Initial Predictors of Survival in Patients with Systemic Sclerosis (Scleroderma)

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Abstract. We conducted a retrospective study of 86 patients with systemic sclerosis (SSc) to clarify the initial predictors of survival at the first visit to the hospital. A life-table analysis of survival was performed concerning 137 items from their histories, physical examinations, and laboratory data. The observed cumulative survival rates were 78.0 percent at 5 years and 68.2 percent at 10 years. Ten items were found to be the initial predictors of survival in patients with SSc. Of these 10 items, 9 items showed significant differences within 5 years of the first visit to the hospital. Patients with resting electrocardiographic abnormalities, such as atrial or ventricular arrhythmias, or conduction disturbances, pulmonary fibrosis on the chest x-ray films, or decreased vital capacity had significantly lower survival rates. However, patients with anti-centromere antibody had a significantly better survival rate. In addition, males, aged patients over 65 years old, and patients with proteinuria, leucopenia, or hypergammaglobulinemia had significantly lower survival rates. Only patients with proximal scleroderma at the first visit to the hospital had a significantly lower survival rate after 8 years. These results are useful in predicting individual patients at risk of shortened survival and in managing these patients. (Keio J Med 41 (3): 141-145, 1992)

Key words: initial symptoms, survival rates, prognosis

Introduction

Systemic sclerosis (SSc: scleroderma) is a systemic connective tissue disease characterized by fibrotic and degenerative changes in the skin and vascular changes, and is accompanied by serious internal organ involvement.1,2 Clinical severity and progression vary among subsets ranging from limited scleroderma to diffuse scleroderma, according to the extent of skin involvement.3 However, patients often have different degrees of visceral involvement and different prognoses even when classified in the same subset.3

Many retrospective studies on survival in SSc patients have been performed.3–15 Clinical manifestations and laboratory data during the entire observation period were analyzed in these studies. Although it is generally accepted that cardiopulmonary and renal involvements have been the main causes of decreased survival, the initial predictors in patients with SSc at the first visit to the hospital are not clear. In this study, clinical and laboratory data at the first visit to the hospital were analyzed to clarify the initial predictors of survival in Japanese patients with SSc.

Patients and Methods

Patients

Eighty-six patients with SSc at Keio University Hospital, Department of Internal Medicine, were studied. These patients were diagnosed with SSc according to the preliminary criteria for the classification of SSc of the American Rheumatism Association (American College of Rheumatology).16 Five patients with complete CREST syndrome were included. However, they were not definitely diagnosed as overlap syndrome with systemic lupus erythematosus, polymyositis or dermatomyositis.
Methods

The medical records of all patients were reviewed. One hundred thirty-seven items from their histories, physical examinations, and laboratory data within one year of the first visit to Keio University, Department of Internal Medicine, were encoded. Nine items of histories, 72 items of physical examinations, and 56 items of laboratory data were included. These items were regarded as the initial clinical manifestations. The most of them were selected from the uniform data base for rheumatic diseases proposed by the Arthritis Foundation.

The life-table method was used for determining the survival of SSc patients.

Sera from all patients were stored at -20°C until use. Serum anti-nuclear antibodies were screened by the indirect immunofluorescence method. Anti-centromere antibody was examined by the indirect immunofluorescence method, while anti-Topoisomerase I antibody and anti-U1 RNP antibody were identified by the double immunodiffusion method.

Results

Patient profiles

Of the 86 patients with SSc studied, 75 were women and 11 were men. All patients were Japanese. The mean age of the patients at the first visit to the hospital was 47.5 years (range, 19 to 76). Six patients over 65 years old were regarded as the aged. The mean observation period was 5.1 years (range, 0 to 15). During the observation period, 46 patients survived, while 25 patients died and 15 patients were lost to follow-up.

Overall survivorship

The observed cumulative survival rates were 78.0 percent at 5 years and 68.2 percent at 10 years (Fig 1).

Initial clinical manifestations and subsequent survival

Survival was examined depending on whether each initial clinical manifestation was present or absent. Ten items were found to be the initial predictors of survival in patients with SSc (Table 1). Out of these 10 items, 9 showed significant differences within 5 years of the first visit to the hospital.

Patients who had resting electrocardiographic abnormalities, such as atrial or ventricular arrhythmias, or conduction disturbances, at the first visit to the hospital had a significantly (P<0.01) lower survival rate, compared with other patients with normal electrocardiographic findings (Fig 2). Similarly, patients with pulmonary fibrosis on their chest x-ray films or patients with decreased vital capacity had significantly (P<0.01) lower survival rates (Fig 3, 4).

