Palindromic Rheumatism with Positive Anticitrullinated Peptide/Protein Antibodies Is Not Synonymous with Rheumatoid Arthritis. A Longterm Followup Study

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ABSTRACT. *Objective.* To analyze longterm progression to rheumatoid arthritis (RA) and the predictive value of anticitrullinated peptide/protein antibodies (ACPA) in palindromic rheumatism (PR).

Methods. We selected all patients in our clinic with PR who had at least 1 ACPA measurement. We included only patients with pure PR, defined as no evidence of associated rheumatic disease at the first serum ACPA measurement. Clinical characteristics, serum ACPA levels, duration of PR until serum ACPA measurement, and total followup time were recorded. The outcome variable was the definitive diagnosis of RA. The prognostic value of ACPA status in pure PR for a definite diagnosis of RA was analyzed by different statistical methods.

Results. Seventy-one patients (54 women/17 men) with a PR diagnosis were included. Serum ACPA were positive in 52.1%. After a mean followup of 7.6 ± 4.7 years since the first ACPA measurement, 24 patients (33.8%) progressed to chronic disease: 22% RA, 5.6% systemic lupus erythematosus, and 5.6% other diseases. The positive likelihood ratio of ACPA status for RA was 1.45, and the area under the receiver-operating characteristic curve of ACPA titers was 0.60 (95% CI 0.45–0.75). Progression to RA was more frequently seen in ACPA-positive than in ACPA-negative patients (29.7% vs 14.7%), but the difference was not significant (hazard ratio 2.46, 95% CI 0.77–7.86). Mean ACPA levels of patients with pure PR did not differ significantly from those of patients who progressed to RA.

Conclusion. ACPA are frequently found in the sera of patients with PR, and a significant proportion of these patients do not progress to RA in the long term. (J Rheumatol First Release Aug 1 2012; doi:10.3899/jrheum.120568)

Key Indexing Terms:
PALINDROMIC RHEUMATISM   ANTICITRULLINATED PEPTIDE/PROTEIN ANTIBODIES
CITRULLINATED   RHEUMATOID ARTHRITIS

Palindromic rheumatism (PR) is a clinical syndrome characterized by attacks of acute arthritis of short duration, usually involving single joints, without residual joint damage[1]. A significant proportion of patients with PR develop a connective tissue disease, mainly rheumatoid arthritis (RA)[2]. Studies have attempted to analyze prognostic indicators for future progression to RA in patients with PR, and identified positive rheumatoid factor (RF) as one such indicator[3,4]. Since our first description of a high prevalence of antibodies against citrullinated peptide/proteins (ACPA) in the sera of patients with PR[5], other groups have confirmed the association between PR and ACPA[6,7], the most specific serological marker of RA[8]. Although ACPA have been shown to be a biomarker for the progression of PR toward RA[6], a significant proportion of patients with PR and high levels of ACPA did not progress to RA during a short-term followup in our original cohort[5]. To expand our knowledge of the prognostic significance of these autoantibodies in PR, we analyzed the longterm clinical progress of 71 patients with PR, and the prognostic utility of the ACPA test.

MATERIALS AND METHODS

Patients with PR attending the Rheumatology Service of Hospital Clinic Barcelona between 1993 and 2010 were included when a typical brief acute attack had been observed by a rheumatologist, other causes of acute arthritis had been ruled out, and an ACPA measurement was available. All

patients fulfilled the PR criteria of Guerne[9]. Patients diagnosed with PR who had progressed to another rheumatic disease at the baseline ACPA measurement were excluded.

Demographic characteristics, duration of PR until serum ACPA measurement, total followup time, and treatment with disease-modifying antirheumatic drugs (DMARD) were recorded in all patients. Serum ACPA were measured by an ELISA using the citrullinated filaggrin-based cyclic citrullinated peptide (CCP1) test until 2002 (normal < 50 IU) and the CCP2 test (normal < 50 IU) thereafter (Immunoscan, Eurodiagnostica; distributed by Diasorin for both tests). RF was measured by nephelometry (normal < 25 IU). All patients were followed until May 2011 to evaluate the development of chronic rheumatic disease and its relationship with ACPA positivity. In most patients, 2 or more ACPA serum determinations were available during the followup. The outcome variable was a definitive diagnosis of RA according to 1987 American College of Rheumatology criteria (progression to RA) or other rheumatic disease besides PR. The study was approved by the Hospital Clinic ethics committee. All patients gave written informed consent to participate.

