Concise report

Investigation of prognostic factors for skin sclerosis and lung function in Japanese patients with early systemic sclerosis: a multicentre prospective observational study

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Abstract

Objective. To clarify the clinical course of SSc in Japanese patients with early-onset disease. It is well known that ethnic variations exist in the clinical features and severity of SSc. However, neither the clinical course nor prognostic factors have been thoroughly investigated in the Japanese population.

Methods. Ninety-three Japanese patients of early-onset SSc (disease duration: <3 years) with diffuse skin sclerosis and/or interstitial lung disease were registered in a multi-centre observational study. All patients had a physical examination with laboratory tests at their first visit and at each of the three subsequent years. Factors that could predict the severity of skin sclerosis and lung involvement were examined statistically by multiple regression analysis.

Results. Two patients died from SSc-related myocardial involvement and four patients died from other complications during the 3-year study. Among various clinical data assessed, the initial modified Rodnan total skin thickness score (MRSS) and maximal oral aperture were associated positively and negatively with MRSS at Year 3, respectively. Additionally, initial ESR tended to be associated with final MRSS. Pulmonary vital capacity (VC) in the third year was significantly associated with initial %VC. Furthermore, patients with anti-topo I antibody tended to show reduced %VC at Year 3.

Conclusions. Several possible prognostic factors for skin sclerosis and lung function were detected in Japanese patients with early SSc. Further longitudinal studies of larger populations will be needed to confirm these findings.

Key words: systemic sclerosis, scleroderma, prognostic factor, skin sclerosis, interstitial lung diseases, treatment

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Introduction
SSc is a CTD characterized by tissue fibrosis in the skin and internal organs. Interstitial lung diseases (ILDs) develop in more than half of SSc patients and are one of the major SSc-related causes of death [1, 2]. The natural course of skin sclerosis and internal organ involvement and identification of prognostic factors have been extensively reported in Europe and the USA [3–6]. However, there are some racial differences in the clinical and laboratory features of SSc [7]. For example, the severity of skin sclerosis is modest in Japanese patients [8]. Furthermore, pulmonary arterial hypertension and renal crisis are rare in Japanese SSc patients [9]. Furthermore, racial differences are found in the distribution of SSc-related serum ANAs [10]. The frequency of anti-RNA polymerases antibody (Ab) is lower in the Japanese population than in US or European patient populations [9]. However, there have been no multiple-centre prospective studies concerning the clinical features of SSc in Japanese individuals.

In most patients, severe organ involvement occurs within the first 3 years of disease and skin sclerosis seldom progresses after 5 or 6 years [3, 11]. Therefore, predicting disease progression is particularly important for SSc patients at their first visit. In the present study, we aimed to determine if any initial clinical or laboratory features were associated with subsequent disease severity in Japanese SSc patients with a short disease duration of <3 years.

Materials and methods

Patients

Patients were grouped according to the degree of skin involvement, based on the classification system proposed by LeRoy et al. (dcSSc vs lcSSc) [12]. In this study, 93 Japanese patients with early SSc (disease duration: <3 years) who had dcSSc or ILD were registered at 12 major scleroderma centres in Japan (Atami Hospital, International University of Health and Welfare; Gunma University Hospital; Kanazawa University Hospital; Keio University Hospital; Kitasato University Hospital; Kumamoto University Hospital; Nagasaki University Hospital; Nagoya University Hospital; Sapporo Medical University Hospital; Tokyo University Hospital; Tokyo Women’s Medical University Hospital; Tsukuba University Hospital).

