

The use of (18F)Fluoro-deoxyglucose positron emission tomography in the assessment of large vessel vasculitis

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multifocal fibrosclerosis.

ABSTRACT

FDG-PET scan has recently been introduced as a diagnostic means to assess large vessel involvement in giant cell arteritis (GCA). Its use in Takayasu arteritis, idiopathic periaortitis and multifocal fibrosclerosis – although more limited, due to the relative rarity of these conditions compared to GCA – is discussed as well.

Introduction

A diagnosis of vasculitis is preferably based on firm histological proof of vessel inflammation. Skin biopsies, nasal biopsies or temporal artery biopsies can readily be obtained without much discomfort for the patient. More invasive procedures are needed to obtain intestinal, kidney, lung, liver or muscle biopsies. Peripheral nerve biopsies are painful and may heal very slowly, while brain biopsies are only performed when all other techniques have failed to demonstrate a suspected central nervous system vasculitis.

Follow-up of patients with vasculitis may include serial measurements of sedimentation rate and C-reactive protein level, anti-neutrophil cytoplasmic antibodies (ANCA) directed against proteinase 3 or myeloperoxidase, renal function, urine microscopic examination, radiological investigations. For obvious reasons, control biopsies to see if vasculitis has disappeared, are almost never performed.

In some forms of vasculitis, histological proof is hard to obtain and one has to be satisfied with a compatible angiographic picture. Whereas classic angiography may produce almost pathognomonic images in classic polyarteritis nodosa, this is not always the case in Takayasu arteritis or isolated central nervous system vasculitis, since the differential diagnosis with atherosclerotic changes can be very difficult.

Even if vasculitis can be diagnosed by angiography, differentiation between an active vasculitic lesion and a late sequel is frequently not possible.

In 1999 (18F) fluoro-deoxyglucose (FDG) positron emission tomography (PET) was introduced in the diagnosis of patients with large vessel vasculitis (1, 2). FDG is a glucose analogue which is transported across the membranes in proportion to the rate of glucose uptake. Increased FDG uptake can be observed in neoplastic processes, but also inflammatory conditions such as infections, sarcoidosis or vasculitis take up more FDG, and hence can be visualized by FDG-PET scintigraphy (3, 4).

The Chapel Hill Consensus Conference distinguished two forms of large vessel vasculitis: giant-cell (temporal) arteritis (GCA) and Takayasu arteritis (5). Although less common, large vessel vasculitis and especially aortitis can be seen in many more conditions (Table I). In a cohort of 1204 surgical aorta specimens (including 1064 aortic aneurysms), Rojo-Leyva *et al.* found 52 cases of idiopathic aortitis, of whom 16 were associated with another systemic disease and 36 were isolated. 67% of idiopathic aortitis patients were female and in 96% of aneurysm formation, aortitis only occurred at the thoracic level (6). From a clinical point of view, aortitis most often presents as a vague syndrome of malaise, fever, weight loss, abdominal pain, while blood examination shows increased inflammatory parameters. Performing FDG-PET scintigraphy in these patients may directly point to aortitis, hence avoiding several time-consuming and unpleasant examinations.

This article will review the clinical experience obtained with FDG-PET scintigraphy in the different forms of large vessel vasculitis. The use of PET

Table I. Causes of aortitis.

Infections
- syphilis
- Salmonella
- Tuberculosis
- Other bacteria
Giant-cell (temporal) arteritis
Takayasu arteritis
Idiopathic periaortitis
Multifocal fibrosclerosis
Aortitis as part of another form of vasculitis
- relapsing polychondritis
- Cogan's syndrome
- Wegener's granulomatosis
- P-ANCAassociated vasculitides
- Classic polyarteritis nodosa
Bechterew's disease (ankylosing spondylitis)
Rheumatoid arthritis
Rheumatoid fever
Reiter's syndrome
Systemic lupus erythematosus
Severe atherosclerosis

scintigraphy in infectious inflammation of the aorta, is beyond the scope of this review. Suffice it to say that FDG-PET scintigraphy can reveal infectious aortitis but that differentiation between infectious and non-infectious inflammation is not possible (7).

Giant-cell arteritis

GCA is the most frequent form of large vessel vasculitis and probably also of all vasculitides. It attacks predominantly elderly people beyond their fifties and there is a clear female preponderance. It involves the extracranial branches of the arteries starting from the aortic arch (8). When typical symptoms like headache, jaw claudication, polymyalgia rheumatica (PMR) or visual symptoms are present, the diagnosis is easily suspected and proven by temporal artery biopsy. This procedure, although invasive, is easily supported by the patients and leaves no sequelae. It can even be repeated on the contralateral side when the first biopsy turns out to be negative and when the suspicion for GCA is high. Nevertheless, since GCA is a focal form of arteritis and skip areas do occur, false negative temporal artery biopsies are reported in up to 16% of patients (9). For that reason, one should always ask the surgeon to take a biopsy of at least 2 cm in length.

