Imaging Techniques: Positron Emission Tomography in GCA and PMR

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9.1 Positron Emission Tomography

Positron emission tomography (PET) is a diagnostic method showing general biodistribution of positron radiotracers, the most widely and routinely used of which is 2-[18F]fluoro-2-deoxy-D-glucose (FDG). FDG is a glucose analogue containing radionuclide fluorine ^{18}F, which decays by positron (β+) emission, with a half-life of 109.7 min. Diagnosis with the use of FDG-PET ("PET") combines high imaging quality (mainly sensitivity and resolution as compared to "conventional scintigraphy") and radiotracers with a favourable biodistribution and a relatively high affinity for both tumour and inflammatory cells. As a result, what is a disadvantage for oncologic imaging is a benefit for imaging of inflammations. PET scanner was adequate to provide a "functional metabolic" image of radiotracer biodistribution, however, without any anatomical-morphological information. The current hybrid PET/CT imaging systems are a combination of both methods (PET and CT), providing the respective image in the same scope and at relatively close time points. PET/CT scanners have also reduced the scanning time by about one half as compared to the initial PET scanners and increased image resolution. CT may be performed both in the low-dose (LD) and in the high-dose (HD) diagnostic mode with the possibility to use both positive and negative contrasts.

(PET/CT scanner in the HDCT mode with the use of intravenous iodinated contrast medium provides maximum diagnostic details.) Availability of the examination is relatively increasing with the growing number of PET centres.

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9.2 GCA

Patients with giant cell arteritis (GCA) may be indicated for PET (PET/CT) examination both for the purpose of initial diagnosing or monitoring of the activity of the already diagnosed disease. In the first case, it is rather a broader differential diagnostic examination within general assessment of a patient with systemic symptoms of an inflammatory condition, with laboratory evidence of active inflammation (high erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels). Such a patient is indicated for examination in order both to reveal an inflammatory condition and to rule out any occult malignancy. Studies of groups of patients examined for fever of unknown origin (FUO) or, more generally, for protracted febrile episodes report about 10–28% of patients with suspected large-vessel vasculitis [1–4]. It highly depends on the composition of the cohort and age of patients. Currently, there exist numerous studies in the literature referring to such groups of patients, with sensitivity values ranging between 77 and 92% and specificity values between 89 and 100% [5]. A typical positive PET scan in GCA patients shows tubular accumulation of radiotracer (FDG), where the arterial lumen remains free of tracer (photopenic area) and only arterial walls are "active". Examination with the use of a hybrid PET/CT scanner may show correlation also with thickening of the arterial wall, sometimes only a fine soft-tissue border in the aortic wall, although these findings may be only vague. Findings of a relatively high FDG uptake in the walls of large arteries in patients with GCA are quite uniform and may be observed in almost all sections of the aorta, with a relatively more frequent involvement of arteries originating from the aortic arch—brachiocephalic trunk, common carotid artery and subclavian artery—with continuation to brachial artery (here also symmetrical) (Fig. 9.1). High FDG accumulation is seen also in the iliac and femoral arteries. With a standard whole body protocol (skull base to mid thighs), the detection capacity of PET (as well as PET/CT) covers the area up to the neck, the carotid artery (approximately at the point of its bifurcation), the cervical part of the vertebral artery and the brachial artery in upper limbs. Meller et al. reported five patients with early aortitis; in all of them, they detected a high FDG uptake in the aortic walls and other arterial regions. High FDG uptake in these patients was found in a total of 28 vascular regions, while only nine of these regions (32%) showed vasculitis also on MRI. In other cohorts, high FDG uptake was demonstrated in the arteries that did not show the signs of involvement according to CTA or MRA [6, 7]. One of the benefits of PET or PET/CT scanning may be the fact that it detects GCA at the time when structural changes relevant for typical angiograms (CTA, MRA) have not developed yet. PET is a metabolic, functional image revealing metabolic activity of inflammation. Thus, examination makes sense only in patients prior to commencement of immunosuppressive or glucocorticoid therapy. In our view, the therapy may induce a relatively rapid decrease in the inflammation activity (and, consequently, impact visualization of FDG uptake in large arteries). There is also evidence of rapid subsidence of signs of inflammation during radiological imaging examinations, and it is recommended to perform these examinations before commencement of immunosuppressive therapy, as sensitivity (not specificity) of both

