Lung involvement in systemic sclerosis (scleroderma): relation to classification based on extent of skin involvement or autoantibody status

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Lung involvement accounts for significant morbidity and is a leading cause of mortality in patients with systemic sclerosis (SSc). It has been shown that different patterns of pulmonary involvement are seen in different subtypes of SSc. This paper reports a retrospective review of 72 patients with SSc to determine whether disease classification according to the extent of skin involvement alone (diffuse vs. limited) or autoantibody status was predictive of pulmonary parenchymal involvement. The diagnosis of interstitial lung disease was based on pulmonary function tests and chest radiographs. Restrictive lung disease was common in both limited SSc (iSSc) and diffuse SSc (dSSc), occurring in 30% and 50% of these patients respectively (P=0.16). Radiographic evidence of significant interstitial disease was also comparable between the groups [nine of 32 iSSc patients (28%) vs. six of 17 dSSc patients (32%), P=n.s.]. No significant difference in mean lung function was found between patients with anti-Scl 70 antibody (n=12) compared to those without (n=60) (TLC 79 0 ± 51% predicted vs. 82.8 ± 2.2, P=n.s.; DLCO 63.0 ± 5.1 vs. 59.7 ± 2.5, P=n.s.). By contrast, statistically significant differences in mean lung function were found between patients with anticentromere antibody (ACA) (n=24) and those without ACA (n=48) (TLC 98.6 ± 9% predicted vs. 79.7 ± 3.1%, P<0.001); and less frequent radiographic evidence of severe interstitial disease (0 of 17 with significant interstitial changes on chest radiograph vs. 15 of 32 (47%), P=0.002). It is concluded that classification of SSc patients on the basis of the distribution of skin involvement poorly predicts the occurrence of interstitial lung disease. On the other hand, ACA is highly associated with the absence of interstitial lung disease.

Introduction

Systemic sclerosis (scleroderma, SSc) is a connective tissue disorder of unknown etiology with heterogeneous manifestations involving skin, peripheral vasculature, heart, kidneys, gastrointestinal tract and lungs. Lung involvement is a major cause of morbidity and a leading cause of death in SSc patients (1–3). Autopsy studies have shown that as many as 79% have interstitial lung disease, while 29% have pulmonary vascular disease (4). Because of the heterogeneity of lung involvement in SSc patients, there has been great interest in clinical markers of disease which could predict patterns of organ involvement. Previous reports have suggested a relation between pulmonary parenchymal or vascular involvement and other clinical features of the disease, such as extent of skin involvement and Raynaud's phenomenon (5–7). For example, patients with the CREST syndrome (having clinical or radiologic evidence of calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, and telangiectasia) variant of SSc appear less likely to have restrictive pulmonary disease but have a higher frequency of isolated pulmonary vascular disease (5). The presence of specific autoantibodies, especially anticentromere (ACA) or anti-Scl 70 (antibodies to toplasmonerase I, a nucleoprotein) (8–12) have also been shown to correlate with the presence of pulmonary parenchymal and vascular abnormalities in SSc patients. Antinuclear autoantibodies (ANA) are detected in virtually all patients with SSc (13). Two specific autoantibodies, anticentromere and anti-Scl 70, occur in approximately 22% and 26% of patients, respectively (8). Although these antibodies usually do not occur together, rare cases demonstrating the presence of both antibodies have been reported (14,15). It has been suggested that interstitial lung
disease is less frequent in SSc patients with ACA than those without this antibody, but this has not been confirmed (8,10). Furthermore, single-breath carbon monoxide diffusing capacity (DLCO) has been shown to be lower in SSc patients with anti-Scl 70 antibodies than in patients without anti-Scl 70, suggesting a greater incidence of interstitial disease in this group (9).

A recently proposed system for classifying SSc identifies patients on the basis of extent of skin involvement as compared to other clinical features such as calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and the presence of telangiectasias (16). Skin involvement appears as scarring (fibrosis) and skin thickening which gives the skin a hidebound appearance. Skin involvement limited to the distal extremities (below the elbow or knee) or the head and neck is classified as limited systemic sclerosis (ISSc). Skin involvement extending to the trunk (shoulders, chest, back, abdomen) or proximal extremities is classified as diffuse systemic sclerosis (dSSc). The latter has been reported to be associated with a more aggressive clinical course of disease and with a greater risk of visceral complications than ISSc patients (8,17).

This study was undertaken to determine whether classification of SSc patients on the basis of the extent of skin involvement or on the basis of autoantibody status was more predictive of interstitial lung involvement. The ability to predict which SSc patients are likely to develop pulmonary involvement would greatly enhance efforts to plan early therapeutic intervention in this disease.

