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Palindromic rheumatism: a unique and enigmatic entity with a complex relationship with rheumatoid arthritis

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Abstract

Introduction: Palindromic rheumatism (PR) is a form of relapsing/remitting arthritis that may evolve to chronic rheumatic disease, mainly rheumatoid arthritis (RA). The exact nature of PR is unclear, as it may be considered a disease in itself, an abortive form of RA or just a pre-RA stage.

Areas covered: The authors review the most relevant epidemiological and clinical aspects of PR, especially the pathogenetic role of autoimmunity in PR, with most patients having a characteristic autoantibody profile similar to that observed in RA. The role of autoinflammation is also discussed. A literature review on the rate of RA progression and its prognostic factors was analyzed. Data on the efficacy of drug therapies used to treat PR is presented. PubMed was searched using the terms “palindromic rheumatism” OR “palindromic arthritis”.

Expert opinion: PR is a disease entity with a close but unclear relationship with RA. In PR there is an unmet need, which is to clarify the clinical spectrum and elucidate the risk factors for evolution to RA. The role of autoimmunity and the autoinflammatory component should be investigated. Since most patients evolve to RA, PR may display a unique therapeutic opportunity to avoid this evolution.

Keywords: citrullinated, drugs, palindromic rheumatism, prognostic, relapsing arthritis, rheumatoid arthritis.

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Article highlights

- Palindromic rheumatism (PR) is an entity with a characteristic clinical presentation of relapsing/remitting arthritis and periarthritis

- There are no agreed diagnostic criteria for PR

- PR may evolve to other chronic rheumatic diseases, mainly RA. However not all patients progress to RA in the long term, even those with positive autoantibodies

- Patients with PR exhibit a similar autoantibody profile to RA patients (RF, ACPA, antiCarP) but with some differences in the immune response repertoire.

- Autoinflammatory genes may play a role in PR, especially in patients without autoantibodies, and this is associated with good response to colchicine.

- The rate of progression to RA and the prognostic factors have been partially identified but the results of studies are not homogeneous.

- No clinical trials have been performed so far in PR, and antimalarials are the most used drugs.

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1. Introduction

Palindromic rheumatism (PR) is an intermittent form of arthritis, and may evolve to a rheumatic chronic disease, mainly RA, in a significant proportion of patients. The term "palindromic" derives from the Greek, palin dromein, which means "returning, recurring", and was used in the original description. PR was first observed in 1928 by Philip Hench, who, in 1944, together with Edward Rosenberg, reported 34 patients with a characteristic clinical presentation of multiple, recurrent, and short-lasting painful attacks of inflammation of the joints and adjacent tissues[1]. The clinical presentation of this type of relapsing/remitting entity is, in general, well known by rheumatologists but not by other medical specialties. Since the original description of PR, only 242 entries have been documented in PubMed as of Jan 1, 2021 (Figure 1). The rate of publications on PR has remained stable over time, although there seems to be more interest in recent years (28 manuscripts since 2015) probably due to the increased interest in the early phases of RA and the pre-RA stage. PR is an interesting and enigmatic entity with a close, but not well understood, relationship with RA.

This review documents the most relevant epidemiological and clinical findings in PR and focuses on new immunologic, prognostic and therapeutic insights. The unmet needs in PR are also analyzed. An extensive literature review in PubMed using the terms "palindromic rheumatism" OR "palindromic arthritis" was carried out.

2. Epidemiology

There are few studies on the prevalence of PR, although it is often considered an uncommon entity. The frequency is significantly lower than that of RA, with some reports suggesting a PR/RA ratio of 1/20[2]. In a retrospective cohort of 4900 patients with musculoskeletal symptoms in a single center over a 10-year period, 127 (2.6%) were found to have PR[3]. A recent Canadian epidemiological survey found that the incidence of PR in a cohort of new cases of arthritis seen in a two-year period was surprisingly high: 1 case of PR for every 1.8 cases of RA[4]. In a recent Korean study using a nationwide, population-based medical registry, an incidence of 7 per 100,000 persons/year was reported[5].

PR affects both sexes, although most studies show a predominance of females. The most frequent age of onset is around 40-45 years[3,6–8] and it is uncommon in children[9]. Familial cases have been reported[10,11]. Periodontitis may be a risk factor for PR according to a recent study[12].

Two recent studies found that 16-18 % of patients with established RA have a history compatible with PR[13,14].A recent survey found a prevalence of intermmitent joint episodes in the year before the

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RA diagnosis of 42%, However the clinical characteristics and duration of attacks were not documented being difficult to ascertain if all these patients suffered from a typical PR [15].