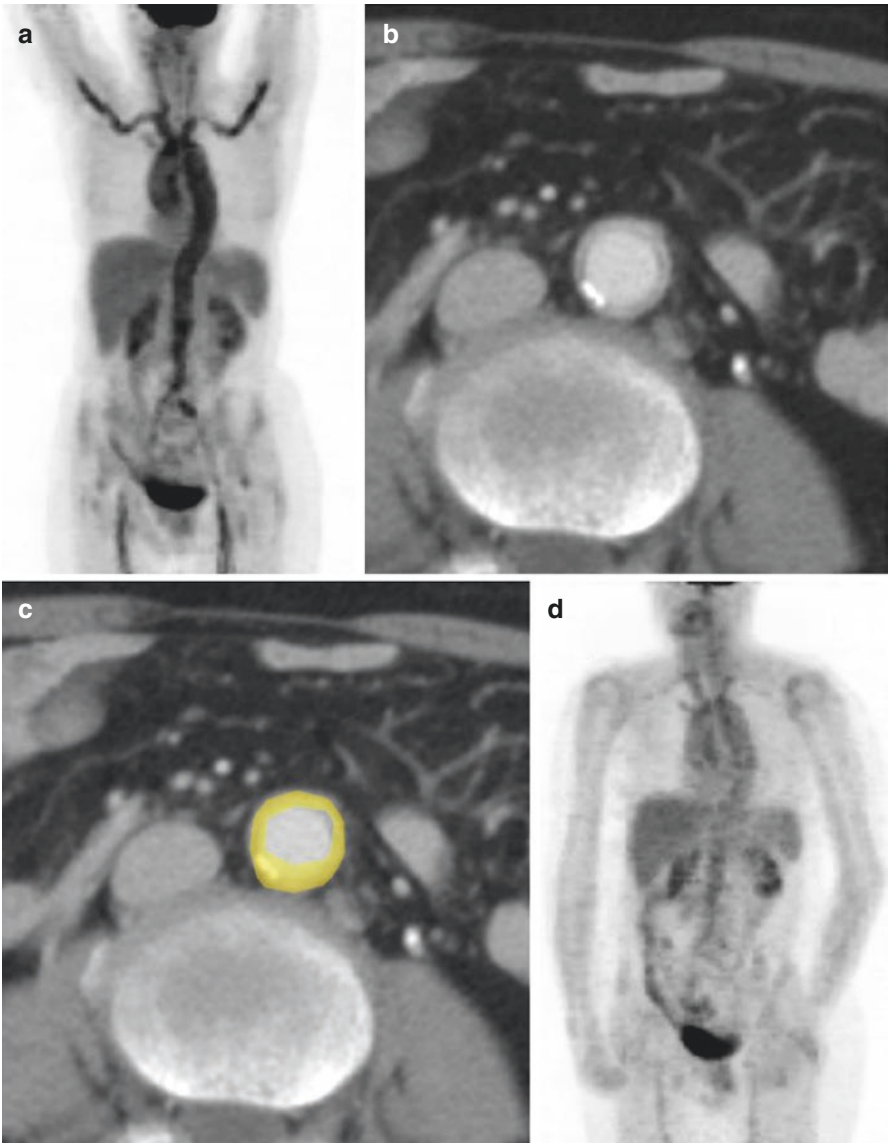

Fig. 9.1 A case study—a 66-year-old woman. (**a**) PET-MIP (maximum intensity projections, summed pseudo 3D image) of the body evidencing active vasculitis. High FDG accumulation in the aorta and large arteries exceeding the reference liver accumulation *t*. (**b**, **c**) CTA was performed due to suspected vasculitis; a fine soft-tissue border in the aortic wall correlates in fusion of both examinations with metabolically active aortic wall (*yellow ring*). (**d**) Follow-up PET examination after 7 months of glucocorticoid therapy demonstrates decrease in FDG accumulation in large arteries

US and MRI decreases from the very first day of the treatment [8]. Unfortunately, there is no information about the effect of the therapy on subsidence of signs that can be visualized by PET (PET/CT) examination. In those patients who are indicated within a broader differential diagnosis of unknown inflammatory condition for PET (PET/CT) examinations, we consider reasonable to begin with immunosuppressive therapy only after this examination in order not to distort signs of vasculitis, if present.

