

research article

PET/CT imaging in polymyalgia rheumatica: praepubic ¹⁸F-FDG uptake correlates with pectineus and adductor longus muscles enthesitis and with tenosynovitis

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Background. The role of ¹⁸F-fluorodeoxyglucose positron emission computed tomography (¹⁸F-FDG PET/CT) is increasing in the diagnosis of polymyalgia rheumatica (PMR), one of the most common inflammatory rheumatic diseases. In addition to other locations, increased ¹⁸F-FDG accumulation has been detected in the praepubic region in some patients. However, a deeper description and pathophysiological explanation of this increased praepubic accumulation has been lacking. The aim of the presented study is to confirm a decrease in praepubic ¹⁸F-FDG accumulation in response to therapy and to describe potential correlations to other ¹⁸F-FDG PET/CT scan characteristics during the course of disease. As a secondary objective, we describe the pathological aspects of the observed praepubic ¹⁸F-FDG uptake.

Patients and methods. A retrospective review of patients with newly suspected PMR undergoing baseline and follow up ¹⁸F-FDG PET/CT between February 2010 and March 2016 is given. Those with a visually detected presence of praepubic ¹⁸F-FDG accumulation were further analysed. The uptake was assessed visually and also semi-quantitatively in the defined region of interest by calculation of target-to-liver ratios. Other regions typical for PMR were systematically described as well (shoulders, hips, sternoclavicular joints, ischiogluteal bursae, spinous interspaces).

Results. Twenty-three out of 89 screened patients (26%) presented with initial praepubic ¹⁸F-FDG PET/CT positivity, 15 of whom also underwent follow up ¹⁸F-FDG PET/CT examination. Five out of 15 patients presented with increased ¹⁸F-FDG accumulation in large arteries as a sign of giant cell arteritis. During follow up examination, decrease in ¹⁸F-FDG accumulation caused by therapeutic intervention was observed in all evaluated locations in all analysed patients and no new positivity was indicated, including periarticular, extraarticular tissues or target large vessels. Praepubic accumulation of ¹⁸F-FDG was diminished in all patients (15/15, 100%) after treatment with steroids.

Conclusions. Increased praepubic ¹⁸F-FDG uptake in patients with PMR is relatively common and this region should be systematically evaluated during differential diagnosis of rheumatic and malignant disease. Praepubic inflammation is probably related to enthesitis and tenosynovitis at the origin of pectineus and adductor longus muscles ventrally from the pubis.

Key words: positron emission tomography, polymyalgia rheumatica, enthesitis, tenosynovitis, fluorodeoxyglucose

Introduction

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease in patients older than 50 years, with a higher incidence in women. PMR shares many pathogenetic and epidemiological features with giant cell arteritis (GCA)¹, and 50% of patients with GCA also develop PMR symptomatology.² The typical symptoms of PMR are bilateral aching of the shoulder girdle, neck and hip girdle, and morning stiffness lasting for 30 minutes or more. These symptoms are probably related to inflammation of the subacromial, subdeltoid and trochanteric bursae, and the glenohumeral or hip joints.^{3,4} 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 several diagnostic and classification criteria have been suggested by some groups.⁵⁻⁹ Each set of criteria has advantages and disadvantages. A PMR-associated ultrasound lesion(s) in the shoulders and/or hips is currently acknowledged as diagnostic criteria for the scoring algorithm in the differential diagnosis of PMR.¹⁰ However, additional imaging methods for assessing rheumatic diseases are warranted.

Prolonged febrile illness with concomitant non-specific symptoms can be also a sign of PMR as well as GCA. Thus, patients may be referred during differential diagnostics of inflammatory or malignant disease to whole body positron emission tomography (PET) or a combination of PET with computed tomography (PET/CT) using ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG).¹¹⁻¹⁴ Both GCA and PMR have their own characteristic ¹⁸F-FDG PET/CT features, which may occur in a non-mutually exclusive manner.

