

# Evidence for Synovitis in Active Polymyalgia Rheumatica: Sonographic Study in a Large Series of Patients

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**ABSTRACT. Objective.** To determine the frequency and localization of synovitis and enthesitis in patients with active, untreated polymyalgia rheumatica (PMR) by ultrasonography (US).

**Methods.** Polyarticular sonographic evaluation was carried out in 50 consecutive patients with PMR at disease onset. Results were compared with 50 consecutive patients with seronegative spondyloarthropathies (SpA) and 50 with seronegative and seropositive rheumatoid arthritis (RA) at disease onset.

**Results.** Synovitis and/or effusion was detected, in at least one joint, in 100% of patients with PMR. The most frequent alterations observed in patients with PMR were effusion in the subacromial-subdeltoid (SA-SD) bursa in 70% of patients, tenosynovitis of the long head of the biceps tendon (LHBT) in 68%, glenohumeral joint effusion in 66%, tenosynovitis of the flexor tendons in the carpal tunnel in 38%, radiocarpal effusion in 18%, wrist extensors tenosynovitis in 18%, coxofemoral joint effusion in 40%, knee effusion in 38%, and ankle effusion in 10%. Enthesitis and tendonitis of the anchoring tendons were relatively rare in all the articular sites. Comparison of the SpA and PMR patients showed that enthesitis (mostly in the elbow, knee, and heel) was significantly more frequent in SpA. There was a significant difference in glenohumeral and coxofemoral effusion between the PMR and SpA patients (66% vs 16% and 40% vs 14%, respectively). Comparison of PMR and RA patients showed no significant difference in the involvement of entheses, shoulder, hip, or wrist flexor tendons in the carpal tunnel. Synovitis of the elbow, knee, and wrist was significantly more frequent in the SpA and RA patients than in those with PMR.

**Conclusion.** Synovitis was detected in at least one site in 100% of patients with PMR. SA-SD bursitis, LHBT tenosynovitis, carpal tunnel syndrome, and glenohumeral, knee and hip synovitis were the most frequent alterations in PMR. Enthesitis was relatively rare at any articular site. (J Rheumatol 2002; 29:123–30)

## Key Indexing Terms:

POLYMYALGIA RHEUMATICA SONOGRAPHY SYNOVITIS ENTHESITIS

Polymyalgia rheumatica (PMR) is a syndrome that prevalently affects elderly subjects and that leads to a clinical picture characterized by morning stiffness, pain, and functional impairment of the neck, shoulders and pelvic girdle. It generally lasts for more than one month, and is often accompanied by increased erythrocyte sedimentation rate (ESR) and systemic symptoms such as fever, weight loss, and anorexia, which respond promptly to low dose corticosteroid therapy. The disease is strictly associated with giant cell arteritis, but its etiopathogenesis is unknown although it

has been hypothesized that cell autoimmunity plays an important role<sup>1,2</sup>.

The cause of the widespread musculoskeletal symptomatology has not been clarified, but the presence of synovitis of the joints and the peripheral and axial periarticular structures has been frequently observed by means of scintigraphy<sup>3,4</sup>, arthroscopy<sup>5</sup>, synovial biopsy<sup>6-8</sup>, ultrasonography (US)<sup>9-11</sup>, and magnetic resonance imaging (MRI)<sup>12-16</sup>, and it could at least partially explain the symptomatic picture. However, there are conflicting data concerning the frequency and prevalent localization of synovitis and enthesitis in PMR<sup>3-28</sup> (Table 1).

Ultrasound examination is an appropriate method for polyarticular screening studies because it is easy to perform, repeatable, inexpensive, and highly accurate for diagnosis<sup>29</sup>. We used articular US to examine a large sample of patients with active PMR at onset to establish the prevalence of synovitis and enthesitis involving the peripheral and axial joints, as well as the anatomic (intra or periarticular) localization.

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Table 1. Prevalence of synovitis in PMR in previous studies, expressed as percentage.