Owing to high FDG uptake in the brain, the small diameter of the vessel and the superficial localisation with high background of the skin, direct evaluation of the temporal arteries is not possible on whole-body PET investigation. These conditions however do not apply to the other vessels which can be involved by GCA such as the aorta, the subclavian, axillary and carotid arteries.

In 1999, the results of FDG-PET scintigraphy in 6 patients with GCA, 5 patients with isolated PMR and 23 age-matched patients with other inflammatory conditions were reported (2). Increased FDG uptake in the thoracic vessels was found in 4/6 patients with GCA and in 4/5 patients with PMR, compared to 1/23 controls ($p < 0.001$). Increased vascular FDG uptake in the upper legs was seen in 8/11 patients with GCA or PMR compared to 8/23 control patients ($p < 0.05$), and in the lower legs in 6/11 patients compared to 6/23 controls ($P =$ not significant). Only 2 of these 8 patients had evidence of atherosclerosis while the only patient with GCA and no vascular FDG uptake suffered from pronounced atherosclerosis. In 4 of the 5 PMR patients, a control PET scan was performed during steroid therapy, at a moment when inflammatory parameters had normalized and patients had become asymptomatic. Vascular FDG uptake had clearly decreased by that time (Fig.1). All these findings argue against atherosclerosis as the main cause for increased vascular FDG uptake in GCA and PMR. In addition, one would expect to find local hot spots in atherosclerosis, corresponding to inflammatory plaques, rather than the smooth, linear picture found in the GCA and PMR patients.

The largest GCA and/or PMR patient group which was studied by FDG-PET scintigraphy thus far was published in 2000 (10). We investigated 25 patients with a diagnosis of GCA/PMR (which was regarded as a single disease; in 13 of them vasculitis was proven on temporal artery biopsy) and 44 age-matched patients who were also suspected initially to suffer from GCA/PMR but in whom another diagnosis was finally made: they served as control subjects.

Again, significantly more patients with GCA/PMR had vascular FDG uptake in their larger thoracic arteries compared to the control patients: 14 of 25 versus 1 of 44 ($p < 0.0001$). Vascular FDG uptake in the legs was seen in 16/25 patients with GCA/PMR and in 10/44 controls ($p < 0.001$). Vascular FDG uptake at any place (chest or legs) was seen in 19/25 patients, compared to 10/44 controls ($p < 0.0001$). Based on these results, we could calculate that thoracic vascular FDG uptake had a sensitivity for GCA/PMR of 56% (95% confidence intervals 35-77%), a specificity of 98% (95% CI 93-100%) and a positive predictive value of 93% (95% CI 79-100%). A negative scan for that parameter had a negative predictive value of 80% (95% CI 69-91%). Vascular FDG uptake in the legs had a somewhat higher sensitivity (64%), but a lower specificity (77%) and positive predictive value (62%). There was no significant difference in age, sex or inflammatory parameters between patients with and without vascular FDG uptake. When patients were divided according to Nordborg presentation form (11), we noted that vascular FDG uptake was most frequent in these patients with predominant systemic symptoms (Nordborg presentation form 4): it was seen in 11/12 such patients, of whom 9 at the thoracic level. In 6 patients with isolated PMR complaints, who all had negative temporal artery biopsies, vascular FDG uptake was seen in 4, of whom 3 at the thoracic level. In the 6 patients with GCA/PMR without increased vascular FDG uptake, there was marked uptake in the shoulders. In some patients, a combination of vascular and shoulder FDG uptake was observed.

These studies demonstrate that vasculitis in GCA clearly involves more arteries than the temporal ones. Although most frequently not clinically apparent, the aorta and its proximal branches seem to participate in the inflammatory reaction in many patients. PET scintigraphy has the advantage to show all sites of increased FDG uptake in the larger vessels within one examination. The synovial FDG uptake at the shoulders may point to synovitis as a con-