Statistical analysis. Patients were described with summary statistics, and Student's t test or chi-square test was used to test differences between groups (ACPA±, RA yes/no). The prognostic value of ACPA status in PR was analyzed based on its sensitivity, specificity, and likelihood ratios. The prognostic value of ACPA serum levels was estimated by the area under the curve (AUC) from receiver-operation characteristic curves where the reference variable was a definite diagnosis of RA. The probability of progressing to RA by year after symptom onset was estimated from Kaplan-Meier failure function curves and life tables. Differences in the time to diagnosis were tested with the log-rank test. Cox regression analysis, after test for proportionality, was used to measure the association of ACPA status and progression to RA by year. All analyses were performed using the Stata/IC 10.1 program (StataCorp LP, 2010). A p value < 0.05 was considered statistically significant.

RESULTS

Demographic and serological characteristics and the length of followup of the 71 patients (54 women, 17 men) are shown in Table 1. Twenty-seven patients from the present series were included in our previous study[5]. The mean duration of symptoms until the first ACPA measurement was 4.5 ± 5.8 years and was significantly shorter in patients with positive than in those with negative ACPA. In 24 patients, ACPA measurement was available within the first year of disease duration. Mean followup time from disease onset

until the last visit was 12.1 ± 7.9 years, with no significant differences by ACPA status. Serum ACPA at baseline, measured by CCP1 in 27 patients and by CCP2 in 44 patients, was positive in 37 patients (52.1%), with mean serum levels of 704.8 ± 592.3 IU. RF was positive in 40 patients (56.3%), with a significantly higher prevalence of positivity in ACPA-positive than negative patients.

During followup, 24 patients (33.8%) progressed to chronic rheumatic or systemic disease: 16 (22.5%) to RA, 4 (5.6%) to systemic lupus erythematosus (SLE), and 4 (5.6%) to other diseases: psoriatic arthritis, undifferentiated spondyloarthropathy, autoimmune hepatitis, and familial Mediterranean fever in 1 case each. Progression to chronic disease was more frequent (54.1%) in patients with symptom duration < 1 year, with 33.3% and 12.5% progressing to RA and SLE, respectively. Progression to RA during the followup was nonsignificantly more frequent in patients with ACPA than in those without (29.7% vs 14.7%; p = 0.109; Table 1). Comparison of patients who progressed to RA (n = 16) with those who did not progress to RA or other rheumatic or systemic disease (n = 47) during the followup revealed significant differences in the frequency of RF and a nonsignificant trend according to ACPA status (Table 2). Eleven of the 16 patients who progressed to RA were ACPA-positive (68.8%). All but 1 of the 5 ACPA-negative patients who progressed to RA was RF-positive. Only 1 out of 20 patients (5%) with negative for both ACPA and RF progressed to RA. All 4 patients who progressed to SLE were ACPA-negative, but 2 were RF-positive. Twenty-six of 37 patients (70.3%) with ACPA-positive PR did not progress to RA during followup. In patients progressing to RA, the diagnosis was established after a mean followup of 3.6 ± 1.2 years, with no statistical difference between ACPA-positive and ACPA-negative patients. Mean ACPA serum levels of patients with persistent or pure PR did not differ significantly from those of patients who progressed to RA (Table 2).

The validity findings of the ACPA status in PR for pre-

Table 1. Demographic and serological characteristics of patients with palindromic rheumatism at the time of first measurement of antibodies against citrullinated peptide/proteins (ACPA).