	Lange <sup>11</sup>	Coari <sup>9</sup>	Salvarani <sup>26</sup>	Koski <sup>10</sup>	Douglas <sup>5</sup>	Chuang <sup>20</sup>	O'Duffy <sup>3</sup>
Glenohumeral effusion	40.9 (US)	65.6 (US)	77 (MRI)	52 (US) (bilateral 50)	89 (AS)	2 (Clin)	80 (SG)
LHBT tenosynovitis	40.9 (US) (bilateral 33%)	15 (US)	54 (MRI)	42 (US) (bilateral 37)			
SA-SD bursitis	10 (US) (bilateral 0)	9.4 (US)	100 (MRI)	15 (US) (bilateral 66)			
Coxofemoral effusion			100 (MRI) (symptomatic patients)	52 (US) (bilateral 60)			
Knee effusion			35 (Clin)			6 (Clin)	36 (SG)
Carpal tunnel syndrome			14 (EMG)			13 (Clin)	
Wrist effusion			38 (Clin)				44 (SG)

US: ultrasound examination, MRI: magnetic resonance imaging, EMG: electromyography, Clin: clinical evaluation, AS: arthroscopy, SG: scintigraphy  
LHBT: long head of biceps tendon, SA-SD: subacromial-subdeltoid.

## MATERIALS AND METHODS

Since January 1998, all patients with suspected PMR attending our outpatient clinics have been evaluated by means of clinical, laboratory, sonographic, and radiological examinations. This study involved 50 patients (37 women, 13 men) with symptoms attributable to PMR who satisfied Healey's classification criteria<sup>30</sup>, including age of > 50 years (mean age 71) plus 3 of the following criteria: (1) pain in the neck, and shoulder and/or pelvic girdles; (2) marked morning stiffness > 1 h; (3) increased ESR; (4) a rapid response to low dose cortisone (< 20 mg prednisone equivalents). In all cases, the symptoms had lasted for more than one month (mean disease duration 80 days). No patient had taken corticosteroids during the 3 months preceding the US examination and laboratory tests. The results of blood chemistry tests were negative for antinuclear antibodies (ANA) and Waaler-Rose; some of the patients had low rheumatoid factor levels (< 60 IU/ml), but none satisfied the revised 1987 American Rheumatism Association classification criteria<sup>31</sup>. The mean ESR at diagnosis was 76 mm/h (normal < 12 mm/h). C-reactive protein (CRP) was positive in 98% of the cases, with a mean value of 4.6 mg/ml (normal < 1). Sixty percent of the subjects had systemic symptoms (fever, anorexia, weight loss). Only 2 patients had concomitant temporal arteritis.

Radiography of various joints (hand, wrist, elbow, shoulder, hip, knee, ankle, foot, and heel) performed at first visit and after 12 and 24 months did not reveal signs of erosive arthritis and/or chondrocalcinosis.

Within one week after the first outpatient examination, patients underwent multi-region US examination of various joints (wrist, elbow, shoulder, hip, knee, ankle, and heel) regardless of the presence of signs or symptoms of inflammatory involvement. The articular and periarticular structures (bursae, tendons, and entheses) were examined for both inflammatory (synovitis and/or effusions, tenosynovitis, enthesitis) and degenerative alterations, even if these were not directly associated with the ongoing disease.

A group of 28 healthy controls with a mean age of 68 years underwent the same multi-region sonographic screening examinations, as did 2 other groups of control patients affected by late onset systemic inflammatory arthropathies, at the onset of disease.

The first of these groups consisted of 50 consecutive untreated patients with late onset peripheral seronegative spondyloarthropathies (SpA) — 21 had psoriatic arthritis, 3 had enteropathic arthritis, and the rest had undifferentiated forms that satisfied the 1991 European Spondylarthropathy Study Group (ESSG) inclusion criteria<sup>32</sup>. The mean disease duration of the SpA control group was 100 days.

The second group consisted of 50 consecutive untreated patients with late onset seropositive (n = 29) or seronegative (21) rheumatoid arthritis (RA)<sup>31,33</sup>. The mean disease duration of the RA control group was 90 days.

The demographic and clinical characteristics of the case patients group and the control patient groups are shown in Table 2.

US examinations were carried out using a Toshiba Tosbee SAL 240 with a linear 7.5 MHz probe and a Kitecho gel pad spacer where necessary. Sonography was performed by 2 experienced operators (both rheumatologists) blinded to diagnosis. The medium rates of concordance between the 2 sonographers were 0.95 for the presence/absence of synovitis/effusion, and 0.92 for enthesitis. Each examination was carried out bilaterally and symmetrically, and every alteration was graded using a semiquantitative scale: grade 1 (mild), grade 2 (moderate), or grade 3 (considerable).