9.3 Monitoring of Therapy

Both PET and PET/CT examination may be used to monitor the course of the disease. Decrease in the radiotracer uptake during glucocorticoid therapy has been documented in correlation with nonspecific inflammation markers (ESR, CRP), platelet count and haemoglobin levels (inverse correlation in case of haemoglobin) [7, 9]. As early as 2006, Blockmans et al. published a study of 35 patients with GCA, in which they performed PET examination initially and 3 and 6 months after glucocorticoid therapy. Already this study has shown that PET is a sensitive marker for GCA and documented a significant decrease in metabolic activity of inflammation after 3 months of therapy that may be also quantified. At the same time, the study has demonstrated that FDG accumulation in large arteries does not further decrease after 6 months of therapy and that GCA relapses cannot be predicted by results of former PET scans (quantification in the initial study) (18 of 35 patients) [10]. PET/CT examination was also used to provide evidence of the disease persisting despite the treatment, in correlation with clinical and laboratory signs of its activity [11]. At the same time, therapeutic response to cyclophosphamide has been also assessed in patients with GCA resistance to glucocorticoids [12]. We are aware that despite a relatively sufficient evidence related to the use of PET (PET/CT) and reasonability of this examination, these methods have not become standard procedures for GCA diagnosis or monitoring yet.

It may be summarized that published studies provide a clear indication of FDG-PET and PET/CT benefits in evaluation of the diagnosis and therapy in patients with GCA, early detection, assessment of the extent of vessel inflammation and specification of the area for biopsy [10, 13, 14]. Several ways to evaluate radiotracer uptake in vessel walls have been proposed. Visual methods are more specific than semiquantitative ones, but they have lower sensitivity. The most commonly used semiquantitative method is SUVmax (maximum standardized

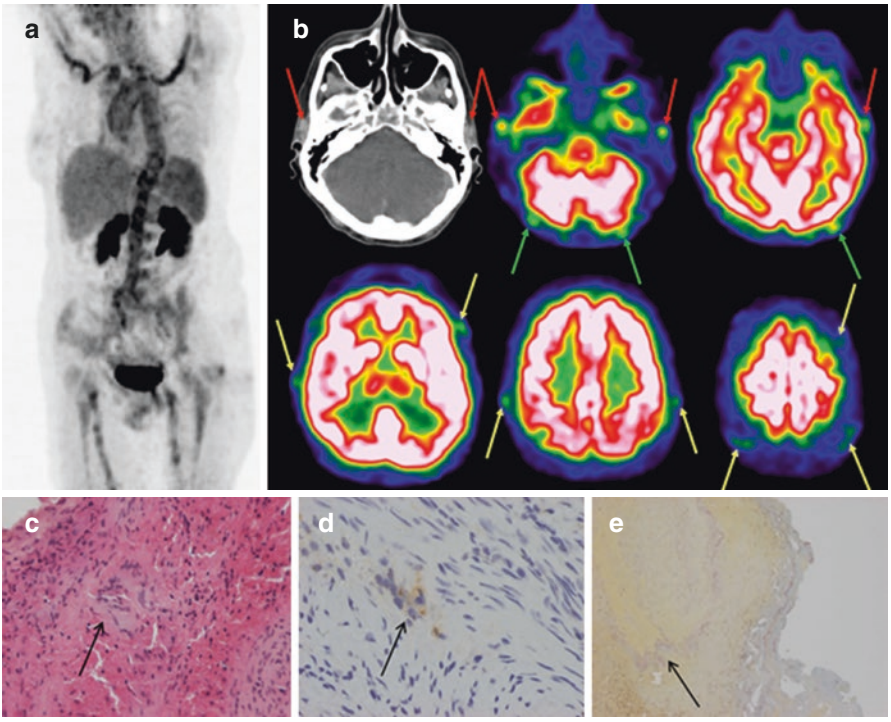

Fig. 9.2 A case study—a 63-year-old woman. (**a**) Hybrid PET/CT examination of the body (PET-MIP) revealed in the patient with fever of unknown origin a high FDG accumulation in aorta and large arteries. (**b**) Additional special brain imaging detected high FDG accumulation also in temporal arteries (*red arrows*), their frontal and parietal branches (*yellow arrows*) and occipital arteries (*green arrows*). Histological examination from excision of the left temporal artery proved giant cell arteritis. (**c**) HE, magnification 200×, stained multinucleated cells, (**d**) immunohistochemical examination—anti CD 68+, magnification 200×, stained multinucleated cells, (**e**) resorcin-fuchsin, magnification 100×, stained disintegration of the internal elastic lamina (elastica)

