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SHORT REPORT

Persistent arthritis develops in joints previously affected by palindromic flares: a longitudinal study investigating the transition from palindromic rheumatism to rheumatoid arthritis

Didem Sahin ,[1,2] Rahaymin Chowdhury,[1,3] Andrea Di Matteo ,[1,2] Laurence Duquenne ,[1,2] Kerem Abacar,[1] Kate Harnden ,[1,3] Jacqueline L Nam,[3] Lucy Thornton,[1,2] Paul Emery ,[1,2] Kulveer Mankia [1,2]

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[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[2]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals Trust, Leeds, UK
[3]Leeds Teaching Hospitals Trust, Leeds, UK

Correspondence to
Dr Kulveer Mankia;
k.s.mankia@leeds.ac.uk

ABSTRACT

Objective To assess whether joint involvement during palindromic rheumatism (PR) flares predicts future arthritis location in patients progressing to persistent inflammatory arthritis (PIA) and to compare rheumatoid arthritis (RA) features in patients with or without a PR prodrome.

Methods In this single-centre longitudinal study, individuals at risk of RA from Leeds research cohorts who progressed to PIA were included. Demographics, clinical features and patient-reported outcomes were collected. In the PR cohort, joint involvement was recorded at initial flare, subsequent visits and at progression to PIA. Joint-level associations were analysed using cross-classified mixed-effects logistic regression model. Comparisons were made between patients with and without PR who eventually met 2010 American College of Rheumatology and European Alliance of Associations for Rheumatology RA criteria.

Results 63 patients with PR progressed to PIA at a median of 13.4 months, with complete joint-level data for 48. Hands and shoulders were most affected at initial flare, with hands predominating across all flares. PIA developed in joints involved at any PR flare in 70.8% of patients. Prior involvement of a joint during a PR flare was associated with a higher risk of developing PIA in the same joint (OR 1.97, 95% CI 1.61 to 2.41; p<0.001). At RA diagnosis, patients with PR had lower Health Assessment Questionnaire and Visual Analogue Scale scores than those without PR, yet showed significantly higher swollen joint counts (4.1 vs 3.2; p=0.045).

Conclusion PR often begins in the hands and shoulders, and joint inflammation during PR usually precedes PIA in the same joints. Despite lower pain and disability, RA patients with PR show greater inflammatory joint burden at progression.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Palindromic rheumatism (PR) is characterised by unpredictable, self-resolving flares of joint pain and swelling. Patients with PR often eventually progress to rheumatoid arthritis (RA), reflecting a transition from intermittent inflammation to persistent synovitis.

WHAT THIS STUDY ADDS

⇒ These prospective data from a large UK PR cohort identified unilateral involvement of the hand and shoulders as the most frequent sites of the initial flare.

⇒ Longitudinal joint-level analysis demonstrated that persistent arthritis usually developed in joints previously affected by flares, supporting a joint-centric transition from transient to chronic inflammation.

⇒ Patients with PR who progressed to RA showed differences in clinical phenotype, but similar disease activity, compared with at-risk individuals without a PR prodrome at the time of progression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The comprehensive joint-level data on initial flare location, from this large disease-modifying antirheumatic drug-naive PR cohort, may aid earlier identification of people with PR amongst the large volume of patients who present to healthcare providers with new musculoskeletal symptoms.

⇒ The strong joint-level association between PR and subsequent persistent arthritis suggests that local tissue-related factors may be critical in driving the transition from PR to RA. This represents a potential role for therapies, which specifically target the local tissue environment in this early phase of the disease.

INTRODUCTION

Palindromic rheumatism (PR) is characterised by recurrent, self-limiting episodes of joint and and extracapsular inflammation, usually affecting one or a few joints with pain, swelling and erythema that resolve without

permanent damage.[1] Despite its transient nature, up to 50% patients with PR develop persistent inflammatory arthritis (PIA), often rheumatoid arthritis (RA).[1–3] RA patients tend to flare in the same joints, suggesting that local factors influence persistent inflammation.[4] Whether PR flare patterns predict subsequent joint involvement in PIA remains unclear.

