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Relationship between abnormalities on high-resolution computerized tomography, pulmonary function, and bronchoalveolar lavage in progressive systemic sclerosis

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Abstract. *Introduction and aim:* Progressive systemic sclerosis (pSS) is a multisystemic connective tissue disease characterized by fibrosis of the skin and internal organs including lung. The mechanisms that leads to progressive lung fibrosis in scleroderma remain obscure. In this study, we aimed to investigate the correlation between HRCT findings and patients' clinical and functional status and the degree of alveolitis based on the BAL results. *Materials and methods:* 65 patients with pSS were evaluated. Thoracic HRCT, pulmonary function tests, and dyspnea measurements were applied, and BAL was performed. The parenchymal abnormalities identified on HRCT were coded, and scored according to Warrick et al. *Results:* Among parameters investigated, a correlation was found between the number of segments with subpleural cysts and the duration of disease. Also there was a correlation between the HRCT score and patient age whereas no correlation was detected between the duration of the disease, manifestation of the symptoms, and the x-ray findings. A correlation was found between the percentage of neutrophils detected in BAL and the extent of the honeycombing on HRCT. *Conclusion:* This study showed a strong correlation between the extent of x-ray abnormalities and FVC, RV, and DLCO, as well as an increase in the percentage of BAL fluid neutrophils in patients with SSc-PI.*(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 349-354)*

Key words: scleroderma, high resolution computed tomography, pulmonary function test

Introduction

Progressive systemic sclerosis (pSS) is a multisystemic connective tissue disease with unknown etiology, which leads to diffuse microvascular and macrovascular damage, and is characterized by fibrosis of the skin and internal organs (1-3). In pSS, lung involvement may occur in two ways: isolated pulmonary hypertension and interstitial lung fibrosis (4-7). Lung involvement is common and is probably the leading cause of death in these patients (8-11). Plain chest x-rays, the pulmonary function test, and thoracic high-resolution computed tomography (HRCT) are standard noninvasive tests used to evaluate suspected lung involvement. It has been suggested that chest x-ray abnormalities are present in up to two-thirds of patients with pSS. Because HRCT is more sensitive than the other standard

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noninvasive tests, lung involvement may be detected on HRCT scans, even though the chest x-ray findings are normal (12). In an HRCT-histopathological correlation, significant inflammation in the open-lung biopsy specimen was almost entirely correlated with ground glass opacity on HRCT scans in a large group of patients (13).

The mechanisms that leads to progressive lung fibrosis in scleroderma remain obscure. Lung inflammation strikes a subset of patients, and its presence, as assessed with the neutrophil or eosinophil bronchoalveolar lavage (BAL) cell differential, indicates greater risk for progressive lung fibrosis and death (14).

In this study, we aimed to investigate the correlation between HRCT findings and patients' clinical and functional status and the degree of alveolitis based on the BAL results.

Materials and methods

In this study, 65 patients with pSS with pulmonary involvement referred to Istanbul University, Cerrahpasa Medical Faculty, Department of Pulmonary Diseases between July 1995 and February 2014 were evaluated. The diagnosis had been established according to the American Rheumatology Association criteria (15). Patients with other collagen diseases in addition to pSS were excluded. Demographic characteristics are displayed in Table 1. Patients with systemic sclerosis in whom pulmonary involvement was suspected and who were referred or attended our clinic were evaluated and followed according to a standard protocol. At the time of the first referral, thoracic HRCT, pulmonary function tests, and dyspnea measurements were applied, and BAL was performed on patients who had no recent history or signs of respiratory infection.

Table 1. Patients' demographic characteristics of the patients

Patients (n)	65
Age (year)	50.3 ± 13.4 (27-80)
Female/male gender (n)	63/2
Duration of disease (year)	11.6 ± 8.0
Duration of respiratory symptoms (year)	2.9 ± 3.4 (median=2)
Smoking status (current smoker-n)	5 (median 15 packs/year)
(ex-smoker-n)	11 (median 6 packs/year)
(nonsmoker-n)	49

Note. Data are presented as mean ± SD or number of patients unless otherwise indicated.
1 pack: 20 cigarettes

The x-rays were evaluated and scored by an independent radiologist who had 5 years of experience in interstitial lung disease radiology and was blinded to the patients' clinical data. The parenchymal abnormalities identified on HRCT were coded, and a score was defined according to Warrick et al. (16). A point value was assigned to each abnormality (Table 2). For each patient, the disease severity score was obtained by adding up the points. The extent of disease score was the total number of bronchopulmonary segments involved (Table 3). Finally, the disease severity and extent of disease scores were summed to form the total HRCT score with a possible range of 0 to 30. For example, a patient with ground glass appearance (disease severity score 1) in the five segments of the right lower lobe (extent of disease score 2) and honeycombing (disease severity score 4) in two segments (extent of disease score 1) would have a total HRCT score of 6. Apart from this scoring, the total number of affected segments in general and the number of segments with each abnormality were also evaluated.

