Various forms of ^{18}F -FDG PET and PET/CT findings in patients with polymyalgia rheumatica

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Aim. Polymyalgia rheumatica (PMR) is a disease presenting with pain and stiffness, mainly in shoulders, hip joints and neck. Laboratory markers of inflammation may bolster diagnosis. PMR afflicts patients over 50 years old, predominantly women, and may also accompany giant cell arteritis.

Patients and Methods. 67 patients, who fulfilled Healey's criteria for PMR in the period between 2004 and 2013 and had positive FDG PET (PET/CT) findings were retrospectively evaluated. FDG uptake was assessed in large arteries, proximal joints (shoulders, hips and sternoclavicular joints), in extraarticular synovial structures (interspinous, ischio-gluteal and praepubic bursae).

Results. Articular/periarticular involvement (A) was detected in 59/67 (88.1%) patients and extrarticular synovial involvement (E) in 51/67 (76.1%) patients either individually or in combinations. Vascular involvement (V) was detected in 27/67 (40.3%) patients only in combination with articular (A) and/or extraarticular synovial (E) involvement. These combinations were: A+E involvement in 30/67 (44.8%) patients, A+V involvement in 8/67 (11.9%) patients, E+V involvement in 6/67 (9%) patients and A+E+V in 13/67 (19.4%) patients.

Conclusions. PMR presents by articular/periarticular synovitis, extraarticular synovitis and can be accompanied by giant cell arteritis. All types of involvement have their distinct FDG PET (PET/CT) finding, which can be seen either individually or in any of their 4 combinations. FDG PET (PET/CT) examination seems to be an advantageous one-step examination for detecting different variants of PMR, for assessing extent and severity and also for excluding occult malignancy.

Key words: FDG, PET, PET/CT, polymyalgia rheumatica, bursitis, vasculitis, synovitis, giant cell arteritis

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INTRODUCTION

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease of the elderly. PMR typically develops in patients older than 50 years, and is more common in women¹. Etiology of PMR is not known. The fact that PMR predominantly affects Caucasians suggests that genetic factors may play some role in the pathogenesis of this disease. Most studies have shown an association with HLA-DRB1*04 alleles². The highest annual incidence rates of PMR were observed in Northern Europe, especially in Scandinavia³. This contrasts with a significantly lower incidence and prevalence in some areas of southern Europe such as northern Italy, north-western Spain and Israel^{4,6}. The average annual incidence

of PMR in Olmsted County, Minnesota was 52.5/100,000 in the population older than 50 years with a significantly higher incidence in females 61.7/100,000 than in males 39.9/100,000 (ref.⁷). The prevalence of PMR in this population was 6/1,000. PMR shares many pathogenetic and epidemiological features with giant cell arteritis (GCA). GCA is reported in 5–30% of patients with PMR (ref.⁸). These two conditions may present together, but may sometimes be separated by long intervals. The typical symptoms of PMR are bilateral aching of the shoulder girdle, neck and hip girdle, and morning stiffness, lasting 30 minutes or more⁸. These symptoms are probably related to inflammation of the subacromial, subdeltoid and trochanteric bursae, and the glenohumeral or hip joints^{9,10}. Onset of PMR symptoms may be acute or gradual. One-

third of PMR patients have systemic manifestations such as low-grade fever, malaise and anorexia, but these are often milder than systemic symptoms in GCA patients. The diagnosis of PMR is made primarily on clinical grounds and is bolstered by laboratory evidence of an acute phase reaction. There is no single diagnostic test for PMR, but sets of diagnostic and classification criteria have been suggested by several groups of investigators¹¹⁻¹⁶. Each set of criteria has its own advantages and disadvantages.

Whole body positron emission tomography (PET) or combination of PET with computed tomography (PET/CT) using ¹⁸F-fluorodeoxyglucose (FDG) is a relatively common examination in patients with fever of unknown origin (FUO) or low-grade fever with non-specific symptoms¹⁷⁻²⁰. Patients with GCA and PMR can therefore undergo these examinations in the course of differential diagnosis of inflammatory or malignant disease.

