Journal of Rheumatic Diseases
Vol. 21, No. 6, December, 2014
http://dx.doi.org/10.4078/jrd.2014.21.6.297

□ Original Article □

Epidemiology of Polymyalgia Rheumatica in Korea

In Young Kim[1*], Gi Hyeon Seo[2*], Seulkee Lee[1], Hyemin Jeong[1], Hyungjin Kim[1], Jaejoon Lee[1], Eun-Mi Koh[1], Hoon-Suk Cha[1]

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine[1], Health Insurance Review and Assessment Service[2], Seoul, Korea

Objective. **Polymyalgia rheumatica is a chronic inflammatory disease that affects people older than 50 years of age. The diagnosis is made based on clinical features, and the current standard of treatment is low-dose glucocorticoids. PMR is more commonly reported in Caucasians and females. However, epidemiological studies of PMR in Asian countries are scarce. We aimed to estimate the epidemiology of PMR in Korea.**

Methods. **This study was conducted by analyzing the Health Insurance Review and Assessment databases. We verified all claims between 2007 and 2012. Cases were included when PMR ICD-10 code (M 35.3) was recorded more than twice, and glucocorticoids were prescribed for ≥30 days.**

Results. **We identified 1,463 newly diagnosed cases of PMR during the 5 years. Among them, 992 (67.8%) were female, and the mean age at diagnosis was 66.9 years old. The annual incidence rate was 2.06 per 100,000 individuals aged over 50 years. The prevalence rate was 8.21 per 100,000 individuals in 2012. Incidence and prevalence appeared to increase with age. Prednisolone was the most commonly prescribed glucocorticoid. In half of the patients, the daily starting dose was 6～15 mg as prednisolone equivalents.**

Conclusion. **This is the first study to investigate the epidemiology of PMR in Korea. The incidence and prevalence appeared to be considerably lower than those in Western populations. Both genetic and environmental factors might influence disease occurrence. In addition, the actual incidence may have been underestimated due to lack of awareness of PMR in clinical practice.**

Key Words. **Polymyalgia rheumatica, Epidemiology, Korea**

Introduction

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease in Western countries. The characteristic clinical features are chronic pain and morning stiffness affecting the shoulder girdle. Pain in the hip girdle or neck muscles is often associated with PMR. Although serum inflammatory markers are typically elevated, they are not specific, and no diagnostic test is available for PMR. Therefore, the diagnosis is based on a clinical assessment, and the response to glucocorticoids is often regarded as a diagnostic clue (1). According to previous Western studies, the incidence of PMR increases progressively with age, peaking at 70～80 years of age (2), and the mean age of onset is 73 years (3). Therefore, PMR has increasing importance in an aging society. PMR occurs throughout the world, but is more commonly reported in Caucasians, with the highest incidences seen in Scandinavian and northern European countries. For example, annual incidence in Norway is 112.6 per 100,000 individuals aged over 50 years (2). In the USA, annual incidence is estimated to be about 60 per 100,000 individuals, and prevalence is approximately 1 case per 133 persons aged over 50 years. Incidence over the past 30 years seems stable (3). However, epidemiological studies of PMR in Asian countries are very scarce, and no such study has been conducted in a Korean population. According to a study performed in Japan in 2012, which evaluated 10 patients with PMR, the calculated prevalence rate was approximately 300 per 100,000 individuals (4). To date, two studies have been conducted on PMR in Korea.

＜Received : August 26, 2014, Revised : September 29, 2014, Accepted : September 30, 2014＞
Corresponding to : Hoon-Suk Cha, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 135-710, Korea. E-mail : hoonsuk.cha@samsung.com
*The first two authors contributed equally to this work.

pISSN: 2093-940X, eISSN: 2233-4718

However, only a small number of patients were included, and the studies were confined to specific tertiary health centers, which cannot represent the general population (5,6). Therefore, it is difficult to determine the actual status and characteristics of patients with PMR in Korea. In this study, we estimated the incidence and prevalence of PMR and the current treatment modalities used to treat PMR in Korea. We expect to establish a database potentiating further understating and investigations of PMR.

