High frequency of capsular knee involvement in polymyalgia rheumatica/giant cell arteritis patients studied by positron emission tomography

Marco A. Cimmino¹, Dario Camellino¹, Francesco Paparo², Silvia Morbelli³, Michela Massollo³, Maurizio Cutolo¹ and Gianmario Sambuceti³

Abstract

Objective. Peripheral arthritis has been described in up to 50% of PMR patients, with knee involvement in the majority. This study was designed to evaluate by PET/CT the knees of patients with PMR and GCA and to identify the knee structures involved by inflammation.

Methods. Twenty-five consecutive patients with PMR (19) or GCA (6) were studied in comparison with 25 age- and sex-matched controls who underwent PET/CT for initial staging of cancer. Clinical features, ESR and CRP were evaluated. Simultaneous FDG-PET and CT imaging from the skull base to the knee was performed after injection of 4.8-5.2 MBq of [¹⁸F]FDG per kilogram body weight. The knee anatomical structures being evaluated included joints, fibrous capsule, synovial recesses and bursae.

Results. At PET/CT, 21/25 patients (84%) showed bilateral diffuse uptake at the knees. The tracer clearly outlined the contour of the fibrous capsule. In 50 knees, 90% of capsular sites were involved by inflammation in comparison with 23% of intracapsular sites and 4.7% of extracapsular sites (P < 0.0001). No correlation was found between PET/CT results and ESR or CRP. FDG uptake, with a pattern similar to that observed in 96% of PMR/GCA patients, was seen in 20% of controls (P = 0.03).

Conclusion. Our findings suggest that bilateral capsulesitis of the knee is detectable in most PMR/GCA patients if a sensitive imaging technique such as PET/CT is used.

Key words: polymyalgia rheumatica, giant cell arteritis, PET, knee.

Introduction

PMR is a common inflammatory disease of the elderly, frequently associated with GCA, of which the causes, development mechanisms and targets of inflammatory damage are still elusive [1]. Synovitis, vasculitis and bursitis have all been demonstrated in PMR. These sites are simultaneously affected in anecdotal observations [2]. In particular, peripheral arthritis has been described in up to 50% of the patients, with knee involvement present in the majority of them [3]. In addition, PMR patients often complain of pain in the popliteal area even if no knee involvement is detected at clinical examination. Imaging may help in the evaluation of patients with PMR and with GCA, which are often associated; in these conditions, imaging can also give indications on pathogenesis, diagnosis and prognosis [4, 5]. This article is concerned with PET/CT evaluation of the knee structures involved in patients with PMR and/or GCA. In particular, the aim of our study was to determine the frequency of knee inflammation and to evaluate its anatomical localization.

Patients and methods

Twenty-five new-onset, consecutive patients (16 women) were studied: 19 fulfilled Bird et al. [7] criteria for PMR [6], 3 the ACR criteria for GCA and 3 those of both diseases; the mean age was 69.1 ± 9.5 years. Eighteen patients had not previously received glucocorticoid treatment, whereas seven had received prednisone (5–15 mg) for less than 7 days or had interrupted steroid treatment at least
1 month before the examination and had experienced disease relapse. Even in this last group, the duration of the previous treatment had not exceeded 20 days. The study was approved by the ethics committee of the University of Genova. After written informed consent was obtained, demographic and disease characteristics were evaluated. Clinical features, including disease duration, duration of morning stiffness, fever, weight loss, new-onset headache and history of pain of the legs, were recorded. Immediately before the PET/CT examination, a standardized clinical examination including search for peripheral arthritis, knee effusion, pain at mobilization of the shoulder and hip girdles, and of the cervical spine, and pain at palpation of the popliteal area was performed. In patients reporting previous episodes of knee pain, bony enlargement of the joint and crepitus at passive motion, attributable to OA, were evaluated. In addition, ESR and CRP were also obtained and the PMR activity score (PMR AS) [8] was calculated at the first visit.

For comparison, 25 sex- and age-matched patients, who underwent PET/CT with the same scan protocol as PMR and GCA patients, for either suspected cancer (seven subjects) or initial staging of cancer (breast cancer in seven patients, melanoma in six, lung cancer in two, sarcoma in two and cancer of the uterus in one), in the absence of metastatic disease, were included as controls. None of them had a history of inflammatory rheumatic conditions. Twelve were women; their mean age was 69.3 ± 5.7 years.

