Respiratory Disorders in Systemic Sclerosis

Pasakorn Jitruckthai, M.D., Emvalee Arromdee, M.D., Suree Sompradeekul, M.D.
Department of Internal Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Respiratory disorders in systemic sclerosis (SSc) are common. They are also a leading cause of morbidity and mortality in this group of patients. Currently, there are no good clinical or serological parameters that would predict respiratory disorders in SSc. The aims of this study are to review the different patterns of respiratory disorder in Thai SSc and to identify the clinical and serological parameters that may be associated with those respiratory disorders. A retrospective medical records review was performed. Out of 137 scleroderma patients seen by the division of rheumatology at Siriraj Hospital Mahidol University from January 1986 to December 2006, sixty-six (48.2%) had respiratory disorders. The most common respiratory disorder was interstitial lung disease (ILD) (81.8%), followed by secondary pulmonary hypertension (PHT) (24%). A few cases of isolated PHT were found (3%). There were no statistically significant differences in the clinical manifestations, disease subtypes or serological parameters between SSc patients who had ILD with or without secondary PHT. Raynaud's phenomenon was very commonly seen in the SSc patients with PHT.

Keywords: Pulmonary hypertension; respiratory disorders; systemic sclerosis

Siriraj Med J 2008;60:74-77
E-journal: http://www.sirirajmedj.com

Systemic sclerosis (SSc) or scleroderma is a connective tissue disorder characterized by thickening and fibrosis of the skin accompanied by varieties of internal organ involvement. Two forms of SSc are classified, by the proximity of skin involvement, as limited and diffuse forms of SSc. The diffuse form is characterized by proximal skin involvement extended to the thorax and the limited form is characterized by distal skin involvement, e.g., below knees and elbows without affecting the thorax. Besides the difference in severity of skin involvement, the diffuse form has a higher prevalence of internal organ involvement causing higher morbidity and mortality.[1]

Respiratory disorder is the second most common organ involved (after the esophagus) in SSc. Over 70% of patients with SSc had respiratory disorders which are the leading causes of morbidity and mortality.[2-3] Diagnosis of lung disease in its earliest stage is crucial because it enables the prompt application of therapies which could halt disease progression before permanent damage occurs. Among the respiratory disorders, interstitial lung disease (ILD) including progressive fibrosis is the most common, affecting approximately 75% of the patients with SSc at autopsy, followed by pulmonary hypertension (PHT), which was found in about 50% of SSc patients.[4] It was also observed that the two forms of SSc described above have different spectrums of pulmonary presentations, eg., ILD typically affected patients with diffuse SSc while PHT affected more patients with limited SSc.[3]

The aim of this study was to identify different patterns of respiratory disorder in Thai SSc patients as well as to determine the clinical and serological parameters that may be associated with those respiratory disorders.

MATERIALS AND METHODS

All medical records of the SSc patients registered at the division of rheumatology, Siriraj Hospital Mahidol University, Bangkok, Thailand between January 1986 and December 2006 were reviewed. Only the SSc patients with at least one respiratory disorder were recruited into this study. (A research protocol (No.093/2549) was sent to the Siriraj Ethic Committee and received approval.) All these patients had the diagnosis of SSc using the American College of Rheumatology (ACR) criteria.[3] They either met one major or 2 or more minor criteria as described below:

Major criteria: proximal scleroderma; symmetric thickening, tightening and induration of the skin of the fingers and skin proximal to the matacarpophalangeal or metatarsophalangeal joints.

Minor criteria: 1) sclerodactyly; 2) digital pitting scars or loss of substance from the finger pad; 3) bibasilar pulmonary fibrosis.

Correspondence to: Emvalee Arromdee
E-mail: exa01@hotmail.com

Demographic data, including age and sex, smoking history, clinical manifestations (arthralgia or arthritis, dysphagia, digital pitting scars, sclerodactyly, Raynaud's phenomenon, and/or renal crisis), laboratory data, serological markers (e.g. antinuclear antibody (ANA) patterns), SSc disease subtypes and patterns of respiratory disorder were recorded.

