

# Is There Subclinical Synovitis in Patients with Palindromic Rheumatism in the Intercritical Period? A Clinical and Ultrasonographic Study According to Anticitrullinated Protein Antibody Status

Sonia Cabrera-Villalba, Julio Ramirez, Georgina Salvador, Virginia Ruiz-Esquide, M. Victoria Hernández, José Inciarte-Mundo, José A. Gómez-Puerta, Juan D. Cañete, and Raimon Sanmarti

**ABSTRACT. Objective.** To investigate the presence of subclinical synovitis by ultrasound (US) and the clinical phenotype in patients with palindromic rheumatism (PR) according to anticitrullinated protein antibody (ACPA) status.

**Methods.** Fifty-four patients with PR were studied. Clinical, demographic, serological, and therapeutic characteristics were compared in ACPA-positive and ACPA-negative patients. US searching for synovial hypertrophy (SH) and power Doppler signal (PDUS) in 22 joints of the hands was performed in the intercritical period. The results were compared according to ACPA status and with a healthy control group (n = 30). In 10 patients, US was performed during the joint attack.

**Results.** Most patients were female (63%) with a mean disease duration of  $11.6 \pm 10.7$  years. Thirty-six patients (66.7%) were ACPA-positive. ACPA-positive patients had a shorter duration of attacks, a younger age, and less knee involvement at disease onset. US examination showed SH grade  $\geq 1$  in 79.6% of patients with PR and 50% of controls. Significant US results (SH  $\geq 2$  or PDUS) were observed in 2.7% and 1.4% of joints assessed and in 33% and 25.9% of patients with PR, respectively. Only 4 patients (7.4%) had US active synovitis (SH  $\geq 2$  plus PDUS) in at least 1 joint. US assessment showed no significant differences between ACPA-positive and ACPA-negative patients. PDUS was observed in 7 out of 10 patients during attacks.

**Conclusion.** Some differences emerged in the clinical phenotype of PR according to ACPA status. Most patients with PR do not have US subclinical synovitis in the intercritical period, even those who are ACPA-positive. (J Rheumatol First Release July 15 2014; doi:10.3899/jrheum.131545)

## Key Indexing Terms:

PALINDROMIC RHEUMATISM  
ULTRASOUND

ANTICITRULLINATED PROTEIN ANTIBODIES  
SUBCLINICAL SYNOVITIS

Palindromic rheumatism (PR) is a clinical entity characterized by intermittent, acute, typically monoarticular

arthritis, lasting for a few days, without residual joint damage<sup>1</sup>. In a variable percentage of cases it may evolve to chronic rheumatic disease, mainly rheumatoid arthritis (RA)<sup>2</sup>. Most patients with PR have the characteristic auto-antibody profile seen in RA: positive rheumatoid factor (RF) and/or positive anticitrullinated protein antibodies (ACPA). After our first description of the high prevalence of ACPA in the sera of patients with PR<sup>3</sup>, other authors confirmed this association<sup>4,5</sup>, and ACPA positivity in the early phases of PR is considered as a biomarker for RA progression<sup>4</sup>. However, a significant proportion of patients with PR do not evolve to RA, even those with high titers of ACPA and a long followup period<sup>6</sup>. Therefore, the question arises as to whether PR is an independent entity or merely a preclinical or abortive form of RA<sup>6,7</sup>.

To better understand the relationship between RA and PR, we addressed the issue of whether patients with PR may have persistent synovitis in the absence of clinical symptoms and whether this could predict progression to

*From the Arthritis Unit, Rheumatology Service, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); Hospital Mútua de Terrassa, Terrassa, Barcelona, Spain; Division of Rheumatology, Immunology and Allergy, Section of Clinical Sciences, Brigham and Women's Hospital, Boston, Massachusetts, USA.*