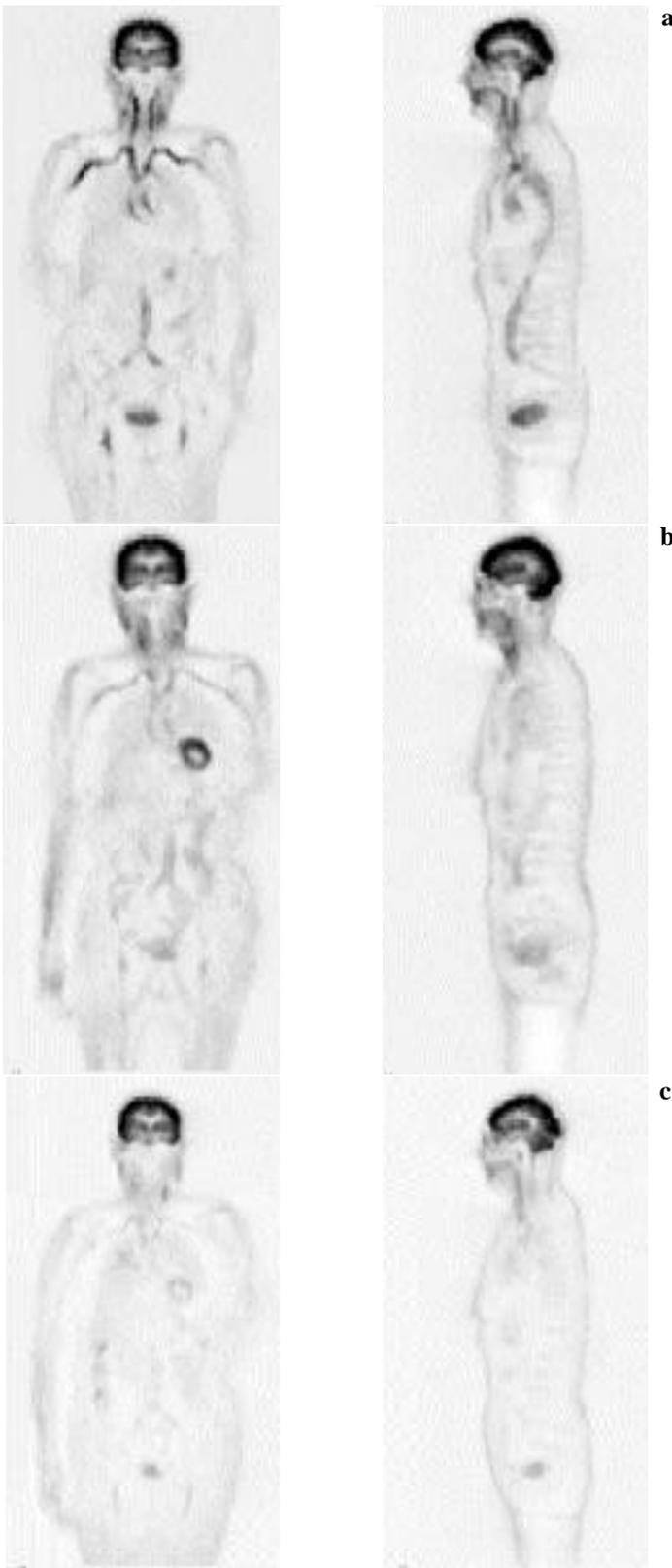


Fig. 1. Sequential FDG-PET scintigraphies in a 76-year-old female patient with GCA. (a) Scintigraphy taken before the start of steroid therapy shows intense FDG uptake in the entire aorta (sagittal plane), the subclavian and axillary arteries, the carotid arteries, the iliac and femoral arteries. (b) Image taken one month later, during steroid therapy, at a time when the patient was asymptomatic and inflammatory parameters had normalized. Vascular FDG uptake, although still visible, was considerably less. (c) Three months after the start of steroid therapy, the larger arteries remain visible, but FDG uptake has further decreased.

tributing factor in PMR.

These initial observations have been confirmed by other investigators, describing single patients or small series (12-14). The lack of larger studies probably relates to the difficulties getting access to PET scan in these conditions, especially in the United States, where this examination is very expensive. We of course do not advise PET scintigraphy to be done in every patient with GCA. In patients with typical clinical features of cranial GCA, temporal artery biopsy is the examination of choice. In patients with atypical symptoms, when fever, weight loss and malaise dominate the clinical picture or in the exploration of an inflammatory syndrome, when GCA is only one of several possibilities, FDG-PET scan may be the technique of choice. Finding increased FDG uptake in the larger thoracic vessels points almost always to GCA (or to another form of large vessel vasculitis, cfr. infra). If not, PET scan may reveal other disorders such as occult tumours or infections. As evidenced by the work of Cornelia Weyand's group, GCA may not be a single entity, but may be divided in cranial GCA and large-vessel GCA (15). Since temporal artery biopsy was negative in 42% of patients with large-vessel GCA, FDG-PET scan may become the diagnostic method of choice in these patients (16).

Takayasu arteritis

This form of large vessel vasculitis is far less frequent than GCA in the Western world and when it occurs, mostly young women are affected. Takayasu arteritis is a vasculitis of the aorta and its proximal branches; the pulmonary arteries may also be involved (17). None of these arteries are accessible for biopsy (except if patients are undergoing resection and grafting for critical ischaemia), and therefore, we have to rely on radiographic examinations to make a diagnosis. Classic angiography can detect stenoses, occlusions and aneurysm formation: these develop when the disease is at an advanced stage, while magnetic resonance imaging (MRI) can detect earlier alterations of the vessel wall (18). MRI provides

