

Original Article

Interstitial lung disease in patients with progressive systemic sclerosis. A study of 58 cases*

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ABSTRACT

Objective: To estimate the frequency of interstitial lung disease in a group of patients with progressive systemic sclerosis, and to describe the clinical, functional and radiological characteristics of the patients studied. **Methods:** Fifty-eight patients diagnosed with progressive systemic sclerosis were submitted to high-resolution computed tomography of the chest, pulmonary function tests and a blood test for anti-Scl 70 antibodies. Comparisons were drawn between patients with interstitial lung disease and those without. Logistic regression with multivariate analysis was used to identify factors predictive of interstitial lung disease. **Results:** Of the 58 patients evaluated, 51.7% presented interstitial lung disease on high-resolution computerized tomography scans. Dyspnea and cough were the most common symptoms (seen in 65.5% and 39.7%, respectively). Bronchiolectasis and honeycombing were the most common tomographic abnormalities (observed in 83.3% and 80%, respectively). When compared to individuals without interstitial lung disease, patients with the condition had a comparable frequency of pulmonary and extrapulmonary symptoms but presented progressive systemic sclerosis of longer duration, a higher frequency of crackling rales, higher rates of anti-Scl 70 positivity, lower vital capacity and reduced total lung capacity. Only forced vital capacity < 80% was found to be a predictor of interstitial lung disease. **Conclusion:** Interstitial lung disease was common in this group of patients with progressive systemic sclerosis. No correlation with symptoms was found, although interstitial lung disease was found to correlate with crackling rales and with anti-Scl 70 positivity. Nevertheless, only reduced forced vital capacity was found to be predictive of interstitial lung disease.

Keywords: Scleroderma, systemic/complications; Scleroderma, systemic/radiography; Lung diseases, interstitial/etiology; Lung diseases, interstitial/radiography; Pulmonary fibrosis; Tomography, X-ray computed; Thorax/radiography; Hypertension, pulmonary

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Submitted: 6 July 2004. Accepted, after review: 24 March 2005.

INTRODUCTION

Interstitial pulmonary involvement is the leading cause of death in cases of progressive systemic sclerosis (PSS).⁽¹⁻³⁾ Reports on the frequency of interstitial lung disease (ILD) among PSS patients present varying results. This can be attributed to the different methods of detection used. However, this variation also results from differences in demographic variables, such as race, and in clinical and laboratory parameters, such as the presence of anti-Scl 70 antibodies, among the populations studied.⁽⁴⁻⁶⁾ In studies using high-resolution computed tomography (HRCT), ILD has been reported in up to 91% of PSS cases.⁽⁷⁻⁸⁾

In the only Brazilian study using HRCT in PSS patients, signs of ILD were reported in 59% of the 22 individuals studied.⁽⁹⁾ However, that study was limited by the sample size, as well as by the fact that 95% of the subjects were Caucasian, which certainly gave the sample an ethnic profile different from that typically found in our milieu.

The main objective of the present study was to determine, through the use of HRCT of the chest, the frequency of ILD among individuals with PSS in a sample of outpatients. Secondly, we sought to characterize this group of patients from a clinical, laboratory, functional and radiological viewpoint in the attempt to identify variables correlated with the presence of ILD.

METHODS

Between April of 2002 and December of 2003, patients diagnosed with PSS⁽¹⁰⁾ were consecutively referred to the interstitial diseases outpatient clinics of the Hospital Santa Izabel (Santa Izabel Hospital) and the Hospital Universitário Professor Edgard Santos (Professor Edgard Santos University Hospital) of the Universidade Federal da Bahia (Federal University of Bahia) for evaluation. These university hospitals are integrated into the network of the national Sistema Único de Saúde (Unified Health System). Patients were evaluated regardless of the presence of symptoms or signs of pulmonary involvement. The interval between the stages of the evaluation of each patient never exceeded 90 days.

