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CASE REPORT

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[^{18}F]fluorodeoxyglucose positron emission tomography is a useful tool to diagnose the early stage of Takayasu's arteritis and to evaluate the activity of the disease

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Abstract Takayasu's arteritis (TA) is a rare disease that can be difficult to diagnose in its early stage. A young woman with a fever and neck pain was thought to have TA, although computed tomographic angiography did not show any specific changes of the arteries. [^{18}F]fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) was performed to detect the source of the inflammation. Specific accumulation of [^{18}F]FDG-6-phosphate in the thoracic aorta and its direct branches was observed, leading to a diagnosis of TA. [^{18}F]FDG-PET is therefore considered to be useful for the diagnosis of early-stage TA.

Key words Diagnosis · Fever of unknown origin · [^{18}F]Fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) · Takayasu's arteritis (TA)

Introduction

Takayasu's arteritis (TA) is a chronic vasculitis that primarily involves the aorta and its main branches. Takayasu's arteritis induces clinically varied ischemic symptoms due to inflammation and stenotic lesions or thrombus formation in the vessels. Acute progression of the disease causes destruction of the media of the arterial wall, leading to the formation of aneurysms or rupture of the involved arteries.[1] During the progression of arterial stenosis, the majority of patients suffer from ischemic disorders, including dizziness, syncope, visual disturbances, an absent pulse, or a difference in the systolic blood pressures of the arms. In the early stages of TA, however, patients usually suffer from only nonspecific symptoms such as fever, general fatigue, and weakness. Early diagnosis and treatment are important to obtain the best possible prognosis for the patient.[2,3] The diagnosis of TA is mainly made based on the characteristic angiographic images seen in advanced cases. Magnetic resonance imaging (MRI) can show subtle inflammatory thickening of the wall of the aorta, even when angiographic results are normal.[4] Therefore, MRI is considered to be a useful tool for the detection of early changes in vessels due to TA. Positron emission tomography (PET) with [^{18}F]2′-deoxy-2-fluoro-D-glucose (FDG) has been developed as a whole-body screening method for malignancies. Recently, this method was reported to be useful for the diagnosis of TA.[5] Here, we report on a patient with early-stage TA, which was diagnosed using [^{18}F]FDG-PET.

Case report

A 16-year-old female patient was referred to our department in January 2005. She complained of a continuous fever and gradually increasing pain in the left side of her neck. Antibiotics were prescribed to treat any potential infection. The symptoms, however, did not improve. She then began to suffer from numbness of her left arm. She was admitted to our hospital on January 17, 2005. The clinical course of the patient is shown in Fig. 1. At admission, both radial pulses were easily palpated. Her blood pressure was 90/60, 86/60, 110/74, and 110/70 mmHg in the right arm, left arm, right leg, and left leg, respectively. No carotid sinus reflex was observed. No cardiac murmur or bruits in her neck or abdomen was audible. Ophthalmological examination, including fundoscopy, did not reveal any abnormalities. Repeated blood cultures were negative. An echocardiogram did not show any evidence of endocarditis and a chest X-ray showed no calcification of her aorta.

The laboratory findings at the time of admission are shown in Table 1. Leukocytosis, anemia, and an increased platelet count were observed. The plasma fibrinogen

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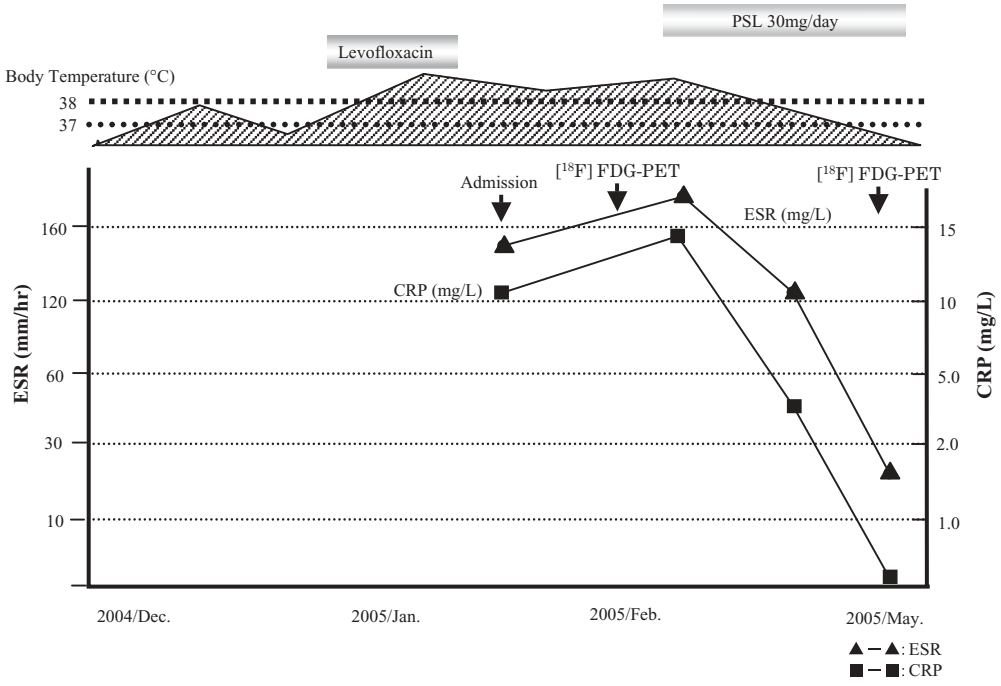

