Easy and Accurate Diagnosis of Rheumatoid Arthritis Using Anti-Cyclic Citrullinated Peptide 2 Antibody, Swollen Joint Count, and C-Reactive Protein/Rheumatoid Factor

TAKASHI YAMANE, AKIRA HASHIRAMOTO, YASUSHI TANAKA, KEN TSUMIYAMA, YASUSHI MIURA, KAZUKO SHIOZAWA, KAZUO CHIHARA, and SHUNICHI SHIOZAWA

ABSTRACT ***Objective.*** To determine an easy-to-use diagnostic criterion for early rheumatoid arthritis (RA) that may be useful for general physicians, using anti-cyclic citrullinated peptide (CCP) antibody.

Methods. We prospectively studied 435 patients who first visited the hospital with arthritic symptoms within 24 months, including 264 visitors within 6 months. The diagnosis was made on their first visit by examination and laboratory tests including anti-CCP antibodies, rheumatoid factor (RF) and C-reactive protein (CRP), and radiograph.

Results. The diagnostic specificity and positive predictive value (PPV) of anti-CCP2 assay were 94.9% and 87.8%, respectively, and those of anti-CCP2 plus RF were 96.9% and 90.9% for the patients who first visited having morning stiffness, arthralgia, and/or joint swelling within 3 months from onset (n = 165). For the patients who first visited later, but within 24 months from onset (n = 260), the diagnostic specificity and PPV were extremely high, 98.7% and 95.5%, when anti-CCP2 assay was coevaluated with RF, CRP, and more than 3 swollen joints. Respective combinations of anti-CCP2 assay plus either 2 of 3 measures were also highly specific.

Conclusion. A diagnostic criterion including anti-CCP2 assay in combination with RF, CRP, and/or swollen joints is less sensitive but highly specific, and accurately predicts future development of RA among those with arthritic symptoms who first consulted doctors within 2 years after onset. It should be highly useful for the general physician without special techniques or devices. (First Release Jan 15 2008; J Rheumatol 2008;35:414–20)

Key Indexing Terms:
RHEUMATOID ARTHRITIS EARLY DIAGNOSTIC CRITERIA ANTI-CCP ANTIBODY

Rheumatoid arthritis (RA) is a chronic polyarthritis of unknown etiology affecting ~1% of the population worldwide[1]. Studies have shown that early initiation of disease modifying antirheumatic drugs (DMARD) definitely improves the sequelae of RA[1,2], and there is an increasing motivation for early and accurate diagnosis of RA. With regard to early diagnosis, however, even the American College of Rheumatology (ACR)[3] classification criteria for RA still lack sensitivity. While the sensitivity and specificity of rheumatoid factor (RF), a constituent of the ACR criteria, are also unsatisfactory[4,5], recent development in assays measuring anti-cyclic citrullinated peptide (CCP) antibody may change the situation[6,7]. In particular, currently available second-generation anti-CCP2 assays show the sensitivity and specificity exceeding 80%-89%[8-12]. Studies show that anti-CCP antibody appears very early in the disease course, even before onset of disease[13-15], and that joint destruction is progressive in the anti-CCP2-positive patients with RA[16-20].

Our study was designed to establish a reliable and easy-to-use predictor of the development of RA in the future using a commercially available anti-CCP2 assay as one of the easy-to-use items to propose a highly specific criterion. We adhered to routine clinical measures for general physicians.

From the Department of Rheumatology, Kobe University Graduate School of Medicine; Rheumatic Diseases Division, Kobe University Hospital; Division of Endocrinology/Metabolism, Neurology, and Hematology/Oncology, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, Kobe; and Rheumatic Disease Centre, Konan Kakogawa Hospital, Kakogawa, Japan.

T. Yamane, MD; A. Hashiramoto, MD, PhD; Y. Miura, MD, PhD; S. Shiozawa, MD, PhD, Investigator of the 21st Century Center of Excellence (COE), Japan, Department of Rheumatology, Kobe University Graduate School of Medicine and Rheumatic Diseases Division, Kobe University Hospital; K. Tsumiyama, MSc, Department of Rheumatology, Kobe University Graduate School of Medicine; Y. Tanaka, MD, PhD; K. Shiozawa, MD, PhD, Rheumatic Disease Centre, Konan Kakogawa Hospital; K. Chihara, MD, PhD, Division of Endocrinology/Metabolism, Neurology, and Hematology/Oncology, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine.