3. Clinical presentation.

The clinical presentation is quite distinctive and is characterized by sudden, recurring attacks of pain and swelling affecting the joints and adjacent structures. Attacks are usually monoarticular, and ≥ 2 joints are involved simultaneously in only a few patients. General symptoms and fever are rare. A substantial proportion of patients show characteristic periarticular inflammation and erythema around the joint. Almost all joints may be affected, although the joints of the hands are the most frequently involved (metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIJ), the wrists), as occurs in RA, followed by the knee and shoulder joints[4,16–18]. Spine involvement is almost never seen[19]. Attacks initiate abruptly, and the degree of pain varies but may sometimes be severe and disabling[1]. There is no evidence of any causative event that may trigger acute attacks, although exercise, psychological stress and some foods have been suggested[20]. The PR episodes last from a few hours to 3 days (most commonly 24-48 hours), although a longer duration, rarely more than a week, has been described. The episodes remit spontaneously and patients are symptom free between them[8,19]. The frequency of attacks varies from a few attacks per year to almost daily in some cases[19]. Some patients may present subcutaneous nodules that disappear within a few days, mainly in the hands, together with the joint manifestations[19,21].

Serum biological parameters of inflammation such as ESR or CRP are characteristically normal between episodes although there may be small increases during acute attacks[19]. Synovial fluid analysis shows varying leucocyte counts[19], and histopathological findings in two patients with PR before RA onset showed mild, nonspecific synovitis[22].

4. Autoantibodies in palindromic rheumatism

The characteristic autoantibodies observed in most patients with RA are one of the most interesting findings in PR. RF positivity was documented in the first descriptions of PR and has been confirmed in various studies[23]. In a 1971 study of 35 patients with PR, RF was positive (latex test) in almost all PR patients during the disease evolution[24]. RF is present from the onset in half the patients[4,16]. RF positivity has been associated with more severe attacks and an increased risk for progression to RA[8].

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Our group was the first to identify serum antikeratin antibodies and ACPA (CCP1 test), the most specific serologic test for an RA diagnosis, in most patients with “pure or idiopathic” PR: i.e., not associated with other rheumatic diseases, including RA [25]. A prevalence of ACPA of 56.6% was found, which was similar to the percentage observed in a control group of patients with early RA (52%). The high prevalence of ACPA in patients with PR, ranging from 39% to 68%, has been confirmed in subsequent studies by other groups from different geographic areas using the most common CCP2 test[4,17,18,26–30]. Only two Taiwanese studies showed very different results, with a surprisingly low rate of ACPA and RF in PR[31,32]. This discrepancy may be explained by different diagnostic or inclusion criteria or ethnic reasons. The prevalence of RF, ACPA and the ACPA test in different studies is shown in table 1.

ACPA positivity in PR patients is associated with some phenotypic characteristics, such as a shorter duration of attacks (typically <72hours), a younger age at onset and less knee involvement at disease onset in one study[17]. Other studies confirm the characteristic short duration of joint attacks in ACPA-positive patients[18], together with a high frequency of hand involvement[18,29]. ACPA levels in PR are similar to those observed in RA in several[7,26] but not all studies[18], a finding not observed in diseases other than RA, where ACPA titers in positive patients are substantially lower[33]. Serial ACPA measurements in PR patients show that ACPA positivity and serum levels remained stable over time and that seroconversion from negative to positive is uncommon, suggesting, as in RA, that ACPA are present in the early stages of PR[7]. Like RF, ACPA have been documented as a biomarker for RA progression in PR[26].

Recently, anti-carbamylated (anti-CarP) autoantibodies, another autoantibody against modified postranslational proteins (AMPA), has been described in PR[34]. A Spanish study of 54 patients with PR found anti-CarP in 24%, lower than the 64% observed in patients with RA. In recent years, anti-CarP have been considered a characteristic RA autoantibody with a similar specificity to ACPA but a lower sensitivity and have been associated with more severe disease[35]. A close relationship was observed between anti-CarP and ACPA in PR patients, but no phenotypic differences were found according to anti-CarP status[34]. These findings confirm that autoimmunity plays a crucial role in most patients with PR and there is a close relationship between PR and RA, on the basis that they share a similar autoantibody profile.

Recently, our group further characterized the ACPA immune response in PR and found substantial differences in comparison with RA. In a study of ACPA fine specificities and isotype usage in 54 patients with longstanding PR and 54 patients with established RA, controlled by age, sex, disease duration and ACPA positivity, a more restricted repertoire was found in PR patients, in whom the number of additional citrullinated peptides recognized by ACPA was significantly lower than in RA, while the immune response to citrullinated vimentin was surprisingly low[36]. In addition, a distinct ACPA isotype profile, with significantly less use of IgA and IgM was demonstrated. Similar results were observed in the isotype usage of anti-CarP[34]. In RA, ACPA and anti-CarP are present several years before the onset of clinical arthritis[37,38] and the fine specificities and titers of both autoantibodies progressively increase until RA onset[37,39]. All ACPA isotypes are found in

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preclinical RA[38] but IgG is the main isotype in this phase and appears earlier than IgM and IgA[40]. Therefore, the ACPA repertoire in PR is closer to that observed in the preclinical phase of RA[41] or in unaffected relatives of RA patients than in that found in RA patients[42]. Whether the more restricted immune response explains a less pathogenic role of these autoantibodies in persistent polyarthritis, such as RA, at least in some PR patients, remains speculative but merits further investigations.

