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

Raul Castellanos-Moreira, Sebastian C. Rodriguez-Garcia, José A. Gómez-Puerta, Virginia Ruiz-Esquide, Oscar Camacho, Julio Ramírez, Andrea Cuervo, Rosa Morlà, Juan D. Cañete, Isabel Haro, and Raimon Sanmarti

ABSTRACT. ***Objective.*** To analyze the prevalence of preexisting palindromic rheumatism (PR) in patients with established rheumatoid arthritis (RA) and to evaluate whether these patients have a distinctive clinical and serological phenotype.

Methods. Cross-sectional study in patients with established RA. Preexisting 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. Included were 158 patients with established RA (78% female) with a mean disease duration since RA onset of 5.1 ± 2.7 years. Preexisting 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, anticitrullinated peptide antibodies, and anticarbamylated protein antibodies were numerically higher in patients with PR. No differences in treatment were observed except for greater hydroxychloroquine (HCQ) 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 disease-modifying antirheumatic drugs.

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 HCQ use and smoking prevalence were identified. Palindromic flares may persist during the RA disease course despite treatment. (First Release January 15 2020; J Rheumatol 2020;47:652–7; doi:10.3899/jrheum.190061)

Key Indexing Terms:

PALINDROMIC RHEUMATISM
ANTICITRULLINATED PROTEIN ANTIBODIES
ANTICARBAMYLATED PROTEIN ANTIBODIES
RHEUMATOID ARTHRITIS
HYDROXYCHLOROQUINE
SMOKING

From the Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; Unit of Synthesis and Biomedical Applications of Peptides, Institute of Advanced Chemistry of Catalonia (IQAC-CSIC), Barcelona, Spain.

This study was supported by a grant from the Hospital Clínic of Barcelona, Research, Innovation and Education Department (Raul Castellanos-Moreira, Premi Fi de residencia: Emili Letang 37933).

R. Castellanos-Moreira, MD, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; S.C. Rodriguez-Garcia, MD, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; J.A. Gómez-Puerta, MD, PhD, MPH, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; V. Ruiz-Esquide, MD, PhD, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; O. Camacho, MD, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; J. Ramírez, MD, PhD, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; A. Cuervo, MD, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; R. Morlà, MD, PhD, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; J.D. Cañete, MD, PhD, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona; I. Haro, PhD, Unit of Synthesis and Biomedical Applications of Peptides, IQAC-CSIC; R. Sanmarti, MD, PhD, Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona.

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

Accepted for publication July 8, 2019.

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]. It is possible that PR forms part of the same spectrum as RA, given the high rate of progression toward RA (in up to 67% of cases in 1 series[4]) and a similar autoantibody profile, including rheumatoid factor (RF) and anticitrullinated peptide antibodies (ACPA)[5]. However, PR is intermittent, periarticular inflammation occurs during flares, and not all patients evolve to RA, suggesting 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 patients with PR do not develop RA in the long term, with intermittent arthritis persisting[8].

Studies have analyzed prognostic factors and progression to RA in patients with PR[7,8,9,10,11], even though none has reported the prevalence of preexisting 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 preexisting PR who presented typical palindromic flares after RA was diagnosed, including patients in clinical remission.

The aims of our study were to analyze the prevalence of intermittent arthritis compatible with PR before RA onset, differences in the clinical phenotype and immunological and therapeutic features among established RA patients with and without preexisting PR and whether typical intermittent arthritis flares continued after RA onset.

MATERIALS 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 according to the 2010 American College of Rheumatology/European League Against Rheumatism 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, extraarticular manifestations (EAMS) according to predefined criteria[12], current disease activity measured by the 28-joint count Disease Activity Score (DAS28), the Simplified Disease Activity Index, and the Clinical Disease Activity Index. Data collected were patient-reported outcomes such as the Routine Assessment of Patient Index Data 3, and disability as measured by the Health Assessment Questionnaire–Disability Index. A pain visual analog scale was administered. The number and distribution of joints involved at RA onset were collected retrospectively: hand and foot radiographs were obtained at study entry and radiographic erosions were evaluated. Previous and current conventional synthetic disease-modifying antirheumatic drugs (csDMARD), biological DMARD (bDMARD), and glucocorticoid use were evaluated.

Current autoantibody status was measured: RF by nephelometry, ACPA by anticyclic citrullinated peptide antibodies (QUANTA Flash CCP3, chemiluminescent immunoassay), and anticarbamylated protein antibodies (anti-CarP) by a homemade 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 were not available during this period, because they are not routinely tested in clinical practice.