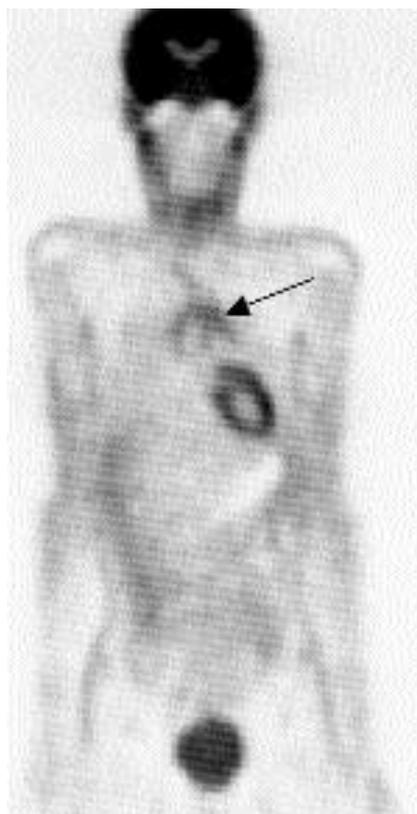


Fig. 2. FDG-PET scintigraphy in a 25-year-old female patient with Takayasu arteritis. There is increased FDG uptake in the aortic arch, although not so intense as in the previous patient with GCA. During steroid therapy, this FDG uptake disappeared.

high-resolution anatomic information, including lumen configuration and vascular wall thickening, and physiological data, such as measurements of the degree of wall enhancement and the presence of edema. Mural edema is considered a characteristic pattern of active and progressive Takayasu arteritis (19-22), although a recent study has cast doubt on the utility of edema-weighted MRI as a sole guide to disease activity and treatment in Takayasu arteritis (23).

Hara *et al.* described their PET findings in a patient with Takayasu arteritis in 1999 (1). There was a marked FDG uptake in the aorta and its proximal branches. We have performed FDG-PET scanning in two young female patients with Takayasu arteritis before steroids were started: there was a moderately increased FDG uptake in the aorta in these patients, which was not so strong as generally seen in patients with GCA and systemic complaints (Fig. 2). Dur-

ing steroid therapy, this uptake gradually disappears. Malik *et al.* performed FDG-scintigraphy in a 32-year old female before and after treatment with pulsed cyclophosphamide and prednisolone. The aortic uptake was dramatically reduced by this treatment (24).

Since the experience with PET-scintigraphy in Takayasu arteritis is still so limited and in face of the recent doubts on the utility of edema-weighted MRI, both investigations (MRI and PET) should be performed in every patient, whenever possible.

Aortitis due to medium sized vessel and small vessel vasculitides

Aortitis has been described in patients suffering from classic polyarteritis nodosa (25), Wegener's granulomatosis (26-28), p-ANCA associated vasculitis (29, 30) and relapsing polychondritis (31). In polyarteritis nodosa and ANCA-associated vasculitis, aortitis can develop due to a necrotizing vasculitis of the vasa vasorum of the aorta (25,29). We described a patient who presented with abdominal aortitis and intramural aortic dissection. He was operated on urgently and the surgeon noted that the abdominal aorta was embedded in a vast retroperitoneal inflammatory process from which it was inseparable. An aortoiliac graft was inserted. Histopathological examination of the resected specimen revealed a necrotizing granulomatous inflammation of the retroperitoneal muscular arteries, invading the aortic wall. On FDG-PET scintigraphy, performed after surgery, there was no FDG accumulation around the operated abdominal aorta, but several hot spots in the lungs and in the nose (Fig. 3). Cytoplasmic ANCA's were positive, a granulomatous vasculitis was seen on bronchoscopic biopsies and there was an axonal neuropathy. A diagnosis of Wegener's granulomatosis was made (27).

Idiopathic periaortitis

Most cases of periaortitis in patients not suffering from systemic vasculitis are believed to be due to an autoim-



Fig. 3. FDG-PET scintigraphy in a 42-year-old patient with Wegener's granulomatosis, who was recently operated on for abdominal aortic dissection, showing several hot spots in the lungs and in the mediastinum [reprinted from Blockmans D, Baeyens H, Van Loon R, Lauwers G, Bobbaers H: Periaortitis and aortic dissection due to Wegener's granulomatosis. *Clin Rheumatol* 2000, vol. 19, pp. 161-164, with the permission of Springer Verlag]

mune reaction to ceroid, an oxidative lipoprotein byproduct normally stored in the atheromatous plaque and thought to leak through the thinned aortic wall (32). In this so-called idiopathic periaortitis, the aorta displays an active chronic inflammatory infiltrate consisting mainly of plasma cells and activated T-lymphocytes (33). When maturing, this periaortic inflammation turns to a dense fibrotic tissue, mainly consisting of fibroblasts and collagen, identical to what is found in retroperitoneal fibrosis. Periaortitis can be regarded as one of the causes of retroperitoneal fibrosis. Other causes of retroperitoneal fibrosis are given in Table II, although it cannot be excluded that aortitis in fact also participates in these other forms of retroperitoneal fibrosis. From a clinical point of view, patients with periaortitis are middle-