PMR presents with increased ¹⁸F-FDG accumulation in periarticular areas of shoulder and hip girdle and of sternoclavicular joints.¹⁵⁻¹⁷ The other location with metabolically active inflammation in PMR patients are the extraarticular synovial structures (bursae). It appears that ¹⁸F-FDG detection of extraarticular bursitis using PET/CT might be routinely achievable for PMR patients, with reasonable sensitivity (85.7%) and specificity (88.2%), by considering high ¹⁸F-FDG uptake in at least 2 of 3 locations (ischial tuberosity, greater trochanter, spinous processes).¹⁸

Contrasting at least in part with PMR, GCA imaging typically reveals increased avidity in the wall of whole aorta, including its branches (subclavian and brachial arteries, brachiocephalic trunk, common iliac arteries and femoral arter-

ies).¹⁹⁻²¹ Importantly, from the clinical point of view, ¹⁸F-FDG uptake in pertinent locations decreases in response to effective treatment in both PMR and GCA. Thus, ¹⁸F-FDG PET/CT evaluation may be used for monitoring therapy and for follow up.^{15,19,22,23}

In our previous study, increased ¹⁸F-FDG accumulation was detected in the praepubic region in some patients.¹⁷ However, a deeper description and pathophysiological explanation of this increased praepubic accumulation is needed. The aim of the present study is to confirm a decrease of praepubic ¹⁸F-FDG accumulation in response to treatment and to describe potential correlations to other ¹⁸F-FDG PET/CT scan characteristics and to the course of disease, and thereby to support the validation of the praepubic avidity within the general ¹⁸F-FDG PET/CT features of PMR. As a secondary objective, we provide a description of the pathological aspect of the observed praepubic ¹⁸F-FDG uptake.

Patients and methods

Patients with suspected new or relapsed PMR who underwent ¹⁸F-FDG PET/CT examination at Masaryk Memorial Cancer Institute in Brno between February 2010 and March 2016 were retrospectively screened for visually detected presence of praepubic ¹⁸F-FDG accumulation. Patients for whom follow up ¹⁸F-FDG PET/CT was performed during corticosteroid therapy within the clinical remission phase were eligible for further analysis. All patient had to meet ACR 2012 diagnostic criteria for PMR. Patients who were previously treated for known PMR (with at least 15 months from the termination of therapy) were eligible as well. All patients initially provided their signed informed consent with participation on further retrospective studies and this analysis was approved by the institutional review board. Treatment consisted by prednisone, methylprednisolone or methotrexate in various dosages as listed in Table 1.

¹⁸F-FDG PET/CT examination was performed utilizing the hybrid scanner Biograph 64 HR+ Siemens Erlangen, Germany. CT scan was performed in low dose CT (25 mAs eff/120 kV) as well as diagnostic or contrast enhanced CT scan (160 mAs eff/12 kV) (intravenous Iomeron 400, BRACCO, Milan, Italy). All patients had standard preparation prior to examination, including restriction of physical activity for 12 h, fasting for at least 6 h, capillary glycemia below 10 mmol/L (180 mg/dL) prior to ¹⁸F-FDG administration and peroral hydration with 500-

TABLE 1. Imaging and laboratory results of all patients. Reported baseline treatment was initiated several days after baseline PET/CT

