Early systemic sclerosis: assessment of clinical and pre-clinical organ involvement in patients with different disease features

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Abstract

Objective. To assess internal organ involvement in early SSc at presentation.

Methods. One hundred and fifteen patients admitted to a tertiary centre because of RP, who did not present any routinely detectable scleroderma-related internal organ involvement, were investigated for ANA and videocapillaroscopy, and underwent history and physical examination to detect symptoms/signs suggestive of SSc. Patients were then subdivided into three groups: (i) early SSc, constituted by patients without clinical manifestations other than RP, but with scleroderma marker autoantibodies and/or typical capillaroscopic abnormalities; (ii) probable SSc, constituted by patients with the same autoantibody and/or capillaroscopic status as early SSc patients, but with any of the following manifestations: digital ulcers/scars, puffy fingers, arthritis, telangiectasia, dysphagia/heartburn, shortness of breath; (iii) UCTD, constituted by patients with a specific (i.e. disease antibody marker) ANA and capillaroscopic findings plus any disease manifestation. All patients were investigated by lung functional study and B-mode echo-Doppler-cardiography. Patients who consented underwent oesophageal manometry.

Results. An inverted mitral E : A ratio (i.e. early scleroderma cardiac involvement) and/or a diffusing lung capacity for CO <80% of the predictive value (i.e. early lung involvement) and/or basal low oesophageal sphincter pressure <15 mmHg (i.e. early oesophageal involvement) were detected in 37/51 probable SSc patients (72%), 8/19 early SSc patients (42%) and 12/45 UCTD patients (27%).

Conclusion. A scleroderma-related internal organ involvement was detected in patients from each group and, more importantly, was pre-clinical in a number of cases.

Key words: Pre-scleroderma, Early systemic sclerosis, Internal organ involvement.

Introduction

SSc is a multisystem CTD characterized by distinct autoimmune abnormalities, microvascular obliterator and small artery proliferative disease and accumulation of collagen and other matrix constituents in the skin and target internal organs [1]. It is easy to diagnose SSc in both the clinical and research settings when a patient is affected by RP associated with fingertip ulcers and/or scars and SSc involving at least the fingers, or with typical organ involvement [2, 3]. However, this approach implies that the diagnosis of SSc and consequently appropriate therapy is delayed until the appearance of skin involvement and/or clinically detectable internal organ involvement [4, 5].

In 1996, the term pre-scleroderma was coined to identify patients with RP plus digital ischaemic changes and typical nailfold capillary changes or disease-specific circulating ANA [6]. Subsequently, LeRoy and Medsger [7] proposed the term limited SSc (lSSc) for cases presenting with RP and either an SSc-type nailfold capillary pattern or SSc-selective autoantibodies. The aim of LeRoy and
Medsgjer [7] was to define criteria for the early diagnosis and classification of SSc in patients who did not satisfy the ACR criteria for SSc [2]. Therefore, they did not mention which other symptom/sign/laboratory/instrumental finding should be considered as an exclusion criterion for a diagnosis of ISSc. In a large prospective study, Koenig et al. [8] found that RP patients with scleroderma marker autoantibodies and/or typical capillaroscopic abnormalities and without any other clinical manifestation are 60 times more likely to develop definite SSc than other RP patients. They called the condition early SSc. The term very early SSc has also been suggested [9]. In this scenario, we carried out an inception cohort study to determine the prevalence and the extent of clinical and pre-clinical organ involvement in patients affected by pre-scleroderma-ISSc—early SSc vs patients affected by UCTD.

Materials and methods

Patients admitted for the evaluation of RP from 1 November 2000 to 31 October 2008 to the outpatient clinic of the Rheumatology Unit of the Second University of Naples, who did not present either X-ray bibasilar lung fibrosis or X-ray oesophageal motility or any ECG abnormality or any finding of scleroderma renal crisis, were considered for the study, and were enrolled after getting their informed written consent. The diagnosis of RP was confirmed if patients fulfilled LeRoy and Medsgjer’s criteria [10], i.e. if a cold challenge induced bilateral, episodic bi- or triphasic (pallor followed by dusky blueness and/or redness) colour changes of fingers.

