Title	The clinical course of polymyalgia rheumatica in Chinese
Author(s)	Li, WL; Lo, Y; Leung, MH; Wong, WS; Mok, MY
Citation	Clinical Rheumatology, 2010, v. 29 n. 2, p. 199-203
Issued Date	2010
URL	http://hdl.handle.net/10722/125081
Rights	The original publication is available at www.springerlink.com

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: _____

AUTHOR'S PROOF!

Metadata of the article that will be visualized in Online

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

35		Address	Kowloon , Hong Kong, China
36		e-mail	
37		Family Name	**Wong**
38		Particle	
39		Given Name	**Woon Sing**
40	Author	Suffix	
41		Organization	The University of Hong Kong
42		Division	Department of Medicine, Queen Mary Hospital
43		Address	Pok Fu Lam , Hong Kong, China
44		e-mail	

| 48 | 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. |

| 50 | Foot note information | | |

BRIEF REPORT

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

Q1

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

Q1

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

JrnlID 10067_ArtID 1315_Proof# 1 - 06/11/2009

66 sedimentation rate (ESR) >40 mm/h at onset. Together with
67 a positive response to corticosteroid therapy, the sensitivity
68 of this diagnostic criteria has been reported to be as high as
69 99.5% [6].
70 However, a number of rheumatic conditions including
71 late onset rheumatoid arthritis (RA) [7], calcium pyrophos-
72 phate deposition disease, inflammatory myositis [8], and
73 fibromyalgia [9] may mimic PMR as they show similar
74 clinical features but carry different prognosis. Seventy-three
75 percent of a large cohort of 100 PMR patients have been
76 reported to develop cranial symptoms related to ischemic
77 events of giant cell arteries after a median of 3 weeks and
78 among these 16.4% of patients resulted in permanent visual
79 loss [10]. Furthermore, 6–17% of PMR patients have
80 been found to evolve into RA subsequently [7]. Anti-
81 cyclic citrullinated peptide (CCP) antibodies that have
82 recently been found to be a specific marker for RA [11]
83 have been suggested to be clinically useful in the
84 prediction of PMR patients who subsequently develop
85 into RA [12, 13]. Our study aimed to compare the clinical
86 characteristics of a Chinese cohort of PMR patients to a
87 Caucasian series and to examine the frequency of anti-
88 CCP antibodies in patients with and without subsequent
89 evolvement into RA.

90 **Methodology**

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

106 Measurement of RF and anti-CCP antibodies

107 RF was performed by latex-enhanced immunonephelometry
108 (BN ProSpec, Dade Behring, Germany) and was considered
109 positive at ≥15 IU/ml. Anti-CCP antibodies were measured by
110 a second-generation anti-CCP enzyme-linked immunosorbent
111 assay (Inova Diagnostic Inc., San Diego, CA, USA) according
112 to the manufacturer's instructions. The cutoff value for
113 positive reaction was set at 20 arbitrary units (AU) as

114 suggested by the manufacturer. The intra-assay variation of
115 the assay was 3.5% with a high-level serum (175 AU) and 6%
116 with a "low-level serum" (21 AU), and interassay variation
117 was 6% for both sera. For patients who presented before
118 the anti-CCP antibody assay was introduced into the
119 hospital serology laboratory in early 2005, the earliest
120 available serum samples after onset of presentation were
121 retrieved and tested.

122 Statistical analysis

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

133 **Results**

134 Presenting features of PMR

135 Forty-four (31 females and 13 males) patients of southern
136 Chinese origin were identified from these two large
137 regional hospitals during 1997–2008. The mean±SD age
138 of these patients was 75.8±9.6 years with a mean duration
139 of follow-up of 4.9±2.9 years. Table 1 shows a summary of
140 the clinical features of these patients compared to those
141 reported in a Caucasian series [6]. There was similar
142 proportion of Chinese patients (75.0%) aged over 65 years

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

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

[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.