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*S. Cabrera-Villalba, MD; J. Ramirez, MD, Arthritis Unit, Rheumatology Service, Hospital Clinic of Barcelona, IDIBAPS; G. Salvador, MD, PhD, Hospital Mútua de Terrassa; V. Ruiz-Esquide, MD, PhD; M.V. Hernández, MD, PhD; J. Inciarte-Mundo, MD, Arthritis Unit, Rheumatology Service, Hospital Clinic of Barcelona, IDIBAPS; J.A. Gómez-Puerta, MD, PhD, Division of Rheumatology, Immunology and Allergy, Section of Clinical Sciences, Brigham and Women's Hospital; J.D. Cañete, MD, PhD; R. Sanmarti, MD, PhD, Arthritis Unit, Rheumatology Service, Hospital Clinic of Barcelona, IDIBAPS.*

*Address correspondence to Dr. R. Sanmarti, Arthritis Unit, Rheumatology Service, Hospital Clinic of Barcelona, IDIBAPS, Villarroel 170, 08036 Barcelona, Spain. E-mail: sanmarti@clinic.cat*

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RA. Musculoskeletal ultrasonography (US) is a valid and reliable tool for measuring synovitis. It is widely used in rheumatologic practice, and has been shown to be more sensitive in detecting synovitis than clinical examination<sup>8,9,10</sup>. There are few imaging studies [with US/magnetic resonance imaging (MRI)] in patients with PR and these have been carried out only during acute attacks and not during the asymptomatic, intercritical period<sup>11,12</sup>.

The aim of our study was to analyze the presence of subclinical synovitis using US, to describe US changes in patients with PR in the intercritical phase, and to determine whether US changes and clinical features differ according to ACPA status.

## MATERIALS AND METHODS

**Patients.** Patients were included who had pure PR, i.e., patients with no associated rheumatic disease at the clinical assessment, and who were attending the Arthritis Unit, Hospital Clinic of Barcelona, from June 2012 to June 2013. All patients fulfilled the criteria for PR of Guerne and Weisman<sup>13</sup>. Patients were excluded if they had other causes of acute monoarthritis (microcrystalline arthritis, seronegative spondyloarthropathies, inflammatory bowel disease, etc.), an initial PR diagnosis that evolved to another rheumatic disease, or erosive radiographic changes. Written consent was obtained from all participants and the study was approved by the Hospital Clinic Ethics Committee, according to the Declaration of Helsinki.

In this descriptive cross-sectional study, the following variables were analyzed in all patients with PR: demographic characteristics, disease duration, smoking status, frequency and duration of attacks, joints involved (at disease onset and during disease evolution), and treatment with disease-modifying antirheumatic drugs (DMARD). Laboratory tests included blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), uric acid, and immunoglobulin levels. Serum ACPA were measured using a commercial cyclic citrullinated peptide antibodies-2 ELISA test [ImmunoScan, Eurodiagnostica; normal values (NV) < 50 IU]. RF was measured by nephelometry (NV < 30 IU) and antinuclear antibody by indirect immunofluorescence assay (NV < 160 units of reference fluorescence).

**Imaging.** Erosive disease was evaluated by radiographs (posteroanterior view) of the hands and feet in all patients, and was scored according to the modified Larsen score in 32 joints to exclude RA diagnosis<sup>14</sup>. All the radiographs were evaluated by the same rheumatologist (RS).

All US assessments were performed during the asymptomatic, intercritical disease phase, defined as the absence of patient-reported symptoms of arthritis and the absence of signs of synovitis on clinical examination. An experienced sonographer (JR) who was blinded to the results of the clinical joint examination and the serological status evaluated 11 joints of each hand [including the proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, and the wrists] for both synovial hypertrophy (SH) and intraarticular power Doppler signal (PDUS), according to European League Against Rheumatism guidelines<sup>15</sup>.

The US equipment used was Esaote My Lab 25 and assessments were made using a frequency range from 8 to 12 MHz. US findings in joints were defined according to published Outcome Measures in Rheumatology Clinical Trials (OMERACT) definitions<sup>16</sup>. The frequency was adapted to each joint assessed. All joints evaluated were scanned for SH and PDUS on the dorsal aspect using the longitudinal midline and transversal planes. Wrists were also examined using longitudinal dorsoradial and dorsoulnar scans.

