Scintigraphic Findings and Serum Matrix Metalloproteinase 3 and Vascular Endothelial Growth Factor Levels in Patients with Polymyalgia Rheumatica

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Abstract: Objective: Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease that affects elderly people and is associated with synovitis. Recently, matrix metalloproteinase 3 (MMP 3) and vascular endothelial growth factor (VEGF) were reported to be involved in the pathogenesis of PMR-related synovitis. New evidence regarding the pathogenesis of PMR has been found; however, the diagnosis and outcomes of PMR remain uncertain. A more valid and standardized set of diagnostic criteria for PMR that preferably include laboratory and radiological assessment is required to facilitate the diagnosis of PMR, which is at present primarily based on the clinical symptoms. Methods: We performed gallium-67 scintigraphy to determine the distribution of inflammation in 6 patients with PMR; we also measured the serum C-reactive protein (CRP), MMP 3, and VEGF levels before and after corticosteroid administration. Results: Symmetrical gallium uptake was observed in the shoulders of all PMR patients, the pelvic girdles of 3 patients, the knees of 5 patients, and the wrists of 4 patients. The serum CRP, MMP 3, and VEGF levels were significantly elevated in pretreated PMR patients. Daily administration of 20 mg corticosteroid promptly and significantly decreased the serum CRP and VEGF levels. Moreover, the serum CRP levels were significantly correlated with the serum VEGF levels. Serum MMP 3 levels were increased in three patients and were decreased in two patients by daily administration of 20 mg corticosteroid. Conclusions: Gallium-67 scintigraphy demonstrated the existence of peripheral articular synovitis as well as proximal articular synovitis, which are common symptoms of PMR, in the study patients. The elevated serum VEGF levels before treatment promptly decreased after corticosteroid administration, suggesting the significant association of VEGF with the pathogenesis of PMR.

Keywords: Gallium-67 scintigraphy, matrix metalloproteinase 3, polymyalgia rheumatica, vascular endothelial growth factor.

INTRODUCTION

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease that affects elderly people [1]. The characteristic presenting feature of PMR is acute or subacute onset of bilateral pain and stiffness in the shoulders, pelvic girdle, and neck [1]. While the cause of PMR is unknown, the occurrence of articular synovitis in patients with PMR has been proven by synovial biopsy [2]. Recently, matrix metalloproteinase 3 (MMP 3) and vascular endothelial growth factor (VEGF) have been reported to be involved in the pathogenesis of PMR-related synovitis [3, 4].

To detect the distribution of inflammation in patients with PMR, we performed gallium-67 scintigraphy instead of technetium-99m bone scintigraphy before the administration of steroid treatment. Further, we measured the serum C-reactive protein (CRP) and VEGF levels in patients with PMR before and after the administration of corticosteroid therapy.

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METHODS

We studied 6 Japanese PMR patients who presented with fever of 38 degrees and clinical signs of synovitis such as pain, stiffness, tenderness, and swelling of multiple joints. The subjects who participated in this study provided informed consent. The diagnoses were made on the basis of Bird's criteria for PMR [5]. Serum rheumatoid factor, anti-cyclic citrullinated peptide antibody (anti-CCP antibody), and antinuclear antibody were not detected in any of the patients. Spinal pain and psoriasis, and pitting edema were not observed in our patients. The distribution of inflammation in the patients was evaluated using whole-body gallium-67 scintigraphy before the administration of steroid therapy. We measured the serum CRP and VEGF levels before and after treatment with steroids for 2 weeks. We also measured the serum matrix metalloproteinase 3 (MMP 3) levels before and after treatment with steroids for two months. All patients were administered 20 mg corticosteroid daily throughout the study period. Their serum CRP and MMP 3 concentrations were measured using a polyclonal (Dade Behring, Marburg, Germany) and monoclonal antibody-based (Daiichi Fine Chemical Co. Ltd., Toyama, Japan) latex-agglutination method, respectively. The serum concentrations of $VEGF_{165}$ (major form of VEGF) were measured using enzyme-linked

