Systemic sclerosis sine scleroderma and limited cutaneous systemic sclerosis: similarities and differences

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ABSTRACT

Objective. *To compare a cohort of patients with systemic sclerosis sine scleroderma (ssSSc) versus patients with limited cutaneous systemic sclerosis (lcSSc).*

Methods. *Forty-five patients with ssSSc and 186 patients with lcSSc were investigated. Demographic, clinical and immunologic features and survival were compared.*

Results. *There were no significant differences between ssSSc and lcSSc in gender, age at onset and interval between onset and diagnosis. ssSSc patients fulfilled the ACR criteria for SSc less than lcSSc patients (13%/77%, p<0.0001). There were no significant differences in articular involvement, myopathy, tendon friction rubs and gastrointestinal, pulmonary, cardiac and renal involvements. There was a trend to higher prevalence of pulmonary arterial hypertension (PAH) in ssSSc patients (29%/19%) but not reach significant difference. The prevalence of antinuclear and anticentromere antibodies and slow capilaroscopic pattern was similar. Sicca syndrome (13%/30%; p=0.024), digital ulcers (16%/50%; p<0.0001), calcinosis (11%/26%; p=0.047) and acroosteolysis (0% /10%; p=0.028) were more frequent in lcSSc. Survival at 5, 10, and 15 yr was not different in ssSSc and lcSSc patients (100%/98%, 100%/98%, and 92%/89%, respectively).*

Conclusion. *ssSSc and lcSSc patients share demographic, clinical and immunologic features. Survival is also similar in both groups. Differences are mainly due to peripheral vascular manifestations. However, despite great similarities, we believe that ssSSc patients should be considered as a different subset in order to avoid misdiagnosis. ssSSc patients should be truly differentiated from early SSc using sensitive and specific studies looking for any asymptomatic organ involvement.*

Introduction

Systemic sclerosis (SSc) is a rare multisystem disorder characterised by widespread accumulation of connective tissue and vasculopathy, which can affect the skin and target internal organs. One of the most remarkable features of the disease is its wide heterogeneity, ranging from a relatively benign condition to a disease with rapid progression of skin thickening and early vital organ involvement.

In 1980, the American College of Rheumatology (ACR) (formerly the American Rheumatism Association - ARA) developed the preliminary criteria to classify patients with definite SSc disease (1). Later, patients with an established disease were classified according to the extent of skin thickening as diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) based on the recommendations of an international panel of experts (2). This 2-subset criteria set was proposed by LeRoy *et al*. (2) to improve the nomenclature of SSc, identify patients at risk of visceral complications, and classify homogeneous groups for clinical research. However, there is a reduced but significant number of patients with similarities in organ involvement to the lcSSc but no skin sclerosis that are usually incorporated into this limited cutaneous subset. Many of them do not satisfy the ARA 1980 preliminary criteria for SSc (1). There is some controversy about considering that group of patients as a separate disorder or being part of the spectrum of the lcSSc. A patient with typical SSc visceral involvement without skin sclerosis was initially reported by Abrams *et al*. (3) in 1954 and Rodnan and Fennel (4) first coined the term "progressive systemic sclerosis sine scleroderma" in 1962. Since then, few cases of this entity have been reported in the literature (3-19) and sometimes

have been called SSc sine scleroderma (ssSSc). Although some authors suggested that patients with ssSSc may be considered as a distinct disorder other authors disagree (2, 20-22). In the largest series to date reported by Poormoghim *et al*. (22), 48 patients with ssSSc were compared with 507 lcSSc patients seen during the same time period at the same institution. The authors concluded that the clinical and serological parameters as well as prognosis in both subsets were not significant enough to consider ssSSc patients as a separate disorder. Whether or not ssSSc and lcSSc are the same or two different subsets require to be confirmed because the accurate identification of disease subsets may improve our ability to predict organ involvement and survival, develop appropriate screening programmes, and guide treatment recommendations.

In the present study we describe a large series of 45 patients diagnosed of ssSSc and compared them with a group of individuals with lcSSc followed up at the same institution during the same period of time. We analysed clinical and laboratory features and survival rates in both groups.