No	Disease status	Date of baseline (B) and follow up (FU) examination	Time to control exam (months)	B/FU praepubic to liver uptake ratio	B/FU FW (mm/h)	B/FU CRP (mg/dL)	B/FU treatment (mg/day)	B/ FU region of positivity of other PMR areas (target-to-liver ratio)	B/FU vascular positivity
1	R	11-18-2014	4.0	1.134	44	23	P 15	S 2.23, H 1.25, Scl 1.13, Isch 1.45	no positivity
		3-20-2015		0.576	16	1.4	P 5	H 1.11	no positivity
2	N	2-23-2010	48.7	1.234	120	49	P 15	S 1.65, H 1.24, Scl 1.24, Isch 1.17, L 1.14	no positivity
		3-15-2014		0.812	26	16.9	M 8	no positivity	no positivity
3	N	9-1-2014	3.2	2.148	120	137	P 60	S 1.87, Scl 1.45, H 2.31, Isch 1.65, L 1.12, Th 1.14, C 1.24	no positivity
		12-8-2014		0.992	35	16.7	P 10	S 1.36	no positivity
4	N	7-24-2010	6.1	1.891	120	56.8	P 40	S 1.78, Scl 1.54, H 1, Isch 2.21, L 1.08	no positivity
		1-25-2011		0.345	30	5.7	P 2.5	no positivity	no positivity
5	N	3-13-2014	12.0	1.772	60	28.5	P 20	S 2.02, H 1.47, Scl 1.24, Isch 2.02, L 1.23	V3/6
		3-13-2015		0.987	7	1	P 0	no positivity	V1/6
6	N	10-14-2013	16.9	1.298	54	45	P 20	S1.78, H1.88, Scl 1.95, L 1.25, Isch 1.16	no positivity
		3-13-2015		0.537	6	5.3	P 2.5	no positivity	no positivity
7	R	1-3-2014	13.1	1.302	77	78.3	M 16	S 1.78, H 1.87, Scl 1.35, Isch 1.65, L 1.12	V4/6
		2-6-2015		0.403	5	1.9	M 2	no positivity	no positivity
8	N	6-9-2012	33.1	1.835	50	76	P 30	S 2.21, H 2.16, Scl 1.8, Isch 1.78, L 1.2	V4/6
		3-13-2015		0.54	14	3.1	P 0	H 1.23	V2/6
9	N	6-3-2015	3.1	1.502	60	41.5	P 15	S 2.36, H 2.24, Scl 2.03, Isch 2.04, C 1.11	no positivity
		9-4-2015		0.76	16	13.4	P 10	no positivity	no positivity
10	N	1-8-2014	21.7	1.209	80	78.3	P 60	S 1.84, H1.78, Scl 1.69, Isch 1.57, L 1.23	no positivity
		10-30-2015		0.395	10	2.5	P 7.5	no positivity	no positivity
11	R	3-4-2015	8.1	1.546	62	16.5	M 48 + MTX 10/week	S 2.66, H 2.74, Scl 2.0, Isch 1.72, C 1.47, L 1.48	V5/6
		11-5-2015		0.811	30	3.3	M 4 + MTX 10/week	H 1.14, C 1.08, S 1.11, Scl 1.07	V3/6
12	N	2-6-2015	8.3	1.789	120	98.7	M 32	S 2.27, H 2.06, Scl 2.16, Isch 3.03, L 1.45	no positivity
		10-16-2015		0.97	40	7.5	M 8	Scl 1.14, Isch 1.21	no positivity
13	N	1-23-2015	14	1.123	70	67.5	P 15	S 1.78, H 1.87, Scl 1.69, Isch 1.57, L 1.24	no positivity
		3-24-2016		0.441	6	1.4	P 5	no positivity	no positivity
14	N	9-16-2015	5.8	1.282	74	52	P 20	S 2.44, H 3.04, Scl 2.07, L 1.21	no positivity
		3-9-2016		0.41	24	3.2	P 7.5	no positivity	no positivity
15	N	10-26-2015	3.2	1.892	80	118.8	P 30	S 2.93, H 2.97, Isch 3.22, C 1.44, L 1.24, Th 1.17, Scl 1.79	V4/6
		2-1-2016		0.678	5	1.3	P20	no positivity	no positivity

B/C = baseline and control; C, L, Th = cervical, lumbar, thoracic interspinous space; FW = Fåhræus-Westergren test; H = hip; M = methylprednisolone; Isch = ischiogluteal bursae; MTX = methotrexate; N = newly diagnosed; P = prednisone; R = relapse; S = shoulder; Scl = sternoclavicular joint; V = vascular uptake with number indicating presence in regions from 6 measured

1,000 mL of plain water. ¹⁸F-FDG (UJV Rez, Czech Republic) was administered in a dose range of 327-434 (median 366 MBq) in the baseline study and in a dose range of 301-400 (median 362 MBq) in the follow up examination. After an *in vivo* accumulation time of 55 to 75 minutes, whole body scanning from the proximal third of thighs to the skull base was performed in baseline as well as follow up study. All images were iteratively reconstructed and corrected for attenuation.

