Demography, Clinical and Laboratory Features of Systemic Sclerosis in a Malaysian Rheumatology Centre

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SUMMARY

A six year retrospective study of the demography, clinical and laboratory features of patients with systemic sclerosis (SSc) was carried out in Selayang Hospital. There were 61 cases seen between January 2000 and December 2005. Of these, 55 (90.2%) were females and 6 (9.8%) were males. Twenty-eight (45.9%) were Malays, 24 (39.3%) were Chinese and 9 (14.8%) were Indians. The mean age of onset was 38.8 years. Thirty-nine (64.0%) had limited cutaneous SSc, 21 (34.4%) had diffuse cutaneous SSc and one had localized morphoea. Raynaud's phenomenon was present in 82.6%, telangiectasia in 45.9%, calcinosis in 11.5%, sclerodactyly in 83.6%, digital pitting scars in 42.6%, digital infarcts/ulcers/gangrene in 23.0%, arthralgia/arthritis in 49.2% and gastroesophageal reflux disease (GERD) in 47.5%. Forty-three (70.5%) patients had interstitial lung disease. Seven patients had associated myositis, 7 systemic lupus erythematosus and 2 rheumatoid arthritis. Three had two other connective tissue diseases. Antinuclear antibodies were positive in 83.6% and anti-Scl 70 antibodies in 34.4%. This study demonstrates that limited cutaneous SSc is more common and there is a high incidence of interstitial lung disease in our population.

KEY WORDS:
Systemic sclerosis, Raynaud's, Limited cutaneous systemic sclerosis, Diffuse cutaneous systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) or scleroderma is a systemic autoimmune disease characterized clinically by different degrees of skin fibrosis and visceral organ involvement [1, 2, 3]. The skin, lungs, gastrointestinal system, heart and kidneys are the major systemic sclerosis targets. The etiology of SSc still remains obscure and the epidemiology is not definitely established due to the rarity of this disease.

The annual incidence (new cases/population at risk per year) of SSc varies largely among different surveys (from 0.6 to 19.1 per million/year). The actual incidence and prevalence of the disease are grossly underestimated. Systemic sclerosis patients have been characterized in the United States [4,5], France[6,7], Japan[8,9], Australia[10], English Canadians[11], French Canadians[12] and in Italian patients[13]. The true prevalence may be more then four fold higher.

There has not been any data published from Malaysia on the prevalence and characteristics of SSc. As Selayang Hospital is the major rheumatology referral centre in Malaysia, we carried out a retrospective study to look into the demography, clinical and laboratory features of systemic sclerosis patients in Selayang Hospital between January 2000 and December 2005.

MATERIALS AND METHODS

This study was carried out to analyse all cases of systemic sclerosis between January 2000 and December 2005. A total of 61 patients were seen during this period and the medical records of all these patients were analysed retrospectively.

All patients fulfilled the preliminary criteria of the American College of Rheumatology (ACR) 1980 for systemic sclerosis which is based on the presence or absence of the major criterion, that is, sclerodermatous skin involvement proximal to metacarpophalangeal joints (including facial skin thickening) or 2 or more of the minor criteria: 1) sclerodactyly 2) digital pitting scars or loss of substance of the distal finger pad and 3) bibasilar pulmonary fibrosis [14]. This classification has 91% sensitivity and more than 99% specificity. At the same time, patients were also classified based on the extent of skin sclerosis according to the two cutaneous subset models [1, 15]. These subsets are:

1. Limited SSc: sclerosis restricted to hands, face, forearms and feet
2. Diffuse SSc: skin sclerosis extending proximal to the elbow, may involve truncal areas.

All 61 patients with a confirmed diagnosis of systemic sclerosis were analysed and the demography, clinical and laboratory features were recorded. The clinical features recorded were that of at the time of referral and cumulative clinical manifestation during the entire follow-up. The duration from first signs and symptoms of systemic sclerosis to the time of first encounter at our clinic ranges from 0 – 13 years. The clinical features were taken from what was written in the medical records by experienced clinicians in our rheumatology unit.

All the serological investigations were done by the laboratory at the Institute of Medical Research (IMR) in Kuala Lumpur. All patients were tested for antinuclear antibodies (ANA) and extractable nuclear antigens (ENA) which includes anti-Sm, anti-RNP, anti-Jo1 and anti-Scl 70.