Patients and methods

Patients

All patients with SSc evaluated by physicians at the Scleroderma Unit in Vall d´Hebron Hospital from 1976 to 2007 were eligible for the study. Data from 1976 to 1989 were collected by retrospective medical chart review, and data from 1990 to 2007 were prospectively obtained, both at the initial visit and follow-up. We identified 45 patients diagnosed of ssSSc and 186 with lcSSc according to the criteria described below. Disease onset was defined as the date of the self-reported first symptom (Raynaud's phenomenon (RP) in the majority of cases), and SSc diagnosis date was considered when the patient accomplished the LeRoy's classification (2). A standardised clinical protocol was filled in for each patient and appropriate complementary tests were requested. Demographic data, age, gender, age at diagnosis, age at first clinical manifestation and age at systemic involvement were collected. Manifestations of SSc were evaluated by criteria detailed below. Patients with SSc overlapping with other systemic autoimmune diseases as rheumatoid arthritis, polymyositis/dermatomyositis or systemic lupus erythematosus were excluded.

Clinical features

Skin involvement: lcSSc was defined by the presence of skin thickening of the extremities distal to elbows and knees and/or the face. ssSSc was defined following Poormoghim's classification (22): clinical diagnosis of SSc with no skin sclerosis on physical examination at the first evaluation and in any time during follow-up, and one or more of the following typical SSc visceral involvements: distal esophageal hypomotility by radiography or manometry, manifestations of small bowel hypomotility by radiography or presence of malabsorption syndrome, pulmonary fibrosis confirmed by radiographic findings, pulmonary artery hypertension (PAH) if systolic pulmonary artery pressure (PAP) was higher than 40 mm Hg by echocardiogram or mean PAP ≥25 mm Hg by right heart catheterisation, heart involvement according to clinical judgment or by identification of arrhythmia by ECG or left ventricular ejection fraction <50%, and/or scleroderma renal crisis following the Traub's criteria (see below) (23).

Peripheral vascular involvement: included the presence of RP, digital pitting scars, fingertip ulcers or acro-osteolysis (tuft resorption secondary to digital ischaemia identified in the radiological study by radiologist).

Skeletal muscle involvement: was defined as proximal muscle weakness on physical examination and raised muscle enzymes level. Once enzymes alteration was confirmed, electromyography and muscle biopsy were performed.

Articular involvement: was recorded if arthralgia, arthritis (defined as synovitis with swelling with or without tenderness to palpation in one o more joints, or tendon friction rubs were present.

Digestive tract involvement: was defined by hypomotility of the lower two thirds of the oesophagus and/or decreased peristalsis confirmed by manometry or cine-radiography. Intestinal manifestations such as diarrhoea or malabsorption syndrome were also recorded and breath test was performed when malabsorption was suspected.

Pulmonary involvement: defined by the presence of pulmonary interstitial fibrosis or PAH or diffusing capacity for carbon monoxide (DCO/VA) <70% of predicted value. ILD diagnosis was established if any of the following criteria were identified: (a) restrictive pulmonary pattern with forced vital capacity (FVC) below 80% of expected value on pulmonary function tests and pulmonary interstitial pattern evidenced by chest radiograph or High-Resolution CT Scan (HRCT), or (b) alveolitis confirmed by bronchoalveolar lavage. PAH was diagnosed when systolic pulmonary arterial pressure was estimated to be above 40 mm Hg by Doppler echocardiogram or when mean pulmonary arterial pressure was found ≥25 mmHg by right–sided heart catheterisation in agreement with other studies (22, 24, 25).

Cardiac involvement: was established when one or more of the following were identified: pericarditis, ischaemic cardiopathy (clinical manifestations and any alterations in nuclear perfusion studies without coronary lesions) in patients with no cardiovascular risk factors, cardiac failure without other cause, reversible thallium perfusion defects after cold stimulation, any change on color-Doppler echocardiography (abnormal left and right diastolic function without PAH, thickening of papillary muscles, mitral regurgitation) with no other cause, electrocardiographic alterations (arrhythmia or conduction disturbances), left ventricular ejection fraction lower than 50% or right ventricular ejection fraction lower than 40% on radionuclide ventriculography (26).

Renal involvement: secondary to SSc was diagnosed when a sclerodermal renal crisis (SRC) defined by the presence of a rapid deterioration of renal function (with concomitant normal urine sediment) within a period of less than one month in the absence of previous evidence of significant kidney disease

or by the combination of abrupt onset or aggravation of moderate to severe arterial hypertension (>160/90 mmHg) accompanied by manifestations of malignant hypertension (hypertensive grade III or IV retinopathy, pulmonary oedema and/or hypertensive encephalopathy) and elevation of peripheral renin activity to at least twice the upper limit of normal (23).

Sicca syndrome: required the presence of xerostomia and xerophtalmia as well as an altered Schirmer test and/or salivary gammagraphy.

Serologic analysis: included antinuclear (ANA) and anticentromere antibodies (ACA) detected on Hep-2cell substrate by indirect immunofluorescence assay and antitopoisomerase-I by immunoblotting. Antibodies to RNP, Ro, La, Sm and Pm-Scl were performed by ELISA.

