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Rheumatoid Arthritis Initiating as Palindromic Rheumatism: A Distinct Clinical Phenotype?

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TITLE: RHEUMATOID ARTHRITIS INITIATING AS PALINDROMIC RHEUMATISM: A DISTINCT CLINICAL PHENOTYPE?

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Key words: palindromic rheumatism, rheumatoid arthritis, hydroxychloroquine, ACPA, anti-CarP, smoking

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Short Running Head: **RHEUMATOID ARTHRITIS AND PALINDROMIC
RHEUMATISM**

ABSTRACT

Objective: To analyse the prevalence of pre-existing palindromic rheumatism (PR) in patients with established rheumatoid arthritis (RA) and evaluate whether these patients have a distinctive clinical and serological phenotype.

Methods: Cross-sectional study in patients with established RA. Pre-existing PR was determined using a structured protocol and confirmed by retrospective review of medical records. Demographic, clinical, radiological, immunological and therapeutic features were compared in patients with and without PR.

Results: 158 patients with established RA (78% female) with a mean disease duration since RA onset of 5.1 ± 2.7 years were included. Pre-existing PR was recorded in 29 patients (18%). The median time from the onset of PR to progression to RA was 1.2 years. No between-group differences in demographic features, current disease activity radiographic erosive disease or disability were observed. Patients with PR had a higher prevalence of smoking (72% vs. 40%). Positive rheumatoid factor, anti-citrullinated peptide antibodies and anti-carbamylated protein antibodies were numerically higher in patients with PR. No differences in treatment were observed except for greater hydroxychloroquine use in patients with PR (38% vs. 6%). Palindromic flares persisted in a significant proportion of patients during the RA course, including patients in clinical remission or receiving biological DMARDs.

Conclusion: Eighteen percent of patients with RA had a history compatible with PR previous to RA onset. No specific clinical or serological phenotype was identified in these patients, although higher hydroxychloroquine use and smoking prevalence were identified. Palindromic flares may persist during the RA disease course despite treatment.

INTRODUCTION

Palindromic rheumatism (PR) is a form of intermittent arthritis that may evolve to chronic rheumatic disease, mainly rheumatoid arthritis (RA) (1). It is unclear whether PR is a separate clinical syndrome, an abortive form of RA or just a preclinical phase of RA (2,3). The high rate of progression towards RA, in up to 67% of cases in one series (4) and a similar autoantibody profile to RA, including rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) (5) suggests that PR form part of the same spectrum as RA. However, the intermittent nature of PR, periarticular inflammation during flares and the fact that not all patients evolve to RA suggests that, in some cases, PR can be considered a distinct disease entity (2,6). Positive autoantibody status is a biomarker for progression to RA (7), although a significant proportion of seropositive PR patients do not develop RA in the long term, with intermittent arthritis persisting (8).

Studies have analysed prognostic factors and progression to RA in patients with PR (7-11), even though none has reported the prevalence of pre-existing PR in patients with established RA or whether these patients have a distinctive clinical and/or serological phenotype. In clinical practice, we have observed various patients with pre-existing PR who presented typical palindromic flares after RA was diagnosed, including patients in clinical remission.

The aims of this study were to analyse the prevalence of intermittent arthritis compatible with PR before RA onset, differences in the clinical phenotype and immunological and therapeutic features between established RA patients with and without pre-existing PR and whether typical intermittent arthritis flares continued after RA onset.

PATIENTS AND METHODS

We conducted a cross-sectional study in consecutive patients attending the Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona, Catalonia, Spain between July 2017 and July 2018. Inclusion criteria were RA patients according to 2010 ACR/EULAR criteria with a disease duration < 10 years since RA onset.

Exclusion criteria were other inflammatory arthritis or connective tissue diseases diagnosed before the inclusion visit according to standard criteria. Medical records were reviewed retrospectively in all patients.