Characteristic	Whole Group, n = 71	ACPA +, n = 37	ACPA –, n = 34	p
Age, yrs	52.4 ± 12.5	51.2 ± 10.2	53.8 ± 14.7	0.38
Female, no. (%)	54 (76.1)	31 (83.8)	23 (67.6)	0.09
Disease duration*, mo, mean ± SD	53.9 ± 69.2	27.1 ± 29.2	82.9 ± 86.9	0.001
Followup**, mo, mean ± SD	90.9 ± 56.6	99.7 ± 60.7	81.2 ± 50.9	0.17
RF+, n (%)	40 (56.3)	26 (70.3)	14 (41.2)	0.01
ACPA+, n (%)	37 (52.1)	—	—	
ACPA values, mean ± SD	704.8 ± 592.3	—	—	
RA during followup, n (%)	16 (22.5)	11 (29.7)	5 (14.7)	0.11
Hydroxychloroquine treatment, n (%)	52 (73.2)	28 (75.7)	24 (70.6)	0.41

* From initial symptoms to first ACPA serum determination. ** From first serum ACPA measurement to last visit. RF: rheumatoid factor; RA: rheumatoid arthritis.

Table 2. Characteristics of patients with palindromic rheumatism who progressed to RA in comparison with those without progression to RA or other rheumatic diseases (persistent PR).

Characteristic	PR to RA, n = 16	Persistent PR, n = 47	p
Age, yrs	56.7 ± 12.5	52 ± 12.5	0.2
Female, n (%)	13 (81.3)	35 (74.5)	0.4
Disease duration*, mo mean ± SD	17.1 ± 17.02	65.4 ± 79.3	0.01
Follow-up time**, mo, mean ± SD	100.8 ± 58.9	89.2 ± 58.2	0.5
RF+, n (%)	14 (87.5)	23 (48.9)	0.006
RF+, mean ± SD[†]	282.5 ± 405.5	169.7 ± 132.9	0.3
ACPA+, n (%)	11 (68.8)	26 (55.3)	0.3
ACPA, mean ± SD[†]	628.4 ± 547.4	737.2 ± 617.8	0.6
Hydroxychloroquine treatment	12 (75)	37 (78.7)	0.5

* From initial symptoms to first ACPA serum determination. ** From first serum ACPA measurement to last visit. [†] Mean values in sera of patients with positive results. RA: rheumatoid arthritis; PR: palindromic rheumatism; RF: rheumatoid factor; ACPA: antibodies against citrullinated peptide/proteins.

dicting RA were sensitivity 68.75%, specificity 52.73%, positive likelihood ratio 1.45, and negative likelihood ratio 0.59. The AUC for the classification efficacy of ACPA serum levels at baseline to predict patients with RA was 0.60 (95% CI 0.45–0.75). The probability of progressing to RA was 7% (95% CI 3.9–16.6), 17% (95% CI 9.9–28.9), and 26% (95% CI 15.9–41.8) at 1, 5, and 10 years after symptom onset, respectively. There were no differences in progression between ACPA-positive and negative patients, as demonstrated by the log-rank test (p = 0.117; Figure 1) and Cox regression analysis, with a hazard ratio (HR) of 2.46 (95% CI 0.77–7.86). The time to ACPA measurement was inversely associated with the probability of RA (HR per year 0.97, 95% CI 0.95–0.99).

Two or more ACPA measurements were made in 57 patients (22 ACPA-positive and 35 ACPA-negative at study entry); seroconversion from negative ACPA to positive ACPA was observed in only 2 patients after 11 and 18 months of followup, respectively, one of whom progressed to RA; the remaining patients showed the same serological status.

The majority of patients were treated with DMARD at some time during the followup, most frequently hydroxychloroquine (73.2%). No significant differences in the use of hydroxychloroquine were observed in patients with PR according to ACPA status or RA progression.

DISCUSSION
This study confirms a high prevalence of ACPA in the sera of patients with PR, more than half of whom were
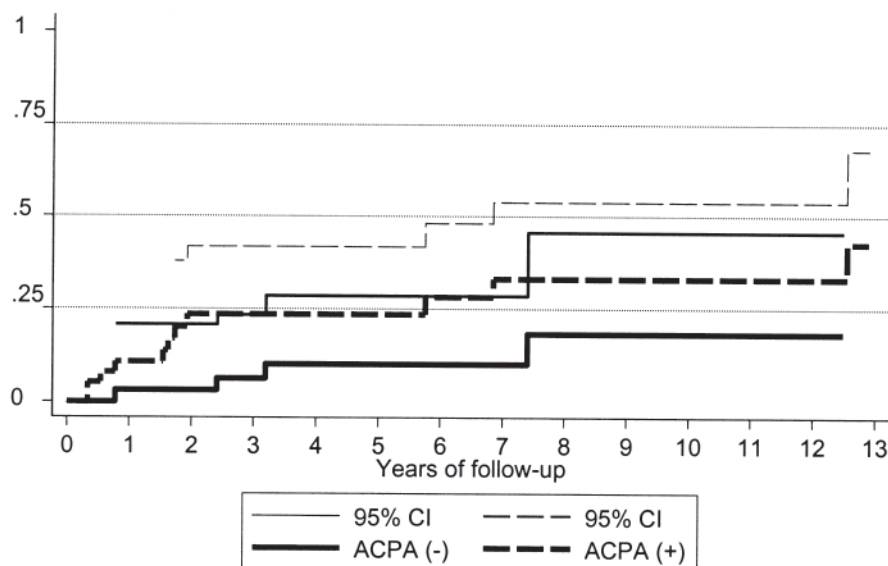

