Predicting the Progression of Palindromic Rheumatism to Rheumatoid Arthritis: The Role of Ultrasonography and Anti-cyclic Citrullinated Peptide Antibodies

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We investigated whether sonography and anti-cyclic citrullinated peptide (anti-CCP) antibodies in Chinese patients with palindromic rheumatism (PR) during active episodes are of predictive value for development of rheumatoid arthritis (RA). Clinically involved regions of 84 PR patients during active episodes were examined with ultrasonography using a 6–13 MHz linear transducer. Serum levels of anti-CCP antibodies were determined by enzyme-linked immunosorbent assay. All patients were followed up monthly for 3 years after investigation. Thirteen (15%) of the PR patients had progressed to RA after a mean of 1.4 years (range, 0.4–3.0 years). Of these 13 patients, 11 patients (85%) had sonographic features of synovitis and 8 patients (62%) had a positive anti-CCP antibody test. The absence of sonographic features of synovitis during active episodes provided a very high 3-year predictive value in excluding the possibility of progression to RA for PR patients with a negative anti-CCP antibody test. Both the sonographic findings of synovitis and a positive anti-CCP antibody test were significant predictors for progression of PR to RA within 3 years by backward stepwise logistic regression analysis. Sonographic examination together with an anti-CCP antibody test during active episodes is useful for predicting the progression of PR to RA.

KEY WORDS — anti-cyclic citrullinated peptide antibodies, palindromic rheumatism, rheumatoid arthritis, sonographic findings

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Introduction

Palindromic rheumatism (PR) is characterized by recurrent attacks of acute arthritis or periarticular inflammation, lasting from a few hours to several days with variable symptom-free intervals, and producing no residual articular damage [1]. It is controversial whether PR is a separate disorder or is a prodrome of rheumatoid arthritis (RA). A number of series of longitudinally followed-up PR patients showed that one third to one half of these cases evolved into RA [2–5]. Anti-cyclic citrullinated peptide (anti-CCP) antibodies are highly specific for RA [6], and appear to be much more predictive of the development of RA than rheumatoid factor (RF) [7,8]. Because recent reports highlight the early onset of structural articular damage in RA patients [9], it could be important to separate PR patients from those who have the potential to develop RA.

As distinct clinical, laboratory or radiological markers have not yet been identified, the diagnosis of PR currently relies on clinical features and on excluding other forms of episodic arthritis [10]. The recent availability of high-frequency transducers (> 7.5 MHz) allows sonographic approaches to the diagnosis and assessment of soft tissue involvement in patients with rheumatic diseases [11–13]. Kasukawa et al [14] reported that sonographic evaluation of synovial membrane proliferation in the knee joints of two PR patients could be used to identify conversion from PR to RA. Therefore, we hypothesized that sonographic evaluation may help predict the progression or non-progression of PR to RA. However, there are no data on sonographic findings of involved joints in a large number of PR patients during active episodes.

In this study, we described the sonographic findings of involved regions during active episodes and determined serum anti-CCP levels in a cohort of 84 unrelated Chinese PR patients. We followed up these patients monthly for 3 years and investigated whether sonographic findings and anti-CCP antibodies during active episodes can be of predictive values for determining the progression to RA from PR.

Patients and Methods

This study was approved by the Ethics Committee of Clinical Research at Taichung Veterans General Hospital (VGHTC). From January to July 2003, we recruited patients who fulfilled the diagnostic criteria for PR as proposed by Guerne and Weismann [10], and were suffering active episodes of PR as determined by Dr. J.-L. Lan, D.-Y. Chen and T.-Y. Hsieh at the rheumatology outpatient clinic of VGHTC. When patients presented with acute onset of painful swelling over articular or periarticular regions without preceding trauma, this was defined as an active episode. Crystal arthritis and infectious arthritis were excluded by synovial fluid analysis if effusion was demonstrated by sonographic examination. A total of 84 PR patients were enrolled in this study. Thirty-two (38%) of these PR patients were treated with hydroxychloroquine only (200–400 mg daily) before their inclusion in this study. Sixteen (19%) of the patients with PR during active episodes had more than one region of attack. We followed up the PR patients monthly for 3 years at the outpatient clinic of VGHTC.