RA evolves through preclinical phases, during which individuals may exhibit musculoskeletal symptoms and immunological abnormalities before developing clinical arthritis. PR, with distinct clinical and imaging features, is considered a pre-RA phenotype.[5 6] Similarly, anti-cyclic citrullinated peptide antibody (anti-CCP)-positive individuals with musculoskeletal symptoms but no clinical synovitis represent another at-risk population.[7–9] Whether the RA phenotype at progression differs between these pre-RA populations remains unclear.

This longitudinal cohort study aimed to investigate whether PIA develops in joints previously affected during PR flares and to compare RA phenotype between patients who developed RA after a PR prodrome and anti-CCP-positive at-risk individuals who developed RA without a PR prodrome, assessing whether different pre-RA pathways result in distinct RA phenotypes.

METHODS

In this single-centre longitudinal study, patients with PR (anti-CCP positive or anti-CCP negative) and anti-CCP-positive at-risk individuals with musculoskeletal symptoms but without PR were recruited and prospectively followed between July 2008 and October 2023 as part of the Leeds PR and CCP cohorts, respectively. The PR and CCP cohorts have been described previously.[5 7] In both cohorts, demographic, clinical (eg, joint tenderness, patient-reported outcomes (PROs) including Health Assessment Questionnaire (HAQ) and Visual Analogue Scale scores) and laboratory data were systematically collected every 3 months during the first year and annually thereafter, with additional visits scheduled if progression to PIA was suspected.

In the absence of consensus criteria, PR was diagnosed by rheumatologists based on 'a documented history or physical examination consistent with joint pain and swelling, which subsequently resolved to normal, in the absence of an alternative diagnosis'.[5] A flare of PR was defined as 'two or more features of pain, swelling and erythema in or around at least one joint region that later normalized'.[5] In shoulders and hips, swelling/erythema was not mandatory. When feasible, patients with PR were also examined during an active flare.

For analysis, joints were grouped into three categories: (1) affected during the first attack of PR (initial flare), (2) involved in subsequent flares occurring after the initial flare and before progression to PIA and (3) affected at progression, defined as one or more persistent swollen joints. At the first visit, initial flare joint involvement was patient-reported based on recall of the first PR flare and recorded using a joint mannequin; subsequent joint involvement was documented via patient mannequins or diaries, and/or physician assessment where possible. At the individual joint level, joints affected in flares prior to progression were compared with joints that developed persistent synovitis at progression.

Demographic, clinical and serological data at progression to RA were compared between patients with and without PR. All progressors included in these group comparisons were restricted to anti-CCP-positive individuals and fulfilled the 2010 American College of Rheumatology and European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for RA.[10] This restriction was employed to minimise serological heterogeneity and to study individuals with a comparable RA-related autoimmune predisposition.

Statistical analysis

Categorical variables were summarised as frequencies and percentages and compared using the χ^2 or Fisher's exact test, as appropriate. Continuous variables were reported as mean±SD or median (25th–75th percentile (Q1–Q3)), and between-group comparisons were performed using the independent samples t-test or Mann-Whitney U test, depending on data distribution. Joint-level associations were analysed using a cross-classified mixed-effects logistic regression model with random intercepts for both patient and individual joint, accounting for within-patient clustering and joint-specific risk.

Additional methodological details are provided in the online supplemental methods.

RESULTS

63 patients with PR with longitudinal data who progressed to PIA were identified (73.0% female; mean age at initial flare 51.5 years, at PIA 53.6 years; median time to progression 13.4 months (Q1–Q3: 6.2–34.3)). 56 patients (88.9%) met 2010 ACR/EULAR RA criteria, while 7 (11.1%) progressed to other forms of chronic arthritis (1 psoriatic arthritis (PsA), 1 enteropathic, 5 undifferentiated arthritis (UA)). Overall, 55 of the 63 progressors (87.3%) were anti-CCP positive, 40 (63.5%) were rheumatoid factor (RF) positive, 56 (88.9%) were positive for either anti-CCP or RF and 39 (61.9%) were double positive (positive for both anti-CCP and RF). PROs and laboratory results at PIA onset across the full PR cohort are presented in online supplemental table 1.

