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ORIGINAL ARTICLE

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Clinical characteristics of polymyalgia rheumatica in Japanese patients: evidence of synovitis and extracapsular inflammatory changes by fat suppression magnetic resonance imaging

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Abstract Polymyalgia rheumatica (PMR) is an inflammatory condition of unknown etiology characterized by diffuse pain and morning stiffness involving neck, shoulder, and pelvic girdles. To facilitate an understanding of PMR and its proper diagnosis, we evaluated clinical symptoms, laboratory data, and radiographic findings of 32 Japanese patients with it. Distal musculoskeletal manifestations were more frequently observed than had been thought before (81% of the patients), and peripheral arthritis was most common (75%). The joints most often affected were knees and wrists, and most episodes were presented as bilateral oligo- or polyarthritis. A swelling of hands was observed in 34% of the patients. Using contrast-enhanced fat suppression magnetic resonance imaging (MRI) of the shoulder, we found the evidence of subacromial and subdeltoid bursitis (100%), glenohumeral joint synovitis (93%), and biceps tenosynovitis (57%) in the PMR patients examined. Inflammatory changes in soft tissues around the joint capsule were prominent. By knee MRI, suprapatellar bursitis and joint synovitis were visualized in all cases examined, and extracapsular abnormalities were also prominent in 90% of the patients. Serum matrix metalloproteinase-3, a parameter of synovial inflammation, was significantly increased in PMR patients. Anticyclic citrullinated peptide antibody was useful for differential diagnosis between PMR and elderly onset rheumatoid arthritis. In conclusion, joint and periarticular synovitis seems to be commonly and primarily responsible for the proximal and distal musculoskeletal symptoms of PMR. The presence of the extracapsular change, probably a nonspecific extension of synovitis, can explain the severe discomfort that radiates toward the periphery. To avoid making a wrong diagnosis, we should be aware that peripheral synovitis is one of the hallmarks of PMR.

Key words Anticyclic citrullinated peptide antibody · Magnetic resonance imaging · Metalloproteinase-3 · Peripheral arthritis · Polymyalgia rheumatica · Synovitis

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Introduction

Polymyalgia rheumatica (PMR) is a clinical syndrome affecting people aged over 50 years and characterized by pain and morning stiffness in the neck, shoulder, and pelvic girdles.[1] Constitutional symptoms including fatigue, fever, anorexia, weight loss, and depression are present in most patients. Usually PMR is dramatically improved with a once-daily low dose of steroids and has a favorable prognosis.[1] Over the past few decades, a sizable number of reports have originated from Europe and the United States.[1] In contrast, the prevalence of PMR in Japan had been thought to be very low until quite recently, and only a few reports regarding Japanese patients were available.[2–4] A variety of clinical diagnostic criteria for PMR has been suggested for many years,[5–7] but there is a lack of universally accepted criteria. A more standardized set of diagnostic criteria for PMR, which may include laboratory and radiological investigations, are needed to reinforce the diagnosis mainly judged from clinical symptoms.

The presence of proximal articular and periarticular synovitis in PMR has been proven by arthroscopy,[8] synovial biopsy,[9,10] ultrasonography (US),[11,12] scintigraphy,[13] and magnetic resonance imaging (MRI).[14] Using US and MRI of the shoulders, Cantini et al. showed that subacromial and subdeltoid (SA-SD) bursal synovitis (= bursitis) is the most frequent and unique lesion present in almost all PMR patients.[11,15] The synovitis of glenohumeral joints and the

tenosynovitis of biceps are present in approximately two-thirds of the patients.[15] Fat suppression MRI is useful to visualize inflammatory sites in bones and soft tissues outside the synovial cavity, since this technique more precisely detects the presence of fluid. Using the fat suppression MRI of shoulder, McGonagle et al. showed that abnormalities in soft tissues around the joint capsules are the most striking findings in PMR.[16] Thus an unanswered question remains whether the primary abnormality in PMR is the articular and periarticular synovitis/bursitis or the capsular/entheseal-based pathogenesis.

