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<th>The clinical course of polymyalgia rheumatica in Chinese</th>
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<td>Li, WL; Lo, Y; Leung, MH; Wong, WS; Mok, MY</td>
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Polymyalgia rheumatica (PMR) is diagnosed based on clinical features that may overlap with other rheumatic conditions like rheumatoid arthritis (RA). Furthermore, a proportion of PMR patients may subsequently evolve into RA. The aim of this study was to examine the clinical characteristics of PMR patients in a Chinese cohort compared to a Caucasian series. Patients diagnosed to have PMR during 1997–2008 were reviewed for clinical features and compared to a reported Caucasian series. Rheumatoid factor (RF) and anticyclic citrullinated peptide (CCP) antibodies were determined by immunonephelometry and enzyme-linked immunosorbent assay, respectively. Forty-four patients of southern Chinese origin were diagnosed to have PMR according to specialist opinion. Seventy-five percent of patients (n = 33) were >65 years of age at diagnosis (mean ± standard deviation, 75.8 ± 9.6 years). The commonest feature at disease onset was elevated erythrocyte sedimentation rate >40 mm/h (100% vs. 95.7%; p = 0.17) and bilateral shoulder pain or stiffness (95.5% vs. 90.8%; p = 0.31), comparable in frequency to the Caucasian cohort. However, Chinese patients had significantly longer duration of symptoms before diagnosis (p < 0.001) but less bilateral upper arm tenderness (p < 0.001) and generalized stiffness (p = 0.01). Twelve (27.3%) patients evolved into RA after a median duration of 2 months from onset of PMR. RF and anti-CCP antibodies were positive in 66.7% and 60% of these patients compared to 9.4% and 6.2%, respectively, among those who did not evolve into RA during the period observed. Chinese patients with PMR have modestly different clinical profile compared to the Caucasian counterpart. RF and anti-CCP antibodies were more likely to be present in those who subsequently developed into RA.

Keywords

- Anticyclic citrullinated peptide antibodies
- Polymyalgia rheumatica
- Rheumatoid arthritis
The clinical course of polymyalgia rheumatica in Chinese

Wai Ling Li · Yi Lo · Moon Ho Leung · Woon Sing Wong · Mo Yin Mok

Abstract Polymyalgia rheumatica (PMR) is diagnosed based on clinical features that may overlap with other rheumatic conditions like rheumatoid arthritis (RA). Furthermore, a proportion of PMR patients may subsequently evolve into RA. The aim of this study was to examine the clinical characteristics of PMR patients in a Chinese cohort compared to a Caucasian series. Patients diagnosed to have PMR during 1997–2008 were reviewed for clinical features and compared to a reported Caucasian series. Rheumatoid factor (RF) and anticyclic citrullinated peptide (CCP) antibodies were determined by immunonephelometry and enzyme-linked immunosorbent assay, respectively. Forty-four patients of southern Chinese origin were diagnosed to have PMR according to specialist opinion. Seventy-five percent of patients (n=33) were >65 years of age at diagnosis (mean±standard deviation, 75.8±9.6 years). The commonest feature at disease onset was elevated erythrocyte sedimentation rate >40 mm/h (100% vs. 95.7%; p=0.17) and bilateral shoulder pain or stiffness (95.5% vs. 90.8%; p=0.31), comparable in frequency to the Caucasian cohort. However, Chinese patients had significantly longer duration of symptoms before diagnosis (p<0.001) but less bilateral upper arm tenderness (p<0.001) and generalized stiffness (p=0.01). Twelve (27.3%) patients evolved into RA after a median duration of 2 months from onset of PMR. RF and anti-CCP antibodies were positive in 66.7% and 60% of these patients compared to 9.4% and 6.2%, respectively, among those who did not evolve into RA during the period observed. Chinese patients with PMR have modestly different clinical profile compared to the Caucasian counterpart. RF and anti-CCP antibodies were more likely to be present in those who subsequently developed into RA.