Of the 63 patients, complete longitudinal joint level data—including joint involvement during the initial and subsequent flares as well as at the time of progression—were available for 48 patients (44 RA, 4 UA).

Across all patients, 195 joints were affected at the initial flare and 793 during subsequent flares. At the initial flare, hand involvement was reported by 23 patients (47.9%), including 16 unilateral and 7 bilateral cases (figure 1), with the second metacarpophalangeal (MCP) joint of

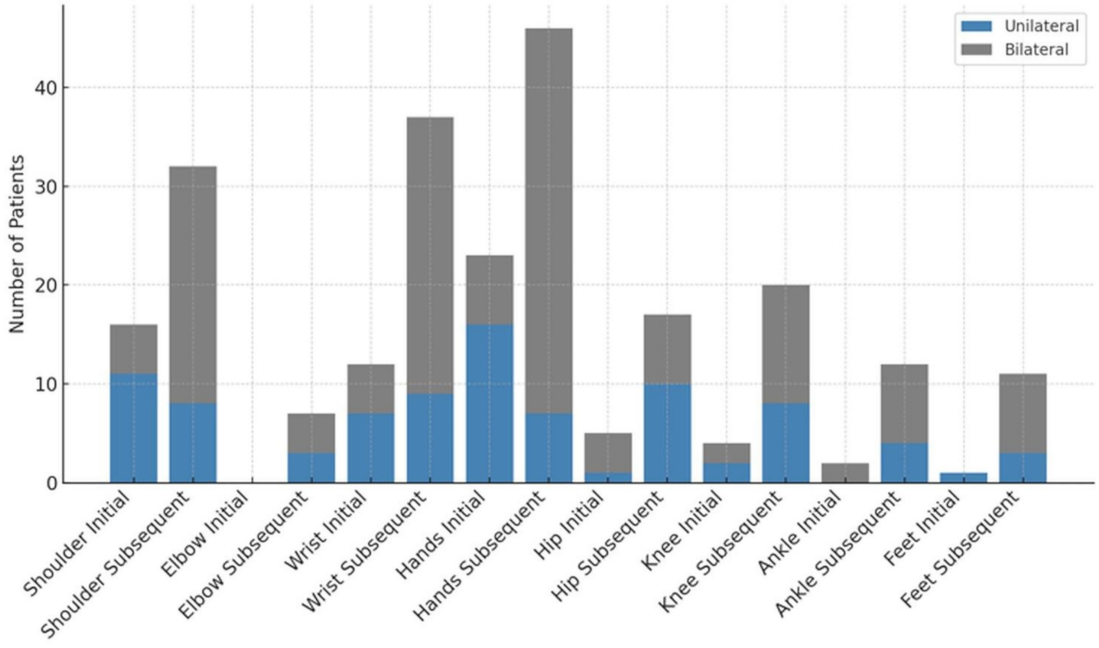

Figure 1 Distribution of initial and subsequent palindromic rheumatism (PR) flares across joints in 48 PR progressors. The figure shows the frequency of joint involvement during initial and subsequent PR flares among patients for whom complete joint data were available (n=48). The bars represent the number of patients with unilateral (blue) or bilateral (grey) involvement. Joint involvement was assessed at the individual joint level; for presentation purposes, results for hands and feet are displayed as aggregated anatomical regions.

the right hand and the third proximal interphalangeal (PIP) joint of the left hand being the most commonly affected joints (n=10 each). Shoulder involvement was reported by 16 patients (33.3%), with 11 unilateral and 5 bilateral cases (figure 1). Across all flares, small joints of the hands were most frequently involved (n=519), with the right MCP2 being the most commonly affected joint overall (n=37). Of 237 joints with synovitis at progression to PIA, 19.0% (n=45) were affected at the initial PR flare and 60.3% (n=143) in subsequent PR flares (figure 2). Among 48 patients with PR with complete joint data, 16 (33.3%) developed PIA in ≥1 joint affected at the initial PR flare, and 34 (70.8%) progressed in ≥1 joint affected in *any* previous PR flare. After accounting for within-patient clustering and joint-specific risk, prior involvement of a joint during a PR flare was associated with a higher risk of PIA in the same joint (OR 1.97, 95% CI 1.61 to 2.41; p<0.001). Analyses focusing on patients who progressed to RA are presented in the online supplemental results.