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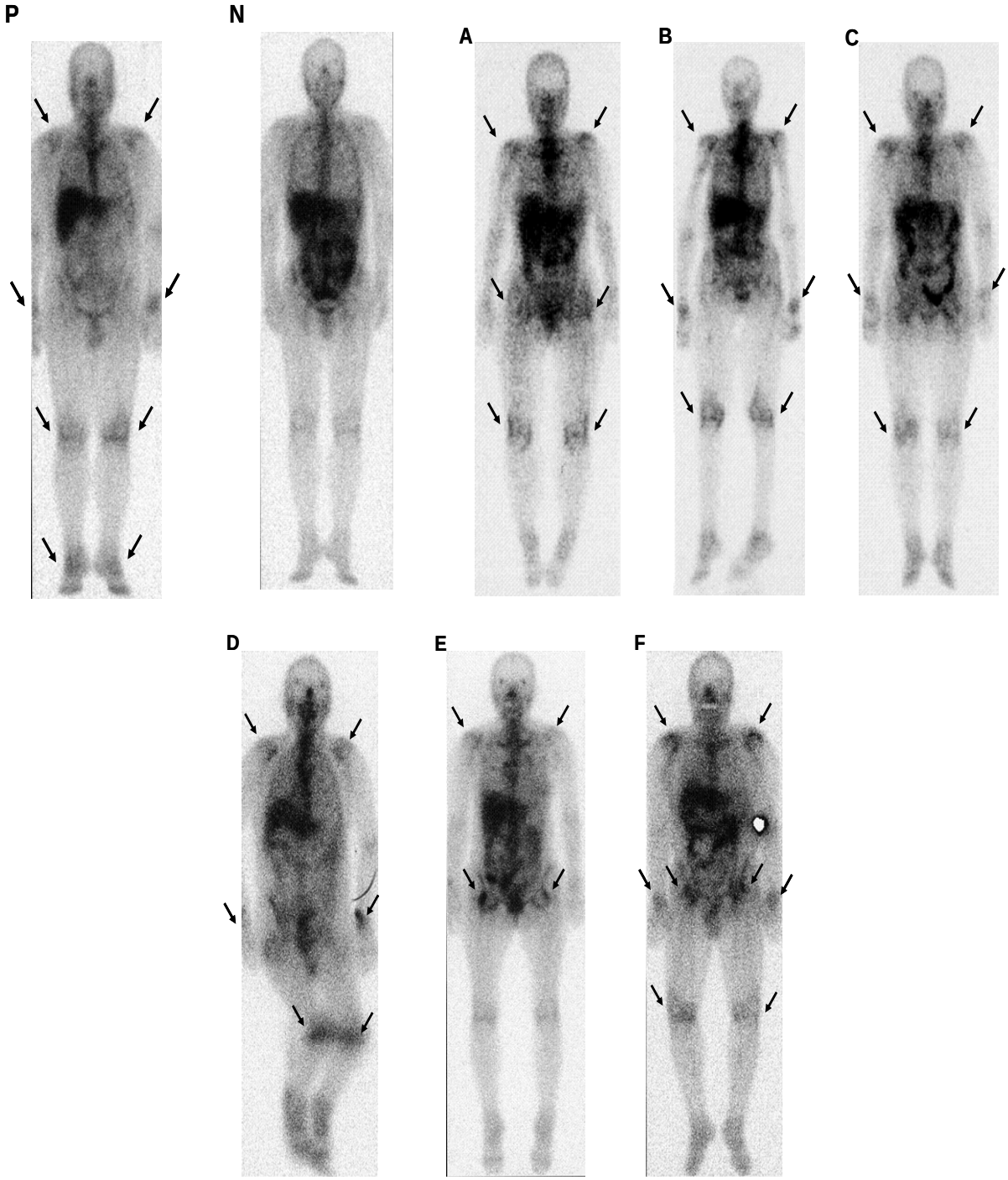

Fig. (1). Gallium-67 scintigraphic findings of patients (A–F) with polymyalgia rheumatica. A–F correspond to patients A–F in Table **1**, respectively. The arrows indicate gallium uptake. P and N indicate gallium-67 scintigraphic findings of patients with active remitting seronegative symmetrical synovitis (positive control) and active adult-onset Still's disease (negative control).

immunosorbent assay (ELISA; $VEGF_{165}$, R&D Systems Inc., Minneapolis, MN, USA). The differences in the serum CRP and VEGF levels before and after steroid therapy were analyzed using Wilcoxon's signed-rank test, and the correlation between the serum CRP and VEGF levels was analyzed using Fisher's Z transformation.

