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Original Research Article

Cardiac involvement in systemic sclerosis- a hospital-based study in tertiary health care centre in Puducherry, India

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ABSTRACT

Background: Systemic sclerosis (SSc) is a complex immune-mediated condition. Systemic sclerosis related cardiac pathologies can be detected in an early stage using various imaging techniques. Aim was to study cardiac involvement in patients with systemic sclerosis.
Methods: The present study was carried out as a descriptive hospital-based study of 31 patients with systemic sclerosis above 13 years of age, of either sex or who fulfilled American Rheumatism Association (ARA) diagnostic criteria. A detailed profile of lab investigations and imaging including inflammatory markers, immunological parameters, ECG and ECHO were done. Data analysis was done using SPSS (statistical package for social sciences) version 21.0. A p value <0.05 was considered statistically significant.
Results: Median age of the study patients was 36 years and 90% females. Nearly 19% of the patients were classified as limited, 39% as early diffuse and 42% as late diffuse systemic sclerosis. Rheumatoid factor was positive in 19% of the patients, while antinuclear antibodies (ANA) was positive in all the patients. Pulmonary arterial hypertension (PAH) was noted in 61%. Right ventricular systolic pressure (RVSP) was relatively higher in limited SSc patients. Patients with late diffuse SSc had higher RVSP than early diffuse SSc. RV systolic function assessed by tricuspid annular plane systolic excursion (TAPSE) showed abnormally low value (<18) in five patients.
Conclusions: Considerable proportion of patients with systemic sclerosis present with cardiac involvement. Tissue Doppler imaging can help in diagnosing subclinical RV dysfunction by measuring TEI index of right ventricle, which can predict PAH.

Keywords: Cardiac involvement, Systemic sclerosis, Tissue Doppler imaging

INTRODUCTION

Systemic sclerosis (SSc) is a complex immune-mediated condition that poses a significant clinical challenge for both patients and doctors as it is characterized by a chronic and frequently progressive course and by extensive patient-to-patient variability. Exact cause of systemic sclerosis remains vague and happens more often in women, with a peak of onset in the fifth decade of life.[1] Despite evidence of improved longevity, particularly for patients with widespread cutaneous systemic sclerosis, systemic sclerosis has a high mortality rate- higher than any other rheumatic condition. For the patient, systemic sclerosis is linked to significant outcome uncertainty and the emergence of potentially fatal or life-impairing symptoms. Due to its uncommonness, systemic sclerosis is classified as an orphan illness with a significant unmet medical need.[2] Primary cardiac involvement, which results from systemic sclerosis, might show up as pericardial,

conduction system, or myocardial fibrosis, as well as, valvular disease less commonly. Furthermore, pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), and kidney pathology may all contribute to the development of cardiac complications in systemic sclerosis as a secondary phenomenon.[3] In the routine cardiovascular system evaluation, clinical examination and common non-invasive investigations like an electrocardiogram (ECG) and a chest x-ray are used, although their sensitivity is reported to be low. Systemic sclerosis related cardiac pathologies can be detected in an early stage using various sensitive techniques such as echocardiography, particularly tissue Doppler imaging (TDI), cardiac computed tomography (CT), single-photon emission CT (SPECT), magnetic resonance imaging (MRI), positron emission tomography (PET), and radionuclide ventriculography.[3-5] The addition of TDI, a contemporary echographic technology that enables precise evaluation of local and global left ventricle (LV) and right ventricle (RV) function, has increased the accuracy and repeatability of regular echocardiography. Dermatological presentation of systemic sclerosis is Indian population is well documented across the country by various different authors.[6,7] However, there is a lack of studies that evaluated the cardiac involvement in systemic sclerosis. The present study was undertaken with an aim to describe the cardiac involvement in patients with systemic sclerosis.