Among the 171 anti-CCP-positive at-risk individuals without PR who progressed to PIA, 151 (88.3%) met RA classification criteria and were compared with 53 anti-CCP positive patients with PR who progressed to RA. Mean age at progression to RA was similar (55.1 vs 55.9 years), with the majority being female. Double positivity was higher in RA patients without PR (82.8% vs 69.8%, p=0.053). At RA onset, functional disability, assessed by HAQ, was significantly lower in RA patients with PR (0.79 vs 1.12, p=0.027). Fatigue and pain levels were also lower, although differences were not statistically significant (table 1). To examine whether background medication use influenced PROs at progression, multivariable linear regression analyses were performed comparing RA progressors with and without PR (online supplemental table 2). In contrast, patients with PR had a higher swollen joint count (28-swollen joint count: 4.1 vs 3.2, p=0.045). No significant differences were observed between the groups at progression in the Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) or erythrocyte sedimentation rate (DAS28-ESR).

DISCUSSION

These joint-level data provide the most comprehensive longitudinal description to date of joint involvement in the transition from PR to RA. Consistent with previous reports, flares of PR frequently involve the small joints of the hands and wrists.[11–13] Notably, we identified a high frequency of initial unilateral shoulder involvement along with unilateral hand involvement, the former supporting previous observations that PR may target large joints at disease onset.[11] These findings may aid earlier recognition of PR in patients presenting with new, non-specific, musculoskeletal complaints.

Local tissue factors and joint-specific responses to cytokines vary among different joints, which may explain their role in the development and recurrence of synovitis.[14] Our study revealed that progression to PIA mostly occurred in joints that had been previously affected during PR flares, with over two-thirds of patients developing PIA in one or more joints that had previously suffered PR flares. Mixed-effects analysis showed that

