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Anticyclic Citrullinated Peptide Antibodies in Rheumatoid and Nonrheumatoid Rheumatic Disorders: Experience with 1162 Patients

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Anticyclic Citrullinated Peptide Antibodies in Rheumatoid and Nonrheumatoid Rheumatic Disorders: Experience with 1162 Patients

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ABSTRACT. ***Objective.*** Anticyclic citrullinated peptide antibodies (anti-CCP) are considered specific markers of rheumatoid arthritis (RA) and have been included in the revised classification criteria for RA diagnosis. However, these antibodies have also been detected in patients with other types of chronic inflammatory rheumatism. Our objectives were to identify the prevalence of positive anti-CCP patients in non-RA diseases, to determine the diagnostic value of anti-CCP for the diagnosis of RA, to specify the clinical characteristics of non-RA patients positive for anti-CCP, and to determine the discriminatory value of the levels of anti-CCP in patients among the various diseases.

Methods. We carried out an observational and descriptive study. All the determinations of anti-CCP requested by the 2 rheumatology departments at Cochin Hospital over a period of 18 months were analyzed. Such determinations were requested for 1162 patients in total. Anti-CCP levels were determined with the Euro Diagnostica ELISA kit, with values ≥ 25 U for this test being considered positive. The diagnosis of rheumatic conditions was the responsibility of the treating physician.

Results. Anti-CCP antibodies were detected in 357 (30.7%) of the 1162 patients. The prevalence of anti-CCP was 292/417 (70.0%) in RA, 13/122 (10.6%) in patients with psoriatic arthritis, 13/62 (20.9%) in patients with unclassified rheumatism, 11/33 (33.3%) in patients with primary Sjögren syndrome, 5/30 (16.6%) in patients with systemic lupus erythematosus, 3/28 (10.7%) in patients with mixed connective tissue disorder, 3/36 (8.3%) in patients with systemic sclerosis, 7/44 (15.9%) in patients with juvenile arthritis, and 6/220 (2.7%) in patients with noninflammatory diseases. In the population of patients positive for anti-CCP, mean anti-CCP levels were 869.4 (± 978.4) U/ml, with no significant difference between RA [854.8 (± 959.8) U/ml] and any of the non-RA conditions [922.7 (± 1070.0) U/ml].

Conclusion. Anti-CCP are a hallmark of RA, but may be observed in other inflammatory, systemic, or mechanical diseases. In this large cohort of patients, the presence of second-generation anti-CCP (anti-CCP2) antibodies is useful in diagnosing RA (70% sensitivity, 91.3% specificity), but examining the levels of these antibodies does not appear to offer further discriminatory power among patients who are anti-CCP2-positive. (First Release Oct 1 2014; J Rheumatol 2014;41:2395–402; doi:10.3899/jrheum.131375)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DIAGNOSIS
ANTICYCLIC CITRULLINATED PEPTIDE ANTIBODIES

Autoantibodies are useful for determinations of the diagnosis and prognosis of the various types of inflammatory chronic rheumatisms. Anticitrullinated protein antibodies (ACPA), like anticyclic citrullinated peptide antibodies (anti-CCP), have proven effective as diagnostic markers for rheumatoid arthritis (RA)[1]. Indeed, they also provide important prognostic information[2,3]. In patients with incipient arthritis, the detection of anti-CCP in serum is highly predictive not only of a diagnosis of RA, but also of the development of a destructive erosive form of the disease[4]. Moreover, the detection of anti-CCP in the serum of a blood donor may indicate that this individual will develop RA later in life[5]. Further, high titers of anti-CCP seem to be indicative of more aggressive radiographic progression and of greater disease severity and RA disease activity[2,3,6,7].

The reported sensitivity of these antibodies for the

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diagnosis of RA varies from 41% to 77%, and their specificity varies from 88% to 100%[8]. They outperform rheumatoid factor (RF) as a diagnostic factor in this context. Given their high specificity, anti-CCP antibodies have been included in the revised classification criteria for RA diagnosis[9]. Anti-CCP2 (second-generation) detection is currently considered the gold standard for ACPA detection[1].