RESULTS

Figure 1 shows the ethnic distribution of all the cases. Figure 2 shows the age of onset and sex distribution. Age of onset

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was considered to be the age at which the first signs and symptoms compatible with the disease appeared. Mean age of onset was 38.8 years. The mean for limited SSc was 40 years and diffuse SSc was 37.1 years. The female to male ratio was 9.2:1. Figure 3 shows the cutaneous subsets of systemic sclerosis.

Table I shows the various clinical features of the cases which are divided into diffuse and limited disease. Only the hands were used to look for subcutaneous calcifications. Gastroesophageal reflux disease (GERD) was diagnosed based on clinical symptoms of heartburn, acid or food regurgitations and in some cases upper endoscopy was performed. There was no specific test carried out to diagnose malabsorption as these tests are not readily available at our centre. It was merely based on the occurrence of chronic diarrhea not responding to antibiotics, abdominal bloating after meals and weight loss. Active alveolitis was diagnosed by the appearance of ground glass opacities in High Resolution Computed Tomography scan of Thorax (HRCT). All cases of interstitial lung disease were confirmed on HRCT. Pulmonary hypertension was diagnosed clinically as evidenced by loud second heart sound as well as echocardiography findings of raised pulmonary artery systolic pressure of above 30mmHg.

Table II: Shows the associated connective tissue diseases.

Table III: Shows the autoimmune markers of systemic sclerosis.

DISCUSSION

There is paucity of information on systemic sclerosis in Asian people. In South-east Asia, the Singapore Scleroderma Databank of patients seen by all the country's rheumatologists had 91 patients as of July 1996 in the city state of 2.9 million people. In Malaysia, since rheumatology

Table I: Clinical features of Diffuse and Limited Systemic Sclerosis

Clinical Features	Number of Cases (n=61)			
	Diffuse SSc	Limited SSc	Total (%)	p value
Telangiectasia	11	17	28 (45.9%)	0.246
Subcutaneous Calcinosis	3	4	7 (11.5%)	0.741
Raynaud's	18	33	51 (83.6%)	0.038**
Sclerodactyly	20	32	52 (85.2%)	0.113
Digital Pitting scars	14	12	26 (42.6%)	0.716
Digital Ulcers/Gangrene/Infarct	9	5	14 (23.0%)	0.687
Arthralgia/Arthritis	11	19	30 (49.2%)	0.156
Gastroesophageal Reflux Disease	11	19	30 (47.5%)	0.156
Malabsorption	0	0	0 (0%)	NA
Interstitial Lung Disease	18	25	43 (70.5%)	0.313
Alveolitis	8	10	18 (29.5%)	0.958
Pulmonary Hypertension	5	2	7 (11.5%)	NA
Cardiac	4	0	4 (6.6%)	NA
Renal crisis	0	0	0 (0%)	NA

NA: not applicable **statistically significant

Table II: Associated Connective Tissue Diseases

Associated Connective Tissue Disease	Number of Cases	Anti RNP +ve
SLE*	7	7
RA**	2	2
Polymyositis	7	4
SLE & RA	1	1
SLE & Polymyositis	1	1
RA & Polymyositis	1	1

*SLE – Systemic Lupus Erythematosus
**RA – Rheumatoid Arthritis

Table III: Laboratory features of Systemic Sclerosis cases

Laboratory Features	Number of Cases		Total (%)
	Diffuse SSc	Limited SSc	
Antinuclear antibody (ANA)	17	34	51 (83.6%)
Anti-Scl70	10	11	21 (34.4%)
Anti-RNP	8	22	30 (49.2%)
Anti-Sm	5	9	14 (23.0%)