Sonographic findings of joint involvement were considered: anechoic joint space widening (interpreted as effusion), and homogeneous echoic or irregularly echoic widening (interpreted as synovial proliferation associated with effusion).

Sonographic findings of tenosynovitis were considered: tendon sheath widening resulting from effusion (anechoic pattern), proliferative synovitis (echoic pattern) or both, and/or irregularity of the tendon margin.

Sonographic findings of enthesitis were considered: heterogeneous hypoechogenicity and thickening of enthesis, possibly associated with enthesophytes, erosions, and peritendinous edema<sup>34</sup>.

Sonographic findings of the clinical picture known as "distal extremity swelling with pitting edema" were considered: subcutaneous edema (anechoic enlargement of subcutaneous tissue) associated with fluid collection in the extensor and flexor tendons synovial sheaths (of the hand or foot)<sup>35,36</sup>.

The various joints were scanned according to standardized methods<sup>37-42</sup>. In particular, the sonographic presence of carpal tunnel syndrome (CTS) was investigated using Buchberger's criteria<sup>43,44</sup>. The periarticular structures of the shoulder were studied according to the technique described by Mack, *et al*<sup>45</sup>, Middleton<sup>46</sup>, and other authors<sup>47-51</sup>, and glenohumeral effusion was evaluated using the transaxillary view according to the technique described by Koski<sup>52</sup> and by posterior transverse scans. The hip was examined using the anterior longitudinal view according to Koski, and by coronal and longitudinal scans<sup>53</sup>.

The percentage of inflammatory involvement (articular and periarticular) was referred to in the number of patients, and not as the total number of articular sites. Further, the percentage of bilaterality of each alteration was calculated in the various groups, because of the frequently asymmetrical nature of the alterations.

The entity of synovitis and the number of affected sites observed in the patients with PMR were correlated with their ESR and CRP levels, age, and sex<sup>54</sup>. The entity was calculated by the sum of all sonographic values recorded for all the articular sites in each patient using a 0-3 semiquantitative scale;

**Table 2.** Demographic and clinical characteristics of the PMR group and controls. No significant difference was noted in clinical and demographic characteristics among the 3 groups, except for significantly lower ESR in the SpA group.

	PMR	SpA Controls	RA Controls	p
No. of patients	50	50	50	
Male/female	13/37	22/28	15/35	NS
Mean age, yrs ( $\pm$ SD)	71 (8)	68 (7.6)	69 (6)	NS
Mean disease duration, days ( $\pm$ SD)	80 (35.2)	100 (53.3)	90 (38.8)	NS
Mean ESR, mm/h ( $\pm$ SD)	76 (9.8)	59 (18.7)	69 (12)	< 0.01
Mean CRP, mg/dl (SD)	4.6 (2.4)	3.8 (2.2)	4.5 (2.3)	NS
Classification criteria	Healey <sup>30</sup>	ESSG <sup>32</sup>	ARA (ACR) 1987 <sup>31</sup>	
Corticosteroid therapy in previous 3 months	No	No	No	

the number of sites was defined as the total number of affected sites in each patient regardless of severity.

Between-group frequencies were compared using Fisher's exact test, and the correlations were calculated using Spearman's rank correlation coefficient. ANOVA was used to compare the clinical and demographic characteristics of the groups.

## RESULTS

The results of US examination (PMR, SpA, and RA groups) are summarized in Figures 1 and 2 and in Table 3. Synovitis and/or effusion were detected in at least one site in 100% of patients with PMR, while enthesitis was detected in at least one site in 10% of cases. The most frequently involved site was the shoulder: effusion in the subacromial-subdeltoid (SA-SD) bursa in 35/50 patients (70%) (Figure 3A), tenosynovitis of the long head of biceps tendon (LHBT) in 34/50 (68%) (Figure 3A), and glenohumeral (GH) joint effusion in 33/50 (66%).