One objective of our study was to identify patients with a history compatible with PR before RA diagnosis. A specific questionnaire (Supplementary Data 1, available with the online version of this article) was administered at study entry, 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. PR flares/symptoms associated with articular or periarticular inflammatory signs (swelling and/or erythema) that 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 regarding 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. Owing to the retrospective design 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.

Our 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 enrollment.

Statistical analysis. We compared the study variables in RA patients with and without preexisting PR. Proportions were calculated using the chi-square test or Fisher's exact test when expected counts were ≤ 5. Continuous variables were analyzed using the parametric Student t 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 SD or median and interquartile range, according to 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

Prevalence of PR before RA 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 h, 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 having inflammatory arthralgia (n = 13) or polymyalgia-like syndrome (n = 5) because of more persistent symptoms (> 1 week) and clinical characteristics after review of medical records. These patients were included and analyzed 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 (percentile 25–p75: 0.5–3.9; Figure 1). Before RA onset, patients with PR were treated with on-demand nonsteroidal antiinflammatory drugs (76%) and glucocorticoids (21%), and 7 patients (24%) received a csDMARD, in most cases hydroxychloroquine (HCQ; 17%).

Clinical, therapeutic, and immunologic features in patients with and without PR. No significant differences were observed in demographic features, disease duration, current disease activity, remission rates, disability indices, and the frequency of erosive disease between patients with and without preexisting PR (Table 1). A significantly higher prevalence of ever smokers (current or previous) was observed in patients with preexisting 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-yrs vs 23.5 ± 14.0 pack-yrs). At RA onset,

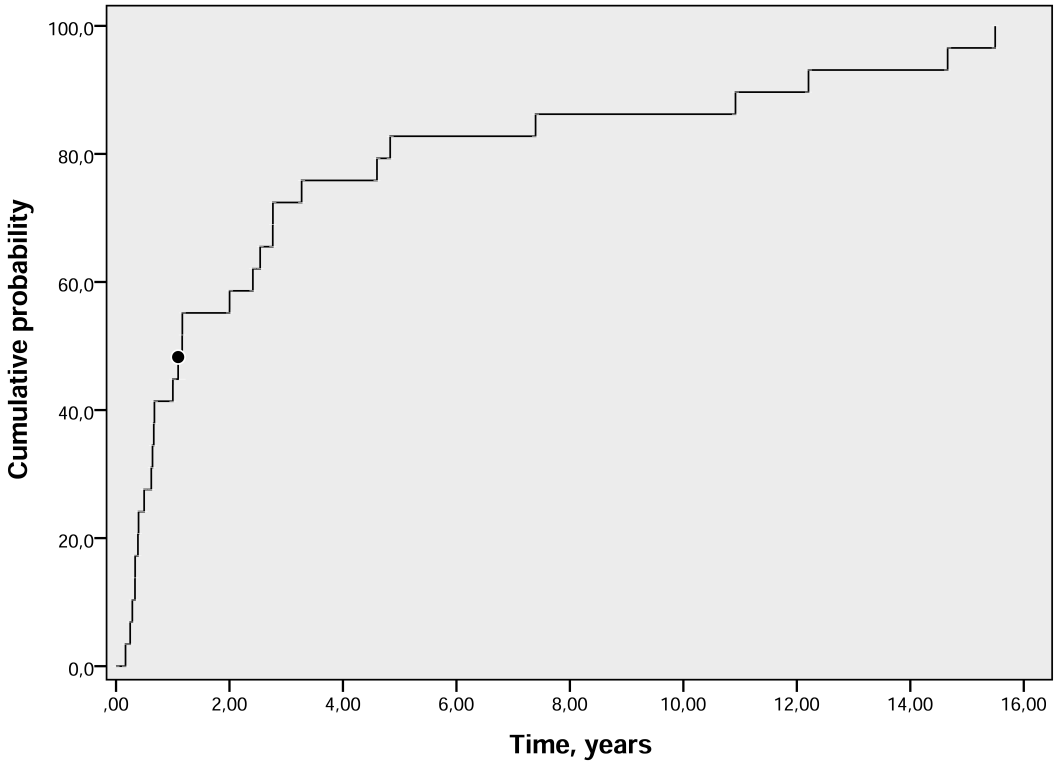

Figure 1. Cumulative probability plot of time (years) from PR diagnosis to RA onset. The median time between PR onset and RA onset was 1.2 (black dot) years (p25-p75: 0.5–3.9). PR: palindromic rheumatism; RA: rheumatoid arthritis.

patients with preexisting 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%), and 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 preexisting 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 1 patient with preexisting PR was seronegative for all 3 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 switched to a negative status.

