Gadolinium-enhanced magnetic resonance imaging in shoulders contributes accurate diagnosis and predicting recurrence to patients with polymyalgia rheumatica

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Abstract

Objective

We aimed to evaluate whether gadolinium-enhanced magnetic resonance imaging (MRI) in shoulders can contribute to more accurate diagnosis and prediction of recurrence in patients with polymyalgia rheumatica (PMR).

Methods

Gadolinium-enhanced MRI and ultrasonography (US) in shoulders were performed in the patients who had bilateral shoulders pain and fulfilled the Bird's Classification Criteria between June 2012 and June 2018. PMR was clinically diagnosed by at least two rheumatologists. MRI and US findings assessed by independent radiologists were compared between the PMR or non-PMR patients. PMR patients were treated with 20 mg/day of prednisolone and were followed-up until June 2019 to determine any recurrences of the disease.

Results

PMR was diagnosed in 58 of 137 patients received gadolinium-enhanced MRI and US examinations. Enhancement of joint capsule, enhancement of rotator cuff tendon and focal bone oedema in humerus heads were frequently found in the PMR patients. If the three findings were used in combination to diagnose PMR, MRI had 76% sensitivity and 85% specificity, higher compared to US findings, which had 50% sensitivity and 72% specificity. During follow-up, PMR recurred in 24 patients. Patients with recurrent PMR were younger in age, had less enhancement of rotator cuff tendon and more synovial hypertrophy findings on their MRI.

Conclusion

Gadolinium-enhanced MRI could display capsulitis, rotator cuff tendonitis and focal bone oedema in humerus heads that was sensitive and specific to patients with PMR, improving diagnostic accuracy in PMR. Rotator cuff tendonitis and synovial hypertrophy on MRI could help predict recurrence in PMR.

Key words

polymyalgia rheumatica, diagnosis, magnetic resonance imaging, shoulder, ultrasonography

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Introduction

Polymyalgia rheumatica (PMR) is an inflammatory disorder that causes muscle pain and stiffness, especially in the shoulders and hips. PMR is clinically diagnosed based on symptoms, although it is difficult to make an accurate diagnosis because the symptoms may occur in many other rheumatologic and inflammatory diseases (1). Bird's Classification Criteria (2) composed of the combination of clinical symptoms is highly sensitive to detect PMR, but is less specific, requiring caution in order to exclude other diseases (3). Recent researches suggest that ultrasonography (US) used in shoulder joints could detect findings specific to PMR, such as biceps tenosynovitis and subdeltoid bursitis (4). EULAR/ACR Provisional Classification Criteria (5) adopting the US findings improved the specificity, but the sensitivity was not enough (6-8). The diagnosis of PMR remains challenging (9). Clinicians need a new diagnostic tool with high specificity and sensitivity for PMR. Besides, we often encounter recurrences of PMR during tapering glucocorticoids, even though PMR is a glucocorticoid-responsive disease. Such a glucocorticoid-dependent case should be concomitantly treated with disease-modified anti-rheumatic-drugs (DMARDs) (1). Clinicians need a marker to predict recurrence of PMR in addition to diagnostic tools (10).

Magnetic resonance imaging (MRI) has the advantage of visualising bone and muscle lesions. Thus, MRI has already been utilised to assess rheumatoid arthritis (RA) (11) or spondyloarthritis (SpA) (12) in clinical practice. However, its application in PMR has not been established yet (9, 13). In this study, we evaluated gadolinium-enhanced MRI findings of shoulders in patients with PMR.

Patients and methods

This study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by local ethics committee (approval number: 20185). All study participants provided informed consent.

Study population and data collection

This study consists of two parts: a cross-sectional study and the follow-up one. In the cross-sectional part, participants included the consecutive patients who had bilateral shoulders pain and fulfilled the Bird's Classification Criteria for PMR (2) between June 2012 and June 2018 at Tomakomai City Hospital in Japan. We excluded patients with contraindications of gadolinium-enhanced MRI. All the study participants underwent gadolinium-enhanced MRI and US examinations on their shoulders. PMR was clinically diagnosed by at least two rheumatologists without referring to MRI/US findings evaluated by independent radiologists. Clinical symptoms, laboratory data and imaging were compared between the PMR or non-PMR patients.

Clinical symptoms data were collected through standardised questionnaires and physical examinations at the first visits. Data regarding laboratory measures, such as rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibody, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and matrix metalloproteinase 3 (MMP-3), were obtained from clinically ordered tests at baseline.