The wrist appeared to be affected by inflammation particularly at the level of the carpal tunnel, with tenosynovitis of

flexor tendons (19/50 patients, 38%), with bilateral alteration in all cases. Radiocarpal effusion was detected in 9/50 cases (18%). Inflammatory involvement of the tendinous structures of the back of the hand was detected in 18% of cases and it was bilateral in more than half (5/9) of the cases; 4 patients (8%) presented bilateral distal extremity swelling with pitting edema, with 3 cases detected at upper limb and one case at lower limb. Only one patient presented elbow effusion (2%).

Knee effusion was detected in 19/50 patients (38%). The hip joints showed effusion in 20/50 patients (40%) (Figure 3B). Enthesitis and tendonitis of the anchoring tendons (without synovial sheaths) were relatively rare in the heel (4/50, 8%) as well as in the other articular sites (epicondyle 0%, epitrochlea 0%, rotator cuff 0%, patellar tendon 0%, trochanteral entheses 2%). All the alterations detected in the group of healthy controls were of the degenerative type and were, therefore, always significantly different from those observed in the case and control patients.

**Table 3.** Prevalence and bilaterality of sonographically revealed inflammatory involvement in the PMR group and controls expressed as percentage.

	PMR		SpA Controls		RA Controls	
	Prevalence	Bilaterality	Prevalence	Bilaterality	Prevalence	Bilaterality
LHBT tenosynovitis	68	55.8	44	72.7	38	84.2
Glenohumeral effusion	66	78.7	16	62.5	54	64.7
SA-SD bursitis	70	77.1	34	70.5	44	90.9
Elbow effusion	2	0	18	22.2	28	35.7
Elbow enthesitis	0	0	18	44.4	6	0
Wrist effusion	18	44.4	48	83.3	90	91.1
Carpal tunnel syndrome	38	100	30	93.3	56	100
Wrist extensors tenosynovitis	18	55.5	20	80	58	75.8
Coxofemoral effusion	40	80	14	85.7	24	91.6
Hip enthesitis	2	0	6	33.3	0	0
Knee effusion	38	57.8	76	63.1	80	100
Knee enthesitis	0	0	22	63.6	0	0
Achilles tendon enthesitis	0	0	12	16.6	0	0
Plantar fasciitis	8	75	28	64.2	0	0
Calcaneal bursitis	0	0	10	20	4	0
Ankle effusion	10	40	6	33.3	26	76.9
Posterior tibial tendon tenosynovitis	6	0	2	0	22	81.8
Foot extensor tendons tenosynovitis	8	50	0	0	4	0
Peroneal tendons tenosynovitis	2	0	0	0	4	0

