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Characteristics of patients with systemic sclerosis living in Qatar

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ABSTRACT

Objective: The aim of this study was to determine the demographic, clinical, and immunological characteristics of patients with systemic sclerosis living in Qatar.

Method: This retrospective study included 42 patients with systemic sclerosis who attended Rheumatology Clinics at Hamad General Hospital in Doha, Qatar, between January 2000 and December 2014. All patients fulfilled the 1980 American College of Rheumatology (ACR) classification criteria for systemic sclerosis.

Results: The 42 consecutively recruited patients of mixed ethnicities consisted of 37 (88.1%) females and 5 (11.9%) males. Of the total 42 patients, 22 (52.4%) had diffuse cutaneous systemic sclerosis (dcSSc) and 20 (47.6%) had limited cutaneous systemic sclerosis (lcSSc). Mean age at onset of first symptoms was 34.5 ± 12 years, and mean age at diagnosis was 36.1 ± 11.5 years. During follow-up, Raynaud's phenomenon occurred in 36 (85.7%) patients, sclerodactyly in 39 (92.9%) patients, digital ulcers in 16 (38.1%) patients, calcinosis in 6 (14.3%) patients, telangiectasia in 16 (38.1%) patients, and arthritis in 13 (31%) patients. The gastrointestinal and respiratory systems were the most frequently affected internal organs. Gastrointestinal involvement was present in 36 (85.7%) patients, and respiratory involvement was found in 30 (71.4%) patients. The majority of patients had positive antinuclear antibodies (ANA; 97.6%). Anti-Scl-70 antibody was found in 66.7% and anti-centromere antibody (ACA) was detected in 14.3% of the patients.

Conclusion: To our knowledge, this is the first study that describes the clinical and immunological profile of patients with systemic sclerosis living in Qatar. This study cohort showed an earlier age of disease onset

and diagnosis than that reported in other international studies. Furthermore, in contrast to several other studies, the diffuse type of scleroderma was more commonly observed than the limited type, which resulted in a high frequency of anti-Scl-70 antibody and interstitial lung disease.

Keywords: diffuse cutaneous systemic sclerosis, limited cutaneous systemic sclerosis, antinuclear antibodies, anti-Scl-70 antibody, anti-centromere antibody

INTRODUCTION

Systemic sclerosis (SSc; scleroderma) is a systemic autoimmune disease that affects different internal organs of the body along with skin involvement. There are three proposed underlying mechanisms that result in various clinical and pathological manifestations. These include vascular damage principally of microcirculation, immune system activation, and fibrosis.[1]

Clinical manifestations and prognosis of scleroderma (SSc) vary, with the majority of patients having skin thickening and variable involvement of internal organs.

The subsets of SSc can be distinguished as limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc), SSc sine scleroderma (SSc without skin involvement), and overlap syndromes in which features of systemic sclerosis coexist with other connective tissue diseases.[2–3]

Raynaud's phenomenon is a universal initial clinical presentation. It results from vasculopathy of the microcirculation of the hands and feet and can be associated with significant morbidity (e.g., digital ulcers and gangrene).[4–5] The lungs and the gastrointestinal (GI) tract are the most commonly involved internal organs in systemic sclerosis. Almost 90% of patients have some degree of GI involvement, and almost any part of the GI tract can be involved.[6]

Approximately 70% of patients can have pulmonary involvement manifesting as either pulmonary arterial hypertension (PAH) or interstitial lung disease (ILD).[7–8] Renal and cardiac involvements are generally life-threatening but are less common.[9–10]

Systemic sclerosis is associated with several autoantibodies, which have diagnostic and prognostic values. Anti-centromere antibody (ACA) often predict a limited skin involvement and development of PAH; the presence of anti-Scl-70 antibodies increases the risk of diffuse skin involvement and pulmonary fibrosis. Anti–RNA polymerase III antibody is commonly associated with scleroderma renal crisis.[11–13]

Currently, there are no published data regarding the characteristics of patients with systemic sclerosis who live in Qatar. To our knowledge, this is the first study to address this topic.