5. Genetic factors

The most investigated genes in PR are those of the HLA system, in accordance with the effect of these genetic factors, especially the HLADR-B04* allele, in susceptibility to RA[43]. The first studies, carried out several decades ago, included few patients and showed unclear and inconsistent results. An Italian study found an association with HLA-B16[44]. Early studies of HLA-DRB1 genes found no association with the HLA-DR4 allele[45], an association only in PR patients who progress to RA[46], or an association with this allele but without differences between patients who evolve or not to RA[47]. The most interesting study of HLA genes and PR was published in 2002[48]. The authors analyzed the distribution of HLA-DRB1 alleles and HLADR04 subtypes using polymerase chain reaction (PCR) amplification and sequence analysis in 147 patients with PR and the results were compared with 149 patients with RA and 149 ethnicity-matched controls. A significantly-increased prevalence of the shared epitope (SE) in PR

(65%) compared with the control group (39%) (odds ratio: 2.9), and similar to the RA group (77%), was found. The HLA-DRB1-0401 and 0404 alleles, but not the HLA- DRB1-01 allele, explain the high proportion of the SE in PR. In the regression analysis, only homozygosity for the SE was associated with RA progression (hazard ratio 2.9).The authors concluded that the immunogenetic profile in PR resembles that found in RA[48].

Subsequently, three further genetic studies were performed in PR, all in Asian populations. In 28 Japanese patients with PR no differences in the distribution of HLDRB04 alleles were found compared with a control population, even in patients who progressed to RA, but an association with the PADI4 haplotype was found[28]. A high prevalence of HLA-DRB1-0803 (59.4% vs 12.2% in controls), but not of HLA-DRB04 alleles, was reported in 110 Korean patients with PR[49] .Given the lack of association of this allele with RA, even in a Korean population, the authors concluded that PR and RA may be independent entities. However, the report did not describe the clinical and serological profile of PR patients[49]. A Taiwanese study found a relationship between persistent PR and mutations in the TNF alpha receptor 1: the TNFRSF1A +36 allele and the TNFRSF1A +36 A/G genotype. However this study, as previously mentioned, had a surprisingly low frequency of RF and ACPA[31].

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Thus, there are few genotyping studies in PR, and most were carried out some years ago in a limited number of patients, making it difficult to draw definitive conclusions. However, there seem to be relevant differences according to ethnic origin and differing inclusion criteria. However, at least in Caucasian patients, PR and RA seem to share a similar immunogenetic background.

6. A possible role for autoinflammation in palindromic rheumatism

There is no doubt about the role of systemic autoimmunity in PR, due to the presence of autoantibodies in most patients and the close relationship with RA. However, a possible role of the innate immune system has also been suggested in PR[50]. The characteristic clinical findings in PR resemble an autoinflammatory disorder rather than a systemic autoimmune disease, on the basis of the aborting relapsing/remitting course of the clinical symptoms. These clinical features are commonly observed in patients with microcrystalline arthritis (gout, calcium pyrophosphate deposition disease) and autoinflammatory disorders such as familial Mediterranean fever (FMF)[51].

To further characterize the role of autoinflammatory genes in patients with PR, we investigated mutations in the MEFV gene in 65 PR patients in a Spanish multicenter study[27]. MEFV gene mutations were studied by PCR amplification and sequential analysis. At least one mutated MEFV allele was found in 8 patients (12.3%). Heterozygosity for different missense mutations was found in seven cases, of whom none had founder MEFV mutations. The frequency of MEFV mutations in ACPA-negative PR patients was 22.3% compared with 5.3% in ACPA-positive patients, suggesting that, in some patients with ACPA-negative PR, autoinflammatory genes may be operative without fulfilling traditional criteria for FMF[27]. MEFV gene mutations have also been found in patients with intermittent hydrarthrosis, a well-defined clinical entity that differs from PR but has a characteristic intermittent course[52].

Therefore, in some patients with suspected PR, especially those without autoantibodies, autoinflammatory genes may play a pathogenetic role and should be investigated. We have recently defined in patients tested for MEFV mutations three groups of patients with palindromic-like arthritis according to the presence or absence of MEFV mutations and autoantibodies and with differences in the disease evolution and therapeutic response (manuscript in preparation). Furthermore a four group of patients with MEFV mutations and a diagnosis of seropositive RA who persist with palindromic flares is described. Therefor the role of MEFV mutations and autoinflammatory genes may be relevant in individual patients with a defined chronic rheumatic disease, such as RA, who present acute and abortive attacks during the disease course conforming a mixed autoimmunity and autoinflammatory component [53].