Address reprint requests to Dr. S. Shiozawa, Department of Rheumatology, Kobe University Graduate School of Medicine, 7-10-2 Tomogaoka, Sumaku, Kobe 654-0142, Japan. E-mail: shioz@kobe-u.ac.jp

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MATERIALS AND METHODS

Patients. Among 1205 outpatients who first visited the Rheumatic Disease Center, Konan-Kakogawa Hospital, from April 2001 until March 2004, we selectively studied 435 patients (mean age 54 yrs; range 18–87; 342 women, 93 men) who first visited within 2 years from onset of arthritic symptoms. Before the first visit to our hospital, no patient received any drugs for arthritic symptoms including nonsteroidal antiinflammatory drugs, corticosteroids, or DMARD. We defined arthritic symptoms as any of the rheumatic complaints including morning stiffness, arthralgia, and/or subjective joint swelling. Of 435 patients, 62 (14%) visited the hospital within 1 month after the onset of arthritic symptoms. Similarly, 165 (38%) and 264 (61%) patients visited the hospital within 3 months and 6 months from onset, respectively. This discrepancy of the duration includes both patient's delay and, in some cases, the delay of judgment of the general physician for recommendation to visit our hospital.

Clinical assessment. The diagnosis was made at the time of the first visit of the patients by evaluating examination, laboratory test, and radiographs. When the diagnosis was uncertain at first visit, the final diagnosis was postponed until respective patients fulfilled the diagnostic criteria including the ACR criteria[3]. The diagnosis of undifferentiated arthritis was made when arthritic conditions still did not meet the ACR criteria during our study[11,14]. In regard to joint swelling, we used the measure of more than any 3, but not fewer than 2, swollen joints out of 68 joints based on previous and present clinical studies[21] (Table 1). RF ≥ 20 IU/ml and C-reactive protein (CRP) ≥ 0.6 mg/dl were considered positive. Serum samples on the patients' first visit were collected and stored at –80°C until assayed. Anti-CCP antibody was measured by using the second generation ELISA kit (Diastat Anti-CCP2; Axis-Shield, Dundee, UK) and referred to here as anti-CCP2 assay. The titer exceeding 5 U/ml was considered positive and the minimal detectable quantity in this assay was 1 U/ml. Sample values below 1.0 U/ml were adjusted to 1.0 U/ml for statistical calculation. The cutoff level 5 U/ml was established based on the result of clinical application of anti-CCP2 assay in all of Japan, via manufacturer's distribution and our original evaluation in the patients with established RA, including the patients in our study (n = 209).

Statistical analysis. Groups were compared using the Student's t-test. The results were expressed as mean ± standard deviation, median, and range. All p values were of 2-sided tests, and p values < 0.01 were considered significant. Positive predictive value (PPV) was calculated as the probability that a person with a positive test is a true-positive. Negative predictive value (NPV) was the probability that a person with a negative test does not have the disease.

RESULTS

Anti-CCP2 antibody in patients with arthritic symptoms. Anti-CCP2 antibody was measured in 435 individuals who first visited the hospital with arthritic symptoms including morning stiffness, arthralgia, and/or subjective joint swelling within 24 months from onset, and their clinical course was prospectively followed for 9.2 ± 11.0 months.

Of 435 individuals, 209 were finally diagnosed with RA, 52 with other rheumatic diseases, 76 with nonrheumatic diseases, and 98 without disease and healthy (Figure 1). Anti-CCP2 antibody was positive in 158 of 435 (36.3%) individuals, in which 137 of 158 (86.7%) anti-CCP2-positive individuals were finally diagnosed with RA. However, the final diagnosis of RA was made in 72 of 277 (26.0%) patients who were anti-CCP2-negative on their first visit (Figure 1).

Anti-CCP2 antibody in sera was 88.8 ± 100.7 U/ml (median 50.9; range 1.1–352.3) in patients with RA. It was 16.8 ± 52.2 U/ml (median 2.2; range 1.0-277.9) and 20.6 ± 56.6 U/ml (median 1.3; range 1.1–247.8) in the patients with other rheumatic diseases and nonrheumatic diseases, respectively (Figure 2). In the healthy individual group, we found one anti-CCP2 antibody-positive individual. The titer of his anti-CCP2 antibody was 6.1 U/ml on first visit; however, he did not develop arthritis subsequently after 3 years of followup.