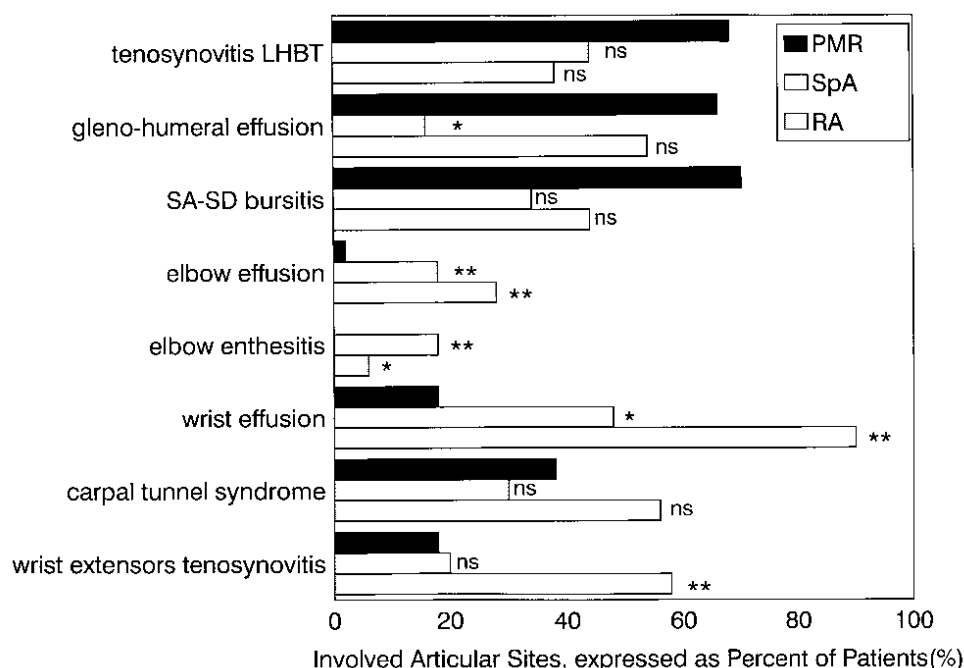


Figure 1. Prevalence of sonographically revealed inflammatory alterations in patients with PMR and 2 control groups. Upper limb. \*p < 0.05, \*\* p < 0.01 (vs PMR group). NS: not significant. LHBT: long head of biceps tendon, SA-SD: subacromial-subdeltoid, SpA: seronegative spondyloarthropathies, RA: rheumatoid arthritis.

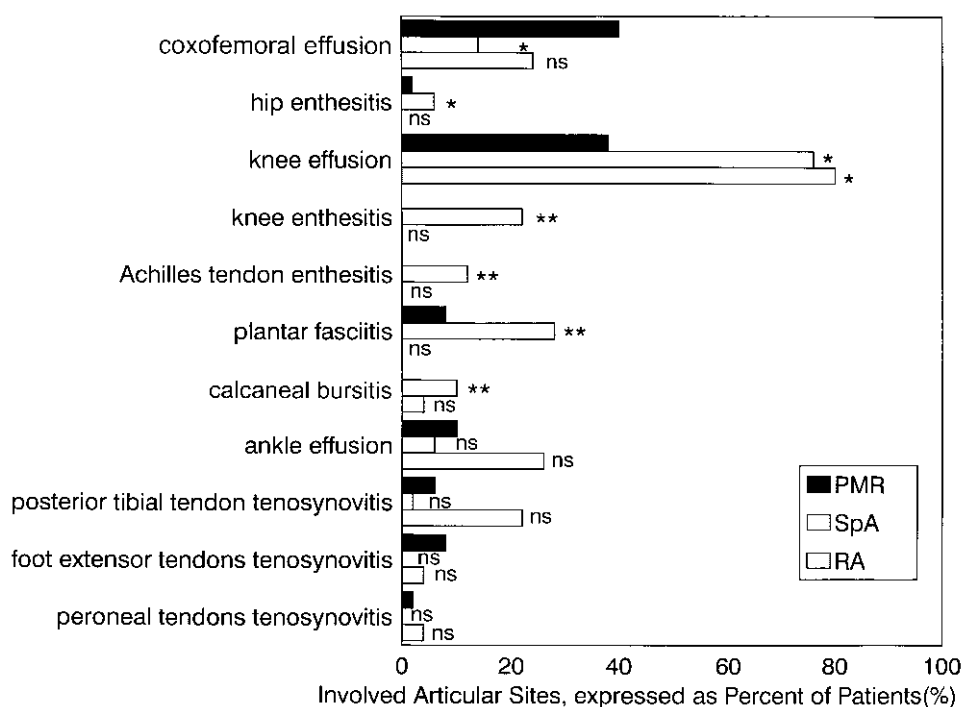


Figure 2. Prevalence of sonographically revealed inflammatory alterations in patients with PMR and 2 control groups. Lower limb. \*p < 0.05; \*\*p < 0.01 (vs PMR patient). NS: not significant.

Comparison of PMR and SpA patients revealed significant differences, particularly in relation to inflammatory involvement of the entheses, which was more marked in the latter

(mostly in the elbow, knee, and heel; p < 0.001). There were no significant differences between the 2 groups in terms of the frequency of the involvement of the tendon of the long head