Among these patients, two died from SSc-related myocardial involvement and four died from complications (ANCA-associated vasculitis, sepsis, thrombotic thrombocytopenic purpura and uterine cancer, respectively) during the 3-year study. Therefore, 87 patients (49 patients had dcSSc with ILD, 27 patients had dcSSc without ILD and 11 patients had lcSSc with ILD) were followed for 3 years. Sixty-four were females and 23 were males; the median (range) age was 50 (3–74) years. All patients fulfilled the criteria for SSc proposed by the ACR [13]. The median (range) disease duration (the period from the development of any symptoms excluding RP to our first assessment) of patients was 20 (1–35) months. With respect to ANA, 56 patients were positive for anti-topo I Ab and 7 patients were positive for ACA. Medical ethics committee of Kanazawa University approved the study. In addition, this study was approved by the ethics committees of International University of Health and Welfare, Gunma University, Keio University, Kitasato University, Kumamoto University, Nagasaki University, Nagoya University, Sapporo Medical University, Tokyo University, Tokyo Women’s Medical University and Tsukuba University. Informed consent was obtained from all patients.

Clinical assessments

Patients had a physical examination and laboratory tests performed at their first visit and at each subsequent year for 3 years. The degree of skin involvement was determined according to the modified Rodnan total skin thickness score (MRSS), as described elsewhere [14]. Organ system involvement was defined as described previously [15] with some modifications: ILD = bibasilar interstitial fibrosis or ground-glass shadow on high-resolution CT (HRCT); pulmonary arterial hypertension (PAH) = clinical evidence of pulmonary hypertension and elevated right ventricular systolic pressure (>45 mmHg) documented by echocardiography in the absence of severe pulmonary interstitial fibrosis; oesophagus = apparent dysphasia, reflux symptoms or hypomotility shown by barium radiography; heart = pericarditis, congestive heart failure or arrhythmias requiring treatment; kidney = malignant hypertension and rapidly progressive renal failure unexplained by certain diseases other than SSc; joint = inflammatory polyarthritis or arthritis; and muscle = proximal muscle weakness and elevated serum creatine kinase. An HAQ modified for Japanese patients [16], digital ulcer, pitting scar, maximal oral aperture (the maximum vertical length of opened mouth) and skin pigmentation/depigmentation were also evaluated. ESR and pulmonary function, including vital capacity (VC) and diffusion capacity for carbon monoxide (DLCO) were also tested.

Statistical analysis

JMP Statistically Discovery Software (SAS institute, Cary, NC, USA) was used for analysis. Potential prognostic factors for the severity of skin sclerosis and lung function were statistically examined by multiple regression analysis. A P < 0.05 was considered to be statistically significant. All values are expressed as the median (range).

Results

The clinical course of SSc in Japanese patients

To provide a comprehensive evaluation of the clinical features of SSc in Japanese patients, we analysed clinical data as well as laboratory test results from 87 patients with short disease duration (Table 1). To assess the degree of skin involvement in patients, MRSS values were calculated; VC and DLCO percentages were used to assess lung involvement. For the patient population as a whole, the median (range) MRSS decreased from 17 (2–42) to 12 (0–41) during the first year. The median (range) MRSS
was 12 (0–41) at the end of Year 2 and 10 (0–47) at the end of Year 3. Median (range) values for %VC did not significantly change during the 3-year evaluation period: 95 (49–144) at first visit, 93 (26–137) at the end of the first year, 95 (49–144) at the end of the second year and 92 (51–137) at the end of the third year. Similarly, median values for %DLCO did not significantly change during the 3 years.

The frequency of patients with ILD or PAH was stable during the evaluation period. Similarly, the number of patients with oesophageal or joint involvement, pitting scar or skin pigmentation/depigmentation did not vary significantly over time. The value of HAQ and maximal oral aperture did not significantly change during the course. The median (range) value of ESR was 18 (2–95) mm/h at the first visit, then it reduced to 16 (2–84), 13 (1–63) and 12 (0.5–122) mm/h, during the subsequent 3 years. Oral prednisolone (~20 mg/day) use was common, with 56 patients starting to take this drug after the first visit and 70 patients having taken it by the end of Year 3. Two patients developed renal crisis during the course of the study (data not shown). Patients with digital ulcer or heart muscle involvement were rare during the course (fewer than 10 patients, data not shown).

