Pulmonary involvement in scleroderma

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Abstract

Aim: The purpose of our study was the identification of pulmonary manifestations in patients with scleroderma, their assessment in relations to immunological alterations, their relations to gender, and the assessment of the sensitivity in the examinations that are used to detect lung injuries.
Methods: This is a cross-sectional study including 58 patients with scleroderma during January-September 2011. Patients' history of disease was carefully extracted and recorded. Patients were underwent immunological tests such as anti-nuclear antibody test, anti-topoisomerase and anti-centromere tests. Furthermore, chest X-ray, pulmonary high-resolution computed tomography, pulmonary function tests and echocardiography Doppler were also performed. Chi-square test was used to assess potentially statistically significant associations.
Results: Mean age of the patients (86.2% females) was 49.38±8.92 years. Mean duration of the disease was 7.29±4.5 years. Pulmonary involvements were found in 42 (72%) patients. Interstitial lung diseases were found in 42 (72%) patients, pulmonary arterial hypertensions in 6 (10%) patients and restrictive ventilator insufficiency in 32 (55%) patients. The proportion of individuals with pulmonary injuries was significantly higher among patients with immunological alterations compared with patient without immunological alterations and among females (both $P<0.001$).
Conclusions: In our study, pulmonary manifestations were common in patients with scleroderma. These injuries are anatomical and functional. Our findings confirm that immunological alterations are an important factor in pulmonary injuries. Sex was also associated with pulmonary injuries in this sample of Albanian patients. High-resolution computed tomography is the most sensitive examination for the detection of pulmonary injuries in scleroderma.

Keywords: interstitial lung disease, pulmonary disease, scleroderma.

Introduction

Pulmonary diseases are an important manifestation in scleroderma (SSc) and 80% of patients have pulmonary injury (1). Lung injuries in scleroderma occur frequently and include interstitial lung disease, vascular, pleural and airways disease (2,3). Pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are the two most common lung manifestations in scleroderma (4,5). Restrictive ventilator insufficiency was observed in patients with scleroderma and pulmonary injury (6,7). Serum anti-topoisomerase (Scl-70) correlates with the development of ILD and is more frequently found in patients with diffuse cutaneous involvement; anti-centromere (ACA) antibody is more frequently associated with limited cutaneous scleroderma and pulmonary vascular disease (8). Unfortunately, systemic sclerosis lung disease is often not detected or diagnosed until the late stages. High resolution computed tomography (HRCT) of the lungs, pulmonary function tests (PFTs), chest x-ray (CXR) and echocardiography Doppler for pulmonary arterial hypertension (PAH) have shown interest in the assessment of scleroderma lung disease.

The purpose of our study was the identification of pulmonary injuries in patients with scleroderma, their assessment in relations to immunological alterations, their relations to gender and the evaluation on the sensitivity of the examinations for the detection of scleroderma lung disease.

Methods

This was a cross-sectional study involving 58 patients with scleroderma during January-September 2011. The patients in this study were recruited from outpatient consultations in the Rheumatology clinic at the University Hospital Center "Mother Theresa" in Tirana and outpatient consultations at the University Hospital Center of Lung Diseases "Shefqet Ndroqi" in Tirana. These patients were then hospitalized in the respective clinics.

We only included patients that met the criteria of the American College of Rheumatology for the diagnosis of scleroderma (9). Scleroderma patients who have suffered in the past or were actually suffering from other diseases (e.g. sarcoidosis, tuberculosis, emphysema, congestive heart failure, congenital heart disease, cirrhosis of the liver) which may influence the pulmonary injuries, smoking patients, pregnant women and those breastfeeding, and also patients with a history of any occupational exposure to inorganic or organic dusts (e.g. asbestosis, silicosis, coal worker's pneumoconiosis) were excluded from the study.