In the follow-up part, patients diagnosed with PMR were prescribed 20 mg/day of prednisone initially, and then this dose was tapered after remission. Prednisolone was increased up to 40 mg/day for the cases complicated with giant cell arteritis or resistant to 20 mg/day of prednisolone. The patients were followed-up until June 2019 to determine any recurrences of PMR defined as reappearance of the symptoms with elevated serum CRP levels. We compared clinical findings and imaging at baseline between the PMR patients with or without recurrences. Patients dropping out within 6 months from initiation of the treatment were excluded from the analysis of the follow-up study.

Gadolinium-enhanced MRI and US procedure

MRI of a dominant shoulder was performed using 1.5 Tesla (Ingenia, Philips, Nederland) equipped with a high-resolution small extremity 8ch

coil. We obtained T1-weighted and fat-suppressed T2-weighted images (both coronal and axial images) of the shoulder. Fat-suppressed T1-weighted coronal, axial and sagittal images were taken after intravenous injection of gadolinium contrast medium (Gadovist, Bayer, Germany) with a dose of 1mmol/kg body weight. The imaging protocol for the T1-weighted images was the following: repetition time (TR), 400 ms; echo time (TE), 14 ms; matrix size, 368 × 368; field of view (FOV), 190 mm; slice thickness, 5 mm; slice gap, 1 mm; number of signals averaged (NSA), 1. The fat-suppressed T2-weighted image parameters were as follows: TR, 3000 ms; TE, 56 ms; matrix, 256 × 256; FOV, 190 mm; slice thickness, 5 mm; slice gap, 1 mm; NSA, 1. The gadolinium-enhanced fat-suppressed T1-weighted image parameters were as follows: TR, 400 ms; TE, 14 ms; matrix, 336 × 336; FOV, 190 mm; slice thickness, 5 mm; slice gap, 1 mm; NSA, 1.

US examination of both shoulders was performed by independent technicians according to a standardised protocol (5) using the Aplio 500 (Canon, Japan) machine with a 10–14 MHz linear probe. US findings of shoulders were evaluated about the three features previously reported to be associated with PMR, including biceps tenosynovitis, subdeltoid bursitis and glenohumeral synovitis. In the study, both shoulders with at least one of these findings were defined as positive US, according to the EULAR/ACR Provisional Classification Criteria.

