A case report of calcific aterosclerosis demonstrated on 18-F-fluorodeoxyglucose positron emission tomography/computed tomography

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Abstract

18F-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG-PET/CT) is a functional imaging technique which is an established tool in oncology, and has also demonstrated a role in the field of inflammatory diseases, such as large vessel vasculitis (LVV). In the last few years, it is known that atherosclerotic lesions with inflammation, detected by FDG-PET, are high-risk structural features and more likely to lead to subsequent progression of atherosclerosis with more clinical complications.

Introduction

18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is a functional imaging technique which is an established tool in oncology, and has also demonstrated a role in the field of inflammatory diseases, such as large vessel vasculitis (LVV) and polymyalgia rheumatica (PMR).

FDG-PET is based on the possibility of detecting enhanced glucose uptake due to high glycolytic activity of inflammatory cells in inflamed arterial walls and synovia/bursa.[1]

Therefore, 18F-FDG PET/CT is a useful tool to diagnose vasculitis (especially when the symptoms of the disease are non-specific), guide biopsy procedures (areas with high glucose consumption), evaluate disease extension and monitor treatment responses.

In general, the diagnostic performance of FDG-PET for the detection of LVV is good and is better in the detection of GCA (Giant Cell Arteritis) than TA (Temporal Arteritis) (87% *vs* 58%, respectively; P<0.0001). However, it is impaired in patients under GC (Glucocorticoids) and/or immunosuppressive treatment at the time of imaging.[2,3]

Furthermore FDG-PET/CT is not disease-specific and results have to be interpreted with caution considering clinical and laboratory data.[4,5]

Atherosclerosis is a biologically active process where vascular risk factors promote vascular endothelial dysfunction, expression of cellular adhesion molecules, and binding of circulating inflammatory cells to the vessel walls.[6]

Monocytes transmigrate into the vessel intima, differentiate into pro-inflammatory macrophages and later engulf oxidized lipoproteins to form 'foam cells'.[7]

Atherosclerotic macrophages secrete inflammatory cytokines and extracellular matrix molecules, which promote further accumulation of lipoproteins, monocytes, and other inflammatory cells within the expanding atheromatous lesion.[8]

Within more advanced plaques, macrophages undergo apoptosis, and release their lipid walls and intercellular contents within the lipid core; and over time, these atheromatous lesions become increasingly hypoxic, undergo neovascularization, and develop microcalcifications.[8]

Within this environment, macrophages release proteolytic enzymes that degrade the protective fibrous cap.[6]

Accordingly, higher-risk atherosclerotic plaques (which are most vulnerable to rupture) are characterized by relatively larger inflammation cells, a necrotic lipid core, micro-calcification, neovascularization, and a thinner fibrous cap, with inflammation playing a central role.[8]

It's well known that in vasculitis, mural thickening usually involves the entire circumference of the vessel wall, whereas in atherosclerosis plaque formation starts from a focal point rather than circumferentially.[9]

A moderate and persistent accumulation of 18F-FDG at the level of the vessell wall in patients with a history of vasculitis, during follow-up or after treatment, requires careful attention to understand to what extent this finding could be secondary to vascular remodeling (such as in aterosclerotic remodelling) rather than to a recurrence of the disease or poor response to treatment.[10]

We report the case of a 70 year-old patient with calcific aterosclerosis demonstrated on FDG-PET/CT.

Case Report

A 70-year-old woman with a history of general malaise, headache and right ophthalmic pain came under our clinical observation. She was also affected by autoimmune hypothyroidism, hypercholesterolemia, arterial hypertension. This patient had a body mass index (BMI) of 30. She had been a smoker of 20 cigarettes a day since adolescence. The medical examination showed numerous positive tender points (14/18). There was no frank engagement of the tracks. The temporal arteries were enlarged and pulsating, not painful on digital pressure.

Laboratory tests showed ESR 30 mm/1 h; C-reactive protein 0.5 mg/dL, ANA and anti-CCP were negative. Complete blood count and liver and kidney functions were normal. The blood tests revealed hyperuricemia, hypercholesterolemia with hypertiglyceridemia and a mild impaired fasting blood sugar.

Since we suspected a rare case of large vessel vasculitis with normal acute phase reactants, we decided to perform a 18-FDG-PET/CT that showed a tenuous and widespread uptake of the radiopharmaceutical at the level of the subclavian arteries and bilateral axillary arteries and of the thoracic aorta, with an uptake gradient slightly lower than that of the hepatic reference (grading 1), to be evaluated to be reported to clinical and laboratory context (Figure 1).

A chest CT scan with contrast medium showed extensive calcifications of the arch of the thoracic aorta and the descending tract of the aorta. Pervius the vascular lumen was patent. Uniform the caliber and course of the aorta. Pervi tthe supra-aortic vessels were patent at their emergence (Figure 2A and B).