No differences were observed in current or previous antirheumatic therapy during the RA disease course, except for greater use of HCQ in patients with preexisting PR (38% vs 6%). Current prescription of glucocorticoids and DMARD is shown in Table 1 and detailed current biologic treatment is described in Supplementary Table 1 (available with the online version of this article).

PR flares after RA diagnosis. At least 1 intermittent flare compatible with PR was recorded in 25 (87%) of the 29 patients with preexisting 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) and in those receiving bDMARD (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 HCQ (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 preexisting PR in disease activity status,

Table 1. Demographic, clinical, and therapeutic features of rheumatoid arthritis patients with and without palindromic rheumatism (PR) before disease onset.

Variables	PR at Initiation, n = 29	No PR at Initiation, n = 129	p
Female	21 (72.4%)	102 (79.1%)	NS
Age at RA onset, yrs, mean (± SD)	51.2 (15.1)	54.3 (12.8)	NS
RA disease duration, yrs, mean (± SD)	4.2 (2.5)	5.3 (2.7)	NS
Extraarticular 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 (± SD)	4.8 (3.1)	6.2 (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, IU, mean (± SD)	152 (199.7)	228.3 (246.8)	NS
ACPA-positive	23 (79.3%)	85 (65.9%)	NS
ACPA titer, IU, mean (± SD)	798.4 (1001.5)	1225.1 (1068.5)	NS
Anti-CarP–positive (%)	15 (51.7%)	58 (45.0%)	NS
Anti-CarP titer, IU, mean (± SD)	1089 (843.9)	924.7 (801.2)	NS
DAS28 mean (± SD)	2.8 (1.1)	2.9 (1.2)	NS
DAS28 remission rate	44.8%	47.3%	NS
DAS28-CRP mean (± SD)	2.7 (1.0)	2.5 (1.2)	NS
DAS28-CRP remission rate	51.7%	66.7%	NS
CDAI mean (± SD)	7.7 (7.1)	8.2 (7.5)	NS
CDAI remission rate	34.5%	21.7%	NS
SDAI mean (± SD)	8.5 (7.4)	9.0 (7.90)	NS
SDAI remission rate	31.0%	23.3%	NS
RAPID-3 mean (± SD)	7.4 (6.6)	7.9 (6.5)	NS
RAPID-3 remission rate	37.9%	31.7%	NS
HAQ-DI mean (± SD)	0.40 (0.45)	0.36 (0.47)	NS
Pain analog scale, mm, mean (± SD)	25.6 (28.4)	31.4 (90.0)	NS
Erosive disease	16 (55.2%)	67 (52.9%)	NS
Current drug therapy			
Glucocorticoid	18 (62.1%)	75 (58.6%)	NS
csDMARD	26 (89.7%)	108 (83.7%)	NS
MTX	20 (69%)	84 (65.1%)	NS
HCQ	11 (37.9%)	8 (6.2%)	< 0.005
bDMARD	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

NS: not significant; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anticitrullinated peptide antibodies; anti-CarP: anticarbamylated protein antibodies; DAS28: 28-joint count Disease Activity Score; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAPID-3: Routine Assessment of Patient Index Data 3; HAQ: Health Assessment Questionnaire–Disability Index; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; HCQ: hydroxychloroquine; bDMARD: biological DMARD; TNF: tumor necrosis factor.

disability, or erosive disease. PR symptoms persisted in a significant proportion of patients during the RA course.

There are few data on the exact prevalence of PR before RA onset. Our results were very similar to those observed in a multicenter 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 analyzed 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 preexisting 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 2 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 and cannot say whether it may reflect the high proportion of seropositive disease observed in these patients, because 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,