The following variables were collected: demographic characteristics, smoking status (current or previous smoking and cumulative exposure), RA duration, extra-articular manifestations (EAMS) according to predefined criteria (12), and current disease activity measured by the Disease Activity Score in 28 joints (DAS28), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI). Patient-reported outcomes, such as the Routine Assessment of Patient Index Data 3 (RAPID3), and disability measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) were collected, and a pain visual analogue scale (VAS) was administered. The number and distribution of joints involved at RA onset were collected retrospectively: hand and foot X-rays were obtained at study entry and radiographic erosions were evaluated. Previous and current conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARD), biological (b) DMARD, and glucocorticoid use were evaluated.

Current autoantibody status was measured: RF by nephelometry, ACPA by anti-CCP3 (QUANTA Flash CCP3, chemiluminescent immunoassay) and anti-carbamylated protein antibodies (Anti-CarP) by a home-made ELISA test using fetal calf serum, as previously described by Montes *et al.* (13). Autoantibody status for RF and ACPA was

also evaluated during the PR phase in patients with available data. Anti-CarP data was not available during this period, as it is not routinely tested in clinical practice.

One objective of the study was to identify patients with a history compatible with PR before RA diagnosis. A specific questionnaire (Supplementary Data 1.) asking patients for the presence of acute intermittent joint attacks of short duration (< 1 week) compatible with PR, defined as pain with or without swelling or erythema, was administered at study entry. PR flares/symptoms associated with articular or periarticular inflammatory signs (swelling and/or erythema) which were directly observed by the treating physician and documented in the medical record were also assessed. In patients with a history compatible with previous PR not explained by other causes, we determined whether these typical acute flares persisted after RA diagnosis until study entry, especially with respect to the number and characteristics of flares in the 12 months before study inclusion. Medical records were completely reviewed to corroborate symptoms compatible with PR before RA onset and whether the flares were observed by the treating physician. Due to the retrospective nature of the study, no specific classification criteria for PR were used. Only patients with both an inclusion visit protocol and medical records compatible with PR were categorized as PR, unless symptoms could not explain by other causes. PR disease duration was defined as date from PR onset to RA onset. RA disease duration was calculated from RA disease onset to the inclusion visit.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Hospital Clinic of Barcelona Clinical Research Ethics Committee (ethics approval number 2017/0679). Signed informed consent was obtained from all patients before study enrolment.

STATISTICAL ANALYSIS

We compared the study variables in RA patients with and without pre-existing PR. Proportions were calculated using the χ^2 test or Fisher's exact test when expected

test or the nonparametric Mann-Whitney U test when there was a non-normal distribution. A cumulative probability plot was constructed to assess the time from PR onset to RA onset. Continuous data are presented as means and standard deviation (SD) or median and interquartile range according the distribution and categorical variables as absolute frequencies and percentages. The level of statistical significance was established as ≤ 0.05 . The analysis was made using IBM® SPSS® for Windows version 23.0.

RESULTS

1. Prevalence of palindromic rheumatism before rheumatoid arthritis onset

A total of 158 patients (78% female) were included, with a mean age of 58.8 ± 13.1 years and a disease duration since RA onset of 5.1 ± 2.7 years. Twenty-nine patients (18%) presented a history compatible with PR before RA onset, with joint flares, typically monoarticular, mostly lasting < 72 hours, which could not be explained by other diseases, such as crystal arthritis. Eighteen patients who reported PR symptoms in the questionnaire were finally classified as inflammatory arthralgia (n:13) or polymyalgia like syndrome (n:5) due to more persistent symptoms ($> one$ week) and clinical characteristics after review of medical records. These patients were included and analysed in the non-PR group.

The mean age at PR diagnosis was 47.9 ± 14.2 years. The median time between PR onset and RA onset was 1.2 years (p25-p75:0.5-3.9) (Figure 1). Before RA onset, patients with PR were treated with on-demand nonsteroidal anti-inflammatory drugs (NSAIDs) (76%), and glucocorticoids (21%) and seven patients (24%) received a csDMARD, in most cases hydroxychloroquine (17%).

