Original Article

A Study on Pulmonary Complications of Systemic Sclerosis in Eastern India

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Abstract

Aim. This study was undertaken to find out the characteristics of clinical, radiological and functional changes affecting the respiratory system in patients with systemic sclerosis (SSc) from eastern India, and the association of these characteristics with pulmonary hypertension.

Methods. This was a cross-sectional, observational study involving 46 patients. Other than the routine tests, anti-nuclear antibody (ANA), spirometry, diffusing capacity of lung for carbon monoxide (DLCO) measurement, chest radiograph, high-resolution computed tomography (HRCT) of thorax, 6-minute walk test and echocardiography were done.

Results. Out of a total of 46 patients, 27 patients had diffuse cutaneous SSc (dcSSc) and 19 had limited cuteaneous SSc (lcSSc). Eleven patients had pulmonary hypertension. The HRCT revealed diffuse parenchymal lung disease (DPLD) in 32 (65%) cases. The ANA was positive in 83% cases. Anti-Scl70 was found in 41% of patients with dcSSc and anti-centromere antibody was found in 47% of patients with lcSSc. Spirometry revealed restrictive pattern in 30 patients; 9 had obstruction; and the rest were normal. The DLCO was abnormal in 38 patients. A strong correlation was found between reduction in DLCO and pulmonary artery systolic pressure (PASP). Also, a strong association was observed between a drop of >4% in oxygen saturation on 6-minute walk test and presence of pulmonary arterial hypertension (PAH).

Conclusions. Majority of the patients with SSc had restrictive lung disease with abnormal DLCO and features resembling non-specific interstitial pneumonia. Nucleolar ANA was predominantly found in patients having PAH. Presence of DPLD had a negative association with presence of anti-centromere antibody. Reduction in DLCO and a fall of >4% in oxygen saturation on 6-minute walk test may be used as predictors of PAH in asymptomatic individuals.

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Key words: Systemic sclerosis, Pulmonary hypertension, Interstitial lung disease.

Introduction

Scleroderma or systemic sclerosis (SSc) is a generalised connective tissue disorder which is characterised by microvascular obliteration and increased deposition of collagen resulting in fibrotic lesions. Pulmonary involvement is a common feature in SSc. Interstitial lung disease (ILD) or currently called diffuse parenchymal lung disease (DPLD) is one of the leading pulmonary manifestations and a leading cause of death in these patients.

This study focuses on the respiratory manifestations — clinical, radiological and functional — in patients with SSc from eastern India.

Material and Methods

Fifty consecutive patients fulfilling the American College of Rheumatology criteria (1980) for diagnosis of SSc,[1] attending the out-patient department and indoor wards of Institute of Postgraduate Medical Education and Research, Kolkata, a tertiary care hospital in eastern India were included in the study. Patients having overlap syndrome, acute left ventricular failure, congenital/valvular heart disease, human immunodeficiency virus (HIV) seropositivity, occupational exposure to organic/inorganic dusts, chronic liver disease with portal hypertension, and pregnancy were excluded from the study. Four patients were excluded from the study on the basis of exclusion criteria. This was a cross-sectional, observational study without any controls. Approval from the Institutional Ethics Committee was obtained, and informed written consent was taken from the study patients.

The patients were classified as having limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc). Limited cutaneous SSc was defined as skin thickening restricted to the sites distal to elbows and knees, but may involve face and neck; while dcSSc was defined with skin thickening on the trunk and proximal extremities in addition to distal extremities and face.

Apart from a detailed history and thorough clinical examination, all patients underwent routine blood tests, such as complete haemogram, HIV serology, random blood sugar, liver function tests, serum urea

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and creatinine. Chest radiograph, electrocardiogram and urinalysis were also done. Anti-nuclear antibody (ANA) by immunofluorescence method, anti-centromere and anti-Scl70 antibodies were tested. A titre of at least 1:80 was considered positive for ANA. All the patients underwent high resolution computed tomography (HRCT) scan of thorax, spirometry, single breath DLCO (diffusing capacity of lung for carbon monoxide), 6-minute walk test with pulse oximetry and Doppler echocardiography.