Nailfold capillaroscopy: was performed on each finger of both hands with Wild M3 stereomicroscopy and Intralux 5000 Volpi. According to Maricq *et al*. (27), two capillaroscopic patterns were distinguished: an active pattern characterised by capillary loss predominance, and a slow pattern characterised by the presence of megacapillaries with no capillary loss.

All SSc patients included in the study were treated similarly taking into account the organ involvements and their severity, independently if the cutaneous sclerosis was present or absent.

The study was approved by the ethics committee of the Vall d'Hebron Hospital.

Statistical analysis

All data collected in the study were transferred to an *Access* database that included data from 317 patients with SSc. Statistical analysis was performed using the SPSS 15.0 for Windows® software (SPSS Inc. Chicago, IL, USA). Comparison of categorical variables was carried out by means of the Fisher exact test. Subgroups differences of continuous variables were compared with the non-parametric Mann-Whitney U-test for non-normal variables and analysis of variance for normal variables. Survival curves were plotted with the Kaplan-Meier method, and subgroup differences in survival between ssSSc and lcSSc have been analysed with the log rank (Mantel-Cox) test. $p \leq 0.05$ was considered statistically significant.

Results

Demographic findings

Two hundred and thirty-one out of 317 SSc patients were classified as having ssSSc (n=45) or lcSSc (n=186). ssSSc patients were referred to the Unit of Scleroderma by pulmonologists (ILD or PAH patients with positive ANA or RP), gastroenterologists (gastro-esophageal reflux or intestinal hypomotility with positive ANA or RP) and from the capillaroscopy unit. There were no significant differences between ssSSc and lcSSc groups with regard to gender (93.3% *vs*. 89.8% were women, respectively), mean disease duration (17.59±11.79 yrs *vs*. 20.85±13.05 yrs), mean time of follow-up (8.87±6.51 yrs *vs*. 11.02±7.69 yrs), mean age at onset of symptoms (46.8±17.2 yrs *vs*. 44.7±15.97 yrs), mean age at diagnosis (55.2±15.13 yrs *vs*. 54.5±14.18 yrs) or mean interval from the first symptom to diagnosis (8.69±11.07 yrs *vs*. 9.85±10.54 yrs). Thus, it seems that the absence of skin changes did not delay the diagnosis of SSc.

Table I. Organ involvement in 45 patients with ssSSc and 186 patients with lcSSc.

		ssSSc	lcSSc	*p*
Peripheral vascular	Raynaud's phenomenon	43 (96%)	179 (96%)	0.414
	Digital ulcers	7 (16%)	94 (50%)	**0.000**
	Telangiectasia	28 (62%)	140 (75%)	0.093
	Calcinosis	5 (11%)	48 (26%)	**0.047**
	Acro-osteolysis	0 (0%)	18 (10%)	**0.028**
Articular and muscular	Global	26 (58%)	132 (71%)	0.108
	Arthralgia	25 (56%)	109 (59%)	0.738
	Arthritis	5 (11.%)	25 (13%)	0.808
	Non-inflammatory myopathy	1 (2%)	5 (3%)	1
	Inflammatory myopathy	1 (2%)	3 (2%)	0.582
	Tendon friction rubs	0 (0%)	2 (1%)	1
Gastrointestinal	Global	32 (71%)	145 (78%)	0.332
	Oesophagus	20 (44%)	110 (59%)	0.094
	Dysphagia	16 (36%)	77 (41%)	0.503
	Pyrosis	16 (36%)	92 (49%)	0.099
	Barret's oesophagus	1 (2%)	3 (2%)	0.582
	Gastric hypomotility	6 (13%)	24 (13%)	1
	Malabsorption	1 (2%)	6 (3%)	1
Liver	Global	5 (11%)	15 (8%)	0.555
	Primary biliar cirrhosis	6 (13%)	9 (5%)	0.083
Pulmonary	Global	38 (84%)	142 (76%)	0.317
	Dyspnea	22 (49%)	78 (42%)	0.956
	Cough	13 (29%)	47 (25%)	0.705
	Interstitial lung disease	16 (36%)	87 (47%)	0.186
	Ground glass pattern[#]	6 (25%)	36 (33%)	0.478
	Reticular pattern	5 (11%)	32 (17%)	0.373
	FVC <70% of predicted	18 (40%)	68 (36%)	0.718
	PAH	13 (29%)	35 (19%)	0.15
	DLCO/AV <70%[##]	14/26 (54%)	56/110 (51%)	0.830
Cardiac	Global	26 (58%)	106 (57%)	1
	Pericarditis	0 (0%)	5 (3%)	0.586
	Ischaemic cardiopathy	13 (29%)	43 (23%)	0.441
	Conduction disturbance	7 (16%)	46 (25%)	0.237
Renal	SRC	1 (2%)	3 (2%)	0.582
Sicca syndrome		6 (13%)	56 (31%)	**0.024**
Neoplasia		4 (9%)	13 (7%)	0.750