2. Clinical, therapeutic and immunologic features in patients with and without

palindromic rheumatism

No significant differences in demographic features, disease duration, current disease activity, remission rates, disability indexes and the frequency of erosive disease between patients with and without pre-existing PR were observed (Table 1). A significantly-higher prevalence of ever smokers (current or previous) was observed in patients with pre-existing PR (72% vs. 40%), although no significant difference was observed in current smoking (24% vs. 16%) or cumulative smoking exposure (24.1 ± 11.8 pack-years vs 23.5 ± 14.0 pack-years). At RA onset, patients with pre-existing PR had a lower mean number of joints involved (4.8 ± 3.1 vs. 6.2 ± 2.8), and a slightly-higher prevalence of large joint involvement (45% vs. 38%), although the differences were not significant. Thirty-six patients presented EAMS, including interstitial lung disease (7% vs 12%), sicca syndrome (21% vs 15%), rheumatoid nodules (14% vs 9%), episcleritis (0% vs 1%) serositis (0% vs 1%), with no significant differences between patients with or without previous PR.

At study inclusion, autoantibody positive status was higher in patients with pre-existing PR, including RF (72% vs. 59%), ACPA (79% vs. 66%) and Anti-CarP (52% vs. 45%) although the differences were not statistically significant. No significant differences in serum titers were found. Only one patient with pre-existing PR was seronegative for all three autoantibodies (Figure 2).

Autoantibody status for RF and ACPA was available in 23 and 21 patients, respectively, during the palindromic phase, before RA onset. RF and ACPA were positive in 11 (48%) and 13 (62%) of these patients, respectively. At study inclusion, positive seroconversion of RF and ACPA was documented in 6 (26%) and 3 (14%) patients, respectively. No patient switch to a negative status.

No differences were observed in current or previous anti-rheumatic therapy during the RA disease course, except for greater use of hydroxychloroquine in patients with pre-

existing PR (38% vs. 6%). Current prescription of glucocorticoids and DMARDs is shown in Table 1., detailed current biologic treatment is described in the

Supplementary Table 1.

3. *Palindromic rheumatism flares after rheumatoid arthritis diagnosis*

At least one intermittent flare compatible with PR was recorded in 25 (87%) of the 29 patients with pre-existing PR after the diagnosis of RA. Fourteen patients (48%) reported PR flares in the 12 months before the inclusion visit: during this period the median number of flares reported was 6 (range: 1-15). Intermittent flares were reported in this 12-month period in patients in DAS28 clinical remission (n=7) or even in those receiving bDMARDs (n=5) at the inclusion visit. In 10 of these 14 patients, direct observation of a palindromic flare associated with articular or periarticular inflammatory signs was documented by the treating physician. During these flares observed by the physician, patients were in remission (30%), low disease activity (40%) or moderate/high disease activity (30%) according to DAS28. No differences in drug treatment, including hydroxychloroquine (40% vs. 36%), were found between patients who did or did not report PR flares in the last 12 months.

DISCUSSION

Our results show that 18% of patients with established RA reported intermittent symptoms compatible with PR before RA onset. No differences were observed between RA patients with or without pre-existing PR in disease activity status, disability or erosive disease. PR symptoms persisted in a significant proportion of patients during the RA course.

There is little data on the exact prevalence of PR before RA onset. Our results are very similar to those observed in a multicentre Catalan study that found a prevalence of 15.8% (14). In the Canadian CATCH early RA cohort study, the reported prevalence was 40%, although the definition of intermittent arthritis possibly reflecting PR was only

analysed using a self-reported questionnaire (15). The latency period of 1.2 years between the onset of PR and the onset of RA confirms that most patients, and

especially those with autoantibodies, develop RA in the first years of PR symptoms (4).

Whether PR represents a specific clinical phenotype of RA is unclear. We found no significant differences in disease activity, remission rates, disability and erosive disease between patients with and without PR. However, we found a higher proportion of smokers in patients with pre-existing PR, although no differences in current smoking or the cumulative exposure were found. The prevalence of current smokers (24%) was similar to that seen in patients with PR in the only two studies that address this issue, which was 21-32% (6,16) and similar to the 25% found in the Spanish RA population in the COMORA study (17) and the 30% in our early RA cohort (18). We have no satisfactory explanation for this finding or whether it may reflect the high proportion of seropositive disease observed in these patients, since a clear trend to RF and ACPA positivity was found in ever smokers. Smoking has been associated with seropositive RA and named as a risk factor for RA in patients with arthralgia and ACPA positivity (19,20). It may be hypothesized that patients with PR, where ACPA positivity is frequent, with a history of smoking during the PR phase and a high cumulative smoking exposure might be more prone to evolve toward RA. A high prevalence of smoking was identified in RA patients with previous intermittent symptoms in the CATCH study (15).