¹⁸F-FDG uptake was assessed visually and also semi-quantitatively in the defined region of interest (ROI) with calculation of target-to-liver ratios. Liver ¹⁸F-FDG uptake (SUVmax) was used as a reference base (measured within the ROI located in the centrum of the right liver lobe). Praepubic ¹⁸F-FDG accumulation was semiquantitatively assessed as SUVmax within elliptic ROI located through both preapubic regions while keeping in the safe distance from the bladder based on the investigator discretion. Praepubic-to-liver ratio (SUVmax) was subsequently calculated.

Other regions typical for PMR were systematically described with measurement of SUVmax: shoulders, hips and sternoclavicular joints and extraarticular sites – in ischial tuberosity and between spinous processes where ischiogluteal and interspinous bursae are often presented, respectively. A target-to-liver ratio higher than 1.0 was considered positive in all mentioned regions. For paired organs, the higher value (from the right or left site) was used for target-to-liver calculation. ¹⁸F-FDG uptake (SUVmax) within the typical sites for GCA was also systematically evaluated, namely in the walls of following arteries: thoracic aorta, abdominal aorta, brachial and subclavian arteries, iliac and femoral arteries. An artery wall-to-liver ratio higher than 1.0 was also considered positive. The number of positive vascular regions out of six evaluated regions is reported. Again, for paired structures, the higher value (from the right or left site) was used for target-to-liver calculation. The same scan evaluation was performed for follow up scans.

Results

Patients characteristic

From 89 screened patients, 23 (26%) presented with initial praepubic ¹⁸F-FDG PET/CT positivity. 15 patients, 10 women and 5 men with a median age of 70 years, range 53 to 78, underwent also follow up ¹⁸F-FDG PET/CT and met inclusion criteria for the presented analysis (Table 2). Twelve out

TABLE 2. Patients' baseline characteristics

Characteristics	Numbers (%) n= 15 (100%)
Sex, n (%)	
females	10 (66.7 %)
males	5 (33.3 %)
Age at the disease onset	
median (min-max)	70 years (53–78)
Time to follow up exam	
median (min-max)	8 months (3-49)

TABLE 3. Changes in analysed laboratory parameters between baseline and follow up examination

	Baseline median (min-max)	Follow up median (min-max)	p-value median (min-max)
CRP	57 mg/l (17–137)	3 mg/l (1–17)	0.001
FW	74 mm/hod (44–120)	16 mm/hod (5–40)	0.001

TABLE 4. Nuclear medicine data at baseline and follow up examination

	Baseline median (min-max)	Follow up median (min-max)	p-value median (min-max)
¹⁸F-FDG	366 MBq (327–434)	362 MBq (301–400)	0.271
Praepubic / liver ¹⁸F-FDG uptake	1.50 (1.12–2.15)	0.58 (0.35–0.99)	0.001