Distal musculoskeletal manifestations have been reported in approximately half of the PMR cases, but they are more variable and less well characterized.[1] They include self-limited, nonerosive mono- or asymmetrical oligoarthritis (predominantly affecting knees and wrists), carpal tunnel syndrome, and distal-extremity swelling with pitting edema over the dorsum of hands and wrists as well as over the ankles and the tops of the feet.[1] An inflammatory involvement of articular and periarticular synovial compartments was evidenced by an MRI of hands in PMR patients.[17] In contrast, McGonagle et al. showed prominent soft tissue edema outside the joint cavity by the aid of the fat suppression MRI of the hands and ankles.[18] The knee is the site of peripheral synovitis most often affected; to our knowledge, however, the MRI findings of the knee in PMR patients have not yet been reported.

In this study, we evaluate the clinical symptoms and laboratory data of 32 Japanese patients who have been diagnosed as definite PMR patients in our hospital. Utilizing fat suppression MRI with contrast enhancement, we examine shoulder and knee joints for the following abnormalities: joint synovitis, tenosynovitis, bursitis, extracapsular inflammatory changes, and edema in bones and soft tissues. Serum levels of matrix metalloproteinase-3 (MMP-3), a synovial-derived inflammatory parameter,[19] are shown. For a differential diagnosis of PMR from elderly onset rheumatoid arthritis (EORA) and elderly onset spondyloarthritis (SpA), enzyme-linked immunosorbent assays (ELISAs) of anticyclic citrullinated peptide antibody (anti-CCP Ab) and HLA-B typing are performed.

Patients and methods

Patients

We reviewed 32 patients (17 males and 15 females) with probable PMR who had been diagnosed at the Departments of Rheumatology, Neurology, and Orthopedic Surgery of Kumamoto Saishunsou National Hospital from September 2001 through October 2006. Diagnosis had been based on Bird's criteria for PMR[5]: (a) bilateral shoulder pain or stiffness, or both; (b) onset of illness within 2 weeks; (c) initial erythrocyte sedimentation rate (ESR) greater than 40 mm/h; (d) duration of stiffness greater than 1 h; (e) age 65 years or older; (f) depression or weight loss, or both; and (g) bilateral upper arm tenderness. If any three or more of these seven criteria were fulfilled, a diagnosis of probable PMR had been made. All of them had shown a positive response to steroid treatment. We therefore considered these patients to have definite PMR. Of 32 patients with definite PMR, 31 had been interviewed and diagnosed by ourselves. Only one patient had been diagnosed by a neurologist of our hospital. Clinical symptoms listed in Table 1 had been evaluated and recorded at first outpatient examinations. To confirm the presence and type of musculoskeletal symptoms, we reviewed outpatient charts of all patients comprehensively.

Magnetic resonance imaging

Several clinical conditions, such as rheumatic disorders, infections, and neoplasms, can mimic musculoskeletal symptoms of PMR.[20] Recent studies demonstrated that evidence of bilateral SA-SD bursitis can be used as a new diagnostic criterion for PMR.[1,11,21] Since 2003, we have used MRI of the shoulder for the detection of SA-SD bursitis. It has been reported that unlike RA, peripheral arthritis in PMR is self-limited and affects mono- or oligojoints.[1,22] However, many of our patients complained of severe and progressive pain of multiple joints. To exclude a possibility of RA complication, we performed an MRI of the knee on patients having "atypical peripheral arthritis." At the first outpatient examinations, patients underwent an MRI of the shoulders and knees. At that time, they had not yet received steroid treatment.

Magnetic resonance imaging was performed with 1.5-T whole-body MRI equipment (Magnetom Symphony, Siemens, Munich, Germany) utilizing a CP flex coil. We obtained fat suppression T2-weighted images (FS-T2W) (repetition time 3600 ms, echo time 100 ms, matrix 215 × 256, field of view 180 mm, slice thickness 4 mm, with an intersection gap of 0 mm), and fat suppression T1-weighted images (FS-T1W) (repetition time 681 ms, echo time 12 ms, matrix 224 × 320, field of view 180 mm, slice thickness 4 mm, with an intersection gap of 0 mm). For contrast-enhanced MRI, gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) was intravenously injected at a dose of 0.1 mmol/kg body weight. Using FS-T2W, we assessed the following regions of shoulder for abnormalities: synovial sheath of biceps tendon, synovial structure of glenohumeral joint, SA-SD bursa, extracapsular region, and insertion tract of rotator cuff. The following region of the knee was evaluated for abnormalities: synovial structure of knee joint, suprapatellar bursa, extracapsular region, and entheseal insertions. The regions corresponding to abnormalities on the FS-T2W images were also evaluated by contrast-enhanced FS-T1W. Scan images were examined by two experienced musculoskeletal radiologists (YK and KI) who were blinded to the patients' diagnoses.