Methods

Patients

Seventy-two patients who were evaluated consecutively at the Thomas Jefferson University Scleroderma Center during 1990 to 1992 were included. Each patient satisfied the American College of Rheumatology criteria for SSc (18). Patients were classified as having either limited or diffuse SSc based on extent of skin involvement (16). Patients with skin involvement confined to the face, hands, forearms, or lower legs were classified as having ISSc. Patients with skin involvement of the trunk or proximal extremities (proximal to the elbow or knee) were classified as having dSSc.

Autoantibody Determination

Dilutions of serum from patients were applied to commercially prepared HEp-2 cells, followed by FITC antihuman immunoglobulin (Cooper, Malvern, PA) using methods previously described (19,20). Anticentromere antibodies were detected by the characteristic fluorescent ANA pattern (large granules dispersed throughout the nucleus of interphase cells segregating with condensed chromosomes in mitotic cells). A titre of less than or equal to 1:40 was considered negative. Antibodies to Scl-70 were identified using rabbit thymus extract (RTE), prepared by resuspension of a commercially prepared thymus extract (Zeus Wampole) in phosphate buffered saline. A titre of less than or equal to 1:40 was considered negative. Antibodies were detected by double immunodiffusion against RTE and compared to sera with known specificity to topoisomerase I.

Pulmonary Function Tests

 Spirometry, lung volumes and DLCO were performed using standardized techniques as described by the American Thoracic Society (21) and expressed as percent of predicted normal. A Collins DS1 (Walter E. Collins, Co, Braintree, Massachusetts) multi-lung analyser was used to measure forced vital capacity (FVC), forced expired volume at 1 s (FEV1), total lung capacity (TLC), and DLCO in each patient. Total lung capacity was measured by closed circuit helium equilibration technique. Predicted normals were obtained from published standards (22–24). Patients were considered to have a restrictive ventilatory impairment if TLC was <80% of predicted normals.

Chest Radiographs

Chest radiographs (standard postero-anterior, and lateral views) were read jointly by two experienced observers (EFC, PWS) who were unaware of the clinical and serologic features of each patient. The distribution of pulmonary parenchymal abnormality was divided by side (right and left) and by zone (upper, middle and lower). The profusion of abnormality in each zone was graded on a 0–3 scale (absent, minimal, moderate and extensive). Profusion, zonal distribution, and symmetry were combined to produce three categories of radiologic parenchymal abnormalities: A, normal or no significant parenchymal abnormality (all zones graded 0 or a solitary zone pair graded no higher than 1); B, minimal abnormality of unknown significance (one bilaterally symmetric zone pair graded no higher than 1); C, significant interstitial abnormality (any involvement exceeding categories A and B).

Statistical Analyses

Mean values for pulmonary function as percent predicted normals were compared using one way
Table 1 Clinical and demographic characteristics of limited and diffuse systemic sclerosis patients

<table>
<thead>
<tr>
<th></th>
<th>Limited SSc</th>
<th>Diffuse SSc</th>
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<tbody>
<tr>
<td></td>
<td>ACA+ (n=21)</td>
<td>ACA− (n=25)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.6</td>
<td>54.5</td>
</tr>
<tr>
<td>Female (%)</td>
<td>21 (100%)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>13-9</td>
<td>9-7</td>
</tr>
<tr>
<td>from first symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>from first non-Raynaud symptom</td>
<td>10-6</td>
<td>6-2</td>
</tr>
<tr>
<td>Smoking history*</td>
<td>8/21</td>
<td>15/25</td>
</tr>
<tr>
<td>Anti-fibrotic therapy†</td>
<td>3/21</td>
<td>7/25</td>
</tr>
<tr>
<td>CREST by clinic evaluation</td>
<td>15/21</td>
<td>12/25</td>
</tr>
</tbody>
</table>

SSc, systemic sclerosis; ACA, anti-centromere antibody; Scl 70, anti-Scl 70 antibody; *defined as current smoker or ex-smoker with greater than 10 pack-years; †D-penicillamine (for 6 months) or, in two patients, extracorporeal photochemotherapy (both diffuse SSc, Scl 70 negative); ‡When compared to ACA− ISSc there were significantly more females in the ACA+ group.