All the patients were clinically verified by a dermatologist and all HRCT scans were cross-checked by a radiologist. Spirometry, DLCO and 6-minute walk test were done according to the American Thoracic Society guidelines. Though static lung volumes were not measured, restrictive lung disease was presumed in those with reduced forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) but a maintained or increased FEV_1/FVC ratio. Pulmonary arterial hypertension (PAH) was diagnosed when pulmonary artery systolic pressure (PASP) was >40mmHg on Doppler echocardiography. The PASP was calculated from the velocity of regurgitant flow across the tricuspid valve by Bernoulli's equation.

Patients with ILD were treated with oral cyclophosphamide, oral prednisolone and N-acetyl cysteine. Patients with PAH were given bosentan. However, patients who could not afford bosentan were given calcium channel blocker (amlodipine). All the patients were given angiotensin converting enzyme inhibitor (Ramipril). Those with prominent skin changes were given hydroxychloroquine. The patients were asked to follow up after six weeks but the findings at follow-up visit were not included in the present study.

Statistical Analysis

Descriptive statistical data are expressed as mean±SD for continuous variables and as frequency with proportion, n (%) for categorical variables. Pearson's coefficient of correlation was used to assess the strength of association between continuous variables and Fisher's exact test and Chi-square test was used to assess the associations between categorical variables. A two-sided P value of less than 0.05 indicated was considered to be statistically significant. Statistical software Statistical Package for the Social Sciences (SPSS; version 17.0) was used for performing all statistical tests.

Results

Of the 46 patients included in the study, 34 were females. The female to male ratio was 2.8:1. Twenty-seven patients belonged to the dcSSc variety and the rest 19 belonged to the lcSSc variety. The mean age of presentation was 38.8±11.8 years. There was no statistically significant difference in the mean age of presentation between the dcSSc and lcSSc group as well as between the gender. The duration of the disease was significantly longer in the lcSSc group (years) than the dcSSc group (9.6±6.9 *versus* 4.5±2.5 years; p=0.009). The maximum duration of the disease in this series was 31 years in a patient with lcSSc, while the minimum duration was one year noted in both the groups. Ten patients (53%) with lcSSc had disease duration of more than 10 years while it was just 1(4%) patient in the dcSSc group.

The group-wise frequency of various respiratory complaints is presented in table 1. The severity of dyspnoea according to the New York Heart Association (NYHA) Functional Classification was as follows: Class I in 7 patients; Class II in 18 patients; Class III in 5 patients; and Class IV in 1 patient. Non-respiratory complaints like fever, constipation, joint pain and weight loss were evenly distributed in both the groups. Heartburns and dysphagia were found in 26 patients with SSc. It was found more commonly in lcSSc (15 patients) as compared to dcSSc group (11 patients). Raynaud's phenomenon (RP) was found in 44 patients. It was the first presenting symptom in 26 patients (16 belonging to the lcSSc group and 10 belonging to dcSSc group) (p=0.04). It preceded the respiratory symptoms in all the cases where it was present. Raynaud's-respiratory gap (RRG), the gap in the duration between appearance of RP and the first respiratory symptom, was significantly higher in the lcSSc than the dcSSc group (7.1±6.4 *versus* 2.5±2.0 years; p=0.001). Maximum RRG in this series was 27 years while minimum was six months.

Table 1. Respiratory symptoms in study patients with SSc

Respiratory Symptom	SSc (n=46)	dcSSc (n=27)	lcSSc (n=19)
Dyspnoea	31 (67%)	21 (78%)	10 (53%)
Cough	36 (78%)	22 (81%)	14 (74%)
Sputum	13 (28%)	8 (30%)	5 (26%)
Chest pain	14 (30%)	6 (22%)	8 (42%)
Chest heaviness	12 (26%)	11 (41%)	1 (5%)

Data presented as, n (%); SSc=Systemic sclerosis; dcSSc=Diffuse cutaneous SSc; lcSSc=Limited cutaneous SSc

Doppler echocardiography was done in all the patients, and the mean MAP was 23.2±11.5 mmHg, slightly higher in lcSSc group than dcSSc group (24.9±12.3 *versus* 22.05±11.05 mmHg). Eleven patients (24%) had PAH (PASP >40mmHg). The PAH was found in 5 patients (26%) having lcSSc, while it was present in 6 (22%) patients with dcSSc (p=0.9). A positive correlation was found between the RRG and the development of PASP [Pearson's r=0.43, <0.01].