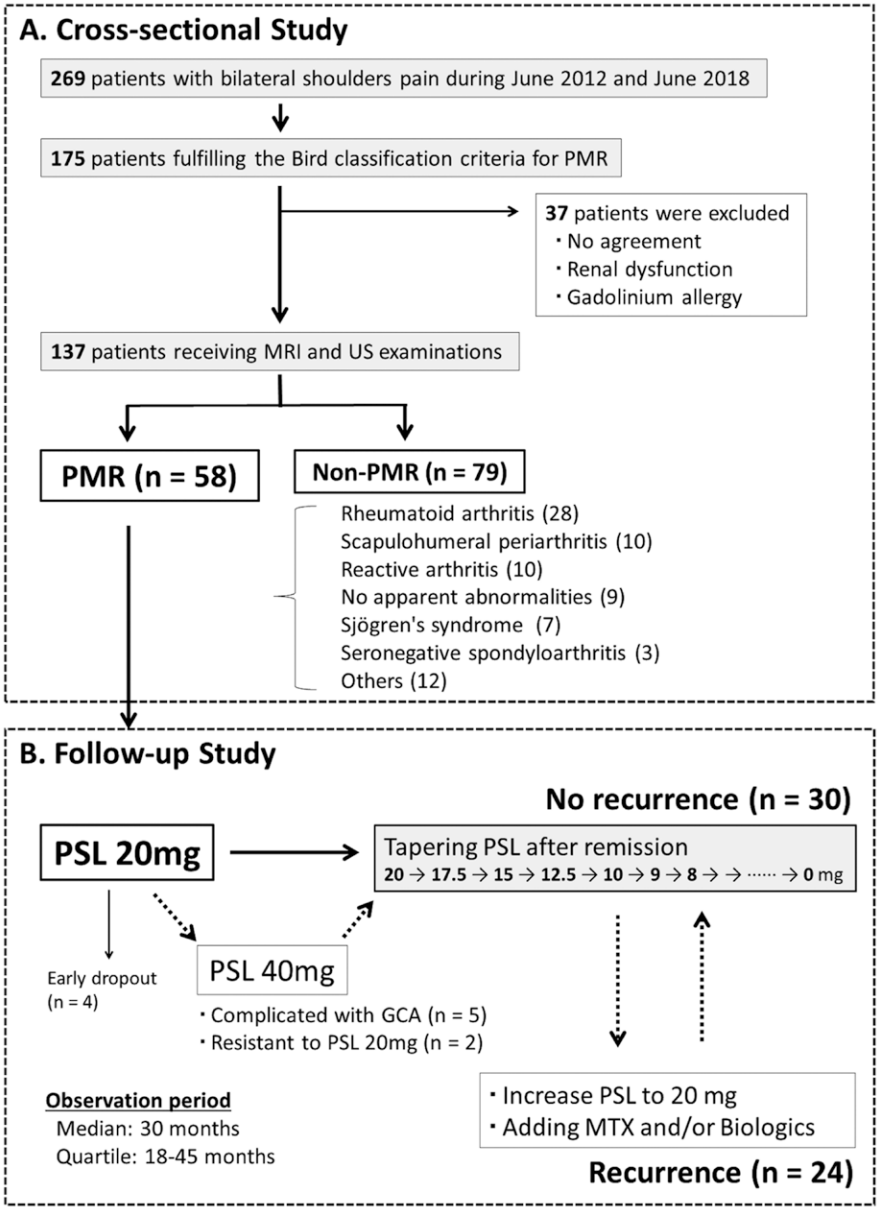

Fig. 1. Study design and patient recruitment.
PMR: polymyalgia rheumatica; PSL: prednisolone.

Statistical analysis

Categorical variables described as percentages, were compared with chi-square test. Continuous variables expressed as the median and quartile, were evaluated with Wilcoxon and/or Cochran-Mantel-Haenszel tests. Diagnostic value was expressed as area under ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). In the follow-up study, we calculated odds ratio (OR) and the 95% confidence interval (CI) for recurrence of the disease. When the *p*-value was below 0.05, the result showed statistical significance. All analyses were performed using the JMP Pro software (v. 12.2; SAS Institute Inc., Cary, NC, USA).

Results

Patients' background

During the study period, 269 patients visited our hospital complaining of bilateral shoulders pain, and 175 of them fulfilled the Bird classification criteria for PMR. Gadolinium-enhanced MRI and US examinations were performed in 137 patients, and PMR was diagnosed in 58 patients. Other diagnoses were given to 79 patients: 28 with RA, 10 with scapulohumeral periarthritis, 10 with reactive arthritis, 9 without apparent abnormalities, 7 with Sjögren's syndrome, 3 with SpA, 2 with systemic lupus erythematosus, 2 with large-vessel vasculitis, 2 with fibromyalgia, 2 with rotator cuff injury, 1 with small-vessel vasculitis, 1 with scleroderma, 1 with mixed connective tissue disease, 1 with adult-onset Still's disease, 1 with uveitis and 1 with pseudogout. Because of disagreement with participation, renal dysfunction or gadolinium allergy, 37 patients were excluded from the study (Fig. 1A).

Age at onset was older in the patients with PMR than in those with non-PMR.

Table I. Clinical findings in the patients with PMR (n=58) or non-PMR (n=79).

	PMR (58) (=Sensitivity)	Non-PMR (79)	*p*-value†	Specificity
Age at onset, years	75 (67-78)	66 (55-74)	**<0.01**	-
Female, %	60	70	0.26	70
Bilateral upper arm tenderness, %	95	62	**<0.01**	38
Hip pain and/or limited range of motion, %	71	25	**<0.01**	75
No other joint involvements, %	55	39	0.06	61
Morning stiffness >1 hour, %	97	78	**<0.01**	22
Depression and/or weight loss, %	97	61	**<0.01**	39
Negative RF or anti-CCP antibodies, %	100	52	**< 0.01**	48
ESR, mm/h	91 (75-116)	46 (17-69)	**<0.01**	-
CRP, mg/dL	6.5 (4.5-8.7)	0.8 (0.3-3.7)	**<0.01**	-
MMP-3, ng/mL	202 (116-325)	87 (50-192)	**<0.01**	-
Ultrasonography in shoulders				
Biceps tenosynovitis, %	43	23	**0.02**	77
Subdeltoid bursitis, %	32	12	**<0.01**	88
Glenohumeral synovitis, %	11	11	0.99	89
Gadolinium-enhanced MRI in shoulders				
Enhancement of shoulder joint capsule, %	69	35	**<0.01**	65
Enhancement of rotator cuff tendon, %	72	32	**<0.01**	68
Enhancement of biceps tendon, %	12	6	0.24	94
Synovial hypertrophy, %	12	15	0.60	85
Shoulder joint effusion, %	64	44	**0.02**	56
Enhancement of glenohumeral joint, %	5	10	0.29	90
Focal bone oedema in humerus head, %	59	19	**<0.01**	81
Diffuse bone oedema in humerus head, %	2	9	0.08	91