7. Diagnostic criteria and differential diagnosis

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There are no agreed classification criteria for PR, and this is one of the main problems hindering exact interpretations of the clinical data and disease course reported in studies, some of which were carried out several decades ago. In some studies, the inclusion criteria were empirical and based on a clinic presentation of relapsing arthritis/periarthritis of short duration, with patients being totally asymptomatic between flares and with no alternative diagnosis. It is crucial to ascertain that the clinical flares in almost all patients with PR are of very short duration (< 72 hours) and most between 12-48 hours, a finding not observed in other diseases causing intermittent arthritis[1,8]. Autoinflammatory disorders and Whipple´s disease also display this phenotypic pattern, and should be taken into account in the differential diagnosis[23]. In our opinion, when the duration of the flares is commonly > 72 hours, other diseases should be considered. Table 2 shows the diseases that can cause intermittent relapsing arthritis.

Diagnostic or classification criteria have been described by several authors, but without validation studies[2,8,19] They all emphasize that other causes of intermittent or recurrent arthritis must be ruled out and that observation of an episode in a clinical examination is important. However, although synovitis or periarticular inflammation may be seen during flares, it is common to observe only pain without swelling in joints other than those of the hands, and almost always in the shoulder or hip joints. Table 3 shows the Guerne and Weisman criteria, the most used current criteria.

8. Imaging findings.

Patients with PR do not show joint damage (radiographic erosions or joint space narrowing), since persistent arthritis does not develop, even in patients with frequent joint attacks, as described in the original report[1]. In recent years, studies using imaging techniques, such as ultrasonography or MRI, have produced interesting results.

Our group investigated subclinical synovitis using ultrasound in 54 patients with persistent PR in the intercritical period and found significant synovitis in only 7.4% of patients, demonstrating the intermittent (relapsing/remitting) nature of PR, even in ACPA positive patients[17]. Mankia et al[30] found similar results when analyzing ultrasound findings in 31 patients with new-onset PR during the acute attack, and reported that the ultrasound pattern differed from that observed in RA, with predominantly periarticular/extracapsular inflammation rather than intrasynovial inflammation, in accordance with the clinical periarthritis traditionally described. These distinctive ultrasound findings are also observed in individual patients at risk for RA with a clinical presentation other than PR, such as seropositive (ACPA+) arthralgia[54]. The authors emphasized that the inflammatory findings in preRA stages, in patients with and without PR, are predominantly in extra-synovial structures, and patients with intra-synovial inflammation may have a higher risk for RA progression. Prospective

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studies in more patients are required to confirm this interesting hypothesis. Other studies have shown predominantly intraarticular synovitis during flares in PR[17,55]. Differences in the disease duration and treatment may account for these discrepancies[56,57].

The few MRI studies in PR have focused on the flares and included a small number of patients. Bone oedema, a hallmark of RA as a risk factor for joint destruction was found in all four ACPA+ PR patients in one report[55], but only in one out 12 patients analyzed by Mankia et al[30].

9. Disease evolution and progression to RA or other rheumatic disease

One of the most intriguing features of PR is that a significant proportion of patients evolve to chronic rheumatic disease, of which RA is, by far, the most frequent. Although the original report by Hench and Rosenberg did not report this finding, all posterior studies have confirmed progression to RA in many patients[6,16,58]. In fact, in the light of the high rate of progression to RA, Ansell and Bywaters et al. considered PR as a mere prodromic phase of RA, and suggested almost all patients will develop RA if followed long-term[58]

In the 1992 review by Guerne et al[19], which analyzed data from nine studies published between 1944 and 1987, the disease evolution of 653 PR patients was described as follows: persistence as PR (48%), progression to RA (33%), persistent remission (15%) and progression to other rheumatic disease (4%). The spectrum of other rheumatic diseases that some patients with PR may evolve to is quite large and includes: systemic lupus erythematosus (SLE), spondyloarthropathy, Wegener's granulomatosis, Sjögren syndrome, psoriatic arthritis, systemic sclerosis, antiphospholipid syndrome, Behçet disease, polymyalgia rheumatica, Whipple disease and FMF, among others[5,19,23,59]. Two recent studies in Asian populations[5,59] estimated the relative risk of different immune-mediated and inflammatory rheumatic diseases in patients with PR compared with those without, using nationwide cohort registries, and found a higher risk for disease progression not only tor RA but also to SLE, Sjögren syndrome, systemic sclerosis, polymyositis, mixed connective tissue disease and spondyloarthropathies including psoriatic arthritis and Behçet disease. As expected, the highest hazard ratio was for RA. The results of the two studies should be interpreted with caution due to genetic differences and the surprising very low frequency of ACPA and RF in these Asian populations[31][32]. In our opinion, at least in PR patients of Caucasian origin, evolution to an immune mediated disease other than RA is found in a minority of patients, with SLE being the most common.