Image acquisition
After a minimum of 6 h fasting, a dose of 4.8–5.2 MBq of \[^{18}F\]fluorodesoxyglucose (FDG) per kilogram body weight was injected through a peripheral vein catheter. The patient was placed in a quiet room and instructed not to move. Data acquisition started between 60 and 90 min after tracer administration. Patients underwent simultaneous FDG-PET and CT imaging from the skull base to the knees visually higher than that of the liver was considered as sign of active inflammation.

The anterior compartment included the following structures (see Figs. 2 and 3 for their localization): a. patellofemoral joint; b. lateral and medial gutters (also known as paracondylar recesses) and patellar retinacula fused with the joint capsule; and c. suprapatellar recess. The posterior compartment included the following: a. posterior fibrous capsule (posterior oblique ligament); b. posterior cruciate ligament synovial recess; c. the fibrous capsule adjacent to the posterior femoral synovial recesses; and d. the bursa common to the gastrocnemius-semimembranosus tendons. The medial compartment included the following: a. medial tibio-femoral joint; b. fibrous capsule and medial collateral ligament; and c. pes anserinus bursa. The lateral compartment included the following: a. lateral tibiofemoral joint; b. lateral/fibular collateral ligament and fibrous capsule; c. the popliteal synovial sheath; and d. bursa of the lateral collateral ligament. CT scans of patients and controls were also evaluated in the coronal plane for the presence of OA, according to the score of Kellgren and Lawrence [9].

Statistical analysis
Means were compared by the Student’s t test or by one-way analysis of variance if their distribution was normal and by the Kruskall–Wallis test when it was non-parametric. Frequencies were compared by the \( \chi^2 \) test. All the calculations were performed using Medcalc version 12.3 (Belgium) as statistical software. PET/CT readings were also performed independently by the two operators to test inter-observer agreement. The results were good, yielding a k value of 0.94.

Results
Clinical and laboratory features
The median disease duration of the 25 patients was 60 days (range 20–540 days). Bilateral shoulder pain was present in 22 PMR and PMR/GCA patients (88%), hip pain in 14 (56%), cervical pain in 9 (36%) and pain in the lower limbs in 8 (32%). Of the three patients with pure GCA, only one had unilateral shoulder and hip pain. Eight patients (32%) had fever, 7 (28%) reported weight loss and 4 (16%) new-onset headache. Median duration of morning stiffness was 45 min (range 0–420 min). At clinical examination, 7 (28%) patients had pain at palpation of the popliteal area, 9 (36%) showed arthritis in a peripheral joint and 5 (20%) had knee effusion, hand tenosynovitis or remitting symmetrical seronegative synovitis with pitting oedema (RS3PE) syndrome. Mean ESR was 62.7 ± 32.5 mm/h and mean CRP was 47.9 ± 35.1 mg/l. All patients had elevated CRP or ESR: one had normal CRP and three had normal ESR. The median PMR AS was 20.9 indicating high disease activity (range 2–60.2). At
the end of the follow-up, which lasted 20.8 months (range 1–39 months), 16/25 patients were in clinical remission, of whom 12 without glucocorticoid treatment; none of the patients had developed RA.

PET/CT results in patients
At PET/CT, most of the patients (24/25, 96%) had capsular uptake of FDG that clearly highlighted the contour of the fibrous capsule (Fig. 1). The pattern was diffuse in 8 patients, focal in 3 and diffuse with discrete areas of focal increased uptake in 13. Intracapsular tracer uptake was present in 16 patients (64%), 15 of whom had also diffuse capsular involvement (Table 1). Extracapsular uptake was seen in four patients (16%), always in combination with capsular and intracapsular uptake. 21/25 patients (84%) showed bilateral diffuse uptake of the knees with or without focal uptake; complete symmetry of the involved structures in both knees was seen in 10 patients (40%). No significant differences in demographic, laboratory or PET/CT data were observed between patients who did or did not have previous glucocorticoid treatment (data not shown).

