SHORT REPORT

Comparison between clinical and immunological features of scleroderma with and without interstitial lung disease

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Abstract

The study was conducted at the Fauji Foundation Hospital, Rawalpindi, Pakistan, from January 1, 2023, to December 31, 2023, and comprised 20 female patients ages 18-55 years having scleroderma. Overall, 14(70%) patients had diffuse scleroderma and 6(30%) had limited scleroderma. The patients with interstitial lung disease were placed in group 1, while those without interstitial lung disease were placed in group 2. Intergroup difference was significant with respect to palpitations, dysphagia, early satiety/reflux, constipation, pulp atrophy, arthritis, tendon friction rubs, digital pitting, digital ulcers, joint contractures, hypertension, positive anti-topoisomerase I antibody, and pulmonary hypertension ($p<0.05$).

Keywords: Systemic sclerosis, Scleroderma, Interstitial lung disease.

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Introduction

Scleroderma, or systemic sclerosis (SSc), is a multi-system, heterogeneous group of connective tissue disorders that is characterised by thickening of the skin and fibroproliferative vasculopathy, leading to fibrosis in the skin and many internal organs. The aetiological and pathological features associated with SSc include microchimerism, autoimmunity and vascular proliferation, leading to vasculopathy.[1,2] Exposure to silica chlorinated solvents may also be involved in the pathogenesis of SSc in minority of patients.[3]

Damage to endothelium may be the initiating factor, but the precise triggering factor for the start of the disease is not confirmed. Endothelin 1 is a potent mediator of vasculopathy in SSc.[2]

SSc is not a common disease, and its worldwide prevalence ranges from 3.1 to 144.5 per 100,000 person years in different areas. The prevalence among men has been reported to be 6.0 per 100,000 person years, and 28.0 per 100,000 person years among women. The prevalence in Asia is the lowest compared to other populations.[4] The involvement of lungs is a common SSc manifestation in 50-60% of patients.

SSc can present with Raynaud's phenomenon, and sometimes it is so severe that it can lead to digital pitting, pulp atrophy, and ulcers of the hands and feet. Other SSc symptoms include heartburn, belching, dyspepsia and dysphagia due to decreased oesophageal motility. Pulmonary arterial hypertension (PAH) is one of the severe complications of SSc. Heart may also be involved in SSc, including dilated cardiomyopathy with decreased ejection fraction (EF), diastolic dysfunction, and conduction blocks. Also included among SSc complications is small intestinal bacterial overgrowth (SIBO) which sometimes leads to diarrhoea along with malabsorption.[5]

Besides, joint pain may also occur, and it can lead to frank arthritis with swelling and early morning stiffness, but the presence of overlap syndrome should be kept in mind because the occurrence of rheumatoid arthritis (RA) symptoms with SSc is common.[6]

Symptoms of increases skin thickening, lung involvement and heart involvement usually occur in the early stage of the disease, mainly in first 4-5 years of the disease, after which the disease becomes inactive, but some of the complications, like PAH and malabsorption, can still occur in the course of the disease even later as well.

There are several types of SSc, and it can be localised and systemic. Systemic SSc includes limited and diffuse forms. Some of the complications are more common in localised SSc, like PAH, while ILD is more common in diffuse SSc. Risk factors of PAH include older age at diagnosis, male gender, anti-centromere antibodies (ACAs), anti-ribonucleic acid polymerase III (RNAP-III), anti-U3-ribonucleoprotein (RNP) autoantibodies, digital ulcers, and severe Raynaud's phenomenon.[7,8]

SSc sine scleroderma (ssSSc) is another type of SSc in which there is no skin involvement, but internal organs are involved, and serology is positive.[9]

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The most common lung manifestation is interstitial lung disease (ILD).[10] It has different patterns, like non-specific interstitial pneumonia and the usual interstitial pneumonia (UIP). Usually, ILD is diagnosed by chest X-ray (CXR), high-resolution computed tomography (HRCT) of the chest showing specific pattern of ILD, pulmonary function tests (PFTs) to document restrictive lung pattern and decreased lung volumes, and six-minute walk test (6MWT).[11] ILD may be an added risk factor for lung cancer in SSc patients.[12]

Screening test is done to assess the presence of antinuclear antibodies (ANAs). Other antibodies that may be positive include anti-topoisomerase I (anti-Scl-70), ACAs and anti-RNAP-I- II- III. Capillaroscopy of SSc patients is also done to find the specific SSc pattern of blood capillaries.

