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Induction of Remission is Difficult due to Frequent Relapse during Tapering Steroids in Korean Patients with Polymyalgia Rheumatica

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Polymyalgia rheumatica is an inflammatory disease affecting elderly and involving the shoulder and pelvic girdles. No epidemiological study of polymyalgia rheumatica was conducted in Korea. We retrospectively evaluated patients with polymyalgia rheumatica followed up at the rheumatology clinics of 10 tertiary hospitals. In total 51 patients, 36 patients (70.6%) were female. Age at disease onset was 67.4 yr. Twenty-three patients (45.1%) developed polymyalgia rheumatica in winter. Shoulder girdle ache was observed in 45 patients (90%) and elevated erythrocyte sedimentation rate (> 40 mm/h) in 49 patients (96.1%). Initial steroid dose was 23.3 mg/d prednisolone equivalent. Time to normal erythrocyte sedimentation rate was 4.1 months. Only 8 patients (15.7%) achieved remission. Among 41 patients followed up, 28 patients (68.3%) had flare at least once. Number of flares was 1.5 ± 1.6. The frequency of flare was significantly lower in patients with remission ($P = 0.02$). In Korea, polymyalgia rheumatica commonly develops during winter. Initial response to steroid is fairly good, but the prognosis is not benign because remission is rare with frequent relapse requiring long-term steroid treatment.

Key Words: Polymyalgia Rheumatica; Symptoms; Treatment; Steroids; Remission; Prognosis

INTRODUCTION

Polymyalgia rheumatica (PMR) is an inflammatory condition affecting elderly people and characterized by aching and stiffness in shoulder and pelvic girdles. Its occurrence is not rare, and reported prevalence rates from European data range from 12.7 to 112.6 cases per 100,000 inhabitants, with a geographical gradient making the disease more frequent in the north (1, 2). Although PMR is generally regarded as a benign disease with no adverse impact on long-term survival, most patients with PMR require long-term steroid therapy, which is associated with various side effects (3, 4).

Diagnosis of PMR is based on a combination of clinical symptoms, raised acute-phase reactants, exclusion of other disease, and response to steroids. Clinical symptoms and laboratory results are not disease specific; therefore, a differential diagnosis is needed in order to exclude neoplastic and other rheumatologic diseases, like elderly rheumatoid arthritis (RA) and seronegative symmetrical synovitis with pitting edema. Therefore, a few sets of diagnostic criteria for PMR were proposed and have been used in clinical practice (2, 5-7).

In most cases of PMR, an initial dose of 10-20 mg per day of prednisone or equivalent is adequate in the absence of associated giant cell arteritis. The response to steroid is usually rapid,

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with complete or nearly complete resolution of musculoskeletal aching and stiffness within a few days (5, 8). A treatment course of 1-2 yr is often required. However, some patients might need low doses of steroid for several years. Therefore, methotrexate has been proposed as a steroid-sparing drug in treatment of PMR, with conflicting results (9-11). Some studies have reported that anti-tumor necrosis factor (TNF) agents had a steroid-sparing effect in treatment of patients who are resistant to steroid therapy (12-14).

Data on the disease course, clinical features, and outcome of PMR have been described in various parts of the world (15-18). However, data on the disease course, ultimate outcome, and therapeutic response of PMR in Korea are limited.

We describe the clinical features of 51 Korean patients with PMR who were treated in 10 tertiary hospitals, and analyze the therapeutic response and remission related factors.