Anti-nuclear antibody was found positive in 38 (83%) cases, similar in frequency between the lcSSc and the dcSSc. The most common pattern observed was speckled (18 cases [47%], followed by nucleolar (12 cases [32%]

and mixed (speckled/nucleolar, homogeneous/nucleolar; 8 cases [21%]). Eight of the 12 patients who had nucleolar type of ANA had PAH. The distribution of ANA among the different groups of patients is shown in figure 1. Anti-Scl70 was positive in 11 (41%) patients

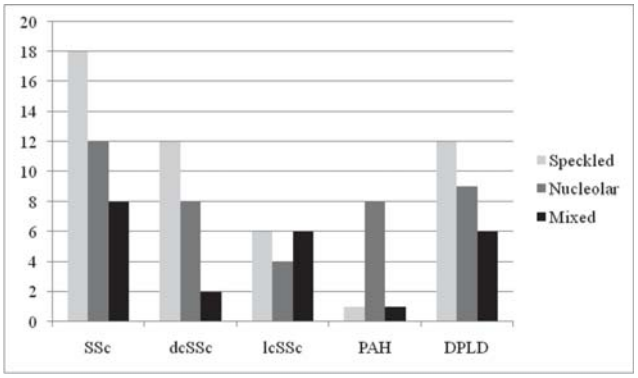

Figure 1. Distribution of ANA
The y-axis depicts the absolute number of patients. ANA=Anti-nuclear antibody; SSc=Systemic sclerosis; dcSSc=Diffuse cutaneous SSc; lcSSc=Limited cutaneous SSc; PAH=Pulmonary arterial hypertension; DPLD=Diffuse parenchymal lung disease

with dcSSc, whereas anti-centromere antibody was found in 9 (47%) patients with lcSSc. Anti-Scl70 had no significant association with the development of DPLD (p=0.13), however, anti-centromere antibody had a significant negative association with the development of DPLD (p=0.015).

Chest radiograph was normal in 15 (33%) patients. Of the 27 patients with dcSSc, 14 (52%) had bilateral reticulo-nodular shadows, 2 had pleural effusion, 1 had bilateral nodular shadows, 1 had hyperinflation, and the rest 9 (33%) had normal findings. In the lcSSc group, of the 19 patients, 7 had normal findings, 2 patients had bilateral reticulo-nodular shadows, 2 had dilated pulmonary artery, 4 had patchy consolidation, and 4 each had ground-glass opacity or apical fibrosis. In 12 patients, the chest radiograph was normal but the HRCT revealed changes. Table 2 shows the HRCT thorax findings in 46 patients; 32 of the 46 patients were diagnosed to have DPLD based on HRCT findings.

Spirometry revealed the presence of restrictive lung disease in majority of the patients. Of the 46 patients, 30 had restrictive features, 9 had obstructive features, and 7 had normal findings. In patients having restrictive finding, 2 had very severe restriction, 6 had severe, 2 had moderate and 20 had mild restriction. All the 10 patients having very severe, severe and moderate restriction had evidence of DPLD. Of the rest, 20 patients had mild restriction, 14 had features of DPLD.

Table 3 shows the distribution of patients as per the severity of restriction. Figure 2 shows the distribution and relationship between patients having DPLD, PAH, and restrictive pulmonary function tests.

Table 2. HRCT thorax findings in study patients

HRCT Findings	SSc (n=46)	dcSSc (n=27)	lcSSc (n=19)
Ground-glass opacities	30 (65%)	23 (85%)	7 (37%)
Reticulo-nodular infiltrates	25 (54%)	18 (67%)	7 (37%)
Honey-combing changes	5 (11%)	4 (15%)	1 (5%)
Bronchiectasis	8 (17%)	6 (22%)	2 (11%)
Septal thickening	7 (15%)	4 (15%)	3 (16%)
Consolidation	4 (9%)	1 (4%)	3 (16%)

Data presented as, n (%); HRCT=High-resolution computed tomography; SSc=Systemic sclerosis; dcSSc=Diffuse cutaneous SSc; lcSSc=Limited cutaneous SSc