Results

The demographic features of the patients are shown in Table 1. Forty-six patients were classified as having ISSc on the basis of extent of skin involvement; 26 patients had dSSc. The mean age was 53 years (range 20–77 years), and 84% were female. The average duration of SSc from the first non-Raynaud symptom was 7.6 years at the time of evaluation. Thirty-six (50%) patients had ACA or anti-Scl 70 antibodies, although no patient had both ACA and anti-Scl 70 detected concurrently (Table 2). Anticentromere antibody was more common in ISSc patients, and anti-Scl 70 was more common in dSSc patients. However, these antibodies did not occur exclusively in either group. Among ISSc patients, 45.7% had ACA, and 38.5% of dSSc patients had anti-Scl 70 antibody. These antibodies were somewhat specific; as the positive predictive value of ACA for ISSc was 87.5%, while anti-Scl 70 had a predictive value of 83% for dSSc. Subgroups based on ACA status did not correspond with the presence of CREST syndrome features (all five features present by history, examination or radiograph) (Table 1). The use of disease modifying anti-fibrotic therapy is also noted in Table 1. Except for the use of extracorporeal photochemotherapy in two dSSc patients, only D-penicillamine was used.

Table 2 Autoantibodies in systemic sclerosis patients

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Limited SSc (n=46)</th>
<th>Diffuse SSc (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA+</td>
<td>21 (45.7%)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>Anti-Scl 70+</td>
<td>2 (4.3%)</td>
<td>10 (38.5%)</td>
</tr>
<tr>
<td>Neither</td>
<td>23 (50%)</td>
<td>13 (50%)</td>
</tr>
</tbody>
</table>

SSc, systemic sclerosis; ACA, anti-centromere antibody; Anti-Scl 70, anti-Scl 70 antibody.

PULMONARY FUNCTION

The frequency of restrictive lung disease did not differ significantly between ISSc and dSSc patients [14/46 vs. 13/26 patients, P=0.16 (n.s.)] as shown in Table 3. In addition, there was no significant difference between ISSc and dSSc patients in the frequency of normal pulmonary function (15/46 vs. 5/26, P=n.s.), or isolated reduction in the DLCO (17/46 vs. 8/26, P=n.s.).

Pulmonary function according to autoantibody status is presented in Figs 1 and 2. There were no significant differences in mean lung function in patients with and without anti-Scl 70 antibody (Fig. 1), but there was a trend toward a lower FVC in those with anti-Scl 70. Additionally, although more patients with anti-Scl 70 had restriction, this difference was not significant (Table 4, P=0.19). However, patients with anti-Scl 70 antibody were more frequently treated with anti-fibrotic agents (83% vs. 30%, P=0.002).

On the other hand, patients with ACA had preserved lung volumes and higher DLCO (Fig. 2). In fact, only three of 24 patients with ACA had
Table 3 Primary patterns of pulmonary function abnormalities in according to skin classification

<table>
<thead>
<tr>
<th></th>
<th>Limited SSc</th>
<th>Diffuse SSc</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=46)</td>
<td>(n=26)</td>
<td></td>
</tr>
<tr>
<td>Normal*</td>
<td>15 (33%)</td>
<td>5 (19%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Isolated reduction</td>
<td>17 (37%)</td>
<td>8 (31%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>in DLCO†</td>
<td>14 (30%)</td>
<td>13 (50%)</td>
<td>P=0.15</td>
</tr>
<tr>
<td>Restriction‡</td>
<td></td>
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</tbody>
</table>

SSc, systemic sclerosis. *Normal defined as FVC, and FEV₁ ≥80%, TLC ≥80%, with DLCO ≥70% predicted normal. †Isolated reduction in DLCO defined as normal except for DLCO <75% predicted. ‡Restricted defined as FVC <80% confirmed by TLC <80% predicted, with or without reduction in DLCO.

Airways obstruction (defined as FEV₁/FVC ≤72%) was noted in both lSSc and dSSc groups: nine of 46 (20%) lSSc patients vs. three of 26 (12%) dSSc patients. There was no difference in the frequency of airways obstruction in patients with ACA compared to those without ACA (12.5% vs. 17%, P=n.s.) or in patients with and without anti-Scl 70 (10% vs. 12.5%, P>0.20). Nearly all patients in the present study population with evidence of large airways obstruction were current or former smokers with greater than 10 pack-years of exposure to tobacco (83%).

RADIOGRAPHY

Thirty-two of 46 lSSc patients and 17 of 26 dSSc patients had radiographs available for review. Overall, the frequency of significant interstitial abnormalities (category C) was comparable between lSSc and dSSc patients (28% vs. 35%, P>0.20) (Table 5). There were no significant differences in the presence of radiographic abnormalities, as indicated by an increase in interstitial markings, between patients with and without anti-Scl 70 autoantibodies (Table 6). Radiographic evidence of interstitial pulmonary disease was, however, less frequent and less extensive in patients with ACA when compared to those without ACA (6% vs. 47%, P<0.002).