Pregnant women and individuals with a history of environmental or occupational exposure recognized as causes of ILD, as well as patients presenting worsening of the symptoms related to

PSS in the last 30 days or presenting another concomitant connective tissue disease, were excluded from the study. The study was evaluated and approved by the Ethics in Human Research Committee of the Santa Izabel Hospital, and all participants gave written informed consent.

Clinical evaluation consisted of completing a standardized questionnaire designed to collect demographic and clinical data on the patient. Duration of PSS was defined as time elapsed since the onset of the first symptom related to PSS, and the criteria established by LeRoy et al. was used to characterize the type of skin involvement.⁽¹¹⁾ Patients were categorized as active smokers if they had smoked cigarettes within the last six months, as former smokers if they had quit smoking more than six months prior and as nonsmokers if they had never smoked. Intensity of smoking was defined in pack-years. Dyspnea was scored using the baseline dyspnea index score described by Mahler et al., which ranges from 0 (worst score) to 12 points (best score).⁽¹²⁾

Blood tests for anti-Scl 70 antibodies were performed using the enzyme immunoassay technique (VAR ELISA Kit - Spain). All patients were submitted to HRCT of the chest in a volumetric (helical) CT device, model CT HISPEED LX/i (General Electric Medical Systems, Milwaukee, WI, USA). The images were obtained with thin (1-mm) cuts using a high-spatial resolution filter (bone filter) to reconstruct the image, in 20-mm increments, in dorsal decubitus and (when indicated for excluding the presence of opacities in the basal segments, resulting from the effects of gravity) ventral decubitus, examining the lungs from the apex to the base, in the inspiratory apnea phase, and complementing this with three sections in the maximum expiratory apnea phase at the following levels: aortic arch, tracheal bifurcation and immediately above the right diaphragmatic dome. We used 120 kV and 200 mA, with one second of cutting time in 360°. The images were obtained and reconstructed in a 512 X 512 matrix and photographed with a window opening that ranged around 1500 H, opening level of approximately -750 H, for the evaluation of the lung fields, and a window opening of 600 H and -40 H for the analysis of the mediastinum.

The HRCT films were evaluated independently by two radiologists who had no previous knowledge of clinical or functional information about the patients. These radiologists indicated presence or

absence of ILD based on the evaluation of abnormalities in any of the compartments of the pulmonary interstitium. Abnormalities that were not correlated to PSS, such as scar processes of infectious granulomatous diseases, were not considered in the final analysis. In addition, the frequencies of the following findings were reported: consolidation, honeycombing cysts, ground-glass opacity, bronchiolectasis and septal thickening, the findings being defined as previously reported.⁽¹³⁾ When there was discordance between the final impressions of the two radiologists, a third radiologist was summoned in order to decide the points in question.

Pulmonary function tests were performed using a Vmax 22 device (Sensor Medics, Yorba Linda, CA, USA) according to the guidelines established by the American Thoracic Society for the acceptance of spirometric curves.⁽¹⁴⁾ Measurement of the lung volumes was performed using the technique of nitrogen lavage with multiple respirations in open circuit, and measurement of the diffusing capacity for carbon monoxide (DLCO) was performed using the single-breath technique, in which the breath is held for ten seconds. Values were expressed as percentage of predicted for age, gender and height, using equations previously described.⁽¹⁵⁻¹⁶⁾ We recorded the proportions of patients presenting reduced forced vital capacity (FVC), reduced total lung capacity (lower than 80% of predicted) and a reduced ratio between forced expiratory volume in one second and FVC, as well as DLCO lower than 75% of predicted, were reported.

Scalar or continuous variables were expressed as means and standard deviations or as medians, and categorical variables were expressed as proportions. For comparison purposes, individuals were divided into two groups based on the presence or the absence of ILD (Groups 1 and 2, respectively). The Mann-Whitney test was used for the analysis of scalar or continuous variables, and the chi-square test (or Fisher's exact test, when necessary) was used to test differences in proportions. In the evaluation of the HRCT scans, the Kappa coefficient value was estimated in order to determine the concordance between the findings of the observers.

