Clinical and Immunological Features of Anti-centromere Antibody-Positive Primary Sjögren’s Syndrome

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ABSTRACT

Introduction: Anti-centromere antibody (ACA)-positive Sjögren’s syndrome (SS) is considered a subtype of SS. ACA-positive SS patients display several features, such as Raynaud’s phenomenon, sclerodactyly, and extraglandular dysfunction. However, information on the features of ACA-positive SS is insufficient and the clinical significance of ACA in SS has not been fully established. The aim of this study was to clarify the features of ACA-positive SS.

Methods: All patients with primary SS who visited our hospital were enrolled. Clinical information and immunological tests were collected and statistically analyzed.

Results: A total of 585 patients were classified as having primary SS. They were divided into four groups by serum ACA and anti-SS-A antibody status as follows: 22 had ACA only (ACA alone), 464 had anti-SS-A antibodies only (SS-A alone), 26 had both ACA and anti-SS-A antibodies (double-positive), and 73 had neither ACA nor anti-SS-A antibodies (seronegative). The proportion of patients with dryness did not differ between the four groups. The proportion of patients with Raynaud’s phenomenon or sclerodactyly was higher in the ACA alone and double-positive groups. The proportion of patients with increased serum IgG or IgA was 0 and 5% in the ACA alone group, 61 and 20% in the SS-A alone group, 52 and 28% in the double-positive group, and 20 and 4% in the seronegative group (p < 0.01 and p < 0.01), respectively. The proportion of patients with leukocytopenia was significantly lower in the SS-A-negative group than in the other groups.

Conclusions: Our study identified characteristics of ACA-positive SS patients that differ from those of anti-SS-A antibody-positive SS patients.

Keywords: Anti-centromere antibody; Anti-SS-A antibody; Sjögren’s syndrome

INTRODUCTION

Primary Sjögren’s syndrome (SS) is a systemic autoimmune disease characterized by symptoms of dry eyes and dry mouth, and by systemic manifestations and damage to multiple organs [1]. The pathogenesis of primary SS remains unclear due to the heterogeneity of clinical phenotypes and pathogenetic mechanisms. Infiltration of lymphocytes into the salivary or lacrimal glands is typically observed.
in patients, which results in destruction and subsequent fibrotic changes [2, 3].

Anti-centromere antibody (ACA)-positive SS is considered a subtype of SS [4]. Past cohort studies reported that the characteristics of ACA-positive SS patients differ from those of ACA-negative SS patients. A recent international, collaborative, large-scale cohort study highlighted several clinical features in ACA-positive SS, such as Raynaud’s phenomenon, sclerodactyly, and extraglandular dysfunction [4, 5].

Assessment of ACA is potentially valuable in establishing a definitive diagnosis of this SS subtype and for medical management in a certain number of patients who meet the current American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria [6]. Information on the clinical and immunological features of ACA-positive SS is insufficient, and the clinical significance of ACA in SS has not been fully established. We therefore sought to clarify the clinical and immunological features of ACA-positive SS.

METHODS

Patients and Data Collection

Six hundred and one patients with primary SS who met the ACR/EULAR classification criteria [6] were enrolled in the study. All patients visited Keio University Hospital between May 1995 and July 2017 and had never been treated with a corticosteroid or immunosuppressant. Patients who had or developed other rheumatic diseases in addition to SS were excluded in this study. All procedures were approved by the medical ethics committee of Keio University Hospital and followed the tenets of the Declaration of Helsinki. All samples and information were collected after patients had provided written informed consent. Clinical parameters including immunoglobulin (Ig) and serum autoantibodies were obtained by clinical laboratory methods. IgG, IgA, and IgM were measured by enzyme-linked immunosorbent assay (ELISA). ACA and anti-SS-A antibodies were measured by ELISA. Rheumatoid factor was measured by latex agglutination turbidimetry, and anti-nuclear antibody was observed in the indirect immunofluorescence. The clinical characteristics of the patients were retrospectively collected from their medical records. Rheumatologists examined the patients and made their diagnosis. Blood test results including Ig and antibodies were evaluated with reference to the reference ranges. We evaluated the extraglandular involvements of SS with reference to the items included in the EULAR primary Sjögren’s syndrome disease activity index [7].