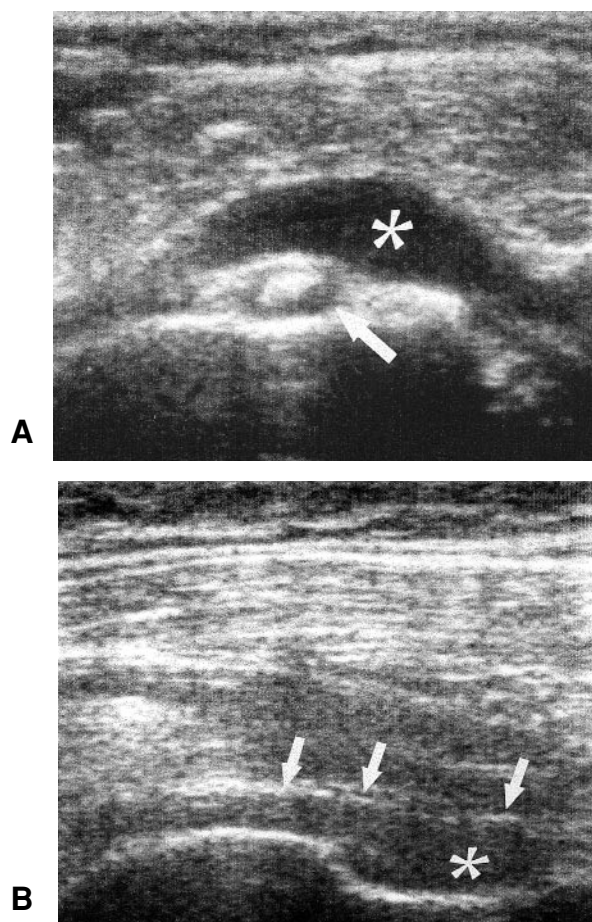


Figure 3. A. Anterior tranverse sonogram of the shoulder in a patient with PMR. A large amount of fluid present within the SA-SD bursa (asterisk) and a moderate amount of fluid surrounding LHBT determine a characteristic "target image" (arrow). B. Anterior longitudinal sonogram of the hip (patient with PMR). Distension of joint capsule (arrows) determined by a moderate amount of hypoechoic effusion (asterisk).

of the biceps (68% vs 44%), SA-SD bursitis (70% vs 34%), or CTS (38% vs 30%), but there was a significant difference ( $p < 0.05$ ) in glenohumeral and coxofemoral effusion between the PMR and SpA patients (66% vs 16% and 40% vs 14%, respectively).

As expected, the comparison of PMR and RA patients revealed no significant differences in enthesitis involvement in any of the examined areas. Important as well was the absence of any significant differences between the 2 groups in terms of the involvement of the LHBT, the SA-SD bursa, the glenohumeral and coxofemoral joints, or the flexor tendons of the carpal tunnel.

The frequency of joint synovitis in the elbow, knee, and wrist was significantly higher in the SpA and RA patients than in those with PMR. Tenosynovitis of the extensor tendons of the back of the wrists was significantly more frequent in the patients with RA than in those with PMR or SpA, but distal extremity swelling with pitting edema was observed only in the patients with PMR.

No significant correlations were found between ESR and CRP levels and the entity of synovitis and the number of affected sites in the PMR patients. There were no correlations between age or sex of patients with PMR and the number of affected sites. A comparison of clinical and sonographic examination results is shown in Figure 4. In many articular sites, especially in deep joints such as the glenohumeral or hip, sonography detects synovitis or enthesitis not revealed by clinical examination. A significant difference ( $p < 0.01$ ) was observed in glenohumeral effusion, SA-SD bursitis, CTS, coxofemoral effusion.

## DISCUSSION

The musculoskeletal manifestations appearing during the course of PMR are often neglected, particularly because of the major myalgic symptoms that characterize the disease, to the extent that synovitis (axial, peripheral, articular, or periarticular) has never been included among the classification criteria.

Nevertheless, there have been increasing reports of the inflammatory involvement of both articular and periarticular synovial structures during the course of the disease, and synovitis detected by means of scintigraphy<sup>3,4</sup>, arthroscopy<sup>5</sup>, synovial biopsy<sup>6-8</sup>, US<sup>9-11</sup>, or MRI<sup>12-16</sup> may play an important role in determining its symptomatic picture.

However, the published data concerning the frequency and prevalent localization of synovitis in PMR are sometimes conflicting. Some papers have described a large case series, but synovitis has been detected clinically<sup>18-26,30</sup> or by means of MRI only in limited skeletal regions such as the shoulder, hand, or foot<sup>12-16</sup>. Some articles report US evaluations of patients with PMR, but only in relation to a few joints<sup>9-11</sup>, and O'Duffy's scintigraphic study using Tc pertechnetate only considered 25 patients<sup>3</sup>.

