Determination of the Subset of Sjögren's Syndrome with Articular Manifestations by Anticyclic Citrullinated Peptide Antibodies

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ABSTRACT. ***Objective.*** To investigate whether anticyclic citrullinated peptide antibodies (anti-CCP) predict the subset of Japanese patients with Sjögren's syndrome (SS) with articular manifestations.

Methods. Eighty-seven patients with SS were enrolled. Prevalence of anti-CCP antibodies, IgM rheumatoid factor, anti-Ro/SSA antibody, anti-La/SSB antibody, and serum IgG concentration and their relation to articular manifestations were examined. Articular manifestations included morning stiffness and the presence of tender or swollen joints.

Results. Eighty-seven SS patients were divided into 3 groups: 14 secondary SS with nonerosive rheumatoid arthritis (RA); 47 primary SS with articular manifestations; and 26 primary SS without articular manifestations. Ten out of 14 secondary SS with nonerosive RA expressed anti-CCP. Anti-CCP was the only statistically proven marker preferentially distributed in patients with articular manifestations (the first 2 groups) compared to primary SS without such manifestations; however, its frequency was low in primary SS. No patient with primary SS without articular manifestations expressed anti-CCP.

Conclusion. Anti-CCP is found in the subset of Japanese with SS with articular manifestations although most of those with anti-CCP-positive SS were classified as secondary SS with RA. (First Release Dec 15 2008; J Rheumatol 2009;36:113–5; doi 10.3899/jrheum.080193)

Key Indexing Terms:
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Erosive arthritis is a hallmark of rheumatoid arthritis (RA), whereas Sjögren's syndrome (SS)-related arthritis is thought to be nonerosive[1]; however, the difference remains obscure. In our previous study, 5 of 52 patients with SS were seropositive for anticyclic citrullinated peptide antibody (anti-CCP)[2]. Extending our previous observations, we observed for the first time in Japanese patients with SS that anti-CCP was found in the subset with articular manifestations, although most of the anti-CCP-positive patients with SS were classified as secondary SS with RA.

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MATERIALS AND METHODS

We prospectively recruited 117 patients from the Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, between August 2004 and September 2007. Informed consent of the 117 patients to the protocol was approved by the Institutional Review Board of Nagasaki University. Figure 1 shows the distribution of the 117 patients. All patients fulfilled the diagnostic criteria of SS according to the American-European Consensus Group[3]. Fifteen SS patients had not come to the hospital regularly, and thus were excluded from the study. Another 15 patients developed SS during the course of established RA, all of whom had bone erosions on hand and foot plain radiography. We focused on the role of anti-CCP in patients with SS complicated with arthropathy. Accordingly, these 15 patients with established RA-SS as well as patients with secondary SS complicated with autoimmune disorders other than RA were excluded at entry. Mean (± standard deviation) followup period of the remaining 87 patients was 1.83 ± 0.88 years. Japan College of Rheumatology-certified rheumatologists examined the patients about every 2 months. Sixty-one out of 87 complained of morning stiffness and tender or swollen joints at more than one site. All patients were previously considered to have primary SS by physicians at the first visit, but 14 of the 87 SS patients fulfilled the 1987 criteria of the American College of Rheumatology for RA[4] after diagnosis of

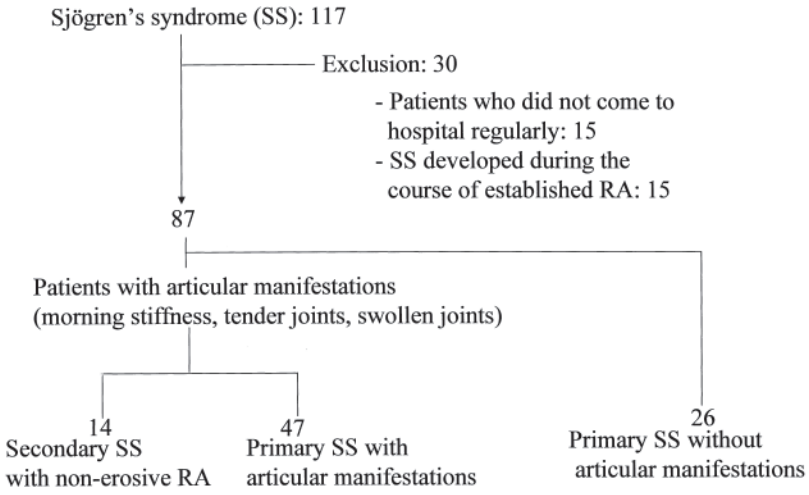

Figure 1. Classification of patients. We recruited 117 patients; 30 were excluded. The remaining 87 patients were classified into one of 3 categories by medical records: secondary SS with nonerosive RA (n = 14), primary SS with articular manifestiations (n = 47), and primary SS without articular manifestations (n = 26).

