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Original Article

Cross-sectional study on clinical features and histopathology of systemic sclerosis

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ABSTRACT

Objectives: To study the cutaneous and systemic manifestations of systemic sclerosis (SSc) and correlate the severity of cutaneous disease with extent of fibrosis on histology.

Methods and Materials: Patients were evaluated for cutaneous and systemic manifestations of SSc. Cutaneous disease was assessed using modified Rodnan Skin Score (mRSS) with mRSS ≥14 indicating severe disease. Masson's trichrome stained skin biopsy specimens were graded semi-quantitatively according to severity and extent of dermal fibrosis. Subsequently, the clinicohistological correlation was assessed.

Results: Thirty-two patients were studied. Eighteen patients had diffuse cutaneous SSc while 14 had limited cutaneous SSc. Ten patients had mRSS <14 while 22 had mRSS ≥14 with a mean mRSS of 15.8. Gastrointestinal system was involved in 56.3%, respiratory system in 53.1%, musculoskeletal system in 31.3%, renal in 6.3%, and cardiovascular in 3.1%. Anti-centromere antibodies were positive in six patients and Anti-Scl-70 in 12. In the histopathological analysis of fibrosis, 40.6% of patients had moderate fibrosis while 59.4% had severe fibrosis. While patients with higher mRSS also had a higher grade of fibrosis histologically, the clinicohistological correlation was not found to be statistically significant.

Limitations: The prognostic significance of mRSS could not be assessed as this was a cross-sectional study.

Conclusion: The cutaneous and systemic involvement observed in this study was comparable to the findings in other studies. The changes observed in frequency of specific manifestations in different population groups point to the role of genetic and environmental factors in the disease process.

Keywords: Systemic sclerosis, Modified Rodnan skin score, Fibrosis

INTRODUCTION

Systemic sclerosis (SSc) is a rare disease of connective tissue with the potential to affect various organs in the body. Skin, often being the initial organ to develop significant changes due to the disease, the patient may be presenting for the first time to dermatologists. The disease process can cause dysregulation of normal functioning of body through pathogenic processes, leading to immune, vascular, and fibrotic disruptions. This study was aimed to assess the cutaneous and systemic manifestations and histopathological features of SSc and to correlate the severity of the cutaneous manifestations with the extent of histopathological change in the form of fibrosis.

METHODS

Thirty-two patients who attended the Department of Dermatology, Government Medical College, Kozhikode, from April 2011 to July 2012 and who fulfilled the American College of

Rheumatology classification criteria for SSc (1980) were included in the study after obtaining clearance from the institutional research and ethics committees and from individual study subject.

Exclusion criteria

Patients who were not willing for skin biopsy and patients who had features of overlap syndrome were excluded.

Data regarding history and clinical features were collected using a preset pro forma. The severity of cutaneous disease was assessed using the modified Rodnan skin score (mRSS). Skin thickness was assessed by palpation and rated on a scale of 0 (normal), 1 (weak), 2 (intermediate), or 3 (severe skin thickening). The total skin score was calculated as the sum of the individual skin assessments in the 17 body areas, giving a possible range of 0–51.[1] In accordance with the recommendations of European Scleroderma Study Group, a value of mRSS ≥14 was taken as indicator of severe cutaneous disease and patients were classified accordingly.[2] Patients manifesting interincisal distance of <35 mm when mouth opened, were considered to have restricted mouth opening.[3]

Investigations including complete hemogram with erythrocyte sedimentation rate (ESR), urine analysis, renal and hepatic function tests, blood sugar, serum electrolytes, chest X-ray, electrocardiogram, and pulmonary function test were carried out in all the cases. Specific investigations for systemic evaluation such as high-resolution computerized tomogram of thorax, echocardiography, and barium studies were done wherever indicated and antinuclear antibody (ANA) profile was done where feasible.

In all the cases, skin biopsy specimens were obtained from the dorsal aspect of middle phalanx of the 3rd or 4th finger of either hand in those with sclerodactyly and from the affected skin in those without sclerodactyly. Specimens were stained with hematoxylin-eosin and Masson's trichrome stains. The presence and distribution of sclerosis were assessed within the various layers of the dermis: Papillary dermis, superficial reticular dermis, median reticular dermis, and deep reticular dermis. Within each of these four dermal layers, the extent of fibrous thickening was assessed semi-quantitatively as followed:[4]

- 0 = No fibrosis
- + = Light fibrosis
- ++ = Moderate fibrosis
- +++ = Extensive fibrosis.

