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Abstract

We analyzed the rate of polymyalgia rheumatica (PMR) and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, both characterized as seronegative inflammatory arthritis in elderly, in an outpatient unit where primary care physicians are working in Japan to better understand the epidemiological characteristics of the diseases in Japan. Consecutive outpatients who newly visited at Department of General Medicine, Asahikawa Medical College Hospital, Japan between April 2004 and March 2010 were analyzed. Each parameter such as age, sex, diagnosis, and biochemical examination was investigated. During the 6 years, 10 or 3 patients were diagnosed as PMR or RS3PE syndrome, respectively. The patients with PMR were 7 females and 3 males and the average age at diagnosis was 69 years old. Out of all patients aged over 50 years old (n= 3347), the rate of PMR was 0.22 % in male or 0.36 % in female, respectively. On the other hand, RS3PE syndrome was diagnosed in 3 males (76, 76 and 81 years old). The rate of patients with RS3PE syndrome was 0.09 % among outpatients aged over 50 years indicating that the rate of PMR in an outpatient clinic in Japan is not far from previous findings reported from western countries. When compared with PMR, the rate of RS3PE syndrome was approximately one third, providing for the first time the rate of RS3PE syndrome when compared with PMR. These epidemiological data might help us pick up the diseases in primary care setting in Japan.

Key word; polymyalgia rheumatica (PMR), remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, primary care, Japan, epidemiology

Introduction

Polymyalgia rheumatica (PMR) is one of the most widespread inflammatory rheumatic disease affecting people aged over 50 years and characterized by pain and morning stiffness in the neck, shoulder, and pelvic girdle [1]. PMR is generally regarded as a benign disease with no adverse impact on long-term survival [2, 3] and represents one of the most common indicators for long-term steroid therapy in the community [4, 5]. Patients with PMR are subjected to wide variations in clinical practice, and may be managed in primary or secondary care by general practitioners [6, 7]. A couple of studies demonstrated the prevalence of PMR in USA and Canada [8-10]. With regard to the reports on PMR in Japan, there are some clinical studies on patients with PMR. For example, five independent research groups demonstrated clinical features in 29, 13, 7, 44 or 32 patients with PMR in Japan, respectively [11-15]. Thus, PMR is observed commonly in Japan. However, the prevalence of the disease is not so far known.

Increasing evidence have suggested that remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome is also one of the inflammatory rheumatic disease of the elderly [16]. RS3PE was described in 1985 by McCarty et al. as an original subgroup of seronegative rheumatoid arthritis [17]. It occurred especially in men older than 60. The onset of the disease was sudden and characterized by a symmetrical polyarthritis associated with pitting edema of the extremities of the upper and lower limbs. According to the report by Olivieri et al [16], the following diagnostic criteria for this syndrome had been proposed. These include 1. bilateral pitting edema of both hands, 2. sudden onset of polyarthritis, 3. age more than 50 years and 4. seronegative rheumatoid factor. So far there are some papers that show patients with RS3PE syndrome in Japan. A couple of independent research groups have demonstrated 7, 13, 11 or 3 Japanese patients with RS3PE syndrome [18-21]. Thus RS3PE syndrome is not very rare in Japan. However, the prevalence of the disease in Japan is not known. Thus little is known

about the epidemiologic feature in patients with PMR and RS3PE syndrome, both characterized as seronegative inflammatory arthritis in elderly [1, 17]. According to the study by Kremers [7], generalists provide the majority of care for patients with PMR. Rheumatologist involvement is generally limited to diagnostic confirmation and management of complications. Thus, primary care physicians have to pay attention to accurately diagnose PMR in the daily practice. A retrospective chart review of 123 PMR patients referred to a tertiary care rheumatology clinic in Canada demonstrated that the accuracy of PMR diagnosis by nonrheumatologists was very low (24 %), and that a large number of inappropriate tests were performed by nonrheumatologists in an effort to reach diagnosis [22]. It is therefore important for general practitioners to understand epidemiological characteristics of PMR in addition to diagnose the disease accurately. Based on these evidence, the present study was performed to clarify the rate of Japanese patients with PMR or RS3PE syndrome in a clinic where primary care physicians are working in Japan.