Patients were investigated for typical microvascular alterations (megacapillaries and/or avascular areas) by wide-field nailfold capillary microscopy (NCM), ANA, SSc and other CTD marker autoantibodies (i.e. anti-DNA-topoisomerase I—anti-Scl-70; ACA; anti-RNA polymerase III; anti-fibrillar; anti-Pm-Scl; anti-Th/To; anti-SSA; anti-SSB; anti-Sm; anti-Jo1; anti-U1RNP; and anti-DNAds antibodies). NCM was carried out while the anti-SSA; anti-SSB; anti-Sm; anti-Jo1; anti-U1RNP; and other CTD marker autoantibodies (i.e. anti-DNAds antibodies) were investigated. The diagnosis of RP was confirmed if patients fulfilled LeRoy and Medsgjer’s criteria [10], i.e. if a cold challenge induced bilateral, episodic bi- or triphasic (pallor followed by dusky blueness and/or redness) colour changes of fingers.

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Patients also underwent a detailed history taking and a physical examination to identify the following features: digital ulcers/scars (ischaemic necrotic ulcers and/or ensuing scars), puffy fingers (increase in soft tissue mass due to dermal imbibition with abolishment of skin contours and skin folds), telangiectasia (dilated small blood vessels visible to the unaided eye), previous or present arthritis, dysphagia/heartburn (difficulty in swallowing either solid or liquid substances and/or sensation of burning located substernally or high in the epigastrium), shortness of breath (difficult or laboured respiration on exertion).

Patients were then divided into three groups: (i) early SSc patients, namely those with a marker autoantibody or a videocapillaroscopic scleroderma pattern or both, without any clinical manifestation other than RP [8]; (ii) probable SSc, namely patients who presented a marker autoantibody or a videocapillaroscopic scleroderma pattern or both, and any other clinical manifestation out of those previously listed, but did not satisfy the ACR for the classification of the disease [2]; and (iii) UCTD, namely patients who had serum ANA, but no marker autoantibody of SSc or any other CTD, no scleroderma videocapillaroscopic findings or any clinical manifestation pathognomonic of any other CTD [13].

Finally, all patients underwent B-mode echocardiography and lung function study, whereas only patients who consented were investigated by oesophageal manometry. Echocardiographic examination was performed as described elsewhere [14]. The detection of diastolic abnormalities (namely an inverted E : A ratio) in the absence of arterial hypertension, coronary artery disease and other symptoms/signs of cardiac disease was considered indicative of early scleroderma cardiac involvement. Lung function was assessed as reported previously [15]. The detection of either a diffusing lung capacity for CO (DLCO) or a forced vital capacity (FVC) <80% of the respective predicted values in the absence of smoking and/or obstructive disease was considered indicative of lung involvement [15]. Stationary oesophageal manometry was performed as described elsewhere [16]. A low (<15 mmHg) basal low oesophageal sphincter (LES) pressure was considered indicative of early oesophageal involvement. Concomitant distal oesophageal hypomotility was recorded. The study was approved by the ethics committee of the Second University of Naples.

Statistics

We used the SPSS for windows software (version 16.0; Chicago, IL, USA) for statistical analysis. Categorical data were analysed by Fisher’s exact test when two groups
were compared, and by contingency table (chi-square) when three groups were considered. Continuous data were compared by analysis of variance (ANOVA). \( P < 0.05 \) was considered to statistically significant. Risk was assessed by odds ratio and step-wise regression analysis.

**Results**

From 1 November 2000 to 31 October 2008, 115 patients with RP who satisfied the entry criteria (109 women, 6 men; aged 12–75 years, median age 42 years; with a disease duration between 0.5 and 33 years, median 4 years) were admitted to our outpatient clinic. Seventy patients were found to have a scleroderma marker autoantibody or a capillaroscopic scleroderma pattern: 13 were anti-Scl-70 positive (10 presented with either megacapillaries or avascular areas); 47 were ACA positive (26 had a typical capillaroscopic pattern); 1 was anti-PmScl positive, 2 anti-fibrillarin positive, 3 anti-Th/To positive (all of them with a typical scleroderma pattern); 1 anti-RNA-polymerase III positive; and 3 had a typical capillaroscopic scleroderma pattern (2 were ANA-positive; 1 was ANA-negative). Out of them, 19 patients presented no clinical manifestation and were considered as early SSc cases; 51 patients presented dysphagia/heartburn, shortness of breath, puffy fingers, digital ulcers/scars, telangiectasia or arthritis, or any combination of these and were labelled as probable SSc.