primary SS. Hand and foot plain radiographs were taken in all 14 patients before entry, and scheduled once per year. None showed erosion after being reviewed by the investigators at entry. Thus, these 14 patients were considered to have secondary SS with nonerosive RA (Figure 1). Plain radiographs also taken in 47 patients with primary SS with articular manifestations were reviewed by the investigators. The followup period from the first diagnosis of primary SS to the diagnosis of definite RA showed a mean value of 3.48 ± 5.83 years. In the group with secondary SS with nonerosive RA (n = 14), 11 patients were treated with disease modifying antirheumatic drugs (DMARD). In the group with primary SS with articular manifestations (n = 47), one was treated with DMARD. In the group with primary SS without articular manifestations (n = 26), no patient was treated with DMARD.

Serum variables examined at entry were the anti-SSA/Ro antibody (anti-SSA) and anti-SSB/La antibody (anti-SSB), IgM rheumatoid factor (RF), anti-CCP, and IgG. Test kits used in these studies were anti-SSA and

Table 1. Clinical characteristics of the study population. Age, duration of disease and serum IgG were expressed as mean ± SD.

	SS with Articular Manifestations, n = 61	SS without Articular Manifestations, n = 26	p
Age, yrs	59.5 ± 12.2	58.9 ± 16.0	NS
Female, no. (%)	56 (92)	25 (96)	NS
Disease duration, yrs	6.8 ± 8.62	9.3 ± 9.25	NS
Serum IgG, mg/dl	1743 ± 556.0	1922 ± 419.4	NS
Anti-SSA (%)	40 (66)	18 (69)	NS
Anti-SSB (%)	17 (28)	11 (42)	NS
IgM-RF (%)	32 (53)	13 (50)	NS*
Anti-CCP (%)	13 (21)	0 (0)	< 0.01**

P value was by Mann-Whitney U test, * chi-square test, and ** Fisher's exact probability test.

Table 2. The presence of anti-CCP antibodies.

	SS with Articular Manifestations		p < 0.01	SS without Articular Manifestations
	Secondary SS+ nonerosive RA, n = 14	Primary SS, n = 47		Primary SS, n = 26
Anti-CCP positive	10 (71%)	3 (6%)		0 (0%)
Anti-CCP negative	4 (29%)	44 (94%)		26 (100%)
	p < 0.00001		NS	
	p < 0.00001			

p value was calculated by chi-square test and Fisher's exact probability test.

anti-SSB; Mesacup SS-A/Ro test and SS-B/La test (Medical and Biological Laboratories, Nagoya, Japan; cutoff value, 30 index and 25 index, respectively), IgM-RF; latex-enhanced immuno-electrometric assay (Dade Behring, Marburg, Germany; cutoff value, 14 IU/ml) and anti-CCP; DIASTAT Anti-CCP (Axis-Shield, Dundee, UK; cutoff value, 4.5 U/ml), respectively.

Differences of variables between groups were examined using the Mann-Whitney U test, chi-square test, and Fisher's exact probability test. A p value < 0.05 denoted the presence of a statistically significant difference.

RESULTS

As shown in Figure 1, all 14 patients with secondary SS with nonerosive RA had articular manifestations. In addition, 47 patients with primary SS had articular manifestations whereas 26 did not. Age, duration of SS to time of study entry, serum IgG concentration, and prevalences of anti-SSA/SSB and IgM-RF did not differ between SS subsets with and those without articular manifestations (Table 1). However, prevalence of anti-CCP was significantly higher in SS with articular manifestations (Table 1).

Table 2 shows the details regarding anti-CCP in all patients. Although anti-CCP was found only in patients with SS with articular manifestations, most patients with SS with articular manifestations were seronegative for anti-CCP, whereas 10 out of 14 secondary SS with nonerosive RA were seropositive (Table 2). None of the 3 anti-CCP-positive primary SS cases with articular manifestations was erosive on hand and foot radiographs (data not shown).

DISCUSSION

Anti-CCP is predominantly distributed in patients with radiographic erosive arthritis in RA[5]. However, a recent study in Caucasians with SS identified subsets of SS, including a subset of patients with secondary SS with nonerosive RA that was anti-CCP-positive[6].

Our data represent the first observation of Japanese with SS to investigate the relationship between serum autoantibodies and articular manifestations. We showed that nonerosive arthritis, including that fulfilling the 1987 RA criteria of the ACR, is present in patients with anti-CCP antibody-positive SS. SS-associated anti-CCP may recognize molecules different from those in erosive RA; thus, radiographic bone erosion might not be found in anti-CCP-positive SS. However, since the mean followup period in our study was short, a serial study would be necessary to identify the association of anti-CCP in SS with radiographic erosion.

It is known that anti-CCP can be present years before the first signs of RA[7]; hence, a prospective analysis of both studies is required to answer the questions raised by our findings.

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