Continuous variables were expressed as the median (quartile). *p*-value†, chi-square test for categorical variables or Wilcoxon test for continuous variables.
CCP: cyclic citrullinated peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MMP-3: matrix metalloproteinase 3; MRI: magnetic resonance imaging; PMR: polymyalgia rheumatic; RF: rheumatoid factor.

Bilateral upper arm tenderness, hip pain and/or limited range of motion, morning stiffness >1 hour and depression and/or weight loss were frequently found in PMR patients, but these clinical symptoms had low specificity (22-39%) except for hip pain and/or limited range of motion (75%). The PMR patients had higher serum ESR, CRP and MMP-3 levels compared with the non-PMR patients (Table I).

Gadolinium-enhanced MRI and US findings

The independent radiologists pointed out enhancement of joint capsule, enhancement of rotator cuff tendon, enhancement of biceps tendon, synovial hypertrophy, shoulder joint effusion, enhancement of glenohumeral joint, focal bone oedema in humerus heads and/or diffuse bone oedema in humerus heads in the study's patients (Fig. 2). Of these MRI findings, enhancement of joint capsule (69% *vs*. 35%, $p<0.01$), enhancement of rotator cuff tendon (72% *vs*. 32%, $p<0.01$), shoulder joint effusion (66% *vs*. 44%, $p=0.02$) and focal bone oedema in humerus heads (59% *vs*. 19%, $p<0.01$) were signifi-