Antinuclear antibodies were screened by indirect immunofluorescence using a Fluorhepana test kit (Medical & Biological Laboratories Co. Ltd., Nagoya, Japan) with Hep-2 cells as the substrate. The determination of anti-CCP antibody was performed by enzyme-linked immunosorbent assay using a commercial kit (INOVA Diagnostics Inc., San Diego, California, USA) [15]. A serum result was considered positive for anti-CCP antibodies if the titer was above 20 IU/mL. Serum levels of RF-immunoglobulin M (IgM) and C-reactive protein (CRP) were measured by nephelometry (Dade Behring, Deerfield, Illinois, USA). A serum result was considered positive for RF when the level was above 22 IU/mL.

Sonographic assessment of the clinically involved regions was performed with a General Electric LOGIQ 500 unit (GE, Milwaukee, Wisconsin, USA) using a 6–13 MHz linear array transducer. Gray-scale ultrasonography (US) and power Doppler US (PDUS) examinations of the involved regions during active
episodes for PR patients were performed. The B-mode frequency used was 11 MHz. The pulse repetition frequency of PDUS was set at 1 KHz with a low wall filter (150 Hz). The color gain of PDUS was adjusted to a level just below that at which all color noise disappeared from regions deep to the cortical bone echo in the corresponding image. Pulsed Doppler spectra were performed to confirm the presence of vessels when the images were unclear. We followed the guidelines for patient positioning and standard scans that were advocated by Backhaus et al in 2001 [16]. Assessment of localized swelling or redness was carried out with longitudinal and transverse planes to clarify its anatomy and relation to adjacent structures. The adjacent joint was also assessed circumferentially to detect any associated pathology, especially synovitis. Bilateral comparison was carried out. The scans were performed by two rheumatologists (H.-H. Chen and G.-D. Hong) who were trained and experienced in musculoskeletal sonography. The examinations of each patient were performed independently and sequentially on the same day. Each sonographer was blinded to the laboratory findings, as well as to the sonographic findings of the other sonographer. They documented and stored digital images of any abnormalities that were noted. All ultrasound images were read in a blinded manner by a radiologist (H.H.-C. Lan) and a rheumatologist (C.-W. Hsieh), who were both experienced in musculoskeletal ultrasonography. The interpretation of the stored images was performed by consensus between the two readers.

The images were interpreted as showing synovitis when effusion was present, or when an abnormal hypoechoic, intra-articular tissue that was non-displaceable, poorly compressible and possibly exhibiting Doppler signals was present within any of the involved joint capsules. Doppler signals were demonstrated in two planes and were confirmed by pulsed wave Doppler spectrum to exclude artifacts. Effusion was characterized by abnormal hypoechoic or anechoic intra-articular material that was displaceable and compressible but did not exhibit Doppler signals [17]. To test the consistency of sonographic patterns in the same patient, 20 patients were examined for a second time during different active episodes in the 3 years following the initial investigation.

Results are presented as the median [inter-quartile (IQ) range] for age at onset, disease duration, and CRP levels. The $\chi^2$ test and Fisher’s exact test were used for testing differences in the frequencies of categorical data between groups. The Mann-Whitney U test was used to test differences in continuous variables between groups. Backward stepwise logistic regression analysis was performed to determine the optimal model for the prediction of progression of PR to RA. A $p$ value of less than 0.05 was considered to be significant. Statistical calculations were performed using the SPSS version 13.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Fifty-two (62%) patients with PR did not receive any medication for at least 3 months prior to enrollment in this study. Positive anti-CCP antibody tests were observed in 11 (13%) patients with PR during active episodes. Positive RF-IgM tests were observed in 12 (14%) of patients with PR during active episodes. CRP levels were increased in 54 (64%) patients with PR during active episodes. Low-titer antinuclear antibodies (1:80–1:160) were found in six (7%) PR patients during active episodes. Radiographs of all involved locations showed an absence of bony erosion or joint space narrowing.

Patients were divided into two groups based on the presence or absence of sonographic features of synovitis. Thirty (36%) PR patients had sonographic features of synovitis in any of the involved regions (Fig. 1). The remaining 54 (64%) PR patients displayed no sonographic features of synovitis in any of the involved regions (Fig. 2). Extra-articular soft tissue inflammation was observed in four of the 54 PR patients without synovitis (three over the left sole and one over the right palm). The other 50 of the 54 patients without synovitis had sonographic findings of tenosynovitis (tendon sheath thickening...
that might exhibit Doppler signals in the involved regions, 32 patients) and/or peri-articular soft tissue inflammation (an abnormally thickened hypoechoic region over peri-articular soft tissue that could potentially exhibit abnormal Doppler signals compared with those exhibited in the corresponding contralateral region, 26 patients). Doppler signals were shown by PDUS in 66 (78%) of the 84 PR patients. Joint effusion was shown in eight (27%) of 30 PR patients who had sonographic findings of synovitis. A thickened hypoechoic synovial membrane was found in 29 (97%) of these patients. No evidence of bone erosion was demonstrated in any PR patients.