However, ACPA have been detected in healthy subjects and in patients with other forms of arthritis, such as psoriatic rheumatism, primary Sjögren syndrome (pSS), systemic sclerosis (SSc), juvenile arthritis, systemic lupus erythematosus (SLE), and dermatopolymyositis[10].

Only a few studies have investigated the prevalence of anti-CCP2 in these diseases. This prevalence has been reported to range from 5% to 20% of patients with non-RA inflammatory rheumatic conditions[1,10,11]. However, the sample size of those studies was generally small. Moreover, the methods and assays used for detection and the definitions of the rheumatic conditions were not uniform across those studies. The specificity of anti-CCP2 and their potential association with non-RA rheumatic conditions remain to be clarified.

The objectives of our study were to identify the diseases other than RA in which anti-CCP may be detected (prevalence of anti-CCP in non-RA diseases), to determine the diagnostic value of anti-CCP2 for the diagnosis of RA, to specify the clinical characteristics of non-RA patients positive for anti-CCP, and to determine the discriminatory value of the levels of anti-CCP among the various diseases.

MATERIALS AND METHODS

Patients. We included consecutive patients seen at the Inpatient Rheumatology Clinic of Cochin Hospital for whom anti-CCP determinations were ordered over an 18-month period, between 2011 and 2012. Such determinations were requested for 1162 patients in total. For 132 patients, determinations were requested several times during the period of interest. For those cases, we took only the result of the first test into account.

The treating physician was responsible for the diagnosis of the rheumatic condition at the time of anti-CCP determination, on the basis of his or her clinical judgment and the various classification criteria. RA diagnosis was based on the American College of Rheumatology (ACR) 1987 classification criteria[12]. We decided to use this classification rather than the ACR 2010 classification[9] because of the great weight given to anti-CCP in this revised classification. The diagnosis taken into account was provided by the treating physician, who was asked to refer to these criteria: the revised ACR criteria[13] for the diagnosis of SLE; the diagnostic algorithm reported by Vitali, *et al*[14] for the diagnosis of pSS; and the classification criteria for psoriatic arthritis (PsA)[15] for the diagnosis of PsA. For patients who might at any time fulfill the criteria for more than 1 rheumatic disease, the whole disease course was analyzed with the treating physician and the predominant clinical presentation was taken into account for classification.

Further, some additional characteristics were recorded for patients with anti-CCP antibodies: arthralgia, arthritis, axial or peripheral involvement, bone erosion, duration of disease, results of RF tests, previous and additional determinations of anti-CCP2 levels between January 2006 and June 2013, and use of disease-modifying antirheumatic drugs (DMARD) or anti-tumor necrosis factor (TNF) agents.

Determination of autoantibodies. A commercial ELISA (ImmunoscanRA, Euro Diagnostica) was used to evaluate the presence of anti-CCP2 IgG antibodies. A cutoff of 25 U/ml was used, as suggested by the manufacturer's protocol. A level ≥ 75 U/ml was regarded as high, as specified in the classification criteria for RA[9]. The assay was reliable up to concentrations of 3200 U/ml; all values above that were analyzed as 3200 U/ml. The samples were not diluted.

All the sera were used concomitantly for the quantification of RF using the ELISA method described elsewhere[16]. RF detection was considered positive for values > 10 U/ml.

Statistical analysis. Descriptive statistics are presented as mean (± SD). Categorical variables are expressed as frequencies and percentages. Continuous variables were compared between groups in a nonparametric test (Mann-Whitney test) and Fisher's exact test was used to compare categorical variables. Spearman's rank correlation test was used to assess the correlations between continuous variables. Values of $p < 0.05$ were considered statistically significant.

The prevalence of anti-CCP for each disease in this population was estimated by dividing the number of patients with a particular diagnosis who tested positive for anti-CCP by the total number of patients with that diagnosis in the population of included patients.

RESULTS

Rheumatologic conditions and the characteristics of the patients. In total, anti-CCP determinations were requested for 1162 patients, and positive results were obtained for 357 patients (30.7%). The mean age of the patients testing positive was 56.5 years (± 14.2), and 302 (84.6%) were women.

