Relationship between histopathological features of non-infectious aortitis and the results of pre-operative 18F-FDG-PET/CT: a retrospective study of 16 patients

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Abstract

Objective

To describe the characteristics of [18]F-fluorodeoxyglucose positron-emission tomography/computed-tomography ([18]FDG-PET/CT) findings before surgery in patients with active, histologically confirmed aortitis, and to correlate the degree of arterial wall inflammation with PETVAS score.

Methods

This was a multiple-centre retrospective study including cases with histologically proven active, non-infectious aortitis who had a [18]FDG-PET/CT performed within one year before surgery for aneurysm repair. PETVAS score was determined by radiologists blinded to the pathology findings. Cardiovascular pathologists reviewed aortic tissue samples and graded the degree of inflammation in the vessel wall.

Results

Sixteen patients were included (8 giant cell arteritis, 4 clinically isolated aortitis, 2 Takayasu's arteritis, 1 relapsing polychondritis, and 1 rheumatoid arthritis). In 5/16 (31%) patients, [18]FDG-PET/CT did not detect the presence of aortic inflammation; two of whom were being treated with glucocorticoids at the time of procedure. Ascending thoracic and abdominal aorta had the highest FDG uptake among the affected territories. Patients without active aortitis on [18]FDG-PET/CT were significantly older (p=0.027), had a lower PETVAS score (p=0.007), and had a lower degree of adventitial inflammation (p=0.035). In contrast, there was no difference between [18]FDG-PET/CT active and inactive aortitis patients as regards the timing between PET/CT and surgery, serum CRP level (during [18]FDG-PET/CT) and, FDG uptake per study site.

Conclusion

In histologically proved aortitis, [18]FDG-PET/CT before surgery did not detect vascular inflammation in 31% patients, and PETVAS score correlated with the degree of adventitial histopathologic inflammation.

Key words

aortitis, fluorodeoxyglucose F18, large-vessel vasculitis, positron emission tomography computed tomography, giant cell arteritis

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Introduction

Aortitis is defined as inflammation of the aortic wall and includes several different diseases, of which the most frequent are systemic vasculitis such as giant cell arteritis (GCA) and Takayasu's arteritis (TAK). Clinically isolated aortitis (CIA) represents a particular subset that is limited to the aorta without signs of systemic disease, although some cases may evolve to GCA (1). Rarely, aortitis may be a complication of rheumatic diseases such as ankylosing spondylitis or relapsing polychondritis (2). Aortitis is associated with significant morbidity and potential mortality related to aneurysmal dilatation, aortic dissection, or rupture (3-6). Histological evidence of aortitis, considered to be the gold standard diagnostic method, is only available after aneurysm surgery. Indeed, most patients with CIA are diagnosed postoperatively following the incidental discovery of aortitis on histopathological analysis. Retrospective case series have reported the presence of aortitis in 3%-6% of surgical specimens from ascending aortic aneurysm repairs (5, 8). In patients with systemic vasculitis such as GCA, aortitis is often diagnosed by imaging studies such as computed tomography angiogram (CTA), magnetic resonance angiogram (MRA) or ^{18}F-fluorodeoxyglucose positron-emission tomography/computed-tomography (^{18}FDG-PET/CT) (7). While PET/CT has excellent specificity and sensitivity for the diagnosis of large-vessel vasculitis (LVV), false negatives (due to glucocorticoids) or false positives (*e.g.* atherosclerosis) may occur (9, 10). No study has correlated preoperative ^{18}FDG-PET/CT findings with pathologically confirmed aortitis in patients undergoing thoracic aortic aneurysm repair. The aim of our study is to describe the ^{18}FDG-PET/CT findings prior to aortic surgery in patients with aortitis, and to report the sensitivity of PET for the detection of pathologically confirmed aortic inflammation.

Patients and methods

Study population

The study comprised patients with pathologically confirmed non-infectious aortitis who had a ^{18}FDG-PET/CT performed no more than twelve months before aneurysm surgery between January 1, 2000, and December 31, 2021, at Mayo Clinic Rochester, Minnesota, USA. French patients from three centres, meeting the same inclusion criteria, were added. Patients without research authorisation and cases of infectious aortitis were excluded from the study.