The most frequently involved intracapsular area was the posterior cruciate ligament synovial recess, where

**Fig. 1** PET examination of the knee in one PMR patient and in one control.

(A and B) PET examination of the knee in a female patient with PMR and GCA in both axial and coronal views. A homogeneous and diffuse uptake of the articular capsule is seen. (C and D) PET examination in a control.

| Table 1 | Pattern of knee involvement evaluated by PET/CT in patients with the PMR/GCA complex |
|---------------------------------------------|---------------------------------|------------------|------------------|------------------|
| Structure involved and pattern of involvement | n + | % | n bilateral | % bilateral |
| Increased uptake | | | | |
| Posterior fibrous capsule | 16 | 64 | 10 | 40 |
| Medial fibrous capsule | 16 | 64 | 10 | 40 |
| Posterior cruciate ligament synovial recess | 14 | 56 | 5 | 20 |
| Bursa of the lateral collateral ligament | 4 | 16 | 1 | 4 |
| Suprapatellar recess | 3 | 12 | 1 | 33.3 |
| Popliteal synovial sheath | 1 | 4 | 0 | 0 |
| Synovial effusion | | | | |
| Lateral and medial gutters | 5 | 20 | 3 | 12 |
| Bursa between gastrocnemius and semi-membranosus | 3 | 12 | 2 | 8 |
| Symmetry | | | | |
| Symmetry (uptake in at least one region in both knees) | 21 | 84 | | |
| Symmetry pattern (uptake in the same regions) | 10 | 40 | | |
**Fig. 2** PET/CT examination of the knee in a PMR patient, axial view.

PET/CT of the knee in a female patient with polymyalgia rheumatica in axial view (A) showing uptake of the posterior cruciate ligament synovial recess (black asterisk) and of the postero-medial area of the capsule (pmc). Note also the diffuse uptake of the capsule. Anatomical landmarks are shown in (B). Mfc: medial femoral condyle; lfc: lateral femoral condyle; pat: patellar tendon; itt: ilio-tibial tract; acl: anterior cruciate ligament; pcl: posterior cruciate ligament; mcl: medial collateral ligament; lcl: lateral collateral ligament; Hfp: Hoffa’s fat pad; pmc: postero-medial capsule; smt: semimembranosus tendon; pt: popliteus tendon. The grey line represents the fibrous capsule and the blue area the synovial membrane.

**Fig. 3** PET/CT examination of the knee in two PMR patients, sagittal and axial views.

PET/CT of the knee in a male patient with PMR in sagittal view (A) showing uptake of the suprapatellar synovial recess (spr) and of the posterior cruciate ligament synovial recess (black asterisk). In (B) the anatomical landmarks are shown; P: patella; f: femur; t: tibia; pat: patellar tendon; qt: quadriceps tendon; mhg: medial head of gastrocnemius muscle; spr: suprapatellar synovial recess; pcl: posterior cruciate ligament. Another PET/CT examination of a different knee in axial view (C) shows uptake of the lateral collateral ligament bursa (arrowhead). The anatomical landmarks are shown in (D): lm: lateral meniscus; mm: medial meniscus; itt: ilio-tibial tract; acl: anterior cruciate ligament; pcl: posterior cruciate ligament; mcl: medial collateral ligament; lcl: lateral collateral ligament; Hfp: Hoffa’s fat pad; pmc: postero-medial capsule; smt: semimembranosus tendon; pt: popliteus tendon. The black asterisk indicates the posterior cruciate ligament synovial recess; the grey line indicates fibrous capsule and blue line indicates synovial membrane.
Fig. 4 Frequency of capsular, intracapsular and extracapsular involvement of the knee in patients and controls.

Frequency of capsular, intracapsular and extracapsular involvement of the knee evaluated by PET/CT in patients with the PMR/GCA complex and in controls. Among all the structures considered in the knee, only two intracapsular (the suprapatellar recess and the posterior cruciate ligament synovial recess) and three extracapsular (the pes anserinus bursa, the popliteal synovial sheath and the bursa of the lateral collateral ligament) structures showed uptake. (A) The bars indicate the total number of possible sites with tracer uptake for each location and the black area the number of sites showing effectively tracer uptake. The percentages within patients and between patients and controls were significantly different from each other ($P < 0.0001$). Pts: patients, Ctrl: controls. (B) Each bar indicates a single patient (P) or control (C); grey bar indicates capsular uptake (maximum two per patient), striped bar indicates intracapsular uptake (maximum four per patient) and dotted bar indicates extracapsular uptake (maximum six per patient).
increased tracer uptake occurred in 56% of the knees (Fig. 2). Fig. 3 shows areas where uptake was infrequently seen, such as the suprapatellar recess where it occurred in 12% of the patients (Fig. 3A), the bursa of the lateral collateral ligament in 16% (Fig. 3C) and the popliteal synovial sheath in 4%.