MATERIAL AND METHODS

All patients with a diagnosis of PMR who had been followed up at the rheumatology clinics of 10 university-based tertiary hospitals were retrospectively evaluated. Diagnosis was based on Bird's criteria for PMR (6): 1) bilateral shoulder pain or stiffness, or both; 2) onset of illness within 2 weeks; 3) initial erythrocyte sedimentation rate (ESR) greater than 40 mm/h; 4) duration of morning stiffness greater than 1 h; 5) age 65 yr or older; 6) depression or weight loss, or both; and 7) bilateral upper arm tenderness. A diagnosis of probable PMR was made if any three or more of these seven criteria were fulfilled. Patients who had other connective tissue disorders like RA and fibromyalgia, systemic infection or abnormal levels of serum creatinine kinase or thyroid-stimulating hormone were excluded. After a detailed history and physical examinations, all patients underwent a series of laboratory tests, including complete blood count (CBC), ESR, C-reactive protein (CRP), rheumatoid factor (RF), anti-nuclear antibody (ANA), liver function tests, and urinalysis. Clinical characteristics, including demographic features, duration of illness before diagnosis, clinical features, treatment, length of follow-up, flares and complications were recorded using a standardized form. Flares were defined as an increase in activity of PMR symptoms sufficient to warrant an increase in steroid dose (16). Remission was defined as the absence of articular and systemic laboratory evidence of disease activity for at least two consecutive months without any kind of drugs and no recurrence.

Statistical analyses were performed using the SPSS software, version 12.0 (Chicago, IL, USA). All data were expressed as the mean ± SD and a *P* value of less than 0.05 was regarded as significant. Predicting factors for remission were assessed using a chi-squared-test and Mann-Whitney U test.

Ethics statement

This study was approved by the institutional review board of Ajou University Hospital (AJOU-MED-MDB-11-180). Informed consent was waived by the board.

RESULTS

Of a total of 51 patients with PMR, 36 patients (70.6%) were female. Age at disease onset ranged from 49 to 89 yr, with a mean of 67.4 ± 10.6 yr. Symptom duration before diagnosis was 4 ± 11.7 months and the follow-up period was 27.6 ± 30.5 months (Table 1).

Symptoms of PMR developed in 10 patients (19.6%) in spring, 13 (25.5%) in summer, 5 (9.8%) in fall, and 23 (45.1%) in winter. Shoulder girdle ache was observed in 45 patients among 50 patients (90%) and pelvic girdle ache was present in 28 patients among 47 patients (59.6%). Other manifestations, in order of decreasing frequency, included peripheral arthritis in 29 patients among 46 patients (64%), morning stiffness in 22 patients among 47 patients (46.8%), weight loss in 12 patients among 46 patients (26.1%), fever in 13 patients (25.5%), headache in 11 patients among 47 patients (23.4%), and depression in 10 patients among 47 patients (21.3%). There were no cases of biopsy-confirmed giant cell arteritis.

Table 2 shows the results of selected laboratory tests. Specifi-

Table 1. Clinical characteristics in 51 patients with polymyalgia rheumatica

Parameters	Mean or number (%)
Age at diagnosis (yr)	67.4 ± 10.6
Sex (F/M)	36 (70.6)/15 (29.4)
Symptom duration (months)	4 ± 11.7
Follow-up period (months)	27.6 ± 30.5
Shoulder girdle pain	45/50 (90)
Hip girdle pain	28/47 (59.6)
Peripheral arthritis	29/46 (64)
Morning stiffness	22/47 (46.8)
Weight loss	12/46 (26.1)
Headache	11/47 (23.4)
Fever	13 (25.5)
Depression	10/47 (21.3)
Giant cell arteritis	0/51 (0)

Table 2. Laboratory findings in 51 patients with polymyalgia rheumatica

Features	Number (%)
Elevated white blood cell count (≥ 10,000/μL)	13 (25.5)
Thrombocytosis (≥ 400,000/μL)	21 (41.2)
Anemia (< 10.0 g/dL)	7 (13.7)
Elevated erythrocyte sedimentation rate (> 40 mm/h)	49 (96.1)
Elevated C-reactive protein (> 0.8 mg/dL)	47 (92.2)
Elevated liver function abnormality	
(AST ≥ 40 U/L or ALT ≥ 41 U/L)	11 (21.6)
Decreased albumin (< 3.5 mg/dL)	20 (39.2)
Elevated alkaline phosphatase (> 120 U/L)	26 (51)
Positive rheumatoid factor	14/50 (28)
Positive antinuclear antibody	19/50 (38)

