Imaging

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Abstract

Conventional digital subtraction angiography (DSA) used to be the "gold standard" for the diagnosis of TAK. However, MR angiography has become the most preferred imaging tool for the diagnosis of TAK and is suggested to be the first-choice of modality in recent EULAR guidelines for imaging in LVV. CT angiography is also helpful as a cheap and fast tool to determine the damage associated with vascular stenosis and occlusion. FDG-PET-CT, detecting the vascular distribution of 18-F-FDG, assesses the metabolic, usually inflammatory activity in aorta and its major branches and demonstrate early vascular changes before occlusions or aneursym development during the clinical course of TAK patients. Finally, Doppler US with contrast enhancement is helpful for carotid lesions. The role of imaging to evaluate disease activity is currently an area of promising research, especially for therapeutic clinical trials.

Keywords

Digital subtraction angiography · MR angiography · CT angiography FDG-PET-CT · CDUS

Angiographic imaging modalities are essential for both the diagnosis and the follow-up of Takayasu Arteritis (TAK) [1]. Ideally, imaging modality in TAK should assess both the arterial lumen and the arterial wall. Luminal changes can be detected only after stenosis, occlusion, or dilatation has occurred. On the other hand, arterial

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wall changes detected with positron emission tomography (PET), magnetic resonance (MR) imaging, ultrasound (US), or computerized tomography (CT) may reveal pre-stenotic disease which is thought to be the earlier phase of disease [2]. The first detectable vascular abnormality in TAK is usually the thickening of the vessel wall caused by inflammation. The vessel wall thickness can be detected with MR angiography (MRA), US, and to a lesser degree, CT angiography (CTA). Contrast-enhanced MRA or CTA allow non-invasive imaging of the aorta and its major branches. Conventional digital subtraction angiography (DSA) which was thought to be the "gold standard" until recently for the diagnosis of TAK, detects well stenosis, occlusions and aneurysms which usually represents the latter stages of TAK. However, it is the least sensitive method for visualizing wall thickness [3] and is not routinely recommended in recent EULAR guidelines for imaging in LVV [4].

10.1 CTA

CTA shows vascular lumen and the arterial wall well and allows early diagnosis before the development of significant luminal remodeling [5]. In a study including patients with suspected TAK, CTA had a sensitivity of 95% and specificity of 100% for diagnosing TAK compared to clinical criteria [6]. While performing CTA, both early "arterial" and "delayed" phase are acquired following infusion of iodinated contrast. The acquisition of "delayed" phase images is needed to assess late contrast enhancement to evaluate the presence of a double-ring appearance. In delayed images, vessel wall thickening with enhancement and low attenuation ring is indicative for active disease [7, 8]. The presence of low attenuation ring have 100% specificity for active disease assessed by clinical evaluation and acute phase reactants; however the sensitivity is quite low (34–57%). On the other hand, wall thickening together with enhancement has a sensitivity of 88% and a specificity of 75% [9, 10]. In a study using electron beam CTA, there was no association between vessel abnormalities and disease activity by the NIH criteria [11]. The same group also published the follow-up data of five TAK patients having new active CTA lesions but considered inactive by clinical criteria. These patients had complications attributable to these lesions during the follow-up with changes in medical therapy leading to improvement in the CTA findings [12].

An important advantage of CTA is its value in differentiating TAK from atherosclerosis. Vascular calcification can be seen with CTA due to several reasons such as chronic renal failure, atherosclerosis, and rarely vasculitis. However, the radiological appearance of aortic calcification caused by vasculitis seems to differ from atherosclerosis. A circumferential calcification pattern is observed only in TAK [13]. Thoracic aorta involvement was also more common in TAK compared to SLE in the same study. Assessing coronary artery calcification is also possible with CTA [14].

The clinical utility of CTA is similar to MRA both in the diagnosis and the assessment during the follow-up of patients with TAK. An important advantage of

CTA over MRA is its shorter acquisition time in daily practice. However, exposure to large amounts of radiation and iodinated contrast limits the usefulness of CTA in routine follow-up [15].

