

Clinical and Radiographic Heterogeneity of Interstitial Lung Disease in Systemic Sclerosis Based on Disease-Specific Autoantibodies

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Abstract

Background: Patients with systemic sclerosis have the presence of several autoantibodies, some of which are systemic sclerosis-specific autoantibodies that are related to the clinical features of this disease. We retrospectively evaluated the clinical and radiological features of systemic sclerosis in patients with interstitial lung disease on the basis of these autoantibodies.

Method: This study comprised 226 patients with systemic sclerosis. We divided patients with systemic sclerosis into 5 clusters based on the systemic sclerosis-specific autoantibodies present and compared the clinical and radiological features of interstitial lung disease among these 5 systemic sclerosis clusters.

Results: Of 226 patients, interstitial lung disease was present in 73 (32.3%) patients. Clustering by Ward cluster analysis subsequently identified 5 major clusters of patients. Clusters of patients with anti-topoisomerase I antibody and without systemic sclerosis-specific autoantibodies had a higher incidence of interstitial lung disease compared to the other clusters (75.0% and 51.9%, respectively). Patients in these two clusters had higher percentages of cough and dyspnea, higher incidence of traction bronchiectasis and honeycomb-like cysts in computed tomography, and a decrease in percentage predicted of vital capacity. In contrast, patients with anti-centromere antibody had few clinical and laboratory findings and the lowest incidence of interstitial lung disease (16.8%). Patients with anti-ribonucleic antibody or nucleolar pattern in anti-nuclear antibody had moderate findings among the 5 clusters.

Conclusion: The results showed that there were differences in clinical and radiological findings among patients with systemic sclerosis-specific autoantibodies.

Keywords: Systemic sclerosis; Interstitial lung disease; Autoantibody; Pulmonary function tests; High-resolution computed tomography; Cluster analysis

Abbreviations: ACA: Anti-Centromere Antibody; DLco: Diffusion Capacity of the Lung for Carbon Monoxide; dSSc: Diffuse Cutaneous Involvement; FANA: Anti-nuclear Antibody; FEV1.0: Forced Expiratory Volume in 1 Second; GGO: Ground-Glass Opacities; HCLC: Honeycomb-like Cysts; HNCB: Honeycombing; HRCT: High-Resolution Computed Tomography; ILD: Interstitial Lung Disease; LO: Linear Opacities; PFT: Pulmonary Function Testing; RNP: Anti-ribonucleic Protein; SSc: Systemic Sclerosis; TBE: Traction Bronchiectasis; Topo-I: Anti-Topoisomerase I; VC: Vital Capacity

Introduction

Systemic sclerosis (SSc) is a collagen vascular disease characterized by microvascular damage and excessive fibrosis of the skin and internal organs including the lungs [1]. The mortality and morbidity of SSc are associated with severe organ involvement of the skin, lung, gastrointestinal tract, heart, and kidney. Survival from SSc has improved over the past two decades because angiotensin converting enzyme inhibitors became available to treat renal crisis [2,3]. Lung involvement, such as interstitial lung disease (ILD) and pulmonary hypertension, is now the major cause of death in SSc [4-6].

ILD complicates in 40-70% of SSc patients [7,8]. Although it occurs predominantly in SSc patients with diffuse cutaneous involvement (dSSc), it also occurs in patients with limited cutaneous involvement (lSSc) [9,10]. High-resolution computed tomography (HRCT) shows bibasilar pulmonary fibrosis. Steen et al. reported that only 15-20% of SSc patients developed severe restrictive lung disease [11]. This finding implies that the progression of pulmonary fibrosis is much slower or ceases in surviving patients.

Patients with SSc have the presence of several autoantibodies, some of which are SSc-specific antibodies associated with the clinical features of SSc [9-13]. The presence of anti-topoisomerase I (topo-I) antibody is associated with the development of skin fibrosis and progressive ILD in SSc. Anti-centromere antibody (ACA) is seen in patients with limited skin disease and is a minor risk factor for the development of ILD. However, it remains unclear whether SSc-specific antibodies are associated with pulmonary function and radiological findings of HRCT. We divided SSc patients into 5 clusters on the basis of SSc-specific autoantibodies present and retrospectively evaluated the clinical and radiological features of ILD among these 5 SSc patient clusters.

