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Identification of a Distinct Imaging Phenotype may Improve the Management of Palindromic Rheumatism

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Keywords

Early rheumatoid arthritis, anti-CCP, magnetic resonance imaging, ultrasonography

Abstract

Objectives

To use high-resolution imaging to characterise palindromic rheumatism (PR) and to compare the imaging pattern observed to that seen in new-onset rheumatoid arthritis (NORA).

Methods

Ultrasound (US) assessment of synovitis, tenosynovitis and non-synovial extra-capsular inflammation (ECI) was performed during and between flares in a prospective treatment-naïve PR cohort. Magnetic resonance imaging (MRI) of the flaring region was performed where possible. For comparison, the same US assessment was also performed in anti-CCP positive individuals with musculoskeletal symptoms (CCP+ at-risk) and patients with NORA.

Results

Thirty-one of 79 PR patients recruited were assessed during a flare. A high frequency of ECI was identified on US; 19/31 (61%) of patients had ECI including 12/19 (63%) in whom ECI was identified in the absence of synovitis. Only 7/31 (23%) PR patients had synovitis (greyscale ≥1 and power Doppler ≥1) during flare. In the hands/wrists, ECI was more prevalent in PR compared to NORA and CCP+ at-risk (65% vs 29% vs 6%, $p<0.05$). Furthermore, ECI without synovitis was specific for PR [42% PR vs 4% NORA ($p=0.003$) and 6% CCP+ at-risk ($p=0.0012$)]. Eleven PR flares were captured by magnetic resonance imaging, which was more sensitive than US for synovitis and ECI. 8/31 (26%) PR patients developed RA and had a similar US phenotype to NORA at progression.

Conclusion

PR has a distinct US pattern characterised by reversible ECI, often without synovitis. In patients presenting with new joint swelling, US may refine management by distinguishing relapsing from persistent arthritis.

Early diagnosis and treatment of inflammatory arthritis (IA) is associated with less joint damage and a higher chance of achieving remission (1). However, identifying and treating IA at the earliest opportunity can be challenging as many patients with disease-specific autoantibodies and/or inflammatory joint symptoms do not necessarily develop persistent arthritis. An important example is patients with palindromic rheumatism (PR).

PR is characterised by intermittent flares of articular and peri-articular inflammation. Up to 50% of PR patients will eventually develop RA, with those that are anti-CCP antibody positive at highest risk of progression (2-4). However, the time to progression is variable and many anti-CCP positive PR patients do not develop persistent arthritis, even after several years of follow up (5). Identifying patients with this favourable prognosis from those with early persistent IA is important; the latter require early disease-modifying therapy whereas the former can often be monitored with a more conservative approach.

In clinical practice, distinguishing true PR from a new presentation of IA can be challenging; many patients require multiple assessments before a diagnosis is made (6). High resolution imaging, particularly ultrasound (US), is recommended as part of the diagnostic workup for suspected RA (7) with many rheumatologists now using US in their routine practice (8).Imaging studies in PR have, however, been limited (9, 10).; this is likely due to the difficulty in capturing this group of patients and the sporadic nature of flares. We therefore aimed to comprehensively describe the imaging phenotype of PR in a prospective treatment-naïve cohort, both during and between flares. We then sought to compare this to the imaging findings in i) anti-CCP positive individuals with musculoskeletal (MSK) symptoms (CCP+ at risk) and ii) patients with new-onset RA (NORA). We hypothesised that both synovial and non-synovial extra-capsular (EC) structures are important disease targets in PR,

and that imaging would reveal a distinct pattern of inflammation which may be used to distinguish PR from patients presenting with early persistent IA.

Methods

Design

A prospective analysis of a regional PR cohort was performed. For comparison, both a prospective and retrospective analysis of a cohort of CCP+ at-risk individuals and NORA patients was also undertaken.

PR patients

PR patients were recruited from rheumatology clinics in Leeds and the Yorkshire region. Some PR patients were also recruited through a national primary care programme adopted by the National Institute for Health Research Clinical Research Network (11).