Fig. 1. Clinical course of the case presented in this study. *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *PSL*, prednisolone; *[18F]FDG-PET*, [18F]fluorodeoxyglucose positron emission tomography

Table 1. Laboratory findings

ESR	152 mm/h	Blood chemistry		Serology (cont'd)	
		TP	7.16 g/dl	C3	195 mg/ml
CBC		Alb	47.8%	C4	34 mg/ml
WBC	9100/μl	α1-glb	5.6%	CH_{50}	68 U/ml
Neut.	69%	α2-glb	12.2%	IC(C1Q)	1.5 μg/ml
Lymph.	22.8%	β-glb	13.2%	IC(C3D)	29.4 μg/ml
Mono.	6.9%	γ-glb	21.2%	ANA	(–)
Baso.	0.7%	BUN	10.5 mg/dl	PR3-ANCA	<10 U
Eosino.	0.6%	CRE	0.5 mg/dl	MPO-ANCA	<10 U
RBC	387×10^4/μl	T-bil.	0.4 mg/dl	RF	(–)
Hb	9.9 g/dl	AST	17 IU/ml	TPHA	(–)
Platelet	53.2×10^4/μl	ALT	23 IU/ml	STS	(–)
		LDH	95 IU/l		
		ALP	385 IU/l	HLA	
Coagulation				HLA-A	A26 (10), A31 (19)
FBG	676 mg/dl	Serology		HLA-B	B46, B62 (15)
FDP	1.3 μg/ml	CRP	11.6 mg/dl	HLA-DR	DR8, DR15 (2)
D-D	0.51 μg/l	IgG	1436 mg/dl		
APTT	41.4 s	IgA	204 mg/dl		
PT%	66%	IgM	120 mg/dl		

ESR, erythrocyte sedimentation rate; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; FBG, fibrinogen; FDP, fibrin degradation product; D-D, D-dimer; APTT, activated partial thromboplastin time; PT%, prothrombin time %; TP, total protein; Alb, albumin; glob, globulin; BUN, blood urea nitrogen; CRE, creatinine; T-bil., total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CRP, C-reactive protein; Ig., immunoglobulin; IC, immune complex; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; RF, rheumatoid factor; TPHA, *Treponema pallidum* hemagglutination; STS, serologic test for syphilis; HLA, human leukocyte antigen

concentration was raised and a slight extension of the blood coagulation time was observed. Both the erythrocyte sedimentation rate (ESR) and the serum C-reactive protein (CRP) concentration were increased. Tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA), and rheumatoid factor were negative, as was a serologic test for syphilis. The human leukocyte antigens were A26, A31, B46, B62, DR8, and DR15.

Based on these findings, infectious diseases and rheumatoid diseases such as rheumatoid arthritis, systemic lupus erythematosus, and ANCA-associated vasculitis were unlikely to underlie the patient's symptoms. The symptoms in her neck and arms together with the inflammatory laboratory data suggested the possibility of TA. Computed tomographic angiography (CTA) of the aorta and its branches revealed no conclusive changes in the vessels, such as dilatation, obstruction, aneurysm, thrombus, or calcification, although narrowing of the subclavian artery could not be completely ruled out (Fig. 2). Unfortunately, because the patient had an allergic reaction to the contrast medium used

in CTA, we could not perform further imaging tests using the contrast medium. No abnormal accumulation of ^{67}Ga was noted by gallium scintigraphy, and no definite changes of the carotid arteries were revealed by conventional sonography. Because no direct evidence of vasculitis was shown by these examinations, malignancies such as lymphoma could not be disregarded as the cause of the fever. Therefore, [^{18}F]FDG-PET was performed and abnormal uptake of [^{18}F]FDG in the bilateral common carotid artery, the bilateral subclavian artery, the bilateral pulmonary arteries, and the thoracic aorta was observed (Fig. 3a).