Patients and Methods

We analyzed consecutive outpatients who newly visited at Department of General Medicine, Asahikawa Medical College Hospital between April 2004 and March 2010. As we have recently demonstrated [23, 24], the hospital consists of 602 beds in which approximately 250 doctors are working to cover almost all of medical problems. Among them, 5 or 6 primary care physicians are working at the Department of General Medicine. All data were drawn from medical records and Computerized Physician Order Entry System in the hospital. Each parameter such as age, sex and diagnosis was investigated from the source.

PMR was diagnosed according to the previous reports [14, 25, 26]. They fulfilled the following clinical and laboratory conditions; age older than 50 years; suffering from severe myalgia and/or stiffness of bilateral neck, shoulders and pelvic girdle for at least 2 weeks; bilateral upper arm

tenderness; a marked increased erythrocyte sedimentation rate (ESR > 50 mm/h). Normal serum creatinine kinase (CK) concentration, and negative for rheumatoid factor (RF) and antinuclear factor (ANA), and a dramatic response to low doses of corticosteroid are observed. According to a previous report [27], patients were included as RS3PE syndrome if they were older than 50 years and satisfied the following diagnostic criteria: symmetrical polyarthritits, pitting edema of the bilateral hands and foots, serological absence of RF and a fast response to steroid therapy.

Results

Out of 6868 patients, PMR or RS3PE syndrome was diagnosed in 10 (0.15 %) or 3 (0.04 %) patients, respectively. Table 1 shows the clinical characteristics of 10 patients with PMR in this study. The patients with PMR ranged from 58 to 82-years old, and were 7 females and 3 males. The average age at diagnosis was 69 years old. All patients had suffered from severe myalgia in at least two parts of the body including the neck, shoulders, and pelvic girdle. The myalgia had persisted for 1-4 months. ESR at initial phase was over 50 mm/h in all patients. RF was negative in all 10 cases. They responded well to PSL at doses of 5-15 mg/day.

On the other hand, RS3PE syndrome was diagnosed in 3 males (76, 76 and 81 years old) in this study. Female patients with RS3PE syndrome have never observed in this analysis. Onset of appearance of edema in extremities with myalgia was sudden in all patients. Clinical characteristics of 3 patients with RS3PE syndrome are showed in Table 2. CRP level was elevated in all cases. However, ESR was high in two cases (No1 and No.2) but normal in one case (No.3). Two patients (No. 1 and No. 3 in Table 2) were initially treated with 20 or 15 mg/day of PSL. The response to the dose of PSL was excellent in the two cases within first week. On the other hand, PSL at the dose of 30 mg was not effective in a patient (No. 2). The patient (No. 2) had been diagnosed as prostate cancer approximately 10 years ago by a doctor in other hospital. He would die 1 year later after the first visit to our clinic because of bone metastasis from

prostate cancer, suggesting that the paraneoplastic factor-induced RS3PE [28, 29] in this case might explain the steroid-resistance observed.

Table 3 demonstrates the distribution of age and sex in patients with PMR or RS3PE syndrome in this study. Out of all patients aged over 50 years old, the rate of PMR was 0.22 % in male or 0.36 % in female, respectively. The rate of patients with RS3PE syndrome was 0.09 % among general population aged over 50 years. When compared with PMR, the rate of RS3PE syndrome was approximately one third.

Discussion

The only population-based study of PMR is from Olmsted County, Minnesota, USA where the prevalence of PMR are given from cumulative incidence rates [8, 9]. Among persons aged over 50 years, the prevalence of PMR was 739 per 100,000. Bernatsky et al. [10] have estimated that the prevalence of PMR in Manitobans, Canada aged over 50 years would be approximately 641 cases per 100,000 in urban area and 864 cases per 100,000 in rural areas. These are compatible with the Olmsted County data. In this study, out of 3347 outpatients aged over 50 years, 10 patients were diagnosed as PMR, estimating for the first time the rate of PMR is approximately 300 per 100,000, suggesting that the prevalence of PMR estimated in Japan is not so far from those in USA and Canada.

Previous studies have shown that women are affected two times more often than are men [30-32]. The present study revealed that the rate of PMR was 0.22 % in male or 0.36 % in female, respectively, indicating 1.6 times higher prevalence in women. The gender difference in Japan observed in this study furthermore supports the previous evidence observed in western countries that PMR is more frequently in women than men. The average age at diagnosis was 69 in this study, being in good agreement with the previous evidence that the mean age at diagnosis of PMR was approximately 70 years old [30-32].

