Clinical features of patients with systemic sclerosis accompanied by rheumatoid arthritis

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ABSTRACT

Objective. To determine the incidence of patients with both systemic sclerosis and rheumatoid arthritis (SSc-RA) and the clinical features of those with SSc-RA.

Methods. All 173 patients with systemic sclerosis in our clinic were investigated.

Results. Of the 173 patients with systemic sclerosis, 9 (5.2%) developed rheumatoid arthritis (RA). At the first visit, arthritis prior to Raynaud’s phenomenon, increased C-reactive protein (CRP), and elevated rheumatoid factor (RF) were seen in patients with SSc-RA at a significantly higher incidence than in those without (44.4% versus 4.8%, p < 0.01; 55.6% versus 13.6%, p < 0.001; 247.2 ± 312.1 versus 47.9 ± 54.3 IU/ml, p < 0.001, respectively). Furthermore, in 8 of the 9 patients with SSc-RA, CRP was increased before the diagnosis of RA.

Conclusion. These results suggest that systemic sclerosis patients with elevated RF and a history of arthralgia prior to Raynaud’s phenomenon should be followed up with serial measurements of CRP due to their risk of developing RA.

Introduction

Connective tissue diseases usually develop without overlap features and remain within definite categories such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). Occasionally, however, two or more connective tissue diseases may develop in the same patient, often sequentially and sometimes concurrently, producing overlap syndromes in which the American College of Rheumatology (ACR) criteria are fulfilled for each component (1, 2). Overlap syndromes most commonly include polymyositis with either SSc or SLE (3). On the other hand, although bony erosion is seen in arthritis associated with SSc (4), overlapping of SSc with RA (SSc-RA) is uncommon (5, 6). However, some cases of SSc-RA have been recently reported. Horiki et al. reported that almost all of these patients had generalized sclerosis of the skin and antitopoisoeraser I antibodies (7). Zimmermann et al. reported on patients with SSc-RA who had limited sclerosis of the skin and anticientromere antibodies (8). They also found that these patients were characterized by an incomplete CREST (calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) syndrome. In addition, their study demonstrated the presence of autoantibodies typical of both diseases and cross-reactivity of anticentromere antibodies with hnRNP-A2/Ro33 in the sera of these patients.

Thus, the clinical features of patients with SSc-RA are still controversial. In the present study we investigated patients with SSc retrospectively and evaluated the incidence of patients with overlapping RA and their clinical features.

Patients and methods

Clinical assessment

All 173 patients with SSc who were evaluated in our clinic during the period from 1990 through 2001 were included in the study. Patients were grouped according to the classification proposed by LeRoy et al. (9): 63 patients had diffuse cutaneous SSc (dcSSc) and 110 patients had limited cutaneous SSc (lcSSc), as described previously (10). All patients fulfilled the criteria proposed by the ACR (11). The diagnosis of RA was also based on the proposed criteria of the ACR (12). SSc patients who were diagnosed with overlapping RA had articular roentgenogram findings such as severe narrowing, osteoporosis, and joint erosions.

The clinical manifestations and laboratory findings of each patient were obtained from the medical records. Patients were evaluated for the presence of gastrointestinal, pulmonary, renal or muscle involvement as described previously (10).

Antinuclear antibodies

Antinuclear antibodies (ANA) were detected by indirect immunofluorescence using HEp-2 cells as the substrate and double immunodiffusion (13).

Measurement of C-reactive protein and rheumatoid factor

Serum C-reactive protein (CRP) was
evaluated by the equilibrium turbidimetric immunoassay (14). Serum CRP levels > 0.3 mg/dl were considered elevated. The latex fixation test was used for the detection of rheumatoid factor (RF) (15, 16). RF > 20 IU/ml were considered elevated.

Statistical analysis
Statistical analysis was carried out with a Student’s t-test for the comparison of means, and Fisher’s exact probability test for the analysis of the incidence. P values less than 0.05 were considered significant.