FVC: forced vital capacity; DLCO/AV: diffusing lung capacity for carbon monoxide corrected for alveolar volume; PAH: pulmonary arterial hypertension; SRC: Sclerodermal renal crisis. [#]HRCT was performed in 24 patients in ssSSc and 108 patients in lcSSc. [##]DLCO/AV was performed in 28 patients in ssSSc and 124 in lcSSc.

As expected, ssSSc patients fulfilled less frequently than lcSSc patients the preliminary ACR criteria for SSc (13% *vs*. 77%, respectively; $p<0.000$).

Clinical findings

Organ and system involvements in both groups are summarised in Table I. RP was the most frequent first symptom of disease referred by both groups with no significant differences between them. It was present at diagnosis in 43 cases with ssSSc and in 175 with lcSSc (96% and 94%, respectively) and in 43 and 179 (96% for both) patients during follow-up. Telangiectasias at any site were not significantly different between ssSSc and lcSSc patients (62% versus 75%, respectively) but the presence of fingertip ulcers (16% *vs*. 50%; $p=0.000$), calcinosis (11.1% *vs*. 26%; $p=0.047$), and acro-osteolysis (0% *vs*. 10%; $p=0.028$) were less common in ssSSc patients.

There were no significant differences between ssSSc and lcSSc subsets in the frequencies of articular involvement (58% *vs*. 71%, respectively) with similar prevalence for arthralgia (56% *vs*. 57%), arthritis (11% *vs*. 13%), inflammatory (2% *vs*. 2%] and non-inflammatory myopathy (2% *vs*. 3%), and palpable tendon friction rubs (0% *vs*. 1%).

Gastrointestinal features were not different between ssSSc and lcSSc patients in (71% *vs*. 78%, respectively) with similar frequencies for distal oesophageal hypoperistalsis (44% *vs*. 59%), gastric hypotonia (13% *vs*. 13%), and malabsorption syndrome (2% *vs*. 3%).

Pulmonary involvement was common in both groups, affecting 84% of ssSSc and 76% of lcSSc patients. The proportions of ILD (35% and 47%, respectively) and reduced forced vital capacity (FVC) were similar in both groups with a mean FVC of 81% and 81%, respectively. Although there was a trend to higher prevalence of PAH (29% *vs*. 19%) and higher mean estimated systolic PAP (47.74±24.3 mm Hg *vs*. 45.33±20.4 mm) in ssSSc than in lcSSc subset these differences were not significant.

Cardiac involvement prevalence was similar in both groups (58% in ssSSc *vs*. 57% in lcSSc), including pericarditis, ischaemic cardiopathy and conduction abnormalities.

No differences were found in the occurrence of SRC.

Sicca syndrome was present less frequently in patients with ssSSc than in patients with lcSSc (13.3% *vs*. 30%, respectively; $p=0.024$).

No differences were found in the rates of neoplasia development (8.9% in ssSSc *vs*. 7% in lcSSc), neither in the histological pattern nor in the localisation of the cancer.

Serum autoantibody findings

Antinuclear antibodies were identified in the great majority of patients with ssSSc and lcSSc (91% *vs*. 97%) and ACA were by far the most frequent SSc-associated autoantibodies in both groups (46% *vs*. 53%). There were no significant differences in the frequency of any other individual autoantibodies between both groups as shown in Table II.

Table II. Serum autoantibodies in patients with ssSSc and lcSSc.

	ssSSc	lcSSc	*p*-value
ANA	41/45 (91%)	180/186 (97%)	0.107
Rheumatoid factor	8/18 (50%)	24/87 (28%)	0.092
Anticentromere	20/43 (46%)	93/175 (53%)	0.497
Anti-Scl70	3/42 (7%)	17/168 (10%)	0.77
Anti-U1RNP	1/37 (3%)	3/151 (2%)	1
Anti-Ro	4/41 (10%)	16/164 (10%)	1
Anti-La	0/40 (0%)	2/161 (1%)	1
Anti-Sm	1/39 (3%)	3/156 (2%)	1
Anti-PM- Scl	1/9 (11%)	3/27 (11%)	1

ANA: antinuclear antibodies.