Data collection

Preoperative clinical and biological data were retrospectively obtained from the patients' electronic health records and a cardiovascular surgical database. Each patient was assigned a clinical diagnosis according to clinical and laboratory information, in accordance with the definitions of each: GCA, TAK, relapsing polychondritis (RP), rheumatoid arthritis (RA), and CIA (11, 12). Aortitis was defined histologically by the presence of an inflammatory infiltrate associated with medial damage.

Radiology review

All the patients in this study underwent FDG-PET/CT scan with standard protocols and comparable scanners including GE Discovery (GE Healthcare, Milwaukee, Wisconsin, USA), Siemens (Siemens Healthcare, Erlangen, Germany) and Philips Medical Systems (Philips Healthcare, Cleveland, OH, USA). After a 4-hour fast, patients were injected with a weight-based dose of ^{18}F-FDG radiotracer. After 1 hour of uptake time, a spiral CT scan followed by a PET emission scan was obtained. PET data and CT images were evaluated using MIM (MIM Software Inc., Cleveland, OH). A nuclear medicine radiologist and a senior radiology resident reviewed all images independently with the findings later compared to confirm the reproducibility.

For quantitative assessment, a volumetric region of interest tool was used to obtain the maximal standardised uptake value (SUVmax) which is calculated from the injected dose and patient weight. The SUVmax was recorded for nine specific arterial territories including: ascending aorta, aorta arch,

