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Concise report

Systemic sclerosis sine scleroderma: distinct features in a large Brazilian cohort

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Abstract

Objective. Systemic sclerosis sine scleroderma (ssSSc) is an infrequent SSc variant characterized by visceral and immunological manifestations of SSc in the absence of clinically detectable skin involvement. We sought to delineate the characteristics of ssSSc in a cohort of Brazilian patients and contrast them with those in the literature.

Methods. SSc patients seen at two academic medical centres in Brazil were retrospectively analysed. Patients were classified as ssSSc if they presented with RP, positive ANAs and at least one visceral involvement typical of SSc in the absence of skin thickening. Demographics, clinical and laboratory data were obtained by chart review. Literature review was performed by searching available original studies up until June 2012.

Results. Among the 947 consecutive patients with SSc, 79 (8.3%) were classified as ssSSc. Oesophagus was the most frequently affected organ (83.1%), followed by pulmonary involvement (63.2%). Compared with the limited cutaneous form of SSc, telangiectasia was the only variable significantly different after multivariate logistic regression analyses (odds ratio 0.46; 95% CI 0.27, 0.81). Compared with the diffuse cutaneous form of SSc, multivariate analyses revealed that ssSSc patients were less likely to be male (odds ratio 0.15; 95% CI 0.04, 0.57), have digital ulcers (odds ratio 0.26; 95% CI 0.13, 0.51) or anti-Scl70 antibodies (odds ratio 0.19; 95% CI 0.07, 0.55) and less frequently treated with CYC (odds ratio 0.23; 95% CI 0.12, 0.43). These features were comparable to those in the published literature.

Conclusion. In this series, patients with ssSSc had a relatively mild disease with good prognosis.

Key words: systemic sclerosis sine scleroderma, epidemiology.

CLINICAL SCIENCE

Introduction

SSc is an uncommon multisystem disease. Autoimmune damage, vasculopathy and extensive fibrosis are considered to be the key etiopathogenic factors [1]. Clinically, there is a broad spectrum of disease manifestations, progression and prognosis. Patients have variable degrees of skin thickening, ranging from involvement limited to the distal extremities and/or face to widespread severe involvement [2]. Systemic sclerosis sine scleroderma (ssSSc) was first described in 1962 by Rodnan and Fennel [3]. ssSSc is defined by specific organ involvement in the absence of skin thickening. There are scarce data for ssSSc in the literature. Poormoghim *et al.* [4] described 48 North American patients from the Pittsburgh scleroderma databank. The German nationwide register described another series with 22 patients [5] and very recently the Spanish registry reported 69 patients [6], giving a total of 139 cases of ssSSc in the literature excluding isolated case reports.

The present report describes a series of 79 consecutive ssSSc patients from two Brazilian cohorts. We compare their characteristics with other SSc subtypes. In addition, this ssSSc population is compared with previous series described in the literature.

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Methods

Study subjects

The authors retrospectively studied the medical records of all SSc patients seen at the Scleroderma Outpatient Clinic at two academic medical centres in Brazil between 2000 and 2010. Follow-up information was collected by chart review or telephone, after approval of the institutional ethics committee (Institutional Ethics Committee of University of São Paulo and University of Campinas). All SSc patients fulfilled the criteria proposed by LeRoy and Medsger [7]. Based on the skin involvement, patients were classified as limited cutaneous subtype (lcSSc; skin involvement distal to the elbows and knees and also affecting face) and diffuse cutaneous subtype (dcSSc; skin involvement affecting upper and lower limbs, face, chest and abdomen) [7]. The diagnosis of ssSSc was based on the criteria proposed by Poormoghim *et al.* [4]: absent skin thickening on physical examination, RP or a peripheral vascular equivalent (digital pitting scars, digital tip ulcers, digital tip gangrene and abnormal nailfold capillaries), positive ANAs, one visceral organ involvement typical of SSc (any one of the following: distal oesophageal hypomotility, small bowel hypomotility, pulmonary interstitial fibrosis, pulmonary hypertension, cardiac involvement typical of scleroderma or renal failure consistent with scleroderma renal crisis) and absence of another defined connective tissue or other disease as a cause of signs and symptoms cited above.