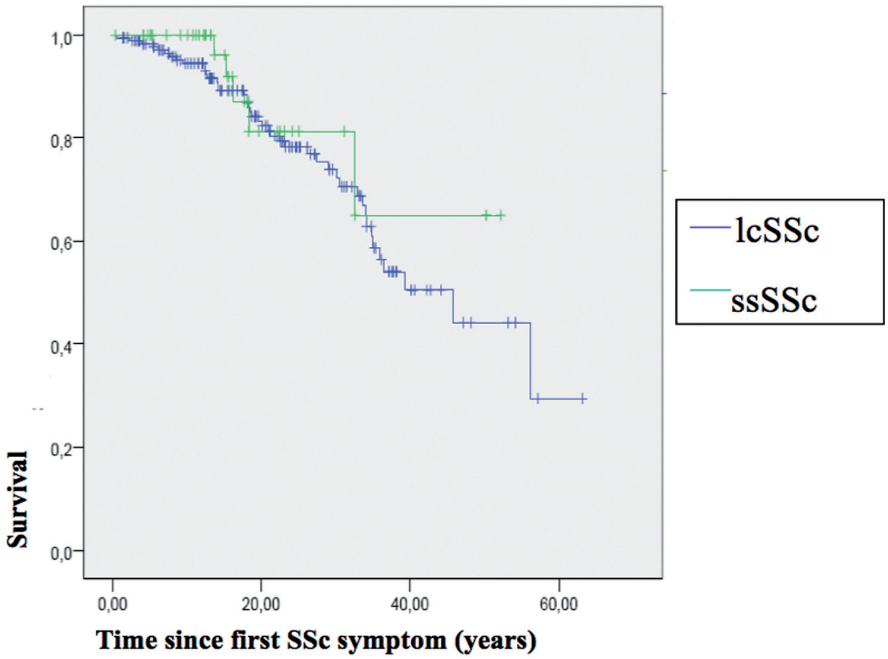

Fig. 1. Cumulative survival at 10th, 20th and 25th year from disease onset were: 100%/95%, 92%/89% and 82%/82% in patients with ssSSc and lcSSc, respectively.

Capillaroscopic findings

The most frequent nailfold capillaroscopic finding was the slow pattern, present in 82% of ssSSc and 83% of lcSSc patients.

Survival

The Kaplan-Meier survival curves were similar in both groups. Thus, Kaplan-Meier cumulative 5-year survival rate was 100% in ssSSc subset (95% CI: 0.95–1) and 98% in lcSSC subset; the 10-year survival rate was

100% and 95% (95% CI: 0.91–0.98) and the 15-year survival rate was 92% (95% CI 0.81–1.03) and 89% (95% CI: 0.84–0.94), respectively. The log-rank χ^2 tests were not statistically significant as shown in Figure 1.

Mortality rates were similar in both groups, with 5 deaths registered in ssSSc subset and 45 deaths in lcSSc subset (11% *vs*. 24%). Pulmonary involvement was the most common cause of death in both groups although less frequent in ssSSc group.

Survival study was performed according to several demographic, clinical and immunological features and confirmed that gender, age, PAH, cardiac involvement, SRC and presence of ACA did not influence survival in the ssSSc group. In the crude analysis of ssSSc patients, the presence of ILD and FVC <70% of the expected value were associated with the shortest survival. Table III shows the 15-year survival rate of ssSSc patients related to the mentioned items.

Table III. Fifteen-year survival of ssSSc patients according to demographic, clinical and immunological features.

		Number	Deceased patients	Cumulative survival	95% CI	*p*-value
nº patients		44	5	92%	0.81-1.03	–
Gender	Male	3	1	100%	1-1	0.067
	Female	41	4	92%	0.8-1.03	
Age at onset	<60	34	3	95%	0.86-1.04	0.084
	≥60	10	2	78%	0.39-1.16	
Age at diagnosis	<60	27	2	100%	1-1	0.234
	≥60	17	3	78%	0.51-1.05	
Respiratory involvement	Absent	7	0	100%	1-1	0.351
	Present	37	5	91%	0.79-1.03	
ILD	Absent	29	1	94%	0.83-1.05	**0.017**
	Present	15	4	87%	0.62-1.11	
FVC	≤70%	18	3	82%	0.5-1.14	**0.006**
	>70%	27	0	100%	1-1	
PAH	Absent	32	3	94%	0.84-1.05	0.342
	Present	12	2	86%	0.6-1.12	
PAPs	<40	14	1	100%	1-1	0.486
	≥40	12	2	86%	0.6-1.12	
Cardiac	Absent	19	2	89%	0.68-1.09	0.540
	Present	25	3	94%	0.82-1.06	
SRC	Absent	43	5	92%	0.8-1.03	0.498
	Present	1	0	100%	1-1	
ACA	Absent	23	3	92%	0.77-1.07	0.878
	Present	20	2	92%	0.77-1.07	

ILD: Interstitial lung disease; FVC: forced vital capacity; PAH: pulmonary arterial hypertension; PAPs: systolic pulmonary artery pressure; SRC: Sclerodermal renal crisis; ACA: anticentromere antibodies.