In the global population, diagnoses were known in 1140 patients and were as follows: 36.6% (n = 417) RA, 10.7% (n = 122) PsA, 6.7% (n = 76) spondyloarthritis (SpA), 5.4% (n = 62) unclassified rheumatism, 3.9% (n = 44) juvenile arthritis, 3.2% (n = 37) SSc, 2.9% (n = 33) SS, 2.7% (n = 31) SLE, 2.4% (n = 25) mixed connective tissue disorder, 1.2% (n = 14) unclassified connective tissue disorder, and 24.3% (n = 279) noninflammatory diseases.

Prevalence of anti-CCP antibodies for each disease. In this population of 1140 patients for whom the diagnosis was known, anti-CCP were detected in 292/417 patients with RA (70.0%), 13/122 patients with PsA (10.7%), 2/76 patients with other types of SpA [2.6%; 1 synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO); and 1 reactive arthritis], 13/62 patients with unclassified rheumatism (20.9%), 11/33 patients with pSS (33.3%), 5/31 patients with SLE (16.1%), 2/25 patients with mixed connective tissue disorder (8.0%), 4/37 patients with SSc (10.8%), 0/14 patients with unclassified connective tissue disorder (0.0%), 7/44 patients with juvenile arthritis (15.9%), and 6/279 patients with noninflammatory diseases (2.1%; 3 with osteoarthritis and 3 with metabolic rheumatism). These results are shown in Figure 1. Two patients who were positive for anti-CCP had unknown diagnoses.

Diagnostic value of anti-CCP2 antibodies for RA. Anti-CCP2 antibodies were present in 292 patients with RA and 63 patients with other diseases. Anti-CCP2 tests were negative in 125 patients with RA and in 660 patients with other diseases. The sensitivity of anti-CCP2 antibodies for

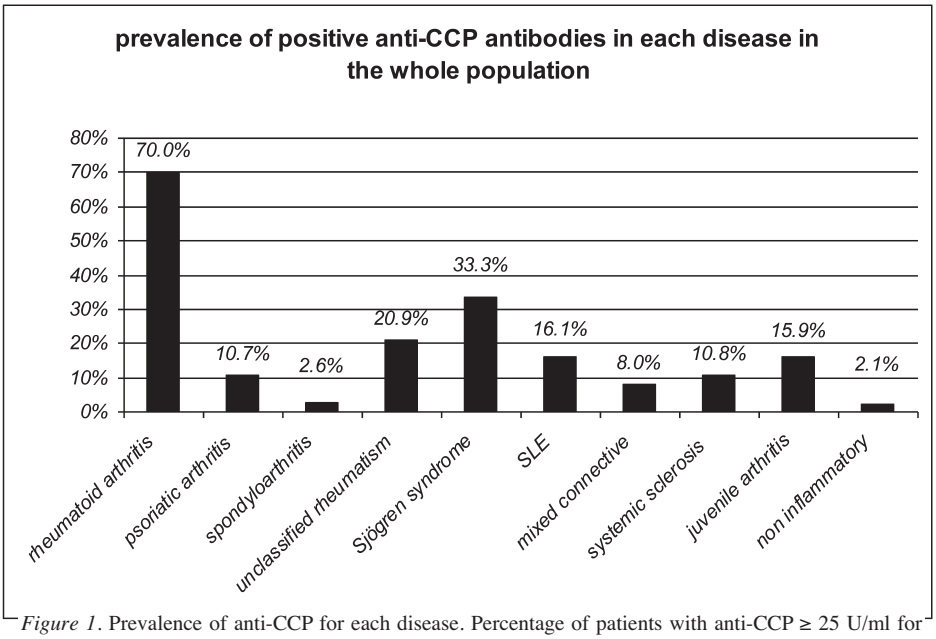

Figure 1. Prevalence of anti-CCP for each disease. Percentage of patients with anti-CCP ≥ 25 U/ml for each disease in the cohort of 1162 patients. Spondyloarthritis included ankylosing spondylarthritis, reactive arthritis, and SAPHO. Noninflammatory diseases included osteoarthritis and metabolic rheumatism. SAPHO: synovitis, acne, pustulosis, hyperostosis, and osteitis; SLE: systemic lupus erythematosus; anti-CCP: anticyclic citrullinated peptide antibodies.

the diagnosis of RA in this population was 70.0%, specificity was 91.3%, positive predictive value was 82.3%, and negative predictive value was 84.1% (Figure 2).