Synovial PDUS was assessed by selecting a region of interest that included the bony margins, joint space, and a variable view of surrounding tissues. PDUS calibrations were adjusted to the lowest permissible pulse repetition frequency (PRF) to maximize sensitivity (500-800 Hz). Doppler

frequency was set higher for the study of small joints and superficial tissues and lower for deep structures. Color gain was set just below the level that causes the appearance of noise artefacts. The sonographer was allowed to modify the machine setting (e.g., gain, PRF) to produce the best quality images, thus allowing each image to be scored appropriately.

SH and PDUS were graded using a 4-grade semiquantitative scoring system from 0 to 3 (grade 0 = none, 1 = mild, 2 = moderate, and 3 = severe) according to the method developed by Szkudlarek, *et al*<sup>17</sup>. The highest SH and PDUS grade detected during the scans was taken as representative of each joint, respectively. To ensure a stringent definition of synovitis by US, only patients with SH grade > 2 plus PDUS were classified as having active synovitis<sup>18</sup>. If any assessed joint met this criterion, the patient was classified as having active synovitis.

A control group of 30 sex-matched and age-matched ( $\pm 5$  yrs) healthy subjects (healthcare professionals), with no history of arthritis, was also studied. All underwent a clinical assessment and US evaluation of both hands, using techniques identical to those carried out in the study group.

We made a double US assessment during the asymptomatic (intercritical) phase in the first 10 patients included in the study. The 2 evaluations were separated by between 24 and 72 h. The same sonographer made both US assessments. The results were calculated as an index of the percentage of agreement between scores at 2 timepoints. The following cutoff values, analogous to  $\kappa$  coefficients, were defined for intrarater reliability: < 0.0 = none, 0.1–0.20 = poor, 0.21–0.40 = modest, 0.41–0.60 = fair, 0.61–0.80 = good, and 0.81–1.00 = excellent. Intrarater agreement was 0.81 for SH and 0.92 for PDUS.

In addition, patients with a clinical flare during the recruitment period were assessed. Clinical examination and US assessment of the joint involved were made according to the same protocol schedule.

**Statistical analysis.** Differences in clinical and demographic characteristics and between-group US findings (ACPA-positive and ACPA-negative) were compared using the parametric Student t test or the nonparametric Mann-Whitney U test when variables had a non-normal distribution. Proportions were calculated using the chi-square test. The level of statistical significance was established at  $\leq 0.05$ . The analysis was performed using SPSS version 20.0 software (SPSS Inc.).

## RESULTS

Sixty-four patients were initially recruited. After careful evaluation, 8 patients were excluded at the initial assessment because of persistent arthritis fulfilling criteria for RA (n = 3), doubts about the diagnosis (n = 1), pyrophosphate arthropathy/chondrocalcinosis (n = 2), gout (n = 1), and systemic lupus erythematosus (n = 1). After radiographic evaluation, 2 further patients were excluded owing to feet radiographic erosions (both in the fifth metatarsophalangeal joints) without persistent clinical synovitis. Therefore, 54 patients with PR were finally included in the analysis.

**Characteristics of patients with PR according to ACPA status.** The clinical, demographic, serological, and therapeutic characteristics of the 54 patients with pure PR are shown in Table 1. Of those, 36 (66.7%) were ACPA-positive and 31 (57.4%) were RF-positive. Mean ACPA titers in ACPA-positive patients were  $528.8 \pm 527.6$  IU. Twenty-seven patients (50%) were both RF-positive and ACPA-positive.

ACPA-positive patients were younger, with shorter attacks ( $\leq 72$  h) and with shorter disease duration compared with ACPA-negative patients (Table 1). There were no significant differences in the number of affected joints, the

Table 1. Clinical, demographic, serologic, and therapeutic characteristics of patients with pure palindromic rheumatism (PR) according to ACPA positivity or negativity.