All patients were assessed at Chapel Allerton Hospital, Leeds, UK and were recruited if the study rheumatologist diagnosed PR. In the absence of accepted classification criteria, PR was defined as *'a confirmed history or physical examination consistent with episodes of joint pain and swelling that returned to normal between episodes in the absence of an alternative diagnosis'*.

Patients underwent clinical and US assessment at baseline and were followed according to patient-reported flares: those patients who were flaring at the initial visit were invited to re-attend when they were not flaring; likewise the patients who were not flaring at the initial

visit were asked to telephone when they were having a flare and were seen within 48 hours. A flare episode was defined as two or more features of pain, swelling and erythema in or around at least one joint region, that later normalised. Patients were divided into two subgroups according to the disease phase at the first assessment: patients in Group A were not in flare at their first assessment (i.e. 'non-flare') whereas patients in Group B were 'in flare' at their first assessment. For both groups patients were re-evaluated at a second visit when the disease phase changed. US was performed at all flare and non-flare visits. Magnetic resonance imaging (MRI) of the most affected region was performed during flare visits where possible. Patients were monitored for the development of persistent arthritis.

Anti-CCP+ at-risk individuals

CCP+ at-risk individuals were recruited through a national primary care programme (11,). This cohort has been previously described (12, 13) and consists of subjects aged >18 years with non-specific MSK symptoms and a positive serum anti-CCP2 test but no clinical synovitis. Clinical and US assessments performed at the baseline visit in this cohort were included in the current analysis.

New-onset RA patients

NORA patients all met American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 classification criteria for RA (14). All NORA patients were anti-CCP positive and DMARD-naïve at the time of assessment. Clinical and US assessments performed at RA diagnosis were included in the current analysis.

Ultrasound evaluation

US evaluation was performed by rheumatologists (RJW, MADA, KM, JLN) and sonographers (LH, KS) with extensive experience in MSK US who were blinded to patient group, symptoms and clinical assessment. All US examiners participated in a training session and agreed on the scanning protocol. A standardised 38-joint, 10-tendon US protocol was used at all visits (see supplementary materials for full details). All available recorded images were scored by a single expert reader (MADA) who was blinded to all patient details and this score was used in the analysis.

US scans were mainly performed using a General Electric (GE) Logiq E9 machine employing a 15-6MHz transducer. Copious gel was used as a standoff to avoid excessive transducer pressure. A small number of US scans were performed using a GE S7 machine. PD was assessed using a pulse repetition frequency set between 0.7-1.0KHz, medium wall filter and gain adjusted until background noise was suppressed. Doppler frequency was 10MHz.

Scoring of grey scale (GS) and power Doppler (PD) synovitis was according to the EULAR Outcome Measures in Rheumatology (OMERACT) scoring system (15, 16). Tenosynovitis was defined according to the OMERACT definition (17) and scored as present or absent. To avoid overestimation, as scoring used for the analysis was based on central reading of images, synovitis was defined as GS ≥1 and PD ≥1.

Non-synovial EC abnormalities were frequently identified in our initial US assessments of PR flares and have previously been observed in PR patients (18). Therefore, the following classification system for EC abnormalities was agreed by consensus (KM, MADA, RJW) after review of a randomised selection of flare images of different joint regions: *Peri-articular inflammation:* localised non-synovial soft tissue inflammation with or without PD signal outside the joint capsule and around the joint region. *Peri-tendinous oedema:* oedema with

or without PD signal occurring around a tendon without a tenosynovium. *Subcutaneous oedema:* diffuse non-synovial soft tissue oedema with or without PD signal occurring outside the capsule and extending beyond the joint region. Figure 2 shows example images for each of these definitions. EC abnormalities were subsequently scored as present or absent.

MRI evaluation

MRI scanning was performed on the most symptomatic region during PR flare. Patients were scanned using a 3T Siemens Verio MRI scanner (Erlangen, Germany) (see supplementary methods for full details).