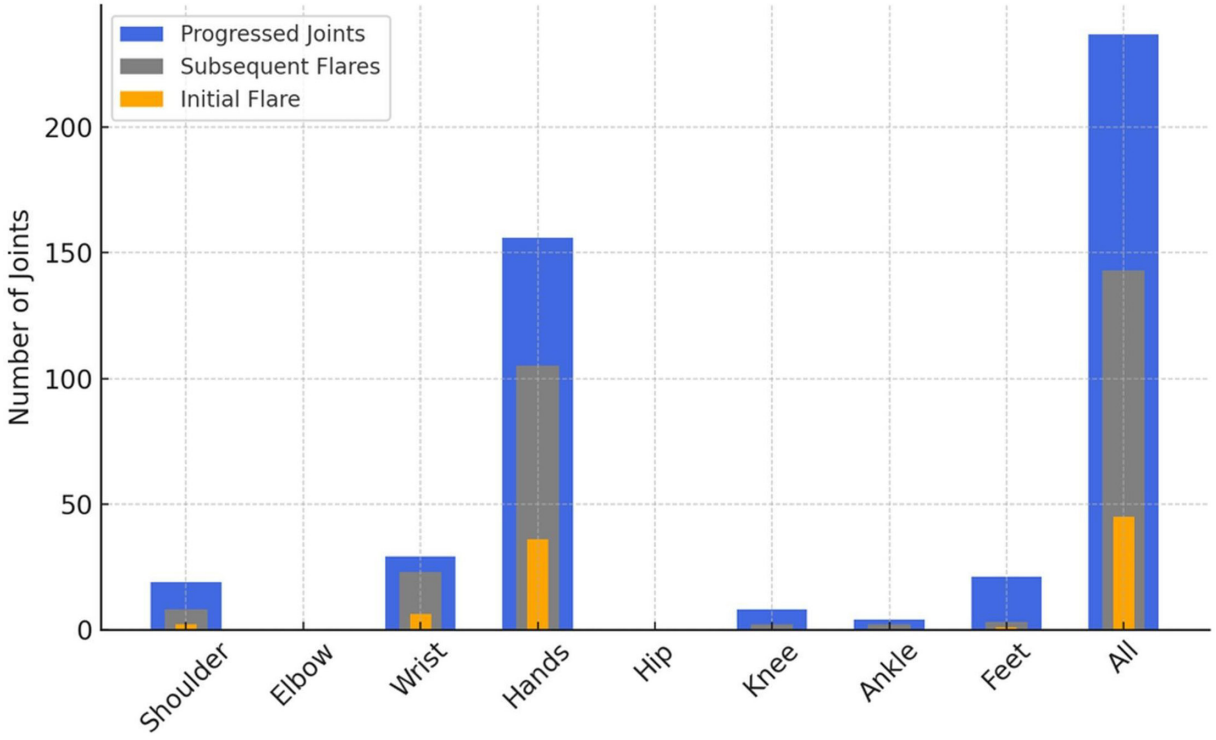

Figure 2 Joints affected at initial and subsequent palindromic rheumatism (PR) flares and at progression to persistent inflammatory arthritis (PIA). The figure shows the number of joints that progressed to PIA in each joint category (blue bars). The grey and orange segments within the blue bars show how many of these joints were also affected during subsequent and initial PR flares, respectively. Joint involvement was assessed at the individual joint level; for presentation purposes, results for hands and feet are displayed as aggregated anatomical regions.

prior joint involvement during PR was associated with approximately twofold higher odds of PIA in the same joint at progression. However, we acknowledge that this association does not establish causality. Indeed, a notable exception was the feet, which were infrequently affected by PR flares despite becoming involved at progression to PIA, an observation that warrants further investigation. Nevertheless, these findings emphasise the importance of joint-level evaluation in people with PR, as clinicians and patients should be especially vigilant for disease progression in previously affected joints. This supports the hypothesis that transient joint and peri-articular inflammation may precede chronic inflammation through local tissue-centric factors. Moreover, people with established RA and PsA tend to flare in the same joints over time, reinforcing the role of local factors in disease progression.[4 15] In this specific at-risk group, the joint-centric nature of disease progression provides a rationale for therapies, which target local tissue factors, such as intra-articular injections targeting the local stroma, which could potentially alter the disease course.

At RA onset, patients with and without PR were of similar age, consistent with previous reports.[16 17] Serological profiles differed slightly, with patients with PR showing less frequent RF positivity than patients without PR, which may be clinically relevant given its association with more aggressive RA presentation.[18]

Patients with PR had significantly higher swollen joint counts at progression, suggesting more overt synovitis. In contrast, they reported lower fatigue, pain and HAQ scores. This may reflect recurrent flares in PR being associated with adaptive changes in pain perception, potentially contributing to lower patient-reported disability at progression. Notably, as demonstrated in previous work, patients with PR have been shown to exhibit US features similar to those of new-onset RA at the time of progression.[5]

Strengths of this study include well-characterised, prospective cohorts and the unique opportunity to analyse joint-level data across the PR-RA transition. Limitations include potential recall bias from patient-reported initial flares, incomplete joint data in some patients and limited power for subgroup comparisons due to small sample sizes.

In conclusion, in patients with PR who progress to PIA, arthritis mostly develops in joints previously inflamed during PR flares, emphasising the importance of thorough joint evaluation during PR for surveillance of future persistent joint involvement. Unilateral involvement of the hands and shoulders was the most frequent initial flare sites. Notably, at progression to RA, patients with PR had more swollen joints but lower disability scores than those without PR despite similar disease activity. This suggests prodromal differences seen in distinct at-risk populations may influence the subsequent RA phenotype.