Among patients with interstitial abnormalities (n=22), 50% had diffuse disease with lower lobe predominance, 27% had isolated lower lobe involvement, 9% had diffuse disease without any predominant zonal involvement, and 14% had isolated mid or upper lung zone involvement.

Eight-five percent of patients who had insignificant or no radiographic interstitial abnormalities (Category A) had normal lung volumes, whereas four had minimally reduced lung volumes (TLC 65–80% predicted). Fifty-seven percent of patients with minimal interstitial abnormalities of uncertain significance (category B) had evidence of restriction with TLC of 73-5% predicted. The remaining patients with minimal interstitial abnormalities had normal lung volumes. Seventy-three percent of patients with significant interstitial abnormalities (category C) on chest radiograph had evidence of restrictive lung disease with mean TLC of 59.3% and mean DLCO of 39-5% predicted.

SPECIAL PATIENT GROUPS

Among dSSc patients with ACA (three patients, who all lacked anti-Scl 70 antibody), only one had evidence of restrictive lung disease. This patient initially presented with limited disease but progressed to diffuse skin involvement with moderate interstitial lung disease (present by chest radiograph and restriction of lung volumes (defined as TLC <80% predicted). Patients without ACA had reduced TLC and FVC values, indicating a significant restrictive impairment. For patients without ACA, 24 of 48 (50%) had restriction (Table 4). Patients with ACA frequently had preserved lung volumes with an isolated reduction in DLCO (12/24 patients, 50%).
Table 4  Patterns of pulmonary function in systemic sclerosis

<table>
<thead>
<tr>
<th></th>
<th>According to ACA</th>
<th>According to Scl 70</th>
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<tbody>
<tr>
<td></td>
<td>ACA⁺ (n=24)</td>
<td>ACA⁻ (n=48)</td>
</tr>
<tr>
<td>Normal*</td>
<td>9 (37.5%)</td>
<td>11 (23%)</td>
</tr>
<tr>
<td>Isolated reduction in DLCO†</td>
<td>12 (50%)</td>
<td>13 (27%)</td>
</tr>
<tr>
<td>Restriction‡</td>
<td>3 (12.5%)</td>
<td>24 (50%)</td>
</tr>
</tbody>
</table>

ACA, anticentromere antibody; Scl 70, anti-Scl 70 antibody. *Normal defined as FVC and FEV₁ ≥80%; TLC ≥80%; with DLCO ≥70% predicted normal. †Isolated reduction in DLCO defined as normal except for DLCO <70% predicted. ‡Restriction defined as FVC <80% confirmed by TLC <80% predicted, with or without reduction in DLCO.

Note: In the limited SSc group, 9/46 (20%) patients had evidence of large airway obstruction with FEV₁/FVC ≤72%. In the diffuse SSc group, 3/26 (12%) had evidence of large airways obstruction.

Table 5  Interstitial abnormalities on chest radiograph according to skin classification

<table>
<thead>
<tr>
<th></th>
<th>Limited SSc (n=32)</th>
<th>Diffuse SSc (n=17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No radiographic abnormalities or radiographically insignificant abnormalities (see Methods)</td>
<td>18 (56%)</td>
<td>9 (53%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Minimal interstitial radiographic abnormalities of uncertain significance</td>
<td>5 (16%)</td>
<td>2 (12%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Significant interstitial radiographic abnormalities</td>
<td>9 (28%)</td>
<td>6 (35%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

ACA, anticentromere antibody; Scl 70, anti-Scl 70 antibody.

Table 6  Interstitial abnormalities on chest radiograph according to antibody status

<table>
<thead>
<tr>
<th></th>
<th>ACA⁺ (n=17)</th>
<th>ACA⁻ (n=32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No radiographic abnormalities or radiographically insignificant abnormalities</td>
<td>16 (94%)</td>
<td>11 (34%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimal</td>
<td>1 (6%)</td>
<td>6 (19%)</td>
<td>=0.012</td>
</tr>
<tr>
<td>Significant</td>
<td>0 (0%)</td>
<td>15 (47%)</td>
<td>=0.002</td>
</tr>
</tbody>
</table>

ACA, anticentromere antibody; Scl 70, anti-Scl 70 antibody.

confirmed at post-mortem examination) and severe pulmonary hypertension. The remaining two patients lacked evidence of interstitial lung disease by chest radiograph. Among 1SSc patients with anti-Scl 70 antibody (two patients, who lacked ACA), both had restrictive lung disease by pulmonary function criteria (chest radiographs were not available).