Results
Incidence and clinical manifestations of SSc patients accompanied with RA
Of the 173 patients with SSc, 9 (5.2%) subsequently developed RA (Table I, Fig. 1 and Fig. 2). The incidence (the number of new cases/N/year) was 0.43%. Four of the 9 patients (44.4%) had dcSSc, and the other 5 patients (55.6%) had lcSSc. All 9 patients were females, and the diagnosis of RA in each patient was posterior to that of SSc. The duration from the onset of arthralgia to the diagnosis of RA in each patient ranged from 1 to 22 years.

Table I. Clinical and laboratory features of 9 patients with SSc-RA.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Skin sclerosis</th>
<th>PF at their first visit (IU/ml)</th>
<th>Age at onset of Raynaud’s phenomenon</th>
<th>Age at onset of arthralgia</th>
<th>Age at diagnosis of SSc</th>
<th>Age at diagnosis of RA</th>
<th>Age at increased CRP</th>
<th>Antinuclear antibodies</th>
<th>Treatment after diagnosis of RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>dcSSc +</td>
<td>732</td>
<td>58y</td>
<td>55y</td>
<td>59y</td>
<td>60y</td>
<td>59y*</td>
<td>Negative</td>
<td>SA</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>dcSSc -</td>
<td>55</td>
<td>53y/6m</td>
<td>53y/3m</td>
<td>54y</td>
<td>60y/9m</td>
<td>60y/1m</td>
<td>Topo-I</td>
<td>PSL, DP, SA</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>dcSSc +</td>
<td>487</td>
<td>39y</td>
<td>66y</td>
<td>39y</td>
<td>70y</td>
<td>64y*</td>
<td>Topo-I</td>
<td>PSL</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>dcSSc -</td>
<td>20</td>
<td>29y</td>
<td>42y</td>
<td>32y</td>
<td>55y</td>
<td>64y*</td>
<td>Topo-I</td>
<td>PSL</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>lcSSc +</td>
<td>46</td>
<td>25y</td>
<td>23y</td>
<td>32y</td>
<td>34y/6m</td>
<td>34y/3m</td>
<td>Others</td>
<td>PSL, SA</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>lcSSc +</td>
<td>54</td>
<td>17y</td>
<td>35y</td>
<td>33y</td>
<td>36y</td>
<td>35y*</td>
<td>Topo-I</td>
<td>PSL, DP, SA</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>lcSSc -</td>
<td>735</td>
<td>45y</td>
<td>44y</td>
<td>61y</td>
<td>66y</td>
<td>61y*</td>
<td>Topo-I</td>
<td>PSL, DP, SA</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>lcSSc -</td>
<td>8</td>
<td>41y/10m</td>
<td>42y/3m</td>
<td>42y/11m</td>
<td>58y</td>
<td>Not elevated</td>
<td>Topo-I, U1 RNP</td>
<td>PSL, DP</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>lcSSc -</td>
<td>88</td>
<td>33y</td>
<td>35y</td>
<td>39y</td>
<td>40y</td>
<td>39y*</td>
<td>U1 RNP</td>
<td>PSL, SA</td>
</tr>
</tbody>
</table>


* Patients had increased CRP at their first visit.

Fig. 1. X-rays of the left hand of a patient with scleroderma and overlapping rheumatoid arthritis. White arrow shows the severe erosive change of PIP joint in thumb.

Fig. 2. Skin sclerosis and marked contracture of the phalanges in a patient with SSc-RA.
Systemic sclerosis with rheumatoid arthritis / M. Jinnin et al.

Table II. The clinical and laboratory findings of SSc patients with and without RA at their first visit.