Anti-CCP2 antibody and disease activity. As shown in Figure 2, there was a small group of non-RA patients who had > 100 U/ml of anti-CCP2 antibody, and their final diagnosis was polymyositis/dermatomyositis (n = 2), CREST syndrome (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasias; n = 1), or reactive arthritis (n = 1) in the other rheumatic disease group (Table 2). However, the diagnosis of undifferentiated arthritis was made in 6 out of 8 (75.0%) patients in the nonrheumatic diseases group. The frequency of the patients with undifferentiated arthritis in the nonrheumatic diseases group was only 5 of 76 (6.6%), and all of the 5 individuals showed ≤ 100 U/ml of anti-CCP2 antibody (data not shown), indicating that the rise of anti-CCP2 antibody is by no means nonspecific but is associated with arthritic condition.

When the frequency of the patients with positive anti-CCP2 antibody was assessed sequentially during the disease course, 50.0% of the patients with the final diagnosis of RA were anti-CCP2-positive as early as 1 month from onset of arthritic symptoms (Table 3). This frequency gradually increased up to 79.5% at 24 months after onset, and thus the disease duration is an important contributor to the rise of anti-CCP2 antibody. In contrast, anti-CCP2 antibody was basically infrequent and did not rise in association with disease course in the groups with diseases other than RA, clearly indicating that anti-CCP2 assay is disease-associated.

The clinical profiles of the patients were compared with each other in relation to anti-CCP2 antibody (Table 4). The presence of anti-CCP2 antibody showed positive correlation with positive RF in the group with the final diagnosis of RA. In contrast, nonspecific inflammatory indices such as CRP and erythrocyte sedimentation rate (ESR), also including RF, showed correlation with anti-CCP2 antibody in the nonrheumatic diseases group, again indicating that the rise of anti-CCP2 antibody is associated with disease activity and/or inflammation. Further data also support this association between anti-CCP and disease activity including bone destruction. When compared with RA patients having < 5 IU/ml anti-CCP2, both Sharp score and Disease Activity Score 28 worsened in patients with > 100 IU/ml anti-CCP2 after 3 years' followup (data not shown).

Prediction of RA. We sought a reliable predictive measure of the development of RA in the future for those who first visited very early in the disease course by the use of routine clinical measures. Such simple measures should be efficiently applicable to the first visitors with any of the arthrit-

Table 1. The specificity, sensitivity, and positive and negative predictive value (PPV, NPV) of clinical measures in relation to disease duration.