All MRI scans were scored by an experienced reader (MADA) who was blinded to all patient and clinical details. The presence or absence of synovitis, bone marrow oedema (BME), tenosynovitis, erosions, peri-tendinous oedema and peri-articular inflammation was reported for the imaged region (i.e. hand, knee, shoulder). Due to interference from coil artefacts, subcutaneous oedema was not included in this analysis. Synovitis and BME were reported according to the OMERACT RA MRI scoring system (RAMRIS)(19). Tenosynovitis was defined according to the OMERACT MRI Tenosynovitis Scoring System (20) and scored as present or absent. In the absence of an accepted definition for EC MRI abnormalities (i.e. peri-articular inflammation and peri-tendinous oedema), these lesions were identified and scored using T1 fat-sat gadolinium enhanced sequences and reported descriptively. Peri-articular inflammation was defined as EC effusion and/or postcontrast enhancement of the EC tissues on axial and coronal sequences over ≥ 3 consecutive slices. Peri-tendinous

oedema was defined as peri-tendinous effusion and/or postcontrast enhancement outside the tendon sheath, seen on axial and coronal sequences over ≥ 3 consecutive slices.

Statistical Analysis

We tested the hypothesis that the frequency of synovial and EC US abnormalities during the flare episode would be different in PR patients compared to anti-CCP +at-risk individuals and NORA patients. Therefore, the proportion of PR patients with US abnormalities during a clinically-defined flare in the hand(s)/wrist(s) was compared with the proportion of anti-CCP+ at-risk and NORA patients with US abnormalities in the hands/wrists using Chi-square or Fisher's exact test (where expected counts were ≤ 5 cases). We also tested the hypothesis that the proportion of PR patients with synovial and EC non-synovial US abnormalities would increase between non-flare and flare disease phases. Therefore, the proportion of PR patients with US abnormalities in the clinically flaring region was compared in flare and non-flare disease phases using McNemar's exact test. Kruskall-Wallis and Fisher's exact tests were used to compare patient characteristics between groups. For significant results, pairwise tests were performed using Mann-Whitney U test for scale variables.

Results

Patients

Seventy-nine PR patients met the study inclusion criteria and were recruited between May 2015 and May 2017. The cohort was followed prospectively according to patient-reported flares (figure 1). Fifteen out of 79 patients were flaring at the initial visit and 11 of these

patients re-attended when they were not flaring. Sixteen out of 64 patients who were not flaring at their initial visit subsequently attended during a flare. In total the 31/79 patients who had an US assessment during a flare episode were included in the analysis. Seven out of 31 (23%) patients developed persistent IA during the subsequent follow up period; all these patients met the ACR/EULAR 2010 classification criteria for RA (14). Of the complete cohort, 13/79 (16%) patients developed persistent IA. 47/79 patients were anti-CCP positive and of these 35 (74%) did not develop persistent IA during the follow up period.

Thirty-three CCP+ at-risk and 24 NORA patients were included as control groups and were matched for age with PR patients. Demographic and clinical characteristics are shown in table 1.

Ultrasound findings in PR patients

US characteristics of PR patients during flare (31 scans recorded) compared with US findings of the same region when the patient was not flaring (27 scans recorded) are shown in table 2 and supplementary online figure 1. US abnormalities were infrequently identified during non-flare and none had GS ≥2 and PD ≥1. Similarly, EC inflammation (ECI) was identified in only 4/27 (15%) of non-flare US scans. GS synovitis, tenosynovitis, peri-articular inflammation and subcutaneous oedema were all less prevalent in non-flare scans compared to flare scans ($p<0.05$). In contrast, there was no difference in the frequency of PD signal and peri-tendinous oedema between flare and non-flare US scans ($p=0.289$ and $p=0.625$ respectively). No erosions were identified on flare or non-flare scans.

Of the 27 patients who had non-flare scans, 11 were performed after the flare scan was captured. There was improvement in US abnormalities in all but one of these patients.

Ultrasound findings during PR flare

In the 31 patients in whom flares were captured, the flaring region was the hands/wrists in 26 patients, the foot/ankle in 1 patient, the knee in 3 patients and the shoulder in 1 patient.