Several studies have addressed the natural history of PR and the time to progression to chronic arthritis. The latency period between PR onset and the development of RA ranged from weeks to more than 10 years, although the risk has been found to be higher in the first years of symptoms[6,7].In a Scandinavian study with a follow up of more than 20 years, RA progression was rarely seen > 10 years after PR onset, and in one third of patients who evolve to RA, progression occurred in the first 2.5 years[6]. Similar results were observed in our series with a mean follow up of 7.6 years; the mean disease duration in patients who evolved to RA was significantly lower than that

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in patients with persistent PR (17 vs. 65 months)[7]. We also found that in patients with established RA with a history of PR, the median lag time between the onset of PR and the onset of persistent polyarthritis was 1.2 years[14]

years. No differences in the clinical phenotype were observed between RA patients with and without previous PR. Interestingly, PR is not only present at the preRA stage, since palindromic flares commonly persist during the RA course, including patients in clinical remission[14,58]

Not all patients with PR evolve to RA or other rheumatic diseases in the long-term, even those with autoantibodies (RF or ACPA)[7]. The rate of progression varies from 10% to 67 % in different studies. Table 4 shows a detailed analysis in studies carried out since 1999.

Several prognostic factors for RA progression have been investigated in PR. Since the first descriptions of PR, RF has been found to be associated with a higher probability of RA evolution[3,6,7,26,28,29]. The hazard ratio for RA progression in RF-positive patients is 2.9 in the study by Koskinen et al[6]. Other studies have shown no association with RF[29] or a lower association than for ACPA[26]. ACPA were associated with a higher risk of RA progression in new-onset PR after 5.4 years of follow up in the study by Rusell et al., with a likelihood ratio 2.6 greater than that observed for RF (1.7), although the highest ratio was observed for double positivity (4.8)[26]. Other studies have confirmed the higher risk for RA progression in ACPA-positive patients[28,29]. However, we reported that 72.8% of ACPA-positive PR patients do not evolve to RA after a mean follow up of 7.5 years from the first ACPA test (CCP2)[7]. This apparent discordance between our study and that by Russell et al. is probably explained by the timing of the ACPA measurement, which was clearly later in our cohort than in the Canadian study (five and one years, respectively)[60], and which may have resulted in a selection bias to a more stable form of PR in our patients[7,60]. The reported prognostic factors for RA progression in PR are presented in table 4.

In summary, it is established that a significant proportion of PR patients evolve to RA, especially those with RA autoantibodies (RF and or ACPA) and that a minority of patients progress to rheumatic diseases other than RA. The exact rate and prognostic factors for RA evolution have been studied and partially identified, although the results are not homogeneous, due to differences in ethnicity, clinical criteria, follow-up time and drug therapy. However, we have observed in clinical practice that some patients with PR, even those with high titers of RF and ACPA, do not evolve to RA in the long-term, an intriguing feature that merits consideration for future studies. On the other hand, patients with a clinical presentation compatible with PR but without evidence of serum autoantibodies probably reflect different disease entities with a different clinical evolution, in whom other factors, such as autoinflammatory genes, may be relevant.

10. Treatment

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There are no controlled trials in PR, in part due to its relative infrequency. The objective of therapy should be to ameliorate the number and severity of acute attacks and try to avoid progression to RA or, in some cases, to another chronic disease. Although various drugs have been used in PR, all are reported in clinical series or observational studies, limiting the interpretation of their true effectiveness. A comprehensive systematic review of drug therapy in PR has recently published[61].

During acute attacks, patients have been treated symptomatically with non-steroidal anti-inflammatory drugs (NSAIDs). Two studies found that NSAIDs may improve symptoms in two thirds of patients[62,63], but another study found substantial benefits during flares in only a minority of patients[8]. We have observed that NSAIDs have only mild efficacy in a significant proportion of patients not treated immediately after symptom onset. In some instances, we used glucocorticoids with good results, as described elsewhere[64]

There is no consensus between rheumatologists about the best therapeutic strategy in PR. As expected, some drugs used in PR were administered because of the benefits obtained in RA. Most studies focusing on these drugs were reported many years ago, such as those with sulfasalazine, penicillamine or gold salts, the last two no longer used as RA treatment[61]. Older studies in small numbers of patients showed a good response with parenteral gold salts in almost 60% of cases[21,65], especially in RF-positive patients, although a response rate of only 20% was found in another study[45].

Currently, antimalarials, mainly hydroxychloroquine, are the drugs most prescribed in PR by rheumatologists, including the main observational therapeutic studies. In a series of 71 patients treated with chloroquine, most improved, with reductions in the frequency, duration and severity of the crisis, but one in five of patients receiving chloroquine evolved to persistent arthritis[66]. In a subsequent retrospective study by the same group[16], the rate of progression to RA according to the use of antimalarials (mainly chloroquine) was analyzed. Of 113 patients with PR, 62 were treated with antimalarials and compared with an untreated control group: 39% of controls progressed to persistent arthritis compared with 32% of the treated group. Although the differences were not significant, an analysis of the latency period for chronic disease progression favored those treated with antimalarials (mean of 162 months in the treated group vs. 56 months in controls). The authors suggested that treatment with antimalarials slows progression to chronicity rather than preventing RA[16]. In an Egyptian study, almost half the patients with PR achieved clinical remission with hydroxychloroquine after one year of follow up[29]. In an uncontrolled Iranian survey of 92 patients with PR that used a treat-to target-strategy (first hydroxychloroquine, then methotrexate and thereafter other DMARDs), the authors claimed that the attacks were completely or partially controlled in most patients (82%), with a low rate of progression to RA and a drug-free remission of 16% [67]. However this study is retrospective and with a mean follow.up less than 3 years, being difficult to ascertain the exact prevalence of persistent remission in PR with and without treatment in those patients who not evolve to RA.