Measurements of anti-CCP Ab and MMP-3 and HLA-B locus typing

Blood samples were collected at the first visit of the patients. To differentiate PMR from EORA, serum levels of anti-

CCP Ab were measured semiquantitatively using an ELISA kit (Axis-Shield Diagnostic, Dundee, UK). A serum was considered anti-CCP Ab positive if the absorbance of subjects was above 8 U/ml. The serum levels of MMP-3 were measured at the SRL (Tachikawa, Japan), using ELISAs. To differentiate PMR from elderly-onset SpA, we investigated whether the patients had HLA-B27 genotype. HLA-B typing was performed at the HLA laboratory, NPO (Kyoto, Japan), using PCR-SSO methods. The ethics committee of our hospital approved a protocol for the genetic study. Written consent was obtained from all DNA donors.

Results

Clinical characteristics of patients with PMR at diagnosis

Table 1 shows the clinical manifestations of 32 patients (17 males and 15 females) at onset who were diagnosed as definite PMR in our hospital. The most frequent symptoms are morning stiffness and shoulder girdle pain. Pelvic girdle pain and muscle pain of upper arms and thighs were less common. Twenty-six patients (81%) showed distal musculoskeletal manifestations, including peripheral arthritis, swelling of hands and feet, and carpal tunnel syndrome. Peripheral arthritis was most common. Serum C-reactive protein (CRP) and ESR were considerably increased. Only three cases were positive for rheumatoid factor (RF), and anti-CCP Ab was negative in all. We performed HLA-B locus typing on 20 patients with peripheral arthritis. No cases showed HLA-B27 allele.

Peripheral arthritis occurred in 24 patients with PMR in a total of 81 episodes, and all episodes were observed at diagnosis. The frequency of monoarthritis, oligoarthritis (2 or 3 joints involved), and polyarthritis (more than 4 joints involved) was 8% (2 patients), 38% (9 patients), and 54% (13 patients), respectively. The distribution of peripheral arthritis was asymmetrical in 5 of 24 patients and symmetrical in 19 of 24. Table 2 shows the joints affected and the numbers of patients and episodes. The knees and wrists were the most frequently involved. Most peripheral arthritis occurred bilaterally. The mean number of affected peripheral joints in a patient was 3.4. No clinical evidence of joint deformity was observed, and none of the radiographs showed erosive changes in the involved joints at onset or during a follow-up period (27 ± 19 months). Whole-body 67-gallium citrate scintigraphy showed significant uptakes in multiple joints of patients having peripheral arthritis (data not shown). Low-dose prednisolone induced dramatic improvements of peripheral joint pain in most of the patients.

Fat suppression MRI of shoulders in patients with PMR

To evaluate the presence of SA-SD bursitis, a fat suppression MRI of the shoulder was performed on 14 patients with PMR: 9 cases with peripheral arthritis and 5 without it. The findings of the shoulder MRI are summarized in Table 3. Subacromial and subdeltoid bursitis was found in all PMR patients tested, regardless of the association of peripheral arthritis. Glenohumeral joint synovitis was also evident in 13 of 14 patients with PMR (93%). Biceps tenosynovitis was observed less frequently (57%), with a difference between two groups: 44% in patients with peripheral arthritis and 80% in patients lacking it. The evidence of prominent extracapsular abnormalities was shown in all patients having peripheral arthritis, but it was present in only one case lacking this association. Figure 1 shows fat suppression MRI films of the right shoulder in a PMR patient with peripheral

Table 1. Clinical and laboratory characteristics of polymyalgia rheumatica (PMR) patients at diagnosis ($n = 32$)