Materials and Methods

Patients and clinical assessment

Study subjects comprised 226 patients with SSc who were outpatients at Osaka Medical College Hospital. All patients fulfilled the criteria of the American College of Rheumatology for the

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classification of SSc [14]. Clinical and laboratory data were obtained from the hospital medical records. The patients were classified as having dSSc or SSc with limited cutaneous involvement according to the classification system [15]. ILD was diagnosed by the presence of radiographic abnormalities consistent with ILD on chest X-ray and/or HRCT. HRCT was performed and assessed in 73 SSc patients with ILD. We excluded patients who had overlap syndrome with systemic lupus erythematosus, polymyositis, or dermatomyositis. Krebs von den lungen-6 (KL-6) is expressed by type 2 pneumocytes. The serum level of KL-6 is increased in patients with ILD and correlated with disease activity [16]. It was measured using an enzyme-linked immunosorbent assay kit at SRL inc. (Tokyo, Japan).

Anti-nuclear antibody

Indirect immunofluorescence tests for anti-nuclear antibody (FANA) were performed using HEp-2 cell lines as substrate according to manufacturer's instructions (Medical & Biological Laboratories, Nagoya, Japan). Ouchterlony double diffusion test was performed for the detection of Topo-I, Ro, La, Sm, and anti-ribonucleic protein (RNP) antibodies (Medical & Biological Laboratories Co., Ltd., Nagoya, Japan). ACA was detected using an enzyme-linked immunosorbent assay kit at SRL Inc. (Tokyo, Japan). Tests for other SSc-specific antibodies were not routinely available and thus were not performed.

Pulmonary function testing

Static and dynamic lung volumes were measured by spirometry (SYSTEM 21; Minato Medical Science, Osaka, Japan). Total lung capacity (TLC) and vital capacity (VC) were determined by the N2 wash-out method. The diffusion capacity of the lung for carbon monoxide (DLco) was determined by the single-breath method. The results of pulmonary function testing (PFT) were expressed as the percentage predicted.

Chest HRCT assessment and scoring

HRCT was obtained with 1.0- or 1.5-mm-thick axial sections at a 1-cm interval throughout the entire lung on a CT system (General Electric Medical Systems, Milwaukee, WI). HRCT of the lung was reviewed for the presence of each of the following signs: consolidation, ground-glass opacities (GGO), linear opacities (LO), traction bronchiectasis (TBE), honeycomb-like cysts (HCLC), honeycombing, reticulation, bulla, and emphysema.

To score the area of ILD, we divided the entire lung to 18 blocks on the HRCT image. Firstly, the thorax was divided to three parts: that above the aortic arch (upper); that between the aortic arch and the origin of pulmonary artery #6 (middle); and that below the origin of pulmonary artery #6 (lower). Then, each part was further divided into 6 pie-shaped blocks; right anterior, right lateral, right posterior, left anterior, left lateral, and left posterior (Figure 1). Each block of the lung was scored as binary variables for the presence of radiographic abnormalities consistent with ILD: consolidation, GGO, LO, TBE, HCLC, reticulation and honeycombing. The scores for each block were summed as the total CT score (minimum 0, maximum 18).

Statistical Analysis

Ward cluster analysis was used to identify groups from all of the study SSc patients with similar SSc-specific autoantibody profiles. A nucleolar pattern of the FANA is not unique to SSc, but when it occurs in SSc, it is associated with three SSc-specific nucleolar ANAs: anti-U3 RNP, anti-Th/To, and anti-Pm/Scl. Thus, the cluster analysis was performed based on the presence of the nucleolar pattern of the FANA

in addition to 3 autoantibodies: anti-Topo-I antibody, ACA, and anti-RNP antibody, as binary variables. Demographic characteristics, clinical and laboratory features, PFT values, and the findings of chest HRCT were compared between the 5 clusters. Clinical and laboratory features were also compared between the findings of chest HRCT. Fisher's exact test was used to compare categorical data, and continuous data were compared using the Mann-Whitney U-test. A p-value of less than 0.05 was considered significant. All statistical analyses were performed with JMP version 7.01 (SAS Institute, Cary, NC) and StatFlex version 6.0 (Osaka, Japan).