Keywords Anticyclic citrullinated peptide antibodies · Polymyalgia rheumatica · Rheumatoid arthritis

Introduction Polymyalgia rheumatica (PMR) is an inflammatory condition of unknown etiology commonly found in the elderly and is often associated with impaired quality of life of these patients [1]. The diagnosis of PMR is mainly based on clinical features such as aches and stiffness in the cervical region, shoulder, and pelvic girdles. There is yet no specific serological marker for this condition. A recent prospective study suggested that PMR is a heterogeneous condition with variable responsiveness to corticosteroid treatment [1]. There is still inconsistency with regard to the guideline on diagnosis, management, and disease response measures in this condition [2]. A number of diagnostic criteria have been proposed to classify PMR [3–5], and the criteria proposed by Bird et al. [3] have been more widely used because of their higher sensitivity [6]. The diagnosis of PMR is regarded as definite if the patient fulfills three or more of the criteria including age >65 years, time from onset of symptoms to full-blown disease of less than 2 weeks, bilateral shoulder pain or stiffness, bilateral upper arm tenderness, stiffness >1 h, depression and/or weight loss, and erythrocyte
sedimentation rate (ESR) >40 mm/h at onset. Together with a positive response to corticosteroid therapy, the sensitivity of this diagnostic criteria has been reported to be as high as 99.5% [6].

However, a number of rheumatic conditions including late onset rheumatoid arthritis (RA) [7], calcium pyrophosphate deposition disease, inflammatory myositis [8], and fibromyalgia [9] may mimic PMR as they show similar clinical features but carry different prognosis. Seventy-three percent of a large cohort of 100 PMR patients have been reported to develop cranial symptoms related to ischemic events of giant cell arteries after a median of 3 weeks and among these 16.4% of patients resulted in permanent visual loss [10]. Furthermore, 6–17% of PMR patients have been found to evolve into RA subsequently [7]. Anticyclic citrullinated peptide (CCP) antibodies that have recently been found to be a specific marker for RA [11] have been suggested to be clinically useful in the prediction of PMR patients who subsequently develop into RA [12, 13]. Our study aimed to compare the clinical characteristics of a Chinese cohort of PMR patients to a Caucasian series and to examine the frequency of anti-CCP antibodies in patients with and without subsequent evolution into RA.

### Methodology

This study has been approved by the ethics committee of the local institutional review board. All patients diagnosed to have PMR by trained rheumatologists at a university affiliated hospital and a large regional public hospital in Hong Kong during 1997–2008 were identified through the clinical data analysis and reporting system (International Classification of Diseases (ICD), i.e., ICD 9 Code 725), and their medical records were retrieved for analysis. Demographic data, clinical features, treatment regimen and response as well as laboratory investigations including ESR, rheumatoid factor (RF) and anti-CCP antibodies at disease onset were recorded. The clinical characteristics of these patients were compared with Caucasian series reported according to the criteria of Bird et al. [3].

**Measurement of RF and anti-CCP antibodies**

RF was performed by latex-enhanced immunonephelometry (BN ProSpec, Dade Behring, Germany) and was considered positive at ≥15 IU/ml. Anti-CCP antibodies were measured by a second-generation anti-CCP enzyme-linked immunosorbent assay (Inova Diagnostic Inc., San Diego, CA, USA) according to the manufacturer’s instructions. The cutoff value for positive reaction was set at 20 arbitrary units (AU) as suggested by the manufacturer. The intra-assay variation of the assay was 3.5% with a high-level serum (175 AU) and 6% with a “low-level serum” (21 AU), and interassay variation was 6% for both sera. For patients who presented before the anti-CCP antibody assay was introduced into the hospital serology laboratory in early 2005, the earliest available serum samples after onset of presentation were retrieved and tested.

### Statistical analysis

Statistical analysis was performed by SPSS 16.0 software (Chicago, IL, USA). Data were presented as mean± standard deviation (SD) unless otherwise stated. Chi-square test or Fisher’s exact test was performed for categorial variables. Mann–Whitney U test was used for comparison on continuous data between groups. Kaplan–Meier survival curve and log-rank test were used to compare the frequency of RF and anti-CCP antibody among patients who had and had not evolved into RA subsequently.