Characteristics	PR, n = 54	PR-ACPA+, n = 36	RP-ACPA-, n = 18	p
Age, yrs, mean ± SD	51.2 ± 11.3	48.6 ± 8.6	56.2 ± 14.4	0.04
Age at onset of PR, yrs, mean ± SD	39.7 ± 11.4	39.4 ± 10.4	40.4 ± 13.4	0.7
Female, n (%)	34 (63)	23 (63.9)	11 (61.1)	0.8
Disease duration, yrs, mean ± SD	11.6 ± 10.7	9.5 ± 7.6	15.8 ± 14.5	0.09
Current smoker, n (%)	17 (31.5)	12 (33.3)	5 (27.8)	0.4
Frequency of attacks, n (%)				
> 1 month	6 (11.1)	5 (13.9)	1 (5.6)	0.6
≥ 1 week	11 (20.4)	9 (25)	2 (11.1)	0.3
Attack duration, h, mean ± SD, n (%)				
≤ 72 h	47 (87)	34 (94.4)	13 (72.2)	0.02
> 72 h, < 1 week	7 (13)	2 (5.6)	5 (27.8)	0.02
Oligoarticular attacks, n (%)	17 (31.5)	12 (33.3)	5 (27.8)	0.7
No. affected joints, mean ± SD	6.1 ± 2.1	6.28 ± 2.2	5.72 ± 1.9	0.4
Joint involvement during PR course, n (%)				
PIP	48 (88.9)	32 (88.9)	16 (88.9)	1
Wrist	46 (85.2)	32 (88.9)	14 (77.8)	0.3
MCP	45 (83.3)	31 (86.1)	14 (77.8)	0.4
Shoulder	44 (81.5)	31 (86.1)	13 (72.2)	0.2
Knee	42 (77.8)	27 (75)	15 (83.3)	0.5
RF+, n (%)	31 (57.4)	27 (75)	4 (22.2)	0.01
ANA+, n (%)	18 (33)	14 (38.9)	4 (22.2)	0.2
CRP, mg/dl, mean ± SD	0.35 ± 0.4	0.38 ± 0.3	0.29 ± 0.54	0.4
ESR, mm/h, mean ± SD	12.5 ± 9.7	12.1 ± 10.7	13.3 ± 7.7	0.6
DMARD treatment				
At the time of assessment	33 (61.1)	25 (69.4)	8 (44.4)	0.08
Hydroxychloroquine	20 (37)	16 (44.4)	4 (22.2)	0.1
Methotrexate	6 (11)	6 (16.7)	0	0.2
Leflunomide	4 (7.4)	4 (12.9)	0	0.3
Others	5 (9.3)	3 (8.3)	2 (11.1)	0.3
During past PR course	46 (85.2)	32 (88.9)	14 (77.8)	0.3

PIP: proximal interphalangeal; MCP: metacarpophalangeal; RF: rheumatoid factor; ANA: antinuclear antibody; ACPA: anticitrullinated protein antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drugs.

frequency of attacks, or the pattern of joint involvement during attacks; the most frequently involved joints in both groups were the small joints of the hands, wrists, shoulders, and knees. The first attack was located in the knee in a higher proportion of ACPA-negative patients (22% vs 2.8%,  $p = 0.02$ ). Six patients were pregnant (4 ACPA-positive) during the disease course, and the attacks remitted in 5 of them during pregnancy.

No significant differences were observed in laboratory tests, including CRP and ESR values, between ACPA-positive and ACPA-negative patients. As expected, RF positivity was significantly more frequent in ACPA-positive patients. After exclusion of the 2 patients with radiographic feet erosions, no erosions were observed in the 54 patients included, and the median Larsen score was 0.

DMARD were being administered to 61.1% of patients at the time of assessment and 85.2% during the past disease course. Hydroxychloroquine was the most used DMARD. No differences were observed in DMARD therapy between groups. Methotrexate (MTX) was being administered to

11.1% of patients at the time of assessment, all ACPA-positive (Table 1).

*US findings.* In the 54 patients with PR, 1188 joints in the hand and wrist were examined by US, of which 10.9% ( $n = 130$ ) had SH detected by US. Of those 130 joints, 8.3% ( $n = 98$ ) were graded as 1, 2.3% ( $n = 27$ ) as 2, and 0.4% ( $n = 5$ ) as 3. A PDUS signal was observed in 1.4% of those joints ( $n = 16$ ).