Table 1 Demographic, clinical and laboratory characteristics of anti-CCP-positive patients at progression to RA, according to the presence or absence of a preceding PR prodrome

	RA without PR n=151	RA with PR n=53	P value
Age, mean (SD)	55.9 (13.9)	55.1 (12.3)	0.682
Sex, female, n (%)	104 (68.9)	37 (69.8)	0.899
CRP≥5 mg/L,* n (%)	78 (55.3)	31 (62.0)	0.412
ESR, median (IQR)	23.0 (21.0)	21.5 (31.0)	0.737
Rheumatoid factor, n (%)			0.233
Negative	24 (18.9)	16 (30.2)	
Low positive	27 (21.3)	11 (20.8)	
≥3×ULN	76 (59.8)	24 (49.1)	
Double positivity,† n (%)	101 (82.8)	37 (69.8)	0.053
HAQ, mean (SD)	1.12 (0.80)	0.79 (0.71)	0.027
VAS Global Health, mean (SD)	42.3 (27.3)	39.7 (28.2)	0.616
VAS Pain, mean (SD)	53.4 (26.5)	46.4 (28.1)	0.178
VAS Disease Activity, mean (SD)	58.1 (26.9)	51.5 (29.4)	0.223
VAS Fatigue, mean (SD)	49.6 (31.0)	40.6 (30.8)	0.151
TJC 53, mean (SD)	8.4 (8.0)	8.6 (6.5)	0.908
SJC 53, mean (SD)	4.0 (3.6)	4.7 (3.6)	0.230
TJC 28, mean (SD)	6.1 (6.0)	6.9 (5.4)	0.443
SJC 28, mean (SD)	3.2 (2.6)	4.1 (3.3)	0.045
DAS28-CRP, mean (SD)	3.8 (1.2)	4.0 (1.2)	0.290
DAS28-ESR, mean (SD)	4.3 (1.3)	4.5 (1.3)	0.477
Any medication use,‡ n (%)	68 (45.0)	25 (47.2)	0.673
NSAIDs, n (%)	62 (41.1)	21 (39.6)	0.855
Glucocorticoids, n (%)	10 (6.6)	6 (11.3)	0.371
csDMARDs, n (%)	7 (4.6)	6 (11.3)	0.202

*CRP was dichotomised due to unavailability of exact values below the reporting threshold (<5 mg/L) and categorised accordingly.
†Double positivity was defined as being seropositive for both anti-CCP and RF.
‡Defined as use of ≥1 of the following at progression: NSAIDs, glucocorticoids or csDMARDs; for csDMARDs, a minimum treatment duration of 1 month was required.
Anti-CCP, Anti-cyclic citrullinated peptide; CRP, C-Reactive protein; csDMARDs, conventional synthetic diseasemodifying antirheumatic drugs; DAS, Disease activity score; ESR, Erythrocyte sedimentation rate; HAQ, Healthassessment questionnaire; NSAIDs, Non-steroidal anti-inflammatory drugs; PR, Palindromicrheumatism; RA, Rheumatoid arthritis; SJC, Swollen joint count; TJC, Tender joint count; ULN, Upper limit of normal; VAS, Visual analogue scale.

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Contributors Study design: KM and DS. Data collection: DS, RC, ADM, LD, KA, KH, JLN, LT and KM. Statistical analysis: DS. Conceptualising and writing of the manuscript: KM, DS, ADM and PE. KM is the guarantor. KA contributed to the Data Collection. ChatGPT was used to generate two figures for the manuscript.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and received ethical approval from the following committees: CCP-Old Generation: NRES Committee Yorkshire & The Humber—Leeds West (06/Q1205/169); RADAR/IACON: NRES Committee Yorkshire & The Humber—Leeds West (09/H1307/98); and CCP-Next Generation: Yorkshire & The Humber—Leeds East Research Ethics Committee (17/YH/0177). Participants gave informed consent to participate in the study before taking part.

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ORCID iDs
Didem Sahin https://orcid.org/0000-0003-3558-5400
Andrea Di Matteo https://orcid.org/0000-0003-0867-7051
Laurence Duquenne https://orcid.org/0000-0001-7631-0986
Kate Harnden https://orcid.org/0000-0003-4699-1498
Paul Emery https://orcid.org/0000-0002-7429-8482
Kulveer Mankia https://orcid.org/0000-0002-7945-6582

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