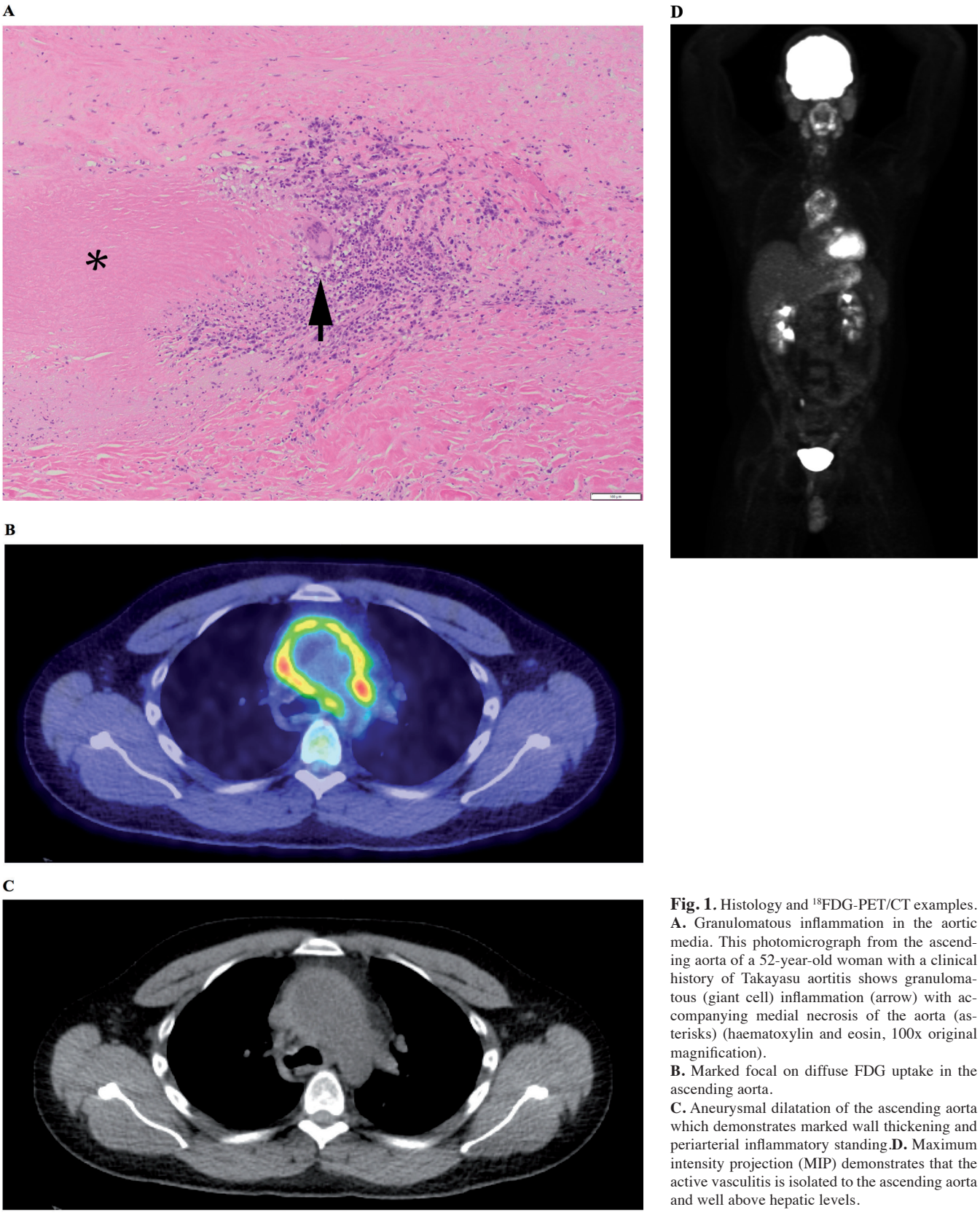

Fig. 1. Histology and ^{18}FDG-PET/CT examples. **A.** Granulomatous inflammation in the aortic media. This photomicrograph from the ascending aorta of a 52-year-old woman with a clinical history of Takayasu aortitis shows granulomatous (giant cell) inflammation (arrow) with accompanying medial necrosis of the aorta (asterisks) (haematoxylin and eosin, 100x original magnification).
B. Marked focal on diffuse FDG uptake in the ascending aorta.
C. Aneurysmal dilatation of the ascending aorta which demonstrates marked wall thickening and periarterial inflammatory standing.**D.** Maximum intensity projection (MIP) demonstrates that the active vasculitis is isolated to the ascending aorta and well above hepatic levels.

descending thoracic aorta, abdominal aorta, innominate artery, right/left carotid arteries and right/left subclavian arteries. The SUVmean of the right hepatic lobe was obtained as an internal reference for subsequent scoring.

PET vascular activity score (PETVAS) was obtained by comparing each vascular segment to the background hepatic uptake. Specifically, a score of 0 = no FDG uptake; 1 = less than liver; 2 = equal to liver; and 3 = greater than

liver. Then the cumulative score was recorded for each patient.
Lastly, the radiologist made an overall impression regarding if active vasculitis was favored to be present or absent. The decision process considered focality of uptake, SUVmax, and non-contrast enhanced CT findings of vessel wall thickening and/or adjacent inflammatory stranding.

Statistical analysis
Quantitative variables were expressed as means and standard deviation. Qualitative variables were expressed as frequencies with percentages. Comparisons were made by Pearson's Chi-2 test, Fisher's exact test, or Wilcoxon test as appropriate for each variable. A *p*-value less than 0.05 was considered to be significant. All calculations were performed using R software v. 3.2.2 (R foundation for statistical computing, Vienna, Austria).

Ethical board approval
For American patients, the study obtained approval from the Mayo Clinic Institutional Review Board. Concerning French patients, the study was conducted in compliance with good clinical practices and the principles of the Declaration of Helsinki. In accordance with French law, formal approval from an ethics committee was not required for this type of retrospective study.

Table I. Comparison between inactive and active vasculitis according to ^{18}FDG-PET/CT findings.