In summary, in a total of 50 knees, 90% of capsular sites were involved by inflammation in comparison with 23% of intracapsular sites and 4.7% of extracapsular sites ($P < 0.0001$) (Fig. 4). SF effusion was seen at CT in eight (32%) patients, of whom five had involvement of the lateral and medial gutters, two of the bursa between the gastrocnemius and semi-membranosus muscles and one had both. Four out of these eight patients had SF effusion detectable also at clinical examination. SF effusion was always associated with diffuse capsular uptake and in three patients extracapsular involvement. No correlation was found between knee involvement by PET/CT and ESR, CRP or PMR AS. When patients were classified according to the diagnosis in 19 with pure PMR and 6 with GCA, inflammatory uptake tended to be more frequent in PMR than in GCA patients at the suprapatellar recess ($P = 0.06$), postero-medial fibrous capsule ($P = 0.02$) and posterior cruciate ligament synovial recess ($P = 0.08$). Among clinical features, morning stiffness tended to be longer in patients with capsulitis of the postero-medial area (median 60 vs 17.5 min, $P = 0.045$) and pain on movement of the pelvic girdle more frequent in patients with suprapatellar recess and gastrocnemius semimembranosus bursa involvement (both $P = 0.027$).

**PET/CT results in controls**

Among the 25 control patients, only 7 (28%) had signs of involvement of the knee’s structures. In one patient, a focal area of uptake was seen at the enthesis of medial head of the gastrocnemius muscle and in another one at the insertion of the distal conjoint tendon of the quadriceps muscle on the superior patellar pole. These findings were different from those observed in PMR/GCA patients. In the other five control patients, a homogeneous capsular pattern of tracer uptake was seen in three (12%) and a focal area of increased uptake of the posterior cruciate ligament synovial recess in two (8%) patients. As a result, a pattern of PET uptake similar to that observed in 96% of PMR/GCA patients was seen in 20% of control patients ($P = 0.03$). Knee effusion was present in one control patient (4%) in comparison with 20% of the PMR/GCA patients ($P = 0.027$). In addition, knee uptake was unilateral in six out of seven controls, whereas it was bilateral in all patients ($P < 0.0001$). Sensitivity for any uptake in the knee was 96% and specificity was 72%; by considering diffuse bilateral capsular uptake, sensitivity decreased to 80%, but specificity increased to 88%.

As expected in view of their age, most patients and controls showed some degree of knee OA when evaluated by CT. The mean Kellgren and Lawrence score was $2.3 \pm 0.8$ in patients and $2.4 \pm 0.9$ in controls ($P = 0.75$). A Kellgren and Lawrence score of 1 was seen in 3 patients and 5 controls, a score of 2 in 14 patients and 9 controls, a score of 3 in 6 and 8, and a score of 4 in 2 and 3, respectively ($P = 0.56$).

**Discussion**

In our small series of patients with PMR/GCA, the frequency of inflammatory knee involvement was extremely high if evaluated by a sensitive technique, such as FDG-PET/CT. Ninety-six per cent of the patients showed increased uptake of FDG in one or more knee anatomical structures. This finding was present also in patients without knee symptoms. The frequency of positive PET/CT of the knee in PMR/GCA patients was even higher than that reported in the literature for RA, where 69% of patients had increased uptake [10]. The absence of patients who developed RA during follow-up and the high percentage of those in clinical remission (64%) confirm that a possible misdiagnosis with RA was not an explanation for the observed knee involvement. This was more frequent in PMR/GCA patients than in controls. Capsulitis and IA synovial inflammation prevailed on bursitis and were slightly more frequent in PMR than in GCA. Capsulitis tended also to be associated with more prolonged morning stiffness, a sign of disease activity. However, associations between clinical features and PET uptake should be taken with caution, in view of the high number of comparisons performed. Tracer uptake was strictly located in the fibrous joint capsule (Fig. 1) contour and highlighted this structure in most patients. This finding is in keeping with the results of an old biopsy study showing evidence of capsular inflammation in the shoulders of PMR patients [11]. Single or multiple focal areas of increased uptake were also seen in the posterior cruciate ligament synovial recess, the bursa of the lateral collateral ligament, the suprapatellar recess and the popliteal synovial sheath. The postero-medial area of the capsule showed the highest uptake rate, probably because the fibrous capsule is thickest at this location. Two regions of the capsule, posterior and medial, were evaluated separately by our methodological approach to the knee structures. Nonetheless, they have the same structure and showed an identical pattern of uptake. Purely extracapsular sites of FDG uptake were observed in only a small minority of the knees examined.