We constructed a model of multivariate analysis, using multiple logistic regression in order to determine the independent impact of each variable on the capacity to determine the presence of ILD. We determined odds ratios and their respective 95%

confidence intervals.⁽¹⁷⁾ In these tests, values of $p < 0.05$ were considered statistically significant (for the rejection of the null hypothesis). Data were entered into a database and processed using the Statistical Package for Social Science (SPSS) program, version 9.0 (SPSS Inc., Chicago, IL, USA, 1998).

RESULTS

A total of 63 individuals were initially evaluated. Of those, 5 were excluded from the study because they presented PSS related to exposure to silica. The final sample analyzed consisted of 58 patients, whose general characteristics are shown in Table 1. Ages ranged from 13 to 69 years (mean \pm standard deviation: 42.8 ± 13.5 years), disease duration ranged from 0.3 to 30 years (median, 4 years), and 63.8% of the patients presented diffuse cutaneous disease. Dyspnea was the most often reported respiratory symptom (38 cases, 65.5%), followed by cough and chest pain. Cracking rales were detected in only 9 individuals (15.5%). Anti-Scl 70 antibodies were detected in only 17 patients (29.3%).

There was discordance between the two radiologists regarding the presence or absence of ILD in only two cases, a Kappa index of 0.86 having been estimated for the evaluation of the HRCT scans. Signs of interstitial pulmonary involvement were detected in 30 patients (51.7%). As described in Table 2, bronchiolectasis was the most often described tomographic finding, found in 83.3% of the ILD patients, followed by honeycombing (80%).

Table 3 shows the results of the HRCT scan comparison between the patients with and without ILD. The ILD patients presented longer disease duration, higher incidence of cracking rales, reduced FVC and reduced total lung capacity, as well as more frequently presenting decreased FVC ($< 80\%$ of predicted). There was no difference between the groups regarding the other variables, including frequency and intensity of dyspnea. Among the ILD patients, 9 (30%) presented no dyspnea, and 6 of those 9 (20% of the total) presented no respiratory symptoms. Cracking rales were detected exclusively in the ILD patients, although in only 30%. There was a significant positive correlation between ILD and positivity for anti-Scl 70 antibodies. Of the 17 patients who presented this antibody, only 1 (5.9%) presented no signs of ILD. Of the 30 ILD patients, 4 (13.3%) presented no decrease in DLCO, 10 (33.3%)

TABLE 1

General characteristics of the 58 patients with progressive systemic sclerosis

Demographic characteristics	
Female (%)	93.0
Mulatto or black (%)	79.3
Age (mean \pm SD in years)	42.8 \pm 13.5
Clinical variables/laboratory test results (%)	
Diffuse skin pattern	62.1
Raynaud's phenomenon	91.4
Sclerodactylia	98.3
Arthralgia	84.5
Teleangiectasis	58.6
Current or former smoker	15.9
Dyspnea	65.5
Cough	39.7
Chest pain	37.9
Crackling rales	15.5
Hissing	6.9
Anti-Scl 70 positive	29.3
Functional variables**	
FVC	77.2 \pm 15.5
DLCO	56.7 \pm 20.6
TLC*	74.8 \pm 14.6
RV*	80.8 \pm 31.1

*n = 43; **% of predicted (mean \pm SD)

presented FVC > 80% of predicted, and only 26.7% presented DLCO < 40% of predicted.

Table 4 shows the results of the multivariate analysis. Of the variables studied, only FVC < 80% of predicted demonstrated a tendency to be predictive of ILD in the group evaluated (odds ratio = 2.99), with borderline statistical significance in the multivariate analysis. However, this variable presented low sensitivity and specificity for the identification of ILD in cases of PSS.