A significantly higher positive rate of anti-CCP antibody [26.7% vs. 5.6%, odds ratio (OR) 6.18, 95% confidence interval (CI) 1.50–25.52, \( p = 0.014 \)] and RF-IgM (30.0% vs. 5.6%, OR 7.29, 95% CI 1.79–29.60, \( p = 0.007 \)) were observed in PR patients who had sonographic features of synovitis compared with those in PR patients without sonographic features of synovitis (Table 1). There was also no significant difference in the positive rate of anti-CCP antibody and RF-IgM tests between PR patients treated with hydroxychloroquine and those in patients not treated with hydroxychloroquine before inclusion in the present study.

CRP levels in PR patients whose PDUS images exhibited abnormal Doppler signals were significantly higher than those in PR patients whose PDUS images did not exhibit these abnormal Doppler signals (median, 1.0 mg/dL; IQ range, 0.7–1.6 mg/dL vs. median, 0.0 mg/dL; IQ range, 0.2–0.3 mg/dL; \( p < 0.001 \)). CRP levels in PR patients who had sonographic findings of synovitis with Doppler signals in thickened synovium were also significantly higher than those in PR patients who had sonographic findings of synovitis without Doppler signals in thickened synovium (median, 1.0 mg/dL; IQ range, 0.6–2.0 mg/dL vs. median, 0.37, IQ range, 0.24–0.40 mg/dL; \( p = 0.007 \)). There was no significant difference in CRP levels between PR patients who had sonographic features of synovitis with effusion and no significant differences in age at onset, the proportion of female, disease duration, frequency of Doppler signals and the proportion of use of hydroxychloroquine between PR patients with or without sonographic features of synovitis (Table 1).
and PR patients who had sonographic features of synovitis without effusion (median, 1.75 mg/dL, IQ range, 0.5–2.3 mg/dL vs. median, 1.00 mg/dL, IQ range, 0.48–1.50 mg/dL; p = 0.396).

Twenty (24%) of the PR patients were available to be examined for a second time during different active episodes within a mean interval of 7.9 months (range, 1–34 months). Nine (45%) of them had sonographic features of synovitis. Eighteen (95%) of them had consistent sonographic patterns. In one patient who had a negative anti-CCP antibody test and had not progressed to RA during 3 years of follow-up, the sonographic features shifted from the presence of synovitis to the absence of synovitis 7 months after the first US scan.

Thirteen (15%) of the PR patients had progressed to RA after a mean of 1.4 years (range, 0.4–3.0 years). Among them, 11 patients (85%) had sonographic features of synovitis, 8 patients (62%) had positive anti-CCP antibody tests and 8 patients (62%) had positive RF-IgM tests. One patient who had a negative anti-CCP antibody test and absence of sonographic features of synovitis progressed to systemic lupus erythematosus. The remaining 70 PR patients were treated with hydroxychloroquine 200–400 mg daily unless remission lasted over 6 months.

The disease duration before investigation in PR patients who had not progressed to RA was significantly longer than that in PR patients who had progressed to RA (median, 7.0 years, IQ range, 4.0–12.0 years vs. median, 3.0 years, IQ range, 1.3–7.4 years; p = 0.008; Table 2). A significantly higher rate of progression to RA was observed in patients with sonographic features of synovitis compared with that in patients without sonographic features of synovitis (37.7% vs. 3.7%, OR 15.05, 95% CI 3.05–74.23, p < 0.001). A significantly higher rate of progression to RA was also observed in patients with positive anti-CCP antibody tests than that in patients with negative anti-CCP antibody tests (72.7% vs. 6.8%, OR 36.27, 95% CI 7.26–181.06, p < 0.001). A significantly higher rate of progression to RA was observed in patients with positive RF-IgM tests compared with that in patients with negative RF-IgM tests (66.7% vs. 6.9%, OR 26.80, 95% CI 5.95–120.76, p < 0.001). There were no significant differences in the frequency of presence of effusion and Doppler signals detected by sonographic examinations, age at onset, the proportion of females, the proportion of use of hydroxychloroquine before investigation and CRP levels between PR patients with progression to RA and those in patients without progression to RA (Table 2).