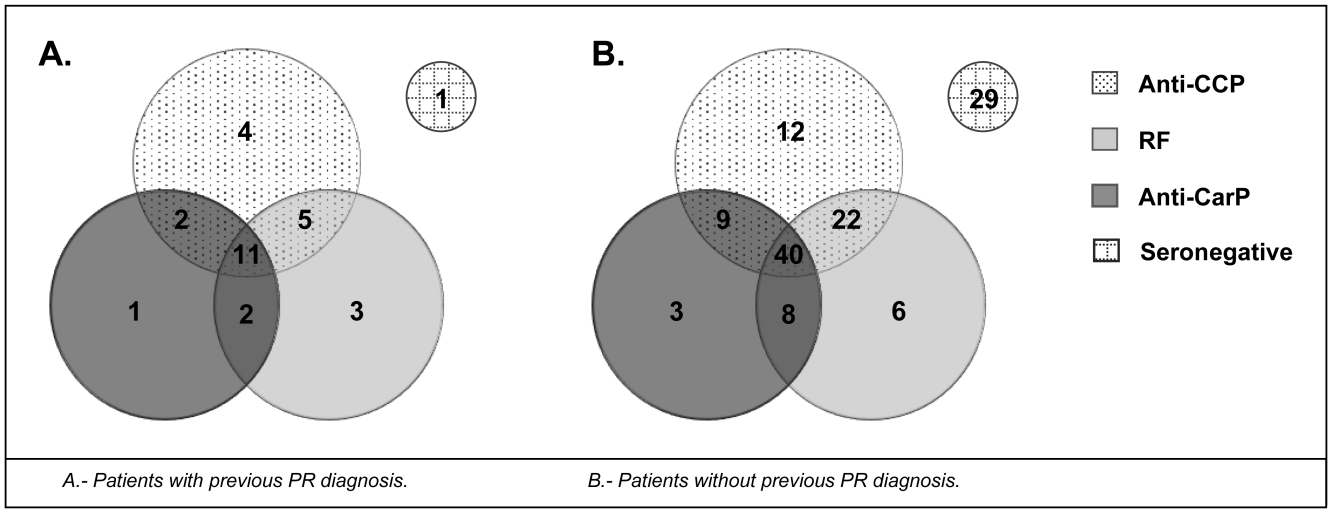

Figure 2. Serum autoantibodies in RA according to the presence of PR at initiation. RA: rheumatoid arthritis; PR: palindromic rheumatism; anti-CCP: anticyclic citrullinated peptide antibodies; RF: rheumatoid factor; anti-CarP: anticarbamylated protein antibodies.

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 patients with PR, 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, because all patients included had established RA (mean duration 5.1 yrs) 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].

A significant proportion of patients with preexisting PR had flares typical of PR after 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 DMARD 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 character, 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 all had seronegative disease (RF or ACPA)[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 analyze autoinflammatory genes, although no other features were recorded, such as fever, cutaneous involvement, or serositis.

No differences in csDMARD, bDMARD, or glucocorticoid use were observed between the 2 groups, although we observed a significantly greater use of HCQ in combination with other DMARD 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 HCQ use may prevent palindromic flares in the RA phase. We found a similar prevalence of persistence of palindromic flares in patients with or without HCQ use, but this may be due to confounding by indication. The study design does not permit definitive conclusions on the effectiveness of HCQ.

The study had some limitations. First, the diagnostic criteria of PR were not applied because of the retrospective design of the study: the definition of palindromic flares was noted 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]. Second, 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. Third, the small sample size is one reason why the conclusions should be considered with caution.

Almost 1 in 5 patients with RA in our cohort had a history compatible with PR previous to RA onset. No differences in

disease severity and no distinctive clinical or serological phenotypes were found in these patients in the RA phase, although palindromic flares may persist in a significant proportion of patients even after the use of DMARD. The role of smoking in PR and the possible effects of HCQ in these patients in aborting palindromic flares merit further investigation.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCE

1. Sanmarti R, Cañete JD, Salvador G. Palindromic rheumatism and other relapsing arthritis. Best Pract Res Clin Rheumatol 2004;18:647-61.
2. Katz SJ, Russell AS. Palindromic rheumatism: a pre-rheumatoid arthritis state? J Rheumatol 2012;39:1912-3.
3. Mankia K, Emery P. What can palindromic rheumatism tell us? Best Pract Res Clin Rheumatol 2017;31:90-8.
4. Koskinen E, Hannonen P, Sokka T. Palindromic rheumatism: long-term outcomes of 60 patients diagnosed in 1967-84. J Rheumatol 2009;36:1873-5.
5. Salvador G, Gomez A, Vinas O, Ercilla G, Cañete JD, Munoz-Gomez J, et al. Prevalence and clinical significance of anti-cyclic citrullinated peptide and antikeratin antibodies in palindromic rheumatism. An abortive form of rheumatoid arthritis? Rheumatology 2003;42:972-5.
6. Mankia K, D'Agostino M, Wakefield R, Nam J, Mahmood W, Grainger A. Identification of a distinct imaging phenotype may improve the management of palindromic rheumatism. Ann Rheum Dis 2018;78:43-50.
7. Russell AS, Devani A, Maksymowych WP. The role of anti-cyclic citrullinated peptide antibodies in predicting progression of palindromic rheumatism to rheumatoid arthritis. J Rheumatol 2006;33:1240-2.
8. Sanmarti R, Cabrera-Villalba S, Gomez-Puerta JA, Ruiz-Esquide V, Hernandez MV, Salvador G, et al. Palindromic rheumatism with positive anticitrullinated peptide/protein antibodies is not synonymous with rheumatoid arthritis. A longterm followup study. J Rheumatol 2012;39:1929-33.
9. Gonzalez-Lopez L, Gamez-Nava JI, Jhangri GS, Ramos-Remus C, Russell AS, Suarez-Almazor ME. Prognostic factors for the development of rheumatoid arthritis and other connective tissue diseases in patients with palindromic rheumatism. J Rheumatol 1999;26:540-5.
10. Tamai M, Kawakami A, Iwamoto N, Arima K, Aoyagi K, Eguchi K. Contribution of anti-CCP antibodies, proximal interphalangeal joint involvement, HLA-DRB1 shared epitope, and PADI4 as risk factors for the development of rheumatoid arthritis in palindromic rheumatism. Scand J Rheumatol 2010;39:287-91.
11. Emad Y, Anbar A, Abo-Elyoun I, El-Shaarawy N, Al-Hanafi H, Darwish H, et al. In palindromic rheumatism, hand joint involvement and positive anti-CCP antibodies predict RA development after 1 year of follow-up. Clin Rheumatol 2014;33:791-7.
12. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol 2002;29:62-7.
13. Montes A, Regueiro C, Perez-Pampin E, Boveda MD, Gomez-Reino JJ, Gonzalez A. Anti-carbamylated protein antibodies as a reproducible independent type of rheumatoid arthritis autoantibodies. PLoS One 2016;11:e0161141.
14. Corominas H, Narváez J, Díaz-Torné C, Salvador G, Gomez-Caballero M, de la Fuente D, et al. Diagnostic and therapeutic delay of rheumatoid arthritis and its relationship with health care devices in Catalonia. The AUDIT study. Reumatol Clin 2016;12:146-50.
15. Ellingwood L, Schieir O, Bartlett SJ, Bessette L, Hitchon CA, Boire G, et al. Characterizing palindromic symptoms in early rheumatoid arthritis: results from the Canadian Early Arthritis Cohort Study [abstract]. Arthritis Rheumatol 2018;70 Suppl 10:2465.
16. Cabrera-Villalba S, Ramirez J, Salvador G, Ruiz-Esquide V, Hernández M, Inciarte-Mundo J, et al. Is there subclinical synovitis in patients with palindromic rheumatism in the intercritical period? A clinical and ultrasonographic study according to anticitrullinated protein antibody status. J Rheumatol 2014;41:1650-5.
17. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch M, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis 2013;73:62-8.
18. Ruiz-Esquide V, Gómez-Puerta J, Cañete J, Graell E, Vazquez I, Ercilla MG, et al. Effects of smoking on disease activity and radiographic progression in early rheumatoid arthritis. J Rheumatol 2011;38:2536-9.
19. Di Giuseppe D, Discacciati A, Orsini N, Wolk A. Cigarette smoking and risk of rheumatoid arthritis: a dose-response meta-analysis. Arthritis Res Ther 2014;16:R61.
20. de Hair M, Landewé R, van de Sande M, van Schaardenburg D, van Baarsen L, Gerlag D, et al. Smoking and overweight determine the likelihood of developing rheumatoid arthritis. Ann Rheum Dis 2012;72:1654-8.
21. Cabrera-Villalba S, Gomara MJ, Cañete JD, Ramírez J, Salvador G, Ruiz-Esquide V, et al. Differing specificities and isotypes of anti-citrullinated peptide/protein antibodies in palindromic rheumatism and rheumatoid arthritis. Arthritis Res Ther 2017;19:141.
22. Castellanos-Moreira R, Ruiz-Esquide V, Gomara MJ, Cabrera-Villalba S, Rodriguez-Garcia SC, Salvador G, et al. ANTI-carbamylated protein antibodies (CARP) in palindromic rheumatism: prevalence and clinical significance [abstract]. Arthritis Rheumatol 2017;69 Suppl 10:480.
23. Cañete J, Arostegui J, Queiró R, Gratacós J, Hernández M, Larrosa M. An unexpectedly high frequency of MEFV mutations in patients with anti–citrullinated protein antibody–negative palindromic rheumatism. Arthritis Rheumatol 2007;56:2784-8.
24. Savic S, Mistry A, Wilson A, Barcenas-Morales G, Doffinger R, Emery P. Autoimmune-autoinflammatory rheumatoid arthritis overlaps: a rare but potentially important subgroup of diseases. RMD Open 2017;3:e000550.
25. Gonzalez-Lopez L, Gamez-Nava JI, Jhangri G, Russell AS, Suarez-Almazor ME. Decreased progression to rheumatoid arthritis or other connective tissue diseases in patients with palindromic rheumatism treated with antimalarials. J Rheumatol 2000;27:41-6.