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In our unit, hydroxychloroquine is the drug of choice for PR. We analyzed the drugs prescribed in 71 patients with PR, and found hydroxychloroquine was used by 73% and with similar proportions in ACPA positive or negative patients[7] We observed a similar percentage of evolution to RA in patients treated with hydroxychloroquine and those that were not in the follow-up (70% vs 78.5%). However, this was an observational study not performed to ascertain the role of antimalarials in avoiding progression to RA and confusing by indication may explain these results. We also commonly use hydroxychloroquine in patients with established RA who continue to have palindromic crises over the disease course, even when the persistent arthritis remains in clinical remission[14] Curiously, there are no consistent published studies on the use of methotrexate or leflunomide in PR[61]

No studies on biologic therapies have been carried out in PR, except for an Indian study with rituximab, a monoclonal antibody against the CD20 molecule expressed in B cells[68]. In this observational study in 33 patients with PR resistant to DMARDs, a rapid and dramatic response of clinical symptoms to rituximab was achieved by all patients after the first drug infusion. Up to half the patients relapsed after the first infusion and required a second treatment with good results. None progressed to RA after a mean follow up of two years[68]. There are no case reports of TNF inhibitor therapies in PR, although three patients with refractory PR in our series were treated with these biologic drugs, with significant improvements (personal observation).

Colchicine was tested in a small older study of patients with PR with good results[69], although no efficacy was found in another study[63]. We have used colchicine in patients with intermittent arthritis resembling PR with MEFV mutations, with significant, rapid clinical improvements[27]. Colchicine might play a role in some patients with PR without autoantibodies in whom an autoinflammatory component is suspected.

To sum up, all studies of drug therapy in PR are observational, the inclusion criteria were not well defined, most are older and almost all include a small number of patients. To date, antimalarials are the most studied drugs and their effectiveness in controlling acute attacks seems proven in a significant proportion of patients, although doubts remain about whether they avoid progression to RA. Biological therapies may provide benefit in PR patients and the impressive effect of rituximab in a recent observational study should be confirmed in new studies with different geographic origins. In patients with an autoinflammatory component, a trial of IL-1 blockers probably merits consideration. However, only randomized clinical trials can answer all these relevant questions. In this sense, an ongoing randomized open clinical trial in recent-onset seropositive PR patients is comparing the efficacy of hydroxychloroquine and abatacept, a fusion protein that inhibits T cell activation, is indicated in RA, and has relevant effects in the immune response to citrullinated antigens (PALABA trial- ClinicalTrials.gov Id: NCT03669367).

11. Conclusion

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PR is a well-defined entity with a characteristic clinical phenotype, but its pathogenesis is poorly understood and the relationship with RA is unclear. The similarities and differences between PR and RA are intriguing. Most, but not all, patients evolve to RA in the long-term and some prognostic factors for RA progression have been identified. Apart from the recognized association with RF, a close association with ACPA and anti-CarP has been documented in PR in recent years, confirming that autoimmunity plays a substantial role and reinforcing the close relationship with RA. However, significant differences have been observed in the immune response to these posttranslational modified proteins between the two diseases. Autoinflammation may be relevant in some cases of PR. The current management of PR is empirical and there is an unmet need for therapeutic strategies aimed at preventing the evolution to persistent, destructive arthritis. Randomized clinical trials in homogeneous populations of PR patients, including the serological status, are warranted.

12. Expert opinion

PR, a clinical entity well-known by rheumatologists, is probably more a syndrome than a disease, and there are doubts about its exact prevalence, rate of progression to RA or other rheumatic diseases, and management. This is in part because the case definition of PR is not homogeneous between studies, due to the lack of validated diagnostic criteria. Most studies have included small numbers of patients and were carried out several decades ago, limiting data interpretation. The inclusion criteria used in some recent studies, with different ethnic origins, may be substantially different. There is an urgent need to validate classification criteria to improve the homogeneity of the patients in order to achieve better and more explainable results in genetics, pathophysiological and clinical studies.