Clinical characteristics of patients positive for anti-CCP and rheumatic diagnoses other than RA. In the patients who were anti-CCP–positive, we noted particular characteristics of their rheumatologic presentation. It should be noted that we did not have the clinical description of patients negative for anti-CCP as a control group.

Among the patients with SpA who were anti-CCP-positive (n = 15), 13 had PsA, 1 had SAPHO syndrome, and 1 had reactive arthritis. The mean age of the patients with PsA and positive for anti-CCP was 54.4 years (± 14.5), not statistically different from patients negative for anti-CCP. All the

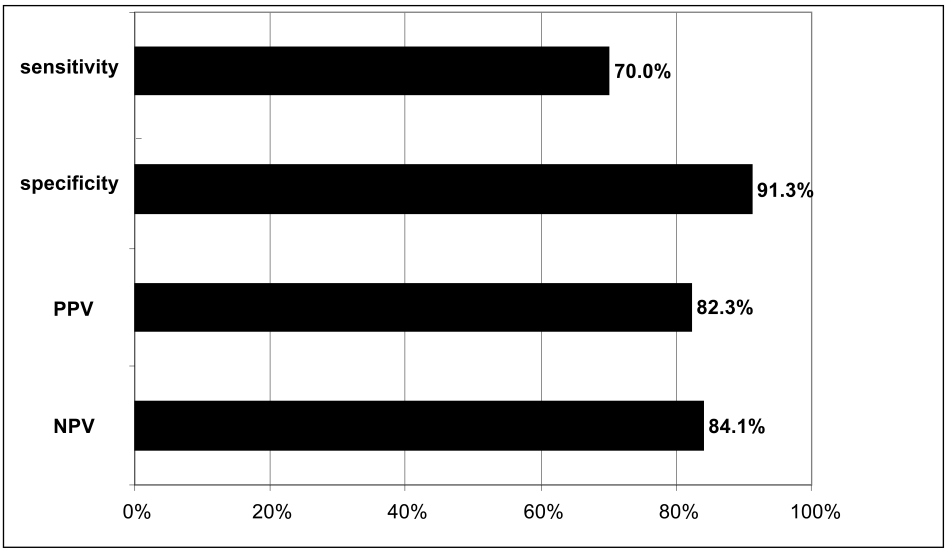

Figure 2. Diagnostic value of anti-CCP2 for RA. Values of sensitivity, specificity, PPV, and NPV of anti-CCP2 for the diagnosis of RA in the 1162 patients. RA: rheumatoid arthritis; PPV: positive predictive value; NPV: negative predictive value; anti-CCP2: anticyclic citrullinated peptide antibodies.

patients with PsA and positive for anti-CCP (n = 13) had peripheral involvement: 9 (69.2%) had symmetric polyarthritis, 4 (30.8%) had asymmetric oligoarthritis, and 1 (7.7%) also had axial involvement. Twelve of these 13 patients (92.3%) had erosions and/or joint space narrowing.

For patients with connective tissue disorders (i.e., SS, SLE, SSc, mixed connective tissue disorder), the mean age was 43.2 years (± 15.0), 18/22 patients (81.8%) had arthritis, but only 3/22 (13.6%) had radiological damage (2 classified as having SLE, 1 as having SSc). Two out of the 5 patients of the SLE group had some radiograph abnormalities, but without typical RA erosions. In the SSc group, 1 out of the 4 patients exhibited radiograph changes that could be evocative of RA-like erosion for carpitis or metacarpophalangeal/proximal interphalangeal damage, but with also distal interphalangeal damage as described in previous studies looking at SSc joint lesions[17]. In addition, this patient had an SSc diffuse cutaneous subtype known to be associated with joint involvement.