The remaining 45 patients were ANA positive, but did not present any CTD marker autoantibody or a typical capillaroscopic pattern, and were labelled as UCTD. No patient was found to be both ANA and capillaroscopy negative. Therefore, no primary RP patient was investigated in the study.

Table 1 shows the main epidemiological and clinical features of the three groups of RP patients identified. Patients with probable SSc were significantly older then those with UCTD patients \( (P = 0.006) \), who in turn did not differ in age from early SSc patients. By definition, no early SSc had any clinical manifestation. Compared with UCTD patients, those with probable SSc had a higher prevalence of puffy fingers, digital ulcers/scars, dysphagia/heartburn and shortness of breath.

Table 2 lists the results of functional investigations carried out in patients from each group. An inverted \( E : A \) ratio was identified in 3 patients with early SSc (2 of whom were >50 years old), 12 with probable SSc (5 of whom suffered from arterial hypertension and further 6 were >50 years old) and in 2 with UCTD (1 of whom is suffering from arterial hypertension). A DLCO <80% was detected in 7 early SSc patients, in 26 probable SSc patients (in 3 cases

<table>
<thead>
<tr>
<th>Feature</th>
<th>Early SSc (( n = 19 ))</th>
<th>Probable SSc (( n = 51 ))</th>
<th>UCTD (( n = 45 ))</th>
<th>( P )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F/M</td>
<td>17/2</td>
<td>50/1</td>
<td>42/3</td>
<td>0.34</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>41 (23–73)</td>
<td>51 (12–75)</td>
<td>35 (14–73)</td>
<td>0.006</td>
</tr>
<tr>
<td>Puffy fingers</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>0.009</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>Digital ulcers/scars</td>
<td>0</td>
<td>17</td>
<td>2</td>
<td>0.006</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>Dysphagia/heartburn</td>
<td>0</td>
<td>35</td>
<td>11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Shortness of the breath</td>
<td>0</td>
<td>19</td>
<td>7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Probable SSc vs UCTD. F: females; M: males.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Early SSc</th>
<th>Probable SSc</th>
<th>UCTD</th>
<th>( P )-value (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E : A ratio &lt;1</td>
<td>1/19</td>
<td>1/51</td>
<td>0/45</td>
<td>0.5</td>
</tr>
<tr>
<td>FVC &lt;80%</td>
<td>0</td>
<td>3/51</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>DLCO &lt;80%</td>
<td>7/19</td>
<td>26/51 (10 with effort dyspnea)</td>
<td>10/45 (2 with effort dyspnea)</td>
<td>0.4</td>
</tr>
<tr>
<td>Basal LES pressure &lt;15 mmHg</td>
<td>4/18</td>
<td>24/43 (21 with dysphagia/heartburn)</td>
<td>4/25 (4 with dysphagia/heartburn)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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\( ^{a} \) Not alternatively explained. P1: early vs probable SSc; P2: early SSc vs UCTD; P3: probable SSc vs UCTD.
Associated with FVC <80% and in 10 UCTD patients. None of them has ever smoked. This lung functional abnormality was significantly more prevalent in patients with probable SSc, but was detected in patients from each of the other two groups (early SSc 37%; UCTD 22%). A basal LES pressure <15 mmHg was detected in 4/18 early SSc patients, in 24/43 probable SSc patients and in 4/25 UCTD patients, who consented to undergo oesophageal manometry. Also, this early sign of oesophageal disease was detected more frequently in patients with probable SSc. Nevertheless, it was found in 22% of early SSc patients and in 16% of UCTD patients. Moreover, concomitant distal oesophageal hypomotility was recorded in 0/4 early SSc, 10/24 probable SSc and 2/4 UCTD patients. Considering the three abnormalities together, functional heart and/or lung and/or oesophageal abnormalities were detected in 8/19 early SSc patients (42%) (1 inverted E:A ratio; 3 reduced DL CO, 4 with both reduced DL CO and reduced basal LES pressure; 15 mmHg was detected in 7 patients. Therefore, the detection of lung, heart and oesophageal involvement in early–probable SSc–UCTD patients based on history-taking is complicated by both false positive and false negative findings.