This study was designed to explore the disease characteristics, the different clinical manifestations, and the autoimmune profile of patients with scleroderma who presented to the Rheumatology Outpatient Clinics of Hamad General Hospital, Doha, Qatar.

PATIENTS AND METHOD

Patient characteristics

This retrospective study included 42 patients with systemic sclerosis who attended the Rheumatology Clinics at Hamad General Hospital in Doha, Qatar, between January 2000 and December 2014. Hamad General Hospital is the only governmental tertiary hospital that receives >90% of outpatient rheumatology referrals. A small number of patients are seen at one of the secondary hospitals which were not included in this study. All patients fulfilled the 1980 American College of Rheumatology (ACR) classification criteria for systemic sclerosis.

Medical records of the patients were reviewed for the following data: date of birth, sex, race, age at onset of first symptoms, date of diagnosis, and duration of disease. This study was approved by the ethical committee of Hamad General Hospital.

Clinical and serological manifestations

The data also included clinical manifestations at presentation and during follow-up, pattern of internal organ involvement, findings on imaging and pulmonary function tests, results of echocardiography, and types of treatment received. All data regarding the different clinical manifestations were collected from patients' charts, which were recorded by the treating rheumatologist from the first encounter till the last with the patients. Gastroesophageal reflux disease (GERD) was diagnosed clinically by the treating rheumatologist based on symptoms of reflux and retrosternal burning requiring antacid therapy. PAH was diagnosed on the basis of the results of transthoracic echocardiography right

ventricular systolic pressure (RVSP) of >35 mm Hg at rest, as the majority of patients did not undergo cardiac catheterization.

The presence of the following autoantibodies was recorded: antinuclear antibodies (ANA), anti-Scl-70 antibodies, ACA, anti-SSA (Ro) antibodies, anti-SSB (La) antibodies, anti-RNP antibodies, and anti-double-stranded DNA (dsDNA) antibodies. ANA were detected through immunofluorescence.

Statistical analysis

Categorical and continuous values were expressed as frequency (proportions/percentage) and mean ± SD or median and range as appropriate. Descriptive statistics were used to summarize the demographic characteristics, disease subtypes and initial manifestations, laboratory parameters, clinical characteristics, and serological manifestations of the patients. The association between two or more qualitative variables (various clinical and laboratory features with systemic sclerosis subtypes dcSSc and lcSSc) was compared using the chi-square test or Fisher's exact test as appropriate. Quantitative data between the two independent groups (dcSSc and lcSSc) were analyzed and compared using an unpaired *t*-test and the Mann–Whitney U test as appropriate. All *p* values were presented as two-tailed, with values <0.05 being considered as statistically significant. All statistical analyses were conducted using the statistical package SPSS 22 (SPSS Inc. Chicago, IL).

RESULTS

Demographic characteristics and clinical subsets

A total of 42 patients of mixed ethnicities included in this study consisted of 37 (88.1%) females and 5 (11.9%) males. There were 22 Arabs (52.4%) and 20 non Arab (47.6%) patients. Mean age at onset of first symptoms was 34.5 ± 12 years, and mean age at diagnosis was 36.1 ± 11.5 years.

A total of 22 (52.4%) patients had dcSSc, and 20 (47.6%) patients had lcSSc (Table 1).

Clinical manifestations during follow-up

Raynaud's phenomenon occurred in 36 (85.7%) patients, sclerodactyly in 39 (92.9%) patients, digital ulcers in 16 (38.1%) patients, calcinosis in 6 (14.3%) patients, telangiectasia in 16 (38.1%) patients, and arthritis in 13 (31%) patients.

The most frequently affected internal organs were the GI and respiratory tracts. GI involvement was present

Table 1. Demographic characteristics, disease subtypes, and initial manifestations.