Based on these findings, the patient was diagnosed with TA. Treatment with prednisolone (PSL) at a dose of 30 mg/day was started. Most of the symptoms disappeared within a week. Laboratory tests indicated the inflammation improved as well. In May 2005, after treatment with PSL for 3 months, the abnormal accumulation of [^{18}F]FDG on the arteries observed with [^{18}F]FDG-PET was found to have disappeared (Fig. 3b).

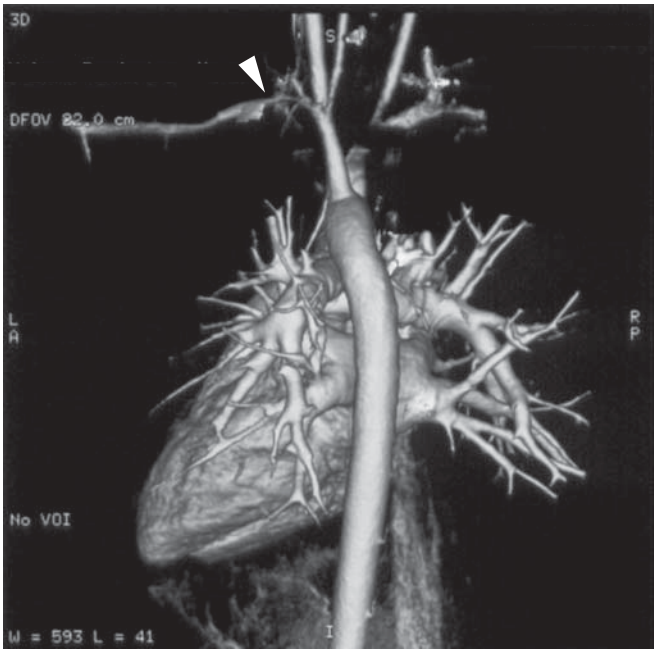

Fig. 2. Three-dimensional computed tomographic angiography. The *arrowhead* marks the left subclavian artery

Discussion

Takayasu's arteritis is a chronic, inflammatory disorder with unknown etiology. This disease primarily affects the aorta and its major branches. In 1908, Takayasu, an ophthalmologist, described unusual retinal arteriovenous anastomoses in a young woman.[6] In 1951, Shimizu and Sano provided a clinical description of this condition and named this it "pulseless disease."[7] In 1954, Caccamise and Okuda renamed the disorder TA.[8] The majority of patients are between 15 and 25 years of age, and the male : female ratio is 1 : 9. Involvement of the subclavian artery has been observed in most cases of TA. Lesions in the abdominal aorta and the ilio-femoral arteries are rare.[9]

Takayasu's arteritis can be clinically divided into two stages. The early stage is characterized by nonspecific symptoms such as malaise, arthralgia, myalgia, fever, and weight loss. In the advanced stage, symptoms caused by the obliterative vascular disorder, such as paralysis of the arms, visual disturbances, and syncope, are observed.[9,10]

Although the American College of Rheumatology criteria for the classification of vasculitis in 1990 (ACR criteria) are considered to be the gold standard, the diagnosis of early-stage TA is often difficult and the ACR criteria do a poor job of identifying this stage of the disease. One of the reasons the diagnosis of early-stage TA is difficult is that specific markers for this disease are not available. In the present case, the patient fulfilled two of the ACR criteria: age and a worsening of fatigue of an upper extremity.

Traditional approaches for the diagnosis of aortitis mainly depend on showing the obstructive changes of the affected arteries in advanced cases.[11] There are several methods for the imaging of affected vessels in TA. Angiographic images can show irregular vessel walls, stenosis, poststenotic dilatation, aneurysmatic transformations, and occlusions. It is difficult, however, to detect these fea-