RESULTS

Symmetrical gallium uptake was observed in the shoulders of all PMR patients, the pelvic girdles of 3 patients, the knees of 5 patients, and the wrists of 4 patients (Fig. **1**). Gallium uptake was not detected in any other region apart from the articular and periarticular regions.

The serum erythrocyte-sedimentation rate (ESR) and CRP, VEGF, and MMP 3 levels were significantly elevated in pretreated PMR patients (Table **1**). Daily administration of 20 mg corticosteroid for 2 weeks promptly ameliorated clinical signs of synovitis. In all patients, morning stiffness, joint pain and swelling were completely disappeared within one week after the treatment started.

Table 1. Age, Sex, and Serum ESR, CRP, and VEGF Levels in PMR Patients Before Treatment

Patients	Age/Sex	ESR (mm/h)	CRP (mg/dl)	VEGF (pg/ml)	MMP 3 (ng/ml)
A	64/female	133	10.2	1,410	92.8
B	89/female	79	9.5	826	75.3
C	75/female	137	8.9	1,260	257.0
D	80/male	127	10.0	1,090	257.0
E	80/female	96	13.4	1,350	189.9
F	74/male	85	6.4	603	315.0
	normal range	3-19	< 0.3	< 115	17.3-59.7

Patients A-F correspond to A-F in Figure 1, respectively. CRP, C-reactive protein; ESR, erythrocyte-sedimentation rate; VEGF, vascular endothelial growth factor; MMP 3, matrix metalloproteinase 3; PMR, polymyalgia rheumatica.

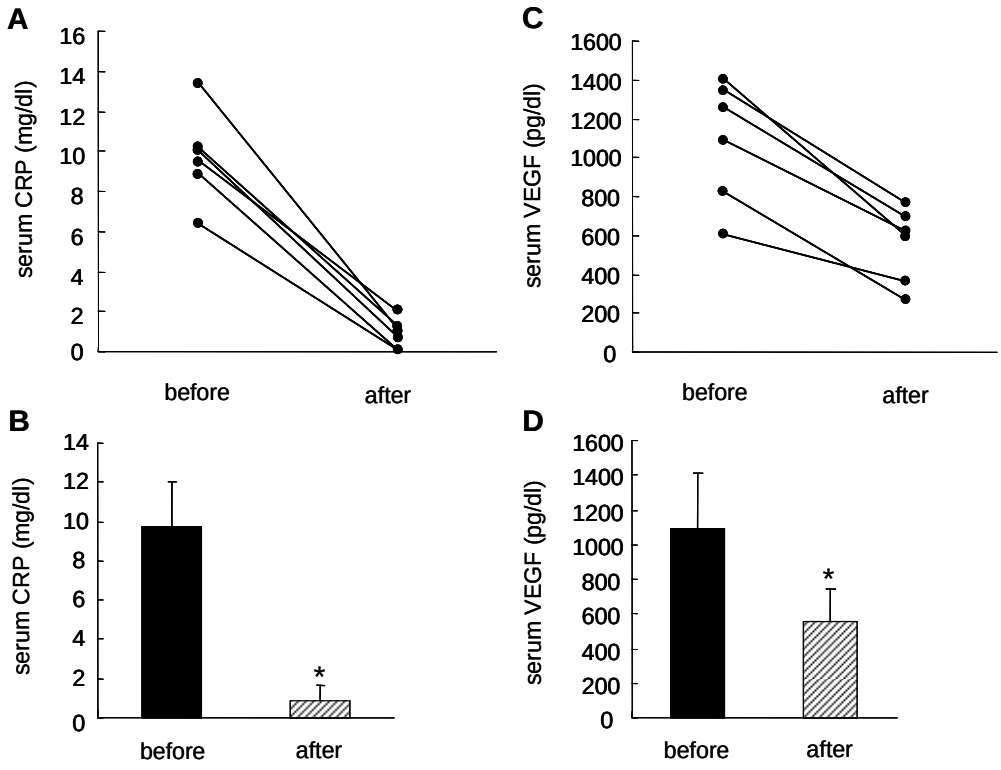

Fig. (2). Changes in serum C-reactive protein (CRP) and vascular endothelial growth factor (VEGF) levels before and after corticosteroid treatment for 2 weeks in patients with polymyalgia rheumatica. **A.** Changes in the serum CRP levels of individual patients. **B.** The Change in the mean serum CRP level (±SD) in the 6 patients. **C.** Changes in the serum VEGF levels of individual patients. **D.** The Change in the mean serum VEGF levels (±SD) in the 6 patients. *$P < 0.05$ vs. Wilcoxon's signed-rank test.