Results

Patient characteristics

Of the 226 patients, 206 (91.1%) were women, with a mean \pm SD age of 59.9 ± 12.1 years (Table 1). Seventy-seven of the 226 patients had dSSc. The time from the appearance of first symptoms to the diagnosis of SSc was 9.1 ± 7.4 years. All patients had positive findings on FANA testing, and ILD was present in 73 (32.3%) patients.

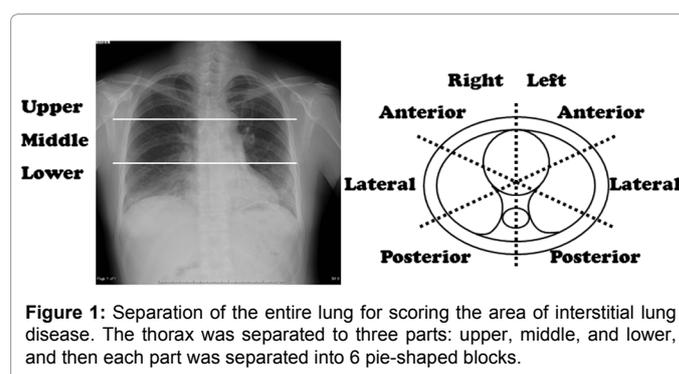
Distribution of ILD in SSc patients and correlation between total CT score and PFT or KL-6 values

To reveal the distribution of ILD in SSc, the number of patients with the presence of ILD was calculated in each block of the lung (Table 2). The affected lung fields of SSc patients with ILD were symmetrical. Bilateral lower posterior blocks were most involved, and bilateral lower lateral and middle posterior blocks were the second most involved.

The total CT score in the SSc patients with ILD was 6.9 ± 4.2 (Table 3). The total CT score correlated positively with the serum level of KL-6 ($p < 0.0001$), whereas the total CT score correlated negatively with %TLC and % VC ($p < 0.0001$) (Figure 2). There was no correlation between the total CT score and % DLco.

Clustering of patients into 5 groups based on SSc-specific autoantibodies

We examined whether SSc patients could be divided into groups based on differences in SSc-specific autoantibody profiles. Clustering by Ward cluster analysis subsequently identified 5 major clusters of patients (Table 1). Cluster 1 (Cent) consisted of 101 patients who were all positive for ACA. Cluster 2 (Nuc) consisted of 37 patients who all had the nucleolar pattern of FANA. Cluster 3 (RNP) consisted of 41 patients who were all positive for anti-RNP antibody. Cluster 4 (Topo) consisted of 20 patients who were all positive for anti-topo-I. Cluster 5 (Non) consisted of 27 patients who were negative for SSc-specific autoantibodies such as ACA, anti-RNP antibody, and anti-topo-I and were without the nucleolar pattern of FANA.



Characteristics	Total	ACA	Nuc	RNP	Topo	Non
Number	226	101	37	41	20	27
Age (yrs)	59.9 ± 12.1	62.9 ± 10.3	59.4 ± 12.6	55.0 ± 14.6*	59.2±13.5	58.9±10.9
Duration* (yrs)	9.1 ± 7.4	9.3 ± 7.4	5.7 ± 4.6	12.0 ± 9.3	9.8±11.0	8.5±7.3
Female sex (%)	91.0	95.0	89.2	95.1	80.0	77.8
Diffuse cutaneous type (%)	34.0	23.8	37.8	36.6	75.0**	29.6
Smoking (%)	31.0	32.5	33.3	24.2	36.8	28.6
SSc-specific autoantibodies						
Anti-centromere Ab	107	101	6	0	0	0
Anti-RNP Ab	49	0	6	41	2	0
Anti-topoisomerase-I Ab	20	0	0	0	20	0
Nucleolar pattern of anti-nuclear Ab	36	0	34	0	2	0
Lung involvement, n (%)	73	17 (16.8)	13 (35.1)	14 (34.1)	15 (75.0)***	14 (51.9)***

*Time from appearance of first symptoms to the diagnosis of SSc

*Values are significantly different from clusters 1.