The severity of fibrosis was then graded as followed:

- Grade 1 = Weak fibrosis defined by the presence of no fibrosis in the papillary dermis and light fibrosis in the superficial reticular dermis or in the median reticular dermis or in the deep reticular dermis.
- Grade 2 = Moderate fibrosis defined by all the cases which do not belong to Grade 1 or 3.
- Grade 3 = Severe fibrosis defined by the presence of severe fibrosis in the deep reticular dermis and in the median reticular dermis irrespective of the degree in the superficial reticular dermis and in the papillary dermis; or severe fibrosis in the deep reticular dermis plus moderate fibrosis in the median and in the superficial reticular dermis as well as in the papillary dermis.

Data was entered in Microsoft Excel and the correlation between the clinical and histological grades was compared using Pearson's Chi-square analysis. $P < 0.05$ was considered statistically significant.

RESULTS

The study group comprised 31 females and one male patient with a male-to-female ratio of 0.03:1. The age of the patients ranged from 5 to 62 years with a mean of 41.3 years. Maximum number of patients belonged to the age group of 41–50 years (11, 34.4%) followed by 31–40 years age (7, 21.9%).

The youngest was a 5-year-old boy with extensive cutaneous involvement and myopathy that was diagnosed by electromyography and muscle biopsy. Detailed work-up failed to reveal any other cause for the myopathy and the ANA profile tested positive only for anti-Scl-70 antibodies.

Maximum number of patients were homemakers (25, 78.1%). None of them were occupationally exposed to physical or chemical agents implicated to cause scleroderma.

The duration of illness ranged from 2 months to 15 years with an average of 3.3 years in the study group. Majority (13 patients, 40.6%) had a disease duration of 2–5 years.

The initial symptom was thickening and tightening of skin in 13 (40.6%) patients while in 7 others (21.9%) the disease began with Raynaud's phenomenon. Initial presentation was generalized edema and pigmentary changes in 4 patients (12.5%) each. In the remaining 4 cases (12.5%), systemic involvement preceded the skin disease.

Three patients gave a history of pulmonary tuberculosis in the past while two each had diabetes mellitus, migraine, and interstitial lung disease. One patient was detected to have carcinoma of the cervix. In the above-mentioned patient, the onset of scleroderma preceded the detection of malignancy by 5 years. The malignancy being inoperable was managed with chemotherapy and radiotherapy, which had no impact on the severity or progression of scleroderma.

None of the patients had a family history of SSc or any other connective tissue disease.

Eleven (34.4%) patients had loss of appetite while 12 (37.5%) cases documented loss of weight after the onset of disease. Eight patients (25%) complained of disturbed sleep.

Eight patients (25%) had menstrual irregularities in the form of oligomenorrhea and hypomenorrhea.

Among the nine patients who attained menopause, three had menopause before the age of 40 years and one was the patient who suffered from carcinoma cervix and received chemotherapy and radiotherapy. Sixteen patients (50%) were on disease-modifying drugs when included in the study.

Pallor was noted in 8 (25%) patients while 3 (9.4%) had clubbing of the fingernails. Two of the three patients (66.7%) with clubbing had pulmonary involvement.

Dermatological manifestations in the study group are depicted in Table 1.

Figures 1 and 2 show the skin changes in the face and hands respectively.

Table 1: Dermatological manifestations in the study group.

Dermatological manifestation	No of patients showing the manifestation (%) of the total
Thickening of facial skin	26 (81.3)
Reduced/absent skin creases over the forehead	22 (68.8)
Difficulty in retraction of the lower eyelid	18 (56.3)
Masklike expressionless face	13 (40.6)
Beaked nose	8 (25)
Pursed appearance of the mouth with reduced mouth opening	13 (40.6)
Sclerodactyly	30 (93.8)
Raynaud's phenomenon	18 (56.2)
Digital pitted scars	
Fingers	21 (65.6)
Toes	10 (31.3)
Active ulcers	
Fingertips	8 (25)
Toe tips	5 (15.6)
Ankle	1 (3.1)
Telangiectasia	
Face	21 (65.6)
Finger nail folds	22 (68.8)
Chest and thigh	5 (15.6)
Pigmentary abnormalities	
Salt and pepper pigmentation	18 (56.3)
Diffuse hyperpigmentation	10 (31.3)
Focal hyperpigmentation	6 (18.8)
Diffuse hyperpigmentation of the buccal and gingival mucosa	5 (15.6)
Calcinosis cutis	2 (6.3)
Calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia (CREST syndrome)	1 (3.1)

Of the 32 patients, 18 (56.2%) had diffuse cutaneous SSc while 14 (43.8%) had limited cutaneous form.

mRSS

The mRSS varied from 2 to 24 with a mean of 15.8. Ten (31.3%) patients had a score <14 while 22 (68.8%) had a score ≥14 indicating severe disease.

