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CARDIOPULMONARY MANIFESTATIONS IN PATIENTS WITH SYSTEMIC SCLEROSIS: A PROSPECTIVE STUDY AT A TERTIARY CARE CENTER IN PAKISTAN

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Abstract:
Introduction: Systemic sclerosis (SSc) is a rare disorder that is characterized by widespread damage in the body due to fibrosis, vascular insult, and autoimmunity. Cardiopulmonary manifestations of this disease are associated with high mortality among patients with SSc.
Objective: This study aims to observe the cardiopulmonary manifestations of SSc patients.
Materials and Methods: A prospective study was carried out at Fatima Memorial Hospital, Lahore, Pakistan after obtaining ethical approval. A total of 58 male and female patients with systemic sclerosis according to ACR-EULAR criteria for SSc between 1st March 2022 to 28th February 2023 in the hospital were included in this study. Two disease groups were established: diffuse cutaneous SSc (DcSS) and limited cutaneous SSc (LcSS). The patients with SSc-like disorders were excluded. Written informed consent was obtained from the participants and data were collected.
Results: There were 7 (12.1%) male and 51 (87.9%) female patients in the study. The mean age of the patients was 34.55 ± 9.85 years. Out of 58, there were a total of 28 (48.3%) DcSS patients and 30 (51.7%) LcSS patients. Systolic dysfunction was present in 3 (5.17%) patients, and diastolic dysfunction in 8 (13.79%) which was statistically insignificant (p-value > 0.05). Manifestations with statistically significant association (p-value < 0.05) included valvular heart disease, interstitial lung disease (ILD), and pulmonary hypertension. ILD was shown to affect the greatest number of patients (45/58).
Conclusion: Systemic Sclerosis affects heart and lungs adversely. The incidence of the cardiopulmonary manifestations was greater in patients with DcSS as compared to LcSS.

Keywords: Systemic sclerosis, cardio-pulmonary manifestations, diffuse cutaneous systemic sclerosis (DcSS), limited cutaneous systemic sclerosis (LcSS).

Introduction

Systemic sclerosis (SSc) or scleroderma is among those rare disorders that are often complicated by lack of timely diagnosis due to limited exposure of the disease to physicians and even at expert centers, difficulty in determining the extent of the disease, ultimately affecting the decision making about the treatment. (1) The global incidence of systemic sclerosis was reported to be 8.64 per 100,000 person-year (1.78-23.57). (2)

The widespread damage caused by the disease in the body is because of three fundamental pathologies: vascular insult, autoimmunity, and fibrosis. Early cardinal symptoms of the disease like gastro-esophageal reflux and musculoskeletal pain mimicking some inflammatory joint disease sometimes divert the critical assessment of the patient's symptoms to other clinical contexts. (1) Cardiopulmonary manifestations along with cutaneous, musculoskeletal, renal, and gastrointestinal complications are present in the later stages of this autoimmune disease. Pulmonary complications involve interstitial lung disease (ILD) and pulmonary hypertension (PAH). Pericarditis, cardiac effusion, and arrhythmia are among the most encountered cardiac complications. (3)

Skin thickening secondary to fibrosis is observed early in the disease course and forms the basis of classification commonly used for systemic sclerosis. Disease with proximal involvement of the skin on limbs is classified as diffuse cutaneous systemic sclerosis (DcSS) while that involving skin distal to the knees and elbows with or without the face and neck involvement is classified as limited cutaneous systemic sclerosis (LcSS). (1) Anti-ribonucleic acid polymerase III (anti-RNAPIII), anti-topo I (anti-Scl-70) and ACA are the autoantibodies commonly seen in systemic sclerosis. Out of these, ACA and anti-topo I are seen in association with pulmonary hypertension and interstitial lung disease respectively. (4)

Complications involving the pulmonary and cardiac systems are leading causes of mortality in the patients. In the patients, this disease does not cause mortality, but it severely affects the quality of life. There is no definitive diagnosis of the disease. However, early diagnosis, prevention of complications, and the management of affected organs and systems have proven to be beneficial. (5,6) In third-world countries where the health facilities are not highly developed equally in all areas, cases of such rare diseases are often ignored and more likely to be seen when complicated, and that too only in tertiary care setups. In this study, we take into account the cardiopulmonary complications of systemic sclerosis patients at a tertiary care center in Pakistan.

Materials and methods

A prospective study was done at Fatima Memorial Hospital Lahore after obtaining permission from the institutional review board. Both male and female patients from all the age groups who were diagnosed with systemic sclerosis between April 2023 to September 2023 at the tertiary care center were included in this study. The diagnosis was in accordance with ACR-EULAR classification criteria for SSc. (7) Patients with scleroderma-like disorders like systemic lupus erythematosus (SLE), polymyositis, eosinophilic fasciitis, nephrogenic sclerosing fibrosis, and scleromyxedema were excluded from the study. Written informed consent was taken from the participants. Data regarding the demographics, onset and duration of disease, and various complications were collected from the patients on the pre-designed proformas. The data were then analyzed using SPSS 26.0. Age and duration of symptoms (quantitative measures) were presented as mean and standard deviation while the qualitative measures like gender and presence and absence of symptoms were presented as frequency and percentages.