uptake value) aorta-to-liver ratio or aortic-to-blood pool uptake ratio [15, 16]. It seems that scanning in 180th minute as compared to standard scanning in 60th minute after the FDG application further improves detection capacity of PET/CT [17]. Addition of head imaging to the brain protocol may contribute to a better detection of inflammation in the region of temporal, vertebral and occipital arteries [18] (Fig. 9.2).

9.4 Coincidence of GCA and PMR

Experience gained in PET and PET/CT examinations also shows that the association between PMR and GCA is very close, and it may emerge as one disease with different manifestations.

Increased accumulation of FDG in the wall of an aorta including rising branches (subclavian and brachial arteries, brachiocephalic trunk and iliac and femoral arteries) is a typical sign of GCA-PET/CT scan. On the other hand, increased FDG accumulation in periarticular (around shoulders, hips and sternoclavicular joints) and extraarticular regions (in synovial structures—bursae between spinous processes in the spine or ischiogluteal bursae) is typical for PMR, including radiotracer uptake in the prepubic location (Fig. 9.3).

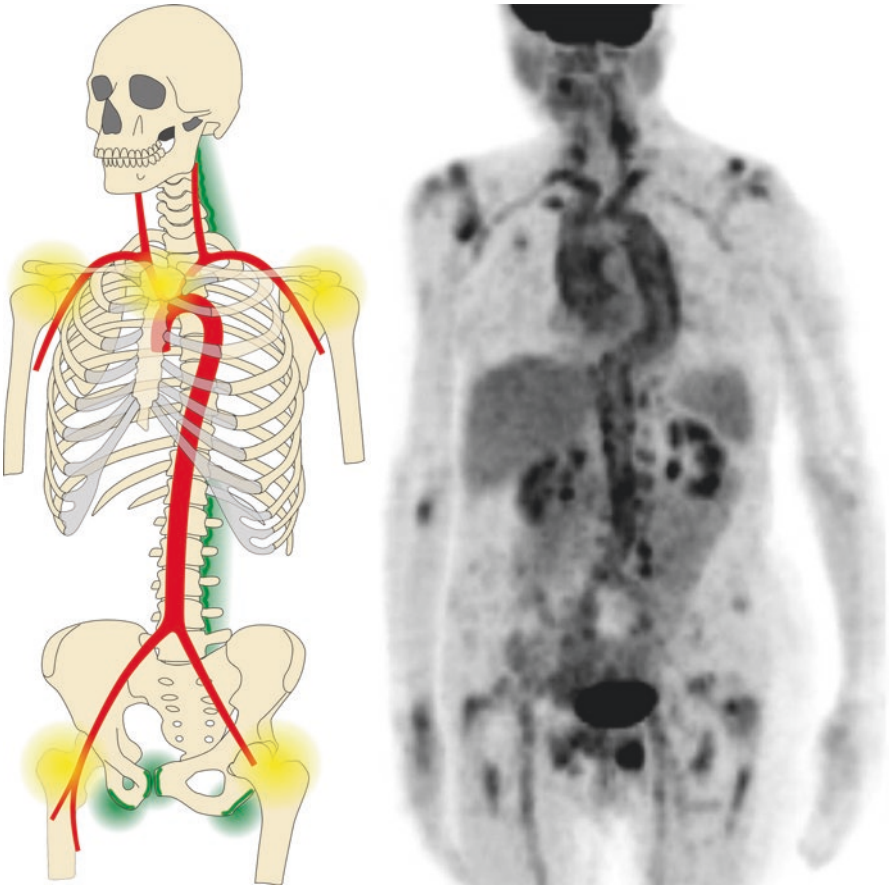

Fig. 9.3 FDG distribution in the torso of a PMR patient with developed signs of coincidental GCA. Schema (*left*) and left anterior oblique view MIP (*right*), with addition of the following colouring: (1) Articular/periarticular FDG uptake (shoulders, hips, sternoclavicular joints)—*yellow colour*. (2) Extraarticular FDG uptake (cervical and lumbar interspinous bursae, ischiogluteal bursae around ischiadic tubers) and prepubic FDG uptake—*green colour*. (3) Vascular FDG uptake (giant cell arteritis)—*red colour*. Adapted with permission of Rehak et al. [20]