Clinical Single Measures	Disease Duration, mo* 3	6	12	24	3 mo PPV	3 mo p† (vs ACR criteria)	3 mo NPV	24 mo PPV	24 mo p (vs ACR criteria)	24 mo NPV
ACR criteria										
Specificity	92.6 (87.7–97.5)**	91.7 (87.2–96.2)	93.5 (89.9–97.0)	93.8 (90.7–96.9)	85.5		83.3	92.2		82.8
Sensitivity	70.1 (59.2–81.1)	75.8 (68.2–83.5)	77.6 (71.4–83.9)	79.9 (74.5–85.3)						
Anti-CCP2 (≥ 5 U/ml)										
Specificity	95.4 (91.4–99.3)	91.0 (86.3–95.7)	91.3 (87.2–95.4)	90.7 (86.9–94.5)	87.8	0.9749	76.9	86.7	0.1341	74.0
Sensitivity	53.7 (41.8–65.7)	58.3 (49.5–67.2)	62.4 (55.1–69.6)	65.6 (59.1–72.0)						
RF (≥ 20 IU/ml)										
Specificity	74.1 (65.8–82.3)	71.5 (64.2–78.9)	69.6 (62.9–76.2)	69.5 (63.5–75.5)	59.4	0.0029	75.5	67.6	< 0.0001	70.7
Sensitivity	61.2 (49.5–72.9)	63.3 (54.7–72.0)	66.5 (59.4–73.6)	68.9 (62.6–75.2)						
CRP (≥ 0.6 mg/dl)										
Specificity	87.0 (80.7–93.4)	86.8 (81.3–92.3)	87.5 (82.7–92.3)	88.4 (84.3–92.7)	75.0	0.2529	79.0	84.7	0.0395	75.5
Sensitivity	62.7 (51.1–74.3)	69.2 (60.9–77.4)	71.8 (65.0–78.5)	69.1 (62.6–75.2)						
Swollen joints (≥ 3)										
Specificity	75.0 (66.8–83.2)	75.0 (67.9–82.1)	76.1 (69.9–82.3)	77.0 (71.5–82.5)	55.7	0.0010	71.1	71.6	< 0.0001	69.0
Sensitivity	50.7 (38.8–62.7)	59.2 (50.4–68.0)	61.8 (54.5–69.1)	62.7 (56.1–69.2)						
Tender joints (≥ 2)										
Specificity	34.3 (25.3–43.2)	25.7 (18.6–32.8)	29.3 (22.8–35.9)	27.0 (21.2–32.8)	46.2	< 0.0001	86.0	53.8	< 0.0001	78.2
Sensitivity	91.0 (84.2–97.9)	95.0 (91.1–98.9)	81.2 (75.3–87.1)	91.9 (88.2–95.6)						
Combination measures										
Anti-CCP2+RF										
Specificity	96.9 (93.5–100.3)	95.1 (91.6–98.7)	95.1 (92.0–98.2)	94.2 (91.2–97.3)	90.9	0.6773	73.9	90.2	0.6499	70.3
Sensitivity	44.8 (32.9–56.7)	49.2 (40.2–58.1)	53.5 (46.0–61.0)	56.9 (50.2–63.7)						
Anti-CCP2+CRP										
Specificity	94.9 (90.5–99.3)	93.1 (88.9–97.2)	94.1 (90.6–97.5)	94.7 (91.8–97.6)	82.1	0.9417	70.1	88.9	0.4485	65.4
Sensitivity	34.3 (23.0–45.7)	38.3 (29.6–47.0)	44.7 (37.2–52.2)	45.9 (39.2–52.7)						
Anti-CCP2+swollen joints										
Specificity	95.9 (92.0–99.8)	95.1 (91.6–98.7)	95.1 (92.0–98.2)	96.5 (94.1–98.9)	82.6	0.9789	68.4	91.9	0.897	64.9
Sensitivity	28.4 (17.6–39.2)	35.0 (26.5–43.5)	40.0 (32.6–47.4)	43.5 (36.8–50.3)						
Anti-CCP2+tender joints										
Specificity	95.9 (92.0–99.8)	92.4 (88.0–96.7)	92.4 (88.6–96.2)	91.6 (88.0–95.2)	87.9	0.9999	73.2	86.9	0.1579	71.4
Sensitivity	43.3 (31.4–55.1)	51.7 (42.7–60.6)	57.6 (50.2–65.1)	60.3 (53.7–66.9)						
Anti-CCP2+RF+swollen joints										
Specificity	98.0 (95.2–100.8)	97.9 (95.6–100.2)	97.3 (95.0–99.6)	97.8 (95.9–99.7)	88.9	0.9784	67.5	92.8	0.8913	60.4
Sensitivity	23.9 (13.7–34.1)	30.0 (21.8–38.2)	35.3 (28.1–42.5)	30.6 (24.4–36.9)						
Anti-CCP2+CRP+swollen joints										
Specificity	98.0 (95.2–100.8)	97.2 (94.5–99.9)	97.3 (95.0–99.6)	97.8 (95.9–99.7)	88.2	0.9113	67.0	93.4	0.9506	61.6
Sensitivity	22.4 (12.4–32.4)	26.7 (18.8–34.6)	34.0 (26.7–41.2)	34.0 (27.6–40.4)						
Anti-CCP2+RF+CRP										
Specificity	96.9 (93.5–100.3)	96.5 (93.5–99.5)	96.2 (93.5–99.0)	97.3 (95.2–99.4)	88.0	0.9651	70.0	93.7	0.8511	64.7
Sensitivity	32.8 (21.6–44.1)	35.0 (26.5–43.5)	41.2 (33.8–48.6)	42.6 (35.9–49.3)						
Anti-CCP2+CRP+tender joints										
Specificity	95.9 (92.0–99.8)	93.8 (89.8–97.7)	94.1 (90.6–97.5)	95.1 (92.3–97.9)	81.8	0.9604	68.0	89.4	0.5492	65.0
Sensitivity	26.9 (16.3–37.5)	36.7 (28.0–45.3)	42.4 (34.9–49.8)	44.5 (37.8–51.2)						
Anti-CCP2+RF+CRP+swollen joints										
Specificity	98.0 (95.2–100.8)	98.6 (96.7–100.5)	97.8 (95.7–99.9)	98.7 (97.2–100.2)	86.7	0.7662	66.3	95.5	0.5363	60.6
Sensitivity	19.4 (9.9–28.9)	23.3 (15.8–30.9)	28.2 (21.5–35.0)	30.6 (24.4–36.9)						

* Disease duration means that individuals first visited at around 3, 6, 12, or 24 months from onset of any arthritis symptoms. ** Percentage of respective measure (95% CI). † Comparison between PPV of measure and PPV of ACR criteria.

ic symptoms whose diagnosis was not yet made. We found that the diagnostic specificity and PPV of anti-CCP2 antibody were 95.4% and 87.8%, respectively, at 3 months from the onset of arthritic symptoms, while the sensitivity and NPV were lower. It was found that even anti-CCP antibody alone amply surpassed the ACR criteria with regards to specificity (Tables 1 and 5), whereas previous studies, lacking patients who visited as early as 3 months after onset, could not reach this conclusion[7]. We found, however, that the specificity and PPV of anti-CCP2 assay declined gradually during the disease course. This was compatible with the previous results, which described the patients visiting later but around 2 years from onset[11].