We excluded the diagnosis of vasculitis and sent the patient to a cardiologist for close follow-up of the inflamed and calcified atherosclerotic lesions at high risk of vascular complications also con-

Figure 1. 18-F-fluorodeoxyglucose positron emission tomography/computed tomography: this image shows a tenuous and widespread uptake of the radiopharmaceutical at the level of the subclavian arteries and axillary arteries bilaterally and of the thoracic aorta with grading 1.

A　　　　　　　　　　**B**
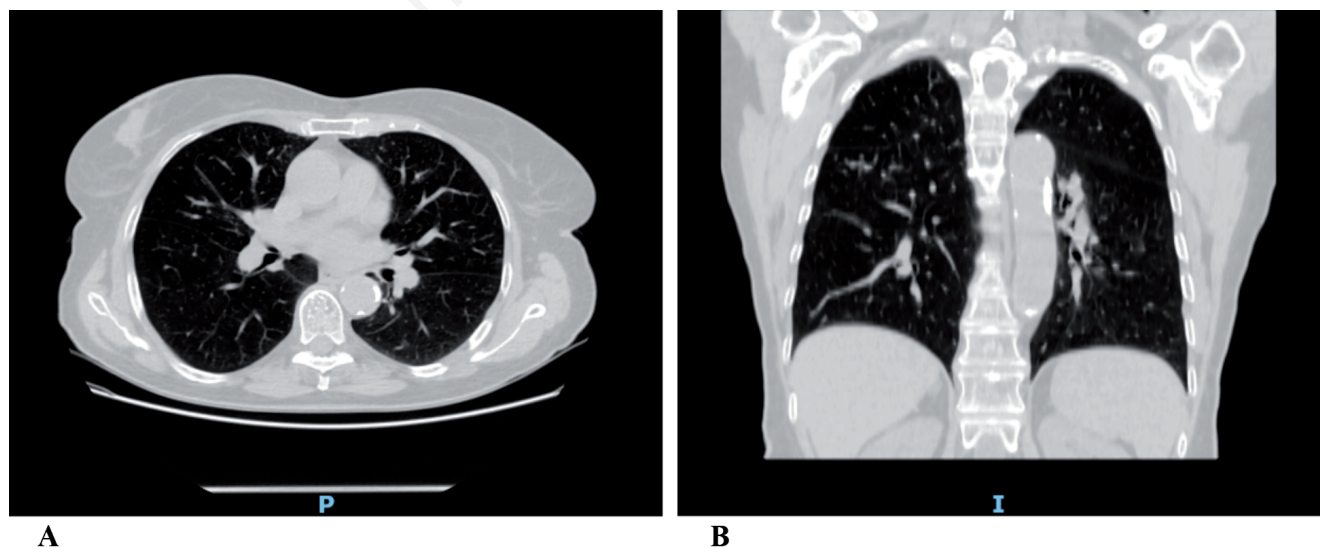
Figure 2. A) A transaxial view of a contrast chest computed tomography in a 70-year-old woman with extensive calcifications of the arch of the thoracic aorta and the descending tract of the aorta. B) Sagittal scan of extensive vascular calcifications.

sidering the underlying metabolic syndrome and their uptake of radiometabolic tracer on 18-F-FDG-PET/CT. We diagnosed trigeminal nevralgia in in this patient with fibromyalgia and started therapy with gabapentin and analgesics.

Discussion

Functional FDG-PET combined with anatomical CT angiography, FDG-PET/CT(A), may have a synergistic benefit for optimal diagnosis, monitoring of disease activity, and evaluating damage progression in LVV. There are currently no guidelines regarding PET imaging acquisition for LVV and PMR.

The European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the PET Interest Group (PIG), and the American Society of Nuclear Cardiology (ASNC) released a joint recommendation for FDG-PET/CT imaging procedures in LVV.

The aim of this group was to provide recommendations and statements based on the available evidence in the literature and consensus among experts in the field for patient preparation, and FDG-PET/CT acquisition and interpretation for the diagnosis and follow-up of patients with suspected or diagnosed LVV and/or PMR.[11]

They recommended some rules for patient preparation and image acquisition for FDG-PET/CT in LVV and PMR, which include fasting for at least 6 h prior to FDG administration and blood glucose levels preferably <7 mmol/L (126 mg/dL).