10.2 MRA

Currently, MRA has become the most preferred imaging tool for the diagnosis of TAK and is suggested to be the first-choice of modality in EULAR guidelines [4]. Lack of radiation exposure allows multiple longitudinal evaluations in young patients. Contrast-enhanced MRA also allow non-invasive imaging of the aorta and its major branches, defining better the features of thickened arterial wall. But this type of assessment needs longer duration compared to standard analysis. In MRA assessment, T1-weighted imaging is used to localize arterial wall lesions. For detecting changes suggestive of active inflammation in arterial vessel wall, T2-weighted and contrast-enhanced T1-weighted imagings are used to assess wall edema and late contrast enhancement, respectively [2]. In a meta-analysis of three studies ($n = 182$) investigating the utility of MRA (1.5 T) for the diagnosis of TAK compared to DSA to detect vessel stenosis, occlusion, or dilatation, the pooled sensitivity and specificities were 79% and 97%, respectively. Vessel wall abnormalities not visualized by DSA were detected by MRA with a specificity of 92% (five studies, total $n = 152$) [15]. Although not yet formally studied, the circumferential or crescentic wall thickening observed in long irregular lesions can be considered pathognomonic for large-vessel vasculitis [5, 16].

MRA can also localize fibro-inflammatory lesions and give detailed information on whether these are limited to the vessel wall or extend to peri-adventitial tissues, determining the disease extent. However, overlap between active and inactive disease remains also challenging with MRA [17]. The wall thickness and enhancement in MRA were proposed to represent active disease. Some studies also defined new vascular dilatation, stenosis, occlusion, or wall irregularity as active disease. Tso et al. [18] performed MRA scans on 24 patients with TAK. The scans of 94% of the patients revealed vessel wall edema during periods of unequivocally active disease and 56% showed them during apparent clinical remission. Andrews et al. [19] and Choe et al. [20] detected that edema and enhancement of vascular wall, as well as a reduction of the mural diameter on MR images are associated with disease activity. Furthermore, these studies suggest that there is a close correlation between wall thickness and/or edema of the vessel, enhancement of wall detected by MR imaging and acute phase reactants. Another study analyzed the imaging manifestations of contrast-enhanced MRA to quantitatively measure and assess disease activity of TAK with an MRA scoring system. MRA scores moderately correlated to CRP, platelet count, and fibrinogen levels ($p < 0.05$) and pointed that the MRA scoring system of lumen stenosis, wall thickness, and wall enhancement could be a non-invasive approach to facilitate assessment in TAK activity [21].

Two other scoring systems aiming to assess vascular damage with MRA for large-vessel vasculitis is also proposed recently. Combined Arteritis Damage Score (CARDS) is a numerical damage index assessing the cumulative number of regions with stenosis, occlusions, and aneurysms [22]. Another composite score also evaluates arterial dilatation and stenosis in 17 arterial territories. Longitudinal changes in these scores correlated with disease activity and mirrored arterial disease evolution [23].

In a recent study, MRA was also found to be active in most patients with clinical remission [24]. In three studies assessing intima media thickness (IMT) by MRA in TAK, IMT was observed to be higher in active patients than inactives (pooled mean difference in IMT of 1.78 mm) [15]. On the other hand, there are a few studies reporting lower association between vessel wall thickening/enhancement and the active disease. Eshet et al. reported a lower sensitivity of 44% and specificity of 65% [25]. Heterogeneity between studies due to lack of validated activity assessment tools and medications lead differences in study results. But it is clear that MRA became the routine imaging method in the longitudinal follow-up of patients with TAK as a safe, non-invasive tool. But it is still a matter of debate whether MRA can reflect disease activity with cross-sectional, single time point assessments of arterial wall edema or post-contrast enhancement. Finally, "pseudostenosis" as an MRA artifact mimicking real arterial stenosis, should also be kept in mind during MRA assessments in LVV [26].

10.3 FDG-PET

FDG-PET-CT is a non-invasive and widely used imaging modality in oncological diseases to detect the regional distribution of 18-F-FDG visualizing the metabolic status of the body. It has promising results in LVV based on the interpretation of FDG uptake by metabolically active inflammatory cells in vessel walls [27]. Some studies used semiquantitative analysis comparing the 18F-FDG uptake of a vascular region of interest (ROI) with that of the liver. The level of large-vessel 18F-FDG uptake was visually graded using a four-point scale: 0 = no uptake present, I = low-grade uptake (uptake present but lower than liver uptake), II = intermediate-grade uptake (similar to liver uptake) and III = high-grade uptake (uptake higher than liver uptake)] [12, 28] while others quantified. 18F-FDG uptake using methods such as standard uptake value (SUV) [29, 30]. Webb et al. [31] were the first to report the diagnostic accuracy of FDG-PET in 18 TAK cases. Their sensitivity was 92%, and specificity was 100%. Kobayashi et al. [29] were the first to establish a cut-off for max SUV (strong accumulation: SUV >2, weak accumulation: SUV: 1.2–2.3) in their study of 14 TAK patients. Their sensitivity was 90.9%, and specificity 88.8%, however with defining active disease as the clinical requirement to use prednisolone. Walter et al. [32] described the qualitative utility of FDG-PET in 26 cases with giant cell arteritis (n = 20) or TAK (n = 6), and the visual grade of FDG uptake (grades I to III) correlated significantly with both CRP and ESR. Arnaud et al. [33] showed a lack of correlation between 18F-FDG uptake, clinical disease activity and