After the diagnosis, immunosuppressive agents are used to improve lung function, including cyclophosphamide, mycophenolate mofetil, tocilizumab, pirfenidone and nintedanib.[13]

The current study was planned to find the different characteristics that may or may not lead to the development of ILD in SSc patients.

Methods and Results

The study was conducted at the Fauji Foundation Hospital, Rawalpindi, Pakistan from January 1, 2023, to December 31, 2023, after approval from the institutional ethics review board. The sample was raised using non-probability consecutive sampling technique. Written informed consent was taken from each patient. SSc was diagnosed according to the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria.[14] Patients who met the ACR criteria and were aged 18-55 years were included. Patients having mix connective tissue disease and overlap of SSc with RA, systemic lupus erythematosus (SLE), Sjogren or myositis were excluded. Presence or absence of ILD was detected on high-resolution computed tomography (HRCT) of the chest. Those with ILD were placed in group 1, while those without ILD were placed in group 2. Two separate proformas were made one for the two groups to collected demographic details, like age, gender, disease duration, weight, modified Rodnan score,[15] Raynaud phenomenon, digital ulcers, dysphagia, early satiety, constipation, dyspnoea, diarrhoea, palpitations and proximal myopathy. the modified Rodnan score[15] was calculated by patient examination conducted by a trained rheumatologist with >3 years of experience in the field of rheumatology. Along with a detailed history of patient's symptoms, a physical examination was carried out to identify clinical signs, like pulp atrophy, sclerodactyly, joint contractures, digital pitting, beaked nose, microstomia, telangiectasias, calcinosis cutis, hypertension, arthritis, crackles in the chest, and signs of PAH in precordium. Blood samples were drawn for serological tests, including ANA by immunofluorescence, ACA, anti-Scl-70, anti-RNAP, anti-double-stranded deoxyribonucleic acid (dsDNA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), complement levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and creatinine kinase.

Group 1 patients were examined to see if they had non-specific interstitial pneumonia/ground glass appearance (NSIP/GGO) pattern or UIP/honey combing pattern. HRCT was done by a radiologist with at least three years of professional experience, while echocardiography was performed by a cardiologist, and PAH was suspected when right ventricular systolic pressure (RVSP) was ≥40mmHg.

Data was analysed using SPSS 23. Categorical variables were presented as frequencies and percentages, while quantitative variables were presented as mean±standard deviation (SD). Comparison of categorical data between

Table-1: Intergroup comparison of demographic data.

Demographic Characteristics	Group 1 SSc without ILD Mean ±SD (n=10)	Group 2 SSc with ILD Mean ±SD (n=10)	*p*-value
Age (years)	40.16±9.47	42.08 ±12.37	0.11
Duration of disease (years)	5.45 ±4.85	5.54 ±3.15	0.82
Weight (Kg)	54.16 ±10.73	52.50±11.13	0.90
Modified Rodnan score	31.58 ±8.18	29.50±5.56	0.36

SSC: Systemic sclerosis, ILD: Interstitial lung disease, SD: Standard deviation.

Table-2: Intergroup comparison of symptoms.

	Group 1 (n=10) SSc without ILD n (%)	Group 2 (n=10) SSc with ILD n (%)	*p*-value
Raynaud's phenomenon	Yes 10(100)	Yes 10(100)	0.00
	No 0 (0)	No 0 (0)	
Digital ulcers	Yes 3 (30)	Yes 5 (50)	0.01
	No 7 (70)	No 5 (50)	
Dysphagia	Yes 7 (70)	Yes 4 (40)	0.04
	No 3 (30)	No 6 (60)	
Early satiety/reflux	Yes 9 (90)	Yes 8 (80)	0.02
	No 1 (10)	No 2 (20)	
Constipation	Yes 2 (20)	Yes 3 (30)	0.02
	No 8 (80)	No 7 (70)	
Diarrhoea	Yes 0 (0)	Yes 1 (10)	0.08
	No 10 (100)	No 9 (90)	
Dyspnoea	Yes 3 (30)	Yes 9 (90)	0.50
	No 7 (70)	No 1 (10)	
Palpitations	Yes 5 (50)	Yes 6 (60)	0.001
	No 5 (50)	No 4 (40)	
Proximal myopathy	Yes 1 (10)	Yes 2 (20)	0.11
	No 9 (90)	No 8 (80)	

SSC: Systemic sclerosis, ILD: Interstitial lung disease.

Table-3: Intergroup comparison of SSc signs.

