

Clinical and laboratory features of scleroderma patients with pulmonary hypertension

K. Yamane, H. Ihn, Y. Asano, N. Yazawa, M. Kubo, K. Kikuchi, Y. Soma and K. Tamaki

Department of Dermatology, Faculty of Medicine, University of Tokyo, Tokyo, Japan

Abstract

Objective. Pulmonary hypertension (PH) is a frequent cause of death in patients with systemic sclerosis (SSc). In this study, we examined the occurrence of PH and investigated the clinical and laboratory features of SSc patients with PH.

Methods. A cross-sectional study of 125 Japanese patients with SSc was conducted using Doppler echocardiography, other multiple cardiopulmonary tests, and laboratory examination.

Results. PH (systolic pressure >40 mmHg) was diagnosed in 20 patients (16%) by Doppler echocardiography. In the six patients who had secondary pulmonary hypertension (SPH), PH was due to severe pulmonary fibrosis; 14 patients had isolated pulmonary hypertension (IPH). An elevated erythrocyte sedimentation rate (ESR) and increased immunoglobulin G (IgG) were found in a significantly greater proportion of the patients with PH than in those without PH. The incidence of pitting scars/ulcers was significantly greater in the patients with SPH than in those without PH.

Conclusion. Elevated ESR and increased IgG were common features of scleroderma patients with PH, and scleroderma patients with SPH were inclined to have pitting scars/ulcers.

KEY WORDS: Pulmonary hypertension, Scleroderma, Doppler echocardiography.

Scleroderma, or systemic sclerosis (SSc), is a generalized connective tissue disease which is characterized by microvascular obliteration and increased deposition of collagen, resulting in fibrotic lesions [1, 2]. Pulmonary involvement is a common feature of SSc, and pulmonary hypertension (PH) is a frequent cause of death in SSc patients [3–5]. PH can be due primarily to pulmonary vascular abnormalities or can be secondary to cardiac or interstitial lung involvement. The former is regarded as isolated pulmonary hypertension (IPH) and is usually found in patients with limited cutaneous SSc and minimal or no pulmonary fibrosis [3, 4]. In contrast, patients with diffuse cutaneous SSc may develop PH due to severe pulmonary fibrosis, but this is uncommon [4].

Many clinical and laboratory features of SSc patients with PH have been reported to date. An isolated reduction in diffusion capacity for carbon monoxide is associated with an increased risk of IPH [5]. We have reported that anti-cardiolipin β 2-glycoprotein I antibody was significantly correlated with the presence of IPH [6]. The presence of other autoantibodies, such as anti-

endothelial cell antibodies, has also been shown to be predictive of IPH [7]. Other studies have shown that the nitric oxide concentration in exhaled air is decreased [8]. In order to identify the common features of SSc patients with PH, we carried out Doppler echocardiography, other multiple cardiopulmonary tests and laboratory examination.

Patients and methods

Clinical assessment

All 125 patients with SSc who were evaluated in our clinic between 1990 and 1999 were included in the study. Patients with SSc were grouped according to the classification system proposed by LeRoy *et al.* [9]: 55 patients had diffuse cutaneous SSc (dcSSc) and 70 patients had limited cutaneous SSc (lcSSc), as described previously [6]. All patients fulfilled the criteria proposed by the American College of Rheumatology [10]. The clinical and laboratory data reported in this study were obtained at the time when Doppler echocardiography was performed. Patients were evaluated for the presence of gastrointestinal, pulmonary, cardiac, renal or muscle involvement, as described previously [6].

Submitted 6 December 1999; revised version accepted 19 May 2000.

Correspondence to: H. Ihn, Department of Dermatology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.

Echocardiographic evaluation

Echocardiographic studies were performed on one occasion at different stages of the patients' disease, as previously described [11]. The criterion for PH was a pulmonary artery systolic pressure of more than 40 mmHg by Doppler echocardiography [12]. According to the results of echocardiography and the severity of pulmonary fibrosis (PF), the patients were divided into three groups [4, 11]: (i) patients with isolated PH (IPH; PH without severe PF); (ii) patients with secondary PH (SPH; PH with severe PF); and (iii) patients without PH. Patients with severe pulmonary fibrosis seen on radiographs or restrictive disease revealed by a pulmonary function test (vital capacity <70% of predicted) were considered to have PH secondary to pulmonary causes. All remaining patients with PH were considered to have primary pulmonary disease or isolated pulmonary hypertension.

Statistical analysis

The Mann-Whitney test was used to compare means and Fisher's exact probability test for the analysis of frequency. Correlations with clinical data were assessed by Spearman's rank correlation coefficient. Two-tailed *P* values less than 0.05 were considered significant.