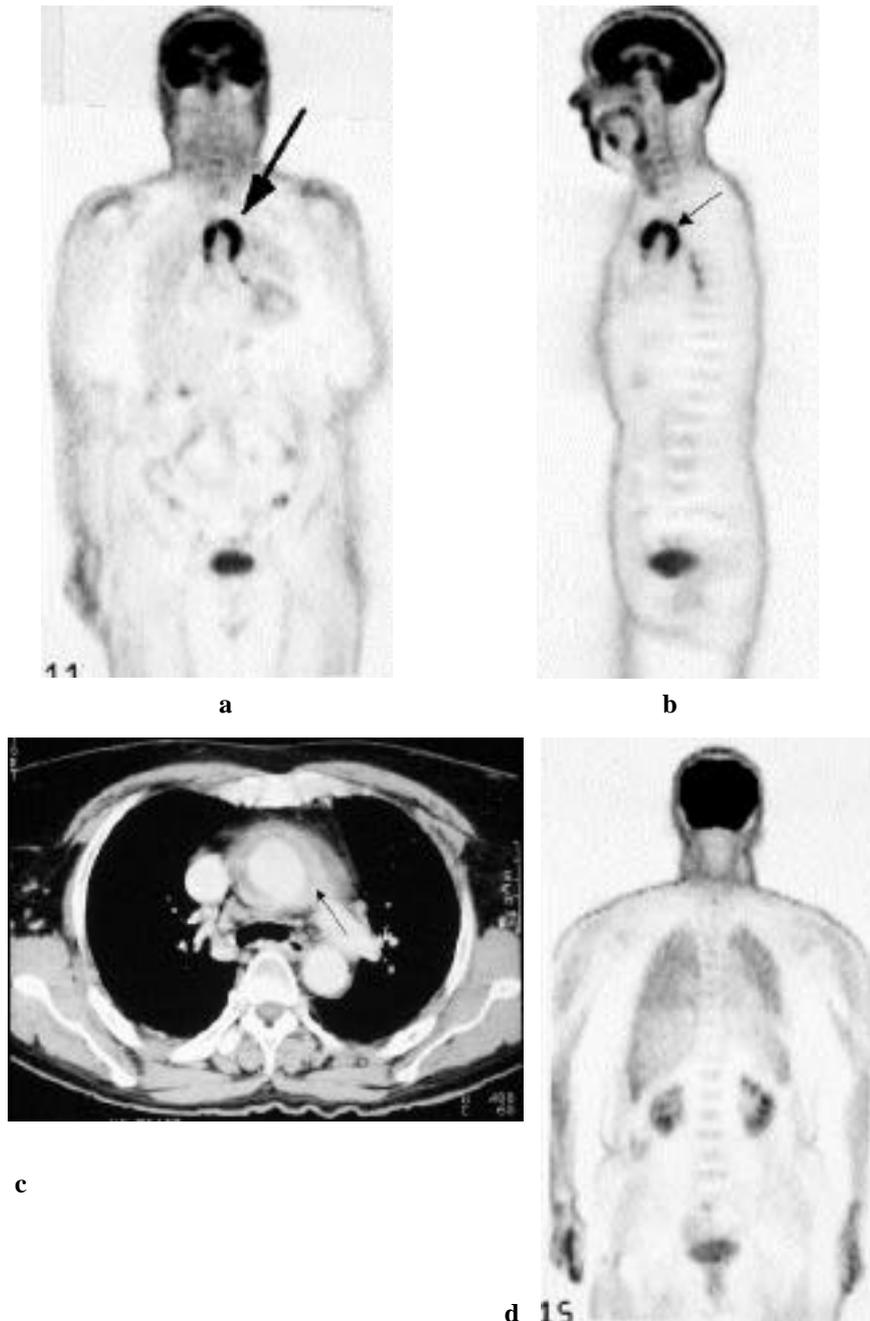


Fig. 4. Very intense FDG uptake in the aortic arch (**a**: coronal plane, **b**: sagittal plane), corresponding to focal thickening of the ascending aorta on CT-scan (**c**). During steroid therapy, FDG uptake in the aortic arch disappeared (**d**) [Figures 4a and 4b are reprinted from Derdelinckx I, Maes A, Bogaert J, Mortelmans L, Blockmans D: Positron emission tomography scan in the diagnosis and follow-up of aortitis of the thoracic aorta. *Acta Cardiol* 2000, vol. 55, pp. 193-5 with the kind permission of the editor of *Acta Cardiologica*.]

aged or older, they have signs of atherosclerosis and have vague complaints such as abdominal discomfort or pain, fever, malaise etc. Idiopathic aortitis in our experience occurs at least as frequent at the abdominal level as at the thoracic level, contrary to the findings of Rojo-Leyva *et al.* in operated patients with aorta aneurysms (6).

Derdelinckx *et al.* reported on a 62-year-old female patient with a one month history of fever exceeding 39° C, night sweats, a dry cough, a vague thoracic discomfort and 10 kg weight loss (34). The CRP level and the sedimentation rate were high. CT-scan and MRI showed a focal thickening of the distal part of the ascending aorta and

Table II. Causes of retroperitoneal fibrosis.