A high frequency of ECI was seen (figures 2 and 3) during flare: in 19/31 (61%) patients, one or more of peri-articular inflammation, peri-tendinous oedema and/or subcutaneous oedema was identified. Interestingly in 12 patients, ECI was seen in the absence of GS (GS ≥2) or PD synovitis. GS alone (GS ≥2) was present in 12/31 (39%) patients. Tenosynovitis and peri-tendinous oedema were detected in 7/31 (23%) and 3/31 (10%) of patients respectively. PD signal was present in only 7/31 (23%) of patients. No differences in either synovial inflammation or ECI was found between in PR patients according to anti-CCP status.

Five patients attended with more than one flare (see supplementary data). Overall US inflammation did not appear to increase with sequential flares (supplementary figure 4).

No patients had tophi, double contour sign, hyperechoic aggregates or any other US features suggestive of crystal arthritis.

Comparison of PR with anti-CCP+ at-risk individuals and NORA patients

US abnormalities identified in PR patients during flares involving the hands/wrists were compared with US abnormalities in the hands/wrists of anti-CCP+ at-risk individuals and NORA patients (table 3 and supplementary figures 2 and 3). PD signal was observed less

frequently in PR patients compared with NORA patients ($p<0.05$). In contrast ECI was identified in the majority (65%) of PR patients but only 7/24 (29%) of NORA patients ($p=0.023$). No PR patients had synovitis on US of the flaring region without ECI also being present. Of note, the identification of ECI without synovitis at the flare site appeared to be specific for PR; 42% of PR patients had this US phenotype but this occurred in only 1 NORA patient ($p=0.003$) and 2 CCP+ at-risk individuals ($p=0.0012$).

Comparison of MRI and Ultrasound

Eleven flares were captured by both MRI and US (in 1 patient 2 flares were captured by both imaging modalities). MRI appeared more sensitive than US for synovitis, tenosynovitis, peri-tendinous oedema and peri-articular inflammation (supplementary figure 5). Synovitis (taken as cut-off of RAMRIS > 1) was identified in 7/11 (64%) flares whereas BME was reported in only one flare. Tenosynovitis and peri-tendinous oedema were identified by MRI in 5/11 (45%) and 6/11 (55%) flares respectively. Peri-articular inflammation was identified by MRI in 6/11 (55%) flares. No MRI erosions were identified.

Ultrasound features at progression to RA

The US phenotype of 7 PR patients who developed RA during the follow up period was similar to the NORA patients who did not have a history of PR. US synovitis and/or tenosynovitis of the hands/wrists was present in 5/7(71%) of patients at progression to RA. In contrast, ECI was only present in 2/7 (29%) of patients (supplementary figure 3).