METHODS

The present study was carried out as a descriptive hospital-based study of patient with systemic sclerosis in Jawaharlal Institute of Postgraduate Medical Education and Research in Puducherry, South India. Patients above 13 years of age, of either sex and who fulfilled American Rheumatism Association (ARA) diagnostic criteria for systemic sclerosis comprised the study population.[8] All 31 patients eligible to participate based on the predefined inclusion and exclusion criteria during the study period comprised the study sample. Patients with autoimmune diseases other than systemic sclerosis, prior pacemaker implantation, congenital or valvular heart disease, pericarditis, known coronary heart disease, diabetes mellitus, hypertension not related to scleroderma renal crisis, history of pulmonary embolization, individuals receiving digitalis, β blockers/other anti-arrhythmic drugs were excluded from the study. Informed written consent was obtained from all study patients and institute ethical committee approval was obtained in advance. A detailed clinical history of all the subjects was noted, especially regarding cutaneous manifestations, occurrence of Raynaud's phenomenon and cardiorespiratory symptoms like chest pain, dyspnoea, palpitations, syncope etc. A detailed physical examination was done including a meticulous cutaneous examination, followed by modified Rodnan skin scoring (MRSS).[9] Based on this, patients were subsequently classified into diffuse/limited systemic sclerosis. Patients with limited cutaneous systemic sclerosis, also known as CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia), are classified to have limited disease. Patients with skin thickening and fibrosis that are more widespread and affect areas beyond the distal extremities, such as the upper arms, thighs, and trunk are classified as early diffuse. Patients having skin involvement that is typically more extensive and can affect larger areas of the body, including the proximal extremities, chest, and abdomen are classified as late diffuse. A detailed profile of lab investigations and imaging including inflammatory markers, immunological parameters [antinuclear antibodies (ANA) profile and rheumatoid factor], ECG, echocardiography (ECHO) [2D, M mode, pulsed wave (PW), continuous wave, colour doppler, TDI] were done.[10] Data entry was done in MS Excel 2013 and data analysis was done using IBM statistical package for social sciences (SPSS) Armonk, NY Version 21.0. Means and proportions were presented for continuous and categorical variables respectively. Normal distribution was tested for continuous variables and appropriate non parametric tests were applied for data that were not normally distributed. Differences in proportions were tested using chi square test for statistical significance. Differences in means were tested using independent sample t test and Mann Whitney U test for parametric and non-parametric data respectively. A p value <0.05 was considered statistically significant.

RESULTS

Median age of the study patients was 36 years and most of them were females (90%). Nearly 19% of the patients were classified as limited, 39% as early diffuse and 42% as late diffuse systemic sclerosis. Salt and pepper pigmentation (23), restricted mouth opening (22), Raynaud's phenomenon (20), dysphagia (18) and arthralgia (17) were the most common features. Median MRS score was measured to be 9, and it was found to be significantly high in case of patients who had diffuse type (p value- 0.003). No significant differences were noted in vital signs between sub classifications of systemic sclerosis. Velcro crepts were recorded in 19 patients and most of whom had diffuse type (18) vide Table 1.

Rheumatoid factor was positive in 19% of the patients, while ANA was positive in all the patients, 23 of them had nuclear pattern and eight had centromere pattern. Anti celomere antibodies were positive in all six patients of limited type of systemic sclerosis. No significant differences were noticed between the subtypes in terms of blood counts, and ESR. Patient with late diffuse type of SSc had higher mean random blood sugar (RBS) values as compared to early diffuse type (p value- 0.004). No significant differences were observed between the subtypes in terms of blood urea nitrogen (BUN), creatinine, electrolytes, and liver function parameters. raised creatine phosphokinase (CPK)- T >170 IU/l was seen in 13 patients (limited 2, early diffuse 5, late diffuse 6) and 9 had myositis (limited 2, early diffuse 4, late diffuse 3). Oesophageal scintigraphy was done in all patients, gastro esophageal reflux disease (GERD) was seen in 23 patients and features of interstitial lung disease (ILD) were noticed in six patients (Table 2).

Table 1: Distribution of study patients based on baseline clinical characteristics (n=31).