The distribution of skin sclerosis among study group is showed in Table 2.

The most common system involved in the present study was the gastrointestinal system in 18 (56.3%), followed by pulmonary (17, 53.1%), musculoskeletal (10, 31.3%), renal (2, 6.3%), and cardiovascular (one patient, 3.1%) systems. The range of systemic involvement in the study group is summarized in Table 3.

Sclerosis of trunk was noted in 11 cases (34.4%) and these patients had a higher rate of pulmonary involvement (6/11, 54.5%) when compared to those without involvement of trunk (7/21, 33.3%); however, this was found to be statistically not significant. The extent of sclerosis was not associated with involvement of other systems.

The abnormalities observed in other investigations were anemia (17, 53.1%), leukocytosis (5, 15.6%), and ESR above 30 mm/h (16, 50%).

ANA profile was done in 24 patients, of which 7 were limited and 17 were diffuse cutaneous SSc. Six patients (25% of the tested) were positive for anti-centromere antibodies (ACA), while 50% of the tested (12 cases) were positive for anti-

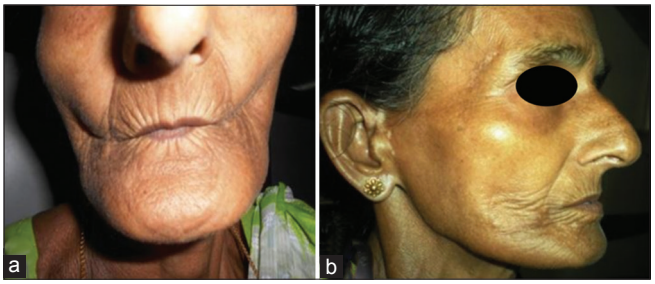

Figure 1: Scleroderma facies (a) radial furrowing around the mouth with pursed mouth appearance; (b) taut skin and beaked nose.

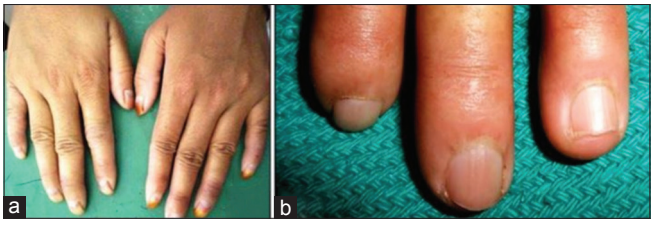

Figure 2: (a) Sclerodactyly tightening of skin with tapering of finger tips and pseudoclubbing (b) nail fold capillary loop enlargement and telangiectasias.

Scl-70 antibodies. Negative serology on ANA profile was obtained in the remaining six that constituted 25% of the tested. Among those tested positive for anti-centromere or anti-Scl-70 antibodies some showed positivity for other antibodies such as anti-Sm (3, 12.5%), anti-Ro-52 (2, 8.3%) and anti-mitochondrial, anti-SS-A, and ribosomal P protein (1 each, 4.2%).

Table 2: Skin sclerosis over different body sites in the study group according to modified Rodnan skin scale.

Site	Grade 0	Grade 1	Grade 2	Grade 3
Face	7	17	7	1
Anterior chest	22	10	0	0
Anterior abdomen	29	3	0	0
Right upper arm	22	9	1	0
Left upper arm	21	10	1	0
Right forearm	6	19	7	0
Left forearm	6	20	6	0
Right hand dorsum	3	16	13	0
Left hand dorsum	3	16	13	0
Right fingers	0	9	13	10
Left fingers	0	9	13	10
Right thigh	23	7	2	0
Left thigh	23	7	2	0
Right lower leg	15	14	3	0
Left lower leg	15	14	3	0
Right foot	8	21	3	0
Left foot	8	21	3	0

Among the seven limited cutaneous SSc patients whose ANA profile results were available, ACA were present in 28.6% (2/7), whereas 23.5% (4/17) of tested diffuse cutaneous cases showed positivity for the same. Anti-Scl-70 was present in 58.8% (10/17) of diffuse cutaneous and 28.6% (2/7) of limited cutaneous forms.

Among the six ACA positive cases, 4 each (66.7%) had pulmonary and gastrointestinal tract (GIT) involvement, respectively, whereas among the 12 Scl-70 positive cases, 5 (41.7%) had pulmonary involvement and 8 (66.7%) had GIT involvement.