levels of markers of inflammation. This study depended exclusively on clinical symptoms without markers of inflammation when assessing clinical disease activity and reported that FDG-PET scan had a sensitivity of 69.2% and a specificity of 33.3% for clinically active TAK [34]. Tezuka et al. [35] measured the mean SUV in the center of the inferior vena cava in all cases and target/background ratio was calculated as max SUV in arterial wall/mean SUV in inferior vena cava. They suggested that max SUV may provide a valid means of comparing patients with active vs. inactive TAK. Max SUV obtained with FDG-PET/CT had a high sensitivity and specificity for detecting subtle TAK activity in this study and ROC curve indicated that this approach may be superior to both ESR and CRP. The diagnostic accuracy of max SUV was also shown in relapsing TAK cases with a max SUV cut-off of 2.1 proposed to discriminate active inflammation of TAK. In another study, Zhang et al. [36] showed that SUV max, SUV mean, and SUV ratios were significantly higher in clinically active group compared to the inactives and with a 2.1 SUV max cut-off they reported 86.2% sensitivity and 90% specificity. Finally, a meta-analysis including eight studies assessing the performance of FDG-PET for detecting vasculitis in LVV showed a pooled sensitivity of 76% (95% CI 69, 82) and specificity of 93% (95% CI 89, 96) [37].

Recently, Grayson et al. Developed a scoring system labeled PETVAS, which is a total quantitative score of most commonly involved nine arteries in LVV. Active FDG-PET/CT differentiated clinically active LVV patients from comparators with a sensitivity and specificity of over 80% in this study. However, more than half of the patients (58%) who were in clinical remission according to NIH criteria were also interpreted to have active FDG-PET-CT. The specificity of FDG-PET-CT in distinguishing clinically active patients was therefore only 42%. In the comparator group who did not have an LVV diagnosis, 17% of patients were also found to have active vasculitic lesions. When a cut-off value of >20 was used, the sensitivity increased to 68% and specificity raised to 71%. Among patients who underwent PET during clinical remission, future clinical relapse was more common in patients with a high PETVAS (>20) compared to low PETVAS group (55% versus 11%; $p = 0.03$) over a median follow-up of 15 months [38]. Previous reports suggested that corticosteroid (CS) treatment reduces the FDG uptake [39]. In the study by Grayson et al., PETVAS scores decreased after CS and/or ISs treatments [38]. However, in a recent study from our center, we did not find any difference in PETVAS scores between patients with and without CS or IS use (*Kaymaz-Tahra S, unpublished*).

In a recent study, Banerjee et al. used a combined assessment of imaging, clinical and biomarker use to observe the effects of treatments in LVV patients. Increases in treatment led to a significant reduction in disease activity, whereas all three assessments of disease activity remained similarly unchanged when treatments were unaltered. When treatment was reduced, PET activity significantly worsened but clinical and serologic activity did not significantly change. Treatment of GCA with tocilizumab and of TAK with tumor necrosis factor inhibitors resulted in significant improvement in imaging and clinical assessments of disease activity, but only rarely did the assessments both become normal [40].

Without an histopathological confirmation, it is difficult to clarify whether increased FDG uptake in the vascular wall in patients with LVV in clinical remission is due to subclinical vasculitis [41] or to secondary processes such as vascular remodeling, hypoxia [42], atherosclerosis [43], or a combination of these factors. The interpretation of FDG-PET-CT has also some technical challenges. One of the main limitations is the lack of standardization for the time interval between the FDG administration and acquisition in LVV. According to the "EULAR recommendations for the use of imaging in LVV in clinical practice," a minimum of 60 min between intravenous FDG administration and acquisition is recommended. However, a delayed acquisition may increase the sensitivity of detecting FDG uptake [4]. Most of PET studies in the literature was performed at 1-h, but the data comparing the first hour and delayed acquisition is conflicting [44, 45] (*Kaymaz-Tahra S, unpublished*). In two recent studies, it was reported that PET assessment at 2 h time point would capture more active patients with LVV compared to 1 h time point assessments [46, 47].