Autoantibody levels in the anti-CCP-positive population, as a function of rheumatological condition. In the group positive for anti-CCP, mean anti-CCP level was 854.8 (± 959.8) U/ml in patients with RA and 922.7 (± 1070.0) U/ml in patients with other diagnoses (for all diagnoses considered together). No significant difference was found in anti-CCP levels (considered as a continuous variable) between patients with RA and patients with other diagnoses in the group of patients positive for anti-CCP (p = 0.865). The proportion of patients with a high level of anti-CCP (≥ 75 U/ml) was 85.3% (249/292) in RA and 79.4% (50/63) in non-RA diagnoses; the difference was not statistically significant (p = 0.24). Details of the levels of anti-CCP for each disease are provided in Figures 3A and 3B.

No correlation was found between anti-CCP level and age, sex, or disease duration. By contrast, anti-CCP levels were found to be correlated with RF levels in the population of patients with RA (p = 0.05), but not in patients with diagnoses other than RA (p = 0.26).

DISCUSSION

In our population of 1162 patients, anti-CCP were present in 70% of the patients with RA, 11.5% of the patients with other chronic inflammatory rheumatisms, and 15.7% of the patients with connective tissue disorder. Analyses in which anti-CCP levels were included as a continuous variable suggested that there was no additional benefit from testing for high titers of anti-CCP in the group of patients with anti-CCP for improving diagnosis.

Several studies showed that among patients with PsA, those with anti-CCP tend to have more involved joints, more erosions, and greater DMARD use than patients without these antibodies[17,18,19,20,21]. Anti-CCP are rarely detected in axial disease: only 14% to 27%[20,21] of PsA cases with axial involvement have anti-CCP. In our study, 69.2% of patients with anti-CCP had polyarticular disease and only 1 patient (7.7%) had axial involvement. All patients were treated with DMARD and 5 of the 13 patients also had a history of anti-TNF treatment.

For SS, 9/11 (81.8%) of our patients had polyarthritis and 2 patients had only arthralgia. None of these patients had radiological erosion. Two studies investigated anti-CCP in patients with SS. Atzeni, *et al*[22] showed that the frequency of arthritis was higher in patients with SS with anti-CCP than in patients with SS without anti-CCP. In contrast, Gottenberg, *et al*[23] found no difference between these 2 groups of patients.

Several studies on SLE have shown that patients with SLE and anti-CCP have more erosive arthritis than patients without anti-CCP[24,25,26,27,28], and the prevalence of erosive or deforming arthritis in patients with anti-CCP has been reported as 50% to 100%[27]. Two of our 5 patients diagnosed with SLE (40%) presented erosions.

Avouac, *et al* showed that 23% of patients with SSc had erosive arthritis[29] but only 2% had anti-CCP. All 3 of our patients with SSc had arthralgia, but no radiological involvement.

We hypothesized at the start of our study that anti-CCP levels might be useful for the stratification of patients who are anti-CCP-positive. However, we found that anti-CCP levels were not useful for distinguishing between patients with RA and non-RA patients with anti-CCP2. Mean anti-CCP levels did not differ significantly, and percentages of patients with high levels (> 75 U/ml) were similar in all types of rheumatisms. Previous studies could be regarded as reporting conflicting results in SLE[30], mixed connective tissue disorder[31], or SS[32]. However, it must be underlined that these previous works did compare the whole populations having various diseases and did not focus only on those positive for anti-CCP. Therefore, because anti-CCP are more common in RA, these studies report higher levels in such patients with RA. We herein rather aimed at comparing the levels of anti-CCP within the groups of patients having various rheumatic conditions. Using this approach, which is relevant from the clinical perspective, we could not show that patients with RA had higher levels among the anti-CCP-positive patients. Therefore, our results suggest that in a patient positive for anti-CCP, the levels of these antibodies cannot guide the clinician to differentiate RA from non-RA diseases.