Regarding ethnicity, patients were considered to be of European ancestry and African Brazilian. The African-Brazilian group included mullatos/mestizos, i.e. originating from a mixture of white and black individuals, and black patients of unmixed ancestry.

Definition of SSc organ involvement

The following definitions were used for visceral involvement: (i) vascular disease: objective history of RP with or without ischaemic digital ulcerations; (ii) nailfold capillaroscopy: scleroderma pattern, as described by Cutolo *et al.* [8]; (iii) articular involvement: either swelling of $\geqslant 1$ joints or tenosynovitis, including palpable tendon friction rubs; (iv) muscle involvement: proximal muscle weakness on physical examination and elevation of muscle enzymes and/or electrophysiological characteristics of inflammatory myositis and/or muscle biopsy; (v) gastro-oesophageal involvement: distal oesophageal hypomotility or aperistalsis (documented by either radiographic or manometric study); (vi) intestinal involvement: diarrhoea and/or faecal incontinence; (vii) interstitial lung disease (ILD): presence of pulmonary interstitial pattern evidenced by chest radiograph or thoracic high-resolution CT (HRCT) and/or restrictive pulmonary functions with forced vital capacity (FVC) $<80\%$ of predicted; (viii) pulmonary hypertension (PH): defined by systolic arterial pulmonary pressure >40 mmHg on Doppler echocardiogram and/or right heart catheterization (mean pulmonary artery pressure at rest $\geqslant 25$ mmHg); (ix) heart involvement: pericarditis, valvular disease and/or myocardial dysfunction on Doppler echocardiogram; (x) peripheral neuropathy: sensory and/or motor neuropathy diagnosed by electromyography; (xi) kidney involvement: rapidly progressive renal failure with abrupt onset of moderate to marked hypertension; (xii) immunological features: ANAs identified by indirect immunofluorescence assays using Hep-2 cell lines and anti-Scl-70 determined by immunoblotting technique.

Statistical analysis

The data were analysed using Microsoft Office Excel 2003 and SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL, USA). Statistical evaluation was performed using contingency table and association tests (χ^2 test or Fisher's exact test) to describe significant associations. Bivariate analysis was performed for comparison of SSc subtypes as well as other studies involving ssSSc registries; χ^2 test was used for verification of associations and *t*-test to compare means of age. We also performed a multivariate statistical analysis by using a logistic regression model.

Results

ssSSc characteristics

Of 947 patients with SSc included in the study, 79 (8.3%) were classified as having ssSSc. Among these 79 patients, 96.2% were female and 75.9% were from European ancestry, with a mean age at disease onset of 46 ± 13.1 years. The mean follow-up was 4.3 ± 3.5 years (Table 1). The mean delay in diagnosis (since the occurrence of RP) was 3.66 ± 4.9 years. ssSSc patients were most often referred from Gastroenterology due to oesophageal hypomotility (33.9%), followed by Internal Medicine (17.8%) for arthralgias, myalgias and RP, Pulmonary Medicine (17.8%) for pulmonary fibrosis and PH, and Vascular Surgery (12.5%) due to digital ulcers and RP.

Despite the absence of skin thickening, skin manifestations were observed. These included telangiectasia (29.1%), ischaemic digital ulcers (24.1%) and calcinosis cutis (7.6%). Oesophageal involvement was most frequent (83.1%), followed by ILD (56.9%) and PH (22.8%). Thirteen patients had ILD plus PH, and five presented with isolated PH. Heart manifestations were present in 11.3%, including five (6.32%) with symptomatic pericarditis and four (5.06%) with diastolic dysfunction. Scleroderma renal crisis occurred in two patients (2.5%) who required dialysis (Table 1).