Published papers provide clear indication of FDG PET and PET/CT benefits in diagnosis and therapy evaluation in patients with GCA, in early detection, in assessment of vessel inflammation extent, for clarifying a possible area for biopsy, and for therapy evaluation²¹⁻²³. Several ways to evaluate FDG accumulation in vessel walls have been proposed, both visual and semiquantitative. The highest interobserver agreement (kappa: 0.96) in an initial study was observed when vascular wall FDG uptake higher than liver uptake was used as a diagnostic criterion²⁴. Visual methods are more specific than semiquantitative ones, but they have lower sensitivity. The most commonly used semiquantitative method is aorta-to-liver ratio²⁴, but a promising alternative is also the aortic-to-blood pool uptake ratio²⁵. There is no consensus on the best evaluation method. There is not a definitive consensus about pattern of FDG uptake in PMR patients and also the total number of PET (PET/CT) examinations in patients with PMR is lower than for patients with GCA.

Our study presents findings of typical FDG uptake patterns in PMR patients identified with FDG PET (PET/CT).

MATERIAL AND METHODS

67 patients, who fulfilled Healey's criteria for PMR (Table 1) in the period between 2004 and 2013 and had positive FDG PET (PET/CT) findings were retrospectively evaluated. Patients without abnormalities in PET (PET/CT) images were not included in our evaluation. Of these 67 patients, 29 were males (43.3%) and 38 females (56.7%), aged between 51 and 83 years (70 years median). All patients had an erythrocyte sedimentation rate (ESR) over 60 mm/h. Apart from Healey's criteria, all patients also had elevated C-reactive protein (CRP) (tab. 2) and 51/67 (76.1%) had at least one other systemic symptom: anemia, thrombocytosis, weight loss, fever. Following examination, 65/67 (97%) were treated with prednisone (Prednison, ZENTIVA, Prague, Czech rep.) and 2 patients with methotrexate (Methotrexat, EBEWE Pharma, Unterach, Austria). None of the patients had corticoid treatment during the 6 months prior to PET (PET/CT) examination.

Examinations were performed using 2 different scanners, either with a PET scanner ECAT ACCEL (Siemens, Erlangen, Germany) in 32/67 (47.8%) patients, between 2004 and 2013, or in the remaining 35/67 (52.2%) patients, a hybrid PET/CT scanner Biograph 64, True Point HR (Siemens, Erlangen, Germany) between 2008 and 2013. When the examination was performed on the hybrid PET/CT scanner, a low-dose (LD) CT protocol was used in 18/35 (51.4%), and a fully diagnostic CT protocol was used in 17/35 (48.6%) with administration of Iomeron 400 intravenous contrast agent (BRACCO, Milan, Italy). Depending on indications from the clinician who requested the examination and also on operational conditions, either the PET or the PET/CT scanner was used from 2008 onward. All patients had standard preparation prior to examination with restriction of physical activity for 12 h, fasting for at least 6 h, capillary glycemia below 10 mmol/L (180 mg/dL) prior to FDG administration and peroral hydration with 500-1,000 mL of plain water. FDG (UJV Rez, Czech Republic) was administered in an activity range of 297-483 MBq (tab 2). After an *in vivo* accumulation time of 55 to 75 min, whole body scanning from the proximal third of thighs to the skull base was performed. Evaluation of body parts outside this area (skull, whole lower extremities) was not performed in this study because these body parts were scanned in only some patients. All images were iteratively reconstructed and corrected for attenuation. FDG uptake was assessed visually, and also semi-quantitatively in the defined region of interest (ROI) with calculation of target-to-liver ratios. Liver FDG uptake was used as a reference base to exclude differences arising from using 2 different scanners. Vascular FDG uptake was considered positive if higher than liver uptake in one of 7 measured locations (ascending aorta, descending aorta, abdominal aorta, brachiocephalic trunk, subclavian artery on both sides, common iliac artery on both sides, common femoral artery on both sides). The number of positive locations was also noted (0-7), in bilateral localizations (subclavian, iliac, and femoral arteries) even if only one side was positive. FDG uptake in articular/periarticular areas of proximal joints (shoulders, hips, sternoclavicular joints) was considered positive if higher than liver FDG uptake on at least one side. FDG uptake in extraarticular synovial structures (interspinous bursae of cervical and lumbar vertebrae, around ischiadic bone prominencies, around greater trochanters, ventral edges of pubic bones) was considered positive if higher than liver FDG uptake on at least one side in case of paired locations.