Of the 73 PR patients with negative anti-CCP antibody tests, a significantly lower rate of progression to RA was observed in patients who had no sonographic features of synovitis than that in

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### Table 1. Clinical characteristics vs. ultrasonography findings in palindromic rheumatism patients*

<table>
<thead>
<tr>
<th>Sonographic findings</th>
<th>Synovitis (–) (n = 54)</th>
<th>Synovitis (+) (n = 30)</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (yr)</td>
<td>40 (29–44)</td>
<td>37 (28–50)</td>
<td>0.751</td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)†</td>
<td>18:36</td>
<td>10:20</td>
<td>1.000</td>
<td>1.00 (0.39–2.58)</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>6.3 (3.9–11.8)</td>
<td>5.5 (2.8–10.6)</td>
<td>0.211</td>
<td></td>
</tr>
<tr>
<td>HCQ (+) (%)†</td>
<td>22 (40.7%)</td>
<td>16 (53.3%)</td>
<td>0.361</td>
<td>1.66 (0.68–4.09)</td>
</tr>
<tr>
<td>Doppler signal (+) (%)†</td>
<td>40 (74.1%)</td>
<td>26 (86.7%)</td>
<td>0.268</td>
<td>2.28 (0.67–7.68)</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.8 (0.3–1.2)</td>
<td>1.0 (0.5–2.0)</td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>CCP (+) (%)†</td>
<td>3 (5.6%)</td>
<td>8 (26.7%)</td>
<td>0.014</td>
<td>6.18 (1.50–25.52)</td>
</tr>
<tr>
<td>RF (+) (%)†</td>
<td>3 (5.6%)</td>
<td>9 (30.0%)</td>
<td>0.007</td>
<td>7.29 (1.79–29.60)</td>
</tr>
</tbody>
</table>

*Values are median (interquartile range) unless designated otherwise; †Fisher’s exact test. OR = odds ratio; CI = confidence interval; M = male; F = female; HCQ = hydroxychloroquine; CRP = C-reactive protein; CCP = anti-cyclic citrullinated peptide antibody; RF = rheumatoid factor of Immunoglobulin M isotype.
patients who had sonographic features of synovitis (0% vs. 29.4%, Table 3, p=0.002). Of the 11 PR patients with positive anti-CCP antibody tests, there was no difference in the rate of progression to RA between patients with sonographic features of synovitis and that in patients without sonographic features of synovitis (Table 3).

The relative values of the presence of sonographic features of synovitis, a positive anti-CCP antibody test and a positive RF-IgM test in relation to the subsequent development of RA within 3 years are shown in Table 4. We used backward logistic regression analysis to determine the optimal model for the prediction of progression to RA within 3 years (Table 5). In this analysis, the presence of sonographic features of synovitis (OR 12.03, 95% CI 1.88–76.98, p=0.009) and a positive anti-CCP antibody test (OR 3.74, 95%, CI 0.35–39.44, p<0.001)
were both significant variables for the prediction of progression of PR to RA within 3 years. However, the presence of sonographic findings of synovial thickening, effusion, the presence of abnormal Doppler signals detected by PDUS and a positive RF-IgM test were excluded from the optimal model for the prediction of progression of PR to RA within 3 years.

**Discussion**

To our knowledge, the present study is the first to attempt to assess sonographic findings in a large number of PR patients during active episodes. The distribution of the joints involved in our patients was similar to that in previous reports [1–5]. When patients present clinically with swelling and redness around the joint, it is often difficult to define anatomic changes of the involved region by clinical examination or conventional radiography. Periarticular inflammation, which often presents with swelling as well as redness and may involve the joint structure, was observed in approximately 30% of PR patients in previous studies [1,5], whereas a higher occurrence rate (64%) was shown by sonography in our PR patients. Consistent with the findings of other reports [18–20], an improved sensitivity in the detection of periarticular inflammation using high-resolution US may have contributed to this discrepancy between studies. In the present study, the mean duration from onset of symptoms to development of RA was 6.6 years.