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

Table 2 The frequency of RF and anti-CCP antibodies among PMR patients who had evolved into RA and those who had not

[a] Test performed by second-generation anti-CCP antibody assay

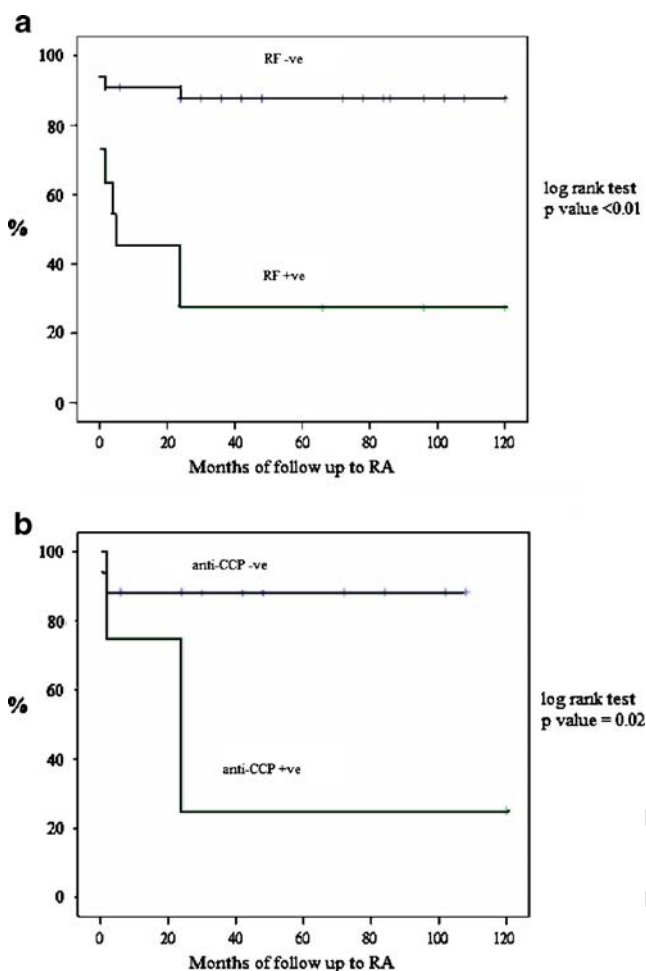|	RF		Anti-CCP antibodies[a]	
	N (%)		N (%)	
	Positive	Negative	Positive	Negative
PMR with evolvement into RA	8/12 (66.7)	4/12 (33.3)	3/5 (60.0)	2/5 (40.0)
PMR without evolvement into RA	3/32 (9.4)	29/32 (90.6)	1/16 (6.2)	15/16 (93.8)

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**)

been found to present with PMR features at disease onset with prevalent involvement of the girdles, high ESR levels, and good response to low-dose steroid treatment [7]. These patients were typically seronegative for RF. A Japanese group has attempted to refine criteria for detection of PMR with higher sensitivity and specificity among their elderly subjects if the patient fulfills all of the following: persistent bilateral muscular pain for >2 weeks involving ≥2 of the neck, shoulder girdle, upper arms, pelvis girdle, and thighs; normal muscle enzyme level; ESR >40 mm/h; and absence of hand joints involvement [16]. However, the sensitivity of diagnosing PMR using such criteria on our cohort was 70% only.

We have explored the role of RF and anti-CCP antibodies as predictive serological markers for subsequent evolvement into RA. We found a high frequency of 67% of RF in those PMR patients who developed into RA, comparable to that observed in elderly onset RA [13]. RF is still present in 9.4% of those patients who had not evolved into RA and is likely related to the increased prevalence of RF in the aged. Indeed, 10–15% of subjects

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.

Disclosures None.