	Vasculitis on PET/CT		*p*-value
	Inactive (n=5)	Active (n=11)	
	Mean ± SD or n (%)		
Age, years	73.8 ± 4.2	59.7 ± 15.2	0.027
Glucocorticoids during PET/CT	2 (40%)	3 (27%)	1.000
Immunosuppressive treatment during PET/CT	2 (40%)	1 (9%)	0.214
CRP during PET/CT, mg/l	23.8 ± 22.9	18.4 ± 22.9	0.497
Time between PET/CT and surgery, months	4.2 ± 4.1	3.8 ± 3.4	0.953
Reason(s) for the realisation of PET/CT			
Constitutional symptoms	1 (20%)	2 (18%)	1.000
Unexplained elevated inflammatory markers	3 (60%)	4/8 (50%)	1.000
Follow-up of known aortitis	1 (20%)	3 (27%)	1.000
Rapid progression of a known aortic aneurysm	2 (40%)	3 (27%)	1.000
Other reasons	0	3 (27%)	0.509
PETVAS score (0 to 3 scale)			
Ascending aorta	1.6 ± 0.9	2.2 ± 0.6	0.157
Aortic arch	1.0 ± 0.0	1.9 ± 0.7	0.015
Descending thoracic aorta	1.2 ± 0.4	2.1 ± 0.8	0.053
Abdominal aorta	1.2 ± 0.4	1.6 ± 0.9	0.446
Right carotid	1.0 ± 0.0	1.1 ± 0.3	0.590
Left carotid	1.0 ± 0.0	1.2 ± 0.4	0.374
Innominate artery	1.0 ± 0.0	1.4 ± 0.5	0.152
Right subclavian artery	1.0 ± 0.0	0.9 ± 0.5	0.739
Left subclavian artery	1.0 ± 0.0	0.9 ± 0.5	0.739
Total PETVAS score (0 to 27 scale)	10.0 ± 1.0	13.3 ± 2.1	0.007
Histology			
Medial inflammation (0 to 3 scale)	1.8 ± 0.8	2.5 ± 0.5	0.108
Adventitial inflammation (0 to 3 scale)	1.4 ± 0.5	2.3 ± 0.6	0.035

PET/CT: 18F-fluorodeoxyglucose positron-emission tomography/computed-tomography; CRP: C-reactive protein.

Results

Demographics
Sixteen patients met the inclusion criteria. Eight had a final diagnosis of GCA. Other diagnoses were CIA (n=4), TAK (n=2), RP (n=1), and RA (n=1). The time interval between ^{18}FDG-PET/CT and surgery was on average 3.9±3.5 months. In most patients (9/16), ^{18}FDG-PET/CT was performed to assess vasculitis disease activity in the context of a known diagnosis of large-vessel vasculitis. Five patients had a ^{18}FDG-PET/CT for unexplained constitutional symptoms and/or persistent inflammatory syndrome. One patient was evaluated with PET/CT for breast cancer and one to characterise a lung nodule. The mean CRP at the time of ^{18}FDG-PET/CT (available for 13/16 patients) was 20±23 mg/l. Six patients were on glucocorticoids/immunosuppressive therapies during ^{18}FDG-PET/CT. The indication for surgery was the presence of an aortic aneurysm for fifteen patients (mean diameter: 54 mm) and aortic dissection for one patient. Consistent with the inclusion criteria for this study, all patients had histologically active aortitis. An illustration of histological proven aortitis is shown in Figure 1.

^{18}FDG-PET/CT findings
^{18}FDG-PET/CT showed no evidence of vasculitis activity in 5/16 (31%) patients, two of whom were being treated with glucocorticoids at the time of the examination. These two treated patients had elevated inflammatory parameters with constitutional symptoms suggesting clinically active vasculitis.
In patients with aortic FDG uptake, the thoracic aorta (10/11, 91% patients) was most frequently involved. The ascending thoracic aorta and abdominal aorta had the highest FDG uptake among the affected territories. In terms of SUVmax, the aortic arch had the highest values. Examples of a ^{18}FDG-PET/CT result is shown in Figure 1. Among patients with active vasculitis on ^{18}FDG-PET/CT, serum CRP level was low (≤11 mg/l) for most (6/8 patients with available CRP).

Comparison between active and inactive ^{18}FDG-PET/CT
Patients without active aortitis on ^{18}FDG-PET/CT (n=5), were significantly older (73.8±4.2 *vs*. 59.7±15.2 years, p=0.027), had a lower aortic arch FDG uptake (1.0±0.0 *vs*. 1.9±0.7, p=0.015) and total PETVAS score (10.0±1.0 *vs*. 13.3±2.1, p=0.007), and had a lower degree of adventitial inflammation (0 to 3 scale) (1.4±0.5 versus 2.3±0.7, p=0.035) (Table I). In contrast, there was no difference in the time between ^{18}FDG-PET/CT and surgery (p=0.953), CRP level during ^{18}FDG-PET/CT (p=0.497), FDG uptake per other study site, or degree of inflammation in the media on pathological examination (p=0.108).