Our study demonstrates that anti-CCP2 assay alone was

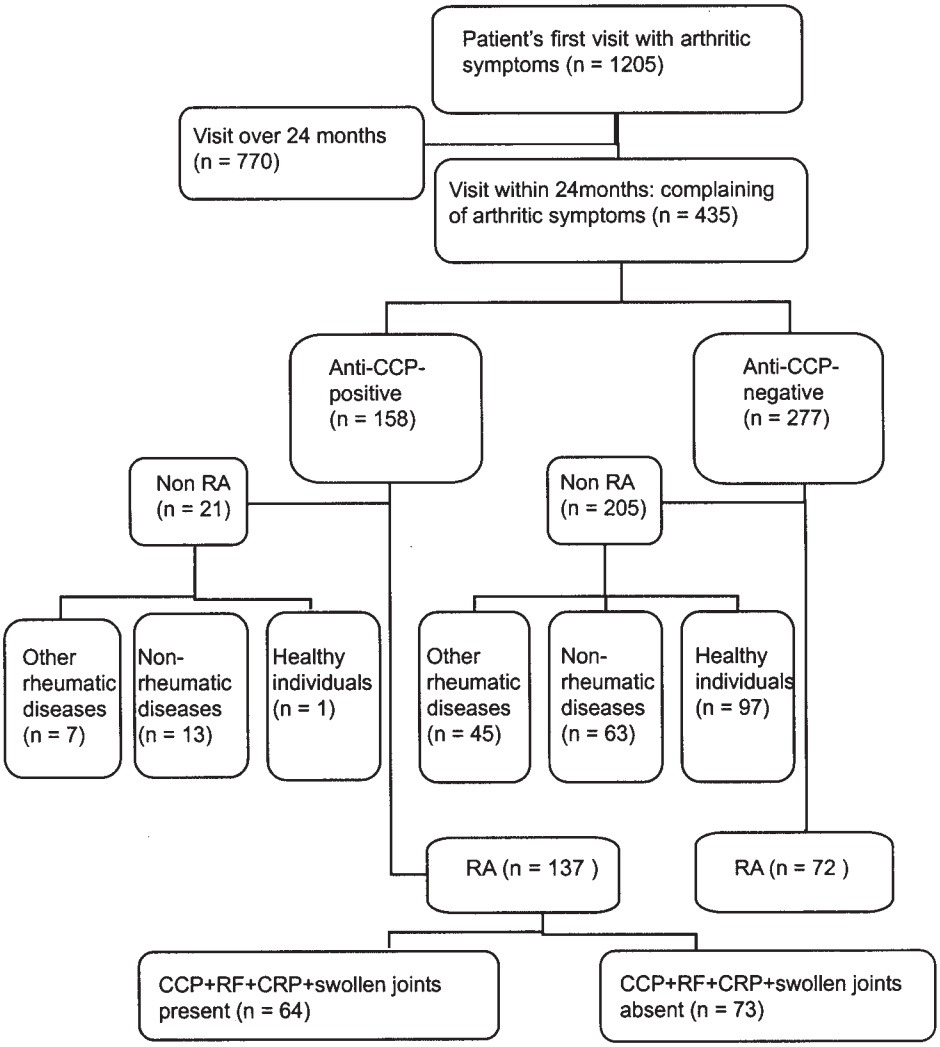

Figure 1. A flow diagram for the specific diagnosis of early RA, showing the relationship between the presence or absence of anti-cyclic citrullinated peptide (CCP)2 antibody and the final outcome of the patients who first visited hospital within 24 months complaining of any arthritic symptoms. Patients with RA are classified into presence or absence of our diagnostic criteria: Anti-CCP+ and rheumatoid factor (RF)+ and C-reactive protein (CRP)+ and more than 3 swollen joints.

