Dear Author

Here are the proofs of your article.

• You can submit your corrections online or by fax.
• For online submission please insert your corrections in the online correction form. Always indicate the line number to which the correction refers.
• Please return your proof together with the permission to publish confirmation.
• For fax submission, please ensure that your corrections are clearly legible. Use a fine black pen and write the correction in the margin, not too close to the edge of the page.
• Remember to note the journal title, article number, and your name when sending your response via e-mail, fax or regular mail.
• Check the metadata sheet to make sure that the header information, especially author names and the corresponding affiliations are correctly shown.
• Check the questions that may have arisen during copy editing and insert your answers/corrections.
• Check that the text is complete and that all figures, tables and their legends are included. Also check the accuracy of special characters, equations, and electronic supplementary material if applicable. If necessary refer to the Edited manuscript.
• The publication of inaccurate data such as dosages and units can have serious consequences. Please take particular care that all such details are correct.
• Please do not make changes that involve only matters of style. We have generally introduced forms that follow the journal’s style. Substantial changes in content, e.g., new results, corrected values, title and authorship are not allowed without the approval of the responsible editor. In such a case, please contact the Editorial Office and return his/her consent together with the proof.
• If we do not receive your corrections within 48 hours, we will send you a reminder.

Please note

Your article will be published Online First approximately one week after receipt of your corrected proofs. This is the official first publication citable with the DOI. Further changes are, therefore, not possible.

After online publication, subscribers (personal/institutional) to this journal will have access to the complete article via the DOI using the URL:

http://dx.doi.org/10.1007/s10067-009-1315-8

If you would like to know when your article has been published online, take advantage of our free alert service. For registration and further information, go to:


Due to the electronic nature of the procedure, the manuscript and the original figures will only be returned to you on special request. When you return your corrections, please inform us, if you would like to have these documents returned.

The printed version will follow in a forthcoming issue.
To: Springer Customer Support 2  
E-mail: CorrAdmin2@spi-bpo.com  
Fax: +1-703-5621873  
SPI  
Re: SPI Building, Sacsac Bacong  
Oriental Negros 6216  
Philippines  
Clinical Rheumatology DOI 10.1007/s10067-009-1315-8  
The clinical course of polymyalgia rheumatica in Chinese  
Li · Lo · Leung · Wong · Mok

Permission to publish
I have checked the proofs of my article and

☐ I have no corrections. The article is ready to be published without changes.
☐ I have a few corrections. I am enclosing the following pages:
☐ I have made many corrections. Enclosed is the complete article.

Date / signature: ____________________________
## Metadata of the article that will be visualized in Online

Please note: Image will appear in color online but will be printed in black and white.