Age in years	72.3
Male:Female	17:15
Laboratory data	
Serum CRP level (mg/dl) (SD)	10.2 (5.8)
ESR (mm/h) (SD)	96 (20)
Subjects with positive RF	3/32
Subjects with positive anti-CCP Ab	0/32
HLA-B27 positive ($n = 20$)	0/20
Clinical symptoms (%)	
Morning stiffness	25/32 (78)
Shoulder girdle aching	25/32 (78)
Pelvic girdle aching	11/32 (34)
Muscle pain of upper arm	9/32 (28)
Muscle pain of thigh	9/32 (28)
Peripheral arthritis	24/32 (75)
Swelling of hands	11/32 (34)
Swelling of feet	2/32 (6)
Carpal tunnel syndrome	2/32 (6)
Fever	8/32 (25)
Depression	8/32 (25)
Temporal arteritis	0/32 (0)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; anti-CCP Ab, anticyclic citrullinated peptide antibody

Table 2. Peripheral joints affected in PMR patients ($n = 24$)

Affected joints	No. of patients	No. of episodes
Knee	19 (13)	32
Wrist	16 (13)	29
Ankle	6 (3)	9
Elbow	4 (3)	7
Hand	4 (0)	4

Numbers of patients who had bilateral joint involvements are shown in parentheses

Table 3. Magnetic resonance imaging findings of shoulders in patients with PMR

Findings	PMR with peripheral arthritis	PMR without peripheral arthritis
SA-SD bursitis	9/9	5/5
Glenohumeral joint synovitis	9/9	4/5
Biceps tenosynovitis	4/9	4/5
Extracapsular abnormality	9/9	1/5
Rotator cuff tear	2/9	0/5

SA-SD, subacromial and subdeltoid

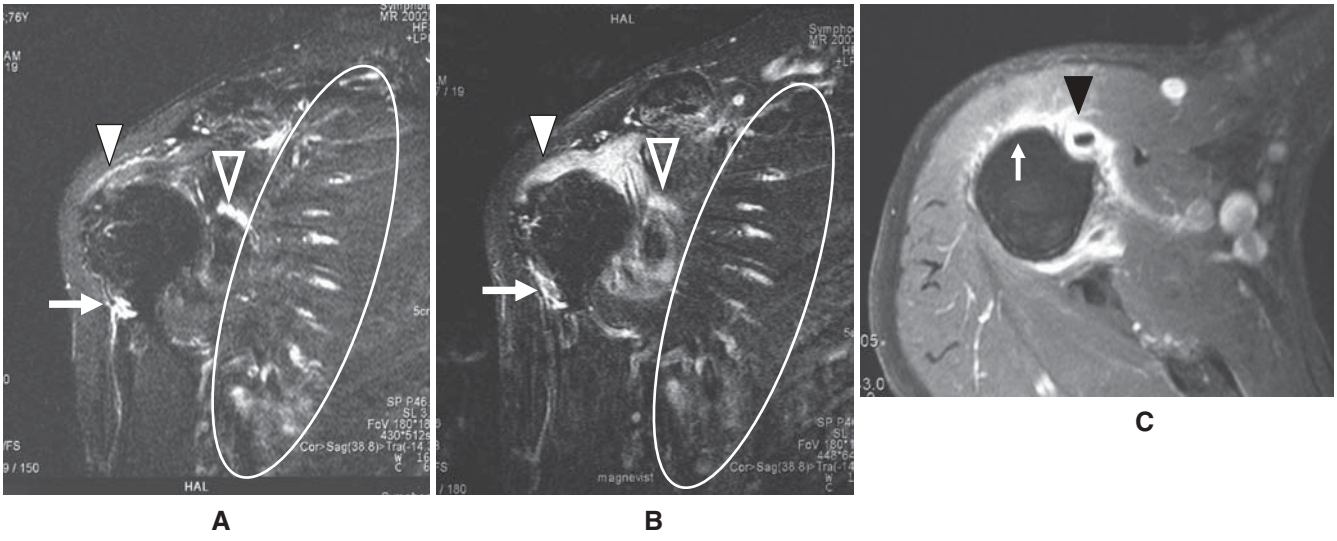

Fig. 1A–C. Fat suppression magnetic resonance imaging (MRI) findings of the right shoulder from a patient with polymyalgia rheumatica (PMR) and peripheral arthritis. The coronal images of fat suppression T2-weighted images (FS-T2W) (**A**) and contrast-enhanced FS-T1W (**B**) show a moderate extent of subacromial (*white arrowhead*) and subdeltoid (*white arrow*) bursitis and of glenohumeral joint synovitis (*open arrowhead*). Notably, high signals are evident in soft tissues around the joint capsule (*open oval*). Besides subdeltoid bursitis (*white arrow*), the axial contrast-enhanced T1W image (**C**) shows tenosynovitis of biceps (*black arrowhead*). No edema/fluid is present in extracapsular sites adjacent to the insertion tracts of the rotator cuffs