	Mean ± SD [median (min–max)] n (%)
Age at onset of symptoms (years)	34.5 ± 12.03 [32 (16–67)]
Age at diagnosis (years)	36.1 ± 11.5 [34.5 (16–67)]
Gender	
Male	5 (11.9%)
Female	37 (88.1%)
Ethnicity	
Arabs	22 (52.4%)
NonArabs	20 (47.6%)
Subtype	
dcSSc	22 (52.4%)
LcSSc	20 (47.6%)
Initial manifestations and manifestation at first encounter with rheumatologist	
Raynaud's phenomenon*	33 (78.6%)*
Sclerodactyly*	25 (59.5%)*
Polyarthralgia/polyarthritis**	11 (26.2%)**
GERD**	02 (4.8%)**
ILD**	06 (14.3%)**
PAH**	01 (2.4%)**

*Initial symptoms to start with.
**Present at the time of first encounter with the rheumatologist in our hospital.

in 36 (85.7%) patients, and respiratory involvement was observed in 30 (71.4%) patients. GERD, the most common GI manifestation, was present in 32 (76.2%) patients; dysphagia in 8 (19%) patients, distal esophageal dilatation in 13 (31%) patients, constipation in 4 (9.5%) patients, and malabsorption was detected in 1 (2.4%) patient.

Respiratory manifestations included ILD in 26 (61.9%) patients and PAH in 12 (28.6%) patients. Of the 12 patients with PAH, eight had concurrent ILD, whereas only four patients had isolated PAH. High-resolution computed tomography (HRCT) of the chest showed abnormal findings in 64.1% (30.8% ground-glass appearance and 33.3% honeycombing) patients. Restrictive defect on pulmonary function tests was observed in 63% of patients.

Cardiac and renal crises were each present in only three (7.1%) patients. Cardiac manifestations included pericardial effusion, which was present in all the three patients, whereas only one patient had cardiomyopathy with congestive heart failure.

Eleven (26.2%) patients were lost to follow-up, three (7.1%) patients died during follow-up (one patient died due to heart failure secondary to scleroderma, one died due to septicemia and cardiorespiratory failure with a background history of severe pulmonary hypertension due to scleroderma, and one patient died due to road traffic accident unrelated to scleroderma).

Only six (14.3%) patients had ILD on initial encounter with the rheumatologist, whereas 26 (61.9%) patients were found suffering from ILD during follow-up. The mean follow-up duration was 4.8 ± 4.9 years. Of the 26 patients, nine (21.4%) showed progression of ILD during the follow-up, which was manifested by radiological progression (assessed by HRCT) and increasing breathing difficulty.

Serological tests

The majority of patients had positive ANA (97.6%). Anti-Scl-70 antibodies were found in 66.7%, ACA in 14.3%, anti-SSA (Ro) antibodies in 16.7%, and anti-SSB (La) antibodies, anti-dsDNA antibodies, and anti-RNP antibodies were each detected in 7.1% of patients.

Type of pharmacologic treatment

A total of 26 (61.9%) patients received treatment for Raynaud's phenomenon and/or digital ulcers. Calcium channel blockers were used by 16 (38.1%), ACE-I/ARBs were used by five (11.9%), PDE-5 inhibitors (sildenafil) by five (11.9%), and endothelial receptor antagonists (bosentan) were used by two (4.8%) patients. Immunosuppressive and disease-modifying agents were prescribed for 26 (61.9%) patients. Some of the patients received more than one immunosuppressive agent during the course of their treatment. A total of 12 (28.6%) patients received methotrexate, 14 (33.3%) received mycophenolate mofetil, seven (16.7%) received cyclophosphamide, and two (4.8%) patients received rituximab. The indication for immunosuppressive treatment was ILD in 15 (35.7%) patients, skin thickening in 10 (23.8%) patients, and arthritis in four (9.5%) patients.

Characteristics based on subsets of scleroderma

GI and respiratory involvements were significantly more common in the dcSSc subgroup than in the lcSSc group [100% of patients in the dcSSc group versus 70% in the lcSSc group had GI involvement ($p = 0.007$) and 86.4% of patients in the dcSSc group versus 55% in the lcSSc group had respiratory involvement ($p = 0.025$)]. Other clinical manifestations in the dcSSc versus lcSSc subgroups were as follows: arthritis in 36.4% versus 25% and renal and cardiac involvements combined in 9.1% versus 5% of the patients, respectively.