Prognostic factors of the progress of skin sclerosis

Next, we evaluated clinical or laboratory factors present at first visit that could predict the severity of skin sclerosis of 3 years later. Investigated factors were as follows: age, gender, disease duration, anti-topo I Ab, ACA, MRSS at the first visit, %VC, %DLCO, existence of each organ involvement (ILD, PAH, oesophagus, joint), pitting scar, skin pigmentation/depigmentation, HAQ, maximal oral aperture, ESR, CS treatment and cyclophosphamide treatment. Cases that have any missing data were excluded and thereby 80 patients were analysed. We performed multiple regression using stepwise way that specified the α-level for either adding or removing a regression as 0.20 (Table 2). As a result, the multiple regression equation predicting MRSS at the third year was as follows: MRSS at the first visit + 0.35 × MRSS at the third year + 0.042 × maximal oral aperture + 0.042 × ESR. Thus, MRSS at the third year was significantly associated with MRSS at first visit (P < 0.001) and was negatively associated with initial maximal oral aperture at first visit (P < 0.01). Additionally, initial ESR tended to be associated with final MRSS (P = 0.17).

Prognostic factors of lung function

We similarly assessed the prognostic factors of impaired lung function to estimate ILD severity. Here, we used %VC as representative markers of lung function. Cases that have any missing data including %VC at the third year were excluded and thereby 58 patients were analysed. We performed multiple regression in a stepped manner that specified the α-level for either adding or removing a regression as 0.20 (Table 3). As a result, the multiple regression equation predicting %VC at the third year was as follows: %VC at the first visit + 0.35 × %VC at the third year + 0.042 × maximal oral aperture + 0.042 × ESR. Thus, %VC at the third year was significantly associated with %VC at first visit (P < 0.001).

| Table 1 The course of clinical and laboratory features in patients with SSc |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | First visit                 | Year 1                      | Year 2                      | Year 3                      |
| MRSS                       | 17 (2–42); n = 87           | 12 (0–41); n = 84           | 12 (0–41); n = 84           | 10 (0–47); n = 87           |
| %VC                        | 95 (49–144); n = 70         | 93 (26–137); n = 55         | 95 (49–144); n = 57         | 92 (51–137); n = 60         |
| %DLCO                      | 70 (11–113); n = 70         | 68 (10–105); n = 55         | 69 (11–96); n = 57          | 68 (10–120); n = 60         |
| ILD                        | 54 (62); n = 87             | 47 (64); n = 73             | 47 (64); n = 73             | 46 (63); n = 73             |
| PAH                        | 9 (10); n = 87              | 9 (12); n = 76              | 8 (11); n = 72              | 11 (13); n = 84             |
| Oesophagus                 | 33 (37); n = 87             | 26 (34); n = 77             | 35 (48); n = 73             | 34 (40); n = 85             |
| Joint                      | 20 (23); n = 86             | 14 (18); n = 77             | 9 (12); n = 73              | 17 (20); n = 84             |
| Pitting scar               | 27 (33); n = 87             | 29 (38); n = 76             | 35 (48); n = 73             | 33 (38); n = 86             |
| Pigmentation/depigmentation| 54 (62); n = 87             | 49 (64); n = 77             | 41 (57); n = 72             | 50 (60); n = 84             |
| HAQ                        | 0.08 (0–2); n = 83          | 0.125 (0–1.75); n = 74      | 0.25 (0–2.5); n = 73        | 0.125 (0–2.25); n = 83      |
| Maximal oral aperture      | 45 (18–70); n = 87          | 45 (28–68); n = 75          | 46 (25–67); n = 72          | 45 (10–67); n = 83          |
| ESR                        | 18 (2–95); n = 80           | 16 (2–84); n = 61           | 13 (1–63); n = 52           | 12 (0.5–122); n = 57        |
| CS                         | 56 (64); n = 87             | 61 (82); n = 74             | 64 (86); n = 74             | 70 (80); n = 87             |
| Cyclophosphamide           | 11 (13); n = 87             | 14 (19); n = 75             | 8 (12); n = 68              | 9 (10); n = 87              |