Furthermore, the prevalence of synovitis in the different studies varies depending on whether the disease is considered at onset in untreated patients or during followup, which explains the large variability of the global prevalence of synovitis described in previous studies. We found 100% prevalence of synovitis in at least one site at the time of disease onset, a much higher figure than that recorded in studies based exclusively on clinical evaluations<sup>17,21,30</sup>, but similar to that observed in studies that used diagnostic imaging techniques<sup>3,4,10,11,14</sup>.

Moreover, the previously described frequencies of the involvement of inflammation in individual articular sites seem to be considerably different (Table 1).

Furthermore, in each individual joint, it is necessary to define more precisely whether the inflammation is predominantly articular or periarticular; this last aspect may be difficult to clarify unless soft tissue imaging techniques are used (mainly MRI and US).

US examination is easy to perform, repeatable, and inexpensive, and it has a high degree of diagnostic accuracy,

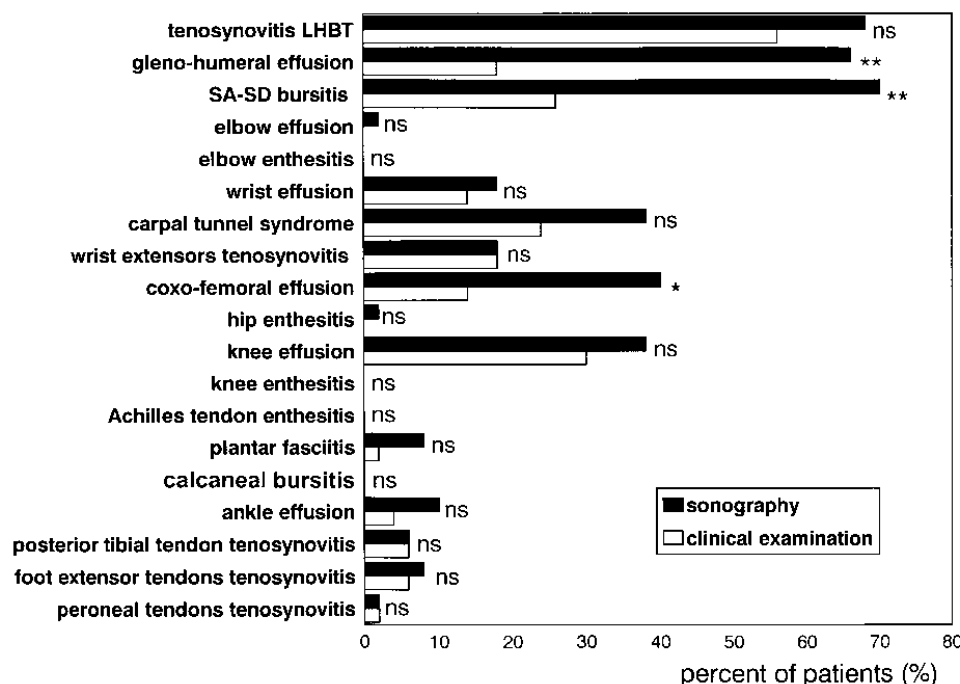


Figure 4. Comparison between sonographic and clinical examination. \* $p < 0.05$ , \*\* $p < 0.01$ ; NS: not significant.

which is why we used it in this large-scale polyarticular screening study.

Our results confirmed the high prevalence of both articular and periarticular synovitis and/or effusion at the onset of PMR (100%). In particular, as in previous studies<sup>1,9-11</sup>, there was a very high frequency of synovitic involvement of the sheaths of the sliding tendons of the shoulder and of the volar side of the wrist. The prevalence of clinically, electromyographically, or MRI detected CTS described in previous studies varies from 6%<sup>30</sup> to 14%<sup>20,21,28</sup>; in our study, the prevalence of acute CTS secondary to flexor tenosynovitis/peritendinous edema, detected sonographically using Buchberger's criteria<sup>43,44</sup>, was 38%.

We found the syndrome picture described in previous studies<sup>35,36</sup> as distal extremity swelling with pitting edema in 4/50 patients (8%), whereas other authors have observed frequencies ranging from 8% to 12%. In the upper limb this clinical picture was always associated with tenosynovitis of the extensor tendons of the wrist (3 cases). In the lower limb it was associated with tenosynovitis of the foot extensor and posterior tibial tendons (one case).