Idiopathic (up to 70%)
Aortitis (see Table I)
Medications (methysergide, beta-blockers, hydralazin, ergotamin-derivatives)
Multifocal fibrosclerosis
Malignancies
Infections
Trauma
Post-radiation
Miscellaneous (Ankylosing spondylitis, Crohn's disease, systemic lupus erythematosus, scleroderma, sarcoidosis, Erdheim-Chester disease)

the proximal part of the aortic arch. FDG-PET scintigraphy showed intense uptake in the aortic arch, which disappeared during high-dose steroid therapy (Fig. 4). An example of FDG-PET scintigraphy in abdominal periaortitis, together with the corresponding magnetic resonance angiography images is shown in Fig. 5 (35).

Multifocal fibrosclerosis

Aortitis can be part of a broader fibrosclerotic disease, in which Riedel's thyroiditis, orbital pseudotumor, sclerosing cholangitis, sclerosing mediastinitis, sclerosing pancreatitis or Dupuytren's contracture are the other features. Drieskens *et al.* described a 41-year old woman, in whom Riedel's thyroiditis had been diagnosed 7 months earlier, who complained of fatigue, anorexia and lower back pain, irradiating to the abdomen. CT scan showed an abdominal mass, which on biopsy was compatible with retroperitoneal fibrosis. FDG-PET images showed an intense hypermetabolic mass surrounding the aorta and increased FDG accumulation in the thyroid. FDG-PET returned to normal during steroid therapy (Fig. 6) (36).

Severe atherosclerosis

Numerous reports from the early nineties onwards suggest that there is an important inflammatory component to the pathogenesis of atherosclerosis (37, 38). Hence, it is not impossible that (severe) atherosclerosis can be visualized on FDG-PETscintigraphy. This may be one of the reasons why vascular FDG uptake in the vessels of the legs was less specific for vasculitis than thoracic vascular FDG uptake in patients with GCA and PMR (cfr. supra), although