Materials and Methods

Study population

We verified all insurance claim data for the population between January 1, 2007 and December 31, 2012, by using the Health Insurance Review and Assessment (HIRA) database. HIRA is a government incorporated organization to build an accurate claims review for the Korean National health Insurance (NHI) program which is the only public medical insurance system in Korea, and covers 100% of the population. HIRA was founded in 2000 and completely computerized its data in 2005.

Methods

Since PMR remains a clinical diagnosis, an epidemiological study is difficult. In this study, we performed a nationwide retrospective review of HIRA insurance claims data. We defined PMR cases by both diagnostic code and concurrent prescription codes simultaneously.

Case definition of PMR

Cases were included when age was more than 50 years and when the PMR ICD-10 code (M 35.3) was recorded more than twice as either a primary or secondary diagnosis. Then, we clarified the PMR cases when glucocorticoids were prescribed within the first 14 days after diagnosis, and when there were more than 30 prescription days within the first 2 months. This reflected that most patients with PMR usually require long-term treatment.

Statistical analysis

The incidence and prevalence rates per 100,000 Korean individuals aged over 50 years were calculated using the number of PMR cases and data reported by the National Statistical Office of South Korea (http://kosis.kr). The annual incidence rate was calculated from total newly diagnosed PMR cases for the 5 years, and the prevalence rate was estimated from the number of patients who had been prescribed glucocorticoids in 2012. Additionally, we reviewed records about currently used treatment modalities.

Results

A total of 14,988 cases were identified with the PMR ICD-10 code (M35.3) as the primary diagnosis, and 14,511 were identified as a secondary diagnosis. After excluding overlapping cases, 25,944 cases remained. Among the 25,944 cases, 17,268 were aged over 50 years. The total number was further decreased to 10,507 when we confined cases to those who had the ICD-10 code more than twice. In total, 2,731 patients were prescribed glucocorticoids within 14 days after diagnosis, and 1,919 had prescribed for more than 30 days. Cases diagnosed before 2008 were excluded. Finally, 1,463 newly diagnosed cases met the operational definition of PMR from 2008 to 2012 (Figure 1). Among them, 992 (67.8%) were females and 471 (32.2%) were males, with a male: female ratio of approximately 1 : 2. Mean age at diagnosis was 66.9±9.4 years old. In addition, only 1.2% (n=17) of all cases had the diagnostic code for giant cell arteritis (GCA) at the

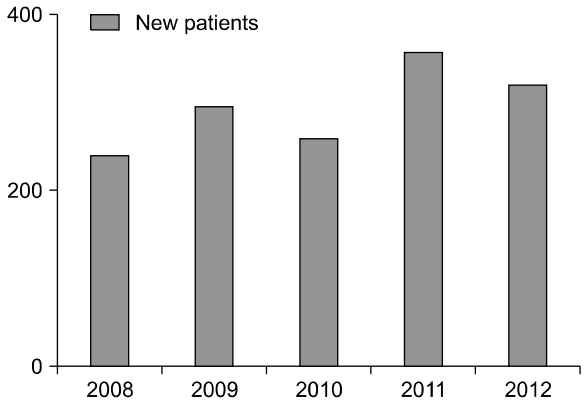

Figure 1. A total of 1,463 polymyalgia rheumatica (PMR) cases were newly diagnosed between 2008 and 2012. More specifically, 238, 294, 258, 354 and 319 were newly diagnosed each year.