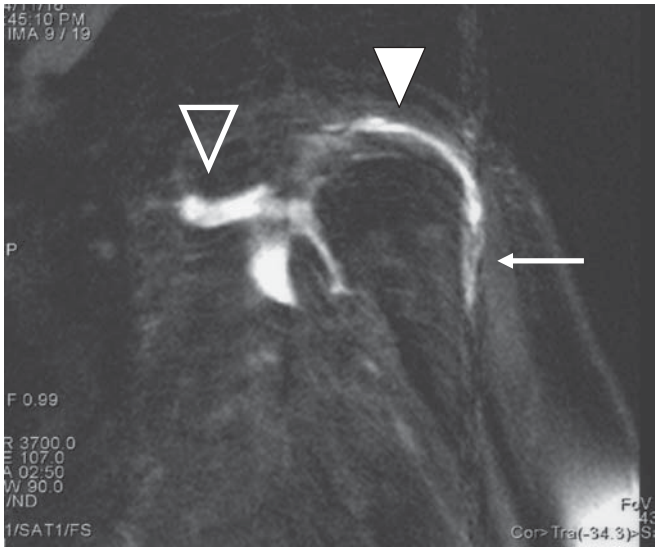

Fig. 2. Fat suppression MRI findings of the left shoulder from a PMR patient without peripheral arthritis. The coronal image of FS-T2W shows subacromial (*white arrowhead*), subdeltoid (*white arrow*) bursitis, and glenohumeral joint synovitis (*open arrowhead*). No abnormalities are visible in extracapsular sites around the shoulder joint

arthritis. On the coronial images of FS-T2W (Fig. 1A) and contrast-enhanced FS-T1W (Fig. 1B), high signals were found in soft tissues adjacent to the joint capsule, thereby showing that these abnormalities appear to be inflammatory changes, but not effusion. No edema was evident in the insertion tract of rotator cuff extending into the tendon and muscle belly of supraspinatus and subscapularis. Subacromial and subdeltoid bursitis and glenohumeral joint synovitis were also prominent. The axial FS-T2W image (Fig. 1C) indicated biceps tenosynovitis as well as subdeltoid bursitis. Figure 2 shows fat suppression MRI films of the left shoulder in a PMR patient lacking peripheral arthritis. Unlike the patient with peripheral arthritis, extracapsular inflammatory changes were not detected.

Table 4. Magnetic resonance imaging findings of knees in patients with PMR and peripheral arthritis

Findings	PMR
Suprapatellar bursitis	10/10
Joint synovitis	10/10
Extracapsular abnormality	9/10

Fat suppression MRI of knees in patients with PMR

A fat suppression MRI was performed for the knees of 10 patients having PMR and peripheral arthritis, and the findings are summarized in Table 4. Suprapatellar bursitis and joint synovitis were found in all patients examined. Joint effusion was evident by a comparison of the sagittal images of FS-T2W and contrasted FS-T1W (Fig. 3). Extracapsular inflammatory changes were also prominent and present in 9 of 10 patients with PMR; however, no edema was visible in soft tissues adjacent to entheseal insertions.

Serum concentrations of MMP-3 in patients with PMR

It has been reported that MMP-3 is a synovial-derived inflammatory parameter.[19] An increase in serum MMP-3 levels is observed in inflammatory rheumatic diseases characterized by joint synovitis, such as RA and PMR. We