PET scan is also an expensive imaging tool. In many countries, even in developed ones, access to PET scanning is very limited in any disease other than malignancies. Radiation exposure during PET-CT scan imaging may be another disadvantage which may be decreased with PET-MRA technique [48]. FDG uptake in all active cells other than inflammatory vessel wall is also an important restriction and there is ongoing research for new ligand options in PET scanning [2]. Therefore, despite the promising results both in the diagnosis and activity assessment, PET scan is still not a standardized imaging tool in TAK and its value in especially long-term follow-up of TAK patients needs to be further investigated.

10.4 Ultrasonography

The role of ultrasonography (US) is less established in TAK compared to other modalities. Doppler US performs well for carotid lesions with a high sensitivity (90%) and specificity (91%) in detecting stenotic lesions [49]. However, aortic and subclavian arteries are more difficult to visualize by US, with poorer detection of lesions. US may also help in determining inflammatory activity, demonstrating hypoechogenicity and mural thickening in active lesions [50]. Contrast-enhanced ultrasound (CEUS) may allow the identification of inflammation-driven hyperemia and neovascularization, a potential marker of disease activity [51]. In a recent study including 159 carotid artery CEUS from 86 patients with TAK, the enhanced intensity of carotid artery wall was higher in active patients and had a high predictive value for disease activity with area under the curve (AUC) of 86.3%, sensitivity of 88.0%, and specificity of 79.1%. This high predictive value did not increase by addition of ESR, CRP, and arterial wall thickness. Qualitative grading of wall vascularization based on the visual appearance of contrast enhancement within the lesion was also found higher in active patients [52]. In a prospective study including 31 patients with LVV, a graded vascularization score with CEUS of the carotid arteries was used as an index of disease activity which correlated closely with

18FDG-PET [53]. There are few case reports showing decreased artery wall thickness after corticosteroid treatment [54].

Being an operator-dependent imaging modality is an important restriction for US and its usage is mainly limited to carotid, vertebral, subclavian, and axillary arteries. However, it may also be used for abdominal aorta [55]. However, as US is a non-invasive, cheap and widely accessable imaging modality, further studies are warranted to confirm the potential of this technique for monitoring disease activity and response to treatment in TAK.

10.5 Conclusion

In summary, conventional angiography is no longer considered as the gold standard for the diagnosis of TAK. Currently, many physicians prefer to use MRA or CTA with FDG-PET-CT in selected cases for establishing the diagnosis of TAK. MRA is the gold standard modality for the longitudinal follow-up patients with TAK. Compared with DSA, three-dimensional MRA can effectively show vessel wall thickening, whereas contrast-enhanced MRA allows better soft-tissue differentiation. Exposure to large amounts of radiation and iodinated contrast limit the usefulness of CTA in routine follow-up. Recently, exciting preliminary reports have come up with PET-MRA with comparable visual and quantitative results to PET-CT. Improved soft-tissue resolution and definition of anatomy was reported with PET-MRA assessment using lower total radiation doses [56, 57]. Further prospective research is needed with PET-MR focusing on clinical activity assessment and changes with immunosuppressive treatments (Figs. 10.1, 10.2, 10.3, 10.4, 10.5, and 10.6).

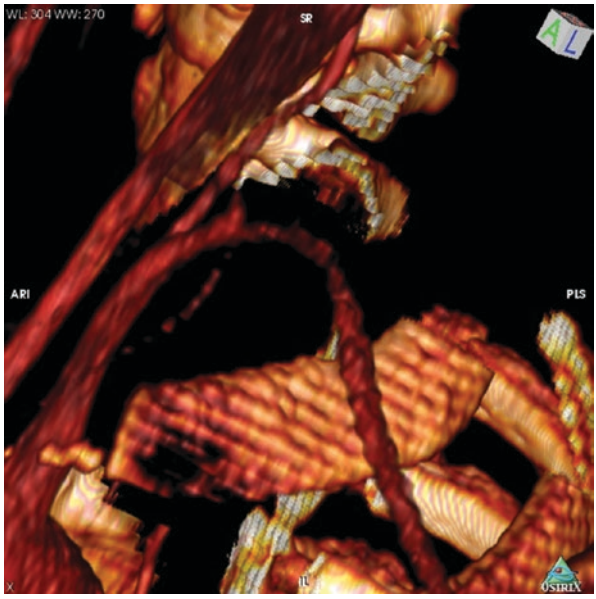

Fig. 10.1 3D reconstruction of CT angiographic data demonstrating a high grade stenosis in left subclavian artery