Discussion

This study is the first which analysed ^{18}FDG-PET/CT before surgery in histologically proved aortitis and highlights the utility of ^{18}FDG-PET/CT for the evaluation of patients with non-infectious aortitis. In this small sample of patients, we show that two third patients with histologically confirmed aortitis had aortic FDG uptake on PET. However, a subset of patients may have a negative a ^{18}FDG-PET/CT despite ongoing histologic evidence of aortitis; ^{18}FDG-PET/CT is not sensitive enough to demonstrate mild inflammation of the aortic wall. Treatment with glucocorticoids may play a role in reducing the sensitivity of PET while the aortitis may still be active (1). Grayson *et al*. showed, comparing 56 patients with LVV to 59 comparator subjects, that ^{18}FDG-PET/CT could distinguish patients with active vasculitis with a sensitivity of 85% (9). Nevertheless, this study correlates ^{18}FDG-PET/CT with clinical disease activity and inflammatory biomarkers (9). The novelty of the present study is that we compared ^{18}FDG-PET/CT with pathology, which remains the gold standard diagnostic assessment for vasculitis.

Patients without active aortitis on ^{18}FDG-PET/CT exhibited a lower degree of adventitial inflammation on histopathological examination compared to those with active aortitis. The onset of the inflammatory process in GCA starts in the adventitia by stimulation of resident dendritic cells (13). The following stages take place mainly in the media with an inflammatory infiltrate composed of lymphocytes and macrophages. The lower intensity of the inflammatory infiltrate observed in the adventitia of ^{18}FDG-PET/CT negative patients might reflect a later stage of disease or may be due to different pathomechanisms of vascular inflammation in these patients. Our findings need to be confirmed in other cohorts and should be considered preliminary.

This present study shows that patients with active aortitis on ^{18}FDG-PET/CT exhibited a higher PETVAS of the aortic arch among the sites of vessels than those without. According to a previous study, aortic arch is the vascular site where hypermetabolism on ^{18}FDG-PET/CT is most marked for patients with active large-vessel vasculitis (9). However, despite the absence of hypermetabolism, patients may have histopathological evidence of active aortitis on surgical specimens. Thus, in select cases, an aortic arch aneurysm, may still be inflammatory in nature even if ^{18}FDG-PET/CT is negative.

The essential reason for using ^{18}FDG-PET/CT pre-operatively in patients with aortic aneurysm and a proven, or suspected condition known to be associated with aortitis is to evaluate disease activity, since a repair surgery should preferably be performed when the inflammatory process is quiescent (14-17). Post-operatively, ^{18}FDG-PET/CT may be used to detect ongoing inflammation in the native aorta, which may increase risk of new events such as aneurysm or aortic rupture. Finally, the follow-up of the graft may be useful, especially in situations of suspected prosthesis infection (18).

The main limitations of our study are the small number of patients, the heterogenous aetiologies of aortitis, and the variable time from imaging to surgery. Indeed, various forms of aortitis may have different pathophysiological mechanisms resulting in variable findings on PET/CT. The delay between PET/CT and surgery in some patients may (at least in part) explain the "false negatives". Most of the PET/CTs (12/16) were performed 6 months before surgery, which limits this gap. Among the negative PET/CT, only one was performed 11 months before surgery (and this patient was on treatment). The 4 other negative PET/CT were performed fairly close to surgery (5, 3, 1 and 1 month respectively) which limits this potential confounder. However, given the rarity of disease and need for surgical intervention to obtain tissue samples, our data are novel and informative. Larger studies and standardisation of radiologic findings are needed to better determine the correlation between nuclear imaging and histologic patterns of inflammation.

In conclusion, our study showed for the first time ^{18}FDG-PET/CT characteristics in patients who underwent surgery a few months later and who had histologic confirmation of aortitis. In a third of cases, aortitis is not identified before surgery. Larger studies are needed to better identify these patients and specify their prognosis.

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