Clinical characteristics	Total (31)	Limited (6)	Diffuse (25)	P value	Early diffuse (12)	Late diffuse (13)	P value
Median age (in years)	36	43	35	0.43	32.5	44	0.34
Median duration of illness	36	18	50	0.34	10	72	36
Median MRSS	9	4	10	0.003	13	10	0.97
Fatigue	12	3	9	0.65	4	5	0.78
Arthralgia	17	5	12	0.18	7	5	0.43
Arthritis	8	3	5	0.16	4	1	0.16
Muscle weakness	7	3	4	0.11	3	1	0.32
Myositis	9	2	7	0.79	4	3	0.67
Digital tip ulcer	14	2	12	0.66	3	9	0.04
Gangrene	4	0	4	0.56	0	4	0.09
Puffy finger	6	2	4	0.56	2	2	0.93
Calcinosis	5	0	5	0.55	3	2	0.64
Raynaud's phenomenon	20	3	17	0.63	7	10	0.41
Telangiectasia	6	1	5	0.85	2	3	0.68
CREST	3	0	3	0.9	1	2	0.58
Salt & pepper pigmentation	23	2	21	0.02	11	10	0.59
Pinched nose	15	0	15	0.01	6	9	0.42
Restricted mouth opening	22	3	19	0.32	10	9	0.64
Dysphagia	18	2	16	0.2	9	7	0.41
Sec Sjogren's	4	0	4	0.56	3	1	0.32
Systolic blood pressure (SBP)	109.74±10.11	116.66±8.16	108.08±9.95	0.06	111±9.81	105.38±9.67	0.06
Diastolic blood pressure (DBP)	75.61±5.57	75±5.47	75.76±5.69	0.76	77.83±6.17	73.84	0.19
Pulse rate	83.16±3.33	82.66±2.42	83.28±3.55	0.69	84 ±3.71	82.61 ±3.4	0.55
P_2 loud	13	4	9	0.2	2	7	0.09
Velcro crepts	19	1	18	0.02	9	9	1.00
GERD	23	4	19	0.63	11	8	0.16
ILD	19	1	18	0.02	9	9	0.74

Table 2: Distribution of study patients based on laboratory parameters (n=31).

Parameters	Total (31)	Limited (6)	Diffuse (25)	P value	Early diffuse (12)	Late diffuse (13)	P value
High high sensitive C reactive protein (hsCRP)	19	3	16	0.65	9	7	0.65
Rheumatoid factor (RF) +ve	6	2	4	0.56	3	1	0.32
Haemoglobin (Hb)	11.19±1.67	10.71±2.03	11.30±1.6	0.44	11.42±1.36	11.19±1.83	0.72
Total leucocyte count (TLC)	8500 (3800-16,500)	6550 (5020-9850)	8800 (3800-8800)	0.04	9150 (5400-16500)	8800 (3800-13800)	0.68
Platelet	2.65 (1.32-4.44)	3.0 (0.152-3.65)	2.65 (13.2-4.44)	0.82	2.955 (1.32-4.44)	2.58 (1.51-3.55)	0.21
Erythrocyte sedimentation rate (ESR)	46 (11-84)	42.5 (18-50)	48 (11-84)	0.42	44 (11-84)	50 (12-84)	0.91
RBS	86 (63-136)	99 (63-120)	79 (65-136)	0.28	75.5	97	0.004
BUN	18 (12-39)	17.5 (16-37)	18 (12-39)	0.49	16 (12- 29)	19 (15-39)	0.08
Creatinine	0.65±0.13	0.75±0.12	0.63±0.13	0.06	0.59±0.11	0.67±0.13	0.10
Na+	138.25±3.57	135.83±2.31	138.84±3.61	0.06	138.08±3.26	139.53±3.9	0.32
STP	6.94±0.7	7±0.44	6.93±0.75	0.63	6.92±0.85	6.94±0.69	0.94
Albumin	3.72±0.49	3.66±0.44	3.73±0.51	0.76	3.64±0.42	3.82±0.59	0.39
Bilirubin (Total)	0.59±0.08	0.63±0.10	0.58±0.08	0.22	0.57±0.06	0.59±0.10	0.62
Aspartate aminotransferase (AST)	27 (14-94)	22.5 (17-88)	27 (14-94)	0.9	30 (14-94)	27 (14-85)	0.62
Alanine amino transferase (ALT)	20 (10-94)	21 (17-87)	20 (10- 94)	0.8	23.5 (15-65)	18(10-94)	0.27
Alkaline phosphatase (ALP)	79 (34-235)	54.5 (37-178)	81 (34-235)	0.47	62 (35-150)	100 (34-234)	0.05
CPK - T	86 (14-915)	97 (35-575)	86 (14-915)	0.9	109 (46-915)	80 (14-419)	0.27

Table 3: Distribution of study patients based on cardiac assessment parameters (n=31).