Spirometry and single-breath carbon monoxide lung diffusion capacity (DLCO) measurements were performed (Sensor Medics Vmax series 22). Lung volumes were measured with ZAN 500 (nSpire Health GmbH, Oberthulba, Germany) plethysmography.

BAL was performed without premedication under local anesthesia with intravenous (iv) 2% lidocaine to the middle lobe or lingular segment using five 20 ml aliquots of normal saline solution. The

Table 2. Point values of the abnormalities on thoracic HRCT

HRCT abnormality	Point value
Ground glass appearance	1
Irregular pleural margins	2
Septal/subpleural lines	3
Honeycombing	4
Subpleural cysts	5

Table 3. Extent of disease scores

Number of bronchopulmonary segments involved	Point value
1-3	1
4-9	2
>9	3

fluid returned was more than 50% of the saline given. In the differential cell count, the percentage of neutrophils, lymphocytes, and eosinophils and the total cell count were determined.

The Medical Research Council (MRC) dyspnea scale was used to measure dyspnea (17). The pulmonary function test results, BAL findings, dyspnea measurements, and HRCT scores were evaluated using the Spearman or Pearson correlation test. The results were defined as the mean value ± standard deviation.

Results

When pulmonary involvement was discovered, 65 patients had spirometric evaluation, 63 patients had diffusion capacity measurements, 18 patients had lung volume measurements, and 38 patients had bronchoalveolar lavage results. All patients already had a dyspnea measurement result. Table 4 illustrates the results of the pulmonary function tests, when pulmonary involvement was definitely diagnosed. In 27 (41.5%) patients and in 56 (86.2%) patients, the forced vital capacity (FVC) and DLCO values, respectively, were below 75%. BAL findings, dyspnea scoring, and thoracic HRCT scores are summarized in Table 5. In 84.2% of patients, alveolitis was detected with BAL, and dyspnea was present with varying severity in 95.4% of patients.

There was a linear correlation between the total HRCT score and age (p=0.04, r=0.26), CT index and FVC % (p=0.026, r=-0.28) and between the HRCT score and DLCO % (p=0.027, r=-0.28). Linear correlations between the total number of affected segments in both lungs and FVC % (p=0.006, r=-0.34), DLCO % (p=0.001, r=-0.41), total lung capacity (TLC) % (p=0.02, r=-0.54), and residual volume (RV) % (p=0.007, r=-0.61) were detected as well as the correlation between the total number of affected segments and the polymorphonuclear leukocytes (PNL) percentage in BAL (p=0.008, r=0.43). The correlation between the number of total segments with ground glass opacity and FVC % (p=0.024, r=-0.28), DLCO % (p=0.007, r=-0.34), and RV % (p=0.045, r=-0.48)

Table 4. Pulmonary function tests when pulmonary involvement was confirmed

	Mean ± SD	%
FVC (mL)	2111 ± 570	77.6 ± 17.7
FEV_1 (mL)	1854 ± 524	76.8 ± 16.2
FEV_1/FVC		84.5 ± 7.0
$FEF_{\%25-75}$ (L/sn)	2.29 ± 1,00	68.5 ± 25.9
PEF (L/sn)	5.37 ± 1.19	87.3 ± 18.1
DLCO (mL/min/mmHg)	12.0 ± 4.7	51.4 ± 16.8
DLCO/VA (mL/min/mmHg)	3.93 ± 0.93	66.8 ± 16.0
TLC (mL)	3458 ± 1099	75.4 ± 20.1
RV (mL)	1253 ± 451	78.6 ± 27.1
FRC (mL)	2236 ± 866	85.5 ± 29.4

FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second, $FEF_{\%25-75}$ = forced expiratory flow over the middle 50% of the FVC, PEF = peak expiratory flow, DLCO = diffusing capacity.