The ILD pattern was defined by using abnormal chest radiograph (CXR) criteria with a restrictive pattern from spirometry or an abnormally high-resolution computerized tomography (HRCT) of the chest.

PHT was defined by the elevated right ventricular systolic pressure (RVSP) of > 35mm Hg estimated by Doppler echocardiography. In this paper, PHT without ILD was termed isolated pulmonary hypertension while PHT secondary to ILD was termed secondary PHT.

Statistical analysis

All the categorical data were presented as a proportion. All continuous variables were presented as a mean or range. A Z-statistic test for dichotomus variables was used to determine the difference of the proportions. Chi-square or Fisher's exact test was used for categorical variables.

RESULTS

Out of 137 scleroderma patients, 66 patients had at least one respiratory disorder (48.2%). The male:female ratio was 3:7. The mean age was 46.4 years (range 19-77 years). Nearly all of the patients were in an inpatient setting. About half of these patients (N=34) were non-smokers, 22% (N=15) were ex-smokers and 4.5 % (N=3) were current smokers. Most patients had diffuse SSc (86%, N=57), the rest had limited SSc (14%, N=9). Sclerodactyly and Raynaud's phenomenon were the two most common manifestations in these groups, followed by digital pitting scars, arthralgia and dysphagia. Scleroderma renal crisis was rare (4.5%) and all patients were in the diffuse SSc group. The patient's gender and disease manifestation are demonstrated in Table 1.

The most common respiratory disorder in our SSc patients was ILD (81.8%, N=54), followed by secondary PHT (24%, N=16). Interestingly, there were very few isolated PHT in these series (3%, N=2). Chest wall restriction, pleural effusion and pneumothorax were very rare. Other coexisting pulmonary disorders commonly observed were pneumonia, tuberculosis, chronic and/or obstructive pulmonary disease (COPD). (Table 2)

Comparison between the group of SSc patients with ILD with or without secondary PHT showed no statistically significant differences in the clinical manifestations, disease subtypes or serological parameters (Table 3). Digital pitting scars, however, seemed to be more prevalent in the former group.

Comparison between the group of SSc patients with isolated PHT and the group with secondary PHT indicated that there were no statistically significant differences in the clinical manifestations, disease subtypes or serological parameters (Table 4).

DISCUSSION

Respiratory disorder in systemic sclerosis is very common. These involvements included interstitial lung disease, pulmonary vascular disease, pleural disease, chest wall restriction, respiratory muscle weakness, aspiration pneumonia, and small airways disease etc.[4-5]

TABLE 1. Gender and disease manifestation of SSc patients.

	dSSc (N=57) No. (%)	lSSc (N=9) No. (%)	Total (N=66) No. (%)
Sex			
Male	18 (31.6)	2 (22.2)	20 (30.3)
Female	39 (68.4)	7 (77.8)	46 (69.7)
Disease manifestation			
Arthralgia	29 (55.8)	4 (80.0)	33 (50)
Dysphagia	30 (55.6)	2 (22.2)	32 (48.5)
Digital pitting scars	39 (79.6)	5 (55.6)	44 (66.7)
Sclerodactyly	56 (98.2)	9 (100)	65 (98.5)
Raynaud's phenomenon	53 (93.0)	9 (100)	62 (93.9)
Sclerodermal renal crisis	3 (5.6)	0 (0)	3 (4.5)

dSSc = diffuse form of systemic sclerosis
lSSc = limited form of systemic sclerosis

The most common type of respiratory disorder is interstitial lung disease, followed by pulmonary hypertension. The prevalence of ILD in SSc patients ranged from 33-90% (the prevalence varied based on the diagnostic criteria for ILD in each study).[6] ILD prevalence in this study was 82% (chest radiograph, HRCT chest and spirometric criteria were used to identify ILD in our study). The prevalence of PHT in SSc patients from earlier studies was 28-35% which was similar to our study at 27%.[6-7] One-fourth of the patients had ILD and PHT.