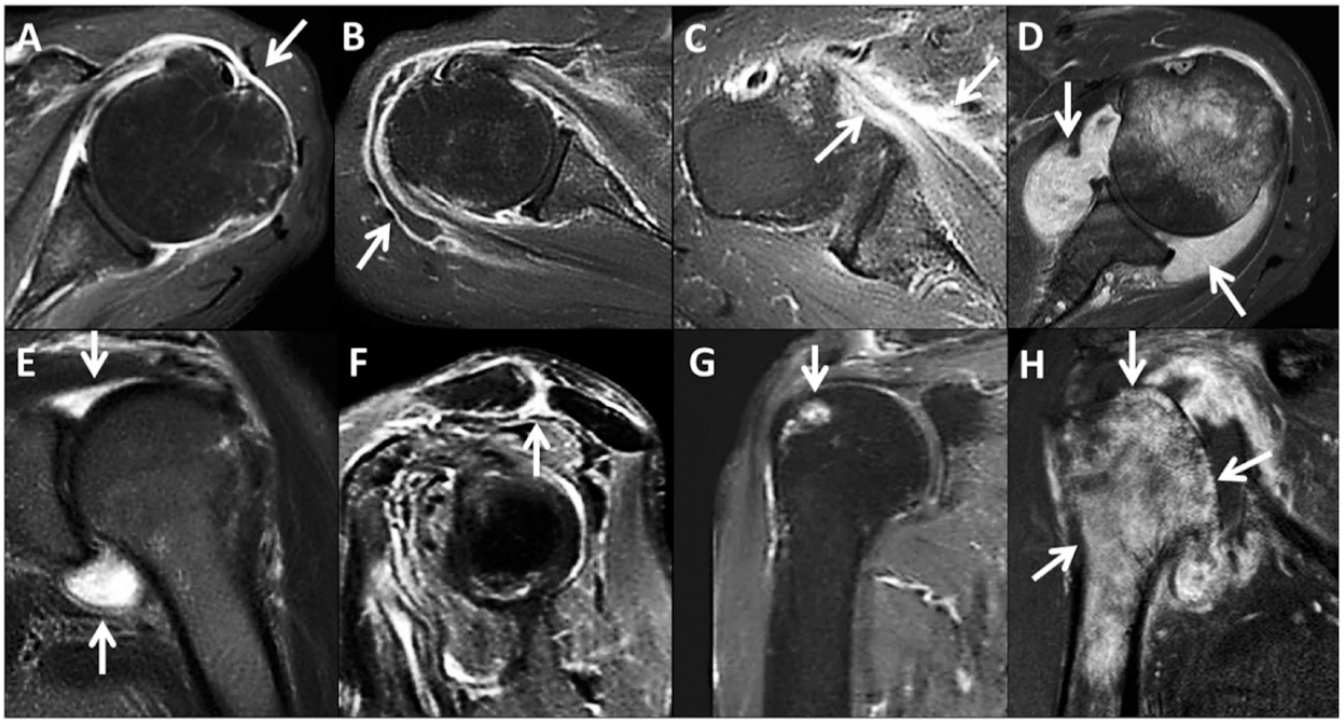

Fig. 2. Representative images of gadolinium-enhanced magnetic resonance imaging in shoulders.
A: Enhancement of shoulder joint capsule, **B**: enhancement of rotator cuff tendon, **C**: enhancement of biceps tendon, **D**: synovial hypertrophy, **E**: shoulder joint effusion, **F**: enhancement of glenohumeral joint, **G**: focal bone oedema in humerus heads and **H**: diffuse bone oedema in humerus heads.