Seventy-nine percent of patients had SH (grade 1 included) in at least 1 joint, and 25.9% had a PDUS signal. SH  $\geq 2$  was observed in 18 patients (33%), and affecting only 1 or 2 joints in all but 2 patients. The joints most affected were the wrist (42.6% for SH and 24.1% for PDUS) and MCP (37% for SH and 1.9% for PDUS; Table 2).

In the control group (63.3% female, mean age  $49.6 \pm 8.7$  yrs), SH was observed in 15 patients (50%), mostly SH grade 1, with grade 2 observed in only 2 patients. No joints with a PDUS signal were observed.

Only 4 patients (7.4%) met the criteria (SH  $\geq 2$  plus PDUS) for US-defined active synovitis. No significant

Table 2. Ultrasound findings in ACPA-positive and ACPA-negative patients with palindromic rheumatism (PR) during the asymptomatic phase.

	PR, n = 54	PR-ACPA+, n = 36	PR-ACPA-, n = 18	p
SH, n (%)	43 (79.6)	29 (80.6)	14 (77.8)	0.8
Grade 1	25 (46.3)	16 (44.4)	9 (50)	0.7
Grade 2	14 (25.9)	11 (30.6)	3 (16.7)	0.3
Grade 3	4 (7.4)	2 (5.6)	2 (11.1)	0.5
SH $\geq$ 2, n (%)	18 (33.3)	13 (36.1)	5 (27.8)	0.5
PDUS, n (%)	14 (25.9)	10 (27.8)	4 (22.2)	0.7
PDUS grade 1, n (%)	13 (24.1)	9 (25)	4 (22.2)	0.7
PDUS grade 2, n (%)	1 (1.9)	1 (2.7)	0	0.7
Total score SH, mean $\pm$ SD	3.33 $\pm$ 3.28	3.28 $\pm$ 3.3	3.44 $\pm$ 3.3	0.8
Total Score PDUS, mean $\pm$ SD	0.37 $\pm$ 0.71	0.36 $\pm$ 0.69	0.39 $\pm$ 0.78	0.9
Total score (SH plus PDUS), mean $\pm$ SD	3.7 $\pm$ 3.5	3.64 $\pm$ 3.61	3.83 $\pm$ 3.49	0.9
SH $\geq$ 2 + PDUS, n (%)	4 (7.4)	3 (8.3)	1 (5.6)	0.8

SH: synovial hypertrophy; PDUS: power Doppler ultrasound; ACPA: anticitrullinated protein antibodies.

differences in US findings were observed between ACPA-positive or ACPA-negative patients (Table 2), and no cases with SH  $\geq$  2 plus PDUS were observed in the control group.

Ten patients were assessed during a joint flare (with the small joints of the hands being affected in 8). All had joint swelling but no significant periarticular swelling on clinical examination. Eight patients had SH (all but 1 with grade  $\geq$  2), 7 had a PDUS signal, and 5 fulfilled criteria for US-defined active synovitis. No significant US periarticular changes were observed.

## DISCUSSION

The results of our study confirm the high prevalence (66.7%) of ACPA in PR, a figure slightly higher than that found in our previous series (56.6%)<sup>3</sup> and in other white populations (55%)<sup>4</sup>. Studies have found lower prevalences of 42%<sup>19</sup> and 46.6%<sup>5</sup> in nonwhite populations, possibly reflecting ethnic differences or different diagnostic criteria. Our patients with PR had not progressed to RA or other rheumatic diseases after a long followup (mean disease duration of 11.6 yrs). We also observed an absence of subclinical synovitis on US in the intercritical period in most patients with PR, even those who were ACPA-positive.

Imaging studies in patients with PR have focused on searching for synovitis during the acute attacks but not during the intercritical period. These studies confirmed synovial inflammation in a significant but variable proportion of cases<sup>11,12,20</sup>, results found in most of our patients during the acute phase. However, although PR is considered an intermittent entity, with no evidence of clinical arthritis during the intercritical phase, there are no studies analyzing subclinical synovitis with imaging techniques, such as US or MRI, during the asymptomatic phase and this is the first study, to our knowledge, to assess synovitis by imaging in the intercritical phase of PR.