Table 3 shows the assessment of the risk of presenting scleroderma-related functional internal organ involvement in 115 RP patients. Considering each group separately, we failed to find any aspect significantly associated with an increased risk in early SSc and UCTD patients, whereas we detected an increased risk in patients with probable SSc presenting typical capillaroscopic findings (odds ratio 3.15; 95% CI 1.7, 8.3) or reporting dysphagia/heartburn (odds ratio 12.5; 95% CI 5, 31).

Considering all the 115 RP patients together, those with marker autoantibodies, a capillaroscopic scleroderma pattern, puffy fingers or dysphagia/heartburn had a higher risk of scleroderma-related internal organ involvement. Stepwise regression analysis pointed out an independently increased risk of scleroderma-related internal organ involvement for marker autoantibodies (P = 0.015); puffy fingers (P = 0.012) and dysphagia/heartburn (P = 0.0001).
we diagnosed early SSc according to Koenig et al. [8], and labelled probable SSC cases with clinical findings suggesting SSC, but not satisfying ACR criteria for the disease [2]. Lastly, we used a strict definition for UCTD because we excluded patients with lung interstitial fibrosis, X-ray oesophageal hypomotility, any marker antibody of CTD, capillaroscopic findings or any clinical manifestation pathognomonic of a major systemic autoimmune rheumatic disease [13].

Since the early 1980s, various groups have evaluated the clinical, serological, capillaroscopic and functional features in patients presenting with RP and predictive of the subsequent development of a full-blown (i.e. satisfying classification criteria) CTD [19–26]. These studies showed that some capillaroscopic findings (megacapillaries and avascular areas) and marker autoantibodies are predictive for the development of definite SSc. Moreover, Kallenberg et al. [20] detected a DLCO <80% of predicted value in 2/24 RP–ACA-positive patients; Gerbracht et al. [21] found that, upon presentation, 10/87 patients with RP had puffy fingers, 4 had digital scars, 2 had digital ulcers, 2 had oesophageal hypomotility (identified with barium X-ray) and 11 had reduced DLCO. Kallenberg et al. [23] found, at admission, one or more findings suggestive of a CTD in 34/85 RP patients, namely sclerodactyly in 13, digital scars in 6, telangiectasia in 9 and oesophageal hypomotility (barium X-ray) in 4; Luggen et al. [24] evaluated 64 patients with one or more findings of a CTD who did not satisfy the classification criteria for any CTD, and found that, at presentation, 25 had dysphagia, 10 had shortness of breath, 15 had hand swelling, 6 had digital ulcers, 2 had sclerodactyly, 22 had oesophageal hypomotility and 17 had abnormal lung function.

Our study is the first to investigate the extent of clinical and pre-clinical organ involvement in patients with a condition referred to as pre-scleroderma–ISSc–early SSC [6–8] by comparing the prevalence of relevant clinical and functional findings in patients with early SSC (i.e. RP with scleroderma marker autoantibodies or typical capillaroscopic findings and no other clinical manifestation) [8], probable SSC (i.e. SSC not satisfying ACR classification criteria) [2] and UCTD, i.e. patients with no disease manifestation or any laboratory finding pathognomonic of a major CTD [13].

As expected, we found a significantly higher prevalence of clinical findings (puffy fingers, digital ulcers or scars, dysphagia/heartburn and shortness of breath) in patients with probable SSC than in patients with UCTD or early SSC (patients presenting no clinical manifestation other than RP). The higher prevalence of any of these findings in patients with probable SSC with respect to those with UCTD is consistent with the reported prevalence of each of them in large series of UCTD patients [27]. In addition, we found functional findings consistent with early scleroderma heart and/or lung and/or oesophageal involvement [14, 16, 31, 32] in 57 RP patients (8 early SSC, 37 probable SSC and 12 UCTD). Again, the prevalence was greater in patients with probable SSC. However, we detected abnormal functional findings in patients with early SSC and in patients with UCTD, who are not currently investigated for these alterations.