	CCP+ at-risk (n=33)	PR (n=31)		NORA (n=24)	P
		During flare (n=31)	During non-flare (n=27)		
Age (Yrs) ,mean (SD)	47 (15)	49 (14)		55 (15)	0.114
Sex (% F)	88% (29/33)	55% (17/31)		58% (14/24)	**0.01*‡**
Anti-CCP positive (%)	100 (33/33)	68% (21/31)		100% (24/24)	**<0.01**
RF positive (%)	18% (6/33)	48% (15/31)		75% (18/24)	**<0.01*‡**
DMARD-naïve (%)	100 (33/33)	90% (28/31)		100% (24/24)	0.06
Current smoker (% Yes)	21% (7/33)	39% (12/31)		29% (7/24)	0.34
Never smoker (% Yes)	58% (19/33)	32% (10/31)		25% (6/24)	**0.03‡**
Alcohol consumer (% Yes)	42% (14/33)	58% (18/31)		67% (16/24)	0.18
FDR with RA (% Yes)	24% (8/33)	13% (4/31)		25% (6/24)	0.43
Duration of symptoms (months)	13 (6,60)	30 (9, 57)	19 (8.5, 46)	14 (10, 40)	0.542
EMS (mins)	0(0,30)	90 (0,120) n=29	0(0,2.5)	60(10, 120)	**<0.01*‡**
Symptoms in hands**	61% (20/33)	84% (26/31)	41% (11/27)	100% (24/24)	**0.01‡**
Symptoms in feet**	33% (11/33)	26% (8/31)	15% (4/27)	58% (14/24)	0.05
Symptoms in large joints**	64% (21/33)	48% (15/31)	44% (12/27)	71% (17/24)	0.23
Pain VAS (mm)	23 (4,50) n=31	58 (25,81) n=19	11 (3,34) n=21	39 (24,59) n=19	**0.03***
Fatigue VAS (mm)	38(6.65) n=31	42 (22,64) n=19	37 (8,58) n=21	42 (23,60) n=19	0.69
Global health VAS (mm)	18(7,40) n=31	41 (16, 55) n=19	20 (8,38) n=21	29(16,50) n=21	0.08
TJC 28	0(0,2)	2 (1,3)	0(0,0)	5(3,9)	**<0.01*‡†**
TJC 53	1(0,2)	1(1,2)	0(0,1)	5(3,7)	**<0.01‡†**
SJC 28	0(0,0)	1(1,2)	0(0,0)	2(1,6)	**<0.01*†‡**
SJC 44	0(0,0)	1(1,2)	0(0,0)	3(2,6)	**<0.01*‡†**
CRP (mg/dL)	1.31 (0.24, 5.24) n=28	9.9 (1.1, 26) n=29	0(0,5.65) n=26	6.5 (0, 9.38) n=23	**0.01***
DAS28CRP	n/a	n/a	n/a	3.48 (3.18, 4.56) n= 21	n/a
DAS28CRP	n/a	n/a	n/a	3.48 (3.18, 4.56) n= 21	n/a

Table 1: Patient characteristics

Baseline characteristics of PR patients seen in flare, CCP+at-risk and NORA patients.

PR,palindromic rheumatism, CCP+ at-risk, anti-CCP positive at-risk individuals; NORA, new-onset rheumatoid arthritis. RF, rheumatoid factor; DMARD, disease-modifying anti-

rheumatic drug; FDR, first-degree relative; EMS, early morning stiffness duration; VAS, visual analogue scale; TJC, tender joint count; SJC, swollen joint count; CRP, C-reactive protein; DAS, disease activity score. Median and IQR are presented for scale variables. P values are given for comparisons between CCP+ at-risk, PR flare and NORA patients (Kruskall- Wallis and Fisher's exact tests). For significant results, pairwise tests were performed (Mann Whitney U test for scale variables). *CCP+ vs PR flare $p<0.05$, ‡ CCP+ vs NORA $p<0.05$, † PR flare vs NORA $p<0.05$. **refers to symptoms over the past week.

	Synovial inflammation n(%)				EC inflammation n(%)				Synovitis only n(%)	EC inflammation only n(%)	Synovitis and EC inflammation n(%)
	GS synovitis (GS≥2)	PD synovitis (PD≥1)	Tenosynovitis	**Synovitis (GS≥1 and PD ≥1)**	Peri-tendinous oedema	Peri-articular inflammation	Subcutaneous oedema	**Any EC inflammation**			
PR non-flare (n=27)	0 (0)	2 (7)	1 (4)	2 (7)	1 (4)	1 (4)	3 (11)	4 (15)	0 (0)	2 (7)	2 (7)
PR flare (n=31)	12 (39)*	7 (23)	7 (23)*	7 (23)	3 (10)	12 (39)*	14 (45)*	19 (61)*	0 (0)	12 (39)*	7 (23)

Table 2: Ultrasound findings during and between flares of palindromic rheumatism

PR,palindromic rheumatism, Ultrasound findings at the clinically flaring site (i.e. hand, foot, shoulder) during flare and non-flare phases. GS, grey-scale; PD, power Doppler; EC, non-synovial extra-capsular. *p<0.05 (PR flare vs non-flare)