Autoantibody status was similar in both groups, but there was a trend to greater autoantibody seropositivity in PR patients, in line with the high prevalence of RF and ACPA in patients with PR without RA (5-11). A lower rate of ACPA fine specificities and isotypes has been reported in PR when compared to RA (21), although we did not evaluate these ACPA features. However, similar ACPA characteristics were expected in this cohort, since all patients included had established RA (mean duration 5.1 years) when autoantibodies were analyzed. Information on Anti-CarP antibodies in PR is scarce, our group recently found that the prevalence of Anti-CarP antibodies in patients with PR was 16.7% (22).

RA onset, to our knowledge a previously unreported finding. This suggests that these patients retain this phenotype after RA onset and may be refractory to DMARDs that might achieve satisfactory control of persistent arthritis but not of palindromic flares. Typical PR flares persist after RA onset in some patients, even though RA itself remained in remission/low disease activity or under biologic therapy. We have no satisfactory explanation for this finding. Palindromic flares, with the abrupt onset and rapid resolution of the crisis, the intermittent nature and the involvement of periarticular tissues may resemble an autoinflammatory disorder; therefore, the pathogenesis of this clinical phenotype, with a more relevant role for the innate immunity than in persistent chronic synovitis, cannot be excluded (3). We have previously reported an unexpectedly-high frequency of MEFV mutations in patients diagnosed as PR, although almost had seronegative (RF or ACPA) disease (23). However, more recently, Savic *et al.* (24) reported a series of patients with seropositive RA with sudden onset of severe self-limiting flares, in whom mutations or single nucleotide polymorphisms of autoinflammatory genes were confirmed, suggesting that, in rare cases, RA and an autoinflammatory disorder may coexist. We did not analyse autoinflammatory genes, although no other features, such as fever, cutaneous involvement or serositis were recorded.

No differences in csDMARD, bDMARD or glucocorticoid use were observed between the two groups, although we observed a significantly greater use of hydroxychloroquine in combination with other DMARDs in patients with RA and PR. This is not unexpected considering that this drug is commonly used in PR with good results (25). It is difficult to establish whether hydroxychloroquine use may prevent palindromic flares in the RA phase. We found a similar prevalence of persistence of palindromic flares in patients with or without hydroxychloroquine use, but this may be due to confounding by indication. The study design does not permit definitive conclusions on the effectiveness

The study had some limitations. First, the diagnostic criteria of PR were not applied due to the retrospective nature of the study: the definition of palindromic flares was recorded in the medical record but focused on the typical symptoms of PR, in which our group have extensive experience (1,5,8,16, 21-23). Secondly, the data on RA features at disease onset were recorded retrospectively and we did not determine whether, in this early phase, the clinical or serological phenotype may differ between patients with or without PR, although we found a lower number of affected joints at RA onset. Thirdly, the small sample size is one reason why the conclusions should be considered with caution.

In summary, almost one in five patients with RA had of our cohort have a history compatible with PR previous to RA onset. No differences in disease severity and no distinctive clinical or serological phenotype was found in these patients in the RA phase, although palindromic flares may persist in a significant proportion of patients even after the use of DMARDs. The role of smoking in PR and the possible effects of hydroxychloroquine in these patients in aborting palindromic flares merit further investigation.

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FIGURE 1. LEGEND:

Cumulative probability plot of time (years) from PR diagnosis to RA onset. The median time between PR onset and RA onset was 1.2 (**dot**) years (p25-p75:0.5-3.9)

FIGURE 2. LEGEND:

ACPA: anti-citrullinated peptide antibodies; RF: rheumatoid factor; Anti-CarP: anti-carbamylated proteins antibodies

FIGURE 1. PREGRESION FROM PALINDROMIC RHEUMATISM TO RHEUMATOID ARTHRITIS

FIGURE 2. SERUM AUTOANTIBODIES IN RA ACCORDING TO THE PRESENCE OF PR AT INITIATION.