Histopathological findings in the skin biopsies included thinning of epidermis with reduced appendages, lymphocytic inflammatory infiltrate, and homogenization of collagen bundles [Figure 3]. According to the semi-quantitative analysis of fibrosis (as mentioned in materials and methods), 40.6% (13/32) of patients had Grade 2 (moderate) fibrosis while 59.4% (19/32) had Grade 3 (severe) fibrosis [Figure 4].

Table 3: Systemic involvement in the study group.

Organ system affected	Symptom pertaining to the system		Abnormality detected in laboratory evaluation	
	Symptom	Number of patients (%) of total	Investigation	Number of patients (%) of total
Gastrointestinal system	Dysphagia	18 (56.3)	Barium swallow – delayed emptying and/or motility disorder	4 (12.5)
	Gastroesophageal reflux	16 (50)	Esophago-gastro-duodenoscopy – Hiatus hernia	1 (3.1)
Pulmonary system	Dyspnea	17 (53.1)	Chest X-ray – Reticular/reticulonodular shadows in the lower zone	12 (37.5)
	*Grade 1 dyspnea	12 (37.5)		
	*Grade 2 dyspnea	5 (15.6)		
	Cough	3 (9.4)	Pulmonary function test – Mild-to-moderate restrictive pattern	11 (34.4)
	Tachypnea or cyanosis	0 (0)		
	Crepitations in lower zone	11 (34.4)	High-resolution ultrasonogram –Reticulations, tiny cystic spaces representing honey combing, and patchy ground glass opacities suggestive of interstitial lung disease	11 (34.4)
	Restricted chest expansion	15 (46.9)		
Cardiovascular system	Palpitation	11 (34.4)	Echocardiography – Mild pulmonary artery hypertension	1 (3.1)
Renal system		0 (0)	Albuminuria and elevated 24 h urine protein	2 (6.3)
Musculoskeletal system	Proximal muscle weakness	3 (9.4)	Elevated serum lactate dehydrogenase indicating Myositis	1 (3.1)
	Arthralgia	6 (18.8)		
	Resorption/shortening of phalanges	4 (12.5)		
	Contractures of interphalangeal joints	5 (15.6)		

*Grade 1 dyspnea – dyspnea on unaccustomed work, Grade 2 dyspnea – dyspnea on accustomed work

The clinicohistological correlation was analyzed by a comparison of mRSS with the histological grade of fibrosis. Six out of the ten (60%) patients with a clinically mild cutaneous disease (as defined by mRSS <14) had moderate/Grade 2 fibrosis histologically, while 4 (40%) had severe fibrosis. On the other hand, 15/22 (68.2%) patients with clinically severe cutaneous disease (mRSS >14) had severe fibrosis histologically and 7 (31.2%) had moderate fibrosis. However, this association between severity of cutaneous disease determined by mRSS with severity of histological fibrosis was not found to be statistically significant.

DISCUSSION

The female predilection observed by us was as reported by others.[5,6] Mean age of the affected in our study was higher than that documented in one North Indian study.[5] Two patients below 20 years of age and one of them being the single male patient in the study group as noted by us was consistent with one previous study but discordant to the findings of Medsger and Masi who observed all male patients to be above 25 years.[5,7] The lack of any occupational triggering factors as documented by us indicates the multifactorial etiology of the disease. The mean disease duration as recorded in this study was comparable to literature; however, certain studies have documented longer disease duration as well.[5,8] Initial symptoms of diseases in study subjects were comparable to existing data.[5,9-12] Sclerosis of skin in 93% of the study group was slightly lower than 96%–100% frequency documented in certain studies, but higher than observed frequency among Caucasians, Hispanics, and African Americans.[5,9-12] Raynaud's phenomenon manifested by only 56.2% of the study group was lower than the observation of many previous studies but was higher than the 28% noted in another South Indian study where the authors have attributed it to the relatively warm climate experienced throughout the year in the Southern parts of the country.[5,9-12] This could explain the lower frequency of Raynaud's phenomenon in our cohort too. Low frequency of active fingertip ulceration recorded in our patients (5% in our patients against 47%–82% noted in other studies) could be attributed to the warmer climate in the state and also to the lack of exposure to triggering factors.[5,9-12]

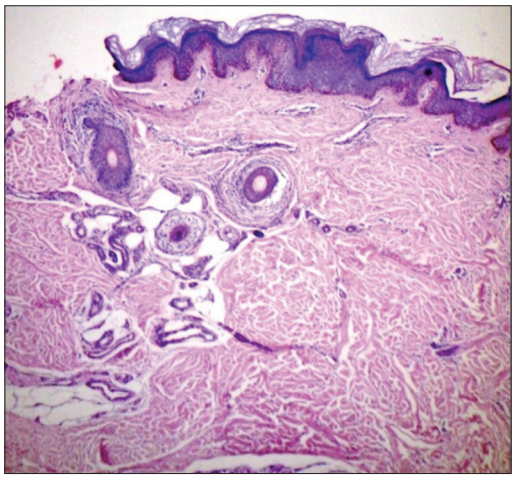

Figure 3: Skin biopsy specimen of systemic sclerosis showing thickened, edematous bundles of collagen in the reticular dermis with pulled up appendages (H & E, x100).