### Results

#### Presenting features of PMR

Forty-four (31 females and 13 males) patients of southern Chinese origin were identified from these two large regional hospitals during 1997–2008. The mean±SD age of these patients was 75.8±9.6 years with a mean duration of follow-up of 4.9±2.9 years. Table 1 shows a summary of the clinical features of these patients compared to those reported in a Caucasian series [6]. There was similar proportion of Chinese patients (75.0%) aged over 65 years among patients who had and had not evolved into RA subsequently.

### Table 1 Presenting features of PMR among the Chinese cohort compared with a Caucasian series diagnosed according to the criteria of Bird et al

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Chinese cohort series*</th>
<th>Caucasian series</th>
<th>p value</th>
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<tr>
<td>Age &gt;65</td>
<td>33/44 (75.0)</td>
<td>171/213 (80.2)</td>
<td>0.40</td>
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<td>Onset of illness &lt;2 weeks*</td>
<td>13/44 (29.5)</td>
<td>148/196 (75.5)</td>
<td>&lt;0.001</td>
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<td>Bilateral shoulder pain/stiffness</td>
<td>42/44 (95.5)</td>
<td>178/196 (90.8)</td>
<td>0.31</td>
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<td>Bilateral upper arm tenderness</td>
<td>5/44 (11.4)</td>
<td>147/195 (75.5)</td>
<td>&lt;0.001</td>
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<td>Stiffness &gt;1 h</td>
<td>30/44 (68.2)</td>
<td>147/173 (84.9)</td>
<td>0.01</td>
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<tr>
<td>Weight loss/depression</td>
<td>13/44 (29.5)</td>
<td>85/213 (40.0)</td>
<td>0.20</td>
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<td>Initial ESR &gt;40 mm/h</td>
<td>444/44 (100)</td>
<td>158/165 (95.7)</td>
<td>0.17</td>
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*Refers to time taken for symptoms to reach their full-blown picture
as the Caucasian counterpart (80.2%; \( p=0.40 \)). Bilateral shoulder pain/stiffness was the commonest symptom for both cohorts (95.5% in Chinese and 90.8% in Caucasian, \( p=0.31 \)). However, Chinese patients had significantly longer period before diagnosis (\( p<0.001 \)), lesser bilateral upper arm tenderness (\( p<0.001 \)), and generalized stiffness (\( p=0.01 \)) compared to the Caucasian counterpart. All our patients had ESR >40 mm/h at disease onset compared to 95.7% of the Western cohort (\( p=0.17 \)), 25 (56.8%) among whom had ESR level above 100 mm/h.

Response to treatment

Two patients (4.4%) responded to nonsteroidal anti-inflammatory drugs (NSAIDs) alone. Most patients (39 of 44, 88.6%) were treated with prednisolone (mean daily dose of 17.2±10.2 mg). There was a rapid response with drop of ESR level by 50% or over from baseline within 2 to 3 months after treatment.

Evolvement into RA

Twelve (27.3%) PMR patients in our cohort subsequently fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA [14] after a median duration of 2 months (range 1–24 months) from diagnosis of PMR. The commonest ACR features fulfilled by these patients included arthritis of three or more joint areas (100%) and symmetrical arthritis (100%), followed by stiffness (83.3%). Arthritis of hand joints and RF was present in 75% and 66.7% at the time of diagnosis of RA.

Predictive role of RF and anti-CCP antibodies in PMR patients who evolved into RA

RF was checked in all patients and anti-CCP antibodies in 21 patients. Among the 12 patients who had evolved into RA, 66.7% were RF positive and 60% were anti-CCP positive. RF and anti-CCP antibodies were present in only 9.4% and 6.2% for those who had not evolved into RA (\( n=32 \)) for the period observed (Table 2). The positive and negative predictive values for RF in the development of RA were 72.7% and 87.9%, respectively, while those for anti-CCP antibodies were 75.0% and 88.2%, respectively.

Figure 1 shows the Kaplan–Meier survival curve with evolvement into RA among PMR patients who were seropositive for RF (Fig. 1a) or anti-CCP antibodies (Fig. 1b) compared to those who were not. Patients who had positive serum RF (\( p<0.01 \)) and anti-CCP antibodies (\( p=0.02 \)) were more likely to develop RA during the period of observation.