The laboratory study showed positive ANA in all ssSSc patients. Anticentromere antibodies (ACAs) were positive in 42.3% of patients, while anti-Scl-70 was positive in only 7.9% ($P < 0.05$) (Table 1). Of the six patients with positive tests for anti-Scl-70 antibody, five had concomitant ILD.

ssSSc compared with the other SSc cutaneous subtypes

Compared with the limited cutaneous SSc subtype, ssSSc had significantly lower frequency of calcinosis cutis, ischaemic digital ulcers and telangiectasia.

Table 1 Demographic and clinic parameters of patients with ssSSc and other subtypes of SSc

Variables	ssSSc ($n = 79$)	lcSSc ($n = 533$)	*P*-value	dcSSc ($n = 294$)	*P*-value
Age at disease onset, mean (S.D.), years	46.1 (13.1)	44.7 (13.8)	0.422	39.1 (14.2)	<0.001*
Gender: women	76/79 (96.2)	482/533 (90.4)	0.091	240/294 (81.6)	0.001*
Ethnicity			0.051		0.225
European ancestry	60/79 (75.9)	427/533 (80.1)		195/294 (66.3)	
African-Brazilian	18/79 (22.8)	98/533 (18.4)		89/294 (30.3)	
Other	1/79 (1.3)	8/533 (1.5)		10/294 (3.4)	
Follow-up period, mean (S.D.), years	4.3 (3.5)	11.1 (8.5)	<0.001*	8.1 (5.8)	<0.001*
Digital ulcers	19/79 (24.1)	204/533 (38.3)	0.014*	155/294 (52.7)	<0.001*
Scleroderma capillaroscopy pattern	24/32 (75)	53/59 (89.8)	0.074	26/27 (96.3)	0.031*
Telangiectasia	23/79 (29.1)	305/533 (57.2)	<0.001*	120/294 (40.8)	0.058
Calcinosis cutis	6/79 (7.6)	116/533 (21.8)	0.003*	36/294 (12.2)	0.246
Oesophageal hypomotility	64/77 (83.1)	390/501 (77.8)	0.294	231/281 (82.2)	0.853
ILD	37/65 (56.9)	221/438 (50.5)	0.330	168/250 (67.2)	0.122
FVC < 80% of predicted	20/63 (31.7)	174/434 (40.1)	0.204	139/226 (61.5)	<0.001*
DL_{co} < 80% of predicted	9/15 (60)	72/118 (61.0)	0.939	49/69 (71.0)	0.538
PH	18/79 (22.8)	132/524 (25.2)	0.981	64/283 (22.6)	0.615
Peripheral neuropathy	4/79 (5.1)	35/533 (6.6)	0.610	21/294 (7.1)	0.512
Arthritis	35/79 (44.3)	244/533 (45.8)	0.806	146/294 (49.7)	0.398
Myositis	10/79 (12.7)	45/533 (8.4)	0.221	50/294 (17.0)	0.350
SRC	2/79 (2.5)	5/533 (0.9)	0.225	16/294 (5.4)	0.384
ACA	33/79 (42.3)	141/461 (30.6)	0.041*	11/270 (4.1)	<0.001*
Anti-Scl-70 antibody	6/76 (7.9)	57/501 (11.4)	0.364	88/268 (32.8)	<0.001*
CYC therapy	24/79 (30.4)	200/533 (37.5)	0.219	209/294 (71.1)	<0.001*

Except where indicated otherwise, values are the number of subjects/total (%). DL_{co}: diffusing capacity for carbon monoxide; SRC: scleroderma renal crisis. **P*-values are statistically significant.

Both subtypes showed similar visceral involvement. ssSSc was associated to a significantly higher frequency of ACAs. Multivariate logistic regression analysis indicated that, after controlling gender, age at diagnosis and time of follow-up factors, only telangiectasia (OR 0.46; 95% CI 0.27, 0.81; $P = 0.006$) differentiated ssSSc from limited SSc.