Daily administration of 20 mg corticosteroid also significantly decreased the serum CRP and VEGF levels in all patients (Fig. **2**). The serum CRP levels were significantly correlated with the serum VEGF levels (Fig. **3**). Serum MMP-3 levels were increased in 3 patients and decreased in 2 patients after the beginning of steroid therapy (Fig. **4**).

After 5 months after the beginning of treatment, the daily dosage of corticosteroid was below 5 mg in every patient. We follow up all patients for one to two years, and we could not find relapse of clinical signs of synovitis and increase in serum CRP in every patient, and we never prescribed disease modifying anti-rheumatic drugs for every patient.

DISCUSSION

There are considerable uncertainties related to the diagnosis of PMR and the outcomes of patients with PMR [6]. A more valid and standardized set of diagnostic criteria for PMR that preferably include laboratory and radiological assessment is required to facilitate the diagnosis of PMR, which is at present primarily based on the clinical symptoms.

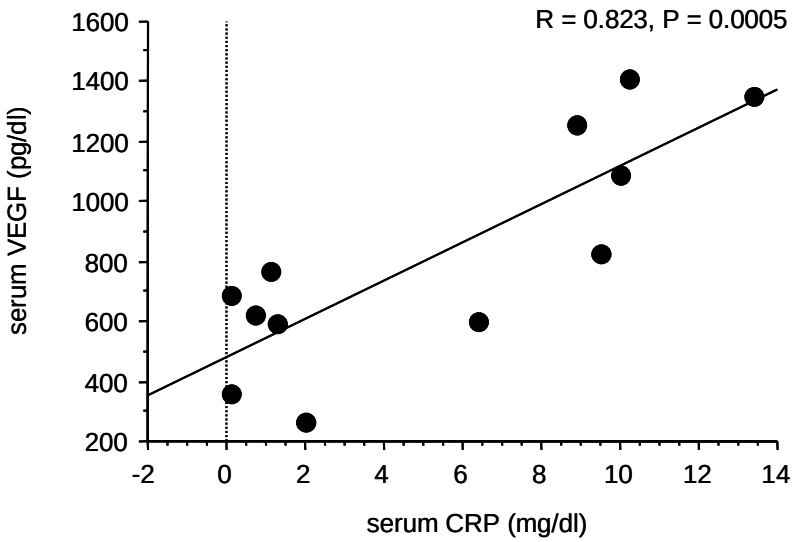

Fig. (3). Correlation between serum C-reactive protein (CRP) and vascular endothelial growth factor (VEGF) levels. R = correlation coefficient. Statistical analysis was performed using Fisher's Z transformation.

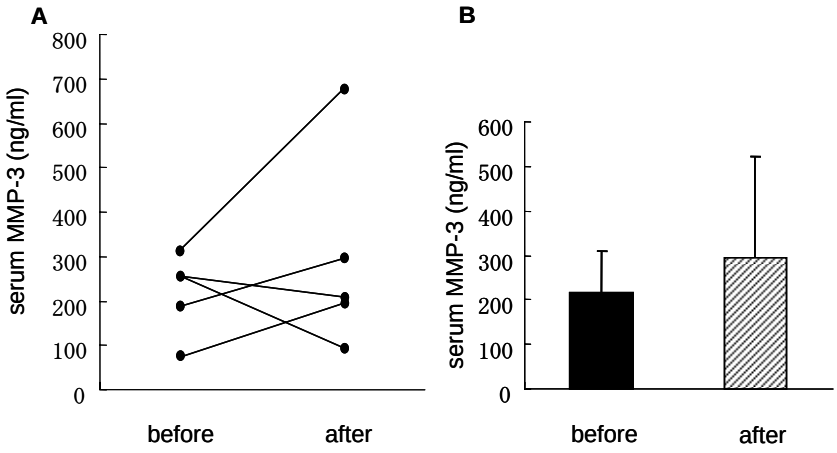

Fig. (4). Changes in serum matrix metalloproteinase 3 (MMP 3) levels before and after corticosteroid treatment for 2 months in patients with polymyalgia rheumatica. **A.** Changes in the serum MMP 3 levels of individual patients. **B.** The Change in the mean serum MMP 3 level (±SD) in the 6 patients. A statistical significant difference between values before and after corticosteroid treatment was not obtained by Wilcoxon's signed-rank test.