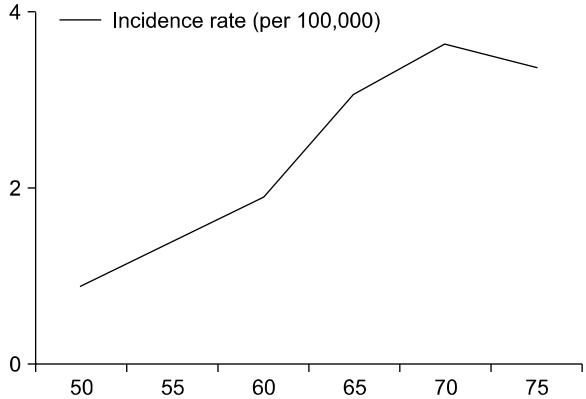

Figure 2. The incidence rates of PMR per 100,000 individuals in each age group.

same time.

Annual incidence rate of PMR in Korea

The age and sex adjusted annual incidence rate of PMR during the 5 years was estimated to be 2.06 per 100,000 individuals aged over 50 years. The rates were 1.45 per 100,000 in males and 2.59 per 100,000 in females. Incidence rates according to age appeared to increase wit age peaking at 70 years, which is similar to reports from western studies (Figure 2).

Annual prevalence rate of PMR in Korea

A total of 1,163 patients were having PMR in 2012. The prevalence rate was calculated to be 8.21 per 100,000 individuals (5.60 per 100,000 in males, 10.42 per 100,000 in females). Table 1 shows prevalence according to sex and age. Prevalence peaked at about 70 years of age.

Treatment

The present mainstay treatment for PMR is low-dose glucocorticoids. As shown in Figure 3A, the majority of glucocorticoids prescribed were prednisolone. The pie chart in Figure 3B indicates that a daily starting dose of 6～15 mg as prednisolone equivalent was given to half of the patients.

Table 1. Detailed prevalence rates of PMR according to age and sex

Age	Number of patients (N)			Prevalence rate (per 100,000)		
	Male	Female	Total	Male	Female	Total
50～54	34	101	135	1.80	5.29	3.55
55～59	43	119	162	3.16	8.46	5.86
60～64	49	122	171	4.64	10.84	7.84
65～69	73	150	223	8.76	15.32	12.31
70～74	87	146	233	12.93	16.35	14.88
75～79	42	93	135	10.23	13.81	12.45
80～84	25	47	72	13.44	11.48	12.09
≥85	11	21	32	11.61	7.72	8.73

Discussion

No specific test exists for making the diagnosis of PMR. Therefore, the diagnosis is mostly based on clinical assessment, making an epidemiological study difficult. In 2012, the collaborative initiative of EULAR and ACR published provisional classification criteria for PMR, which was not meant for diagnostic purposes but helps to distinguish PMR from other disorders (7,8). To conduct a retrospective review using the HIRA database, we had to clarify the PMR cases. Thus, we devised an operational definition for PMR. Cases were included only when the age at diagnosis was ≥50 years old, as the diagnosis is unlikely in individuals younger than 50 years of age (9). Next, a prescription for glucocorticoids was incorporated as a required condition. Glucocorticoids are the cornerstone of treatment for PMR, and some authors have suggested that prompt response to low-dose of glucocorticoids is a clue for the diagnosis (10,11). As patients with PMR require long-term treatment usually for 1～2 years, we confined PMR cases when the prescription days were ≥1 month.

Epidemiological studies performed in Asia on PMR are scarce. Our results demonstrate a considerably lower incidence of PMR in Korea compared to that in Western countries. For example, the annual incidence rate in Korea is one-30th the incidence in the USA. It seems apparent that Koreans have low susceptibility to PMR. The geographic distribution of PMR with higher incidence in a north-south gradient in