Results

Clinical and serological features of each subgroup of patients with SSc

Twenty of the 125 patients (16%) with SSc were diagnosed as having PH. The clinical and laboratory features of each subgroup of the patients with SSc are shown in Table 1. There was no significant difference between these groups in sex, age, or duration of the disease. Fourteen patients had IPH; five patients had dcSSc and nine patients had lcSSc. All of these patients had IPH without other antecedent pulmonary or cardiac conditions. Six patients had SPH; five patients had dcSSc and one patient had lcSSc. All of these patients had severe pulmonary fibrosis. The incidence of pitting scars/ulcers was significantly greater in the patients with SPH than in those without PH (100 vs 49%, *P* < 0.05).

Anti-topoisomerase I antibody was found in a significantly greater proportion of the patients with SPH than of those with IPH and of those without PH (83 vs 14%, *P* < 0.01 and 83 vs 32%, *P* < 0.02, respectively). An elevated erythrocyte sedimentation rate (ESR) and increased immunoglobulin G (IgG) were found in a significantly greater proportion of the patients with SPH than of those without PH (100 vs 49%, *P* < 0.02 and 67

TABLE 1. Clinical and laboratory features of each subgroup of patients with systemic sclerosis

	Patients with IPH (<i>n</i> = 14)	Patients with SPH (<i>n</i> = 6)	Patients without PH (<i>n</i> = 105)
Sex (male, female)	1, 13	0, 6	10, 95
Age (yr)	45.4	43.8	42.9
Duration of disease (yr)	9.1	4.7	7.4
Type (diffuse, limited) (<i>n</i>)	5, 9	5, 1	45, 60
Clinical features			
Pitting scars/ulcers	36	100 ^e	49
Short sublingual frenulum	36	83	53
Contracture of phalanges	36	67	48
Pigmentation	50	67	47
Calcinosis	7	17	10
Telangiectasia	43	67	41
Organ involvement			
Oesophagus	50	50	42
Lung	36	100 ^b	33
Decreased %DLco	71 ^c	83 ^d	34
Decreased % vital capacity	21	100 ^a	19
Heart	7	0	4
Kidneys	21	0	6
Muscles	14	0	11
Joints	29	50	38
Antinuclear antibody specificity			
Anti-topoisomerase I	14	83 ^d	32
Anti-centromere	36	0	25
Anti-U1RNP	14	33	13
Laboratory findings			
Elevated ESR	79 ^e	100 ^d	49
Increased C-reactive protein	21	33	12
Increased IgG	57 ^e	67 ^e	24

Unless noted otherwise, values are percentages of patients.

U1RNP, U1 ribonucleoproteins.

^a*P* < 0.0001, ^b*P* < 0.001, ^c*P* < 0.01, ^d*P* < 0.02, ^e*P* < 0.05 vs patients without PH.

vs 24%, $P < 0.05$, respectively). In addition, elevated ESR and increased IgG were found in a significantly greater proportion of the patients with IPH than of those without PH (100 vs 49%, $P < 0.02$ and 67 vs 24%, $P < 0.05$, respectively).

Discussion

In the present study we investigated the clinical and laboratory features of 125 SSc patients. The frequency of patients with IPH was 11.2%, which is less than in previous reports [3, 13]. However, in those reports PH was diagnosed according to the presence of a pulmonary artery systolic pressure >35 or 30 mmHg by Doppler echocardiography. Koh *et al.* [14] pointed out that the occurrence figures for PH in SSc are heavily influenced by the extent of the investigations carried out. There was no significant difference between the different subgroups in the duration of the disease. We also determined the disease stages in the different subgroups. The proportion of patients at the atrophic stage was larger in patients with IPH than in those with SPH (36 vs 17%), but the difference was not significant. This result is consistent with the longer disease duration of the patients having IPH compared with those having SPH.

PH has been reported to be clinically unsuspected in patients with SSc [3]. It is of interest that the frequency of pitting scars/ulcers was significantly greater in the patients with SPH than in those with IPH and in those without PH. This suggests that SSc patients with SPH tended to have pitting scars/ulcers.

Although anti-phospholipid antibody is known to be associated with PH, few other laboratory features have been reported to be useful for detecting PH in patients with SSc. In this study, we found that elevated ESR was significantly correlated with PH in patients with SSc. ESR is known to be elevated in patients with inflammation, anaemia or hypergammaglobulinaemia. In this study, there was no significant difference in the frequency of anaemia between the different subgroups (data not shown). This indicates that inflammation or hypergammaglobulinaemia may cause elevated ESR in SSc patients with PH. In fact, elevated IgG was also found in a significantly greater proportion of the patients with PH than in those without PH. There were no significant differences in the levels of serum IgA and IgM among the different subgroups (data not shown). There is a possibility that increased IgG may be associated with coagulation due to hyperviscosity.

In this cross-sectional study, we have shown that elevated ESR and increased IgG were common in SSc patients with PH. Moreover, SSc patients with SPH

tended to have pitting scars/ulcers. We conclude that these features are common in SSc patients with PH.

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