Values are represented as median (range) or as number of positive cases with percentage within parentheses, in total patients in whom those data are available.
TABLE 3 Factors predicting %VC at the third year determined by multiple regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>10.94</td>
<td>8.54</td>
<td>0.20</td>
</tr>
<tr>
<td>%VC at the first visit</td>
<td>0.85</td>
<td>0.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-topo I Ab (+)</td>
<td>2.32</td>
<td>1.64</td>
<td>0.19</td>
</tr>
</tbody>
</table>

The multiple regression equations predicting %VC at the third year are as follows: %VC at the third year = 10.94 + 0.85 × %VC at the first visit + anti-topo I Ab (+) → 2.32 (R² = 0.70, P < 0.0001). Thus, %VC at the third year was significantly associated with the value of %VC at first visit (P < 0.0001). In addition, %VC at the third year tended to be lower in patients with anti-topoisomerase I Ab (P = 0.19).

Discussion

To our knowledge, this study is the first multi-centre, longitudinal prospective study to investigate the clinical course of Japanese patients. For this study, 87 patients with early-onset SSC (<3 years) were followed over 3 years. Median MRSS was reduced 5 points during the first year, and continued to decrease through the third year. This trend was similar to that identified in our previous, single-centre prospective observational study of Japanese SSC patients [17]. Although the reason for the prominent first-year reduction in MRSS in our current study is unknown, our previous single-centre study [17] indicated that the dose of oral CS was related to the decrease of MRSS. However, in this multi-centre observational study we could not perform a similar analysis of prednisolone dose in patients at each centre. In addition, other therapies including cyclophosphamide were also used in a part of patients in our observational study. Previous large studies demonstrated that MRSS naturally reduced during the disease course and time was a significant predictor of MRSS [3-6]. Therefore, the effect of CS therapy for MRSS remains unclear from our data. Since it has been suggested that CS therapy can induce renal crisis, high doses of CSs have not been recommended for the treatment of SSC [18]. However, renal crisis is not as common in Japanese patients [9], and only two patients (one had been taking low-dose CS, whereas the other had not) developed renal crisis during the course of our study.

The main aim of this study was to define the prognostic factors of skin sclerosis and ILD. The multiple regression equation was defined to predict the MRSS at the third year among multiple factors presenting at the first visit. MRSS at the first visit was significantly correlated with MRSS at the third year in all patients. Maximal oral aperture was correlated inversely with MRSS in the third year. Thus, the current skin sclerosis likely reflects the extent of skin sclerosis of 3 years later independent of other organ’s involvement or treatment. Additionally, ESR tended to be associated with final MRSS. The presence of autoantibodies such as anti-topo I Ab and ACA was not shown to have value as a prognostic indicator of MRSS. However, this may be due to population bias in our study, since most patients were positive for anti-topo I Ab and negative for ACA.

The current study revealed that %VC and %DLCO remained nearly constant or slightly reduced during the 3-year period. Since patients with progressive ILD received immunosuppressive treatment, including cyclophosphamide therapy in the participating facilities, this may have affected the stabilization of lung function in our cases. The frequency of ILD detected by HRCT was not increased during the course of the study, indicating ILD is usually detected early in the disease course and rarely develops later. In consistent with generally stable course of %VC, %VC at their first visit highly associated with the %VC at the third year in all patients with or without treatment. Patients with anti-topo I Ab tended to show reduced %VC at the third year. Although these findings are not surprising, we first confirmed them in Japanese patients.

Our study has some limitations. The population is not large and the follow-up period is not long. This is an observational study and therefore the treatment is heterogeneous. In addition, other parameters including CRP could not be analysed due to the lack of data. We should also include disease activity variables [19] and disease severity scale [20] in our future study. Further longitudinal studies in a larger population will be needed to clarify the natural course and prognostic factors in Japanese SSc patients.

Rheumatology key messages

- Initial ESR tended to be associated with skin score at Year 3 in Japanese scleroderma patients.
- Japanese scleroderma patients with anti-topo I Ab tended to show reduced %VC at the third year.

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