Table 3. Severity of restrictive lung disease in study patients

Grade, (% Predicted FVC)	SSc (n=30)	dcSSc (n=22)	lcSSc (n=8)
Mild (≥60%)	20 (67%)	14 (64%)	6 (75%)
Moderate (50%-59%)	2 (7%)	2 (9%)	–
Severe (35%-49%)	6 (20%)	4 (18%)	2 (25%)
Very severe (<35%)	2 (7%)	2 (9%)	–

Data presented as, n (%); FVC=Forced vital capacity; SSc=Systemic sclerosis; dcSSc=Diffuse cutaneous SSc; lcSSc=Limited cutaneous SSc

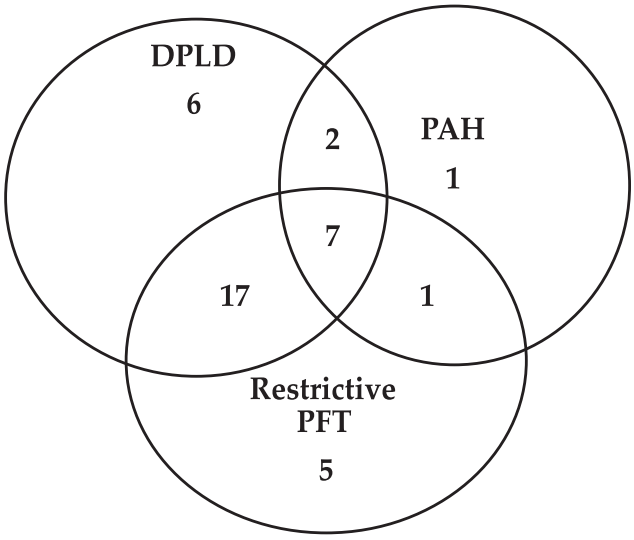

Figure 2. Venn diagram depicting the relationship between DPLD, PAH and restrictive pulmonary function defect

DPLD=Diffuse parenchymal lung disease; PAH=Pulmonary arterial hypertension; PFT=Pulmonary function test

The DLCO test was done in 46 patients; and abnormal results (<75% of predicted) were found in 38 (83%) patients. Most patients (25 [54%]) had DLCO in the 60%-74% of the predicted range. Severe reduction of DLCO was found in 9 (20%) patients, the lowest being 39% of the predicted. All the patients with severe reduction of DLCO had PAH on echocardiography. A strong negative correlation was found between the DLCO value of the patients and PASP (p<0.001).

All the patients underwent 6-minute walk test. Mean distance covered was 317.0±72.5 metres. There was no significant difference between the lcSSc and

dcSSc groups. The saturation of oxygen fell in all; 10 of them had saturation fall >4%; and 9 of these 10 patients had PAH. The mean saturation fall was 3.6±2.2%. Six-minute walk distance had a significant positive correlation with PASP values ($r=-0.74$; $p<0.001$). Significant positive association ($p<0.001$) was found between a fall in saturation of more than 4% on 6-minute walk test and the presence of PAH.

Table 4 summarises the comparison between the patients having PAH with the rest.

Table 4. Comparison between No-PAH and PAH groups

	No PAH Group (n=35)	PAH Group (n=11)
Male gender	9 (26%)	3 (27%)
lcSSc	14 (40%)	5 (45%)
dcSSc	21 (60%)	6 (55%)
Raynaud's phenomenon	33 (94%)	11 (100%)
Anti-nuclear antibody	29 (83%)	9 (82%)
Speckled pattern	17/29 (59%)	1/9 (11%)
Mixed pattern	7/29 (24%)	1/9 (11%)
Nucleolar pattern	5/29 (17%)	7/9 (78%)
Anti Scl-70 antibody	7 (20%)	4 (36%)
Anti-centromere antibody	7 (20%)	2 (18%)
Presence of DPLD	23 (66%)	9 (82%)
DLCO<50%	—	9 (82%)
DLCO 50%-59%	2 (6%)	2 (18%)
DLCO 60%-74%	25 (71%)	—
DLCO ≥75%	8 (23%)	—
Fall in saturation of >4% during 6-minute walk	1 (3%)	9 (82%)

Data presented as, n (%); PAH=Pulmonary arterial hypertension; SSc=Systemic sclerosis; dcSSc=Diffuse cutaneous SSc; lcSSc=Limited cutaneous SSc; DPLD=Diffuse parenchymal lung disease; DLCO=Diffusing capacity of lung for carbon monoxide