References

1. Hutchings A, Hollywood J, Lamping D, Pease CT, Chakravarty K, Silverman B, Choy EH, Scott DG, Hazleman BL, Bourke B, Gendi N, Dasgupta B (2007) Clinical outcomes, quality of life, and diagnostic uncertainty in the first year of polymyalgia rheumatica. Arthritis Rheum 57:803–809

2. Dasgupta B, Hutchings A, Matteson EL (2006) Polymyalgia rheumatica: the mess we are now in and what we need to do about it. Arthritis Rheum 55:518–520

3. Bird HA, Esselinckx W, Dixon AS, Mowat AG, Wood PH (1979) An evaluation of criteria for polymyalgia rheumatica. Ann Rheum Dis 38:434–439

4. Chuang T-Y, Hunder GG, Ilstrup DM, Kurland LT (1982) Polymyalgia rheumatica: a 10-year epidemiologic and clinical study. Ann Intern Med 97:672–680

5. Healey LA (1984) Long-term follow-up of polymyalgia rheumatica: evidence for synovitis. Semin Arthritis Rheum 13:322–328

6. Bird HA, Leeb BF, Montecucco CM, Misiuniene N, Nesher G, Pai S, Pease C, Rovensky J, Rozman B (2005) A comparison of the sensitivity of diagnostic criteria for polymyalgia rheumatica. Ann Rheum Dis 64:626–629

7. Caporali R, Montecucco C, Epis O, Bobbio-Pallavicini F, Maio T, Cimmino MA (2001) Presenting features of polymyalgia rheumatica (PMR) and rheumatoid arthritis with PMR-like onset: a prospective study. Ann Rheum Dis 60:1021–1024

8. Pego-Reigosa JM, Rodriguez-Rodirguez M, Hurtado-Hernandez Z, Gromaz-Martin J, Taboas-Rodriguez D, Millan-Cachinero C, Hernandez-Rodriguez I, Gonzalez-gay MA (2005) Calcium pyrophosphate deposition disease mimicking polymyalgia rheumatica: a prospective followup study of predictive factors for this condition in patients presenting with polymyalgia symptoms. Arthritis Rheum 53:931–938

9. Hwang E, Barkhuizen A (2006) Update on rheumatologic mimics of fibromyalgia. Curr Pain Headache Rep 10:327–332

10. Hernandez-Rodriquez J, Font C, Garcia-Martinez A, Espiqol-Friqole G, Sanmarti R, Cariete JD, Grau JM, Cid MC (2007) Development of ischemic complications in patients with giant cell arteritis presenting with apparently isolated polymyalgia rheumatica: study of a series of 100 patients. Medicine 86:233–241

11. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, Saigo K, Morinobu A, Koshiba M, Kuntz KM, Kamae I, Kumagai S (2007) Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 146:797–808

12. Ceccato F, Roverano S, Barrionuevo A, Rillo O, Paira S (2006) The role of anticyclic citrullinated peptide antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. Clin Rheumatol 25:854–857

13. Lopez-Hoyos M, Ruiz de Alegria C, Blanco R, Crespo J, Pena M, Podriguez-Valverde V, Martinez-Taboada VM (2004) Clinical utility of anti-CCP antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. Rheumatology 43:655–657

14. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315–324

15. McCracken LM, Matthews AK, Tang TS, Cuba SL (2001) A comparison of blacks and whites seeking treatment for chronic pain. Clin J Pain 17(3):249–255

16. Nobunaga M, Yoshioka K, Yasuda M, Shingu M (1989) Clinical studies of polymyalgia rheumatica. A proposal of diagnostic criteria. Jpn J Med 28(4):452–456

17. Zendman AJW, van Venrooij WJ, Pruign GJM (2006) Use and significance of anti-CCP autoantibodies in rheumatoid arthritis. Rheumatology 45:20–25

18. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, Heyse SP, Hirsch R, Hochberg MC, Hunder GG, Liang MH, Pillemer SR, Steen VD, Wolfe F (1998) Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 41:778–799

AUTHOR QUERY

AUTHOR PLEASE ANSWER QUERY.

Q1. Please check authors' affiliations if presented correctly.