Recently, the members of the American College of Rheumatology have proposed criteria for the classification of PMR [7]. Over 70% of the survey respondents agreed on the importance of 7 core criteria. These were (1) age ≥ 50 years, (2) duration of symptoms ≥ 2 weeks, (3) bilateral shoulder and/or pelvic girdle pain, (4) duration of morning stiffness > 45 min, (5) elevated ESR, (6) elevated CRP, and (7) rapid response to steroid treatment (>75% global response within 1 week of daily treatment with 15–20 mg prednisolone). Our 6 PMR patients satisfied these 7 core criteria. Late-onset seronegative rheumatoid arthritis (RA) can mimic PMR in its early stages. Daily administration of 20 mg corticosteroid promptly ameliorated morning stiffness, pain and swelling of joints, and decreased the serum CRP within one week after the treatment started. After 5 months after the beginning of treatment, the daily dosage of corticosteroid was below 5 mg in every patient. We follow up all patients for one to two years, and we could not find any relapse of clinical signs of synovitis and increase in serum CRP in every patient, and disease modifying anti-rheumatic drugs was not required to prescribe for every patient. Although it is difficult to differentiate PMR from seronegative RA, the clinical course, a complete agreement with criteria for the classification of PMR (7), an absence of anti-CCP antibody, a presentation with fever, in our patient may suggest that our patients had PMR. However, we have to mention the possibility that the study cohort was not necessarily classical PMR, and that the number of subjects studied was too small to draw conclusion.

Further, gallium-67 scintigraphy revealed symmetrical gallium uptake in the shoulders of all patients, supporting the importance of bilateral shoulder pain in patients with PMR [7]. Although proximal musculoskeletal manifestations are considered to be the characteristic features of PMR, symmetrical gallium uptake in peripheral articular regions, including the wrists and knees, was observed in 5 of the 6 patients. Thus, physicians should be aware of the possibility of peripheral synovitis in patients with PMR in order to avoid misdiagnosis. Since several infectious and malignant disorders can present with symptoms similar to those of PMR, gallium-67 scintigraphy, not technetium-99m bone scintigraphy, should be used to determine the location of synovitis and to rule out infectious and malignant diseases.

Serum MMP-3 has been proposed as a synovial derived marker of inflammation [3]. Serum MMP-3 levels were elevated in our PMR patients before a steroid therapy, however, a corticosteroid therapy increased serum MMP-3 levels in 3 patients and decreased those in 2 patients. The mechanisms by which steroids increase serum MMP-3 levels in PMR patients should be revealed in the future.

VEGF has been shown to play an important role in the development of synovitis [4]. Serum VEGF levels were elevated before treatment, and the daily administration of 20 mg corticosteroid for 2 weeks decreased the serum VEGF levels in all patients. Furthermore, the serum CRP levels were significantly correlated with the serum VEGF levels. These results suggest that VEGF is significantly associated with the pathogenetic mechanism underlying PMR-related synovitis.

We consider that follow-up gallium-67 scintigraphy should be performed in patients with PMR in order to confirm the regression of synovitis. In the future, we intend to use ultrasonography as a less-invasive imaging technique for the follow-up of patients with PMR.

CONCLUSIONS

Gallium-67 scintigraphy demonstrated the existence of peripheral articular synovitis as well as proximal articular synovitis, which are commonly observed symptoms of PMR, in the study patients. Thus, physicians should be aware of the possibility of peripheral synovitis in patients with PMR. The serum VEGF levels before treatment were elevated; these levels rapidly decreased after the administration of steroid therapy. Further, the serum CRP and VEGF levels were significantly correlated, suggesting that VEGF may be associated with the pathogenesis of PMR.

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