PR is a unique and enigmatic entity which probably forms part of the clinical spectrum of RA, since progression to RA is seen in most patients during the follow up. The autoantibody profile, which is similar to that of RA, is also a strong argument favoring this concept. However, not all PR patients, even those with autoantibodies, evolve to RA and significant differences in the autoantibody immune response repertoire have been shown. Clinical and imaging findings suggest a more relevant role of periarticular inflammation than intrasynovial synovitis, as occurs in RA. These findings emphasize the complex relationship between PR and RA. In addition, some patients evolve to another rheumatic disease .Furthermore the role of autoinflammation may be relevant, especially in autoantibody-negative patients. Testing for autoinflammatory genes (MEFV mutations) or a therapeutic trial of colchicine in these patients even in those who evolved to RA but in whom palindromic attacks persist may be of interest. At the same time, a search for other autoinflammatory gene variants responsible for typical flares in patients without MEFV variants but with a good response to colchicine is needed to uncover the extent of autoinflammation-related PR.

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A limitation in the study of PR is the characteristic very-short duration of episode which make the collection of biological samples, and imaging and clinical data during the flare difficult. This limitation is relevant in the search for prognostic biomarkers of progress to RA.

Modern genetic studies and better characterization of the immune response profile are crucial to better understanding of PR. Large observational studies in homogeneous PR populations with a long-term follow up may provide the most reliable information about the frequency of progression to RA and its prognostic factors. In-depth genetic analysis of the HLA-DRB region and single-cell analysis of the B-cell autoantibody profile could increase our knowledge of the differences in the B-cell repertoire and its relevance to the transition from PR to RA.

The management and therapeutic strategies in PR patients are empirical at present. There is an unmet need in the treatment of PR patients, who should be considered a risk population for RA, and the therapeutic strategy should influence this outcome. Thus, preventive strategies should be pursued in all patients until the diagnosis of PR is confirmed. Effective treatment in this phase may avoid progression to chronic arthritis. Antimalarials are the most used drugs and observational studies confirm their effectiveness in clinical symptoms, but their role in preventing progression to RA is unclear. There is little data on biologic therapy in PR, but preliminary findings are encouraging. Randomized clinical trials in the early phases of PR are warranted.

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Declaration of interest

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Papers of special note have been highlighted as:

* of interest

** of considerable interest

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Reference annotations:

1.* *Original description of palindromic rheumatism. Detailed analysis of the first 34 cases reported. The authors proposed the term palindromic rheumatism for this entity.

6. **The longest-term follow-up (more than 20 years) described so far in PR, demonstrating that two thirds of patients evolved to RA.

7.* Observational survey in patients with palindromic rheumatism showing that a significant proportion of patients, even those with autoantibodies, do not progress to rheumatoid arthritis in the long-term.

16.* Observational study in patients with palindromic showing the clinical efficacy of antimalarials in clinical symptoms and in delaying rather than avoiding RA progression.

19.** A review of different aspects of palindromic rheumatism with a literature review of the disease course of nine series of patients between 1944-1987. Diagnostic criteria for palindromic rheumatism are proposed.

25.* First evidence that serum antibodies against citrullinated peptides (ACPA) are present in most patients with palindromic rheumatism.

27.* Spanish multicenter study in patients with palindromic rheumatism, demonstrating an unexpectedly high presence of MEFV mutations, especially in autoantibody-negative patients.

30.* Imaging studies (ultrasound and MRI) in the acute phase of PR showing preeminent extracapsular inflammatory findings that differ from the intrasynovial inflammation characteristic of rheumatoid arthritis.

36.* Characterization of the immune response to citrullinated antigens in palindromic rheumatism, showing a more restricted antibody response than in rheumatoid arthritis.

48*. HLA study in patients with palindromic rheumatism showing a similar frequency of the shared epitope as in RA.

50. **Interesting review about the relationship between palindromic rheumatism and rheumatoid arthritis, with its similarities and differences.

61.** Comprehensive systematic review of the different drugs used to treat palindromic rheumatism until now.

66* Editorial commentary on the pros and cons of palindromic rheumatism as a pre-RA stage.

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Tables and figures

Table 1: Prevalence of rheumatoid factor and ACPA in palindromic rheumatism

Author (year)	Country	Number cases	Mean symptom duration months	RF+ %	ACPA+ %	ACPA test
Salvador et al. (2003)[25]	Spain	32	90	42	56	CCP1
Russell et al. (2006)[26]	Canada	61	<12	51	55	CCP1
Lu L-Y et al. (2007)	Taiwan	56	171	1,8	3,6	CCP
Cañete JD et al. (2007)[27]	Spain	65	101	35	59	CCP2
Powell et al. (2008)[4]	Canada	51	42	53	49	CCP2
Chen HH et al. (2009)[32]	Taiwan	84		13	14	CCP
Tamai et al. (2010)[28]	Japan	28	63	82	46	CCP2
Khabazzi et al. (2012)[18]	Iran	69	47	46	42	CCP
Emad et al. (2014)[29]	Egypt	90	15	33	39	CCP2
Cabrera-Villalba et al.[17] (2014)	Spain	54	139	57	67	CCP2
Mankia et al. (2018)[30]	UK	31	19 to 30	48	68	CCP2

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Table 2: Differential diagnosis with diseases that can cause intermittent arthritis/periarthritis

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Crystal arthropathies (gout, calcium pyrophosphate deposition disease, hydroxyapatite arthritis)
Reactive arthritis
Arthritis associated with inflammatory bowel disease (Crohn's disease, ulcerative colitis)
Celiac disease
Palindromic rheumatism
Behcet's disease
Sarcoidosis
Relapsing polychondritis
Whipple's disease
Systemic autoinflammatory disorders
i. Familial Mediterranean fever
ii. TRAPS syndrome
iii. Hyper IgD syndrome
IV. CAPS syndrome
Familial Hyperlipoproteinemia
Intermittent hydrarthrosis
Hereditary angioedema
Lyme arthritis

Modified with permission from Sanmarti et al[23].