TABLE 2

Frequency of abnormalities detected in the 30 patients in whom alterations were seen on the high-resolution computed tomography scan of the chest

Abnormality	Frequency (%)
Bronchiolectasis	83.3
Honeycombing	80.0
Ground-glass opacity	66.7
Septal thickening	20.0
Consolidations	16.7

DISCUSSION

Early detection of ILD seems to be relevant for the treatment of PSS patients, and the clinical approach may be insufficient.⁽¹⁸⁾ Similar to what has been seen in other studies,^(8,19-20) dyspnea was the most often reported respiratory symptom in our group, with similar frequency and intensity in patients with and without ILD, which reduced its usefulness in detecting this complication. This finding might be explained by the fact that a portion of the individuals with ILD probably present an incipient form of the disease (not yet radiologically detectable), which would in turn explain the high proportion of patients with normal FVC in this group. However, cracking rales were found exclusively in patients with significant ILD, a correlation previously reported in other studies.^(8-9,19) This indication, which is highly specific for the diagnosis of ILD in individuals with PSS, lacks sensitivity since it was found in only 30% of the ILD patients in our study.

As has been reported in other studies, ILD patients presented significantly reduced FVC and total lung capacity.^(8,13) Although lower, DLCO values and the proportion of patients with a significant reduction in DLCO (less than 40%) were not significantly different in ILD patients, representing a divergence from the findings of other studies.^(8,13) The presence of pulmonary vascular disease in patients without pulmonary fibrosis may, in addition to making tomographic detection possible in cases of incipient ILD, reduce DLCO, which explains why there was no difference in DLCO between the groups of PSS patients with and without ILD.⁽²¹⁾

In the present study, the frequency of ILD was high despite being lower than that found in most reports involving HRCT scans of PSS patients. In a prospective study evaluating 23 PSS patients, it was demonstrated that 91% of the individuals presented signs of ILD.⁽⁷⁾ The population evaluated in that study presented longer disease duration than did our group. Similar high frequencies were also reported in three other studies.⁽²²⁻²⁴⁾ In the study with the greatest number of patients, ILD was reported in 63.7% of the 91 individuals evaluated, this value being closer to the results of most of the studies currently available.^(8-9,26-28) In that study, the authors only included patients who presented respiratory symptoms and were,

TABLE 3
Demographic, clinical and functional characteristics - Comparison between patients with interstitial lung disease and those without

Parameters	ILD (n = 30)	no ILD (n = 28)	p
Demographic, clinical or laboratory test variables			
Age (years)	45.1	40.3	NS
Duration of PSS (years)	8.5	6.1	0.05
Diffuse skin pattern (%)	73.3	53.6	NS
Dyspnea (%)	70.0	60.7	NS
Cough (%)	43.3	35.7	NS
Dysphagia (%)	46.7	50	NS
Regurgitation (%)	48.0	43.3	NS
Baseline dyspnea index (score)	7.8	8.1	NS
Crackling rales (%)	30	0	0.001
Anti-Scl 70 positive (%)	53.3	3.6	0.0003
Functional characteristics			
FVC*	72.7	80.1	0.02
FEV ₁ *	70.1	77.5	NS
DLCO*	53.8	59.8	NS
TLC*	69.2	80.1	0.01
FVC < 80%**	66.7	35.7	0.02
TLC < 80%**	71.4	54.5	NS
DLCO < 75%**	86.7	81.5	NS

*% of predicted (mean \pm standard deviation); **frequency (%)

ILD: interstitial lung disease; PSS: progressive systemic sclerosis; NS: not significant; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; DLCO: lung diffusing capacity for carbon monoxide; TLC: total lung capacity

therefore, more likely to present pulmonary involvement. In the only study in which a lower frequency of ILD than that of the present study was found, interstitial involvement was detected in only 39.5% of the 43 cases evaluated.⁽²⁹⁾