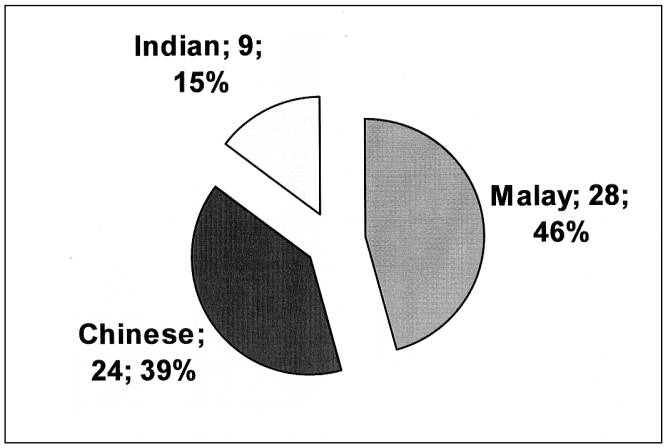

Fig. 1: Ethnic Distribution of Systemic Sclerosis cases

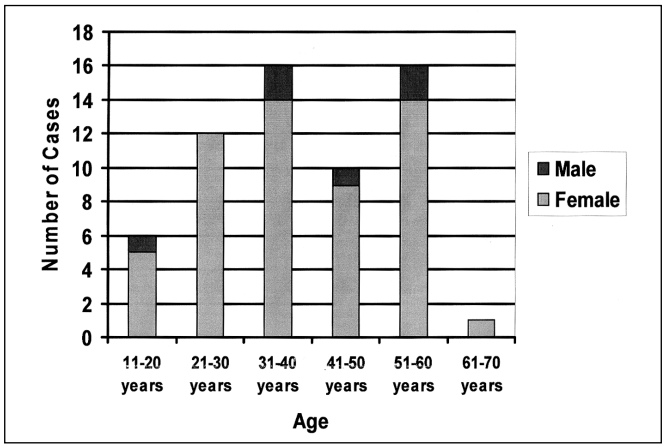

Fig. 2: Age and Gender Distribution

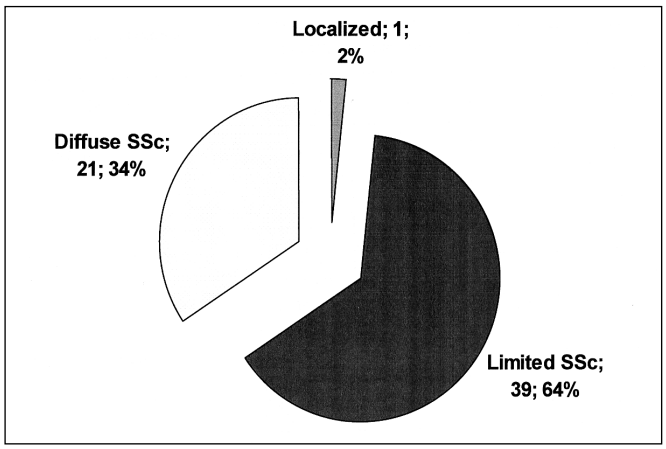

Fig. 3: Subsets of Systemic Sclerosis

is relatively a new field of medicine, there has not been any data collected on systemic sclerosis.

The clinical features of systemic sclerosis patients seen in Asia are much like those in other countries. Systemic sclerosis is 3-4 times more common in women with a peak incidence between ages of 45 and 64 years [2,3]. However, in this study it was noted that the age group seems to be younger with a peak incidence of between 21 and 60 years old. The female to male ratio remained high as expected, even higher than the ratio of 5.3:1 reported by the European scleroderma study group [16]. The mean age of onset of 38.8 years appeared to be similar to the Singapore data which was 38.2 years and the European data of 41 years [16].

Limited systemic sclerosis represents the most frequent subset of SSc in all studies including this review in which 64% of the patients had limited SSc which gives a ratio of 1.9: 1 to diffuse type. Most studies gives a ratio of between 1.5 to 6 [17, 18, 19,20, 21]. The Malay and Chinese population were affected the most, comprising almost 85% of the total patients seen. This was actually a close reflection of the racial composition of patients seen at our institution.

The commonest clinical features noted in limited SSc were telangiectasia, Raynaud's phenomenon, sclerodactyly, arthralgia/arthritis, GERD and interstitial lung disease. However, only Raynaud's phenomenon is statistically significant ($p<0.05$). These findings seem to correlate with the older term of CREST syndrome which is considered a variant of systemic sclerosis. CREST syndrome consists of subcutaneous calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly and telangiectasia. However there was a very low incidence of subcutaneous calcinosis in our population, noted only in 11.5% of the patients. Generally subcutaneous calcinosis is seen in about 40% of patients with long standing limited SSc. This could be because of the failure of the clinicians to pay attention to this clinical feature and thus it may not have been routinely picked up. Raynaud's phenomenon is known to be the initial complaint in approximately 70% of patients with SSc and in virtually all patients whose condition is destined to evolve into SSc with limited SSc [22]. In this review 83.6% of the patients had Raynaud's phenomenon with 65% of them in the limited SSc subset.