Spontaneous pneumothorax is a rare complication of respiratory disorder in SSc patients, most likely caused by the rupture of subpleural cysts secondary to cicatricial emphysema.[3,8] Only one of our patients had pneumothorax which occurred 6 years after diagnosis of scleroderma with ILD and secondary PHT.

SSc is associated with an increased incidence of various cancers, e.g. breast cancer, lung cancer, tongue cancer or lymphoma, etc. It was hypothesized that overexpression of oncogenes and a reduction in the level of tumor suppression genes may be related to the cancerous features of SSc.[5,9] We found 1 non-smoker patient with tongue cancer and pulmonary metastasis at the same time as her SSc diagnosis. Her SSc manifestation may be a

TABLE 2. Respiratory disorders in SSc patients (66 cases).

Respiratory disorders	No. (%)
Related respiratoy condition	
Interstitial lung disease	54 (81.9)
Interstitial lung disease (evidence by CXR)	45 (68.2)
Non specific interstitial pneumonia (evidence by HRCT)	5 (7.6)
Usual interstitial pneumonia (evidence by HRCT)	4 (6.1)
Isolated pulmonary hypertension	2 (3.0)
Secondary pulmonary hypertension (with ILD)	16 (24.2)
Chest wall restriction	4 (6.1)
Pneumothorax	1 (1.5)
Pleural effusion	1 (1.5)
Co-existing respiratory condition	
Pneumonia	6 (9.1)
Pulmonary tuberculosis	4 (6.1)
COPD	3 (4.0)
Empyema thoracis	1 (1.5)
Chemical pneumonitis	1 (1.5)
Metastatic cancer	1 (1.5)

CXR= chest radiograph, HRCT= high resolution computerized tomography
ILD= interstitial lung disease, COPD= chronic obstructive pulmonary disease

TABLE 3. Clinical and serological characteristics of SSc patients with isolated interstitial lung disease(ILD) and secondary pulmonary hypertension(PHT) from ILD.

	Isolated ILD (N=38) No. (%)	ILD with PHT (N=16) No. (%)	Total No. (%)	p value
Sex				
Male	10 (26.3)	5 (31.3)	15 (27.8)	0.747
Female	28 (73.7)	11 (68.8)	39 (72.2)	
Disease subtype				
Diffuse form	32 (84.2)	15 (93.8)	47 (87)	0.660
Limited form	6 (15.8)	1 (6.3)	7 (13.0)	
ANA pattern				
Negative	2 (6.7)	1 (6.7)	3 (6.7)	1.00
Positive	28 (93.3)	14 (93.3)	42 (93.3)	
Homogeneous	5 (16.7)	4 (26.7)	9 (20.0)	
Nucleolar	2 (6.7)	0 (0)	2 (4.4)	
Speckle	20 (66.7)	10 (66.7)	30 (66.7)	
Peripheral	1 (3.3)	0 (0)	1 (2.2)	
Disease manifestation				
Arthralgia	19 (57.6)	6 (46.2)	25 (54.3)	0.527
Dysphagia	16 (44.4)	9 (56.3)	25 (48.1)	0.551
Digital pitting scars	23 (65.7)	13 (92.9)	36 (73.5)	0.075
Sclerodactyly	37 (100)	16 (100)	53 (100)	-
Raynaud's phenomenon	35 (92.1)	16 (100)	51 (94.4)	0.547
Renal crisis	2 (5.7)	1 (6.3)	3 (5.9)	1.00

paraneoplastic symptom.

In SSc patients with ILD alone or ILD with PHT, there are no specific disease manifestations, disease subtypes or ANA patterns that would separate these two groups. Among those with ILD, about 30% had secondary PHT associated with ILD. It is notable that digital pitting scars were found in most patients with ILD but none in those with isolated PHT. However, there are very few SSc patients (N=2) with isolated PHT. Interestingly, Raynaud's phenomenon was found in all patients with PHT. This may reflect the linkage between peripheral vascular and pulmonary vascular lesions.