TABLE 1. DEMOGRAPHIC, CLINICAL AND THERAPEUTIC FEATURES OF RHEUMATOID ARTHRITIS PATIENTS WITH AND WITHOUT PALINDROMIC RHEUMATISM BEFORE DISEASE ONSET

	PR at initiation n: 29	No PR at initiation n: 129	p value
Female	21 (72.4%)	102 (79.1%)	NS
Age at RA onset mean ($\pm$ SD)	51.2 ($\pm$ 15.1)	54.3 ($\pm$ 12.8)	NS
RA disease duration mean ($\pm$ SD)	4.2 ($\pm$ 2.5)	5.3 ($\pm$ 2.7)	NS
Extra-articular manifestation	6 (20.7%)	30 (23.3%)	NS
Smoking (past or current)	21 (72.4%)	51 (39.5%)	<0.005
RA family history	6 (20.7%)	16 (12.4%)	NS
Large joint involved at onset (%)	13 (44.8%)	48 (37.5%)	NS
Joint number involved at RA onset, mean ($\pm$ SD)	4.8 ($\pm$ 3.1)	6.2 ($\pm$ 2.8)	NS
Hand joint involvement at RA onset (%)	28 (96.6%)	108 (85.0%)	NS
RF positive (%)	21 (72.4%)	76 (58.9%)	NS
RF titer mean ($\pm$ SD), IU	152 ($\pm$ 199.7)	228.3 ($\pm$ 246.8)	NS
ACPA positive	23 (79.3%)	85 (65.9%)	NS
ACPA titer mean ($\pm$ SD), IU	798.4 ($\pm$ 1001.5)	1225.1 ($\pm$ 1068.5)	NS
Anti-CarP positive (%)	15 (51.7%)	58 (45.0%)	NS
Anti-CarP titer mean ($\pm$ SD), IU	1089 ($\pm$ 843.9)	924.7 ($\pm$ 801.2)	NS
DAS28 mean ($\pm$ SD)	2.8 ($\pm$ 1.1)	2.9 ($\pm$ 1.2)	NS
DAS28 remission rate	44.8%	47.3%	NS
DAS28 CRP mean ($\pm$ SD)	2.7 ($\pm$ 1.0)	2.5 ($\pm$ 1.2)	NS
DAS28 CRP remission rate	51.7%	66.7%	NS
CDAI mean ($\pm$ SD)	7.7 ($\pm$ 7.1)	8.2 ($\pm$ 7.5)	NS
CDAI remission rate	34.5%	21.7%	NS
SDAI mean ($\pm$ SD)	8.5 ($\pm$ 7.4)	9.0 ($\pm$ 7.90)	NS
SDAI remission rate	31.0%	23.3%	NS
RAPID3 mean ($\pm$ SD)	7.4 ($\pm$ 6.6)	7.9 ($\pm$ 6.5)	NS
RAPID3 remission rate	37.9%	31.7%	NS
HAQ-DI mean ($\pm$ SD)	0.40 ($\pm$ 0.45)	0.36 ($\pm$ 0.47)	NS
Pain Analogue Scale mean ($\pm$ SD), mm	25.6 ($\pm$ 28.4)	31.4 ($\pm$ 90.0)	NS
Erosive disease	16 (55.2%)	67 (52.9%)	NS
Current drug therapy:			
• Glucocorticoid	18 (62.1%)	75 (58.6%)	NS
• csDMARDs	26 (89.7%)	108 (83.7%)	NS
○ MTX	20 (69%)	84 (65.1%)	NS
○ HCQ	11 (37.9%)	8 (6.2%)	<0.005
• bDMARDs	8 (27.6%)	32 (24.8%)	NS
○ Anti-TNF	6 (20.7%)	18 (14.0%)	NS
○ Non anti-TNF	2 (6.9%)	14 (10.9%)	NS

TABLE 1. LEGEND:

PR: palindromic rheumatism; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; Anti-CarP: anti-carbamylated proteins antibodies; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; .RAPID3: Routine Assessment of Patient Index Data 3; HAQ: Health Assessment Questionnaire Disability Index; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs: biological disease-modifying anti-rheumatic drugs.