		Synovial inflammation n(%)				EC inflammation n(%)				Synovitis only n(%)	EC inflammation only n(%)	Synovitis and EC inflammation n(%)
		GS synovitis (GS≥2)	PD synovitis (PD≥1)	Tenosynovitis	**Synovitis (GS ≥1 and PD ≥1)**	Peri-tendinous oedema	Peri -articular inflammation	Subcutaneous oedema	**Any EC inflammation**			
CCP+ at-risk (n=33)		10 (32)	4 (13)	4 (13)	4 (12)	0 (0)	1 (3)†	1 (3)†	2 (6)†	4 (12)	2 (6)†	0 (0)†
PR flare (n=26)		9 (35)	6 (23)	7 (27)	6 (23)	2 (8)	12 (46)	13 (50)	17 (65)	0 (0)	11 (42)	6 (23)
	Anti-CCP+ (n=19)	7 (37)	4 (21)	3 (16)	4 (21)	2 (11)	8 (42)	9 (47)	12 (63)	0 (0)	8 (42)	4 (21)
	Anti-CCP- (n=7)	2 (29)	2 (29)	4 (57)‡	2 (29)	0 (0)	4 (57)	4 (57)	5 (71)	0 (0)	3 (43)	2 (29)
NORA (n=24)		20 (83)*	17 (71)*	18 (75)*	17 (71)*	4 (17)	2 (8)*	5 (21)*	7 (29)*	11 (46)*	1 (4)*	6 (25)

Table 3: Ultrasound findings according to patient group.

PR,palindromic rheumatism; CCP+ at-risk, anti-cyclic citrullinated peptide antibody positive at-risk individuals; NORA, new-onset rheumatoid arthritis. For comparative purposes only PR flares involving the hands/wrists are included. GS, grey-scale; PD, power Doppler. EC, non-synovial extra-capsular; *$p<0.05$ (PR flare vs NORA), †$p<0.05$ (PR flare vs CCP+ at risk); ‡$p=0.057$ (anti-CCP- vs anti-CCP+)

Discussion

In the early stages of IA, identifying patients with persistent disease from those with a better prognosis can be difficult. While the presence of anti-CCP antibodies in patients with early synovitis is generally associated with poor prognosis (21, 22), many patients with anti-CCP positive PR do not develop persistent IA (5, 6). Indeed 74% of anti-CCP positive PR patients in our cohort did not develop IA during follow up. In clinical practice these patients may be inappropriately treated (e.g. with methotrexate) as they often meet ACR/EULAR criteria for RA (14).

To our knowledge, this is the first study to demonstrate high resolution imaging, especially US, may be used to distinguish PR from NORA at a single assessment. Isolated ECI appears to be specific for PR whereas synovitis and tenosynovitis is more frequently identified in NORA. This is important as PR carries a more favourable prognosis but often takes several assessments to diagnose clinically; we have identified a specific imaging phenotype which may facilitate earlier identification and therefore more appropriate management of these patients.

This is also the first study to use imaging to characterise ECI, synovitis and tenosynovitis in both flare and non-flare phases of PR. The high prevalence of peri-articular soft tissue inflammation and subcutaneous oedema on US during flare may explain clinical peri-arthritis in these patients. Tenosynovitis and peri-tendinous oedema, both identified on US and MRI, could also cause this. The specific US phenotype of ECI without synovitis suggests firstly that intra-articular inflammation may often not be responsible for the clinical features of PR flare and secondly that ECI may be mechanistically important rather than a secondary

effect of an adjacent synovitis. This highlights the value of US in identifying the site of inflammation, particularly as most studies (including ours) have identified PR patients clinically as having recurrent 'joint' swelling. Extra-articular abnormalities have been previously described in PR patients who do not have US synovitis (18). However, contrary to our findings, a relatively high frequency of GS and PD synovitis has previously been reported (9, 10, 18, 23). Differences in patient characteristics may be one explanation. Our patients were comparatively early in their disease course (median 2.5 years) and all but three were DMARD-naïve at the time of imaging. In contrast, patients in the other studies had experienced several years of disease (9, 10, 23) and 45% - 61% were on DMARD therapy at the time of assessment (9, 23). It is possible that the phenotype we have described reflects *de novo* PR and this may change towards an RA phenotype with more prolonged disease duration and/or under the influence of immunomodulation.