Our results clearly show that most patients with PR do not have subclinical synovitis by US, confirming the intermittent nature of the disease. No significant differences in US results were observed according to ACPA status. Most US findings in the joints assessed were SH grade 1, which was also observed in a high percentage of control subjects without arthritis, and which is considered nonspecific and without clinical significance by some groups<sup>21</sup>. Nevertheless, one-third of patients had SH grade 2 or 3 in at least 1 joint, and one-fourth had a PDUS signal. Although these findings were observed in only a very few joints, these percentages are higher than those seen in healthy subjects in our and other studies<sup>21,22,23</sup>, suggesting the presence of subclinical monoarticular or oligoarticular synovitis in some patients with PR. However, the stringent definition of subclinical active synovitis by US (SH grade  $\geq$  2 plus PDUS) was only met by 7.4% of patients. Using the same approach, another study by our group found that 45.4% of patients with RA in clinical remission had US active synovitis<sup>18</sup>.

The results also confirm the predominance of females in PR, as described in most recent studies<sup>5,6,24</sup>, a mean age of onset around 40 years, similar to that observed in some studies<sup>19</sup> but earlier than that found in others<sup>13,24</sup>, and a pattern of joint involvement with a predominance of the small joints of the hands, as described in almost all studies<sup>1,13,25,26</sup>.

Whether PR patients with autoantibodies represent a different clinical entity from PR without antibodies is an unaddressed question. ACPA or RF positivity have been shown to be biomarkers for the development of RA in PR<sup>4,25</sup>, but few studies have focused on determining whether there are clinical differences in the phenotypic expression of the disease according to autoantibody status<sup>3,6,19</sup>. Some patients from our previous report are included in the present series. In our previous report, we

found no differences in the pattern of joint involvement in ACPA-positive or ACPA-negative patients with PR<sup>3</sup>, a finding confirmed in our present study, except for more frequent involvement of the knee joint at disease onset in ACPA-negative patients. However, an Iranian study found some differences in PR according to ACPA status, including an older age at diagnosis, more frequent acute episodes, and shorter attack duration in ACPA-positive patients<sup>19</sup>; only the last finding was confirmed in our patients, in whom the attacks were of shorter duration ( $\leq 72$  h) in almost all ACPA-positive patients. The clinical implications of this finding are unknown, but the short duration of attack might represent the typical phenotype described in the classical series of PR<sup>2,13</sup>. No significant differences in the therapeutic approach were found between groups in our study, and most patients were treated with DMARD (mostly antimalarials) during the disease course.

Our study had some limitations. First, the sample size, especially of ACPA-negative patients, was small, but sufficient to find some differences between the groups. Second, given that most patients were receiving DMARD, mainly antimalarials and in a few cases other DMARD including MTX, the possibility that subclinical synovitis was masked or suppressed by DMARD use cannot be ruled out. DMARD treatment was mandatory in those patients to avoid or minimize the frequency or intensity of joint flares; most of them have been treated with antimalarials, which have been shown to be effective in PR<sup>27</sup> and can delay the progression to RA in patients with PR<sup>28</sup>. Finally, the cross-sectional design of the study could not determine whether subclinical synovitis in PR might be a marker for RA progression. US synovitis in autoantibody-positive arthralgia patients is considered a potential risk factor for the development of RA<sup>29</sup>. At the time of writing, 2 of our patients (both ACPA-positive) had progressed to RA after 4 and 5 years of symptom duration, respectively, but neither showed US synovitis at study entry. In addition, the long disease duration of our patients with PR might result in a selection bias toward a more stable form of PR with a lower risk of progression to RA<sup>6</sup>.

Patients with longstanding PR are frequently ACPA-positive. We observed some clinical differences according to ACPA status. Most ACPA-positive patients do not have significant synovitis on US in the intercritical disease period, a feature observed in both ACPA-positive and ACPA-negative patients, confirming the intermittent nature of PR. However, only prospective studies in the early phases of PR would help determine whether subclinical synovitis on US could be a marker of future progression to RA in those patients.

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