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ORIGINAL ARTICLE

Pulmonary Arterial Hypertension and Systemic Sclerosis Relation: A Single Centre Experience

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Aim In systemic sclerosis (SSc), this single-centre study aimed to define the frequency and association of pulmonary arterial hypertension (PAH), occurring either alone in SSc-PAH or together with interstitial lung disease (ILD-PH).

Material-Methods SSc cases between the years 1990-2011 were reviewed, retrospectively. Patients' clinical, laboratory findings, Modified Rodnan Skin Score and Medsger score, 6-minute walk distance (6MWD), carbon monoxide diffusion test (DL_{CO}), echocardiography, thorax HRCT, and right heart catheterisation findings were recorded.

Results One hundred and forty-one cases (F/M:124/17, diffuse cutaneous SSc (DcSSc)/limited cutaneous SSc (LcSSc): 84/57) were included in the study with the mean age of 52.70±15.17 years and disease duration of 107.07±99.44 months. PaO_2, FEV1 and FVC were lower in DcSSc ($p<0.05$) as compared to LcSSc, but DL_{CO} and 6MWD did not differ significantly, between the two forms. Ground glass opacity (64.7%) and interlobular septal thickening (58.8%) were the most frequent findings on HRCT of such subjects. PAH was detected in 34 subjects (24.1%). Seven of them had SSc associated PAH (SSc-PAH) and 27 ILD-PH. Both frequencies were similar between DcSSc and LcSSc. Mean sPAP was higher in SSc-PAH.

Conclusion PAH was observed in approximately one fourth of patients; therefore advanced cardio-pulmonary investigation should be routinely performed in the SSc patients' management.

Keywords Systemic sclerosis • Diffuse cutaneous scleroderma • Limited cutaneous scleroderma • Pulmonary arterial hypertension • Interstitial lung disease

Introduction

Approximately half of systemic sclerosis (SSc) related deaths are known to be associated with pulmonary involvement. Recently, pulmonary complications have been more frequently seen as the main cause of morbidity in advanced stage of disease [1–5]. Over 30 years, while the prevalence of deaths due to renal crisis has been decreasing, deaths due to pulmonary fibrosis have increased from 6% to 33% [6]. Pulmonary fibrosis unrelated pulmonary hypertension has also been increasing significantly during this period. These observations demonstrate that the most common

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cause of SSc deaths are either due to pulmonary hypertension or pulmonary fibrosis.

Pulmonary arterial hypertension (PAH) associated with SSc is a common complication and an important mortality cause. PAH due to pulmonary vascular remodeling can either occur alone (SSc-PAH), or may develop secondary to pulmonary parenchymal involvement appearing as interstitial lung diseases (ILD-PH). Among the most frequent and serious complications of SSc, ILD is observed in up to 75% of cases and has also an important role in PAH development, whereas SSc-PAH is found in 8-12% of SSc patients [1–4].

Interstitial lung disease is more frequent in diffuse cutaneous SSc (DcSSc) and is often complicated with pulmonary hypertension. Isolated PAH (SSc-PAH) is similar to idiopathic PAH (IPAH) histologically, and it is more common in limited cutaneous SSc (LcSSc) when compared to DcSSc [7]. Despite the histopathological similarity, SSc-PAH shows a worse prognosis than that of IPAH [5]. SSc-PAH subjects are at higher risk of death than IPAH patients. Haemodynamic patterns and management of both subjects are similar; however, estimated one-year survival rates are 55% and 84%, respectively [8].

In most SSc cases, pulmonary involvement cannot be diagnosed until advanced stages of the disease. For optimal management of serious pulmonary complications of SSc, early detection and intervention with advanced therapies have become more important recently [1].

The aim of this single centre study was to define the prevalence and association of SSc-PAH and ILD-PH in DcSSc and LcSSc in patients registered in our institution.

Patients and Methods

Study Design

One hundred and sixty registered patients with SSc followed up in our institution through the years 1990-2011 were reviewed retrospectively. The data of 141 cases were obtained and recorded via Systemic Sclerosis Data Registry Form. This form included demographic data, clinical features like the disease duration, co-morbidities, pulmonary and extrapulmonary symptoms, dyspnoea score, physical examination findings, and Raynaud's phenomenon, and laboratory findings such as complete blood count, routine biochemical analysis, C-reactive protein, erythrocyte sedimentation rate, and immunologic markers. The patients were diagnosed with SSc according to American College of Rheumatology criteria and allocated into DcSSc and LcSSc groups according to LeRoy criteria as described previously [9,10]. Modified Rodnan skin scores (MRSS) and Medsger scores of all patients were evaluated by a rheumatologist. For MRSS evaluation a total of 17 skin sites were evaluated, including face, upper arms and forearms, dorsum of the hands, fingers, chest, abdomen, thighs, legs and feet. The maximum total score was 51 (MRSS-51) and the grading was done accordingly: 0, normal skin; 1, thickened skin; 2, thickened and unable to pinch; and 3, thickened and unable to move. Medsger score, an accepted severity scoring system for disease activity and damage in SSc, was used. Accordingly we assessed disease involvement in nine organ systems, namely, general health, peripheral vascularity, skin, joint/tendon, muscle, gastrointestinal tract, lungs, heart, and kidneys. Each organ system was scored separately from 0 to 4, depending on whether there was no, mild, moderate, severe, or end-stage involvement [11,12].

All patients were asked to grade their breathlessness on the Modified Medical Research Council (mMRC) dyspnoea scale: grade I: I only get breathless with strenuous exercise; grade II: I get short of breath when hurrying on the level or up a slight hill; grade III: I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level; grade IV: I stop for breath after walking 100 yards or after a few minutes on the level and grade V: I am too breathless to leave the house [13].

Thorax high resolution computed tomography (HRCT), pulmonary function test (PFT), diffusion capacity of carbon monoxide (DLco), arterial blood gas analysis (ABG), 6-minute walk distance (6MWD) results were evaluated. The PFT was carried out according to the standards of the joint ATS/ERS Task Force. The DL_{CO} values were corrected for the patient's haemoglobin concentration. All results were expressed as percent of the predicted values [14,15]. The 6MWT was performed following ATS guidelines [16].

Any fibrotic, ground glass appearance and/or honeycombing changes on HRCT was assessed as interstitial involvement of the disease and the patients evaluated along with their PFT findings as described previously [17,18].

Pulmonary arterial systolic pressure (sPAP) $\geq$ 40 mmHg on echocardiography (echo) (n:118) or $\geq$25 mmHg on right heart catheterisation (RHC) (n:13) was defined as PAH [19]. However, TAPSE or other echo assessments were not available during the follow-up period. Only 13 patients had undergone RHC. All the study subjects were evaluated for the presence of PAH and ILD. Subjects with high sPAP on echo and pulmonary interstitial involvement on HRCT and restrictive PFT findings were considered as ILD-PH. Subjects with high sPAP on echo but with normal HRCT and PFT finding were considered as SSc-PAH. A patient-flow diagram for the evaluation of ILD and PAH in SSc patients is seen Fig. 1.

Statistical analysis: Data were analysed by using SPSS for Windows release 10.0.1 (SPSS, Chicago, IL). Values were expressed as mean $\pm$SD. The chi-square test was used to compare categorical variables. T-test was used to compare the mean differences in independent samples. In addition, case summary reports and frequency charts were used to analyse the group variables. All p values were two-tailed and any p value < 0.05 was considered statistically significant.

Ethical approval for this study was obtained from Local Ethics Committee (04.DEC.2010/16-356).