Table 1 The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

Items	Sub-categories	Weight/Score†
Item Sub-item(s) Weight/score Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere Anti–topoisomerase I Anti–RNA polymerase III	3

* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy). † The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of 9 are classified as having definite SSc.

Results

The demographic information of the patients who participated in our study is given in Table 1 below. A total of 58 patients diagnosed with systemic sclerosis were included in the study. Out of them, 7 (12.1%) were male while 51 (87.9%) were females. Average age of the patients was 34.55 ± 9.85 years. Two disease patterns, diffuse cutaneous systemic sclerosis (DcSS) and limited cutaneous systemic sclerosis (LcSS) were observed with a total of 28 (48.3%) patients with DcSS and 30 (51.7%) patients with LcSS. The prevalence of a number of systemic symptoms is given in the Table 2.

Table 1: Distribution of Variables

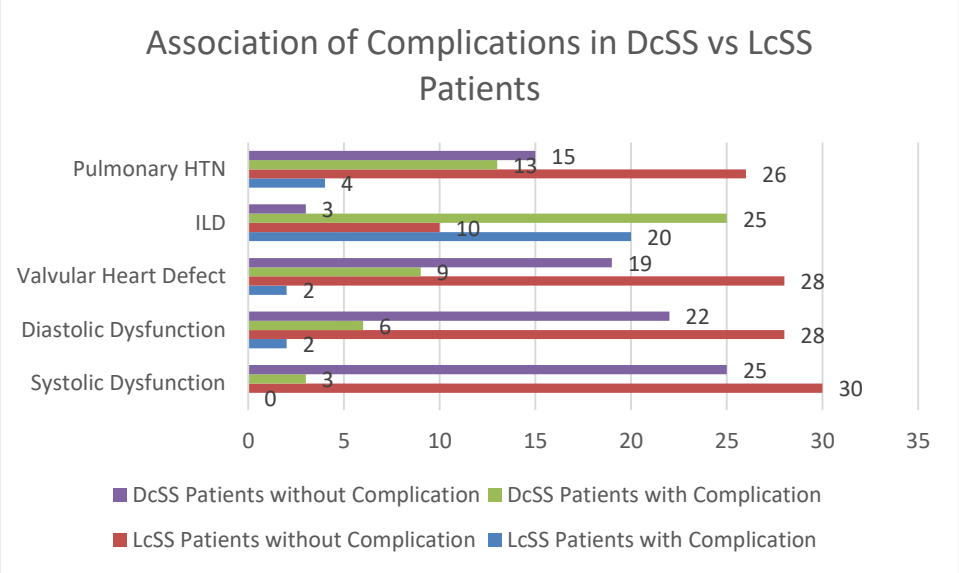
Variables	Distribution	
	Frequency (n)	Percentage (%)
Age	34.55 ± 9.85	
Gender		
Male	7	12.1
Female	51	87.9
Marital status		
Married	41	70.7
Unmarried	17	29.3
Duration of disease	68.55 ± 43.21	
First symptom of Raynaud's — Yes	53	91.4
First symptom of Raynaud's — No	5	8.6
Palpitations		
Yes	30	51.7
No	28	48.3
Chest pain		
Yes	10	17.2
No	48	82.8
Shortness of breath		
Yes	45	77.6
No	13	22.4
Pattern of disease		
LcSS	30	51.7
DcSS	28	48.3
Systolic dysfunction		
Yes	3	5.2
No	55	94.8
Diastolic dysfunction	8	13.8
Yes	50	86.2
No		
Valvular defect		
Yes	11	19.0
No	47	81.0
ILD		
Yes	45	77.6
No	13	22.4
HRCT pattern		
Normal	13	22.4
NSIP	18	31.0
UIP	24	41.4
Bronchiectasis	3	5.2
First PFT severity grade of ILD — Normal	13	22.4
First PFT severity grade of ILD — Mild ILD	6	10.3
Moderate ILD	17	29.3
Severe ILD	14	24.1
Very Severe ILD	8	13.8
Pulmonary HTN		
Yes	17	29.3
No	41	70.7

Of all these, systolic dysfunction, diastolic dysfunction, interstitial lung disease (ILD), pulmonary hypertension (PAH) and valvular heart disease were of special interest (Table 2). Among 58 patients, systolic function was present in 3 (5.17%) patients with DcSS (LR = 4.54). In patients with LcSS, systolic dysfunction was absent. However, p-value was 0.066 so the association of the manifestation was not statistically significant. Similarly, the manifestations of diastolic dysfunction were observed in 8 (13.79%) patients (LR= 2.75) but p-vale was found to be 0.103 which was not statistically significant. Manifestations with statistically significant association included valvular heart disease (LR= 6.48, p-vale 0.013), ILD (LR= 4.46, p-value 0.039) and Pulmonary HTN (LR= 7.93, p-value 0.006). ILD was shown to affect the greatest number of patients (45/58) of all other complications. The incidence of these manifestations was greater in patients with DcSS as compared to LcSS.