ANA were positive in 100% of patients in the dcSSc group versus 95% in the lcSSc group. The frequency of anti-Scl-70 antibody was significantly higher among patients with dcSSc than among patients with lcSSc (86.4% versus 45%, $p = 0.005$), and that of ACA was significantly higher among patients with lcSSc than among patients with dcSSc (25% versus 4.5%, $p = 0.058$) (Table 2).

DISCUSSION

There is a paucity of data regarding the characteristics of patients with systemic sclerosis from the Middle East. To the best of our knowledge, this retrospective study is the first to evaluate the clinical and serological features of patients with systemic sclerosis living in Qatar. A potential limitation of this study is the inclusion of a heterogeneous group of patients from different ethnic backgrounds. However, this is a true representation of the general population living in Qatar.

Table 2. Clinical characteristics based on systemic sclerosis subtype.

Variable	dcSSc (n = 22)	lcSSc (n = 20)	*p* value
Gender			
Male	03 (13.6%)	02 (10%)	0.716
Female	19 (86.4%)	18 (90%)	
Ethnicity			
Arabs	12 (54.5%)	10 (50%)	0.768
Non Arabs	10 (45.5%)	10 (50%)	
Raynaud's phenomenon			
Yes	18 (81.8%)	18 (90.0%)	0.449
No	04 (18.2%)	02 (10.0%)	
Sclerodactyly			
Yes	21 (95.5%)	18 (90%)	0.598
No	01 (4.5%)	02 (10%)	
Digital ulcer			
Yes	09 (40.9%)	07 (35.0%)	0.694
No	13 (59.1%)	13 (65.0%)	
Polyarthralgia			
Yes	17 (77.3%)	11 (55.0%)	0.126
No	05 (22.7%)	09 (45.0%)	
Arthritis			
Yes	08 (36.4%)	05 (25.0%)	0.426
No	14 (63.6%)	15 (75.0%)	
Respiratory involvement			
Yes	19 (86.4%)	11 (55.0%)	0.025
No	03 (13.6%)	09 (45.0%)	
ILD			
Yes	17 (77.3%)	09 (45.0%)	0.031
No	05 (22.7%)	11 (55.0%)	
PHTN			
Yes	04 (18.2%)	08 (40.0%)	0.118
No	18 (81.8%)	12 (60.0%)	
GI (Gastrointestinal) involvement			
Yes	22 (100%)	14 (70.0%)	0.007
No	00 (00%)	06 (30.0%)	
Renal involvement			
Yes	02 (09.1%)	01 (05.0%)	0.607
No	20 (90.9%)	19 (95.0%)	
Cardiac involvement			
Yes	02 (09.1%)	01 (05.0%)	0.607
No	20 (90.9%)	19 (95.0%)	
ANA			
Yes	22 (100.0%)	19 (95.0%)	0.288
No	00 (000.0%)	01 (05.0%)	
Anti-Scl-70 antibody			
Yes	19 (86.4%)	09 (45%)	0.005
No	03 (13.6%)	11 (55%)	
Anti-centromere antibody			
Yes	01 (04.5%)	05 (25.0%)	0.058
No	21 (95.5%)	15 (75.0%)	

Systemic sclerosis is more commonly observed in females. Female predominance is observed in various regional and international cohorts of patients. The female-to-male ratio was 7.4:1 in our cohort, and other studies have also reported ratios of 9:1 in Iraqi and Malaysian cohorts, 4.3:1 in an Egyptian cohort, 6.7:1 in an Iranian cohort, 10:1 in an Indian cohort, and 7:1 in a Spanish cohort.[14–18]

Our study cohort exhibited an earlier age of disease onset than that reported in other Asian and European studies. In our study, the mean age at onset of first symptoms was 34.5 ± 12 years compared with 42.6 ± 13.4 years in a Malaysian study, 47 ± 0.7 years in a Japanese study, and 45.0 ± 15.2 years in a Spanish study.[18–20] Similarly, age at diagnosis was earlier in our study than in other Asian and European studies, which was 36.1 ± 11.5 years in our study compared with 51 ± 0.6 years in Japan and 51.2 ± 15.2 years in Spain.[19–20]