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Table 3: Guerne and Weissmann classification criteria for palindromic rheumatism[19]

1) 6-month history of brief, sudden-onset, recurrent episodes of monoarthritis or, rarely, polyarthritis, or of soft tissue inflammation.
2) Direct observation of one attack by a physician.
3) Three or more joints involved in different attacks
4) Absence of erosions on radiographs.
5) Exclusion of other arthritides

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Table 4: Rate of progression and prognostic factors for RA progression in recent series with PR

Author (ref)	year	Country	Number patients	Mean Symptom duration (months)	Mean follow-up (months)	Females (%)	Mean age	RF/ACPA (%)	RA progression (%)	Prognostic factors for RA	Criteria	Comments
Gonzalez-Lopez et al[3]	1999	Canada	127	72	40	65	40	40/NR	28	RF, PIP joints and wrist involvement, female, age of onset	own	8-fold increase for RA if female plus RF ACPA not available at this time
Salvador et al[25]	2003	Spain	33	90	35.1	78.8	42.6	42/56	10	NR	Guerne et al	Patients who evolved to RA or other diseases before serum measurement were excluded (n=30)

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Russell et al[26]	2006	Canada	61	NR	64.8	NR	NR	50/54	47.5	ACPA LR: 2,6 RF LR 1,7 ACPA+RF: LR 4,8	ownl	Three patients evolved to (one each to Behçet disease, psoriatic arthritis and SLE)
Koskinen et al[6]	2009	Finland	60	NR	>240	55-60%	49	50-77/NR	66.6	RF-positive was 77% in those evolving to RA and 50% in those who did not	own	The largest follow-up series
Tamai et al[28]	2010	Japan	28	63	38	71.4	47	82.1/46.4	39.2	ACPA, PIP involvement	Guerne et al	RF and shared epitope not associated with RA progression
Sanmarti et al[7]	2012	Spain	71	54	90	76.1	52	56.3/52.1	22.5	RF, symptom duration	Guerne et al	Most ACPA+ patients do not evolve to RA

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Emad et al[29]	2014	Egypt	90	14,8	12	55.6	39.1	33/38.5	27.5	ACPA, hand involvement	own	PPV for RA progression higher for ACPA than RF (73.4 vs 48%)

RF: rheumatoid factor; ACPA: antibodies against citrullinated peptides; PIP: proximal interphalangeal; NR: not reported.

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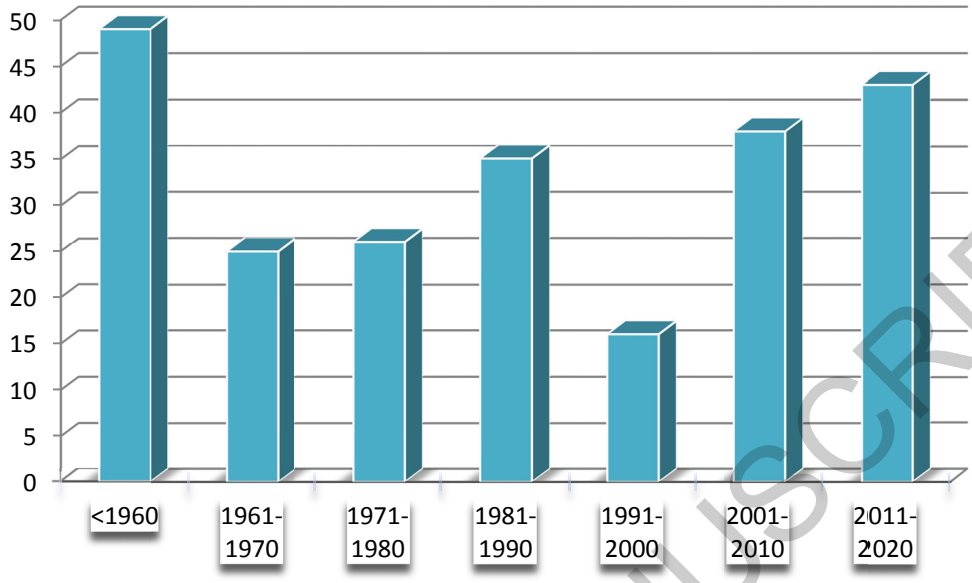
Figure 1: PubMed entries for palindromic rheumatism from the original report by decade from 1944 to 2020.



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