Table 2: Association of Complications

Association		Pattern of Disease		P-value
		LcSS	DcSS	
Systolic dysfunction	Yes	0	3	0.066
	No	30	25	
Diastolic dysfunction	Yes	2	6	0.103
	No	28	22	
Valvular heart disease	Yes	2	9	0.013
	No	28	19	
ILD	Yes	20	25	0.039
	No	10	3	
Pulmonary HTN	Yes	4	13	0.006
	No	26	15	

Fig 1: Association of Complications in DcSS vs LcSS Patients



Discussion

Systemic involvement in scleroderma and activation of immune system can cause silent damage in many organs and still go unnoticed. One typical example is scleroderma renal crisis where the presenting patients are often normotensive, however, acute onset arterial hypertension leads to progressive renal failure. (7) Involvement of cardiovascular system is of particular concern since it leads to significant disability and ultimately death in the patients with SSc. Pulmonary hypertension is among end-stage SSc complications that are associated with high mortality. Even the management of such a patient requires multi-disciplinary involvement for assessment of multiple organs at the

same time. (8) There are a number of cardio-pulmonary complications that were covered under the spectrum of our study from chest pain to diastolic dysfunction and from shortness of breath to pulmonary HTN and ILD. However, our focus is on those cardiopulmonary manifestations that are associated with higher morbidity and mortality like systolic dysfunction, pulmonary hypertension, diastolic dysfunction, interstitial lung disease and valvular defect in SSc patients and their association with a particular disease pattern-either DcSS or LcSS.

Only 3 patients with DcSS were seen to be associated with systolic dysfunction. The association was found to be statistically insignificant (p-value 0.066). A study at Oslo University Hospital comprising a large cohort, howewer, reported the prevalnce of systolic dysfunction to be higher than our study and even many other studies. (9) One possible explanation of the contradiction can be what the study claimed to be a limitation of those studies-a small cohort. This is seconded by some other studies comprising a small cohort but with high sensitivity tools to detect the subclinical disease. (10-11). In our study, no participant with LcSS presented with systolic dysfunction. Number of individuals with diastolic dysfunction in our study were 6 in DcSS group and 2 in LcSS group. So, in our cohort, cardiac involvement was more prevalent in DcSS patients as compared to LcSS patients. Also, diastolic dysfunction was present in greater number of patients as compared to systolic dysfunction. Our results were similar to a study conducted by Tennøe et. al. They observed that the diastolic dysfunction was present in 17% of the 275 SSc patients. Also, they found it to be associated with high mortality as 57% of the patients with diastolic dysfunction died during follow up. (12) However, in our study, this association was statistically insignificant (p-value 0.103).

Valvular heart defect was present in 11 out of 58 patients of SSc (2 in LcSS and 9 in DcSS). The result was statistically significant (p- value 0.013). From literature we find that the valvular defects are present in significant number of patients with SSc. A multi-center cohort conducted by Colaci et. al in Italy showed that valvular defect was a common presentation in their cohort of SSc patients. 85% of the SSc patients developed mitral valve insufficiency and 91% developed tricuspid valve insufficiency. (13) Another study reported the presence of valvular abnormalities (mitral valve) in at least 20% of SSc patients. (14)

Pulmonary involvement is yet another feared complication of this multi-organ, autoimmune disease. In our study, 17 out of 58 patients were reported with pulmonary hypertension (PH). p-value was 0.006, so the results were statistically significant. Again, number of individuals having pulmonary HTN with DcSS was greater (13) than those with LcSS (4). Another sever pulmonary manifestation observed in study was interstitial lung disease (ILD). This complication, by far, affected the greatest number of patients (45 out of 58) in our study. Results were also statistically significant (p-value 0.039). One reason to discuss ILD along with PH is that literature has reported the presence of these manifestations together and their co-existence in a patient are associated with a poor prognosis. (15,16) Several studies have reported that interstitial lung disease and pulmonary HTN are frequently observed manifestations in systemic sclerosis. (17-21)
As observed with cardiac complications, pulmonary complications in our SSc patients are also more frequently associated with DcSS than LcSS. However, there are limitations of our study as well. Our study is based on a single tertiary care center. Due to the disease being rare and limited number of patients being encountered, it is hard to study a large sample size in our setting. Also, our study was not controlled. Although the study has highlighted important considerations about the complications in SSc patients in our setting, a multi-center and controlled study with a larger and diverse cohort is recommended.

Conclusion

Patients with systemic sclerosis have multi-organ complications at later stage of the disease. Cardiopulmonary complications are common in SSc patients which include systolic and diastolic

dysfunction, valvular defect, pulmonary hypertension and interstitial lung disease. These complications were more often manifested in diffuse type of systemic sclerosis than in limited type.

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