Figure 1. Cumulative probability of a diagnosis of rheumatoid arthritis from determination of anticitrullinated peptide/protein antibodies (ACPA). Kaplan-Meier failure function by ACPA status.

ACPA-positive, mostly at high titers, as we and others have described[5,6,7]. As expected, as occurs in RA[10,11], ACPA are clearly associated with RF positivity, although some discrepancies were found. Seroconversion from negative to positive results is uncommon in PR and it was observed in a minority of our patients with serial serum ACPA measurements, suggesting that as in RA[12], ACPA are present in the early phases of the disease and remain stable over time.

Since its original description, a significant proportion of PR cases have been associated with progression to other diseases, including SLE and especially RA[1,2]. Different prognostic factors for progression to RA have been identified, including clinical and demographic data, RF positivity[3,4], and most recently ACPA[6,7]. In our cohort, ACPA positivity in patients with pure or persistent PR at the first serum measurement was also associated with a 2-fold but non-significant risk of RA progression at followup compared with ACPA-negative patients. Indeed, the sensitivity of ACPA for progression to RA was low. Only one-third of ACPA-positive patients progressed to RA, suggesting that the majority of ACPA-positive patients with PR do not progress to RA or another rheumatic or systemic condition after a longterm followup (mean 7.5 yrs after baseline ACPA measurement). Serum ACPA levels of patients with and without RA progression were high and were not significantly different, as described[6]. Progression to RA in some patients in the future cannot be excluded, although the probability is low because of the longterm followup and because progression to RA is clearly higher during the first years of development of PR[13]. We also confirmed that the probability of RA progression is very low in the absence of autoantibodies, since only 5% of patients negative for both ACPA and RF progressed to RA. ACPA negativity may alert clinicians to the possibility of progression to a systemic condition other than RA, such as SLE or other uncommon diseases such as arthritis associated with *MEFV* gene mutations, as our group has confirmed in a collaborative study[14].

The percentage of patients who progressed to a chronic condition or RA (33.8% and 22.5%, respectively) is within the lower range of the proportions described in other series of patients with PR, where the percentage of progression to RA ranged from 28% to 66.7%[3,6,13,15]. Most of our patients had received antimalarial drugs, whose effect in reducing the rate of progression to RA in this type of patient has been documented[16], although their effect in our patients was uncertain and difficult to establish. Considering ACPA status, our results contrast with those observed by Russell, *et al*[6], where ACPA positivity at the presentation of PR was strongly predictive of RA, with 71% of ACPA-positive patients progressing to RA after a mean of 5.4 years. The different symptom duration until serum measurements between the 2 studies (within 1 year of disease presentation in comparison with a mean 4.5 years in our series) may explain the discrepancies, with a selection bias toward a higher probability of pure or persistent PR in our patients. The higher percentage of disease progression in our patients 1 year after presentation of PR, together with a significantly shorter disease duration of PR symptoms in patients progressing to RA, supports this reasoning.

ACPA are frequently found in sera of patients with PR, and although they can be considered a marker of RA progression, especially in the early phases of palindromic symptoms, a significant proportion of patients with persistent PR do not progress to RA or another rheumatic condition, not even those with high ACPA titers and after a long followup. Therefore, PR may be considered an abortive form of RA, and emerges as a clinical entity that merits further investigations to ascertain the mechanisms leading to the intermittent disease course rather than to a chronic and aggressive disease as in RA.

ACKNOWLEDGMENT

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