There is considerable debate on the possibility that PMR could be a bursal disease [12], or rather a capsular-entheseal disease [13]. Data on imaging of the shoulder and pelvic girdles have been inconclusive, with either hypothesis supported in different studies. The majority of MRI studies emphasize the role of synovitis of the bursae, joints and tendon sheaths as primary localization of the disease [14]. However, these studies have been criticized because fat-suppressed MRI, which can evaluate possible extracapsular changes, was employed only rarely [13]. McGonagle et al. [15] have proposed a dichotomy between synovial and entheseal/capsular forms of arthritis. The latter form of inflammation was observed also in PMR [13]. In PMR patients, the hands show both entheseal inflammation [16] and extracapsular tenosynovitis [17]. Our results in a different peripheral joint, such as
the knee, strongly support the capsular origin of inflammation in this disease. However, due also to the limitation of spatial resolution of PET/CT, knee entheseal areas were not specifically involved in this series.

Since the fibrous capsule is tightly connected to the subintimal layer of the synovial membrane, these structures cannot be easily differentiated. However, it is unlikely that synovitis was the primary location of inflammation in our PMR/GCA patients because tracer uptake was limited to a very thin rim of the structure. This pattern is clearly different from that observed in RA, the prototype of synovial arthritis [15], where synovial uptake is more intense, and usually involves also the suprapatellar pouch [18, 19]. Although the literature on PET uptake in arthritis is scanty, a small study has suggested that the capsular pattern could be similar to that seen in seronegative spondyloarthritis [20], the prototype of entheseal inflammation [15]. Knee uptake in OA was also frequently periarticular, but with occasional focal distribution in the subchondral area corresponding to bone oedema or osteophytes on MRI and, sometimes, to secondary synovitis [21]. Other sites of focal accumulation were seen in the intercondylar notch, with extension to the posterior cruciate ligament in 4/15 (26.6%) of OA knees. Both pericapsular and posterior cruciate ligament uptake was similar to, but often milder than, that observed in PMR. To explain the OA findings, ligament tears, periligamentous synovitis, enhanced chondrocyte metabolism and bone marrow oedema have been advocated [21]. Among our PMR/GCA patients, only two presented with symptomatic, secondary, post-traumatic OA of one knee, according to the clinical ACR criteria [22]. The Kellgren and Lawrence score of knee OA was however similar in patients and controls, excluding that OA could be an explanation for the increased knee uptake seen in PMR patients.

SF effusion of the knee occurred more frequently in PMR/GCA than in controls. It was not accompanied by synovial membrane tracer uptake, suggesting that effusion was not a consequence of synovitis, but rather a reaction to capsulitis. This observation is in keeping with the finding that in PMR synovitis is absent or mild [23] and SF shows a relatively low inflammatory component [3].

There are few limitations of this study that deserve mention. A minority of PMR/GCA patients received glucocorticoid treatment before PET/CT examination. This is common in studies on PMR/GCA because it is increasingly difficult to see untreated patients in tertiary referral centres. Although glucocorticoids are effective in abolishing disease signs and symptoms, the short duration of treatment or the long interval between treatment and investigation most probably reduced interference. In fact, the treated and untreated patients did not differ in terms of clinical features and PET/CT results.

We did not consider a control group of healthy subjects because their involvement was considered unethical. However, we feel that, by considering patients undergoing initial staging of cancer or investigation for suspected cancer, we obtained an unbiased sample of normal-for-

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**Rheumatology key messages**

- Bilateral knee capsulitis is frequently detected by PET/CT in PMR, also in patients without symptoms.
- Our data support the view that PMR inflammation is capsular rather than synovial.

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