<table>
<thead>
<tr>
<th>Initial Predictors</th>
<th>Percent of Patients Positive</th>
<th>P</th>
<th>Follow-up Period (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting Electrocardiographic Abnormalities</td>
<td>8</td>
<td>&lt;0.01</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary Fibrosis</td>
<td>52</td>
<td>&lt;0.01</td>
<td>4</td>
</tr>
<tr>
<td>Decreased Percent Vital Capacity</td>
<td>24</td>
<td>&lt;0.01</td>
<td>4</td>
</tr>
<tr>
<td>Negative Anti-centromere Antibody</td>
<td>86</td>
<td>&lt;0.01</td>
<td>3</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>3</td>
<td>&lt;0.05</td>
<td>1</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>29</td>
<td>&lt;0.05</td>
<td>4</td>
</tr>
<tr>
<td>Hypergammaglobulinemia</td>
<td>30</td>
<td>&lt;0.05</td>
<td>4</td>
</tr>
<tr>
<td>Males</td>
<td>13</td>
<td>&lt;0.05</td>
<td>4</td>
</tr>
<tr>
<td>Age Over 65 Years Old</td>
<td>7</td>
<td>&lt;0.05</td>
<td>4</td>
</tr>
<tr>
<td>Proximal Scleroderma</td>
<td>55</td>
<td>&lt;0.05</td>
<td>8</td>
</tr>
</tbody>
</table>
Patients with anti-centromere antibody had a significantly (P<0.01) better survival rate, from the viewpoint of anti-nuclear antibodies.

Males, aged patients, patients with proteinuria, leukopenia (white blood cell count less than 4000/µl), or hypergammaglobulinemia (serum gammaglobulin more than 2 g/dl) had significantly (P<0.05) lower survival rates.

In addition, patients with proximal scleroderma had a significantly (P<0.05) lower survival rate, compared with patients with only sclerodactyly 8 years after the first visit to the hospital.

Discussion

Various kinds of internal organ involvement as well as fibrotic and degenerative changes in the skin have been found in patients with SSc. These involvements were related to the prognoses and the subsets of these patients. Tuffanelli and Winkelmann reported that the 5-year survival rate in patients with SSc was only 70.3% in 1961. However, the 5-year survival rate in patients with SSc was recently estimated to be 75 or 77%. In this study, the 5-year survival rate was 78.0%. Therefore, this study confirmed recent advances in the management of SSc patients, including the development of new drugs such as vasodilators and angiotensin-converting enzyme inhibitor, and the current concept of better quality of life.

Many retrospective studies on survival among patients with SSc have been published. All of the authors have agreed that the development of serious visceral involvement, such as heart or lung, portends early mortality in patients with SSc. We have already shown that the incidence of cardiac failure and respiratory failure as causes of death were high in SSc patients who died within 5 years of their first visit to the hospital.

In this study, resting electrocardiographic abnormalities, pulmonary fibrosis on the chest x-ray films, and reduced vital capacity were able to serve as initial predictors of survival at the first visit to the hospital. Although ambulatory electrocardiography was recommended in the management of patients with SSc, this study emphasized the clinical usefulness of resting electrocardiography at the first visit to the hospital. Arrhythmias and conduction disturbances may be caused...
by myocardial fibrosis, leading to cardiac failure.\textsuperscript{24} In addition, pulmonary fibrosis can cause cardiac failure as a result of pulmonary hypertension and respiratory infection. Moreover, non-invasive studies, such as echocardiography and myocardial perfusion scanning, are necessary to evaluate these points.

Patients with anti-centromere antibody had better survival rates. This finding was compatible with the report by Steen et al,\textsuperscript{20} and confirmed the clinical importance of anti-nuclear antibodies. It was recently reported that other anti-nuclear antibodies, such as anti-7-2 RNP (Th) antibody and anti-RNA polymerase complex antibodies, are capable of serving as predictors of the prognosis in patients with SSc.\textsuperscript{18} Various kinds of anti-nuclear antibodies should be identified to predict the survival of these patients.

Males and aged Japanese patients had lower survival rates. This finding confirmed the results of previously reported foreign studies.\textsuperscript{3,6–10,12,15,22} Proteinuria may be a sign of scleroderma renal crisis. Otherwise, proteinuria, leukopenia, and hypergammaglobulinemia suggested overlapping features of systemic lupus erythematosus. Careful clinical assessment is necessary to treat these patients.

In the literature, the extent of skin involvement has been unclear in terms of prognosis. Barnett et al, reported the association between the prognosis and the early extent of clinical skin involvement.\textsuperscript{13} However, Cunningham et al, found that mortality was unrelated to the extent of skin involvement.\textsuperscript{11} Although patients with proximal scleroderma at the first visit to the hospital had a lower survival rate, the difference was only found to be significant after 8 years. Therefore, our results suggest that the degree of visceral involvement has a more important role than skin involvement.

In this study, initial predictors of survival in patients with SSc were found. These findings are useful in predicting individual patients at risk of shortened survival and in managing these patients. Further studies are necessary to analyze other factors and various kinds of therapy.

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References