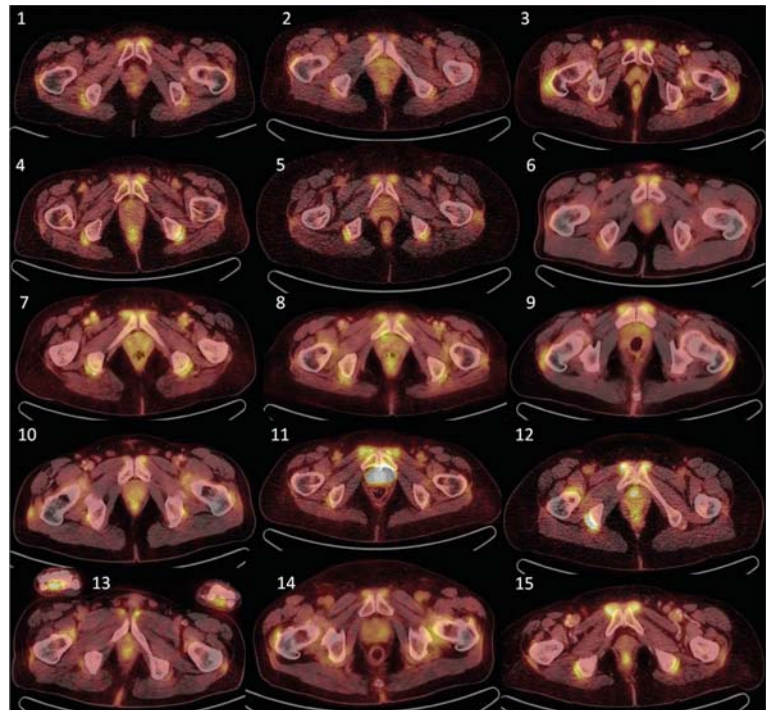


FIGURE 1. Initial ¹⁸F-FDG-PET/CT examination of all 15 examined patients, showing transversal planes through maximal praepubic uptake. Visually detectable accumulation can be observed in all patients.

of 15 patients were classified as newly diagnosed; prior to the initiation of corticosteroid therapy, the other three patients had been previously treated for known PMR (with at least 15 months from the termination of therapy). Laboratory values for FW and CRP were obtained for all patients, \pm 14 days around ^{18}F -FDG PET/CT (Table 3). Patient number 5 had accompanied giant cell arteritis confirmed histologically by temporal artery biopsy.

Baseline ^{18}F -FDG PET/CT characteristics

^{18}F -FDG PET/CT characteristic including ^{18}F -FDG dosage are summarized in Table 4. Increased ^{18}F -FDG accumulation (positivity) was observed at baseline in all patients in the praepubic region, with praepubic-to-liver ratios higher than 1.0. This accumulation was obvious by visual evaluation only, as presented in Figure 1, and this finding was always accompanied by additional positivity in ^{18}F -FDG PET/CT scans (Table 1). Other sites with increased accumulation were as follow: around the shoulder girdle in all 15 patients, around the hip girdle in 15 patients, and around sternoclavicular joints in 14 out of 15 patients. ^{18}F -FDG PET/CT positivity was observed also in extraarticular synovial structures, in ischiogluteal bursa in 14 patients and

between spinous processes of the vertebrae in 14 patients, most commonly within lumbal region in 13 patients.

Five out of 15 patients presented with increased ^{18}F -FDG accumulation in large arteries as a sign of large vessel vasculitis of GCA. In those with large vessel vasculitis, ^{18}F -FDG PET/CT positivity was at least in 3 of 6 evaluated vascular regions. Increased values of FW and CRP were detected in all patients during initial examination and were correlated to newly diagnosed PMR or to its relapse (Table 3).

Follow up ^{18}F -FDG PET/CT characteristics

Given the retrospective nature of this study, it was not possible to keep a strict interval between baseline and follow up ^{18}F -FDG PET/CT scans. Follow up examinations were timed by clinical purposes rather than by experimental needs. Follow up ^{18}F -FDG PET/CT (median time 8 months, range 3-49) revealed continuing positivity around the shoulder girdle in only 2/15 patients, around hip joints in 3/15, around the sternoclavicular joint in 2/15, in extraarticular synovial structures in ischiogluteal bursae in 1/15 and in interspinous regions of cervical vertebrae in 1/15 patients. In three out of 15 patients, positivity in continuous large vessels was observed, maximally in 3 vessel regions out of 6 measured. In all evaluated locations in all analysed patients, a decrease in ^{18}F -FDG accumulation (target-to-liver ratio) was observed, and no new positivity was indicated, including periarticular, extraarticular tissues or target large vessels. Praepubic accumulation of ^{18}F -FDG was diminished in all patients after treatment with steroids. Praepubic-to-liver ratio was lower than 1.0 post therapy and this decrease in accumulation was clear by visual assessment (Figure 2).