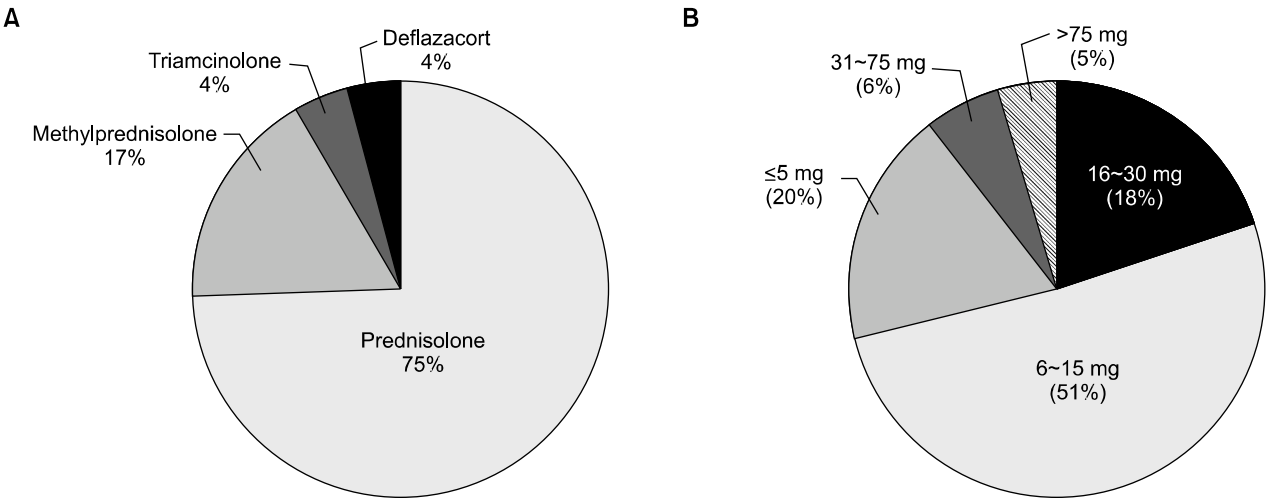

Figure 3. (A) Glucocorticoids prescribed for treating PMR in Korea. (B) Daily glucocorticoids starting doses, as prednisolone equivalents to treat PMR in Korea.

Europe, suggest that the disease is affected by environmental and genetic factors (2). The results of our study also support this concept, although the pathogenesis and genetic role of PMR have not been fully unraveled. Until now, PMR has been considered a multi-genetic disease associated with systemic activation of the immune system. Associations with several polymorphisms such as intercellular adhesion molecule 1, interleukin (IL)-1 receptor antagonist, IL-6, and TNF-alpha have been suggested (12,13). In addition, an association with HLA-DR4 has been reported in discrete populations (9,14,15). Taken together, it seems that multiple genes contribute to susceptibility to PMR. Furthermore, the associations with polymorphisms may vary in different populations (16). Further investigations into the molecular pathogenesis are needed to better understand PMR etiology.

Another possibility for the low incidence in Korea is that the actual incidence may have been underestimated owing to a lack of awareness of PMR in clinical practice. The absence of objective diagnostic criteria could amplify this error. Furthermore, as this study was solely based on insurance claim data, it brings inevitable doubts whether these claim data reflect the true burden of PMR in Korea. Moreover, as we devised an operational definition of PMR to include glucocorticoids therapy without exception, some patients who were not prescribed glucocorticoids for certain reasons including comorbidities may have been omitted. However, this portion would be small, as the initial starting dose is usually low, which most patients can tolerate. These are the inherent limitations of a study design using the HIRA database. In this study, we could not validate the accuracy of the case definition for PMR and it was impossible to access personal information and medical records of patients from HIRA database. However, considering that almost all of the Korean population is under the coverage by the of NIH system, these results are worthy.

The basic demographic characteristics of age and sex predispositions were similar to reports from Western populations. Studies have noted that age is the major risk factor for PMR and that incidence increases with age. The incidence and prevalence of PMR in Korea also appeared to increase with age, peaking at about 70 years old. Furthermore, female predominance corresponded with findings of preceding studies (3). Although detailed prevalence rate according to sex and age groups showed higher prevalence rate in male than female when aged over 80, the actual number of patients was higher in the female group. It could be explained by the fact that the total number of females was more than twice as many as that of males in elderly people aged over 80.

