



FDG PET/CT used in identifying adult-onset Still's disease in connective tissue diseases

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Abstract

Purpose To explore the ¹⁸F-fluoro-dexoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) imaging characteristics of adult-onset Still's disease (AOSD) and its significance in differential diagnosis from other connective tissue diseases (CTDs).

Methods FDG PET/CT images of 54 patients with AOSD and 66 with other CTD from patients suffering from fever of unknown origin (FUO) were retrospectively studied and compared with 40 healthy controls. Clinical and PET/CT characteristics of AOSD and other CTDs were compared, and SUV_{max} (maximum standardized uptake value) was used to analyze the differences of FDG uptake in the blood pool, liver, spleen, bone marrow, and hyperplastic lymph nodes between the AOSD and other CTDs. The SUV_{max} ratios of the spleen, bone marrow, and lymph nodes to the liver were used to establish the diagnostic criteria for differential diagnosis of AOSD, and its diagnostic efficiency was evaluated.

Results Positive findings are presented in 53/54 (98.1%) AOSD patients and 61/66 (92.4%) other CTD patients in PET/CT imaging. AOSD manifested as diffusely increased FDG uptake in the spleen and bone marrow, and multiple reactive hyperplasia lymph nodes are symmetrically distributed mainly in the neck and axilla, while other organs were seldom involved. Although these abnormalities could be seen in other CTDs, its incidence and uptake value were both higher in AOSD. If two or more of the following three standard were met, the sensitivity, specificity, and accuracy of diagnosing AOSD could reach 90.7%, 92.4%, and 91.7%, respectively: ① spleen SUV_{max}/liver SUV_{max} ≥ 1.2 and/or bone marrow SUV_{max}/liver SUV_{max} ≥ 1.4; ② symmetrically distributed reactive hyperplastic lymph nodes mainly in the neck and axilla with a lymph node SUV_{max}/liver SUV_{max} ≥ 1.8; and ③ no other abnormal uptake found in other organs.

Conclusion Characteristic manifestations in AOSD were found on FDG PET/CT. These findings could help to identify AOSD from the other CTDs, especially in cases of fever of unknown origin, where it can assist in identifying the cause.

Key Points

- Image characteristics of FDG PET/CT in adult-onset Still's disease were described.
- FDG PET/CT helps in identifying adult-onset Still's disease from the other connective tissue diseases.
- FDG PET/CT imaging standard for diagnosing adult-onset Still's disease were established.

Keywords ¹⁸F-fluoro-dexoxyglucose · Adult-onset Still's disease · Connective tissue disease · Fever of unknown origin · Positron emission tomography/computed tomography

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Introduction

Adult-onset Still's disease (AOSD) is a multisystemic connective tissue disease (CTD), which mainly manifests as fever, rash, joint pain, and pharyngeal pain. Patients were often considered as fever of unknown origin (FUO) upon their first visits to the hospital. Although clinical diagnosis of AOSD is based on the current classification criteria [1, 2], early diagnosis is still challenging since patients are often lack of characteristic clinical manifestations. In recent years, more

and more clinical attentions have been attracted to the use of ^{18}F -fluoro-dexoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in inflammatory diseases [3–8]. Relevant studies on the AOSD have also been reported [9–12]. For patients with FUO, FDG PET/CT is useful in detecting malignant tumors or infectious lesions with its advantages of high sensitivity and wide field imaging [13–16]. However, whether FDG PET/CT can help in diagnosing different types of CTD remains unknown. Since AOSD accounts for the most common cause in CTDs in FUO, it is of great significance to understand PET/CT characteristics in AOSD. In this study, we retrospectively investigated a group of patients with CTDs who presented as FUO and underwent FDG PET/CT, in order to explore the PET/CT imaging characteristics of AOSD and its significance in differential diagnosis among CTDs.