During follow up ^{18}F -FDG PET/CT examination, all patients were undergoing steroid treatment and they reported subjective improvement in health condition, and disease remission was confirmed by attending rheumatologist. The laboratory signs of inflammation, FW, and CRP were decreased as well (Table 3).

Discussion

In the presented retrospective analysis of ^{18}F -FDG PET/CT findings in patients with proven PMR, 25.8% patients presented with praepubic ^{18}F -FDG uptake with fifteen patients from our cohort being able to undergo follow up ^{18}F -FDG PET/CT

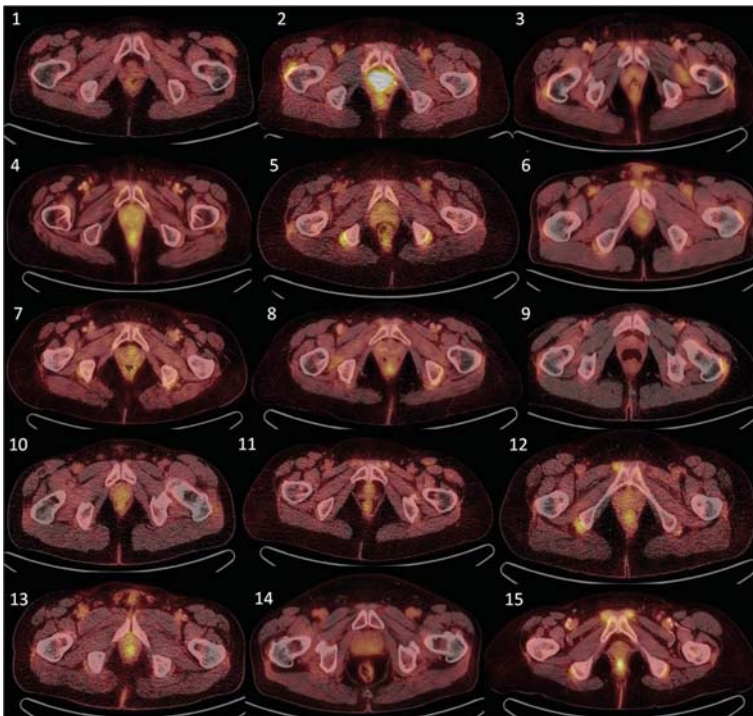


FIGURE 2. Control ^{18}F -FDG-PET/CT examination showing corresponding transversal slices as in Figure 1. Compared with Figure 1, decrease or complete diminishment of ^{18}F -FDG accumulation is observable in all patients.

examination. We were not able to perform follow up ¹⁸F-FDG PET/CT scan in a prospectively defined phase of treatment; instead, the aim was to obtain ¹⁸F-FDG PET/CT study during disease remission. During this follow up ¹⁸F-FDG PET/CT exam, praepubic accumulation of ¹⁸F-FDG was diminished in all 15 patients after treatment with steroids.

In our previous study, praepubic positivity was described only in 5/67 (8%) PMR patients representing only a relatively rare sign of the disease.¹⁷ However, 32/67 (48%) patients were examined on an older PET scanner with the rest undergoing examination in a newer hybrid PET/CT scanner with better image resolution. Lower detectability of targeted lesions may have occurred on ¹⁸F-FDG PET scanner alone and also underevaluation of accumulation quantification may result in false negativity (praepubic-to-liver ratio < 1.0). Even if visual accumulation was clearly positive, no patient from our previous cohort met the criterion for positivity. Given the above findings, it is reasonable to speculate that the percentage of positive praepubic accumulation in patients with active PMR would be higher when examined on a hybrid ¹⁸F-FDG PET/CT rather than a PET camera. The overall number of patients with initial praepubic ¹⁸F-FDG PET/CT positivity was 23/89 (25.8%). Thus, praepubic accumulation should not be considered a constant and frequent sign of ¹⁸F-FDG PET/CT results as it is in periarticular ¹⁸F-FDG accumulation in shoulders and hips. In cohorts from previous studies, accumulation in the shoulder groin girdle was observed in 33/35 (94%), in 12/14 (86%) and in 58/67 (87%) and in the hips in 31/35 (89%), in 12/14 (86%) and in 47/67 (70%) PMR patients, respectively.¹⁵⁻¹⁷