Parameters	Total (31)	Limited (6)	Diffuse (25)	P value	Early diffuse (12)	Late diffuse (13)	P value
PAH	12	4	8	0.17	2	6	0.2
RVSP (CW doppler)	30 (15-105)	37.5 (20-86)	30 (15-105)	0.49	30 (15-65)	35 (17-105)	0.6
Tei index	0.38 (0.05-1.76)	0.42 (0.05-0.61)	0.38 (0.11-1.76)	0.68	0.38 (0.13-1.76)	0.38 (0.11-1.39)	0.76
TAPSE	22 (11-29.5)	23.75 (11-26.4)	22 (16-29.5)	0.57	22 (18.9-29)	22 (16-29.5)	0.38
RVEF (TAPSEx3.2)	70.4 (35.2-94.4)	76 (35.2-84.48)	70.4 (51.2-94.4)	0.42	70.4 (60.48-92.8)	70.4 (51.2-94.4)	0.38
Left ventricular internal diameter in diastole (LVIDD)	4.19±0.79	4.09±0.82	4.22±0.80	0.72	4.28±0.69	4.23±0.91	0.93
Left ventricular internal diameter in systole (LVIDS)	2.75±0.67	2.48±0.78	2.81±0.65	0.19	2.69±0.49	2.92±0.77	0.39
Fractional shortening (FS)	35.5 (24.5-51.6)	41.95 (27.9-51.6)	33 (24.5-48.5)	0.05	35.65 (24.5-46)	27.8 (25.4-48.5)	0.09
LVEF	63.3 (50-83)	72.1 (53.9-83)	62.2 (50-77.9)	0.08	65.8 (54.4-77.9)	55 (50-70)	0.03
Mitral S'	10.1 (5.3-28)	10.15 (6.43-28)	10.1 (5.3-27)	0.88	8.95 (5.3-15)	10.5 (9-27)	0.01
E	0.77±0.23	0.75±0.17	0.77±0.24	0.83	0.85±0.24	0.70±0.24	0.15
A	0.66±0.16	0.69±0.13	0.66±0.16	0.65	0.69±0.19	0.66±0.14	0.92
E/A	1.18±0.32	1.09±0.2	1.21±0.34	0.43	1.35±0.31	1.08±0.33	0.04
E'/A'	1.00 (0.55-3.26)	1.06 (0.72-3.26)	1 (0.55-2.34)	0.82	1.2 (0.63-2.34)	0.95 (0.55-2.05)	0.4
Deceleration time (DT)	130 (53-201)	127 (85-192)	133 (53-201)	0.68	131.5 (107-183)	137 (53-201)	0.97

ECG showed, left ventricular hypertrophy (LVH) in three patients, right ventricular hypertrophy (RVH) in three patients while, three patients had ventricular premature contractions (VPC's), 'p' pulmonale in two patients, 'p' mitrale in 2 patients and RBBB in one patient. Out of three patients with VPC's, one had frequent VPC's in couplets, triplets (early diffuse group) while the rest 2 had VPC's in singles. Significant tricuspid regurgitation was seen in 5 patients (1 in limited; 3 in early diffuse; 1 in late diffuse), 1 patient in early diffuse subtype had posterior mitral leaflet (PML) prolapse, 1 patient in late diffuse subtype had anterior mitral leaflet (AML) prolapse and 1 patient in late diffuse subtype had mitral annular calcification. On 2D ECHO, 5 patients had dilated right atrium (RA), right ventricle (RV) 4 patients had pulmonary arterial hypertension (PAH), 1 patient had mildly dilated RA, RV without PAH, 1 patient in limited subtype had grossly dilated RA, RV with right ventricular ejection fraction (RVEF) of 35.2%, 2 patients had paradoxical septal motion and 3 patients had concentric LVH. Tei index >0.32 in 23 patients (limited 4, diffuse 19; p=0.63). E/A<1 was seen in 6 patients (Limited -2, Diffuse- 4, p=0.56) and E'/A'<1 in 15 patients (limited 3, diffuse 12; p=0.92). E/A <1 was seen in 4 patients (early diffuse- 1, late diffuse- 3, p=0.59) and E'/A'<1 in 12 patients (limited 5, diffuse 7; p=0.69). Decelaration time was <160 ms in 23 patients (limited 5, diffuse 18) vide (Table 3).

DISCUSSION

The present study was an attempt to document the cardiac manifestation of systemic sclerosis. The study findings revealed that SSc was predominant in females (90%), patients with limited SSc had higher age at presentation (43 years versus 35 years) and, patients with late diffuse SSc had higher age at presentation than early diffuse SSc (44 years versus 32.5 years). Pradhan et al in their study from western India reported that there was a male:female ratio of 1:10 in systemic sclerosis from their study, where mean age at evaluation was 34.7±10.7 years and a mean disease duration was 43.7±35 months.[11] Nearly 40.9% had diffused cutaneous lesions, 29.1% had limited cutaneous lesions, and 30%had other autoimmune overlaps. Gosh et al in their research report from eastern India noted that Raynaud's phenomenon was present in 84.8% patients, inability to open the mouth was seen in 82.6% and fingertip ulceration and scarring in 63%.[12] Arakkal et al studied 28 patients with SSc in a tertiary care center in South India and observed that 17 had diffuse systemic sclerosis and 11 had limited systemic sclerosis.[13] Also, ILD was diagnosed in 21 patients. This demographic and clinical pattern observed in patients with SSc in the above discussed studies were similar and comparable to that of those observed in the present study.