Patients were examined by immunological tests such as: anti-nuclear antibody (ANA), anti-topoisomerase and anti-centromere test. Chest X-ray and high resolution computed tomography of the lung were also performed and their findings were recorded in consultation with the radiologist. Patients were considered to have ILD when they showed CXR and HRCT of the lung findings compatible with ILD such as: nodular, reticular, reticulonodular, ground-glass opacities, honeycombing, dominantly on lung bases (10). Lung function was measured with a spirometer. Indicators of pulmonary function included forced vital capacity (FVC), forced expiratory volume in the first, second (FEV1), and FEV1/ FVC ratio. Based on the American Thoracic Society criteria, patients with normal FEV1/ FVC ratio and decreased FVC <80% were diagnosed as having restrictive disease (11). These data were expressed as percentages of the predicted values, based on patient's sex, age, height and weight. The patients were referred to the pulmonologist for spyrometry and interpretation of the related findings. Furthermore, patients were examined with echocardiography Doppler for PAH and were referred to the cardiologist for interpretation of the findings. The systolic pressure in the pulmonary artery was evaluated based on tricuspid regurgitation peak flow velocity m/ s using the Bernoulli equation 4 x (tricuspid regurgitation jet)^2 + right atrial pressure of 5 mm/ hg. The value of pulmonary artery systolic pressure (PASP) >36 mm/ hg was considered as PAH (12).

To determine if the immunological alterations were associated with pulmonary injury, patients were classified into two groups. The first group included patients with positive anti-nuclear antibodies, positive anti-topoisomerase and positive anti-centromere. The second group included patients with negative antinuclear antibodies,

negative anti-topoisomerase and negative anti-centromere. Sex-specific analyses were performed to assess the scale of pulmonary injuries.

Statistical analysis

Continuous variables were expressed as mean values and their respective standard deviations. Categorical variables were presented in absolute values and their respective percentages. Differences between the categorical variables were assessed with the chi-square test. A p-value d"0.05 was considered as statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 19.0.

Results

Mean (±SD) age of the patients was 49.38±8.92 years. Mean (±SD) duration of disease was 7.29±4.55 years. There were 50 (86.2%) female patients and 8 (13.8%) male patients. Patients with positive anti-nuclear antibodies were 46 (79%), anti-topoisomerase positive were 23 (40%) and anti-centromere positive were 16 (28%) patients. Lung X-ray changes were observed in 10 (17%) patients, pulmonary injuries in HRCT were found in 42 (72%) patients, pulmonary arterial abnormalities were found in 6 (10%) patients with echocardiography Doppler and pulmonary function tests abnormalities were found in 32 (55%) patients. Lung injuries were more prevalent in HRCT compared with CXR and pulmonary function tests. ILD was identified in 42 (72%) patients and pulmonary arterial hypertension was found in 6 (10%) patients. ILD was significantly different (P<0.001) in patients with scleroderma versus PAH (Table 1).

Table 1. Pulmonary manifestations in scleroderma

Condition	Number of patients	Column percentages	P-value
ILD	42	72.4	<0.001
PAH	6	10.4	
Normal	10	17.2	
Total	***58***	***100.0***	

Pulmonary function tests abnormalities were observed in 32 (55%) patients and all patients had restrictive ventilator insufficiency. There were 46 (100%) patients with positive anti-nuclear antibodies, anti-topoisomerase positive and anti-centromere positive, of whom 39 (85%) represented pulmonary injuries whereas 7 (15%) patients were normal (group 1). Conversely, in group 2, of 12 (100%) patients who did not have positive anti-nuclear antibodies, anti-topoisomerase and anti-centromere, only 3 (25%) patients had pulmonary injuries and 9 (75%) patients were normal. The proportion of patients with pulmonary injuries was significantly higher among patients with immunological alterations compared to patient without immunological alterations (P<0.001) (Table 2).

Among 8 males, 2 (25%) had pulmonary injuries and 6 (75%) resulted normal. In 50 females, 40 (80%) had pulmonary injuries and 10 (20%) were normal. The proportion of patients with pulmonary injuries was significantly higher among females (P<0.001) (Table 3).