Discussion

Our study was conducted on a large case series of 45 patients diagnosed of ssSSc and the main objective was to compare demographic, clinical, immunological features and survival rate of these patients to a group of patients with lcSSc at the same institution during the same period of time. Several peripheral vascular findings, particularly finger tip ulcers and calcinosis were more common in lcSSc patients. In agreement with other authors we also found a trend to higher pulmonary vascular involvement in ssSSc respect to lcSSc patients suggesting that it could be statistically significant in a larger cohort study. However, no more differences were found in internal organ involvement and immunological features with influence in survival rates.

In 1980, the preliminary criteria to classify patients with definite SSc disease were proposed by the ACR. It has been an essential component of SSc research as they have ensured that patients recruited for studies have similar features and allow results to be compared across studies. More recently, different subsets have been recognised within the spectrum of SSc, according to their singularities in disease expression, response to therapy, prognosis, and morbidity. Thus, LeRoy *et al*. (2) proposed in 1988 a 2-subset criteria with good feasibility, acceptable face validity, and good predictive validity (28) and nowadays they are widely used worldwide. In that classification ssSSc patients were included within the lcSSc subset because of many features were shared by both groups. Poormoghim *et al*. and some other authors agreed that both subsets of patients are part of a simple disease spectrum rather than a separate entities (2, 20, 22). Nevertheless, it is of great importance to determine whether ssSSc patients are really similar to lcSSc patients because the accurate identification of SSc subsets may improve our ability to predict early organ involvement and prognosis, develop appropriate screening programmes, and guide treatment recommendations (28, 29). In this sense, our results confirm the absence of major differences between ssSSc and lcSSc in relation to organ involvement, immunological features, and average survival rates although we observed a trend toward a higher frequency of PAH in ssSSc patients. In agreement with Poormoghim *et al*. (22), only fingertip ulcers, and calcinosis were significantly less frequent in ssSSc subset. It is possible that skin changes present in lcSSc, including atrophy of the epidermis, loss of elasticity, flexion contractures, and microtraumatisms may contribute to the apparition and poor regeneration of the vascular lesions and to persistent digital ischaemia.

The mean interval from the first symptom to diagnosis was similar for ssSSc and lcSSc patients (8.7yr and 9.8 yr respectively) suggesting that the absence of skin changes did not delay the diagnosis of SSc. When ssSSc patients were stratified according to age at onset, gender, and disease duration from

Table IV. Comparison between cohorts of patients with sSSc and lcSSc of the Vall d'Hebron and Pittsburgh.

	Pittsburgh patients			Vall d'Hebron patients		
	ssSSc	lcSSc	*p*-value	ssSSc	lcSSc	*p*-value
n°	48	507	–	45	186	–
Women (%)	85%	86%	NS	93%	90%	0.582
Age at diagnosis (years)	51 (17-78) 1st visit	NA	–	55.2±15.1	54.5±14.18	0.76
ARA criteria fulfillment	12.5%	NA	–	13%	77%	**<0.0001**
Raynaud's pnenomenon	98%	97%	NS	93%	96%	0.414
Digital ulcers	33%	59%	**<0.001**	16%	50%	**<0.0001**
Calcinosis	29%	49%	**<0.03**	11%	26%	**0.047**
Telangiectasia	73%	90%	**<0.0002**	62%	75%	0.093
Articular	44%	47%	NS	58%	71%	0.108
Gastrointestinal	79%	73%	NS	71%	78%	0.332
Liver	NA	NA	-	11%	8%	0.555
Lung involvement	68%	60%	NS	84%	76%	0.317
Dyspnea [FC III-IV]	65%	33%	**<0.0004**	49%	42%	0.956
DLCO<70% of expected	77%	64%	NS	54%	51%	0.830
PAH	23%	13%	0.103	29%	19%	0.153
FVC <70% of expected	35%	31%	NS	40%	36%	0.718
ILD	39%	37%	NS	36%	47%	0.186
Cardiac	9%	9%	NS	58%	57%	1
Renal	0%	1%	NS	4%	4%	0.689
Sicca syndrome	NA	NA	NA	13%	30%	0.024
Antinuclear Ab	94%	94%	NS	91%	97%	0.107
Anticentromere Ab	31%	54%	<0.09	46%	53%	0.497
Antitopoisomerase Ab	6%	10%	NS	7%	10%	0.557