The difference between the frequency found in this series and those found in other studies may be due to the heterogeneity of demographic characteristics (such as race), as well as of the

clinical and immunogenetic characteristics, of the individuals evaluated. All of the studies previously mentioned evaluated almost exclusively Caucasian individuals. Despite having evaluated patients with different characteristics from those evaluated in the present study, the Brazilian study reported a higher frequency of ILD.⁽⁹⁾ In that study, 95% of the patients were white and presented more prolonged ILD, which can result in different clinical

TABLE 4
Potential predictors of interstitial lung disease in the 58 progressive systemic sclerosis patients studied - Logistic regression analysis

Variable	Univariate	Multivariate (95% CI)	OR (%)	Sensitivity (%)	Specificity
DLCO < 50%	0.17	NS	ND	ND	ND
FVC < 80%	0.06	0.05**	2.99 (1.12-6.95)	64	60
TLC < 80%*	0.36	NS	ND	ND	ND
BDI score < 6	0.42	NS	ND	ND	ND
PSS duration > 4 years	0.05	NS	ND	ND	ND

*n = 43; **p values

OR: odds ratio; 95% CI: 95% confidence interval; DLCO: lung diffusing capacity for carbon monoxide; NS: not significant; ND: not determined; FVC: forced vital capacity; TLC: total lung capacity; BDI: baseline dyspnea index; PSS: progressive systemic sclerosis

expressions of the disease.⁽⁴⁻⁵⁾ A close correlation between human leukocyte antigen haplotypes and expression of autoantibodies such as anti-Scl 70 has been described.^(4,30) The anti-Scl 70 antibody was detected in a third of our group and seems to be correlated with the presence of ILD.^(4,31-32) However, this marker also presented low sensitivity since it was positive in only half of the ILD patients. It is unclear whether anti-Scl 70 is only a marker of involvement or an etiopathogenic determinant.

The identification of factors predictive of ILD in PSS patients may be important for clinical management. Multivariate analysis revealed that the clinical and functional variables studied were of little use in the prediction of ILD, which underscores the importance of radiological evaluation using HRCT. Among the variables studied, only abnormal FVC (< 80% of predicted) tended to be predictive of ILD in this group of PSS patients, with borderline significance. The confidence interval correlated with this variable was wide and sensitivity and specificity were not high. The correlation between reduced FVC and interstitial involvement is frequent but not constant. Evaluation with HRCT was routinely performed in a group of patients that were not selected and therefore may have presented an incipient form of ILD, with few repercussions for the functional evaluation. In addition, restriction patterns may also occur in patients without ILD,⁽¹⁹⁾ resulting from the dysfunction of the respiratory muscles or alterations in chest cavity compliance. Despite the more prolonged PSS duration seen among the ILD patients, multivariate analysis failed to demonstrate a significant correlation between PSS duration and ILD. This relationship has been described in previous studies,^(8,26) in which the existence of more prolonged PSS in patients presenting interstitial pulmonary involvement was also mentioned. In a prospective cohort study, severe pulmonary fibrosis was reported to occur more often in the three first years of disease. Therefore, we should evaluate our findings with caution since they result from an evaluation made at a specific point in time.

In summary, the frequency of ILD was high in our group of PSS patients. From a practical viewpoint, the data presented in our study may indicate that PSS patients who present reduced FVC, presence of anti-Scl 70 and cracking rales

should be monitored more rigorously, using, for example, HRCT. However, it is important to emphasize that the present study was carried out in tertiary-care facilities and that, therefore, our sample may not be representative of the total population of PSS patients. In future studies, the inclusion of patients from primary-care facilities and private clinics should be encouraged in order to improve the sample representativeness and thereby establish a frequency of ILD that is more reliable in view of the broad clinical spectrum of PSS patients. The presence of ILD on HRCT scans does not necessarily indicate clinically significant disease, and this study did not evaluate the magnitude of the tomographic findings. Longitudinal, long-term follow-up studies are necessary in order to determine the impact of these findings on the prognosis and clinical evolution of PSS patients.

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