The prevalence of SA-SD bursitis observed in our study (70%) was markedly less than the 100% reported by Salvarani, *et al*<sup>14</sup>. The reason may be that US is less sensitive than MRI; on the other hand, the findings of SA-SD bursitis cases revealed in previous US studies (18% by Koski<sup>10</sup>, 10% by Coari, *et al*<sup>9</sup> in patients undergoing treatment) are fewer than those we observed. It is likely that, as noted by Salvarani, *et al*, corticosteroid therapy rapidly improves the anatomical lesions of patients with PMR. Thus, sonographic findings in

steroid treated patients with PMR may not show the real frequency and severity of shoulder lesions<sup>55</sup>. In any case, the difference in relation to RA did not appear to be significant, at least partly because of the many cases of SA-SD bursitis observed in our patients with RA.

The control group comparisons showed the difference between PMR and SpA, particularly in terms of the absence of enthesitis involvement in PMR and the presence of articular synovitis in SpA in sites that are rarely involved in patients with PMR (elbow, wrist, knee, and calcaneal bursae). We noted significantly higher prevalence of both glenohumeral and coxofemoral articular synovitis in PMR than in SpA (66% vs 16%, and 40% vs 14%, respectively), which was not mirrored in the comparison between the PMR and RA groups. The frequency of coxofemoral synovitis and/or effusion in our patients with PMR was similar to that observed by Koski<sup>10</sup>, who reported 42% frequency of hip synovitis in treated patients. The reason for this result may have been that our fixed frequency 7.5 MHz probe does not allow correct coxofemoral visualization in particularly robust or overweight subjects because of the depth of the joint; in such cases a small effusion may have escaped our notice.

Joint synovitis of the elbow, wrist, and knee was more frequent and more frequently bilateral in our patients with RA than in those with PMR, but enthesitis involvement was rare in both groups.

Tenosynovitis of the back of the wrist was significantly more frequent in the RA than in the PMR patients, but the presence of pitting edema of the upper limb was only observed in 3 of the patients with PMR.

Sonographically detected differences may be useful in the differential diagnosis of the 3 diseases considered. In the case of PMR and RA, the articular sites showing the most significant difference in terms of synovitic involvement were the elbow (joint effusion), the wrist (joint effusion and dorsal tenosynovitis), and the knee (joint effusion). In the comparison between PMR and SpA, the most significant differences were observed in relationship to the elbow (joint effusion), the knee (joint effusion and enthesitis), and most of all in the calcaneal entheses and bursae.

Comparison between the results of US and clinical examination revealed that US is more sensitive than clinical examination for the assessment of synovitis or enthesitis, particularly in deeper joints such as the glenohumeral or coxofemoral. In clinical practice, the predominance of myalgic symptoms in PMR probably overshadows the less well characterized and more variable proximal and distal synovitis of joints and tendons. Moreover, both articular structures and periarticular soft tissues may be involved with very similar symptoms; US can help to identify the site of anatomic alteration more precisely than a clinical examination, and it can be useful in choosing local treatments<sup>55</sup>.

In conclusion, our data showed that articular and periarticular synovitis and/or effusion in both axial and peripheral sites can frequently be detected at the onset of PMR. Although our US investigation could not confirm whether the synovial inflammation was primary or secondary to initial capsular/enthesal involvement, as suggested by McGonagle, *et al*<sup>16,56</sup>. However, in our experience, it is clear that pure enthesitis of anchoring tendons, such as calcaneal, patellar, and epicondylar tendons, is rare during the course of PMR.

On the other hand, peritendinous synovitis of the sheaths of sliding tendons (e.g., the long head of the biceps and the flexors and extensors of the fingers), as well as bursal and intra-articular synovitis, are very frequent, confirming that synovial inflammation is a fundamental factor in the pathogenesis of PMR and it contributes to the cause of its characteristic painful symptoms.

We believe our results should be taken into account when considering a possible new nosologic reclassification of PMR and, in any case, in terms of differential diagnosis with other late onset systemic inflammatory arthropathies, such as senile RA, remitting seronegative symmetrical synovitis with pitting edema, and spondyloarthritides<sup>12,16,56</sup>.

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