ARA: American Rheumatism Association; ssSSc: Systemic sclerosis sine scleroderma; lcSSc: limited cutaneous systemic sclerosis; PAH: pulmonary arterial hypertension; FVC: forced vital capacity; Ab: antibodies. FC: functional class; ILD: Interstitial lung disease; NS: not significant; NA: not available.

onset no differences were found in the frequencies of organ involvements.

In Pormooghim's *et al*. study, severe dyspnoea was referred more frequently by ssSSc than lcSSc patients but surprisingly this difference did not correlate with the prevalence of PAH (23% and 23%, respectively) and ILD(39% and 37%, respectively) (22). In this sense, our study also showed a tendency of a higher prevalence of dyspnoea in ssSSc patients but interestingly we also identified a non-significant higher prevalence of PAH in ssSSc (28.9% *vs*. 18.8%), but not ILD. It suggests that PAH could be more frequent in ssSSC than in lcSSc but the potency of both studies separately did not allow identifying it (Table IV). Otherwise, there were no other major differences between both groups and only sicca syndrome was less frequent in ssSSc than in lcSSc. As expected, higher frequencies of slow capillaroscopic pattern and ANA positive were found. Ninety-one percent of patients had positive ANA, similarly to results reported by Poo moghim *et al*. (22) and Toya *et al*. (30). The most common autoantibodies in both groups were ACA.

Survival analysis revealed analogous cumulative survival rates after 5, 10 and 15 years of follow-up in both subsets. In our study, ILD was associated with poor prognosis in ssSSc subset. Recently, Toya *et al*. (30) reported a meta-analysis of 108 published cases of ssSSc. Lung involvement was present in 66% of cases and gastrointestinal manifestations in 82%. The authors revealed that the great majority of ssSSc patients have RP, frequently preceding other disease manifestations. Therefore, the presence of RP in a patient with respiratory symptoms should pay particular attention to the possibility of an underlying ssSSc (30).

Only 22 (1.5%) of all registered patients of the German Network Registry (31) were diagnosed of ssSSc and 50% of them presented dyspnea. ILD was detected in 59% of patients and PAH (determined by echocardiography and/or by right heart catheterisation) was only identified in 13.6%. Unfortunately, because of the low frequency seen in the registry, ssSSc subset was excluded from further statistical analysis. The Spanish Network SSc Registry (32) showed no differences in the prevalence of ILD and PAH in ssSSc and lcSSC subsets but the mean FVC was significantly lower and the mean estimated systolic pulmonary pressure was higher in ssSSc than in lcSSc patients. Moreover, cardiac involvement, in particular ischaemic cardiopathy, was more frequent in ssSSc than in lcSSc and dcSSc subsets (32). We carried out survival analysis in Spanish Network SSc Registry and no statistical significant differences were observed between curves for lcSSc and ssSSc (manuscript under review).

Recently, a series of 79 consecutive ssSSc patients from two Brazilian cohorts (33) were compared with lcSSc and dcSSc subtypes. Esophagus was the most frequently affected organ (83.1%), followed by pulmonary involvement (63.2%) in ssSSc subtype. Compared with the lcSSc, ssSSc had significantly lower frequency of calcinosis, digital ulcers and telangiectasia. Both subtypes showed similar visceral involvement. These results are similar to the present study. Multivariate logistic regression analysis indicated that, after controlling gender, age at diagnosis and time of follow-up factors, only telangiectasia differentiated ssSSc from lcSSc. Survival analysis was not made.

Patients diagnosed of ssSSc, unlike lcSSc patients, never satisfy the major criterion nor one of the minor ACR criteria for SSc because skin sclerosis is absent by definition. As expected, only 13% of ssSSc patients fulfilled the preliminary ACR criteria for SSc at any time in contrast to the significant 77% of patients with lcSSc. In a recent incidence study of SSc spectrum disorder none of ssSSc patients fulfilled ACR 1980 criteria (34). Obviously, ACR criteria perform poorly for the classification of ssSSc patients and therefore new classification criteria incorporate characteristics of these patients to improve the sensibility (35). In this sense, we agree with Poormoghim *et al*. (22) and other experts (29) that any patient