The overall frequency of ANA in SSc patients from the study by Pradhan et al was measured at 85.5%.[11] Furthermore, in the same study it was also noted that the proportion of anti-Scl70, anti-centromere, anti-endothelial cell antibodies (AECA), and anti-keratinocyte antibodies (AKA) was 62.7%, 22.7%, 30%, and 40.9%, respectively. Gosh et al study also documented that 78.2% of their patients tested positive for ANA.[12]

In the present study PAH was noted in 19 patients (61%). RVSP was relatively higher in limited SSc patients (Median -37.5 versus 30). Patients with late diffuse SSc had relatively higher RVSP than early diffuse SSc (35 versus 30). RV systolic function assessed by TAPSE showed abnormally low value (<18) in 5 patients (1 in limited, 4 in diffuse). Overall RVEF calculated from TAPSE was preserved (median-m70.4). RVEF was relatively lesser in diffuse SSc (70.4 versus 76). However, one patient in limited SSc group had markedly reduced RVEF of 35.2%, this patient also had hugely dilated RA and RV. Overall Tei index was showing a rising trend (median 0.38) in 23 patients, pointing towards decreased right ventricular myocardial performance. Thus, subclinical cases can be picked up earlier by using TEI index. Overall, 6 patients had grade I diastolic dysfunction with E/A <1 (limited 2, diffuse 4). Patients with late diffuse SSC had significantly lesser E/A compared to early diffuse SSc (1.08 versus 1.35, p=0.04). 1 patient in diffuse subtype had grade 2 diastolic dysfunction with pseudo-normalisation pattern (E/A =0.61 but E/E' 10.83).

Even though it is asymptomatic in 70% of cases, cardiac involvement is indicative of a more aggressive pathology.[14] Additionally, the heart is the main component of the cardiovascular system and exhibits a complex fractal organisation. Because of this, it may be possible to target the heart early to detect systemic involvement and to predict clinical aggression and evolution. Arakkal et al in their research article reported that two-dimensional ECHO was abnormal in 17 of 28 patients with valvular abnormalities being the most common finding.[13] Interventricular septal thickness and left ventricular posterior wall thickness were found to be higher in patients compared to controls in a study from New Delhi by Handa et al.[15] Low early diastolic filling velocities and a low early diastolic atrial filling ratio were also present in patients with limited SSc. These numbers, however, were unrelated to the patient's age or the length of the illness. D'Alto et al in their longitudinal study from Italy documented that SSc patients exhibit biventricular systolic and diastolic dysfunction and increased sPAP.[16] Patients had mild LV and RV systolic dysfunction at baseline compared to controls (Sm 13.7 2.7 versus 15.4 3.2 cm/second; St 11.5 cm/second in 16/74 patients versus 0 controls; p=0.0031); and higher pulmonary artery systolic pressure (sPAP) (26.1±6.0 versus 24.1±5.1, p=0.040).There was disagreement on the presence and frequency of decreased myocardial contractility in SSc patients. While up to 46% of the patients had LV dysfunction when the LVEF was also measured during exercise, other researchers have reported a low prevalence of depressed LVEF in SSc patients at rest.[15,17] Most of the earlier investigations have indicated that patients with SSc may have diastolic dysfunction.[9,18-20] Poanta et al found no evidence of cardiac involvement, abnormalities in the ECG or SE, or poor LV filling in 20 SSc patients.[21] Using both SE and TDI, Lindqvist et al assessed 26 asymptomatic SSc patients and found that the RV had normal systolic but impaired diastolic performance, as well as an increase in RV wall thickness and RA area.[22] These findings imply that thorough cardiac studies should be performed on all SSc patients. One of the possible limitations of the present study is the relatively smaller sample size.

CONCLUSION

Considerable proportion of patients with systemic sclerosis present with cardiac involvement. Tissue Doppler imaging can help in diagnosing subclinical RV dysfunction by measuring Tei index of right ventricle, which can predict PAH.

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