**Values are significantly different from the other 4 clusters.

***Values are significantly different from clusters 1, 2, and 3.

Data are presented as the mean ± standard deviation or number of subjects. Categorical data and continuous data were compared using Fisher's exact test and Mann-Whitney U-test, respectively.

Ab: Antibody; ACA: Patients with Anti-centromere Ab (cluster 1); Nuc: Patients with Nucleolar Pattern of Antinuclear Antibody (cluster 2); RNP: Patients with Anti-ribonucleic Protein (cluster 3); Topo: Patients with Anti-topoisomerase I (cluster 4); Non: Patients Negative for Antinuclear Antibody and Negative for Systemic Sclerosis-Specific Antibodies (cluster 5)

Table 1: Baseline Patient Characteristics.

Lung area	Right			Left		
	Anterior	Lateral	Posterior	Anterior	Lateral	Posterior
Upper	3	7	23	5	8	20
Middle	6	14	51	6	17	50
Lower	23	53	73	29	54	72

Table 2: Distribution of Interstitial Lung Disease in Systemic Sclerosis.

Characteristics	Total	ACA	Nuc	RNP	Topo	Non
Number	73	17	13	14	15	14
Respiratory symptoms						
Cough	18	0**	1**	4	5	8
Dyspnea	20	1**	2**	1**	7	9
KL-6 (IU/ml)	930 ± 985	608 ± 382*	876 ± 575	1005 ± 1047	973 ± 458	1259 ± 1819
Pulmonary function testing						
%Vital capacity	87.7 ± 19.4	100.7 ± 18.1 [‡]	97.3 ± 16.8	86.2 ± 18.6	87.3 ± 1.3	74.2 ± 22.1
FEV1.0%	80.2 ± 6.9	75.5 ± 5.6	82.4 ± 6.1	77.8 ± 6.5	83.9 ± 5.4	79.7 ± 8.2
%DLco	48.1 ± 16.6	49.6 ± 18.6	51.7 ± 15.1	49.4 ± 10.6	49.3 ± 12.3	39.3 ± 20.8
Total CT score	6.9 ± 4.2	3.9 ± 2.4* ^{‡§}	5.3 ± 2.6* [‡]	7.6 ± 4.7	8.3 ± 3.4	10.0 ± 4.8
HRCT findings						
consolidation	1	0	0	0	0	1
honeycombing	2	0	0	0	1	1
honeycomb-like cysts	39	4**	7	7	11	10
traction bronchoectasis	38	1**	6	7	12	12
ground-glass opacity	25	5	6	6	4	4
linear opacity	20	4	5	3	4	4
reticulation	40	8	9	8	7	8
bullae	17	4	4	3	2	4
emphysema	5	2	2	0	1	0

*Values are significantly different from Topo (clusters 4)

[‡]Values are significantly different from Non (clusters 5).

[§]Values are significantly different from RNP (clusters 3).

Data are presented as the mean ± standard deviation or number of subjects. Categorical data and continuous data were compared using Fisher's exact test and Mann-Whitney U-test, respectively.

Table 3: Clinical and Laboratory Characteristics of SSc patients with ILD.

Sex and the percentage of smoking were similar in the subjects across all groups. Patients in cluster 3 (RNP) were younger than those in cluster 1 (ACA). The incidence of dSSc in cluster 4 (Topo) was significantly greater than that in the other clusters.

Clinical and laboratory manifestations among the 5 autoantibody clusters

The clinical and laboratory manifestations of ILD among the 5 autoantibody clusters in the SSc patients are shown in Table 1. There was a significant difference in the incidence of ILD among the 5 clusters.