AST, aspartate transaminase; ALT, alanine transaminase.

cally, an elevated ESR (> 40 mm/h) was observed in 49 patients (96.1%), an elevated CRP (> 0.8 mg/dL) in 47 patients (92.2%), leukocytosis (≥ 10,000/μL) in 13 patients (25.5%), thrombocytosis (≥ 400,000/μL) in 21 patients (41.2%), elevated alkaline phosphatase in 26 patients (51%), positive ANA in 19 patients (38%), and positive RF in 14 patients (28%). RF titers of positive patients were low (14-27.3 IU/mL). The ANA titer was < 1:320, except for one case. For ANA positive patients, the diagnosis of SLE could be excluded according to American College of Rheumatology criteria.

Drugs used singly or in combination included oral steroids (50 patients, 98%), non-steroid anti-inflammatory drugs (34 patients, 66.7%), and disease modifying antirheumatic drugs (DMARDs) (26 patients, 51%). Methotrexate was the most commonly used DMARD (16 patients, 31.4%); however, other DMARDs were used, including hydroxychloroquine in 12 patients (23.5%) and sulfasalazine in 3 patients (5.9%). Initial steroid dose was 23.3 ± 11.5 mg prednisolone equivalent. Time to normal ESR was 4.1 ± 5.4 months.

Malignancy was diagnosed in six patients (11.8%). Malignancies preceded PMR in five patients (three patients, stomach cancer 2, 4, and 10 yr ago; one patient, prostatic cancer 7 yr ago and sigmoid cancer 4 months ago; one patient, colon cancer 8 yr ago). Patients diagnosed as PMR did not experience cancer recurrence. One patient developed ovarian cancer 1 yr after diagnosis of PMR.

During the follow-up period (27.6 ± 30.5 months), only 8 patients had stopped steroids, 10 patients were lost to follow-up, and 33 patients still received steroids. Of the 41 patients, 28 (68.3 %) had flare at least once during the follow-up period. Number of flares was 1.5 ± 1.6. Follow-up duration of eight patients defined as remission was 26.5 ± 17.9 months, and their flare frequency was 0.5 ± 0.5. Their cumulative steroid dose was 2,306.6 ± 1,314.6 mg prednisolone equivalent.

Although the number of patients with remission was small, we evaluated clinical features and treatment between patients with remission and patients without remission (Table 3). No difference was observed in follow-up duration and clinical features. In addition, no significant difference was observed in initial steroid dosage and cumulative dose of steroids between them. However, the frequency of flare was significantly higher in patients without remission (P = 0.02).

Evaluation of clinical features and treatment between patients treated with methotrexate and patients treated without methotrexate showed no difference in follow-up duration and clinical features. In addition, no significant difference was observed in initial steroid dosage. However, patients treated with methotrexate had higher cumulative steroid dosage (P = 0.046).

Table 3. Predicting factors for remission in 41 patients with polymyalgia rheumatica

Factors	Patients with remission No. (%) or mean ± SD	Patients without remission No. (%) or mean ± SD	P value
Number of patients	8	33	
Fever	1 (12.5)	10 (30.3)	0.416
Weight loss	3 (37.5)	8 (19.5)	0.68
Depression	2 (25)	8 (19.5)	0.676
Headache	4 (50)	6 (18.2)	0.181
Peripheral arthritis	4 (50)	8 (19.5)	0.394
Hip girdle pain	2 (25)	12 (36.4)	0.684
Morning stiffness duration (min)	75 ± 123.2	96.5 ± 269.2	0.829
Follow-up duration (months)	26.5 ± 17.9	36.6 ± 36.7	0.554
Flare frequency	0.5 ± 0.5	1.9 ± 1.8	0.02
Initial VAPS	6.3 ± 2.2	6.1 ± 2.3	0.496
ESR (mm/h)	87.7 ± 21.1	69.6 ± 27	0.069
CRP (mg/dL)	8.9 ± 5.3	7.2 ± 7.6	0.534
Duration to normal ESR (months)	5 ± 3.3	3.5 ± 5.3	0.472
Initial steroid dose (mg/d)	25.6 ± 15.9	21.7 ± 10	0.371
Cumulative steroid dose (mg)	2306.6 ± 1314.6	6523.5 ± 10241	0.288
DMARDs medication	5 (62.5)	22 (66.7)	1.0
Methotrexate medication	1 (12.5)	15 (45.5)	0.224