Statistical Analysis

We used commercial statistical software (JMP 13 system®, SAS Institute Inc., Cary, NC, USA). The Wilcoxon rank sum test was used to assess the statistical significance of differences between groups, and the Kruskal–Wallis test and Dunn’s test were used for multiple comparison procedures. A p value < 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics of Primary SS Patients

The clinical characteristics of patients at the initial visit are shown in Table 1. This study included 585 patients with primary SS, of whom 38 were male (6%) and 547 were female (94%). Mean age was 55 ± 15 years, ranging from 17 to 90 years. Patients were divided into four groups by serum ACA and anti-SS-A antibody status. Only ACA positivity (ACA alone) was detected in 22 patients (3.8%), while only anti-SS-A antibodies with no ACA (SS-A alone) were detected in 464 patients (79.3%). Twenty-six patients (4.4%) had both ACA and anti-SS-A antibodies (double-positive), while 73 had neither ANA nor anti-SS-A antibodies (seronegative) (Table 2). On statistical comparison, the proportion of patients with dryness did not differ between the four groups, nor did salivary gland function evaluated by salivary gland scintigraphy. There was no difference of the mean average of the Greenspan “focus score” in
four groups (3.5 vs. 3.2 vs. 3.1 vs. 3.3, p = 0.38). The proportion of patients with Raynaud’s phenomenon or sclerodactyly was higher in the ACA alone and double-positive groups (p < 0.01 and p < 0.01, respectively). Extraglandular involvement of SS was significantly lower in the ACA alone than in the SSA alone or double-positive groups (p < 0.01).

**Clinical Parameters**

Table 3 shows the clinical parameters of primary SS patients at the initial visit. The proportion of patients with increased serum IgG or IgA was 0 and 5% in the ACA alone group, 61 and 20% in the SSA alone group, 52 and 28% in the double-positive group, and 20 and 4% in the seronegative group (p < 0.01 and p < 0.01), respectively. Existence of anti-SS-A antibodies, but not ACA, was associated with a high concentration of IgG or IgA, while there was no difference in IgM between the four groups (p = 0.26). There was no difference in the proportion of patients with low C3, C4, or CH50 between the four groups. Remarkably, the proportion of patients with leukocytopenia and thrombocytopenia in the ACA alone group was significantly lower than the proportion with leukocytopenia and thrombocytopenia in the other groups (p < 0.01). The presence of rheumatoid factor was significantly lower in the ACA alone and seronegative groups (p < 0.01).

**Organ Involvement**

Extraglandular major visceral involvement and complications in primary SS patients are shown in Table 4. Thirty-six patients (6%) were found to have pulmonary diseases, including interstitial pneumonia, pleuritis, and bronchiolitis.
Thirty-one patients (5%) had articular involvement. Twenty-three patients (4%) had annular erythema and/or malar rash. Cardiac and renal involvement was seen in eight and seven patients. Six patients had pulmonary hypertension and they had only anti-SS-A antibodies. Seventy-four patients (13%) had thyroid diseases such as hyperthyroidism.
hypothyroidism, or thyroid tumor. Four patients and six patients had autoimmune hepatitis and primary biliary cholangitis, respectively. There were few SS patients with other involvement in our study. No differences in organ involvement or complications were found between the four groups. Seventeen patients had lymphoma, but nobody had lymphoma in ACA alone. There was no difference of the frequency of lymphoma in four groups ($p = 0.86$).

**DISCUSSION**

In this study, we focused on the difference between ACA- and anti-SS-A antibody-positive primary SS patients, and we investigated and newly showed the differences between four SS groups according to ACA and anti-SS-A antibody status: ACA-positive, SSA-positive, double-positive, or seronegative. We described extraglandular major visceral involvement and complications in primary SS patients in long-term follow-up.

ACA-positive SS is considered a distinct clinical subgroup of SS [8, 9]. ACA is often detected in sera in other autoimmune diseases, such as limited cutaneous systemic sclerosis and primary biliary cholangitis [10]. The prevalence of ACA and double (ACA and anti-SS-A antibody) positivity in our cohort of primary SS was both 5%. The characteristics of ACA-positive SS patients have been reported to differ from those of ACA-negative SS patients [4, 8, 9].