Cases of diffuse SSc seem to have more digital pitting scars, digital ulcers/gangrene/infarct, pulmonary hypertension and cardiac manifestation. All patients with pulmonary hypertension in this study had interstitial lung disease and no primary isolated pulmonary vasculopathy was identified. As a rule, patients with diffuse SSc are at risk for progressive interstitial fibrotic lung disease. In limited SSc, interstitial lung disease (ILD) may also develop but there is also a risk for progressive pulmonary hypertension in the absence of interstitial change [23]. There seem to be a very high incidence of ILD in our population which is almost 70.5% of the patients. The usage of HRCT to detect ILD has been reported to have increased the prevalence by as much as 90% [24], thus this could account for the high prevalence in this study where HRCT was used.

Furthermore the majority of them (58%) were in the limited SSc subgroup but no statistical significance was noted. The European scleroderma study group also reported a high 74% incidence of ILD among their 290 patients[16]. Even though in their study, the diffuse SSc group had a higher incidence of ILD, the difference was actually minimal (limitedSSc/diffuse SSc: 67%/72%). It is known that in limited SSc, ILD develops quite late in the course of the disease. Since our centre is a major referral centre for Malaysia, most of the patients were

referred to us after they have developed some form of complication. Some of the limited SSc patients were referred to us when these patients developed lung complications despite having the disease for many years. As such, the late presentation of these patients to our centre could be responsible for the higher incidence of ILD in limited SSc as it is also well known that the onset of ILD is usually within the first three years of disease in most patients [25, 26, 5]. There have also been reports that Blacks and Japanese races have a more severe restrictive lung disease and that the ethnic background is an independent determinant of severe lung disease [25, 27]. It is interesting to note that 17 of 43 patients (39.5%) who had ILD had associated connective tissue diseases. There is a possibility that the association of other connective tissue diseases may increase the likelihood of developing ILD in our population but this needs further evaluation.

The four cases that had cardiac manifestations presented with pericardial effusion. One of them also had concomitant cardiomyopathy. These were only seen in the diffuse type. There were no cases of nephropathy or renal crisis noted in our patients. Similar findings were noted from Singapore which is dissimilar to series reported from Northern Europe and the United States [28, 29]. Asians seem less likely to have renal involvement than to Caucasians. There were also no cases of clinical malabsorption reported here.

Anti nuclear antibody (ANA) were found in 83.6% of the patients in this series. Generally it is reported that ANA is present in the sera of more then 90% of patients with SSc. It is also reported that 20-40% of patients with SSc are anti-Scl70 positive[30]. This corresponds to our study as 34.4% of the patients had anti-Scl70. As many as half of the SSc patients whom pulmonary fibrosis develops will have anti-Scl70 autoantibodies[13,17,31,32]. In this study, 15 of 21 patients (71.4%) with anti-Scl70 had interstitial lung disease.

As a rule, SSc patients lack anti-Sm antibodies [33], although it has been described as occurring uncommonly in patients with SSc [34-36] and only about 20% have anti-RNP [37]. In this review there were 14 (23.0%) patients who had anti-Sm. Out of these, seven patients had overlap with SLE, three patients had polymyositis and one patient had rheumatoid arthritis.

Only three patients did not have any associated connective tissue disease. Anti-Sm is considered to be highly specific for SLE. There is also a very high incidence of anti-RNP antibodies (49.2%) in this review. Sixteen out of 30 (53.3%) patients with anti-RNP had associated connective tissue disease. There is a possibility that SSc patients who were anti-Sm or anti-RNP positive but did not have other connective tissue disease may develop it later in their lives.

Since Selayang Hospital is a major rheumatology referral hospital in the country, only patients who have severe diseases are referred to us. As such the data could be biased in terms of severity of the clinical features.

CONCLUSION

This study demonstrates that patients from our population tend to develop systemic sclerosis at a younger age and have a high incidence of interstitial lung disease. However, they are less likely to develop any renal crisis or clinical malabsorption syndrome.

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