VAPS, visual analogue pain score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DMARDs, disease modifying antirheumatic drugs. These data were assessed using χ^2-test and Mann-Whitney U test.

DISCUSSION

No epidemiological study of PMR in the Korean population has been conducted. Given the lack of awareness and the absence of biomarkers to aid in clinical diagnosis, it is possible that we are under diagnosing PMR. Therefore, in the present study, we described the clinical features of 51 Korean patients with PMR and analyzed the therapeutic response and remission related factors.

PMR is an inflammatory disease that characteristically affects old people and women more often than man. In this study, the mean age at disease onset was 67.4 yr, and 70.6% of patients

Table 4. Clinical and laboratory findings among the Korean cohort compared with Caucasian, Chinese and Japanese series

Parameters	Korean cohort No. (%) or mean ± SD	Caucasian cohort (21) No. (%) or mean ± SD	Chinese cohort (17) No. (%) or mean ± SD	Japanese cohort (15) No. (%) or mean ± SD
Total patients	51	213	44	32
Age (yr)	67.4 ± 10.6	70.3	75.8 ± 9.6	72.3
Females	36 (70.6)	124 (70.5)		15 (46.9)
Shoulder girdle pain	45/50 (90)	178/196 (90.8)	42 (95.5)	25 (78)
Hip girdle pain	28/47 (59.6)	82/213 (38.5)		11/32 (34)
Peripheral arthritis	29/46 (64)			24 (75)
Morning stiffness	22/47 (46.8)	147/173 (84.9)	30 (68.2)	25 (78)
Weight loss or depression	18/50 (36)	85/213 (40)	13 (29.5)	8 (25)
Fever	13 (25.5)			8 (25)
ESR (> 40 mm/h)	49 (96.1)	158/165 (95.7)	44 (100)	
CRP (> 0.8 mg/dL)	47 (92.2)			
Positive RF	14/50 (28)		8 (18.1)	3 (9.3)

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor.

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were women, similar to previous studies (19, 20). Table 4 shows a summary of the clinical and laboratory data of Korean patients, compared to those reported in Caucasian (21), Chinese (17), and Japanese patients (15). Shoulder girdle pain, weight loss, and depression were prevalent symptoms, similar to other reports (15-17, 21). Incidences of morning stiffness and peripheral arthritis were lower; however, the incidence of hip girdle pain was higher. These differences could be explained by racial differences and different natures of study. In this study, some patients with headache or fever were evaluated with temporal artery biopsy. However, there was no biopsy-proven giant cell arteritis. Giant cell arteritis is the most frequent type of vasculitis in western countries, and European population-based studies of PMR have demonstrated the presence of biopsy-proved giant-cell arteritis in 16 to 21 percent of patients (5). However, giant cell arteritis is very uncommon in Asian population. The prevalence of giant cell arteritis in Japan was only 1.47 per 100,000 populations (22). There has been no study evaluating the incidence of giant cell arteritis in PMR patients in Asia.

Elevated levels of ESR, CRP, and alkaline phosphatase were the most frequent laboratory findings. In addition, the frequencies of thrombocytosis and hypoalbuminemia were high. Frequencies of positive RF and ANA were higher than in previous reports (15, 23). However, their titers of RF were low. In addition, the ANA titer was < 1:320, except for one case.