When we compared the clinical and functional findings of internal organ involvement in our RP patients, we found that history taking is complicated by both false-negative and false-positive results in the detection of oesophageal (dysphagia/heartburn) or heart/lung involvement (shortness of breath). Whereas the false negativity was somewhat expected, the false positivity in 24 patients (9 reported shortness of breath and 15 reported dysphagia/heartburn) means that clinical findings referred by patients at history taking should be confirmed by appropriate functional studies.

Three conclusions may be drawn from the above-reported results.

(i) Patients with early SSC, who have recently been shown to have a 60-fold higher risk of developing definite SSC with respect to other asymptomatic RP patients, [8] can have pre-clinical sclerodermic internal involvement already at presentation.

(ii) Patients with strictly defined UCTD can have pre-clinical sclerodermic internal organ involvement at presentation.

(iii) Internal organ involvement must be assessed in patients presenting with early SSC, probable SSC and UCTD by sensitive and specific functional studies because both false-positive and false-negative findings can emerge from history taking.

We investigated the 115 patients enrolled in this study for features associated with an increased risk of deranged internal organ function (i.e. an E : A ratio <1 and/or a DLCO <80% and/or a basal LES pressure <15 mmHg). Patients with scleroderma marker autoantibodies, puffy fingers, dysphagia/heartburn had a significantly higher risk of internal organ involvement. We found no independently increased risk either in patients with a typical capillaroscopic pattern or in those with digital ulcers/scars, but 42 of the former [42/45 (93%)] and 9 of the latter [9/19 (47%)] presented a marker autoantibody profile.

From a clinical point of view, several studies of other CTDs found that marker autoantibodies are detectable in serum before the disease is manifest [31, 32]. This is also the case for SSC. From a therapeutic point of view, we do not know whether calcium channel blockers or other vasoactive drugs commonly used in RP are able to block the disease progression in this stage. Nevertheless, pre-SSc patients with a low LES pressure should be treated with proton pump inhibitors. Similarly, pre-SSc patients who suffer from alveolitis, as confirmed by high-resolution CT of the lung and/or broncho-alveolar lavage analysis should be treated with cyclophosphamide. Moreover, when an anti-fibrotic agent becomes available, the pre-SSc stage is the one in which the clinician should start therapy at least in those patients presenting an autoantibody profile consistent with a diffuse disease [33, 34].

From a taxonomic point of view, our study suggests that patients with early SSC or UCTD in whom...
scleroderma-related functional internal organ involvement has been detected should be labelled as being affected by SSc. These patients should be separated from patients with SSc sine scleroderma, who already present a clear-cut clinical involvement of internal organs but have not developed skin sclerosis [18].

The relationships between UCTD and major CTDs including SSc have been debated in the past few years. At present [13, 28], the presence of any marker autoantibody as those detected in early and probable SSc inhibits the diagnosis of UCTD. Therefore, the three groups of RP patients investigated by us can be considered mutually exclusive.

Our study was conducted on a small number of patients. In addition, it was confined to patients admitted to a tertiary centre, who do not necessarily reflect the reality of all early SSC patients. Actually, we did not investigate patients with primary RP, who would represent an interesting control group. The ongoing multicentre studies planned by the European League Against Rheumatism (EULAR) Scleroderma Trial and Research Group [9] is likely to overcome these limitations, and to identify factors associated with an increased risk of functional internal organ involvement, at presentation, in patients with RP.

In conclusion, we have investigated patients suffering from RP for scleroderma-related capillaroscopic findings, marker autoantibodies, clinical manifestations and internal organ functional abnormalities. We have found that a significant percentage of patients satisfying criteria for early SSc or UCTD present a scleroderma-related heart and/or lung and/or oesophageal functional abnormality, which is often pre-clinical. At present, our findings are an aid to clinicians in their evaluation of patients with early SSc or UCTD. In future, when an anti-fibrotic drug becomes available, the data will help to identify the proper time to start therapy.

Rheumatology key messages

- Patients with early SSC should be investigated for pre-clinical internal organ involvement.
- Patients with strictly defined UCTD can present scleroderma-type internal organ involvement.

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