Systemic sclerosis is classified into limited and diffuse subtypes based primarily on the clinical picture and the autoantibody profile. The limited form is the most common subset reported in Asian, African, and European patients. The lcSSc subtype was reported in 81.3% of Egyptian patients, 70% of Iraqi patients, 71% of Malaysian patients, 66.7% of Japanese patients, and 61.8% of Spanish patients.[14,15,18–20] In contrast, the diffuse type was more commonly observed in our cohort comprising 52.4% of patients versus 47.6% of patients with the limited type. Anti-Scl-70 was the most frequent antibody present in our cohort, reflecting the high frequency of the diffuse type of scleroderma.

The most frequent initial manifestation of SSc in our cohort was Raynaud's phenomenon, which was observed in 78% of patients. This result was similar to that found in the Egyptian study, where 77% of patients had Raynaud's phenomenon as part of their initial presentation.[15] Similar results were obtained in the Spanish study, where 83.6% of patients with SSc presented initially with Raynaud's phenomenon.[20]

During the follow-up, Raynaud's phenomenon was found to be one of the commonest manifestations of the disease occurring in 85.7% of our patients. Such a high frequency of Raynaud's phenomenon has been similarly reported in other cohorts, e.g., in 97.3% of Egyptian patients, 95% of Iranian patients, and 76.5% of Indian patients.[15–17]

Involvement of the GI tract was observed in a significant proportion of our patients (85.7%). Symptoms of GI involvement were found in all our patients with dcSSc and 70% of patients with lcSSc. The Spanish study also reported comparable results, where 80% of patients with dcSSc and 69% of those with lcSSc had involvement of the GI tract.[20] Similarly, the Egyptian study reported symptoms of dysphagia and GERD in 68% and 38% of patients, respectively.

In this study, we found that 61.9% of patients had ILD, which was more commonly seen in patients with dcSSc (77%) than in patients with lcSSc (45%). This result is similar to that reported in the Egyptian and Spanish studies (78.6% versus 47.5% and 70% versus 39.3%, respectively).[15,20] On the other hand, the Iranian and Malaysian studies did not report any significant difference.[16,18]

Arthritis was reported in 36% of our patients with dcSSc and 25% of patients with lcSSc. This was in contrast to the result reported by the Malaysian study, where 55.5% of patients with dcSSc and 72.7% of patients with lcSSc had joint involvement.[18]

The present study demonstrates a high prevalence of ANA positivity in patients with SSc (97.6%), which is in accordance with several other studies. The prevalence of anti-Scl-70 antibody was also higher in our study cohort (66.7%) than in other Asian cohorts (32.3% in the Malaysian cohort and 23.5% in the Japanese cohort)[18–19] but lower than that in the Iranian cohort (71%).[16]

In our study, anti-Scl-70 antibody was more prevalent in patients with dcSSc than in those with lcSSc (86.4% versus 45%, $p = 0.005$) and was associated with the development of ILD. Several previous studies have also confirmed this association. Anti-Scl-70 antibody was found to be associated with ILD in the Iranian, Malaysian, and Japanese cohorts of systemic sclerosis.[16,18,19] Furthermore, data from a European study reported a similar association.[20]

CONCLUSION

This study has described the clinical and serological characteristics of patients with systemic sclerosis living in Qatar. Earlier age of disease onset and diagnosis was observed in this cohort compared with other international studies. The diffuse type of SSc was more commonly observed, which was also reflected on the autoantibody profile and the high

frequency of ILD. Our study has some limitations. It is a retrospective investigation with a small sample size and the data were collected from patients' medical records. Therefore, further prospective studies are needed to examine different systems involvement and their association with different antibodies in patients with scleroderma living in Qatar.

Disclosures

There is no conflict of interest for all authors.

Ethical approval

The study conforms to the 1995 Declaration of Helsinki and was approved by the ethical committee of Hamad General Hospital.

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