<table>
<thead>
<tr>
<th></th>
<th>SSc patients with RA (n=9)</th>
<th>SSc patients without RA (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male: female)</td>
<td>0.9</td>
<td>15.149</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>7.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Mean age at onset (years)</td>
<td>36.9</td>
<td>43.5</td>
</tr>
<tr>
<td>Type (diffuse: limited)</td>
<td>4.5</td>
<td>60.104</td>
</tr>
<tr>
<td>Clinical and features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitting scars/ulcers</td>
<td>66.7</td>
<td>49.7</td>
</tr>
<tr>
<td>Nailfold bleeding</td>
<td>50.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>71.4</td>
<td>56.5</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>25.0</td>
<td>19.5</td>
</tr>
<tr>
<td>Sicc symptoms</td>
<td>50.0</td>
<td>51.6</td>
</tr>
<tr>
<td>Patients with arthralgia before Raynaud’s phenomenon</td>
<td>44.4*</td>
<td>4.8</td>
</tr>
<tr>
<td>Organ involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>44.4</td>
<td>39.4</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>66.7</td>
<td>54.3</td>
</tr>
<tr>
<td>Heart</td>
<td>0</td>
<td>5.8</td>
</tr>
<tr>
<td>Kidney</td>
<td>0</td>
<td>7.8</td>
</tr>
<tr>
<td>Muscle</td>
<td>14.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Laboratory features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased CRP</td>
<td>55.6**</td>
<td>13.6</td>
</tr>
<tr>
<td>ESR (mm/hour)</td>
<td>33.3</td>
<td>26.1</td>
</tr>
<tr>
<td>Rheumatoid factor (IU/ml)</td>
<td>247.2**</td>
<td>47.9</td>
</tr>
<tr>
<td>ANA specificity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topo-I</td>
<td>55.5</td>
<td>31.7</td>
</tr>
<tr>
<td>Centromere</td>
<td>0</td>
<td>31.1</td>
</tr>
<tr>
<td>U1 RNP</td>
<td>11.1</td>
<td>12.2</td>
</tr>
<tr>
<td>DMARD medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>44.5</td>
<td>19.7</td>
</tr>
</tbody>
</table>

Values are percentages unless otherwise indicated.

*P < 0.01; **P < 0.001 versus SSc patients without RA.

SSc: systemic sclerosis; RA: rheumatoid arthritis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibodies; Topo-I: antitopoisomerase I antibody; centromere: anticentromere antibody; U1 RNP: anti-U1 ribonucleoprotein antibody; DMARDs: disease-modifying anti-rheumatic drugs.

Table II shows the clinical and laboratory features of the patients at their first visit. There were no significant differences in gender, duration of disease, mean age at onset, or type of skin sclerosis between SSc patients with RA and those without. On the other hand, SSc patients with RA developed arthralgia prior to Raynaud’s phenomenon at a significantly higher incidence than those without (44.4%, p < 0.01). Furthermore, increased CRP at the first visit was significantly more frequent and RF was significantly higher in patients with SSc-RA (55.6% versus 13.6%, p < 0.001; 247.2± 312.1 versus 47.9±54.3 IU/ml, p < 0.001, respectively). However, there were no significant differences in the erythrocyte sedimentation rate (ESR) or in the DMARD medications since their first visit between SSc patients with RA and those without.

Discussion

The early diagnosis of RA is often difficult in patients with SSc because arthritis is a common clinical feature of both disorders (7). Symmetric polyarthritis and flexion contractures of the joints are frequently observed in both diseases, but some of the clinical and pathologic features of articular involvement are different between RA and SSc. The radiographic articular manifestations of SSc are less severe than those of RA, and are usually limited to mild joint narrowing, osteoporosis, and small discrete erosions at the periarticular margins. Pathologically, there is only a slight tendency to form pannus in SSc, and synovial lesions are characterized initially by inflammation of synovium and later by severe fibrosis of the tissue (17).

SSc-RA has been reported to occur in 4.3% of patients with SSc (18), which is similar to our results. On the other hand, epidemiologically RA occurs in 0.65% of the general population (19). Thus, SSc patients have a nearly 10-fold risk of developing RA and it is clinically important to check for the occurrence of RA in patients with SSc.