In a recently published report of 15 patients with PMR and of 9 patients with Elderly-Onset Rheumatoid Arthritis (EORA), praepubic ¹⁸F-FDG uptake was recommended as one of the signs to enable differentiation between these two conditions.²⁴ The incidence of praepubic ¹⁸F-FDG uptake (pectineus enthesitis) was relatively high with 9 patients from 15 evaluated which may be related to sample size bias. Patients with PMR developed significantly higher uptake compared to those with EORA.²⁴ Patients in the present study represent a retrospectively described cohort of patients with praepubic ¹⁸F-FDG PET/CT positivity that includes post-treatment follow up examination. In light of these findings, it seems possible that increased praepubic accumulation may have been present in previously published case reports including those where axial slices indicating ischiogluteal bursitis were published.^{18,25-27} Sondag *et al.* observed

¹⁸F-FDG uptake in 11/50 (22%) patients; however, the cohort was a mixture of those with and without treatment with 22/50 (44%) with administration of steroids.²⁸ Mackie *et al.* published the first MRI findings of inflammation in the front of the symphysis in patients with PMR in 2015.²⁹ A similar observation was observed in our cohort (patient number 11); data not shown.

It is difficult to exactly determine the pathological background of increased ¹⁸F-FDG uptake in the praepubic region in patients with PMR. The described accumulation seems to be relatively bordered and with spheric shape in some patients, while with blurry margins in others. MRI may be helpful in further evaluation of this region. Based on the MRI finding presented by Mackie *et al.* and Wakura *et al.*, we assume another type of extraarticular inflammation is responsible for the observed PET findings.^{24,30} Namely, it appears to represent features of enthesitis and tenosynovitis of pectineus and adductor longus muscles. There is probably no bursa in the locations under the tendons of these muscles, which is also supported by findings on MRI, where no fluid collection with evidence of thickened wall suggestive for bursitis was observed. However, some reports have recently suggested a combination of PMR and tenosynovitis in other locations, namely in the long head of biceps brachii³¹ or in extensor tenosynovitis of the hand³² or in the vicinity of the entheses of the rectus femoris.²⁴

Our observations confirm that ¹⁸F-FDG PET/CT examination seems to be an advantageous one-step diagnostic modality for detecting different variants of PMR, for assessing extent and severity, and for excluding occult malignancy. The follow up exam may be useful in monitoring disease activity including the praepubic location. It is conceivable that the praepubic region will become part of targeted examination for other imaging strategies as is US or MRI and that clinical significance and correlations will be further discovered.

Conclusions

Increased praepubic tracer accumulation is becoming an integral part of ¹⁸F-FDG PET/CT evaluation of polymyalgia rheumatica, and is probably a correlate of enthesitis and tenosynovitis at the origin of pectineus and adductor longus muscles ventrally from the pubis. The findings described here were consistently presented in combination with other periarticular accumulations (shoulder and hip gir-

dle and surrounded bursae, sternoclavicular joint) and other extraarticular bursae at some distance from joints such as the ischiogluteal bursae and interspinous bursae in spine. Some patients presented with signs of large vessels vasculitis of GCA. In accordance with other ¹⁸F-FDG PET/CT positive locations, praepubic accumulation was decreased in relation to PMR treatment. Our findings support the clinical value of ¹⁸F-FDG PET/CT examination of patients with suspected or proved PMR.

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