The mechanism of ECI in PR is unclear and requires investigation; clinically, there are similarities with autoinflammatory diseases (6, 24) and the role of autoinflammation in PR is an important area for future research.

The low frequency of US abnormalities when patients were not flaring supports the notion that flares of PR are truly relapsing-remitting and are important to distinguish from early IA. This is consistent with previous published data (23).

The use of MRI is a strength of this study. In the majority of cases, MRI findings concurred with US findings as well as identifying additional abnormalities. Also, 2/11 patients had ECI on MRI in the absence of synovitis. The absence of erosions on MRI and identification of BME in only one patient confirms a distinct imaging pattern to early RA. Previous reports of MRI findings in PR flare are limited to a case report (25) and a study of four patients in

whom BME was identified in all cases and synovitis in three (10). Both studies describe a phenotype more akin to RA than we have observed.

Due to the transient and unpredictable nature of flares, it was not possible for the same US examiner to perform all scans. However, all sonographers were trained in the same centre and followed the same US protocol. In addition all US and MRI scans were scored by an expert reader who was blinded to all clinical details. We acknowledge that the reliability of the proposed classification system for ECI should be assessed in future work; our findings should also be validated in other PR cohorts.

In conclusion, we identified a specific imaging phenotype in PR, which may be used to distinguish true PR from persistent IA in patients presenting with early arthritis. These findings may refine diagnosis and improve the management of this important condition.

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Competing Interests

No competing interests declared

Contributorship

KM designed the study, collected and analysed the data and wrote the manuscript. MADA designed the study, scored the ultrasound and MRI images and helped write the manuscript. RJW helped design the ultrasound protocol and performed some of the ultrasound scans. JLN was one of the study clinicians and performed some of the ultrasound scans. WM helped with data analysis. AJG was responsible for MRI protocols. PE designed and led the study. All co-authors read and revised the manuscript.

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Ethics approval

NHS Health Research Authority National Research Ethics Service Committee Yorkshire & the Humber – Leeds West.

Figure legends

Figure 1: Flow chart showing patient visits for the palindromic rheumatism cohort

PR; palindromic rheumatism, RA, rheumatoid arthritis; the cohort was followed according to patient-reported flares. Patients in Group A were not in flare at visit 1 and were in flare at visit 2. Patients in Group B were in flare at visit 1 but not at visit 2. Ultrasound assessments were performed at both visit 1 and visit 2. Ten out of 15 (67%) PR patients who were flaring at the initial visit had US abnormalities. Eleven of these patients subsequently attended a non-flare visit where only 1 (9%) patient had US abnormalities. Of the patients who were not in flare at the initial visit and who subsequently attended for a flare visit, 9/16 (56%) had US abnormalities. MRI assessments were performed during flare where possible. Patients were monitored for the development of persistent arthritis.

Figure 2. Ultrasound findings in flares of palindromic rheumatism.

Representative images of the different types of ultrasound pathology detected at the flaring region are shown in the panels. 1. Peri-articular inflammation shown at a PIPJ in a) longitudinal (LT) and b) transverse (TV). Joint effusion is also present; 2. Peri-tendinous oedema shown at a) a PIPJ in longitudinal (LT) and b) a MCPJ in transverse (TV); 3. Subcutaneous oedema (indicated by }) shown at a MCPJ and midfoot; 4. Flexor tenosynovitis shown in a) longitudinal (LT) and b) transverse (TV). Subcutaneous oedema is also present; 5. Synovitis shown at a) MCPJ and b) wrist intercarpal joint (ICJ).

Figure 3. MRI findings in flares of palindromic rheumatism.

Representative images of the different types of MRI pathology (highlighted by arrows) detected at the flaring region are shown in the panels. 1. Peri-articular inflammation (shown for 4th PIPJ with clinical photograph insert); 2. Peri-tendinous oedema (shown for 3rd extensor tendon at MCPJ level, the patient also has MCPJ synovitis); 3. Synovitis (shown for 2nd and 3rd MCPJs); 4. Tenosynovitis (shown for 2nd flexor tendon).

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