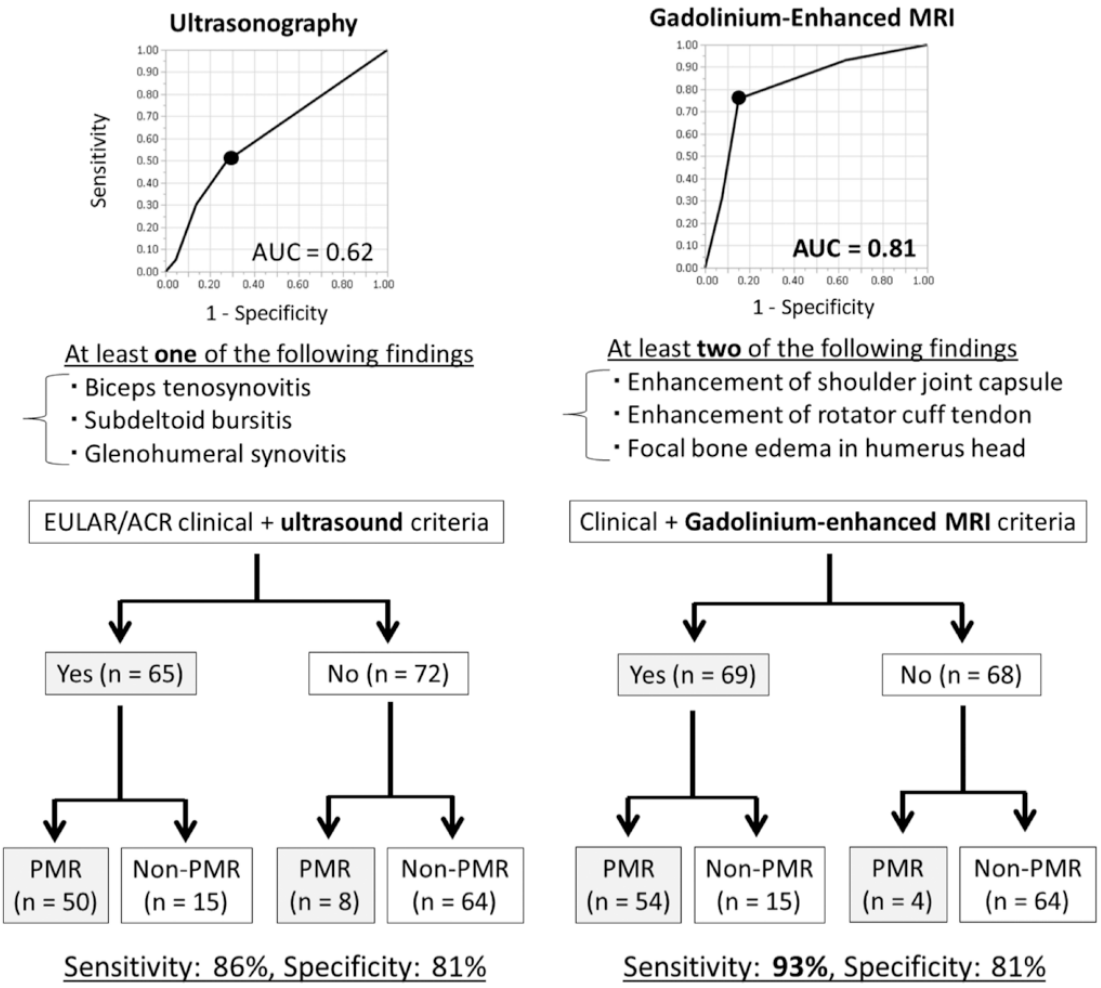

Fig. 3. Comparison of diagnostic value between ultrasonography and gadolinium-enhanced MRI for the diagnosis of PMR.

cantly more frequent in the PMR patients. Those MRI findings had both high sensitivity (59-72%) and specificity (56-81%). Biceps tenosynovitis (43% *vs*. 23%, p=0.02) and subdeltoid bursitis (32% *vs*. 12%, p<0.01) on US were also significantly more frequent in the PMR patients. However, these US findings had high specificity (77–88%) but low sensitivity (32-43%) (Table I).

If the enhancement of joint capsule, enhancement of rotator cuff tendon and focal bone oedema in humerus heads on MRI were used in combination to diagnose PMR, AUC was 0.81. When the cut-off value was set as at least two of the three findings, sensitivity and specificity for PMR diagnosis were 76% and 85%, respectively, higher than 50% and 72% of US criteria findings. PPV and NPV of MRI were 79% and 83%, respectively, also higher than 61% and 63% of US. Moreover, if the MRI criteria were used instead of US criteria in our cohort, the sensitivity of EULAR/ACR Provisional Classification Criteria increased to 93% from 86%, whereas the specificity remained the same level (81%) for PMR diagnosis (Fig. 3).

Follow-up study

Of 58 PMR patients, 54 were included in the follow-up study, excluding 4 patients who dropped out early. The median observation period was 30 months (quartile: 18-45 months). Prednisolone was increased to 40 mg/day in 5 patients complicated with giant cell arteritis and 2 patients resistant to 20 mg/day of prednisolone. PMR recurred in 24 patients (44%) during tapering prednisolone (Fig. 1B). The median time to recurrence was 10 months (quartile: 2–13 months). The patients with recurrent PMR were significantly younger in age, had less enhancement of rotator cuff tendon and more synovial hypertrophy findings on their MRI. These MRI abnormalities were still significant using Cochran-Mantel-Haenszel test stratified by age at onset. The patients with enhancement of rotator cuff tendon had low odds (OR: 0.2), while the patients with synovial hypertrophy had high odds (OR: 7.6) for recurrence of the disease. Laboratory data and US findings did not significantly differ between the PMR patients with or without recurrences (Table II).

Discussion

In this study, we evaluated gadolinium-enhanced MRI findings in shoulders of 58 PMR patients and 79 control subjects, and identified three findings that were sensitive and specific to patients with PMR. We subsequently assessed the diagnostic value of gadolinium-enhanced MRI for PMR by comparing with the existing classification criterions, especially with US criteria.

The symptoms defined by Bird's Classification Criteria for PMR were non-specific consisted with the previous reports (6-8). Thus, the criteria led to

Table II. Factors associated with recurrences in the patients with PMR.

Recurrence	No (n=30)	Yes (n=24)	*p*-value†	*p*-value††	OR (95% CI)
Age at onset, years	76 (71-82)	72 (66-77)	**0.04**		
Female, %	53	75	0.10		
ESR, mm/h	87 (80-113)	99 (71-126)	0.68		
CRP, mg/dL	6.4 (3.3-8.4)	7.0 (5.3-9.9)	0.11		
MMP-3, ng/mL	238 (132-333)	196 (113-403)	0.69		
Positive ultrasonography, %	52	52	0.97		
Gadolinium-enhanced MRI in shoulders					
Enhancement of shoulder joint capsule, %	77	67	0.41	0.40	0.6 (0.2-2.0)
Enhancement of rotator cuff tendon, %	87	58	**0.02**	**0.01**	**0.2 (0.1-0.8)**
Enhancement of biceps tendon, %	10	12	0.77	0.93	1.3 (0.2-7.0)
Synovial hypertrophy, %	3	21	**0.04**	**0.04**	**7.6 (0.8-70.5)**
Shoulder Joint effusion, %	60	67	0.61	0.51	2.6 (0.2-31.0)
Focal bone oedema in humerus head, %	53	63	0.50	0.38	1.5 (0.5-4.4)

