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. (First Release Aug 1 2012; J Rheumatol 2012;39:1929–33; doi:10.3899/jrheum.120568)

Key Indexing Terms: PALINDROMIC RHEUMATISM ANTICITRULLINATED PEPTIDE/PROTEIN ANTIBODIES CITRULLINATED RHEUMATOID ARTHRITIS
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. The mean duration of symptoms until the first ACPA measurement was 4.5 ± 5.8 years and was significantly shorter in patients with PR and persisting PR compared to those with PR and remission at the first measurement of antibodies against citrullinated peptide/proteins (ACPAs). All but 1 of the 5 ACPA-negative patients who progressed to RA were 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-
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

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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).

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

* 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.

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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. As expected, as occurs in RA, 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, 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. Different prognostic factors for progression to RA have been identified, including clinical and demographic data, RF positivity, and most recently ACPA. 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 follow-up 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 long-term follow-up (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. Progression to RA in some patients in the future cannot be excluded, although the probability is low because of the long-term follow-up and because progression to RA is clearly higher during the first years of development of PR. 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 MEVF gene mutations, as our group has confirmed in a collaborative study.

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%. 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, 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., 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 follow-up. 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.

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REFERENCES