Standard descriptive statistics were used to summarise the sample data set. Gender and imaging technique as well as number of localizations with positive findings were characterised by the number of occurrences and percentages. Age at date of examination and FDG dose are characterised with median, minimum and maximum. Statistical significance of differences in examination results between women and men as well as between PET and PET/CT was assessed by Fisher-exact test.

Ethical issues: none, as it is a retrospective evaluation of PET (PET/CT) scans that had already been performed

Table 1. Criteria for PMR developed by Healey et al.(ref.¹⁵) - all six criteria are required.

Persistent pain (for at least 1 month) involving two of the following areas: neck, shoulders and pelvic girdle
Morning stiffness lasting more than 1 h
Rapid response to prednisone (≤ 20 mg/day)
Absence of other diseases capable of causing the musculoskeletal symptoms
Older than 50 years
Erythrocyte sedimentation rate (ESR) greater than 40 mm/h

Table 2. Baseline characteristics.

	Total (n = 67)
Gender, n (%)	
- Men	29 (43.3)
- Women	38 (56.7)
Age at the date of examination	
- median (min-max)	70 yrs (51-83)
Imaging technique, n (%)	
- PET	32 (47.8)
- PET/CT	35 (52.2)
FDG dose	
- median (min-max) [MBq]	349 (297-483)
Patient weight	
- median (min-max) [kg]	78.8 (48-95)
Blood glucose	
- median (min-max) [mmol/L]	5.7 (4.0-6.7)
- median (min-max) [mg/dL]	102.6 (72-120.6)
ESR	
- median (min-max) [mm/h]	82 (60-120)
CRP	
- median (min-max) [mg/L]	79.7(39.9 - 116.8)
Disease duration before examination	
- median (min-max) [month]	5.1 (3-12)

Table 3. Examination results.

	Total (n = 67)
Vascular involvement, large arteries, n (%)	27 (40.3)
Number of affected locations, median (min-max)	4 (3-7)
Articular/periarticular proximal joint involvement, n (%)	59 (88.1)
Shoulders	58 (86.6)
Sternoclavicular joints	31 (46.3)
Hips	47 (70.1)
1 positive location	11 (16.4)
2 positive locations	19 (28.4)
3 positive locations	29 (43.3)
Extraarticular synovitis, n (%)	51 (76.1)
Cervical interspinous bursae	13 (19.4)
Lumbar interspinous bursae	38 (56.7)
Ischiogluteal bursae	35 (52.2)
Praepubic bursae	5 (7.5)
1 positive location	24 (35.8)
2 positive locations	15 (22.4)
3 positive locations	11 (16.4)
4 positive locations	1 (1.5)
Various types of involvement, n (%)	
1 type of involvement	10 (14.9)
V: vascular involvement	0
A: articular/periarticular involvement	8 (11.9)
E: extraarticular synovitis, bursitis	2 (3.0)
2 type of involvement	44 (65.7)
A+V: articular/periarticular + vascular involvement	8 (11.9)
E+V: extraarticular synovitis + vascular involvement	6 (9.0)
A+E: articular/periarticular + extraarticular synovitis	30 (44.8)
3 type of involvement	13 (19.4)
A+E+V: articular/periarticular + extraarticular synovitis + vascular involvement	

in clinical indications as part of standard procedures. All patients signed informed consent for the examination procedure and research purposes of data processing.