There is a well-known association between PMR and GCA, also known as temporal arteritis. GCA is an inflammatory vasculitis affecting the large arteries. These conditions are closely related and have many similarities. Some authors have suggested that they might be the same disease with a common pathophysiology but with different manifestations. Those authors suggested that PMR is a variant of GCA characterized by dominance of systemic inflammation over the vascular component. The most significant risk factor for both diseases is old age, suggesting an important role for environmental factors in the pathogenesis. These two diseases can occur together or apart, and PMR occurs approximately two or three times more frequently than GCA (17,18). In general, it is reported that 40～60% of patients with GCA have PMR at diagnosis, whereas 16～21% of patients with PMR have coexisting GCA (19). The reported incidence of GCA in the USA is approximately 20 per 100,000 individuals ≥50 years (20). In the present study, only 17 patients (1.2%) of the 1,453 PMR cases had the diagnostic code for GCA simultaneously. Considering prior studies that almost 20% of patients with PMR had GCA at diagnosis, this finding differs from the results of Western countries. But we could not investigate whether the pathologic confirmation were made in these patients from HIRA database. In fact, there have been only a few case reports of GCA in Korea. Among them, only two cases presented symptoms compatible with PMR (21-23). Lee et al (6). performed a retrospective review of 78 patients with PMR at a tertiary hospital, and no single case was accompanied with GCA. Another study of 51 patients with PMR also had no coexisting cases of GCA (5). It is probable that GCA is under-diagnosed in clinical practice, as well as PMR. Further investigations into GCA in Korea are needed. In practice, it is recommended that patients with PMR be carefully evaluated for the possibility of concurrent GCA. Moreover, patients must be warned about the potential for PMR to progress to GCA and should be monitored for the emergence of vasculitis, which may develop even years later.

Although there are no controlled clinical trials demonstrating efficacy, PMR treatment is based on low-dose glucocorticoids that usually induces dramatic improvement within a few days (24). In this study, half of the patients were prescribed daily starting doses of 6～15 mg prednisolone equivalents. However, approximately 10% of patients were prescribed an unusually higher dose exceeding 30 mg. It was difficult to define and evaluate the treatment duration in this study since there were discontinuity of prescriptions and possibilities of coexistence of other diseases indicated glucocorticoids therapy during follow up period.

According to one study, other diagnoses should be considered when there is no improvement after 30 mg per day prednisone for 1 week (19). The British Society for Rheumatology published a set of guidelines and suggested that prednisolone, or its equivalent, be used at 15 mg daily for the first 3 weeks, and then tapered over several weeks (25). Dose adjustment is currently based on clinical course, and many patients are able to stop treatment 6 months to 2 years after disease onset. However, more long-term treatment is required in some cases for several years to prevent relapse. (26,27). About 50% of patients experience relapse, and higher initial doses and faster tapering are predictors of relapse (28,29). In 2003, the EULAR proposed a core set of response criteria for PMR, which include erythrocyte sedimentation rate, C-reactive protein, pain, the physician's global assessment, early morning stiffness, and the degree of elevation of upper limb (30). Later, new definitions of remission and relapse were proposed based on the PMR activity score (PMR-AS) (31,32). Long-term glucocorticoid treatment leads to concerns about potent adverse events. However, there is no consensus about glucocorticoids sparing agents for PMR. Trials of various agents including methotrexate have shown conflicting results (33). Usage of second-line treatment agents other than glucocorticoids was not evaluated in this study because of medical insurance issues.

Although this study has limitations mainly arising from the nature of the retrospective review using insurance claim data, our results are significant because we attempted to identify PMR epidemiologic data in Korea for the first time. This study revealed a very lower incidence of PMR in Korea than that reported in other countries. However, demographic characteristics were similar with those of Western populations. We expect to establish a database potentiating further understanding and investigations of PMR, and hopefully, for the large vessel vasculitis including GCA in the future. Further studies on the outcomes and comorbidities caused by PMR, or from long-term use of glucocorticoids are anticipated. As PMR may be under-recognized and under-diagnosed in clinical practice, clinicians must raise suspicion for the diagnosis of PMR if elderly patients present with shoulder pain and increased level of inflammatory markers.