In our study, the prevalence of ACA positivity, including ACA positivity and double positivity, in our study of primary SS was 10% and did not differ from that reported in a previous study [4]. We evaluated ACA-positive primary SS after the exclusion of patients diagnosed with systemic sclerosis based on the 2013 classification criteria [11]. We confirmed that patients with ACA-positive primary SS had Raynaud’s phenomenon and scleroderma. SS patients with ACA have a significantly higher frequency of

| Table 4 Extraglandular major visceral involvement and complications in 585 primary SS patients |

| All $(n = 585)$ | ACA alone $(n = 22)$ | SSA alone $(n = 464)$ | Double-positive $(n = 26)$ | Seronegative $(n = 73)$ | $p$ value |
|----------------|---------------------|----------------------|--------------------------|------------------------|-----------|
| Pulmonary involvement, $n$ (%) | 36, 6% | 1, 5% | 27, 6% | 3, 12% | 5, 7% | 0.67 |
| Articular involvement, $n$ (%) | 31, 5% | 0, 0% | 22, 5% | 3, 12% | 6, 8% | 0.19 |
| Skin involvement, $n$ (%) | 23, 4% | 1, 5% | 22, 5% | 0, 0% | 0, 0% | 0.18 |
| Cardiac involvement, $n$ (%) | 8, 1% | 0, 0% | 7, 2% | 1, 4% | 0, 0% | 0.46 |
| Renal involvement, $n$ (%) | 7, 1% | 0, 0% | 5, 1% | 1, 4% | 1, 1% | 0.59 |
| Thyroid disease | 74, 13% | 2, 9% | 59, 13% | 4, 15% | 9, 12% | 0.93 |
| Autoimmune hepatitis | 4, 1% | 0, 0% | 3, 1% | 0, 0% | 1, 1% | 0.84 |
| Primary biliary cholangitis | 6, 1% | 0, 0% | 5, 1% | 1, 4% | 0, 0% | 0.39 |

The Kruskal–Wallis test was used to assess the statistical significance of differences between groups. ACA anti-centromere antibody, SSA anti-SS-A antibody.
clinical findings that are seen in systemic sclerosis.

SS patients with ACA significantly differed from those with anti-SS-A antibodies in immunological and clinical characteristics. Existence of anti-SS-A antibodies, not ACA, was associated with a high concentration of IgG or IgA, while there was no difference in IgM between the four groups. The proportion of patients with leukocytopenia and thrombocytopenia in the anti-SS-A antibody-positive groups was significantly higher than the other groups. Primary SS patients with both ACA and anti-SS-A antibodies had Raynaud’s phenomenon and sclerodactyly, and they had leukocytopenia and thrombocytopenia, similar to SS patients with anti-SS-A antibodies.

There was no difference in salivary gland dysfunction between ACA- and anti-SS-A antibody-positive patients in our study. It is considered that there is no change in histological findings between patients with ACA and those with anti-SS-A antibodies because the presence of focal lymphocytic sialadenitis in the labial salivary gland and focus score are necessary for diagnosis in anti-SS-A antibody-negative, ACA-positive SS patients in the new classification criteria [6]. A previous study highlighted the presence of extraglandular dysfunction in ACA-positive SS [4]. We consider that achieving an early diagnosis of SS associated with the presence of only ACA before glandular destruction is difficult.

We note four limitations of our study. First, the number of patients was relatively small, although it was large enough to provide statistically significant data. Second, this study may have a participant selection bias since we collected the patients voluntarily visited our hospital. However, we estimated that this study avoided a participant selection bias because each patient was chosen by chance and each patient of the population had an equal chance, or probability, of being selected. Third, this study was a retrospective study and we did not fully evaluate clinical findings in the patients. A long-term prospective study on these patients is needed. Finally, we did not evaluate glandular dysfunction in patients with ACA-positive SS compared with those with anti-SS-A antibodies.

Also, the histological differences between ACA-positive and anti-SS-A antibody-positive SS need to be clarified in future studies.

CONCLUSIONS

ACA-positive SS patients have a higher frequency of Raynaud’s phenomenon and sclerodactyly, as seen in systemic sclerosis, and a lower frequency of hematological findings, including leukocytopenia and thrombocytopenia. Primary SS patients with ACA and anti-SS-A antibodies display the clinical characteristics of both ACA-positive patients and anti-SS-A antibody-positive patients. Our study identified distinct clinical and immunological characteristics of ACA-positive SS patients, which differ from those of anti-SS-A antibody-positive or seronegative SS patients.

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**Compliance with Ethics Guidelines.** All procedures were approved by the medical ethics committee of Keio University Hospital and followed the tenets of the Declaration of Helsinki. All samples and information were collected after patients had provided written informed consent.

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