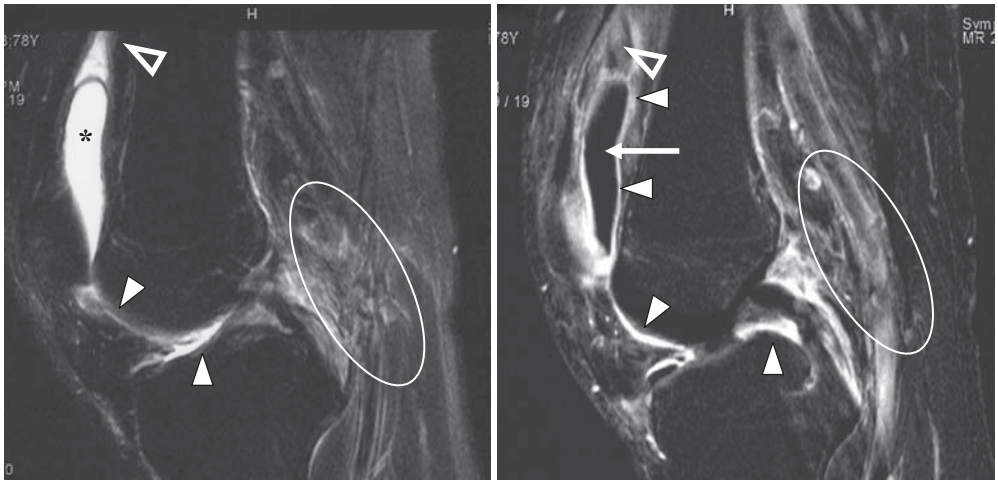

Fig. 3A,B. Fat suppression MRI findings of the right knee in a patient with PMR and peripheral arthritis. The sagittal sections of FS-T2W (**A**) and contrast-enhanced FS-T1W (**B**) show joint synovitis (*white arrowhead*), suprapatellar bursitis and effusion (*open arrowhead*), and extracapsular inflammatory changes (*open oval*). Joint effusion is also prominent in FS-T2W (*asterisk*) and contrast-enhanced FS-T1W (*white arrow*). There is no edema adjacent to the entheseal insertion

measured serum MMP-3 levels in 21 patients with PMR (10 males and 11 females). Most of the patients with PMR showed significantly high levels of serum MMP-3, and the averages were 226.2 ng/ml in females and 185.9 ng/ml in males.

Discussion

The etiology of PMR is poorly understood. In this study, SA-SD bursitis and glenohumeral joint synovitis were both observed in shoulder MRI of almost all PMR patients. Biceps tenosynovitis was also present in more than half of the patients (Table 3). These findings support the idea that synovial structures of proximal joints, tendon sheaths, and bursas are the main inflammatory sites involved, which may contribute to discomfort in the shoulder girdle. Salvarani et al. suggested a correlation between proximal bursitis and shoulder girdle symptoms because corticosteroid therapy improved the abnormal findings of shoulder MRI, parallel to the resolution of clinical symptoms.[1,14] Based on a similar concept, inflammatory changes of hip synovial structures, such as iliopectineal bursa and hip joint, may account for the clinical symptoms of pelvic girdle in PMR.[21] However, the pain and stiffness of shoulder and pelvic girdles are severe and diffuse, radiating toward elbows and knees. Can the limited inflammatory involvement simply explain such diffuse discomfort? Using fat suppression MRI, McGonagle et al. showed the presence of bone and soft tissue edema outside synovial compartments in approximately 50% of shoulders in PMR[16] and therefore suggested that the prominent edema may contribute to the diffuse nature of musculoskeletal symptoms in this disease. Using the same MRI technique, Cantini et al. showed the absence of extracapsular abnormalities in the early shoulder disease of PMR.[15] In ultrasonographic studies, Falsetti et al. also showed that enthesitis was relatively rare at any articular sites.[23] By fat suppression MRI with contrast enhancement, we have found inflammatory changes in soft tissues around the shoulder joint cavity in 72% of PMR patients, but there was no edema in the insertion tract of the rotator cuff of the shoulder (Table 3 and Fig. 1). Our data may suggest that the extracapsular lesion observed here is a nonspecific and secondary extension of articular and periarticular synovitis to surrounding soft tissues. The association of extracapsular inflammatory changes can contribute to the diffuse discomfort in the proximal extremities. We have discovered through experience that an injection of steroids into the subacromial bursa of PMR patients induces only a partial and transient improvement of shoulder symptoms.[20] This knowledge also suggests the involvement of extracapsular lesions in the characteristic musculoskeletal manifestations of PMR.