Thirty (36%) of the PR patients in the present study showed sonographic features of synovitis (Fig. 2B). Twenty patients (87%) exhibited Doppler signals in the thickened synovium on PDUS images. The introduction of PDUS allows the detection of smaller degrees of synovitis with a reported accuracy equal to that of dynamic MRI [21]. Using histopathology as gold standard, Koski et al [22] found that a negative Doppler signal did not exclude the

<table>
<thead>
<tr>
<th>Significant variable</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>Excluded variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis (+)</td>
<td>12.03 (1.88–76.98)</td>
<td>0.009</td>
<td>Synovial thickening (+)</td>
</tr>
<tr>
<td>CCP (+)</td>
<td>28.99 (4.52–185.91)</td>
<td>&lt;0.001</td>
<td>Effusion (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Doppler signal (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RF (+)</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; CCP = anti-cyclic citrullinated peptide antibody; RF = rheumatoid factor of immunoglobulin M isotype.
possibility of synovitis and a positive Doppler signal in the synovium was an indicator of an active synovial inflammation in patients. Moreover, a significant correlation between the power Doppler signal and the degree of vascularity of the synovial tissue has recently been reported [23]. In our study, we found significantly higher CRP levels in PR patients with sonographic features of synovitis who had Doppler signals in the synovium compared with patients who did not have Doppler signals in the synovium, and this could be because of the presence of more active synovial inflammation in these patients.

There is no standard laboratory test to diagnose PR. In our study, 54 (64.3%) of the patients with PR had elevated CRP levels during active episodes. The significantly higher CRP levels in PR patients with sonographic features of synovitis compared with patients without sonographic features of synovitis suggests a higher degree of inflammation in synovitis. However, CRP is neither specific nor sensitive enough for the diagnosis of PR. The lower positive rate of anti-CCP antibodies in our patients than those reported previously [8,24] may be due to a longer mean ± SD disease duration (8.2 ± 6.4 years) before investigation in our PR patients (which may have excluded some PR patients who progressed more rapidly to RA), and population characteristics or target epitopes of citrulline used in the detection method.

In the present study, a lower positive rate of anti-CCP antibodies was found in patients with no sonographic features of synovitis. In contrast, a higher positive rate of anti-CCP antibodies was observed in patients with sonographic features of synovitis. Accumulating evidence suggests that the immune response to citrullinated peptides could play a significant role in the pathogenesis of synovitis in RA [25,26]. However, this hypothesis needs to be confirmed by further investigation and a large prospective cohort study.

A longer disease duration was found in our PR patients who had not progressed to RA compared with that in patients who had progressed to RA. However, the wide variation of duration from onset to progression of PR to RA limits the use of disease duration in predicting progression of PR to RA. Some investigators have attempted to search for biologic markers that might predict the progression to RA in PR patients. Recently, a positive anti-CCP antibody test was found to be highly specific for RA [6], and it appears to be much more predictive of the development of RA than RF [7].

In the present study, we followed up our PR patients for 3 years after US examinations and anti-CCP antibody tests during active episodes. Only 15% of our PR patients had progressed to RA. The rate of progression to RA in our PR patients is lower than that reported previously [8,23]. This disparity may be because of a longer disease duration before investigation, population characteristics or shorter duration of follow-up. However, the mean duration (6.6 years) from onset of symptoms to development of RA in our PR patients is consistent with data reported previously [7,8].

The positive predictive value was 73% for a positive anti-CCP antibody test in our study, which is consistent with previous data [8]. The high specificity and negative predictive values for a positive anti-CCP antibody test are also consistent with previous reports [27,28]. We found that the negative predictive value was high for both the presence of sonographic features of synovitis and a positive anti-CCP antibody test. We found that in PR patients with a negative anti-CCP antibody test, there was a significantly lower rate of progression to RA in those patients without sonographic features of synovitis compared with that in those with sonographic features of synovitis (Table 3). The absence of sonographic features of synovitis during active episodes provided a very high 3-year predictive value in excluding the possibility of progression to RA for PR patients with a negative anti-CCP antibody test. In addition, we used backward logistic regression analysis to determine the optimal model for the prediction of progression of PR to RA within 3 years and found that both the presence of sonographic features of synovitis and a positive anti-CCP antibody test were significant variables. Therefore, the sonographic
findings of involved regions in PR patients during active episodes could be valuable for helping clinicians to predict future development of RA within 3 years.

Some limitations of our study should be highlighted. First, our study was conducted in accordance with daily clinical practice. Patients were treated without hydroxychloroquine or with various doses of hydroxychloroquine before recruitment and during the 3-year follow-up period. Therefore, we could not compare the predictive value of PDUS variables depending on the medication received. Second, we were not always able to perform US scanning when patients presented active episodes; we only performed US scanning when patients happened to have active episodes during their scheduled follow-up. Therefore, the data about the consistency of the sonographic patterns in the same patient were limited.

In conclusion, our results demonstrate that sonographic examination, which is a quick, inexpensive, and easily accessible technique for assessment of synovial and periarticular tissues of PR patients during active episodes, together with a test for anti-CCP antibody are useful for predicting progression to RA within 3 years.

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References