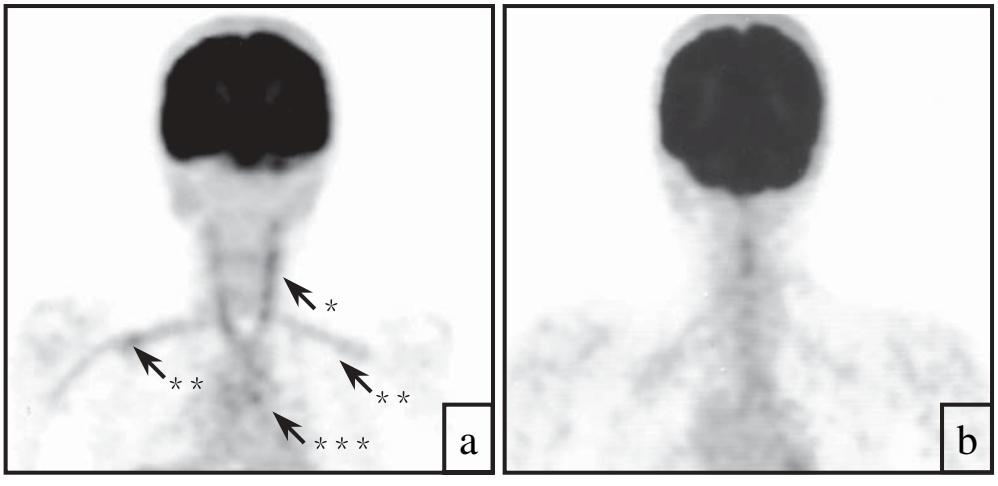

Fig. 3a,b. [^{18}F]Fluorodeoxyglucose positron emission tomography. **a** A scan made in February 2005. Abnormal accumulation in the left common carotid artery (*asterisk*), the bilateral subclavian arteries (*double asterisk*), the bilateral pulmonary arteries, and the thoracic aorta (*triple asterisk*) is shown. **b** A scan from May 2005. The accumulation of [^{18}F]fluorodeoxyglucose seen in **a** was not detectable

tures by angiography in the early stage of TA. Recently, CTA and MRI have been more frequently used for the diagnosis of TA. Both methods are useful to detect vascular wall thickening of large arteries.[12,13] Muthumala et al. reported that CTA is useful as a noninvasive means of monitoring the activities of the disease in patients with TA who are undergoing treatment.[14] Computed tomographic angiography is considered useful for the diagnosis of TA when the patient suffers from occlusive lesions of the vessels or thickening of the aortic wall. This, however, was not the case for the patient in this report. Magnetic resonance angiography is reported to allow the detection of subtle inflammatory wall thickening of the aorta and its branches, which can be associated with early-stage TA. Recently, MR angiography has been used instead of conventional angiography for evaluation of the advanced disease.[15,16] Due to the allergic reaction to the contrast medium, however, it was not possible to perform MR angiography in the present case. In addition, conventional sonography has been widely applied for measuring the thickness of the walls of the carotid arteries. In the diagnosis of the early stage of TA, however, it is difficult to detect subtle changes in vessels or to evaluate inflammation of the vessels by this method.[12,13] Changes in the carotid arteries were not evident in the present case.

[^{18}F]FDG-PET is a well-established method to detect malignancies by locating the increased glycolytic activity of neoplastic cells via the accumulation of [^{18}F]FDG-6-phosphate. Moreover, inflammatory cells are also known to display increased glucose metabolism. [^{18}F]FDG-PET has been considered to be useful for the detection of infection and inflammatory processes.[17] Recently, [^{18}F]FDG-PET was also reported as a sensitive and noninvasive method for the diagnosis of early-stage TA.[18–22] However, there are few reports from Japan that evaluate cases of TA using [^{18}F]FDG-PET. Meller et al. have reported that inflammatory aortic lesions, which could not be detected by CTA, gallium scintigraphy, or sonography, were successfully identified using [^{18}F]FDG-PET.[2] [^{18}F]FDG-PET is considered to be more useful than CTA to detect inflamed vessels and their distribution when the disease does not progress to stages with morphological changes that can be detected by other imaging tests. Moreover, as contrast medium is not necessary for [^{18}F]FDG-PET, this method can be used for patients that are allergic to the contrast medium or have compromised renal function.

The distribution of [^{18}F]FDG in positive scans has been reported to be linear and continuous on arterial walls. This pattern is typically seen for the early stage of TA. On the other hand, the pattern was reported to be patchier with a linear distribution for the later stage of TA.[23] The distribution of the abnormal accumulation of [^{18}F]FDG on the aorta and its direct branches in the present case was linear and continuous without patchy lesions, suggesting early-stage TA. Additionally, the patient mainly complained of symptoms in her left arm and the left side of her neck. Although the accumulation of [^{18}F]FDG did not show a significant difference between the left and right subclavian arteries, it was stronger in the left common carotid artery than in the right common carotid artery. Therefore, the level of accumulation of [^{18}F]FDG may reflect the level of inflammation. Kobayashi et al. also reported that [^{18}F]FDG-PET is useful for both the diagnosis of TA and for the assessment of the activity of TA, and the [^{18}F]FDG accumulation observed in TA cases directly indicated the degree of inflammation in the vascular wall.[24] Andrews et al. reported that low-level accumulation of [^{18}F]FDG remained detectable in a patient who was considered to be clinically in remission.[3] These data suggest that [^{18}F]FDG-PET may be a more sensitive method to assess continuing vascular inflammation than conventional clinical markers, such as CRP and ESR.

In conclusion, [^{18}F]FDG-PET is a useful tool for the diagnosis and assessment of the activity of early-stage TA. In addition, this method is also useful when contrast medium cannot be used because of an allergy or impaired renal function of the patient. At the same time, because [^{18}F]FDG-PET is expensive and the required instrument is not widely available, the full range of diagnostic options should be considered for the diagnosis of TA.

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