Table 5. Patients' BAL results, HRCT scores, and dyspnea scores when pulmonary involvement confirmed

	Mean ± SD
Dyspnea score	1.6 ± 1.1
BAL findings	
Neutrophils (%)	10.8 ± 7.1
Lymphocytes (%)	8.4 ± 4.6
Eosinophils (%)	0.7 ± 1.3
Alveolitis (n, % all cases)	32 (84.2%)
Neutrophilic alveolitis	25 (65.8%)
Lymphocytic alveolitis	1 (2.6%)
Mixed alveolitis	6 (15.8%)
X-ray findings	
HRCT score	14.7 ± 7.4
Total segments involved	8.8 ± 4.0
Segments with ground-glass appearance	7.4 ± 3.8
Segments with honeycombing	3.4 ± 3.5
Segments with subpleural cysts	0.9 ± 1.7
Segments with septal/subpleural lines	3.8 ± 2.7
Segments with irregular pleural margins	2.5 ± 2.3

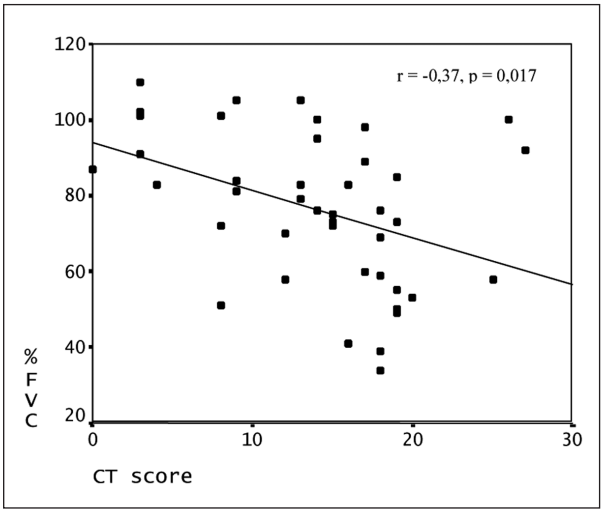

Fig. 1. Relation between FVC (%) and CT score

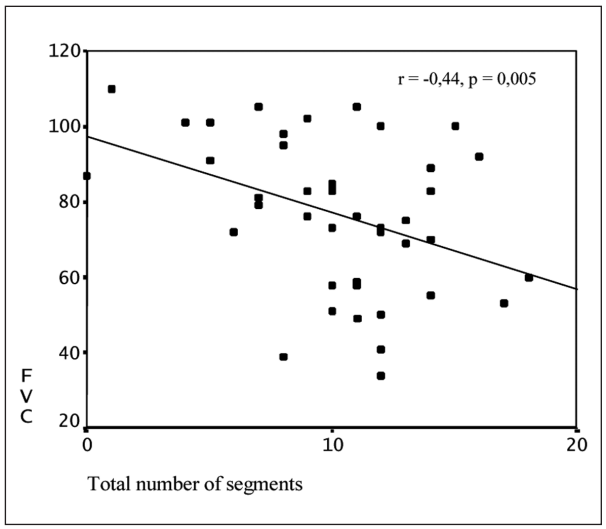

Fig. 2. Relation between FVC (%) and segments involved on CT

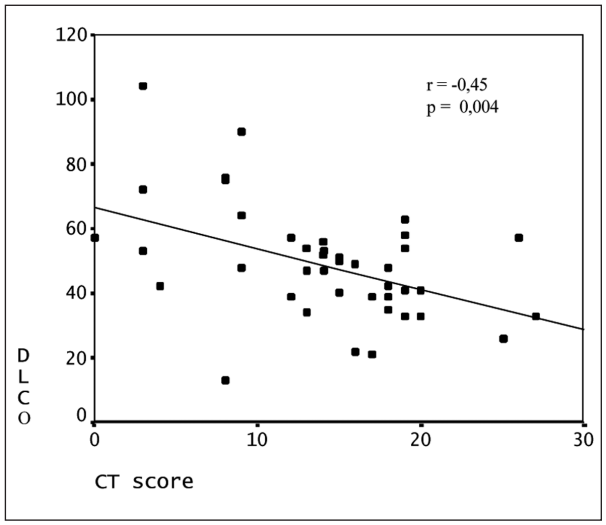

Fig. 3. Relation between DL_{CO} (%) and HRCT score

were statistically significant. The relation between the number of total segments with irregular pleural margins and age (p=0.03, r=0.27), dyspnea score (p=0.03, r=0.26), and FVC % (p=0.001, r=-0.41) were statistically significant as well as the relation between the total number of segments with subpleural cysts and the duration of the disease (p=0.042, r=0.32). Finally, there was a correlation between the total number of segments with honeycombing and DLCO % (p=0.003, r=-0.37), TLC % (p=0.04, r=-0.49), and RV % (p=0.04, r=-0.50).