Discussion

Our study showed that Chinese patients with PMR presented with similar features as the Caucasian counterpart including age at onset, bilateral shoulder pain or stiffness, constitutional symptoms, and ESR >40 mm/h. However, our patients were found to complain less of bilateral upper arm tenderness and generalized stiffness. Our patients also had longer duration of symptoms before seeking medical help. This may be due to the lack of awareness of an underlying rheumatic disease as nonspecific musculoskeletal rheumatism are frequent complaints in the elderly or that Chinese patients may demonstrate a different health care seeking behavior. Indeed, cultural and social influences have been demonstrated to affect the experience and adjustment to pain among subjects of different racial or ethnic groups [15].

Our study showed that 27.3% of Chinese patients with initial diagnosis of PMR subsequently evolved into RA after a median of 2 months (range 1–24 months) since disease onset. This frequency was higher than the Western cohort where 6–17% of patients have been reported to develop into RA after a period of 3 to 5 years [12]. This may be related to the small sample size of our study and may also be explained by the more subjective items in the criteria of Bird et al. that lead to variations in different populations. Furthermore, PMR patients who had milder symptoms and those who readily respond to NSAIDs alone may have been managed at the primary care instead of being referred to our tertiary care units. It is also possible that we have included more patients with late onset RA into our cohort as PMR and elderly onset RA can be difficult to discriminate. A proportion of patients with late onset RA have

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<th>The frequency of RF and anti-CCP antibodies among PMR patients who had evolved into RA and those who had not</th>
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<td><strong>RF</strong></td>
<td><strong>Anti-CCP antibodies</strong></td>
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<td>Negative</td>
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<td>PMR with evolvement into RA</td>
<td>8/12 (66.7)</td>
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<td>PMR without evolvement into RA</td>
<td>3/32 (9.4)</td>
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\*Test performed by second-generation anti-CCP antibody assay
older than 65 years of age have been reported to have positive RF [12]. On the other hand, anti-CCP antibodies were not present in 93.8% of patients who had not evolved into RA during the time of observation suggesting a high specificity and a role to predict development of RA. In this study, only a marginally better sensitivity and positive predictive value of anti-CCP antibodies was demonstrated compared to RF which is probably related to the small sample size of our study. Anti-CCP antibodies have recently been found to be a specific serological marker for RA. The second-generation anti-CCP antibodies assay has comparable sensitivity as serum RF (80%) while demonstrating almost absolute specificity for the diagnosis of RA [17]. The production of anti-CCP antibodies has been found to be an early process in RA development, and their presence is predictive of the development of the disease [10].

Our result complemented the conclusions from a previous study which showed that anti-CCP antibodies were useful in the differential diagnosis of elderly onset RA and PMR [13]. In that study, 65% elderly onset RA patients showed increased serum titer for anti-CCP antibodies compared to none of the healthy subjects and PMR patients. Thus, anti-CCP antibodies may be a clinically useful marker to be tested at the onset of patients with PMR such that these patients can be followed up for the development of RA which requires different treatment modalities and carries different prognosis.

The average annual age- and sex-adjusted incidence of PMR aged 50 and older has been quoted as 54.8 per 100,000 population in the USA [18]. There has not been any large scale epidemiological study in the Chinese population. However, in the small number of patients we were able to retrieve from the clinical data analysis and reporting system involving databases in two large public hospitals over an 11-year-period, PMR does not appear to be a common condition in our locality. It remains possible that we are under diagnosing the condition given the lack of awareness at the levels of both patients and doctors and the absence of biomarker to aid clinical diagnosis. Education on the public, carers, and health care professionals is needed to raise awareness of this condition and the associated giant cell arteritis among different rheumatic problems encountered in the elderly so that they can be brought to medical attention earlier in their disease course. In conclusion, our study demonstrated that the spectrum of clinical features of PMR in Chinese patients is similar to that of the Caucasian counterpart. Larger prospective studies are warranted to delineate the role of clinical usefulness of anti-CCP antibodies in the early diagnosis and differentiation of PMR and RA.

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Disclosures None.
References


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