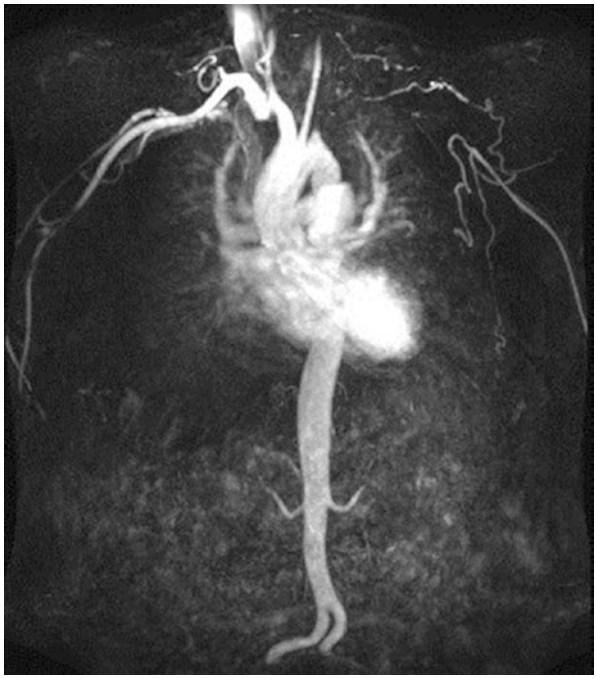

Fig. 10.2 CT angiographic image demonstrating occlusion in left subclavian artery

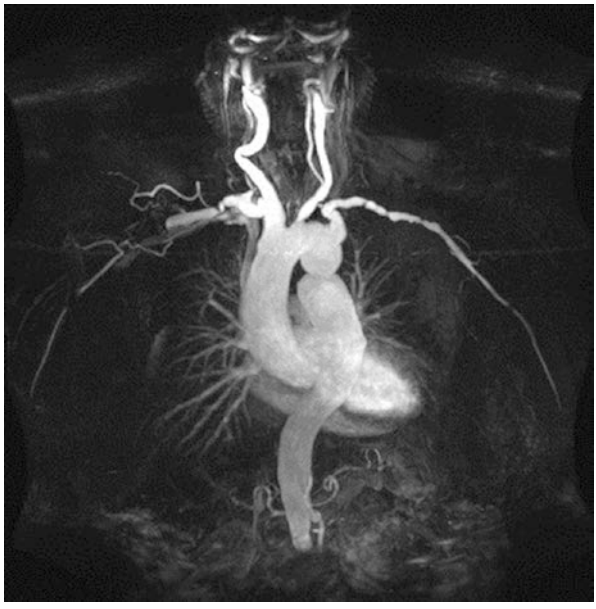

Fig. 10.3 MR angiographic image demonstrating a high grade stenosis in right subclavian artery and brachial artery

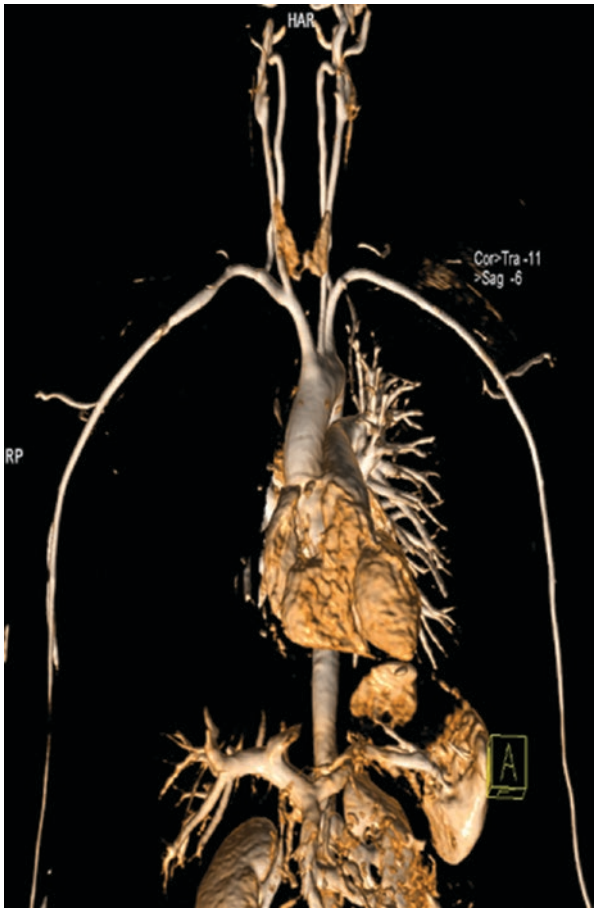

Fig. 10.4 MR angiographic image demonstrating bilateral common carotid artery stenosis and right subclavian arteriel stenosis