Table 2. Pulmonary injuries by immunological alterations

Patients' group	Total	Pulomonary injury	No pulmonary injury	P-value
Group 1	46 (100.0)	39 (85.0)*	7 (15.0)*	<0.001
Group 2	12 (100.0)	3 (25.0)	9 (75.0)	

* Absolute numbers and row percentages (in parentheses).

Table 3. Pulmonary injuries by sex

Sex	Total	Pulomonary injury	No pulmonary injury	P-value
Female	50 (100.0)	40 (80.0)*	10 (20.0)*	<0.001
Male	8 (100.0)	2 (25.0)	6 (75.0)	

* Absolute numbers and row percentages (in parentheses).

Discussion

The main finding of this study was that pulmonary injuries are more frequent in patients with scleroderma and in our opinion this indicates that pulmonary manifestations are important complications in such groups of patients. Pulmonary involvements in this study were found in 72% of the patients. The rate of this kind of injuries is reported at the level of 70%-90% in the literature (13). This study showed that in patients with scleroderma pulmonary anatomical injuries such as parenchymal and vascular injuries occur quite frequently. ILD and pulmonary arterial hypertension are often found in this type of patients. Some authors have noted that interstitial lung disease and pulmonary arterial hypertension are the two most common lung manifestations in scleroderma (4,5). In the present study, ILD was found in 72% of the patients and pulmonary arterial hypertension in 10% of the patients. ILD is reported to be present in nearly 60% of SSc patients with clinical involvement and approximately 80% of SSc patients in the autopsy (14). Pulmonary arterial hypertension is a frequent and serious form of pulmonary complication affecting 10%-20% of SSc patients (15,16). Pulmonary arterial hypertension occurs in at least 10% of SSc patients, and is associated with high mortality (17).

Another finding of this study is that pulmonary anatomical injuries are associated with injuries of pulmonary function, which are not always manifested with pulmonary anatomical injuries. In our study, 55% of the patients had pulmonary function testing abnormalities. Other authors have reported that 40%-75% of scleroderma patients have changes in pulmonary function tests (18). Different studies show that pulmonary injury in scleroderma is associated with restrictive ventilator defect (6,7). It has been estimated that 40% of the patients with scleroderma have a predicted FVC of less than 75%, indicating the presence of ILD (19).

A finding of this study is that scleroderma pulmonary injuries occur more frequently in patients with alterations of the immune system. According to our study, in patients with positive antinuclear antibodies, anti Scl-70 positive and anti-centromere positive pulmonary manifestation occurred frequently in 85% patients. Other authors have shown that the presence of anti-topoisomerase positive and anti-centromere positive in patients appear to be associated with the development of ILD and pulmonary arterial hypertension (8). Specific autoantibodies such as the anti-topoisomerase, ribonucleoprotein and anti-histone antibodies have been reported to be associated with an increased risk of ILD in SSc (20). Anti-centromere antibodies, known to be associated with limited SSc, are also linked to SSc-PAH (21). In our study, the pulmonary manifestations of scleroderma were observed more frequently in women than in men. In this study, HRCT were more sensitive than the chest X-ray and PFTs. HRCT is the standard method for the noninvasive diagnosis of SSc-ILD and can detect mild abnormalities even when chest the X-ray and pulmonary function tests result normal. HRCT is more sensitive than chest X-ray and is the imaging technique of choice for detecting and characterizing ILD (22).

Study limitations

The patients in our study were selected from a university hospital, which could potentially be prone to selection bias by including patients with more severe stages of the disease compared to patients at the community level. However, we tried to minimize this bias by recruiting also all the patients from the hospital's outpatient consultation clinics.

Conclusion

In conclusion, pulmonary manifestations are common in scleroderma. These injuries are anatomical and functional. ILD and restrictive ventilator insufficiency are injuries that occur more frequently in patients with scleroderma. Immunological alterations are important factors in pulmonary injuries. Sex is a factor that might be associated with the pulmonary injuries. Finally, HRCT is the most sensitive examination for the detection of pulmonary injuries.

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