Despite a 20-year data review, the limitations of this study were the small number of SSc patients and nearly all were in an in-patient setting (of interest, the number of patients with limited form SSc in our series was only nine), therefore these results may not represent the overall SSc population in Thailand. Since this is a retrospective study, some of the data, especially those from the fields of diagnostic methods for ILD and pulmonary hypertension such as HRCT, echocardiogram, serological markers were not fully accessible during the earlier years of the retrospective study. Full analysis of the tests mentioned may therefore not be possible.

CONCLUSION

Respiratory disorders in Thai SSc patients are common. Interstitial lung disease followed by secondary PHT are the first two disorders most frequently observed. No definite clinical manifestations or serological markers were found to predict different types of respiratory disorder.

TABLE 4. Clinical and serological characteristics of scleroderma patients with isolated and secondary pulmonary hypertension.

	Isolated PHT (N=2), No. (%)	Secondary PHT (N=16), No. (%)	Total No. (%)	p value
Sex				
Male	0 (0)	5 (31.3)	5 (27.8)	0.639
Female	2 (100)	11 (68.8)	13 (72.2)	
Disease subtype				
Diffuse form	1 (50)	15 (93.8)	16 (88.9)	0.221
Limited form	1 (50)	1 (6.3)	2 (11.1)	
ANA pattern				
Negative	1 (50)	1 (6.7)	2 (11.8)	0.074
Positive	1 (50)	14 (93.3)	15 (88.2)	
Homogeneous	0 (0)	4 (26.7)	4 (23.5)	
Nucleolar	1 (50)	0 (0)	1 (5.9)	
Speckle	0 (0)	10 (66.7)	10 (58.8)	
Peripheral	0 (0)	0 (0)	0 (0)	
Disease manifestation				
Arthralgia	2 (100)	6 (46.2)	8 (44.4)	0.327
Dysphagia	1 (50)	9 (56.3)	10 (55.6)	0.880
Digital pitting scars	0 (0)	13 (92.9)	13 (72.2)	0.058
Sclerodactyly	2 (100)	16 (100)	18 (100)	-
Raynaud's phenomenon	2 (100)	16 (100)	18 (100)	-
Renal crisis	0 (0)	1 (6.3)	1 (5.6)	0.914

REFERENCES

1. White B, Denton CP, Black CM. Pulmonary fibrosis and pulmonary vascular involvement in systemic sclerosis. In: Clements PJ, Furst DE. Systemic Sclerosis, 2nd ed. Lippincott, Williams & Wilkins, 2003:163-93.
2. Korn JH. Clinical manifestation and evaluation of scleroderma lung disease. UpTo Date 2005.
3. Seibold JR. Scleroderma. In: Harris E, Budd R, Firestein G, et al. Kelley's textbook of Rheumatology, 7th ed. W.B. Saunders, 2004:1279-320.
4. Crestani B. The respiratory system in connective tissue disorders. Allergy 2005;60:715-34
5. Denton CP, Black CM. Scleroderma-clinical and pathological advances. Best Pract & Res Clin Rheumatol 2004;18:271-90.
6. Charabaty S, Stern V. Pulmonary complications are the leading causes of scleroderma - related death - Managing lung involvement in systemic sclerosis. J Musculoskel Med 2006;23:575-81.
7. de Azevedo AB, Sampaio-Barros PD, Torres RM, Moreira C. Prevalence of pulmonary arterial hypertension in systemic sclerosis. Clin Exp Rheumatol 2005;23:447-54.
8. Zeuner M, Müller-Laduer U, Mohr VD, Lang B. Spontaneous pneumothorax in a patient with systemic sclerosis. Clin Rheumatol 1996;15:211-13.
9. Kanaji N. Fujita J, Bandoh S, et al. Small cell lung cancer associated with systemic sclerosis. Intern Med 2005;44:315-8.