In our study, arthritis prior to Raynaud’s phenomenon and increased CRP and RF at the first visit were observed in patients with SSc-RA at a significantly higher incidence than in those without. It is well known that the initial manifestation of SSc is usually Raynaud’s phenomenon. However, in patients with SSc-RA, significantly more patients had arthralgia prior to Raynaud’s phenomenon. These patients may already have developed RA, which is difficult to differentiate from the manifestation of SSc. Careful interviews of the symptomatic history, especially the history of arthralgia, are needed in patients with SSc.

On the other hand, increased CRP was found in 92.2% of RA patients (20), and several studies have shown that radiologic progression correlates more closely with serial measurements of CRP than clinical joint counts (21, 22). Aho et al. investigated 19,072 healthy adults and concluded that serum CRP did not predict RA (19). However, in our study increased CRP at the first visit was present significantly higher in patients with SSc-RA than in those without. In addition, CRP was increased in 8 of 9 patients at the time of the diagnosis of RA. Contrary to SLE or RA, SSc patients with elevated CRP are relatively rare. In our study, the ele-

- treated orally with disease-modifying anti-rheumatic drugs (DMARDs) such as predonine and D-penicillamin, or with intramuscular injections of sodium aurothiomalate. Arthralgia and CRP levels in all of these patients have improved gradually.

Clinical features of SSc accompanied by RA

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vated CRP in patients without RA was thought to be due to bacterial infection of their leg ulcers. In SSc patients, CRP may be a predictor of overlapping RA.

Approximately 65–70% of patients with RA show positive serologic tests for rheumatoid factor (23) and it is included into the criteria of RA proposed by the American Rheumatism Association (12). SSc patients with elevated RF at their first visit may have the higher risk of developing RA. There was, however, no significant difference in ESR between patients with SSc-RA and those without. Its clinical significance is controversial even in patients with RA alone (21, 24). Additionally, although Zimmermann et al. suggested that DMARDS may be associated with the occurrence of overlap disorders in patients with SSc-RA (8), in our study there was no significant difference in the medications of DMARDS since their first visit between patients with SSc-RA and those without.

However, in previous reports almost all SSc-RA patients had generalized sclerosis of the skin, severe seropositive polyarthritis, pulmonary fibrosis, antitopoisomerase I antibodies, and HLA-DR4, -DR53 (7). In the present study, diffuse sclerosis of the skin, pulmonary fibrosis, and antitopoisomerase I antibodies were observed only in 44.4%, 44.4%, and 55.5% of our patients with SSc-RA, respectively. Furthermore, the patients with SSc-RA who had limited sclerosis of the skin and anticcromere antibodies were reported (8). However, in our study there were no SSc-RA patients with anticentromere antibodies. These differences may be due to the small number of SSc-RA patients studied, to their heterogeneity, or to the criteria for SSc used in each study. Previous reports did not always specify the criteria used. In the present study, we used the preliminary classification criteria of the ACR for the definition of SSc. This may be inadequate for the identification of lcSSc and cause inevitable bias such as the absence of SSc-RA patients with ACA. Moreover,

the ACR criteria for RA have not been validated for classification of overlap syndrome and patients may fulfill some RA criteria due to the presence of symptoms of SSc. There have been no reports investigating the prevalence of SSc-RA overlap in patients with SSc using the same criteria that we adopted. It appears that further studies are needed.

In conclusion, 5.2% of our SSc patients subsequently developed RA. Arthritis prior to Raynaud’s phenomenon, increased CRP, and elevated RF were observed in SSc patients with RA at a significantly higher incidence than in those without. SSc patients who had arthritis prior to Raynaud’s phenomenon and elevated RF should be followed up with serial measurements of CRP because of the risk of overlapping with RA.

References