should be considered to have ssSSc if the subject meet all of the following features: 1) RP, or a peripheral vascular equivalent: digital pitting scars, fingertip ulcers, digital-tip gangrene, SSc-type nailfold capillary pattern, 2) positive antinuclear antibodies 3) one or more of the following typical SSc visceral involvement: distal esophageal or small intestinal hypomotility, ILD, PAH, typical SSc cardiac involvement or SRC and 4) no other defined connective or other disease as a cause of the previous items. These criteria allow to classifying patients with ssSSc and differentiating them from other subset of patients who have early SSc or prescleroderma that was named limited SSc by LeRoy and Medsger (33). This SSc subset with neither cutaneous involvement nor SSc organ involvement is defined by the presence of RP, scleroderma-type nailfold capillaries and/or SSc marker autoantibodies (29, 36, 37). Therefore, early SSc patients differ from ssSSc only by the identification of a typical organ involvement in the latter subset, thus all patients included in this study met criteria for ssSSc because established visceral involvement was always present. We must consider that patients classified as early SSc may correspond to an initial stage of any other SSc subset, frequently ssSSc or lcSSc, but also dcSSc. Thus, it is of great importance to assess the presence or absence of distinct typical SSc clinical manifestations because ssSSc patients do not have skin thickening although progressively develop organ involvements with similar prognosis to lcSSc patients (29, 36, 37, 38). Before classifying any patient as an early SSc, any typical internal organ involvement must be ruled out at presentation by sensible and specific studies. Esophageal manometry, lung function test and echocardiography should be assessed in all patients because pre-clinical visceral involvement may already be present at presentation and therefore patients' classification may change from early SSc to definite SSc (37, 38). Furthermore, it is also recommendable to assess yearly lung function test and echocardiography studies. Thus, Valentine *et al*. (38) demonstrated that preclinical scleroderma-type cardiopulmonary or esophageal abnormalities were common in patients with early SSc. Moreover, 92% of patients with early SSc developed manifestations consistent with definite SSc at 5 years of follow-up but only 10% developed skin sclerosis (sclerodactyly in 3 cases and skin sclerosis proximal to the elbows in only one). Recently, researchers from the European Scleroderma Trials and Research (EUSTAR) group proposed criteria for the very early diagnosis of SSc(VEDOSS) (39), namely RP, puffy hands, marker autoantibodies and typical capillaroscopic alterations. These experts proposed that any patient classified as very early SSc should be sent to a referral centre to investigate preclinical, functional internal organ involvement and to put them under strict surveillance.

In a recent study, laser speckle perfusion imager was used to investigate microvascular reactivity in SSc. When SSc patients were stratified according to early and established SSc, a peculiar difference in the ischaemic challenge was noticed. Early SSc patients showed a significant increase in the amplitude of the hyperaemic response. This peculiar alteration lends support to the hypothesis that the disease starts with the beginning of RP rather than with the appearance of the first non-RP symptom) (40).

This study has several limitations. Although our case series is the second largest one reported to date in a single center, it could be insufficient to identify more differences between both groups. However, its importance lies in providing more information to improve understanding of this population and deal with the heterogeneity of this entity. Another limitation lies on the retrospective collection of the patients before 1989 although they were followed-up prospectively thereafter and organ involvements could be identified properly.

In summary, we report a large series of cases with ssSSc and compare them with an equivalent cohort of lcSSc seen in the same institution during the same period of time. Only fingertip ulcers, calcinosis and acro-osteolysis were significantly less frequent in ssSSc patients. There was a trend to have more pulmonary vascular involvement in ssSSc patients, but this observation did not reach significance. Despite similarities between ssSSc and lcSSc subsets, we believe that ssSSc patients should be considered as a different subset within SSc spectrum to avoid misdiagnosis and to be taken into account in some syndromes as PAH and ILD that may be related to SSc with no skin changes. As the ssSSc patients are not easily recognised by the non-expert in SSc clinicians, it's very important that SSc expert clinician who follow a large number of SSc patients participate in commissions and meetings about PAH, ILD and others syndromes related to SSc because it's necessary an early and adequate diagnosis of ssSSc for general practioners, pneumologists and gastroenterologists. Furthermore, since pulmonary manifestations are the leading cause of mortality and morbidity in SSc and can be the first manifestation, it's imperative that in the guidelines for the diagnosis of ILD and PAH should search for associations that would suggest underlying SSc, including RP, abnormal capillaroscopy, positive ANA and gastro-esophageal reflux. Moreover, ssSSc patients should be truly differentiated from early SSc using sensitive and specific studies looking actively for any asymptomatic organ involvement. Its recognition avoids misclassification and allows to truly classify these patients as having a subset of SSc.

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