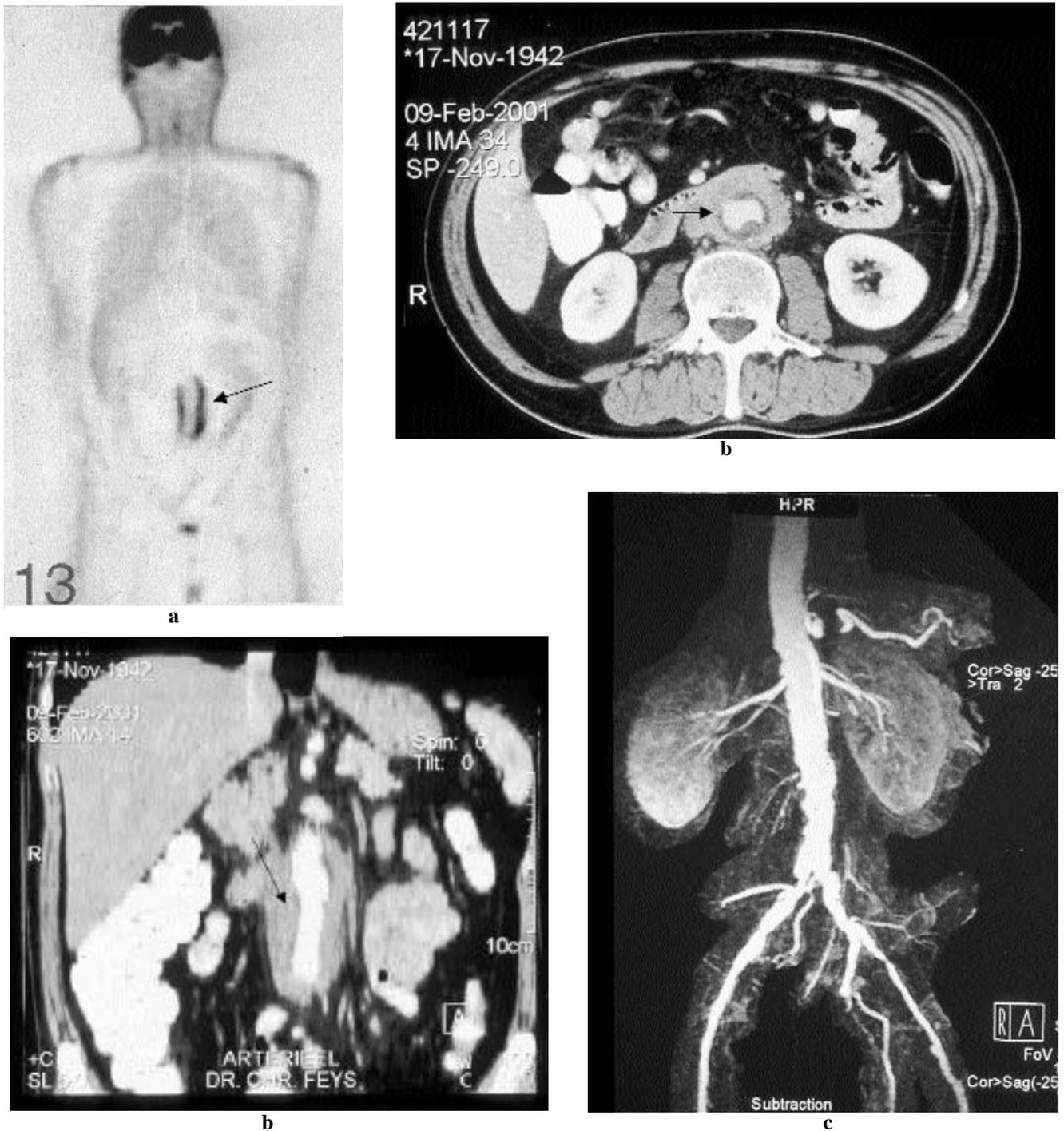


Fig. 5. A 58-year-old man complained of fatigue, anorexia, weight loss and pain in the lumbar region and lower abdomen. The erythrocyte sedimentation rate was 70 mm/1 hour. Findings of a chest radiograph and abdominal ultrasound were normal. FDG-PETscintigraphy revealed intense uptake around the abdominal aorta (a). On T2 weighted images, the aorta was surrounded by an inhomogeneous mass, extending from 1 cm below the renal arteries to the iliac bifurcation (b: transverse plane, c: sagittal plane). MR angiography showed very irregular large vessels, resulting from severe atherosclerosis (d). [Reprinted from Blockmans D, Van moer E, Dehem J, Feys C, Mortelmans L: Positron emission tomography can reveal abdominal periaortitis. *Clin Nucl Med* 2002, vol. 27, pp. 211-212 with the permission of Lipincott Williams &Wilkins, Inc.]

there was no correlation with atherosclerosis on clinical grounds (2). The disappearance of vascular FDG uptake in GCA and Takayasu patients, in idiopathic periaortitis and in multifocal fibrosclerosis during steroid treatment

(cfr. supra) is in favour of true vasculitis, and would be very unusual if FDG uptake was due to atherosclerosis. Yun *et al.* reported FDG vascular uptake in up to 70% of 156 patients, referred for various clinical indications, with at least

one risk factor for atherosclerosis. Age and hypercholesterolemia most consistently correlated with FDG uptake in the abdominal aorta (39). Since the percentages reported are so high, also in patients without atherosclerotic risk fac-

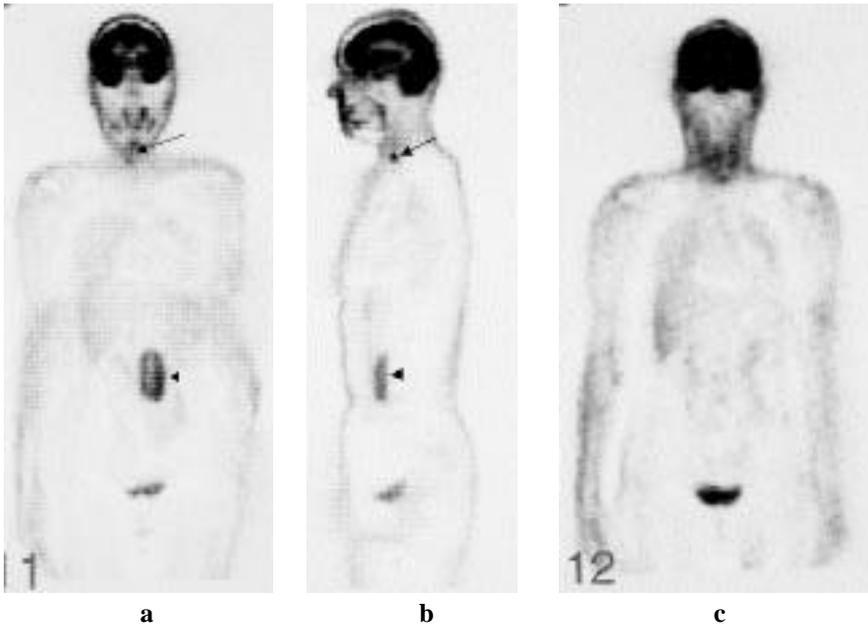


Fig. 6. FDG-PETscintigraphy showing increased FDG uptake in the thyroid gland (**arrow**) and surrounding the aorta (**arrowhead**) (**a**: coronal plane, **b**: sagittal plane). A control PETscan after 4 months of steroid therapy had normalized (**c**). [Figures 6a and 6c are reprinted from Drieskens O, Blockmans D, Van den Bruel A, Mortelmans L: Riedel's thyroiditis and retroperitoneal fibrosis in multifocal fibrosclerosis. Positron emission tomographic findings. *Clin Nucl Med* 2002, vol. 27, pp. 413-415 with the permission of Lipincott Williams &Wilkins, Inc.]

tors, these cases may have very moderate FDG accumulations, not judged significant by our nuclear medicine specialists. Nevertheless, slight to moderate FDG

accumulation is seen from time to time, without obvious vasculitis. In Fig. 7a, the FDG-PET scintigraphy is shown of a 78-year old patient with an inflamma-

tory syndrome of unknown origin. There was moderately increased FDG uptake in the aortic arch and subclavian arteries, two temporal artery biopsies were negative, there was severe atherosclerosis with calcifications but no signs of periaortitis on CT-scan and the inflammatory parameters subsided spontaneously. Whilst still in hospital, the patient died suddenly from an acute cerebrovascular accident. On autopsy, the wall of the aortic arch was highly atherosclerotic (Fig. 7b and c).