**Discussion**

This study was undertaken to determine whether classification of SSc patients according to the extent of skin involvement could predict the presence or absence of pulmonary involvement and restrictive lung disease. The present data indicate that
classification according to skin involvement alone is only weakly predictive of restrictive lung disease, as 14/46 (30%) ISSc patients had restriction compared to 13/26 (50%) of dSSc patients. Thus, restrictive lung disease is common in both ISSc and dSSc patients. This study's definition of restrictive lung disease was arbitrary (TLC < 80% predicted), it was believed to conservatively identify patients with pulmonary parenchymal abnormalities and it was applied consistently between all groups. Moreover, there was a correspondence between the pulmonary function abnormalities and radiographic abnormalities, as only four of 27 patients with normal chest radiographs had reduced TLC values and only seven of 30 patients with normal TLC values had abnormal radiographs.

A notable finding in this study was the observation that restrictive disease occurred infrequently in patients with ACA (3/24, 12.5%). In contrast, among patients without ACA, restriction was common, occurring in 24 of 48 patients (50%). The lower frequency of interstitial disease based on measurements of FEV₁, FVC and chest radiographs in patients with ACA has previously been noted (8-10). The present study supports and extends these observations insofar as the evaluation of ILD included measurement of static lung volumes (TLC) and DLCO together with a blinded analysis of chest radiographs (observers unaware of clinical and serologic features of each patient). Additional studies are necessary to determine whether patients with ACA are 'protected' against the development of interstitial involvement, or if such involvement is mild and not detected by routine pulmonary function testing and chest radiography.

Whereas ACA was almost exclusively identified in ISSc patients, a statistically significant difference in the frequency of restrictive lung disease between ISSc and dSSc might be expected if greater numbers of patients were studied. Nevertheless, the occurrence of restrictive lung disease appears to be unrelated to the pattern of skin involvement; rather the presence of ACA appears to be associated with the absence of restrictive lung disease. The demonstration of a moderately reduced DLCO in ACA positive patients may indicate early pulmonary vascular disease, as others have suggested (5). The finding of infrequent restriction among patients with ACA is not attributable to the frequency of CREST syndrome features, as those features were frequently present in limited SSc patients with and without ACA.

Patients with dSSc who have ACA (only three of 72 patients in the present study) represent a rare population. Two of the three patients with this pattern lacked physiologic or radiographic evidence of interstitial lung disease. Thus ACA appears to be protective in dSSc as well. Limited SSc patients with anti-Scl 70 antibody might be expected to have ILD because they lack ACA, and indeed both such patients in the present study had restrictive lung disease.

In contrast to ACA, anti-Scl 70 antibody status was not predictive of lung function in the study population. This contrasts with other reports of an association between anti-Scl 70 antibodies and interstitial lung disease (8, 9). This discordance could be explained by the effects of anti-fibrotic therapy in those with anti-Scl 70 antibody, and the small number of patients with this antibody in the present study. In all but two of the patients receiving anti-fibrotic therapy in this cohort, D-penicillamine was employed. Two patients who received extracorporeal photochemotherapy had diffuse SSc and lacked Scl 70 and ACA antibodies. Anti-fibrotic therapy, D-penicillamine in particular, has been associated with improvement in DLCO, and prolonged survival, in addition to improvement in skin sclerosis (26-29). Further study of larger populations with anti-Scl 70 may be required, given the small number of patients in this report.

Radiographic involvement was primarily in the lower lobes, as previously reported (31). However, among patients with interstitial disease noted on chest radiograph, three patients (14%) had isolated mid-lung or upper lobe abnormalities. This observation suggests that abnormalities in the mid and upper lung zones may be seen in this disease and should not be dismissed as unrelated parenchymal abnormalities.

The observation that the presence of ACA has greater predictive value for interstitial lung involvement in SSc than the extent of skin involvement highlights the complex immunopathogenesis of SSc. Moreover, it is remarkable that the presence of an autoantibody appears to be protective against the development of lung fibrosis as the authors are aware of no other such autoantibody. One hypothesis for the protective effect of ACA could be its association with specific major histocompatibility complex antigens. Pulmonary fibrosis in SSc has been shown to be strongly associated with DR52a haplotype (32). This haplotype has been shown to be associated with the anti-Scl 70 antibody. In contrast, ACA is associated with DR1 and DR4 haplotypes which may be protective against the development of pulmonary fibrosis. It is not surprising that the autoantibodies discussed here, as well as others, such as antihistone antibodies, are the focus of recent investigations into
the pathogenesis of SSc (33,34). Studies of potential differences in the regulation of lung tissue injury and repair in patients with and without ACA may shed light on the pathogenesis of pulmonary inflammation and fibrosis in SSc.

Acknowledgments

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