A discontinuation or delay of glucocorticoids are useful until PET is completed, unless there is a risk of ischemic complications, as in the case of GCA with temporal artery involvement. FDG-PET within 3 days after the start of GC is optional as a possible alternative.[12,13] The patient must be placed in a supine position with arms next to the body. The scans must be performed from head to the feet. A minimum of 60 min between intravenous FDG administration and acquisition has been recommended for an adequate tracer biodistribution.[14] Delayed acquisitions (3 h) increase the vascular-to-blood pool ratio, thus increasing contrast resolution,[15] and could make the measured vascular uptake more accurate.[16]

However, as the majority of LVV studies have been performed at 60 min, PET-positive criteria at delayed time points have not yet been evaluated in this setting and may differ slightly from those defined at the standard time interval.

In contrast to FDG-PET studies evaluating metabolic activity of atherosclerotic lesions, studies comparing early (1 h) *versus* delayed (3 h) imaging in LVV are scarce.[17]

The recently published EANM position paper on the use of FDG-PET in atherosclerosis has recommended an interval of 2 h between FDG administration and acquisition.[18]

Currently, there is not enough evidence to apply the same time window for LVV. At this time, we recommend an uptake interval of at least 60 min. Standardization of the time interval is essential, especially when using semiquantitative analyses and comparing FDG uptake in follow-up studies and between centers.

Several factors may significantly influence the arterial wall FDG uptake, and must be taken into consideration for interpretation of FDG-PET in LVV and PMR.

Riemer H.J.A. Slart *et al.* proposed the use of a standardized 0-to-3 grading system as follows: 0 = no uptake (≤ mediastinum); 1 = low-grade uptake (< liver); 2 = intermediate-grade uptake (= liver), 3 = high-grade uptake (> liver), with grade 2 as possibly indicative and grade 3 as positive for active LVV.[11-20]

A total vascular score (TVS) can be determined, for instance, at seven different vascular regions (thoracic aorta, abdominal aorta, subclavian arteries, axillary arteries, carotid arteries, iliac arteries, and femoral arteries) as negative (0) or positive. This can be further scored semi-quantitatively as 1 (minimal but not negligible FDG uptake), 2 (clearly increased FDG uptake), or 3 (very marked FDG uptake). Therefore, a TVS could be calculated ranging from 0 (no vascular FDG uptake in any of the seven vascular regions) to 21 (vascular FDG uptake scored 3 in all seven territories).[11]

Visual qualitative methods are most commonly used, but semi-quantitative methods such as the vascular/blood ratio and vascular/liver ratio using standardized uptake values (SUVs) are gaining ever more relevance.

FDG-PET/CT(A) may be of value for evaluating response to treatment by monitoring functional metabolic information and detecting structural vascular changes (evidence level III, grade C), but additional prospective FDG-PET/CT(A) studies are warranted.[11]

The main limitations of the functional FDG-PET are the relatively low spatial resolution of the tomograph, which can lead to false-negative results in the presence of small-vessel vasculitis, and risk of false positive results, especially in the presence of atherosclerosis and post-treatment vascular remodeling.

The atherosclerosis activity may also interfere with the FDG-PET signal in patients with LVV.[11-21] In fact the atherosclerotic vessels, above all those with a larger diameter, tend to capture the tracer of glucose metabolism, due to the macrophage component of the atherosclerotic plaque. The atherosclerotic vascular uptake[22,23], which is frequent when aging, may be a source of false positives in LVV evaluation, despite a classical "patchy" uptake pattern. Uptake in iliofemoral arteries should be interpreted with caution, because this is a frequent site of atherosclerosis. Taking these considerations into account, vascular inflammation in LVV on FDG-PET classically appears as a smooth linear pattern, involving the aorta and its main branches (subclavian, carotid or vertebral arteries, pulmonary arteries), but not all main branches have to be involved. Arterial inflammation is as a predictor of plaque progression and adverse cardiovascular outcomes. In atherosclerotic lesions, arterial inflammation (by FDG-PET) comes with high-risk structural features, and locations with more intense inflammation are more likely to lead to subsequent atherosclerosis progression (*e.g.* calcium deposition).[24,25] Therefore, due to an increased uptake of atherosclerotic plaques, the results of functional FDG-PET need to evaluate in a comprehensive manner. Finally, when atherosclerotic lesions with inflammation are detected, it is necessary to refer the patient to a specialist for appropriate management, given the high risk of cardiovascular complications.

Conclusions

Although FDG-PET/CT(A) has proven to be an important imaging modality for the diagnosis of large vessel vasculitis, recent studies have shown that atherosclerotic plaques can give false positives in 18F-FDG PET/CT. Distinguishing between atherosclerosis and vasculitis may be difficult, especially in patients with important risk factors for atherosclerotic plaque development, such as age, hypertension, diabetes, hypercolesterolemia and smoking. Therefore, history, clinical, laboratory and instrumental data must be combined to lead to a confirmed diagnosis.

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