	Group 1 (n=10) **SSc without ILD** n (%)	**Group 2** (n=10) **SSc with ILD** n (%)	***p*-value**
Skin involvement			
Limited	3 (30)	3 (30)	
Diffuse	7 (70)	7 (70)	
Arthritis/arthralgia	Yes 7 (70)	Yes 5 (50)	0.01
	No 3 (30)	No 5 (50)	
Pulp atrophy	Yes 2 (20)	Yes 4 (40)	0.02
	No 8 (80)	No 6 (60)	
Sclerodactyly	Yes 4 (40)	Yes 90 (90)	0.41
	No 6 (60)	No 1 (10)	
Joint contractures	Yes 5 (50)	Yes 3 (30)	0.01
	No 5 (50)	No 7 (70)	
Scleroderma renal crisis (SRC)	Yes 1 (10)	Yes 1 (10)	0.08
	No 9 (90)	No 9 (90)	
Digital pitting	Yes 4 (40)	Yes 5(50)	0.001
	No 6 (60)	No 5(50)	
Beaked nose	Yes 10 (100)	Yes 10 (100)	0.00
	No 0 (0)	No 0 (0)	
Microstomia	Yes 10 (100)	Yes 10 (100)	0.00
	No 0 (0)	No 0% (0)	
Telangiectasias	Yes 4 (40)	Yes 8 (80)	0.42
	No 6 (60)	No 2 (20)	
Calcinosis cutis	Nil	Nil	0.00
Tendon friction rubs	Yes 3 (30)	Yes 1 (10)	0.003
	No 7 (70)	No 9 (90)	
Hypertension	Yes 2 (20)	Yes 1 (10)	0.531
	No 8 (80)	No 9 (90)	
Interstitial lung disease pattern			
• Ground glass appearance		4(40)	
• Honey combing appearance		3 (30)	
• Mixed pattern		3(30)	
Pulmonary arterial hypertension	Yes 1 (10)	Yes 2 (20)	0.01
	No 9 (90)	No 8 (80)	

SSC: Systemic sclerosis, ILD: Interstitial lung disease.

the groups was done using chi-square test. For continuous data, student's t-test was employed, along with Mann-Whitney U test when the data did not follow a normal distribution. Stratification of the data was done for SSc type. Logistic regression model was applied for clinical associations using chi-square test. P<0.05 was considered statistically significant.

Of the 20 female patients, 10(50%) were in group 1 with mean age 40.16±9.47 years. There were 10(50%) patients in group 2 with mean age 42.08±12.37 years. There was no significant difference between the groups at the baseline (Table 1). Intergroup differences with respect to symptoms (Table 2), signs (Table 3) and other investigations (Table 4) were generally significant (p<0.05).

Table-4: Intergroup comparison of investigations related to SSc.

	Group 1 (n=10) **SSC without ILD** n (%)	**Group 2** (n=10) **SSC with ILD** n (%)	***p*-value**
ANA	9 (90)=Positive	10(100)=Positive	0.33
Anticentromere antibodies	1 (10)=Positive	0(0%)=Positive	0.33
Anti-Scl70 antibodies	2 (20)=Positive	3 (30)=Positive	0.003
Anti-RNP	1 (10)=Positive	1(10)=Positive	0.11
Anti-Ro	1(10)=Positive	0 (0)=Positive	0.33
Anti-LA	0 (0)=Positive	0 (0)=Positive	0.00
Anti-dsDNA	0 (0)=Positive	0(0)=Positive	0.00
Anti-Sm	0 (0)=Positive	0 (0)=Positive	0.33
Complement levels	Normal	Normal	0.00
RA factor	1 (10)=Positive	0 (0)=Positive	0.33
Anti-CCP	0 (0)=Positive	0 (0)=Positive	0.00
Conduction block	0(0)=Positive	0 (0)=Positive	0.00
Left ventricle diastolic dysfunction (LVDD)	0 (0)=Positive	1(10)=Positive	0.33
Raised creatinine kinase	0 (0)=Positive	2 (20) = Positive	0.00
Elevated acute phase reactants	4 (40)=Positive	8(80) = Positive	0.31

SSC: Systemic sclerosis, ILD: Interstitial lung disease, Scl70: Topoisomerase I , RNP: Ribonucleoprotein, Ro: , LA: , dsDNA: Double-stranded deoxyribonucleic acid, Sm: , RA: Rheumatoid arthritis, CCP: Cyclic citrullinated peptide.