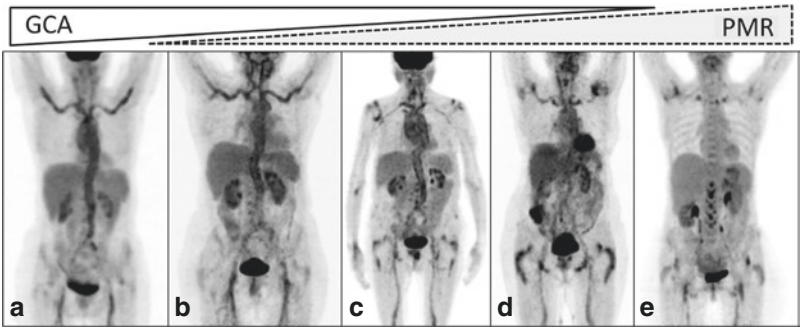

Fig. 9.4 FDG-PET/CT, MIP (maximum intensity projections)-PET scans of torso in patients with GCA and PMR. Cases **a** and **b** are typical for GCA and cases **d** and **e** are typical for PMR cases, while case **c** represents a mixture of features. Lesser mixtures of PMR and GCA signs are also seen in cases **b** and **d**, with predominance of only a subset of components. This demonstrates that the characteristic signs of GCA and PMR are frequently not clear or exact

In 2006 and 2007, Blockmans et al. published two PET 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%) patients [10]. 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 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 patients [19]. These two studies with GCA and PMR patients were the first to visualize the possible accompanying vasculitis and the association of polymyalgia rheumatica, using PET. Also in our study, large-vessel vasculitis was found in 27/67 (40.3%) patients [20]. Thus, we have arrived at a similar conclusion as Blockmans et al. (Fig. 9.4). We have also detected metachronous PET/CT presentations of active GCA and PMR. Yamashita et al. presented the case of a patient with high FDG uptake in the shoulders, near ischial tuberosities and lumbar spinous processes who was treated with nonsteroidal 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 examination [21].

9.5 Periarticular Accumulation

Periarticular accumulations are the most common type of FDG pattern in PMR patients. In FDG-PET examinations, Blockmans et al. detected high FDG uptake in shoulders in 33/35 (94.3%) patients and in hips in 31/35 (88.6%) patients [19]. 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 hips [22]. In our study, high articular/periarticular FDG uptake in shoulders was detected in 58/67 (86.6%) patients and in hips in 47/67(70.1%) patients [20]. Recent PET/CT studies revealed positivity in shoulders

in 16/18 (88.9%) and in hips in 17/18 (94.4%) patients and in 11/15 (73.3%) and in 11/15 (73.3%), respectively [23, 24].

It is difficult to distinguish shoulder or hip girdle synovitis and periarticular bursitis in PET or PET/CT examinations. High FDG uptake can spread from articular capsule to surrounding tissues including peribursitis locations. Nonetheless, it is possible to assess this FDG accumulation not only in shoulders and hips but also in near bursae [24, 25].

The other prominent sites exhibiting increased FDG accumulation are sternoclavicular joints, presenting positivity in 6/14 (42.8%), 31/67 (46.3%) and 13/18 (72.2%) patients, respectively [20, 22, 23].

9.6 Extraarticular Accumulation: Interspinous and Ischiogluteal Bursitis

PMR can be accompanied by extraarticular synovial involvement, i.e. as in bursitis. Blockmans et al. were first to describe high FDG uptake surrounding vertebral spinous processes of vertebrae in approximately half of their PMR patient population, 18/35 (51.4%) [19]. These observations were confirmed by other groups showing the increased FDG uptake near the cervical spinous processes in 13/67 (19.4%) patients [20] or in 10/18 (55.6%) patients [23] or uptake in lumbar spinous processes in 38/67 (56.7%) patients [20] or in 13/18 (72.2%) patients [23]. Furthermore, the radiotracer uptake was detected in intervertebral joints [24, 26].