The incidence of ILD was significantly greater in cluster 4 (Topo) and cluster 5 (Non) than that in the other clusters. Patients in these two clusters had higher percentages of cough and dyspnea, increased serum level of KL-6, and a higher CT score (Table 3). In addition, PFT showed a decreased value of %VC. Patients in cluster 3 (RNP) had also increased serum level of KL-6, and a higher CT score. In contrast, no significant difference was observed among the 5 clusters for FEV1.0% (forced expiratory volume in 1 second) and % DLco.

Radiological findings among the 5 autoantibody clusters

Radiological findings of chest HRCT among the 5 autoantibody

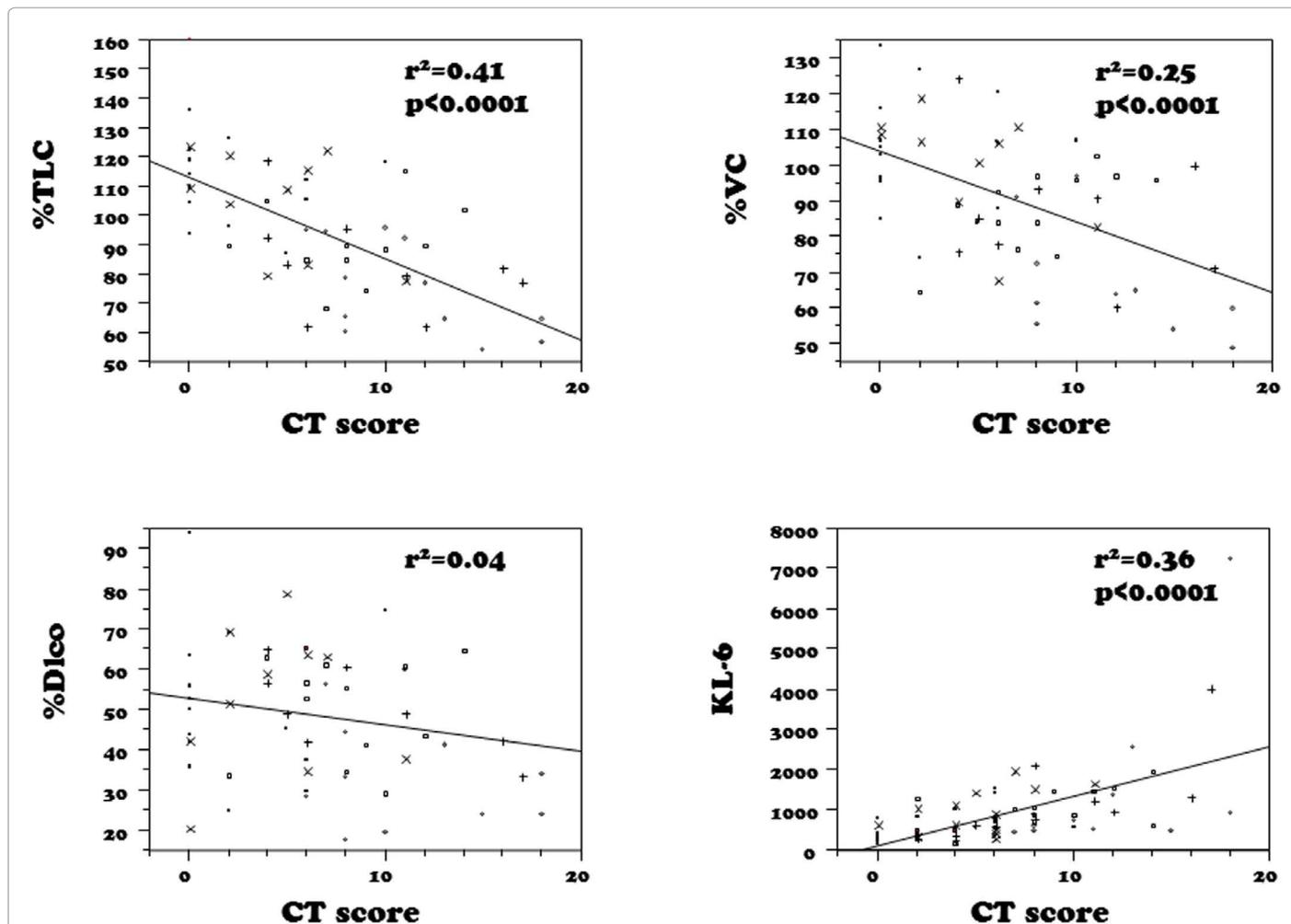


Figure 2: Correlation of total CT score with clinical parameters. %TLC: total lung capacity, %VC: percentage predicted of vital capacity, %DLco: diffusion capacity of the lung for carbon monoxide, CT: computed tomography.

clusters in the SSc patients are shown in Table 3. The presence of TBE and HCLC in cluster 4 (Topo) and cluster 5 (Non) was significantly greater than that cluster 1 (ACA). No significant differences among the 5 clusters were observed for the other findings of HRCT.

Discussion

We showed the distribution of ILD in SSc patients and its association with clinical and laboratory findings and evaluated the clinical features of autoantibody clusters in these patients. SSc showed heterogeneous clinical manifestations and several SSc-specific autoantibodies [9-13]. SSc-specific autoantibodies were associated with the clinical and laboratory findings of ILD in patients with SSc. All autoantibodies in this study can be measured routinely in most medical institutions. The associations between SSc-specific antibodies and the present study findings may be useful for the management of ILD in SSc patients.

ILD in SSc distributes predominantly in the bilateral and lower lung fields [15,17]. Our study also showed the lung involvement was symmetrical and predominantly bibasilar. HRCT findings of ILD were assessed by several methods [18,19], and its assessment depends on the evaluators. The assessment of HRCT in this study was done with binary variables for the presence of radiographic abnormalities consistent with

ILD. The total CT score correlated with KL-6 level, %TLC, and %VC. Our method may be simple and useful for the assessment of ILD in SSc. Although %DLco was reduced in patients with ILD, it did not correlate with the total CT score. This discrepancy may be due to the presence of other factors such as anemia and pulmonary hypertension in SSc.