To our knowledge, there is no evidence on the prevalence of RS3PE syndrome in not only Japan but also other countries. Based on

this study, the rate of patients with RS3PE syndrome in Japan was 0.09 % among outpatients aged over 50 years. When compared with PMR, the rate of RS3PE syndrome was approximately one third. However, the number of patients with RS3PE syndrome is quite small in this study, thereby suggesting that a much larger survey should be performed to more accurately estimate the prevalence of RS3PE syndrome in future.

Paiva et al. have demonstrated that patients presented clinical characteristics suggestive of paraneoplastic RS3PE had a poor response to corticosteroid therapy [29]. In patients with RS3PE, the presence of systemic symptoms along with resistance to low doses of corticosteroid therapy as shown in the present study (No. 2 in Table 2) should alert the physician to the possible presence of malignancy. In fact, the present patient who did not respond to steroid had advanced prostate cancer. Although the serum level of vascular endothelial growth factor (VEGF) or the expression of VEGF in the prostate cancer cells was not examined in this study, we would speculate that increased expression of VEGF in the prostate cancer cells might play a role in the key molecule that induces RS3PE syndrome in the No. 2 patient in this study as following. A couple of reports demonstrated that prostate cancer cells overexpress VEGF [33-36] and overexpression of VEGF increases growth and alters the metastatic potential of prostate cancer cells [37]. Recent evidence have suggested that VEGF may be implicated in the pathogenesis of RS3PE syndrome [21]. These results suggest that VEGF produced by prostate cancer cells is capable of inducing not only tumor development but RS3PE syndrome including pitting edema in the present case (No. 2).

In conclusion, the present study demonstrated that out of 3347 consecutive outpatients aged over 50 years, 10 (0.3 %) or 3 (0.09 %) patients were diagnosed as PMR or RS3PE syndrome, respectively in an outpatient clinic where primary care physicians are working in Japan. This epidemiological evidence might help us understand the characteristics of the diseases in primary care setting in Japan.

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Table 1 Clinical characteristics of 10 patients with polymyalgia rheumatica (PMR)

Age	Gender	Symptom duration (months)	WBC (/mm ³)	CRP (mg/dl)	ESR (mm/h)	PSL dose (mg)
69	f	1	7690	1.18	85	5
82	f	2	9520	15.35	87	5
76	m	3	5030	5.1	85	10
58	f	4	6100	10.3	98	15
68	m	1	5550	3.53	84	15
70	f	5	8210	4.89	79	5
58	f	1	10870	5.95	94	10
73	f	2	6180	8.66	94	10
75	f	1	6010	4.15	91	15
67	m	2	6840	0.67	56	15

PSL, prednisolone

Table 2 Clinical characteristics of 3 patients with remitting seronegative symmetrical synovitis with pitting edema (RS3PE)

No.	Age	Gender	Symptom duration (months)	WBC (/mm ³)	CRP (mg/dl)	ESR (mm/h)	PSL dose (mg)
1.	76	m	2	6580	5.1	61	20
2.	82	m	1	8750	9.82	88	30 *
3.	76	m	2	6690	0.47	4	15

* This patient did not respond to PSL probably because of paraneoplastic (prostate cancer) factor-induced disease. PSL, prednisolone

Table 3 Age and gender distribution of patients with PMR and RS3PE

	Age	(A) Patients	(B) PMR (B/A)	(C) RS3PE (C/A)
Male	0-	44	0	0
	10-	166	0	0
	20-	471	0	0
	30-	479	0	0
	40-	299	0	0
	50-	406	0	0
	60-	440	2 0.45%	0
	70-	389	1 0.26%	2 0.51%
	80-	141	0	1 0.71%
	0 -49	1459	0	0
50-	1376	3 0.22%	3 0.22%	
overall	2835	3 0.11%	3 0.11%	
Female	0-	22	0	0
	10-	232	0	0
	20-	692	0	0
	30-	687	0	0
	40-	430	0	0
	50-	593	2 0.34%	0
	60-	589	1 0.17%	0
	70-	530	3 0.57%	0
	80-	258	1 0.39%	0
	0 -49	2062	0	0
50-	1971	7 0.36%	0	
overall	4033	7 0.17%	0	
Both	0-49	3521	0	0
	50-	3347	10 0.30%	3 0.09%
	Total	6868	10 0.15%	3 0.04%