Discussion

In the current study, patients without ILD were younger compared to their counterparts in the ILD group. This may have been so because ILD may occur in patients who have disease for a longer period. The duration of disease was longer in patients with ILD compared to others in the current study. Weight was less in patients with ILD in comparison with those without ILD. This may be explained by the fact that due to chronic inflammatory changes and hypoxia leading to cachectic state, there is a decrease in appetite and, consequently, weight loss. The Modified Rodnan score was higher in the non-ILD group compared to the ILD group. This cannot be explained simply as an increase associated with diffuse SSc which is usually associated with ILD in most cases. In the current study, the increase was associated with less chance of ILD. This factor needs validation through further studies.

Although Raynaud's phenomenon occurred equally in both arms of the study, digital ulcers were seen more in ILD patients (50%) compared to the non-ILD group (30%), probably because of chronic hypoxia along with vasoconstriction.[16] Another interesting finding is that both diffuse and limited SSc had equal incidence of ILD, which was in contrast to the belief that ILD is usually associated with diffuse disease.[17] This may have been a coincidence, and further studies with larger sample sizes are needed for concrete evidence.

Symptoms of dysphagia, early satiety with reflux secondary to oesophageal dysmotility/patulous oesophagus was more common in the non-ILD group, while symptoms of

diarrhoea, constipation, dyspnoea and proximal myopathy were more in the ILD group.

Clinical signs, like arthritis, joint contracture, tendon friction rub and systemic hypertension, were found more in the non-ILD group, while sclerodactyly, pulp atrophy, digital pitting, telangiectasias and PAH were found more in the ILD group. Beaked nose and microstomia were seen equally in both the groups.

In a local study conducted in Lahore, ILD was more common in diffuse SSc than limited SSc, but in the current study, both diffuse and limited SSc has an equal chance of ILD. ANA was present in 100% ILD patients and 90% non-ILD patients, while only 78% patients included in the Lahore study had positive ANA. Anti-Scl-70 positive was 30% the current ILD group and 20% in the non-ILD group, while it was positive in 63.2% of the patients in the Lahore study. Only 10% patients in the current non-ILD group had positive ACA compared to 52.3% in the Lahore study.[18]

In a study in China, ILD was more common in diffuse SSc case, while in the current study, ILD was equal in both limited and diffuse SSc. Weight was more in the ILD group than non-ILD group in the Chinese study, while the current non-ILD group had more weight compared to the ILD patients. Like the current study, the duration of disease was more in the ILD group than non-ILD group in the Chinese study. Telangiectasis and digital ulcers were more common in the ILD group, but the Rodnan score was higher in ILD group, which was in contrast to the current study. The PAH, LVDD and sclerodactyly values were higher in the current ILD group, which was in line with the Chinese study.[19] Anti-Scl-70 was more common in the ILD group, and ACA among those without ILD. Anti-Scl-70 positivity resulted in major organ involvement, especially ILD, in most studies.[20]

In a study conducted in South Korea with 108 patients, 49(45.4%) had diffuse type and 59(54.6%) had limited type SSc. There was difference in the ILD group for disease duration, positive anti-Scl-70 and ACA, white blood cell, platelet, ESR, and the presence of PAH.[21]

As can be seen, a few findings are very consistent in all the relevant studies, which suggests that an algorithm is needed to predict the incidence of ILD in patients with SSc, like the one used to predict PAH incidence.[22,23] This will help the rheumatologists in predicting the onset of ILD in SSc patients earlier, leading to proper investigations and timely management with the usage of minimal resources. As ILD in SSc is a preventable and treatable complication with good prognosis, an early diagnosis can facilitate treatment with immunosuppressives.[24,25]

If an algorithm is devised using simple signs, symptoms and basic investigations in SSc patients, it will be helpful for rheumatologists and physicians to initiate early investigations and treatment within the window period where it can be slowed down and possibly reversed in some cases.[26,27]

The strength of the current study is that, to the best of our knowledge, it is the first of its kind in the local population. However, the current study has several limitations as it had a single-centre data with a small sample size which only had female patients. Besides, the study did not explore the effect of treatment on ILD progression.

Conclusion

There were several significant differences in clinical and laboratory characteristics between SSc patients with or without ILD. Age, duration, telangiectasis, raised ESR, CRP, LVDD, pulmonary arterial hypertension (PAH), and anti-Scl-70 antibodies could be associated with SSc in patients with ILD. The presence of these features predicts ILD in SSc patients, and the absence of these features results in lower incidence of ILD in SSc.

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Author Contribution:

MSM: Design, statistical analysis, review, editing, final approval and responsible for integrity of research.
HG: Design, statistical analysis, data collection, writing, editing, responsible for integrity of research.
MUD & SS: Review and final approval.
MK: Data collection and writing.