Conclusion

This study was designed to determine the epidemiology and basic demographic characteristics of PMR in Korea based on the HIRA database. This is the first study that has investigated PMR epidemiology in Korea. The population analyzed was the largest among those of studies published in East Asia so far. PMR cases from 2008 to 2012 were retrospectively identified by both diagnostic code and prescription codes for glucocorticoids.

The incidence and prevalence rates of PMR in Korea appeared considerably lower than those of Western populations. However, the sex and age predisposition was similar to that of Western populations. This finding suggests both genetic and environmental factors influence the disease pathogenesis. Another possibility is that the true incidence may have been underestimated due to the lack of awareness of PMR in clinical practice.

GCA coexistence in PMR patients also seemed greatly lower than that of western studies. Further investigations into GCA in Korea are needed.

References

1. Kermani TA, Warrington KJ. Polymyalgia rheumatica. Lancet 2013;381:63-72.
2. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Filloy JA, Gonzalez-Juanatey C, Martin J, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 2009;61:1454-61.
3. Doran MF, Crowson CS, O'Fallon WM, Hunder GG, Gabriel SE. Trends in the incidence of polymyalgia rheumatica over a 30 year period in Olmsted County, Minnesota, USA. J Rheumatol 2002;29:1694-7.
4. Okumura T, Tanno S, Ohhira M, Nozu T. The rate of polymyalgia rheumatica (PMR) and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome in a clinic where primary care physicians are working in Japan. Rheumatol Int 2012;32:1695-9.
5. Kim HA, Lee J, Ha YJ, Kim SH, Lee CH, Choi HJ, et al. Induction of remission is difficult due to frequent relapse during tapering steroids in Korean patients with polymyalgia rheumatica. J Korean Med Sci 2012;27:22-6.
6. Lee JH, Choi ST, Kim JS, Yoon BY, Kwok SK, Kim HS, et al. Clinical characteristics and prognostic factors for relapse in patients with polymyalgia rheumatica (PMR). Rheumatol Int 2013;33:1475-80.
7. Dasgupta B, Cimmino MA, Maradit-Kremers H, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis 2012;71:484-92.
8. Hutchings A, Hollywood J, Lamping DL, Pease CT, Chakravarty K, Silverman B, et al. Clinical outcomes, quality of life, and diagnostic uncertainty in the first year of polymyalgia rheumatica. Arthritis Rheum 2007;57:803-9.
9. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 2002;347:261-71.
10. Jones JG, Hazleman BL. Prognosis and management of