RESULTS

Articular involvement (A) in proximal joints was found in 59 (88.1%) patients, specifically of shoulders in 58/67 (86.6%) patients, hips in 47/67 (70.1%), and sternoclavicular joints in 31/67 (46.3%) patients. All articular locations of high FDG uptake were visually symmetric. Vascular involvement (V) was seen in 27/67 (40.3%) patients, in 3-7 (with median of 4) monitored locations. In none of the patients did we see vascular involvement alone without abnormal positivity in other notable locations. Extraarticular synovial involvement (E) was present in 51/67 (76.1%) patients, specifically in these locations: around ischiadic tuberosities, or more precisely in ischiogluteal bursae in 35/67 (52.2%) patients, around symphysis and ventral to pubic bones in 5/67 (7.5%) patients. Those findings were symmetric. Furthermore, we observed elevated FDG uptake in spinous interspaces of

cervical vertebrae in 13/67 (19.4%) patients and of lumbar vertebrae in 38/67 (56.7%) patients. All findings are presented in table 3. Articular and extraarticular involvement was seen individually and also in combinations; on the other hand, vascular involvement (V) was observed only in combination with articular (A) and/or extraarticular synovial (E) involvement. Combination of articular and

extraarticular synovial involvement (A+E) was detected in 30/67 (44.8%) patients, combination of articular synovial and vascular involvement (A+V) in 8/67 (11.9%) patients, combination of extraarticular synovial and vascular involvement (E+V) in 6/67 (9%) patients and combination of articular, extraarticular synovial and vascular involvement (A+E+V) in 13/67 (19.4%) patients. There were more positive results in the arteries in women than in men ($P = 0.006$). No statistically significant differences were observed between women and men in proximal joints synovitis (A) ($P = 0.125$) and extraarticular synovial bursitis (E) ($P = 0.574$). There were no statistically significant differences between patients examined with PET (32 patients) and PET/CT (35 patients) in articular involvement (A) ($P = 0.711$) and vascular involvement (V) ($P = 0.804$). In case of extraarticular synovitis (E), there were more positive results in patients examined with PET/CT - 32/35 (91.4%) than in patients examined with PET - 19/32 (59.4%) ($P = 0.003$). PET/CT examination provided for more precise and easier localization of high FDG uptake foci.

DISCUSSION

The patients in our study were older than 51 years, with a slightly higher percentage of women 38/67 (56.7%). This is to be expected regarding the age-related incidence of PMR (ref.²⁶). All patients were examined in this study because of significant symptomatology in the differential diagnosis of FUO, or to exclude malignancy in patients with symptoms considered possibly paraneoplastic. Values of ESR were relatively high, with the lowest value being 60 mm/h. Therefore, it may be that our patient group more likely represents patients with more developed (more severe) PMR. Only patients with a confirmed diagnosis of PMR were included in our study. Patients were in the care of a rheumatology specialist with confirmed laboratory and clinical response to corticosteroid therapy (prednisone) or methotrexate. In this retrospective analysis, another 36 patients were found with a positive PET finding (increased FDG uptake) on large arteries without clinical symptoms of PMR (no pain in shoulder and pelvic girdles or cervical spine, absence of stiffness). Those latter patients were not included in our study group, although their response to corticosteroid treatment, high ESR and age over 50 were similar to the patients included in this study. We consider the excluded patients to have giant cell arteritis (GCA). The distinction between PMR and GCA is not clear, and for PMR patients, meeting of all Healey's criteria was a requirement. No control group comparison with asymptomatic patients or with patients with a different inflammatory disease was performed.

The association between PMR and GCA is very close, and it may emerge as one disease with different manifestations. In 2006 and 2007, Blockmans et al. published 2 studies. In the first study with 35 GCA patients, a clearly increased shoulder FDG uptake was seen in 11/35 (31.4%) patients. On FDG-PET, large vessel vasculitis was found in 29/35 (82.9%) patients²². In the second study,

Blockmans et al. presented FDG-PET examinations of 35 patients with PMR and detected vasculitis in only 11/35 (31.4%) patients, and this only in the form of a mild increase in FDG uptake; however, high FDG uptake in shoulder and hip joints was detected in almost all patients²⁷. These two studies with GCA and PMR patients^{22,27} were the first to visualize with PET the possible accompanying vasculitis and the association of polymyalgia rheumatica. In our study, large vessel vasculitis was found in 27/67 (40.3%) patients. Thus, we have arrived at similar conclusions as Blockmans et al., while supported by a larger patient group.