In our study, we estimated the prevalence of anti-CCP for each non-RA disease. This was possible because almost all the patients admitted for suspected chronic inflammatory diseases or connective tissue disorders were tested for anti-CCP. For most diseases, our findings were consistent with previous reports: between 0% to 20% for small cohorts of patients with PsA[17,18,33,34,35,36], 4% to 13% for SSc[10,31,37,38,39,40], and 13% to 38% for SLE[31,41,42], with higher values for erosive arthritis[24,25,26,43], about 9% in

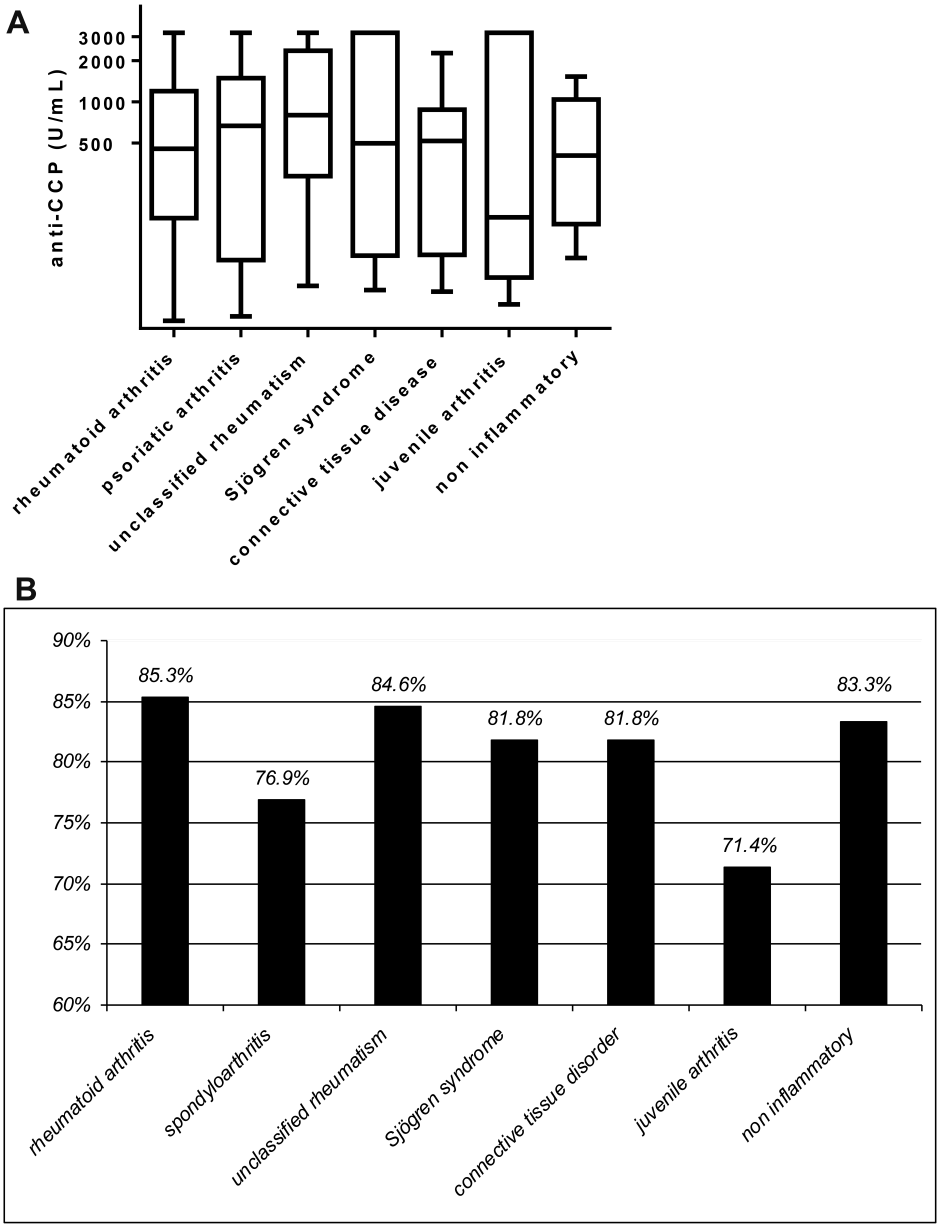

Figure 3. A. Levels of anti-CCP in patients with RA, and with non-RA diseases in patients positive for anti-CCP. Spondyloarthritis included 13 patients with psoriatic arthritis, 1 with reactive arthritis, and 1 with SAPHO syndrome. Connective tissue disorder included 5 patients with SLE, 4 with systemic sclerosis, and 2 with mixed connective tissue disease. Noninflammatory diseases included 3 patients with OA and 3 with metabolic rheumatism. B. Prevalence of patients with anti-CCP level ≥ 75 U/ml among the patients positive for anti-CCP in each disease. Spondyloarthritis included 13 patients with psoriatic arthritis, 1 with reactive arthritis, and 1 with SAPHO syndrome. Connective tissue disorder included 5 patients with SLE, 4 with systemic sclerosis, and 2 with mixed connective tissue disease. Noninflammatory diseases included 3 patients with OA and 3 with metabolic rheumatism. SAPHO: synovitis, acne, pustulosis, hyperostosis, and osteitis; SLE: systemic lupus erythematosus; anti-CCP: anticyclic citrullinated peptide antibodies; RA: rheumatoid arthritis.

mixed connective tissue disease[31], and about 20% in juvenile arthritis[44,45,46,47,48]. However, for SS, the prevalence of these antibodies was higher in our cohort (33.3%) than in previous studies, which reported a prevalence of 3% to 18%[22,23,31,49].

In our study, including patients from rheumatology units,

the patients with positive anti-CCP antibodies had RA in 82.1% of cases, other inflammatory or connective tissue disorder in 16.2% of cases, and noninflammatory diseases in 1.7% of cases. We are aware of 2 other studies[50,51] with a design similar to that of our study and with large cohorts, focusing on patients for whom anti-CCP determinations were requested. In these studies, the patients with anti-CCP had RA in about 65% and 75% of cases, other inflammatory rheumatism or connective disease in 30% and 5% of cases, and noninflammatory disease in 5% and 20% of cases, respectively. However, in 1 of these previous studies[51], the included patients originated from various clinical departments rather than just from rheumatology units, potentially accounting for the high proportion of noninflammatory diseases in our study.