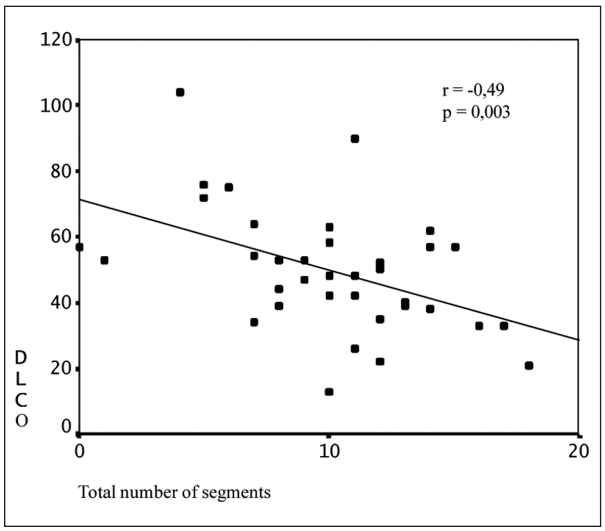

Fig. 4. Relation between DL_{CO} (%) and segments involved on CT

Discussion

The aim of our study was to evaluate whether there was a relation between the histopathologically proven alveolitis and the x-ray and functional findings in pSS. Different results for the effectiveness of HRCT on its own in detecting disease severity as well as functional impairment have been reported, and accordingly, the adequacy of HRCT in planning the management of the treatment (18-22). In this study, among the parameters investigated, the only correlation found was between the number of segments with subpleural cysts and the duration of disease. This correlation can be explained by the possibility that findings related to pulmonary involvement proceed at different speeds in the patients. Some studies showed that pulmonary involvement in patients with pSS progress in the first 3 years and then is usually followed by a remission period (23-25). That may be why we did not find a correlation between the duration of the disease, manifestation of the symptoms, and the x-ray findings. In addition, some of our patients were under immunosuppressive treatment until the pulmonary involvement was discovered, which may change the course of the disease.

However, we found a correlation between the HRCT score and patient age. The lack of a correlation between the duration of the disease, manifestation of the symptoms, and the x-ray findings but a correlation with age gives the impression that the

disease has a more progressive course radiologically in patients who have late onset.

When pulmonary involvement was discovered in our patients with pSS, there was a significant correlation between the HRCT scores and the respiratory function tests. The relation between the diffusion capacity and the x-ray features was stronger. Although there was a relation between the number of segments with ground glass opacity and diffusion capacity and FVC, only DLCO was correlated with the number of segments that had honeycombing. However, irregular pleural margins correlated only with FVC. When these findings were evaluated together, there was a correlation between disease progression and the pulmonary functional tests and the x-ray findings. Solitiris et al. also reported a relation between startup FVC and functional progress (26). In a study of 17 patients, Warrick et al. found no correlation between FVC and HRCT, but the DLCO and HRCT were correlated (16). A correlation between DLCO and HRCT scoring was reported in a 52-patient study conducted by Diot et al. in which the Warrick scoring was used (27). The lack of a correlation between FVC and HRCT may be related to the small number of patients. Diot et al. did not evaluate FVC (27).

In the present study, there was a correlation between the percentage of neutrophils detected in BAL and the extent of the honeycombing. The lack of a correlation between the ground glass opacity and BAL does not confirm the assessment that this finding indicates active alveolitis. Warrick et al. also detected a correlation between neutrophil percentage in BAL fluid and HRCT score, but this result was based on BAL measurements for only 7 patients. Soh et al. detected a correlation between neutrophilic alveolitis and mortality (28). Kowal-Bielecka et al. concluded that patients with pSS with neutrophilic alveolitis respond better to iv cyclophosphamide treatment (29). Sanchez evaluated induced sputum, a more noninvasive method than BAL, and concluded it was related to early pulmonary involvement (30). In light of these findings, we conclude that neutrophilic alveolitis is an important factor that affects mortality and response to treatment in patients with pSS. In this study, it was also related to the extent of honeycombing on HRCT.

We detected a correlation between the dyspnea score and irregular pleural margins only among the HRCT scores. Dyspnea measurement, a subjective method, can fail to reflect disease severity. Warrick et al. also found the same result (16). The result showing any relation of the pulmonary functional tests with dyspnea score also supports this idea.

Among the parameters we evaluated, diffusion capacity measurement was the best correlating laboratory parameter with x-ray findings. In particular, the relation between the fibrosis results and diffusion capacity was evident. The ground glass opacity seen on HRCT did not reflect active alveolitis but was an early finding of fibrosis. As the extent of honeycombing increases, the number of neutrophils in the BAL fluid also increases. It can be hypothesized that there is neutrophilic inflammation in patients with pSS and this is progressive or as the honeycombing develops, the nature of the inflammation changes. Additional studies are needed to clarify this hypothesis.

In conclusion, this study showed a strong correlation between the extent of x-ray abnormalities and FVC, RV, and DLCO, as well as an increase in the percentage of BAL fluid neutrophils in patients with SSc-PI. In an ongoing study, we are investigating the change in this correlation in response to therapy.

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