sufficient for the patients visiting within 3 months after onset of RA, but was apparently insufficient for the prediction of RA for those who first visited later than 3 months but within 24 months from onset. Accordingly, we adopted clinical detection of more than 3 swollen joints as a measure: we found swollen joints to be fairly specific for RA throughout the disease course (Table 1). We therefore constructed the new criteria by adopting more than 3 swollen joints, RF, and CRP for the patients who visited later but within 24 months from onset. We found that the specificity and PPV of the criteria surpassed 98% and 95%, respectively, when anti-CCP2 antibody was coevaluated with RF, CRP, and more than 3 swollen joints (Table 1). Coevaluation of anti-CCP2 assay with (1) RF plus swollen joints, (2) CRP plus swollen joints, or (3) RF plus CRP also affords specificity and PPV exceeding 96% and 92%, while the sensitivity and NPV were lower again. It should be noted that most of these criteria again surpassed the specificity of ACR criteria.

DISCUSSION

In our study, we first demonstrate that anti-CCP2 antibody does not rise without arthritis and/or inflammation: first, 6 of 8 (75.0%) individuals in the nonrheumatic disease group who presented with > 100 U/ml of anti-CCP2 antibody achieved the final diagnosis of undifferentiated arthritis; second, the clinical profile of patients showed that anti-CCP2 antibody was raised as early as 1 month from onset in a significant proportion (50%) of patients with the final diagnosis of RA, and anti-CCP2 antibody was gradually raised during the disease course solely in the patients with

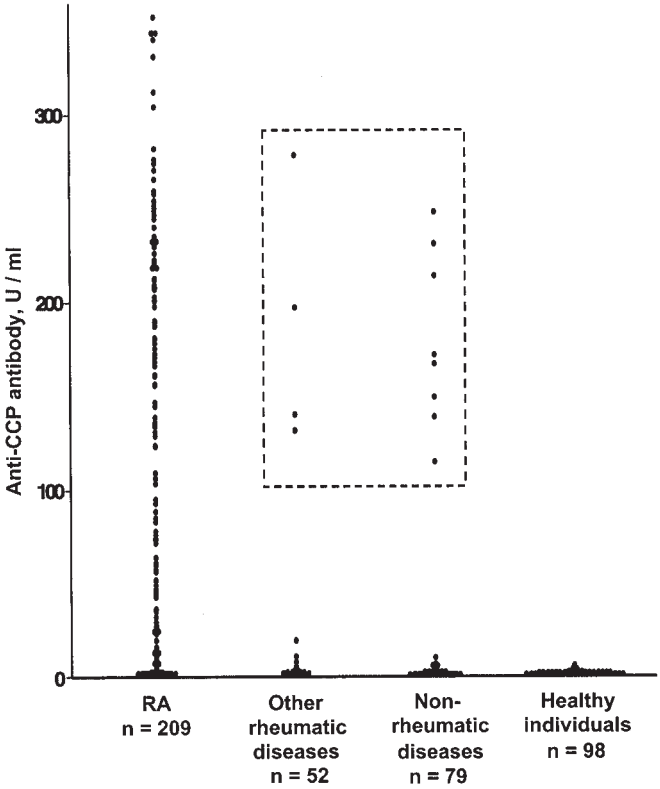

Figure 2. Serum level of anti-CCP antibody: titers in patients with RA and other conditions as measured on first visit to hospital. Groups were categorized according to the final diagnosis. Inner rectangle shows individuals with > 100 U/ml of anti-CCP2 antibodies.

Table 2. Final diagnosis of individual non-RA patients who presented with > 100U/ml of anti-CCP2 antibody.

Diagnosis	Anti-CCP Antibody Titer (U/ml)
Other rheumatic disease (n = 4)	
Polymyositis/dermatomyositis	131.2
Polymyositis/dermatomyositis	139.7
CREST syndrome	197
Reactive arthritis	277.9
Nonrheumatic diseases (n = 8)	
Osteoarthritis	114.6
Tenosynovitis	138.2
Undifferentiated arthritis	149.1
Undifferentiated arthritis	166.4
Undifferentiated arthritis	171.3
Undifferentiated arthritis	213.8
Undifferentiated arthritis	230.9
Undifferentiated arthritis	247.8

the final diagnosis of RA (Table 3); third, the presence of anti-CCP2 antibody showed a positive correlation with RF in the patients with RA (Table 4); and fourth, the inflammatory indices including ESR and CRP also showed positive correlation with anti-CCP2 antibody in the groups other than those with RA. Thus, we conclude from clinical observation that anti-CCP2 antibody is raised by no nonspecific means, and the disease condition associated with arthritis and/or inflammation definitely contributes to the rise of anti-CCP2 antibody.