The frequency of distal musculoskeletal manifestations in PMR is still controversial, ranging from 6% to 60% in previous reports.[1,22,24–27] In this study, 26 patients (81%) showed distal musculoskeletal involvement, and peripheral arthritis was the most frequent one (75%) (Table 1). Several authors reported an association of mono- or asymmetrical oligoarthritis with PMR;[1,22,24] however, we have found that most episodes of peripheral arthritis are presented bilaterally, and polyarthritis is the most common form (Table 2). Similar to previous findings, the most frequently involved distal joints were the knees (79%) and wrists (67%). These percentages are higher in our study than were previously reported.[1] This may be explained by the fact that peripheral synovitis had not been widely acknowledged as a PMR manifestation until 1998,[22] and most studies had been done retrospectively. Further, the values obtained before may vary when more sensitive imaging techniques such as US and MRI are used. To facilitate a proper diagnosis of PMR, we should be aware that distal musculoskeletal involvement is one of the symptomatic features of this disease. With knee fat suppression MRI with the contrast enhancement, we found that prominent suprapatellar bursitis and joint synovitis were present in all patients. Prominent extracapsular abnormalities were also observed in 90% of PMR patients, but no edema/fluid was evident in soft tissues adjacent to entheseal insertions (Fig. 3 and Table 4). Like shoul-

der joints, synovitis/bursitis of knee seems to be a primary abnormality in PMR, and the extracapsular inflammation may be the secondary site of disease localization.

Salvarani et al. have proposed that the presence of peripheral synovitis in PMR could constitute a more severe subset because it is associated with a longer duration of steroid therapy and a higher frequency of relapse and recurrence.[22] On the contrary, Ceccato et al.[26] and Narvaez et al.[24] suggested that PMR patients with peripheral synovitis would not represent a high-risk subgroup with more severe disease, since they found no significant differences in clinical symptoms or laboratory data between patients with and without peripheral synovitis. In our study, a more frequent incidence of extracapsular abnormalities in shoulders was observed in PMR patients having peripheral arthritis (Table 3). This finding may suggest that the presence of peripheral arthritis in PMR is related to the severity of disease.

Several studies proposed a need for diagnostic criteria for PMR specific to the Japanese, since there are particularly characteristic symptoms in Japanese patients.[3,4] In a retrospective study, Nobunaga et al. showed that thighs are more frequently involved in Japanese patients with PMR, as compared with the Caucasian population.[4] They also proposed an absence of hand joint swelling as a criterion for PMR.[4] In our study, the myalgia of thighs and upper arms was a less frequent complaint (28%) on comparison with a previous report from the Japanese association for PMR, where the involvement of thighs and upper arms was 77% and 53%, respectively.[3] Moreover, 34% of patients showed a swelling of hands at the onset (Table 1). In this regard, we can say that the criterion of "no swelling in hand joints" should not be included in the differential diagnosis of PMR from RA.

The occurrence of peripheral arthritis in PMR may create some difficulties in a differential diagnosis between PMR and EORA. Some cases of EORA have a PMR-like appearance, characterized by shoulder/pelvic involvement, an absence of RF, and a nonerosive course.[13,28–30] Anti-CCP Ab may be useful in the differential diagnosis because of the excellent specificity to RA.[31,32] In this study, all patients were negative for anti-CCP Abs (Table 1). The absence of anti-CCP Ab appears to be a key feature for the PMR diagnosis. Although an absence of RF has been considered one criterion in PMR diagnosis, we have found that 3 patients (9%) have a positive titer of RF (Table 1). RF positive is reported to increase with age, and 12% of healthy people over the age of 60 are estimated to be RF positive,[33] which may be unreliable in the differentiation between PMR and EORA.

Elderly-onset SpA is characterized by asymmetrical peripheral oligoarthritis occurring with pitting edema, minimal involvement of the axial skeleton, constitutional symptoms, and elevated ESR.[34,35] Some cases developing PMR-like proximal symptoms have been described.[35] Several reports suggested that the HLA-B27 association may allow the differentiation of PMR from elderly-onset SpA.[36,37] We showed that no patients examined had the HLA-B27 allele (Table 1). Furthermore, peripheral enthesitis, one of the most typical extra-articular manifestations of SpA,[38] was not found in the fat suppression MRI of knees in our patients (Fig. 3).

In conclusion, joint and periarticular synovitis appears to be the common and primary abnormality that is responsible for the proximal and distal musculoskeletal symptoms of PMR. The secondary extracapsular changes can explain the severe and diffuse discomfort. The distal musculoskeletal manifestations, especially peripheral arthritis, were more frequently observed than had been previously thought. A recognition of peripheral arthritis as the PMR symptom helps to make an early diagnosis for this disease.

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