<table>
<thead>
<tr>
<th></th>
<th>Article Title</th>
<th>The clinical course of polymyalgia rheumatica in Chinese</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Article Copyright - Year</td>
<td>Clinical Rheumatology 2009&lt;br&gt;(This will be the copyright line in the final PDF)</td>
</tr>
<tr>
<td>4</td>
<td>Journal Name</td>
<td>Clinical Rheumatology</td>
</tr>
<tr>
<td>5</td>
<td>Corresponding Author</td>
<td>Mok</td>
</tr>
<tr>
<td>6</td>
<td>Family Name</td>
<td>Mok</td>
</tr>
<tr>
<td>7</td>
<td>Given Name</td>
<td>Mo Yin</td>
</tr>
<tr>
<td>8</td>
<td>Suffix</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Organization</td>
<td>The University of Hong Kong</td>
</tr>
<tr>
<td>10</td>
<td>Division</td>
<td>Department of Medicine, Queen Mary Hospital</td>
</tr>
<tr>
<td>11</td>
<td>Address</td>
<td>Pok Fu Lam, Hong Kong, China</td>
</tr>
<tr>
<td>12</td>
<td>e-mail</td>
<td><a href="mailto:temy@hkucc.hku.hk">temy@hkucc.hku.hk</a></td>
</tr>
<tr>
<td>13</td>
<td>Author</td>
<td>Li</td>
</tr>
<tr>
<td>14</td>
<td>Family Name</td>
<td>Li</td>
</tr>
<tr>
<td>15</td>
<td>Given Name</td>
<td>Wai Ling</td>
</tr>
<tr>
<td>16</td>
<td>Suffix</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Organization</td>
<td>The University of Hong Kong</td>
</tr>
<tr>
<td>18</td>
<td>Division</td>
<td>Department of Medicine, Queen Mary Hospital</td>
</tr>
<tr>
<td>19</td>
<td>Address</td>
<td>Pok Fu Lam, Hong Kong, China</td>
</tr>
<tr>
<td>20</td>
<td>e-mail</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Author</td>
<td>Lo</td>
</tr>
<tr>
<td>22</td>
<td>Family Name</td>
<td>Lo</td>
</tr>
<tr>
<td>23</td>
<td>Given Name</td>
<td>Yi</td>
</tr>
<tr>
<td>24</td>
<td>Suffix</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Organization</td>
<td>The University of Hong Kong</td>
</tr>
<tr>
<td>26</td>
<td>Division</td>
<td>Department of Medicine, Queen Mary Hospital</td>
</tr>
<tr>
<td>27</td>
<td>Address</td>
<td>Pok Fu Lam, Hong Kong, China</td>
</tr>
<tr>
<td>28</td>
<td>e-mail</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Author</td>
<td>Leung</td>
</tr>
<tr>
<td>30</td>
<td>Family Name</td>
<td>Leung</td>
</tr>
<tr>
<td>31</td>
<td>Given Name</td>
<td>Moon Ho</td>
</tr>
<tr>
<td>32</td>
<td>Suffix</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Organization</td>
<td>Queen Elizabeth Hospital</td>
</tr>
<tr>
<td>34</td>
<td>Division</td>
<td>Department of Medicine</td>
</tr>
</tbody>
</table>
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

Received: 30 April 2009 / Revised: 12 October 2009 / Accepted: 27 October 2009

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

W. L. Li · Y. Lo · W. S. Wong · M. Y. Mok (✉)
Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Pok Fu Lam, Hong Kong, China
e-mail: temy@hkucc.hku.hk

M. H. Leung
Department of Medicine, Queen Elizabeth Hospital, Kowloon, Hong Kong, China
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 
categorical 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 

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Chinese cohort Number (%)</th>
<th>Caucasian seriesa Number (%)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65</td>
<td>33/44 (75.0)</td>
<td>171/213 (80.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Onset of illness &lt;2 weeksa</td>
<td>13/44 (29.5)</td>
<td>148/196 (75.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilateral shoulder pain/stiffness</td>
<td>42/44 (95.5)</td>
<td>178/196 (90.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Bilateral upper arm tenderness</td>
<td>5/44 (11.4)</td>
<td>147/195 (75.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stiffness &gt;1 h</td>
<td>30/44 (68.2)</td>
<td>147/173 (84.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight loss/depression</td>
<td>13/44 (29.5)</td>
<td>85/213 (40.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Initial ESR &gt;40 mm/h</td>
<td>44/44 (100)</td>
<td>158/165 (95.7)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

\( a \)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.

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

| Table 2 The frequency of RF and anti-CCP antibodies among PMR patients who had evolved into RA and those who had not |
|---|---|---|
| **RF** | **Anti-CCP antibodies** |
| **N (%)** | **N (%)** |
| **Positive** | **Negative** | **Positive** | **Negative** |
| PMR with evolution into RA | 8/12 (66.7) | 4/12 (33.3) | 3/5 (60.0) | 2/5 (40.0) |
| PMR without evolution into RA | 3/32 (9.4) | 29/32 (90.6) | 1/16 (6.2) | 15/16 (93.8) |

*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.

Acknowledgment We would like to thank Prof. N.G. Patil for his kind help to furnish the English of this paper.

Disclosures None.

Fig. 1 Kaplan-Meier survival curve showing evolvement of PMR patients into RA among patients who were seropositive for RF (a) or anti-CCP antibodies (b).
References


AUTHOR'S PROOF!

AUTHOR QUERY

AUTHOR PLEASE ANSWER QUERY.

Q1. Please check authors’ affiliations if presented correctly.