Discussion

Diffuse parenchyal lung disease and PAH have been recognised as the major pulmonary complications in patients having SSc. Other manifestations of pulmonary involvement, such as pleural effusion, malignancy, aspiration pneumonitis and bronchiectasis have also been described. In our study, most of the patients belonged to the dcSSc group (58.7%), which is similar to those found in both Indian and western medical literature.[2] The mean age of presentation of the disease was 6.6±5.4 years which is similar to the other Indian studies,[2] but lower than the data of western literature.[3] There was a significant female preponderance, but it was lower than the ratio found in other Indian studies.[2,4] The mean duration of the disease was similar to the other studies.[2,3] The disease duration was found significantly higher in the lcSSc group than the dcSSc group.

Most common presenting respiratory symptom was cough, followed by dyspnoea and chest pain. The cough was mostly non-productive in nature. The most common non-respiratory symptom was Raynaud's phenomenon, present in 95.6% cases, which is similar to other studies from India and western literature, except the study reported from the southern part of India,[5] it was reported to be 28.2%, probably due to hot climate prevalent throughout the year. There was a positive correlation between RRG and PASP. Among other non-respiratory complaints joint pain was found to be slightly higher in the dcSSc group, while dysphagia and heartburn were found significantly higher in the lcSSc group.

Anti-nuclear antibody was positive in 83%, similar in frequency between the lcSSc and the dcSSc group. This is at par with the results found in previous studies from India,[4,6] but higher than the western reports.[7] The higher frequency of nucleolar pattern found in our study was also observed in another Indian study[2] and it predicted PAH in our series. Anti-Scl70 was positive in 41% patients with dcSSc, similar to other studies.[2] However, anti-centromere antibody was less frequent when compared to other studies, mostly due to lesser number of lcSSc cases and the small sample size in our study. No association with PAH or increased severity of pulmonary involvement could be demonstrated with either of the two auto-antibodies. However, development of DPLD showed no significant association with the presence of anti-Scl70 antibody but a significant negative association with the presence of anti-centromere antibody.

Spirometry showed that 65% of cases had a restrictive pattern while 20% had obstructive features. This finding was slightly higher compared to western countries,[3] as most patients seen in tertiary referral centres have more severe respiratory symptom as well as more number of dcSSc. All the patients who had restrictive pattern and two patients with obstructive pattern were found to have DPLD in various stages on HRCT. Severe and very severe restriction was found in 17.7% cases, belonging to the dcSSc group.

Frequency of DPLD in the present study was similar to that observed in an earlier Indian study[8] but higher than that from the western studies[9] which had more number of lcSSc cases. The DPLD was found significantly higher in the dcSSc (88.9%) compared to lcSSc (42.1%) group ($p=0.02$). Only 11% of cases showed honey-combing on HRCT, confirming the fact that the predominant DPLD type in SSc is non-specific interstitial pneumonia which has infrequent honey-combing on HRCT.[10]

Our study also revealed a predominance of nucleolar type of ANA in patients having PAH. All patients of PAH had RP. Strong association was found between a fall of >4% in arterial oxygen saturation (SpO_2) values in 6-minute walk test and the presence of

PAH. Distance covered in 6-minute walk test had a significant negative correlation with PASP values, though it was not consistently found in other studies.[11] All patients with severe reduction of DLCO to <50% of predicted had PAH. A strong negative correlation was found between the DLCO (% predicted) and PASP, similar to other studies.[12] So, reduction in DLCO may be used as a predictor for the presence of PAH in asymptomatic individuals. The prevalence of PAH was found to be lower in our study than the previous Indian study,[8] which might be attributed to the lower cut-off of PASP (>35mmHg) used in that study. However, this result was similar to the findings in studies from the West.[9]

Conclusions

The present study offers a glimpse of the Indian patients having respiratory manifestations of SSc. Studies from India on SSc are very few. The present study also describes about PAH in these patients, an issue which has been less extensively studied in Indian patients. The main drawback of our study is its small sample size. Also, we could not do right heart catheterisation to evaluate PAH, due to resource limitations. Further, since this was a cross-sectional study, we could not present any follow-up data for these patients. Further studies are required with large sample size of patients.

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