When comparing ssSSc with the diffuse cutaneous subtype, ssSSc presented significantly lower frequencies of male gender, ischaemic digital ulcers, diarrhoea, altered FVC at the pulmonary function test, scleroderma-pattern capillaroscopy, anti-Scl-70 and use of cyclophosphamide (CYC), while it was associated with higher frequencies of positive ANA and ACAs. Multivariate logistic regression, after correcting for age at diagnosis and time of follow-up, revealed that male gender (OR 0.15; 95% CI 0.04, 0.57; $P = 0.005$), ischaemic digital ulcers (OR 0.26; 95% CI 0.13, 0.51; $P < 0.001$), use of CYC (OR 0.23; 95% CI 0.12, 0.43; $P < 0.001$) and anti-Scl-70 (OR 0.19; 95% CI 0.07, 0.55; $P = 0.002$) differentiated ssSSc from diffuse SSc.

Brazilian ssSSc patients compared with published ssSSc series

To compare the characteristics of ssSSc among different populations, we compared our data with published series in the literature [3, 5, 6]. Compared with the Pittsburgh series, we observed a higher frequency of female gender, and despite similar clinical and laboratory characteristics, a significantly lower mortality rate. Patients in the German SSc registry showed similar demographic, clinical and laboratory features compared with the patients in the Brazilian series. The comparison with the Spanish SSc registry revealed further differences, showing a higher frequency of oesophageal, articular and muscular involvement in our population (Table 2).

Discussion

Although ssSSc was described in 1962 [3], for 40 years the literature consisted of case reports [9]. In 2000, Poormoghim *et al.* [4] described the first ssSSc series (9%), and recently the German [5] and Spanish [6] SSc registries described their ssSSc population (1.5% and 7.5%, respectively). The true prevalence of ssSSc is likely to be underestimated in these studies due to the difficulty in its diagnosis by the absence of skin thickness, the characteristic hallmark of the SSc. The present study was undertaken to gain further understanding into the clinical features of ssSSc in a large series.

ssSSc patients presented many similarities with the limited SSc variant. In fact, the multivariate logistic regression analysis revealed that only telangiectasia differentiates one clinical variant from the other. However, whether ssSSc is a different subset of SSc still needs to be clarified. Poormoghim *et al.* [4] consider ssSSc to be a part of the lcSSc continuum rather than a separate disorder. We also found no major difference in organ involvement between these two SSc subtypes. Moreover, the lcSSc-specific ACA antibodies were also highly prevalent in ssSSc patients. There is no specific

TABLE 2 Comparison of ssSSc series reported in the medical literature with Brazilian ssSSc patients

Variables	Brazilian	Pittsburgh	*P*	German	*P*	Spain	*P*
Age at disease onset, mean (S.D.) or mean (range)	46.04 (13.1)	51 (17–78)	0.058[a]	NR		44.9 (18.2)	0.671[a]
Female	76/79 (96.2)	41/48 (85)	0.041[b,*]	20/22 (90.9)	0.398[b]	62/69 (89.8)	0.189[b]
Digital ulcers	19/79 (24.1)	16/48 (33)	0.256[c]	7/22 (31.8)	0.461[c]	10/69 (14.5)	0.209[c]
Articular	35/79 (44.3)	21/48 (44)	0.951[c]	7/22 (31.8)	0.293[c]	9/69 (13)	<0.001[c,*]
Muscular	10/79 (12.7)	2/48 (4)	0.132[b]	3/22 (13.6)	>0.999[b]	2/69 (2.9)	0.036[b,*]
Oesophageal dysmotility	64/77 (83.1)	37/48 (77)	0.475[c]	16/22 (72.7)	0.367[b]	31/69 (44.9)	<0.001[c,*]
ILD	37/65 (56.9)	32/47 (68)	0.230[c]	16/22 (72.7)	0.189[c]	44/69 (63.7)	0.418[c]
PH	18/79 (22.8)	11/48 (23)	0.986[c]	3/22 (13.6)	0.349[c]	17/69 (24)	0.791[c]
ACA	33/79 (41.8)	15/45 (33)	0.354[c]	8/22 (36.4)	0.648[c]	27/69 (24.6)	0.977[c]
Mortality rate	6/79 (7.6)	19/48 (40)	<0.001[c,*]	NR		6/69 (8.7)	0.806[c]