The results showed that the diagnostic specificity and PPV of anti-CCP2 assay were considerably higher in the patients who first visited the hospital within 3 months from onset. We simultaneously noted that the diagnostic specificity and PPV of anti-CCP2 assay gradually declined to 90.7% and 86.7% at 24 months from onset (Table 1), this finding clearly indicating that sole measurement of anti-CCP antibody is insufficient as a predictor of RA for those who first visited later than 3 months after disease onset. This is consistent with the suggestion of Vittecoq, *et al*[12] and suggests that extremely high specificity of anti-CCP2 assay is masked by the operation of factors other than anti-CCP2 at time periods later than 3 months from disease onset. The diagnostic specificity and PPV remained at 92.5% and 88.4% and did not improve when the RF of the ACR criteria was replaced by anti-CCP2 antibody. We therefore tried to find a more accurate predictor for the development of RA in future apart from the ACR criteria. Since all of the previously established criteria adopting anti-CCP antibodies[19,20,22,23] required either consultation by specialists or additional expensive instruments such as magnetic resonance imaging, we intentionally focused on the very routine measures, and found that the use of RF, CRP, and/or clinical detection of more than 3 swollen joints significantly improved the diagnostic specificity (Table 5). For the patients who first visited later but within 24 months from onset, we found that the specificity and PPV were extremely high at 98% and 95%, respectively, when anti-CCP2 assay was coevaluated with RF, CRP, and swollen joints. They are clearly superior to the ACR criteria. Further, for routine clinical use, we may also use (1) RF plus swollen joints, (2) CRP plus swollen joints, or (3) RF plus CRP in combination with anti-CCP2 assay. All 3 combinations do afford high enough values, surpassing the ACR criteria. We emphasize here that, although less sensitive, the combination of RF, CRP, and/or swollen joints with anti-CCP2 assay is instead highly specific and accurate: it is easy to use for physicians and thus beneficial to patients.

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Table 3. Disease course and frequency of anti-CCP2-positive individuals.

	Anti-CCP2+/RA (%)*, N = 209†	Anti-CCP+/Other Rheumatic Disease (%), N = 52†	Anti-CCP+/Nonrheumatic Diseases (%), N = 76†	Anti-CCP+/Healthy Individuals (%), N = 98†	Anti-CCP+/Total (%), N = 435†
Disease duration, mo					
0–1**	6/12 (50.0)	1/10 (10.0)	2/14 (14.3)	0/26 (0.0)	9/62 (14.5)
2–3	30/55 (54.5)	1/10 (10.0)	1/13 (7.7)	0/25 (0.0)	32/103 (31.1)
4–6	34/53 (64.2)	3/13 (23.1)	5/16 (31.3)	0/17 (0.0)	42/99 (42.4)
7–12	36/50 (72.0)	1/9 (11.1)	1/17 (5.9)	1/15 (6.7)	39/91 (42.9)
13–24	31/39 (79.5)	1/10 (10.0)	4/16 (25.0)	0/15 (0.0)	36/80 (45.0)

* The number of anti-CCP2-positive individuals divided by the number of individuals with indicated final diagnosis. † Number of individuals with respective final diagnosis. ** Respective disease duration includes individuals who first visited at 0–1, 2–3, 4–6, 7–12, or 13–24 months from onset of any arthritic symptoms.

Table 4. Presence or absence of anti-CCP2 antibody and profiles of patients. Data are mean ± SD.