A correlation between interspinous bursitis seen as high-contrast enhancement (MRI) and high FDG uptake (PET/CT) was published in 2012 by two author groups [22, 27]. A hypothesis of interspinous bursitis as one of the signs of PMR was evaluated using MRI on patients in 2008. In 12 patients with active PMR, bursitis in C5–C7 cervical interspinous spaces was described on MRI and was significantly more frequent in patients with PMR than in controls with various inflammatory and noninflammatory disorders [28]. Soft-tissue dense infiltration surrounding vertebral spinous processes with overlap to the subcutaneous tissue can be detected by FDG-PET/CT [20]. Other published case reports of patients examined on PET/CT scanners noted high FDG uptake in surrounding vertebral spinous processes and in other extraarticular synovial structures (bursae around ischial tuberosities and femoral trochanters). These were found either individually or in combination with proximal joint involvement or with vasculitis or in a combination of all three. For example, FDG uptake positivity was reported near ischial tuberosities in 17/18 (94.4%) patients [23], in 35/67 (52.2%) patients [20], in 12/14 (85.7%) patients [22] and in 14/15 (93.3%) patients [24].

It appears that extraarticular involvement (bursitis) detected using FDG-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 two of three locations (ischial tuberosities, greater trochanters, spinous processes) [22].

9.7 Extraarticular Accumulation: Enthesitis and Tenosynovitis

An infrequent sign of PMR in PET/CT is increased accumulation of FDG in front of pubic bones (Fig. 9.5) [20, 23, 24].

MRI findings of inflammation in front of the symphysis in patients with PMR were published in 2015 [29]. It is reasonable to suspect that this correlates with features of enthesitis and tenosynovitis of the pectineus muscle and adductor longus rather than bursitis.

In patients with developed signs of the disease (always with high periarticular FDG uptake near shoulders, hips and sternoclavicular joints), including high radiotracer uptake in ischiogluteal or interspinous bursae and in the prepubic region, it is sometimes possible to detect increased FDG uptake in front of the anterior inferior iliac spine. This inflammation in PMR patients related to the rectus femoris muscle confirms the pioneer observation of Wakura et al. in 2016 [24].

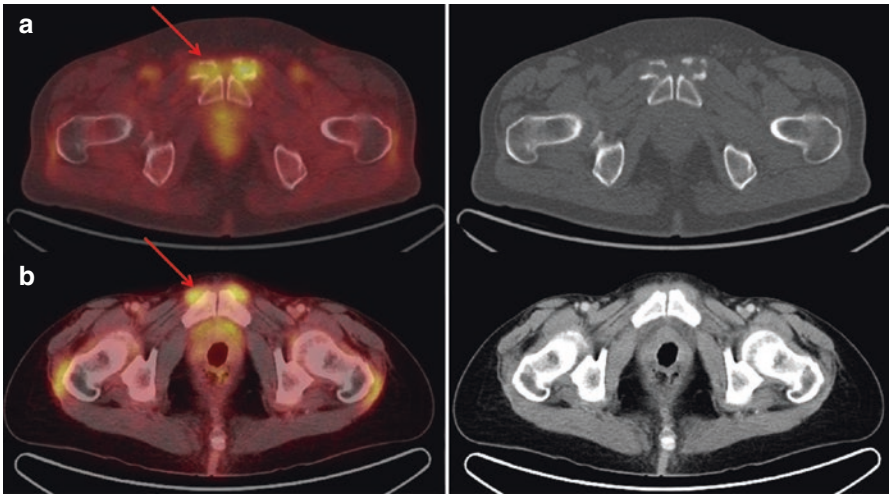

Fig. 9.5 Axial slices with a positive prepubic findings in two different patients ((**a**) a 73-year-old man, (**b**) a 54-year-old woman) detected by FDG-PET/CT. FDG uptake hot spot in the fused image (*left*, *arrow*) corresponds to metabolically active inflammation in the insertions of the muscles located in front of the symphysis (pectineus, adductor longus muscle)

9.8 Monitoring of Therapy

Decreasing FDG accumulation, as a reaction to effective treatment (corticosteroids) and in concordance with clinical and laboratory remission (decrease of ESR and CRP levels), has been documented in separate case reports and also in a cohort of patients examined using PET alone or PET/CT [19, 22, 26]. Recently, this reaction was also described in a patient undergoing therapy with the targeted monoclonal antibody tocilizumab [23]. Also, disease relapse may be mirrored by re-accumulation of FDG. This relapse is often presented as only a partially positive disease (not in all previously impaired locations) and often with sidedness asymmetry (Fig. 9.6). It may be reasonable to use FDG-PET/CT examination as follow-up monitoring, as in GCA.