On the basis of SSc-specific autoantibodies, SSc was divided to 5 autoantibody clusters, which were different from each other in the incidence, clinical and laboratory findings, and HRCT findings of ILD. Patients with anti-Topo-I antibody have the highest incidence of ILD [9-13], and our results confirmed this. Moreover, the distribution of ILD was wider, the serum level of KL-6 and the presence of TBE and HCLC in HRCT were higher, and the results of PFT were worse in these patients. In contrast, patients with ACA had few clinical and laboratory findings and the lowest incidence of ILD. The distribution of ILD in patients with ACA was the smallest, and the serum level of KL-6 and the presence of TBE and HCLC in HRCT were the lowest. Patients with anti-RNP antibody or nucleolar pattern in FANA testing had moderate findings among the 5 SSc clusters. Thus, clinical and radiological features of ILD were heterogeneous in SSc based on disease-specific antibodies. TBE and HCLC in HRCT may be useful findings for the assessment of ILD in SSc compared with findings of GGO, LO, and honeycombing.

Patients without SSc-specific autoantibodies frequently had ILD, similar to the patients with anti-Topo-I antibody. Most patients in this cluster (Non) had respiratory symptoms such as dyspnea and cough and were referred to our hospital because of their symptoms. It is possible that this cluster (Non) may contain patients with ILD-dominant SSc. Recently, several autoantibodies such as anti-Th/To antibody and anti-synthetase antibodies were reported to be related to ILD [20-22]. Although these antibodies were not measured in this study, some patients may have autoantibodies related to ILD, and additional studies are needed to confirm the presence of these autoantibodies.

This study was a retrospective and observational study performed at a single center. We did not show the progression of ILD and therapeutic effects in patient clusters of SSc. Our results showed that there were differences in clinical and laboratory findings among patients with SSc-specific autoantibodies. The incidence of disease-specific autoantibodies and clinical manifestations show racial differences in SSc. Thus, further analyses based on disease-specific autoantibodies as in the present study are needed to evaluate the features of SSc.

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