Except where otherwise indicated, values are the number of subjects/total (%). NR: not reported. [a]Student's *t*-test. [b]Fisher's exact test. [c]χ^2 test. **P*-values are statistically significant.

antibody that is reported to be specific for the ssSSc subtype, although anti-Th/To antibody can be associated with ILD in this variant [10, 11].

In the study by Poormoghim *et al.* [4], 18 patients classified as ssSSc subsequently developed sclerodactily during a follow-up period of 3.9 years and were reclassified as lcSSc. As the early diagnosis of sclerodactily can be subjective, especially when there are many investigators involved, we restricted the final diagnosis of ssSSc to two board-certified rheumatologists in each institution. It has been proposed that only patients with more than 5 years of ssSSc diagnosis can be considered as a true ssSSc, while a patient with less than 5 years of diagnosis can still develop cutaneous involvement and be classified as lcSSc [2, 12]. In the present study, no patients have developed clinical skin thickness during a 4.6-year follow-up period. This fact reinforces the need to monitor these patients closely to evaluate further skin involvement and the need for specific therapy.

Our ssSSc cohort showed lower mortality rates than previously published series. Moreover, despite similar frequency of visceral manifestations as compared with the other SSc subtypes, a recent study analysing mortality in the same cohort showed improved survival in ssSSc compared with dcSSc, while similar to the lcSSc group [13].

There is a growing interest in early diagnosis of SSc. In 2001, LeRoy and Medsger [14] proposed classification criteria for early SSc. In 2009, the EULAR scleroderma trials and research group (EUSTAR) emphasized the need for a very early diagnosis [15], with the proposition of classification criteria published in 2011 [16]. In this setting, ssSSc plays an important role, as 1.5–8.3% of SSc patients will present with this clinical picture where the clinical phenotype of skin fibrosis is absent.

Recognition of ssSSc cases that are hidden under the appearance of an undifferentiated CTD should be common knowledge for all clinicians leading to an early referral to the rheumatologists and a more specific management of the disease. We observed in this study that most of the ssSSc patients have visited other specialists prior to seeing the rheumatologist, which led to a significant delay in diagnosis. As oesophageal involvement is the most prevalent visceral manifestation in SSc, we could assume that gastroenterologists are aware of this manifestation, which could have contributed to the higher reference rate of our ssSSc cases from the gastroenterology clinic. Furthermore, since pulmonary manifestations are the leading cause of mortality and morbidity in SSc and can be the first manifestation of CTD, pneumologists should search for associations that would suggest underlying SSc, including RP, abnormal capillaroscopy, positive ANA, anti-Th/To antibodies and gastro-oesophageal reflux [17].

In conclusion, analysis of our cohort suggests that ssSSc can be considered a subset of SSc, and while it shares several features with lcSSc, it should be separated in terms of severity of organ manifestation and potential treatment. It should be mandatory for general clinicians to investigate SSc in patients presenting with typical visceral manifestations in the absence of skin involvement. Further analysis of the clinical features and prevalence of ssSSc will allow more robust comparison with other SSc subtypes in order to investigate the role of gene expression as well as other factors that could be responsible for and predict the thickness of the skin.

Rheumatology key messages

- ssSSc is a subset of SSc.
- In spite of the absence of skin thickening, ssSSc shares several features with limited cutaneous SSc.
- Recognition of ssSSc hidden as an undifferentiated CTD will contribute to its diagnosis.

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