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Pulmonary function tests, high-resolution computerized tomography, α1-antitrypsin measurement, and early detection of pulmonary involvement in patients with systemic sclerosis

Received: 18 June 2000 / Accepted: 20 November 2000 / Published online: 17 February 2001
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Abstract Objective: Pulmonary disease represents a major complication of systemic sclerosis (SSc). However, pulmonary involvement is commonly silent. In this study, we investigated the relationship between serum α1-antitrypsin and other means of assessing pulmonary involvement. Methods: Twenty-two patients affected by SSc were studied (mean age 37.6 ± 14.3 years, mean duration of disease 9.9 ± 11.9 years). Fourteen had the diffuse form of disease (dSSc) and eight had the limited form (ISSc). All patients underwent pulmonary function tests, high-resolution computed tomography (HRCT) of the lungs, echocardiography, and serum assessment of α1-antitrypsin. Results: Mean percentage of predicted values of forced vital capacity was lower in patients with dSSc than with ISSc (72.3 ± 17.8 vs 74.5 ± 8, P = NS). Mean percentage of predicted values of forced expiratory volume in 1-s forced vital capacity (FEV1/FVC) was lower in patients with ISSc (79.8 ± 7.5 for ISSc vs 84.4 ± 7.8 for dSSc, P = NS). The overall HRCT score was 5.6 ± 5.9 with no significant difference between disease subgroups. Pulmonary hypertension was detected in two cases, both with dSSc. Alpha1-antitrypsin was significantly higher in patients than in controls (P < 0.01), with no significant difference between disease subgroups, and correlated significantly with ground glass opacities in HRCT (P < 0.05) and the detection of diffusion defects (r = -0.61, P < 0.01). No significant correlation was observed between skin score or degree of dyspnea with HRCT score, lung volume, or carbon monoxide diffusing capacity. Conclusion: Restrictive lung disease was more pronounced in patients with dSSc. Alpha1-antitrypsin levels correlated significantly with ground glass opacities, an early finding of pulmonary involvement in SSc. Extent and severity of skin involvement and degree of dyspnea were not related to pulmonary involvement.

Key words Systemic sclerosis · High-resolution CT · Restrictive lung disease · Alpha1-antitrypsin · BORG dyspnea score

Introduction

Systemic sclerosis (SSc) is a multisystemic autoimmune disease of unknown etiology characterized by vascular changes and progressive fibrosis of the skin and visceral
organs. Renal, myocardial, and pulmonary involvement represent the major complications [1].

Lung disease may remain clinically silent for a long time [2], although pulmonary hypertension was recently reported as the most frequent cause of death [3]. Few data exist on the relationship between pulmonary and extrapulmonary involvement in SSc.

As patients with earlier stages of disease respond more frequently to treatment, it is of utmost importance to assess lung involvement in asymptomatic patients [4]. Chest radiography has a limited role in the detection of earlier stages of lung involvement, and pulmonary function studies are of paramount importance in early detection.

Alpha₁-antitrypsin is a glycoprotein. Comprising 90% of the α₁-globulin, it functions in the lungs as an antiprotease that inhibits neutrophil elastase [5]. In many patients with SSc, bronchoalveolar lavage (BAL) reveals elevated proportions of neutrophils, [6] which are the source of elastase, and although antiproteases can bind and inactivate elastases in the lower respiratory tract, they lead overwhelmingly to progressive lung damage [7].

The aim of this study was to assess pulmonary involvement in patients with systemic sclerosis and the correlation between conventional tests and serum α₁-antitrypsin levels.

### Materials and methods

#### Patients

Twenty-two nonsmoking patients affected by SSc (21 women, mean age 37.6 ± 14.3 years, range 14 to 60) were referred to the Kasr Eleni Hospital Department of Rheumatology and Rehabilitation from February 1998 to April 1999. All patients met the American Rheumatism Association preliminary criteria for diagnosis of SSc [8]. Ten normal nonsmoking volunteers (nine females, mean age 39.7 ± 10.4 years) served as controls for α₁-antitrypsin measurement and lung function analysis.

Fourteen patients were affected by diffuse scleroderma (dSSc) and eight by the limited form (lSSc) [8,9] (mean duration 9.9 ± 11.9 years, range 0.5–30).