Disease Group	Anti-CCP2+,	Anti-CCP2–,	p
RA (final diagnosis; N = 209)	N = 137	N = 72	
Male, n (%)	40 (29.2)	23 (31.9)	
Age, yrs	56.4 ± 14.6	56.9 ± 15.0	0.85
Anti-CCP, U/ml	136.1 ± 95.9	1.8 ± 0.8	< 0.01
Disease duration, mo	8.6 ± 6.7	6.1 ± 5.7	< 0.01
Serum CRP, mg/dl	3.0 ± 4.7	3.5 ± 4.7	0.49
Serum MMP-3, ng/ml	92.2 ± 129.5	64.9 ± 104.7	0.12
ESR, mm/h	59.3 ± 35.6	58.2 ± 38.5	0.85
RF, IU/ml	201.4 ± 377.7	31.6 ± 83.1	< 0.01
No. swollen joints	6.6 ± 6.3	5.9 ± 7.0	0.43
No. tender joints	7.7 ± 6.3	6.4 ± 5.8	0.17
Other rheumatic diseases (final diagnosis; N = 52)	N = 7	N = 45	
Male, n (%)	1 (14.2)	7 (15.6)	
Age, yrs	56.4 ± 7.4	51.1 ± 16.4	0.49
Anti-CCP, U/ml	111.9 ± 104.6	1.9 ± 0.8	< 0.01
Disease duration, mo	5.0 ± 3.8	6.7 ± 6.1	0.54
Serum CRP, mg/dl	4.6 ± 4.9	1.3 ± 2.7	0.01
Serum MMP-3, ng/ml	32.7 ± 24.7	38.7 ± 63.9	0.80
ESR, mm/h	74.7 ± 33.7	43.2 ± 35.4	0.04
RF, IU/ml	151.3 ± 139.6	50.8 ± 104.3	0.05
No. swollen joints	3.6 ± 1.5	3.3 ± 4.2	0.86
No. tender joints	5.0 ± 2.2	3.3 ± 3.1	0.24
Nonrheumatic diseases (final diagnosis; N = 76)	N = 13	N = 63	
Male, n (%)	1 (7.7)	9 (14.3)	
Age, yrs	49.6 ± 14.7	54.2 ± 10.6	0.24
Anti-CCP, U/ml	113.0 ± 94.1	1.5 ± 0.6	< 0.01
Disease duration, mo	8.4 ± 6.5	7.0 ± 6.0	0.37
Serum CRP, mg/dl	0.8 ± 1.6	0.3 ± 1.4	0.24
Serum MMP-3, ng/ml	16.3 ± 23.5	13.6 ± 20.2	0.67
ESR, mm/h	29.4 ± 22.1	16.9 ± 14.0	0.02
RF, IU/ml	53.9 ± 92.8	35.1 ± 84.9	0.49
No. swollen joints	1.3 ± 1.7	1.2 ± 1.6	0.86
No. tender joints	3.4 ± 2.8	3.7 ± 3.0	0.80

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Table 5. Comparison between selected measures and ACR diagnostic criteria (summary of Table 1).

Clinical Measures	Disease Duration, mo				3 mo		24 mo	
	3	6	12	24	PPV	NPV	PPV	NPV
ACR criteria								
Specificity	92.6 (87.7–97.5)	91.7 (87.2–96.2)	93.5 (89.9–97.0)	93.8 (90.7–96.9)	85.5	83.3	92.2	82.8
Sensitivity	70.1 (59.2–81.1)	75.8 (68.2–83.5)	77.6 (71.4–83.9)	79.9 (74.5–85.3)				
Anti-CCP2 (≥ 5 U/ml)								
Specificity	95.4 (91.4–99.3)	91.0 (86.3–95.7)	91.3 (87.2–95.4)	90.7 (86.9–94.5)	87.8	76.9	86.7	74
Sensitivity	53.7 (41.8–65.7)	58.3 (49.5–67.2)	62.4 (55.1–69.6)	65.6 (59.1–72.0)				
Anti-CCP2+RF								
Specificity	96.9 (93.5–100.3)	95.1 (91.6–98.7)	95.1 (92.0–98.2)	94.2 (91.2–97.3)	90.9	73.9	90.2	70.3
Sensitivity	44.8 (32.9–56.7)	49.2 (40.2–58.1)	53.5 (46.0–61.0)	56.9 (50.2–63.7)				
Anti-CCP2+RF+swollen joints								
Specificity	98.0 (95.2–100.8)	97.9 (95.6–100.2)	97.3 (95.0–99.6)	97.8 (95.9–99.7)	88.9	67.5	92.8	60.4
Sensitivity	23.9 (13.7–34.1)	30.0 (21.8–38.2)	35.3 (28.1–42.5)	30.6 (24.4–36.9)				
Anti-CCP2+CRP+swollen joints								
Specificity	98.0 (95.2–100.8)	97.2 (94.5–99.9)	97.3 (95.0–99.6)	97.8 (95.9–99.7)	88.2	67.0	93.4	61.6
Sensitivity	22.4 (12.4–32.4)	26.7 (18.8–34.6)	34.0 (26.7–41.2)	34.0 (27.6–40.4)				
Anti-CCP2+RF+CRP+Swollen joints								
Specificity	98.0 (95.2–100.8)	98.6 (96.7–100.5)	97.8 (95.7–99.9)	98.7 (97.2–100.2)	86.7	66.3	95.5	60.6
Sensitivity	19.4 (9.9–28.9)	23.3 (15.8–30.9)	28.2 (21.5–35.0)	30.6 (24.4–36.9)				

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