Continuous variables were expressed as the median (quartile). *p*-value†, chi-square test for categorical variables or Wilcoxon test for continuous variables. *p*-value††, Cochran-Mantel-Haenszel test stratified by age at onset.
OR: odds ratio; CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Enhancement of shoulder joint capsule, %7767MMP-3: matrix metalloproteinase 3; MRI: magnetic resonance imaging.

many false-positive results in our cohort, unless careful diagnosis of exclusion was done. Inflammatory markers, such as CRP, ESR and MMP-3, were also non-specific, although they may be helpful for the diagnosis of PMR (14). Biceps tenosynovitis and subdeltoid bursitis were specific to PMR, but US examination could not detect the findings with enough sensitivity. On the other hand, gadolinium-enhanced MRI was highly sensitive to detect abnormalities of bones and muscles in shoulders. In particular, gadolinium-enhanced MRI specifically displayed enhancement of joint capsule, enhancement of rotator cuff tendon and focal bone oedema in the humerus heads in our patients with PMR. These MRI findings had higher sensitivity and specificity for the diagnosis of PMR than US findings in our cohort. Previous reports have indicated effusion around joint capsule and/or rotator cuff tendon on non-enhanced MRI in patients with PMR (15-17). US also detects such an extracapsular effusion in patients with PMR (4). Our study showed gadolinium-enhanced MRI could clearly display capsulitis and/or rotator cuff tendonitis without effusion on non-enhanced images. Besides, MRI could reveal focal bone oedema in subcortex of humerus heads in our patients with PMR. MRI was highly sensitive to detect such a small bone abnormality. We demonstrated that gadolinium-enhanced MRI could improve diagnostic accuracy in PMR when the specific and sensitive MRI findings were used in combination. Our proposed MRI criteria could be superior to existing US criteria for the diagnosis of PMR. Clinicians can diagnose PMR with confidence using gadolinium-enhanced MRI with high sensitivity and specificity, which will lead to decreasing misdiagnosis of PMR. The follow-up study showed patients with synovial hypertrophy on MRI had frequent recurrences of PMR. Differential diagnosis between PMR and seronegative RA is often complicated, but synovial hypertrophy is thought to be a finding to suggest RA-like phenotype rather than typical PMR (1). Thus, clinicians have to be cautious when making a clinical diagnosis of PMR in patients with synovial hypertrophy on their shoulder MRI. Those patients would have true, even undifferentiated, inflammatory arthritis in their shoulders. Clinicians may consider using DMARDs from the early stage for the patients with synovial hypertrophy. In contrast, the patients with enhancement of rotator cuff tendon had less recurrences of PMR. The fact suggests that rotator cuff tendonitis may be a typical finding of PMR to guarantee a good response to glucocorticoids. A previous work reported extracapsular findings on MRI was associated with complete glucocorticoid responsiveness for PMR (16). Our study showed that gadolinium-enhanced MRI could be useful for predicting recurrences of PMR, whereas US findings did not relate to the recurrences.

There were several limitations in the study. First, we could not evaluate asymptomatic or atypical PMR patients who did not fulfill the Bird's Criteria. Second, we did not evaluated hip joints by both MRI and US in the study. Third, sensitivity of US examination depends on skills of operators, although our US technicians had standard skills. The sensitivity of US examination may be underestimated in our cohort compared with the studies performed by US experts. Finally, gadolinium-enhanced MRI has some disadvantages: high cost, adverse effects of gadolinium contrast medium and unavailability in some clinics. US is more feasible than MRI. We need to validate, optimise and standardise the gadolinium-enhanced MRI procedure for the diagnosis of PMR to be applied in real-world clinical practice.

In conclusion, gadolinium-enhanced MRI displayed capsulitis, rotator cuff tendonitis and focal bone oedema in shoulders sensitively and specifically in patients with PMR. Besides, rotator cuff tendonitis and synovial hypertrophy on MRI were associated with recurrences of the disease. Our study showed that gadolinium-enhanced MRI of the shoulder could play a useful clinical role in patients with PMR, contributing to diagnostic accuracy and prediction of recurrence in patients with this rheumatic disease.

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