Conclusions

FDG-PET scintigraphy can be helpful in the diagnosis and follow-up of large vessel vasculitis, involving the aorta or its proximal branches, regardless of the precise nature of the vasculitis. Since many patients with large vessel vasculitis present with vague symptoms of fatigue and malaise, weight loss and fever in the presence of raised inflammatory parameters, FDG-PET scintigraphy may directly point to large vessel vasculitis or to occult inflammatory or neoplastic disorders causing these symptoms. The lack of data correlating PET-findings with tissue evidence of

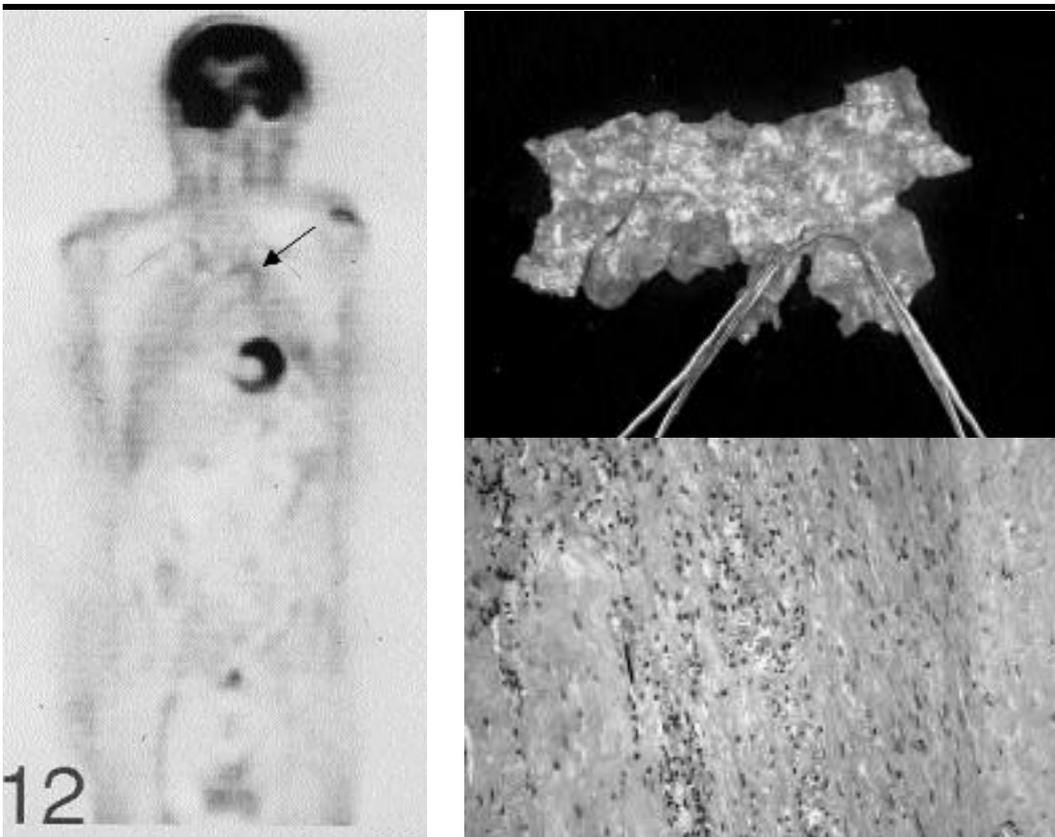


Fig. 7. Moderately increased FDG uptake in the aortic arch (**a**), corresponding to a severely atherosclerotic aorta (**b**). On microscopic examination, there was, apart from severe atherosclerosis, a limited dissection of the aortic wall filled with granulomatous tissue (**c**). Compared to the previous FDG images from patients with true aortitis, vascular FDG uptake in this severely atherosclerotic patient is much less pronounced.

inflammation remains a major caveat. Severe atherosclerosis may result in some FDG-accumulation in the vessels, but probably not to the same intensity as seen in true vasculitis. An increased accessibility to this non-invasive whole-body examination is needed. In our institution, FDG-PET scintigraphy has replaced Gallium-scintigraphy in the work-up of patients with inflammatory syndromes or fever of unknown origin (40). Future directions of research in this area may be the use of serial PET scintigraphies during treatment protocols to see if PET-results have any prognostic value in terms of length of treatment or relapse risk. In order to do so, a more quantitative approach of vascular FDG-accumulation is highly wanted.

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