Our study has several limitations that merit further consideration. First, ours was a transverse study without longitudinal followup of the patients. The final diagnosis was made at the time of anti-CCP determination, on the basis of clinical, biological, and radiological data. However, the symptoms or radiological data may change during patient followup, leading to a reevaluation of the diagnosis after several years. For example, a patient with arthralgia and sicca syndrome might initially be diagnosed with SS, but many years later, arthritis and radiological erosions might appear, resulting in a modification of the diagnosis to RA. Moreover, longitudinal followup of the patients with unclassified rheumatism in this cohort might have led to a precise diagnosis for these patients. However, mean disease duration at the time of antibody quantification was 13.2 years (± 10.5), quite a long period, potentially limiting this bias.

Prospective followup might also be useful to monitor changes in anti-CCP production in patients with diseases other than RA. Nevertheless, in 15 patients with anti-CCP2, further determinations were requested. In 11/15 patients (73.3%), the results of subsequent tests were also positive, but in the remaining 4 patients, no antibodies were detected in later tests. For these 4 patients, the initial positive result may be considered a false positive because the levels were low (27, 33, 41, and 68 U/ml). The results of previous determinations were also positive in 18 patients, and all but 1 of the results of those tests were also positive. Another potential limitation relates to the criteria used to define the various rheumatic conditions. We did not collect all the data required to check the various diagnoses, but all the patients were followed in our tertiary center by highly experienced rheumatologists, ensuring the accurate definition of rheumatic conditions.

Anti-CCP2 are known to be a hallmark of RA and of erosive disease. Nevertheless, these antibodies may be observed in other rheumatic diseases, particularly chronic inflammatory diseases. Our results indicate that the presence of anti-CCP2 are useful in diagnosing RA (70% sensitivity, 91.3% specificity), but examining the levels of these antibodies does not appear to offer further discriminatory power among patients who are anti-CCP2-positive.

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