Ultrasound and MRI can be used to confirm girdle synovitis in shoulder, pelvis, and in periarticular spaces. It is relatively common to find subacromial and subdeltoid bursitis, long-head biceps tenosynovitis, glenohumeral synovitis in shoulder girdle examinations, and synovitis and trochanteric bursitis in pelvic girdle examinations. Both MRI and US are approximately similar in their respective sensitivity and specificity above 90% (ref.^{10,28-31}). In FDG PET examinations, Blockmans et al. detected high FDG uptake in shoulders in 33 of their 35 patients (94.3%) and hips in 31 of their 35 (88.6%) patients²⁷. In another hybrid PET/CT study published in 2012, high FDG uptake in shoulders and hips was detected in 12/14 (85.7%) patients with relatively low specificity, 24.9% for shoulders and 64.7% for hips³². In our patient group, high articular/periarticular FDG uptake in shoulders was detected in 58/67 (86.6%) patients and in hips in 47/67 (70.1%), either individually or in combinations. Our findings (with a 2 or 5 times larger patient group, respectively) confirm results published by Blockmans et al. and Yamashita et al. regarding FDG uptake in PMR patients in shoulder girdles. In pelvic girdles, we noted a slightly lower incidence than in the aforementioned studies^{27,32}. It is difficult to distinguish shoulder girdle synovitis and periarticular bursitis in PET or PET/CT examinations. High FDG uptake can continuously overlap from articular capsule to surrounding tissues (Fig. 2). High FDG uptake in sternoclavicular joints of PMR patients was published in both a case study³³ and a group of 6/14 (42.8%) patients³², which is confirmed in our patient group with positivity in 31/67 (46.3%).

PMR can be accompanied by extraarticular synovial involvement, bursitis that was confirmed by both US and MRI in trochanteric bursitis and, less commonly, iliopsoas and ischiogluteal bursitis¹⁰. Blockmans et al. were first to describe high FDG uptake surrounding vertebral spinous processes of lumbar, dorsal and cervical vertebrae in approximately half of their PMR patient population (18/35, 51.4%). In their study, FDG uptake was assessed in large arteries, proximal joints and vertebral spinous processes. Other locations that were included in our assessment of extraarticular synovial structures were either not detected or evaluated in the study of Blockmans et al.²⁷. Other published case studies of patients examined on PET/CT scanners noted high FDG uptake surrounding vertebral spinous processes and in extraarticular synovial structures (bursae around ischial tuberosities and femoral trochanters). These were found either individually or in combination with proximal joint involvement

Fig. 1. Six whole body ^{18}F -FDG PET MIP images and a schema, left anterior oblique view, with added coloring.

A: Articular/periarticular FDG uptake (shoulders, hips, sternoclavicular joints) – yellow colour,

E: Extraarticular synovial FDG uptake (cervical and lumbar interspinous bursae, ischiogluteal bursae around ischiadic tubers, bursae around pubic bones) – green colour,

V: Vascular FDG uptake (aorta and large arteries) – red colour.

Fig. 2. ^{18}F -FDG PET/CT: fused axial slices of a patient with a positive finding surrounding proximal joints – shoulders (left), sternoclavicular joints (middle), hips (right). In both the shoulder and hip image, FDG uptake overlap to surrounding tissues is notable (from hips up to subtrochanteric bursa).