All patients had complete clinical examination including evaluation for gastrointestinal, pulmonary, cardiac, renal, and muscle involvement. The grade of dyspnea (if present) was determined based on the Sherwood Jones classification [10]: 1a able to do housework or job with moderate difficulty or b with great difficulty, 2a confined to chair or bed but able to get up with moderate difficulty or b only with great difficulty, 3 totally confined to chair or bed, and 4 moribund. Dyspnea was also measured by a modified Borg dyspnea score [11]: 0 nothing at all, 0.5 very, very slight (just noticeable), 1 very slight, 2 slight, 3 moderate, 4 somewhat severe, 5 severe, 7 very severe, 9 very, very severe (almost maximal), and 10 maximal (score numbers 6 and 8 have no accompanying descriptive term).

Routine laboratory examinations included complete blood picture and assessment of erythrocyte sedimentation rate (ESR), liver and kidney functions, and creatinine phosphokinase (CPK). Antinuclear antibodies (ANA) were detected by immunofluorescence. Esophageal manometric studies were carried out on all patients.

#### Skin-tethering assessment

A semiquantitative scoring system was used to evaluate skin involvement [12]. The body was divided into ten regions (face, chest, back, abdomen, upper arms, forearms and wrists, hands, thighs, legs, and feet). The degree of skin involvement in each region was rated as follows: 0 normal skin, 1 mildly thickened, 2 moderately thickened, and 3 hidebound. The highest possible score was 30.

#### Pulmonary function tests

Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC, and forced expiratory flow 25–75% (FEF25–75%) were measured using compact velocigraph spirometry. Carbon monoxide diffusing capacity (DLCO) was measured using the single-breath technique. All values were evaluated as percentage of predicted values [13]. Restrictive lung disease was diagnosed if FVC < 80%, and obstructive pattern was diagnosed if increased FEV1/FVC was reduced in equal proportion. Small airway obstruction was diagnosed if FEF25–75% < 80% [14]. Abnormal diffusing capacity was present if DLCO was < 80% of predicted value.

#### High-resolution computed tomography

Pulmonary interstitial disease was assessed by high-resolution computed tomography (HRCT) using either X-Vision (Toshiba, Otawa, Japan) or Somatom Plus-S (Siemens, Erlangen, Germany) CT units. Reconstruction with high-resolution algorithm for the lungs was done in all cases, and standard soft-tissue algorithms for mediastinal evaluation were done in 11. Patients underwent scanning in the supine position. No intravenous contrast material was used. The scanned lungs were divided into upper, middle, and lower zones; the upper zones were defined as those above the level of the carina, the middle zones between the level of the carina and the level of the inferior pulmonary veins, and the lower zones under the level of the inferior pulmonary veins. The following scores were used and added together for each patient: 0 normal, 1 any lung lesion due to scleroderma apart from honeycomb lung (e.g., ground glass opacities or emphysema), 2 subpleural micronodules, 3 septal or nonseptal linear opacities, bronchiectasis, bronchiolectasis, pleural thickening, and subpleural plaques), and 4 honeycombing. This scoring system was modified from that used by Morelli et al. [2]. The duration and severity of each case were not known at the time of CT interpretation, nor were the results of other investigations.

#### Doppler echocardiography

A two-dimensional method and Doppler echocardiography techniques were applied for all patients. Imaging was performed with a Sonos 1000 equipped with 2.5-mHz and 3.5-mHz phased pulsed array transducers (Hewlett-Packard, USA). Doppler studies were performed for assessment of the mitral flow and measurement of maximal early diastolic flow velocity (peak E, m/sec), maximal late diastolic flow velocity (peak A, m/sec), and E/A ratio. Guided with color flow imaging, pulsed wave (PW) was used to detect and quantify the magnitude of mitral and tricuspid regurgite (MR and TR). In the presence of TR, continuous wave (CW) Doppler was used to estimate the pulmonary artery systolic pressure. First, the tricuspidal systolic pressure gradient (TSPG) was estimated according to the modified Bernoulli equation [15] to calculate pulmonary artery systolic pressure, and 10 mmHg (estimated systolic right atrial pressure) was added to the TSPG. Pulmonary systolic hypertension was defined as >35 mmHg. If no TR could be detected, pulmonary artery systolic pressure was presumed normal.

Alpha₁-antitrypsin was assessed by single radial immunodiffusion.

#### Statistical analysis

Data were reported as mean ± standard deviation. Student’s t- and chi-squared tests were used when appropriate. Correlation analyses...