Previous findings related to seasonality have been somewhat inconsistent; however, seasonal patterns of incidence of PMR have been proposed as evidence to support an infectious etiology (4). Clustering of diagnoses in the early summer months has been reported, while other studies have reported peaks in the winter months (4, 24, 25). However, other studies have reported no seasonal pattern (26, 27). In this study, we observed higher rates in the winter. These findings support an infectious etiology related to seasonal variation in incidence.

Steroid is the drug of choice in treatment of PMR. In the absence of giant cell arteritis, an initial dosage of 10-20 mg/day of prednisone or equivalent is adequate in most cases (5). Steroids are often needed for two to three years, and a subset of patients may relapse within 10 yr and require longer courses of treatment (28). A recent study reported that a higher plasma viscosity in PMR increases the risk of prolonged steroid therapy and late giant cell arteritis. The authors of the study also suggested that starting patients on > 15 mg prednisolone showed an association with prolonged steroid treatment (16). Adjuvant steroid sparing agents, such as methotrexate and anti-TNF agents, have been suggested for prevention of steroid related adverse events (9-13). Findings from a randomized controlled trial have suggested that methotrexate can be effective in treatment of PMR when the drug is started at disease onset and given for at least 1 yr at a dose of at least 10 mg per week (11). Two pilot studies reported on a steroid-sparing effect of anti-TNF agents (infliximab and etanercept) in patients who were resistant to steroid therapy (12, 14). However, a recent randomized controlled trial showed that infliximab was ineffective in newly diagnosed patients with PMR (29). In this study, only one patient did not use steroid because of patient denial. Initial steroid dose was 23.3 ± 11.5 mg prednisolone equivalent and the response was good, with improvement of symptoms and normalization of ESR in 4.1 ± 5.4 months. Methotrexate was the most commonly used DMARDs (16 patients, 31.4%). Patients treated with methotrexate showed a higher cumulative steroid dosage than those who were not (P = 0.046). These results could be explained by the fact that methotrexate was needed for control of disease activity in steroid dependent patients.

Some patients have a more chronic, relapsing course and may require low doses of steroid for several years. Two recent studies reported a relapse frequency of 50% in patients with PMR (25, 29). Another study showed that increased initial doses of steroids and faster tapering were substantial predictors of relapse. Therefore, they recommended keeping the initial steroid dose as low as possible, and that it should be discontinued slowly (28). Other studies suggested that persistently raised concentrations of CRP and interleukin 6 were helpful in identification of patients with relapsing disease (30). In this study, 28 patients (68.8%) had flare at least once during the follow-up period. The number of flares was 1.5 ± 1.6. Flare frequency of our patients was higher than that reported in previous studies. These differences could be explained by different flare or relapse standards. Kremers et al. (28) defined relapse as an exacerbation of PMR symptoms requiring an increase in steroid dose ≥ 5 mg/d occurring at least 30 days after the incidence rate. Salvarani et al. (30) defined relapse or recurrence as reappearance of clinical symptoms in association with elevated ESR or CRP in a patient receiving steroids or after discontinuation of treatment. We evaluated clinical features in patients with PMR according to achievement of remission. The frequency of flare was significantly higher in patients without remission than those with remission (P = 0.02). These results suggest that whether flare develops or not during tapering of steroid could be an important predicting factor for remission. Larger prospective studies are needed in order to reveal therapeutic responses and prognostic factors of PMR in Korea.

In conclusion, Korean patients commonly develop PMR in the winter and show more seropositivity, although the titer is low. The response to steroid is fairly good; however, tapering is not easy due to frequent flare. Approximately 15.7% of patients went into remission and the frequency of flare was significantly lower than patients without remission. More than half of patients required second-line treatment in order to reduce the steroid dose, which is most commonly methotrexate. The course of PMR is not benign, because remission is rare and relapse occurs frequently with long-term steroid treatment.

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