or with vasculitis, or in a combination of all three (Fig. 3,5) (ref.³³⁻³⁹). Correlation of cervical interspinous bursitis seen as high-contrast enhancement (MRI) and high FDG uptake (PET/CT) was published in 2012 by two author groups^{32,40}. A postulated theory of interspinous bursitis as one of the PMR signs was evaluated using MRI on patients in 2008. In 12 patients with active PMR, bursitis in C5-7 cervical interspinous spaces was observed on MRI, and was significantly more frequent in patients with PMR than in controls with various inflammatory and non-inflammatory disorders⁴¹. Recently, the same author group verified interspinous bursitis in the lumbar spine of PMR patients using MRI (ref.⁴²). Signs of active interspinous bursitis were detected in metabolic PET im-

ages with morphologic CT correlates in our patient group, both in cervical and in lumbar spine. It was observed as soft tissue dense infiltration surrounding vertebral spinous processes with overlap to subcutaneous tissue (Fig. 3,4) (ref.³⁷). This finding is consistent with studies performed using MRI. It appears that extraarticular bursitis detected using PET/CT might be typical for PMR patients, with reasonable sensitivity (85.7%) and specificity (88.2%) when considering high FDG uptake in at least 2 of 3 locations (ischial tuberosities, greater trochanters, spinous processes) (ref.³²). In a more recent study, it has been shown that signs of interspinous bursitis (with high FDG uptake) are relatively common in PMR patients, and do not correlate with severity or appearance of spinal pain⁴³.

Fig. 3. ^{18}F -FDG PET/CT: fused axial slices in patient with a positive finding in the interspinous spaces of the lumbar spine (left image) and large arteries (a. iliaca comm. l. dx. – left image, ascending and descending thoracic aorta – right image).

Fig. 4. ^{18}F -FDG PET/CT: sagittal slice in a patient with a positive finding in the interspinous spaces of cervical spine. Soft tissue dense infiltration was observed on CT (left) with an FDG uptake hot spot in the fused image (right).

Fig. 5. ^{18}F -FDG PET/low-dose CT: fused axial slices in a patient with a positive finding surrounding the symphysis and peritrochanteric area (left image) and in ischiogluteal bursae (more clearly observed in the right image).

Previously published studies and our FDG PET (PET/CT) findings show that active PMR (with articular and extraarticular synovial involvement) can be synchronously accompanied by large vessel vasculitis. We have also detected metachronous presentation of active vascular and extraarticular synovial inflammation. Yamashita et al. presented the case of a patient with high FDG uptake in the shoulders, ischial tuberosities and lumbar spinous processes who was treated with non-steroidal anti-inflammatory drugs and salazosulfapyridine (and not with corticosteroids) and who experienced remission after 6 months. Two years later after another febrile episode (with CRP and ESR elevation), high FDG uptake in large arteries was present, with isolated vasculitis but without high FDG uptake in proximal joints and in extraarticular synovial structures as seen in the preceding examination⁴⁴.

It is clear that further studies will be needed to evaluate the role of PET/CT in patients with PMR, either in initial diagnosis or in post-therapy follow-up, and also in relapse. An ongoing challenge lies in determining whether different manifestations (articular, extraarticular or vascular involvement) of PMR are correlated with different clinical outcome, for example in choosing the best treatment strategy and when assessing patient prognosis.

CONCLUSION

PMR may present by articular/periarticular synovitis of shoulders, hips and sternoclavicular joints and involvement of extraarticular synovial structures/bursitis around ischiadic tuberosities, in spinous interspaces and ventral to pubic bones. PMR can also be accompanied by giant cell arteritis. All types of involvement (periarticular, extraarticular synovial and vascular) have their distinct FDG PET (PET/CT) finding, which can be seen not only individually (articular and extraarticular synovial involvement) but in any of their 4 combinations. FDG PET (PET/CT) examination seems to be an advantageous one-step diagnostic modality for detecting different variants of PMR, for assessing extent and severity and also for excluding occult malignancy. In contrast to other imaging modalities (ultrasound and magnetic resonance imaging), PET (PET/CT) does not need targeting to a limited body part and can provide whole body examination. Understanding the variations of possible symptoms and their imaging correlations could be helpful not only in patients with newly diagnosed PMR, but also in patients in post-therapy follow-up.

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