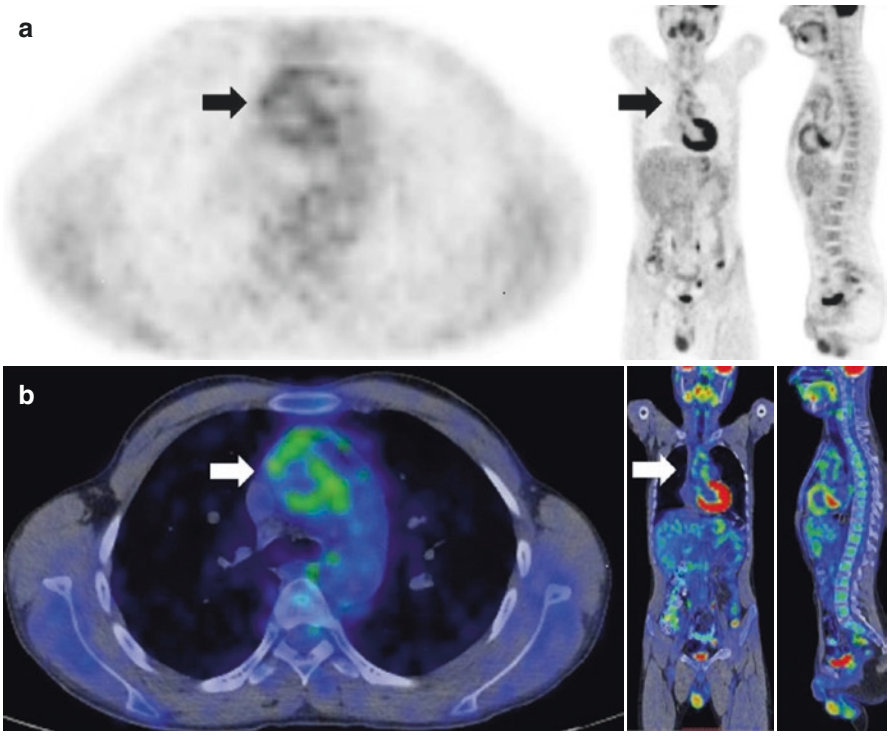

Fig. 10.5 Axial, coronal and sagittal positron emission tomography (PET) (**a**) and PET/CT fusion (**b**) images of the same patient shows fluorine-18 fluorodeoxyglucose (FDG) uptake at the level of the ascending aorta and the aortic arch (arrows) consistent with activated disease

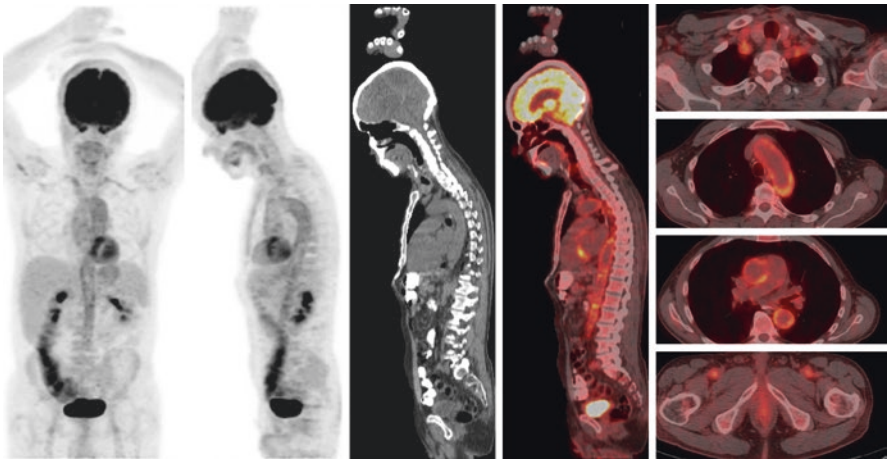

Fig. 10.6 PET/CT Images of a patient showing increased 3 fluorine-18 fluorodeoxyglucose (FDG) uptake (higher than liver uptake) in biateral carotid, subclavian, axillary, iliac, femoral arteries and assending-arcus-abdominal aorta

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