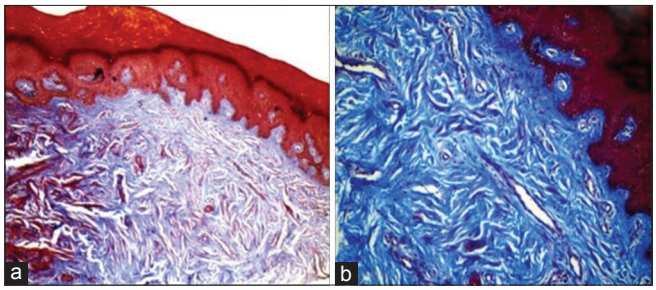

Figure 4: Skin biopsy specimen of systemic sclerosis patient showing (a) Grade 2 fibrosis - moderate fibrosis in deep reticular dermis (Masson's trichrome, x100) (b) Grade 3 fibrosis - severe fibrosis throughout the dermis (Masson's trichrome, x100).

Pigmentary abnormalities documented in our cases fell between 36.3%–91% noted in the previous studies.[5,9-12] Salt and pepper pigmentation noted as the most common pigmentary abnormality by us (18/32, 56.3%) was discordant to the observation of Sharma *et al.*, who reported diffuse pigmentations as the most common pigmentary abnormality (88.1%).[5]

Most common site of telangiectasia being the periungual area as noted by us was comparable to previous data; however, our observation of the same in nearly 70% of the study subjects was higher than that reported in literature (9.5%–58%).[5,9-12]

Mean Rodnan skin score in this study was comparable to many previous studies, but a higher mean score was reported by Sharma *et al.*[5,12] Higher mean Rodnan skin score in Sharma *et al.*'s study could be a reflection of most of their study population having a longer disease duration (6.75 years) than that documented in our cases (3.3 years).[5]

Frequency of GIT and pulmonary involvement (based on clinical symptoms) in our study population was consistent with certain studies but was higher than the reported frequency in some other studies.[5,9,10,12] GIT being the predominant system involved by us was contrary to the data of one North Indian study.[5]

The frequency and pattern of renal involvement recorded in the study was concordant to existing Indian data but lower than the western literature.[5,9,11] This once again highlights the racial variations observed in disease pattern of SSc.

The percentage of patients affected by arthritis in the current study was lower than that in a study from Ukraine.[6] Documented frequency of calcinosis cutis (6.3%) in the study was also lower than that recorded previously (25%).[13]

Chest X-ray abnormalities detected in the study group were consistent with most other studies; however, one study had documented greater percentage of patients manifesting the former.[5,8,9,11] Percentage of patients detected to have barium swallow and pulmonary function test abnormalities in this study was lower than the reported frequency in most other studies.[5,8,9,11] Higher percentage of patients manifesting GIT symptoms, despite normal investigation results in our study could be due to the habit of intake of spicy food which is prevalent in the state. Similarly, the presence of pulmonary system involvement in greater number of patients than those diagnosed to have pulmonary involvement after evaluation could be due to the restricted chest expansion due to the sclerosis of skin of the chest among the affected. Although not statistically significant, the association observed between the sclerosis of trunk and pulmonary symptoms in our study subjects supports this argument.

Although not significant statistically, the association noted between clinical and histological severity of skin sclerosis by us was comparable to existing literature.[14]

Limitations

Being a cross-sectional study, we could not assess disease progression or to identify predictors of bad prognosis. Moreover, the current study does not add to data on response to treatment.

Despite these limitations, we were able to study the clinical profile of scleroderma in this part of the country and we agree with the observation of previous authors that clinical profile of scleroderma is similar in different population groups; however, the frequency of individual clinical feature shows variations among different population groups which could be due to the interplay of genetic and environmental factors.[14]

CONCLUSION

The cutaneous and systemic involvement observed in this study was comparable to the findings in other studies. The changes observed in frequency of specific manifestations in different population groups point to the role of genetic and environmental factors in the disease process.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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