscle signal that may be doubtful due to the potential of coexistent low-grade myositis [17,27].

CMR has developed great usefulness in the evaluation of cardiac morphology, function and the detection of myocardial inflammation and fibrosis [25]. It is deemed the technique of choice for the assessment of the pathophysiologic process of cardiac disease in systemic autoimmune disorders including SLE [8,30]. CMR has surpassed other imaging techniques in its capability of tissue characterization. It is also highly reproducible, operator-independent [25,26].

In the present study, regarding to ejection fraction, there was a significant correlation between EF measured by echocardiography and CMR. Also, no significant differences were found in pericardial effusion between ECHO and CMR which is in agreement with Plazak, et al., in 2011 [31].

Five cases had wall motion abnormalities detected by echocardiography, two of them were found to have myocardial edema by MRI study. Echocardiographic studies cannot accurately diagnose myocarditis, but global hypokinesia, in the absence of other known causes, is strongly suggestive. Segmental areas of hypokinesia can be also indicative of the disease [32]. The systolic function may be preserved until late in the course of the disease limiting the potential of echocardiography to screen for early involvement. It may be insensitive for diagnosis of pericarditis when it is not associated with effusion or thickening [22,32,33].

Echocardiography is a cheap, widely obtainable, bedside technique capable of providing data about atrial and ventricular function, wall motion, and valvular features [33]. Echocardiographic assessment is still considered the gold standard for pericardial and valvular evaluation [34]. It remains the mainstay of non-invasive techniques for the regular evaluation of cardiovascular involvement in SLE and should be done on a yearly interval, regardless symptoms in every single SLE patient [28].

Endomyocardial biopsy has been considered as the cornerstone for myocardial evaluation, yet it cannot be carried out regularly and frequently, especially in subclinical cases. So, the prevalence of myocardial involvement in SLE patients may be notably overlooked and remains a direct contributor to the cardiovascular morbidity and mortality known to be increased in SLE even in young individuals. Also, it may have hazardous complications [35].

CONCLUSION

T2-double IR black blood imaging identified the worthy percentage of myocardial edema in active SLE patients, even in absence of clinical symptoms, denoting early myocardial involvement. Thus, cardiac MRI is a potential non-invasive diagnostic tool for cardiac surveillance in SLE patients.

DECLARATIONS

Acknowledgment

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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