polymyalgia rheumatica. Ann Rheum Dis 1981;40:1-5.
11. Healey LA. Long-term follow-up of polymyalgia rheumatica: evidence for synovitis. Semin Arthritis Rheum 1984;13:322-8.
12. González-Gay MA, Amoli MM, Garcia-Porrua C, Ollier WE. Genetic markers of disease susceptibility and severity in giant cell arteritis and polymyalgia rheumatica. Semin Arthritis Rheum 2003;33:38-48.
13. Gonzalez-Gay MA, Hajeer AH, Dababneh A, Garcia-Porrua C, Mattey DL, Amoli MM, et al. IL-6 promoter polymorphism at position -174 modulates the phenotypic expression of polymyalgia rheumatica in biopsy-proven giant cell arteritis. Clin Exp Rheumatol 2002;20:179-84.
14. Gonzalez-Gay MA, Garcia-Porrua C, Ollier WE. Polymyalgia rheumatica and biopsy-proven giant cell arteritis exhibit different HLA-DRB1* associations. J Rheumatol 2003;30:2729.
15. Cid MC, Ercilla G, Vilaseca J, Sanmarti R, Villalta J, Ingelmo M, et al. Polymyalgia rheumatica: a syndrome associated with HLA-DR4 antigen. Arthritis Rheum 1988;31:678-82.
16. Pipitone N, Salvarani C. Update on polymyalgia rheumatica. Eur J Intern Med 2013;24:583-9.
17. Frearson R, Cassidy T, Newton J. Polymyalgia rheumatica and temporal arteritis: evidence and guidelines for diagnosis and management in older people. Age Ageing 2003;32:370-4.
18. Franzén P, Sutinen S, von Knorring J. Giant cell arteritis and polymyalgia rheumatica in a region of Finland: an epidemiologic, clinical and pathologic study, 1984-1988. J Rheumatol 1992;19:273-6.
19. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008;372:234-45.
20. Salvarani C, Crowson CS, O'Fallon WM, Hunder GG, Gabriel SE. Reappraisal of the epidemiology of giant cell arteritis in Olmsted County, Minnesota, over a fifty-year period. Arthritis Rheum 2004;51:264-8.
21. Chang HK, Hur SH, Chung HR. A Case of Giant Cell Arteritis developed in Polymyalgia Rheumatica. J Korean Rheum Assoc 2000;7:72-6.
22. Seo JW, Hur J, Kim HO, Jeon DH, Baek JH, Kim JH, et al. A case of atypical giant cell arteritis presenting as raynaud's phenomenon and diagnosed by random temporal artery biopsy. J Korean Rheum Assoc 2010;17:278-82.
23. Kang MI, Park HJ, Jeon HM, Kang Y, Lee SW, Lee SK, et al. A case of atypical giant cell arteritis presenting as a fever of unknown origin. J Rheum Dis 2012;19:299-301.
24. Hernández-Rodríguez J, Cid MC, López-Soto A, Espigol-Frigolé G, Bosch X. Treatment of polymyalgia rheumatica: a systematic review. Arch Intern Med 2009;169:1839-50.
25. Dasgupta B, Borg FA, Hassan N, Barraclough K, Bourke B, Fulcher J, et al; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guidelines for the management of polymyalgia rheumatica. Rheumatology (Oxford) 2010;49:186-90.
26. Gabriel SE, Sunku J, Salvarani C, O'Fallon WM, Hunder GG. Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica. Arthritis Rheum 1997;40:1873-8.
27. Barraclough K, Liddell WG, du Toit J, Foy C, Dasgupta B, Thomas M, et al. Polymyalgia rheumatica in primary care: a cohort study of the diagnostic criteria and outcome. Fam Pract 2008;25:328-33.
28. Salvarani C, Cantini F, Niccoli L, Macchioni P, Consonni D, Bajocchi G, et al. Acute-phase reactants and the risk of relapse/recurrence in polymyalgia rheumatica: a prospective followup study. Arthritis Rheum 2005;53:33-8.
29. Kremers HM, Reinalda MS, Crowson CS, Zinsmeister AR, Hunder GG, Gabriel SE. Relapse in a population based cohort of patients with polymyalgia rheumatica. J Rheumatol 2005;32:65-73.
30. Leeb BF, Bird HA, Nesher G, Andel I, Hueber W, Logar D, et al. EULAR response criteria for polymyalgia rheumatica: results of an initiative of the European Collaborating Polymyalgia Rheumatica Group (subcommittee of ESCISIT). Ann Rheum Dis 2003;62:1189-94.
31. Leeb BF, Rintelen B, Sautner J, Fassl C, Bird HA. The polymyalgia rheumatica activity score in daily use: proposal for a definition of remission. Arthritis Rheum 2007;57:810-5.
32. Binard A, de Bandt M, Berthelot JM, Saraux A; Inflammatory Joint Disease Working Group of the French Society for Rheumatology. Performance of the polymyalgia rheumatica activity score for diagnosing disease flares. Arthritis Rheum 2008;59:263-9.
33. Caporali R, Cimmino MA, Ferraccioli G, Gerli R, Klersy C, Salvarani C, et al; Systemic Vasculitis Study Group of the Italian Society for Rheumatology. Prednisone plus methotrexate for polymyalgia rheumatica: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2004;141:493-500.