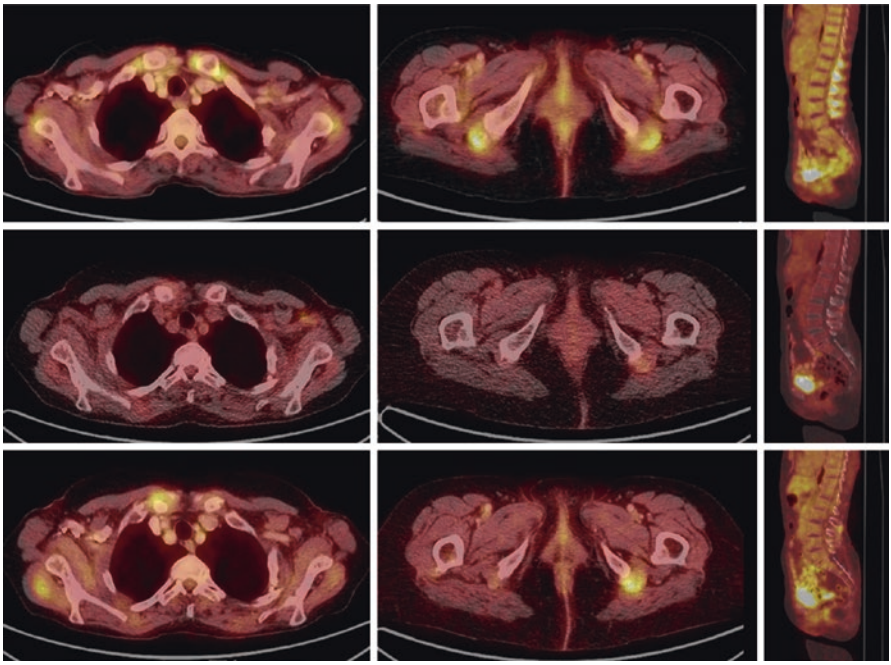

Fig. 9.6 FDG-PET/CT images of axial and sagittal slices from a unique patient. Signs of disease are present in the region of sternoclavicular joints (*left column*), ischiogluteal bursae (*middle column*) and lumbar spinous interspaces (*right column*). The upper row represents the status prior to steroid therapy and is compared with findings after therapy as presented in the middle row. The lower row demonstrates PMR relapse two years after termination of steroid therapy. Together with laboratory measurements showing the patient's increase in concentration of CRP and elevated FW, an FDG accumulation was observed around the right sternoclavicular joint, around the left ischiogluteal region and in one lumbar spinous interspace

9.9 Conclusion Concerning PMR

It is possible to use FDG-PET/CT examination in treatment-naïve PMR patients. Most commonly, periarticular signs of pathology around shoulders and hips as well as sternoclavicular joints have been reported. However, accumulation also presents exraarticularly between spinous processes in the spine, in ischial tuberosities, in the prepubic region and sometimes in unique combination. Approximately 30–40% of PMR patients present with signs of giant cell arteritis. In the regions described above, it is possible to detect a decrease or even complete disappearance of pathological FDG uptake in response to effective treatment, which can be useful for monitoring treatment as well as for detection of PMR relapse.

FDG-PET/CT examination seems to be an advantageous one-step diagnostic modality for detecting different variants of PMR involvement, for assessing extent and severity and also for excluding occult malignancy. In contrast to other imaging modalities (ultrasound and magnetic resonance imaging), PET/CT does not need targeting to a limited body part and can provide whole body examination. However, PET/CT has several disadvantages in routine examination of PMR patients: (1) high cost, (2) a worse accessibility of non-cancer slots in PET centres and (3) not inconsiderable radiation exposure.

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