Patients and methods

Study subjects

From January 2013 to June 2018 in Peking University people's hospital, FDG PET/CT examination was performed in 266 FUO patients for the determination of etiology. FUO was defined as an illness of more than 3 weeks in duration, temperature exceeding $38.3\text{ }^{\circ}\text{C}$ on more than three occasions, and diagnosis uncertain despite appropriate investigations, after at least three outpatient visits or 3 days in the hospital [17]. Among the 266 FUO patients, 120 (45.1%) were eventually diagnosed as having CTDs, and 54 of the CTDs were AOSD.

AOSD was diagnosed based on the Yamaguchi's criteria [1]. Final clinical diagnosis of other CTDs was based on the patient's medical history as well as laboratory, image, and histopathological examinations, which meet their respective clinical classification criteria. Table 1 listed the final clinical diagnosis for all of the 266 FUO patients. All patients were provided with laboratory examination data within 3 days before and after the PET/CT examination and the results of more than 1 year of clinical follow-up. The 54 patients with AOSD and 66 patients with other CTDs were studied and compared with the 40 cases with negative PET/CT findings that underwent PET/CT examination for the purpose of health examination. Table 2 shows the general information of the study subjects.

FDG PET/CT imaging

All patients were fasted at least 6 h before PET imaging, and the blood glucose of the patients was controlled below 200 mg/dL. ^{18}F -FDG (provided by Atom High-Tech Co., Ltd., Beijing, China) was injected intravenously at 5.55 MBq/kg (0.15 mCi/kg). Fifty minutes later, the patients lied in a supine position in the examination bed with both upper limbs placed at the sides of the body. Imaging ranging from the base of the skull to the middle of the tibia was acquired for each patient by using Discovery VCT PET/CT Scanner (GE Healthcare, Milwaukee, WI, USA). Images were reconstructed as three-dimensional PET, CT, and fusion images with a slice thickness of 3.3 mm. According to the patient's situation, the range of image acquisition is appropriately increased from head to toe, sometimes an additional chest high resolution CT or local contrast CT is added.

Table 1 Clinical diagnosis and etiological classification in 266 patients with FUO

Etiological classification	Case number	Proportion	Clinical diagnosis
Connective tissue disease	120	45.1%	AOSD (54), systemic vasculitis (16), idiopathic inflammatory myopathy (IIM)(11), systemic lupus erythematosus (SLE) (10), undifferentiated connective tissue disease(UCTD) (6), rheumatoid arthritis (RA) (5), rheumatic polymyalgia (5), panniculitis (2), Sjogren's syndrome (SS) (2), IgG4-related diseases (2), recurrent polychondritis (2), remitting seronegative symmetrical synovitis with pitting edema syndrome (RS3PE) (2), reactive arthritis (1), antiphospholipid syndrome (APS) (1), and autoinflammation syndrome (1)
Infection	75	28.2%	Infection site: lung (25), urinary tract (7), periprostheses (2), lymph node (2), peritoneum (3), bone (2), intestinal tract (2), pericardiac (1), muscle (1), spleen (1), meninges (2), multiple sites (9), uncertain (18)
Malignancy	35	13.2%	Lymphoma (24), leukemia (6), myelodysplastic syndrome (2), other malignant neoplasms (3)
Miscellaneous	22	8.3%	Drug allergy (10), histiocytic necrotizing lymphadenitis (4), Castleman disease (2), primary hemophagocytic syndrome (2), inflammatory bowel disease (2), limbic encephalitis (1), hyperthyroidism (1)
Unknown	14	5.3%	Uncertain (14)

Table 2 Age and gender distribution of study subjects

	AOSD (54 cases)	Other CTDs group (66 cases)	Control group (40 cases)
Range of ages (years)	18–73	18–84	36–74
Mean age (years)	40.9 ± 14.9	58.3 ± 17.2	52.8 ± 9.9
Male to female ratio	9/45 (1:5)	28/38 (1:1.4)	29/11 (2.6:1)

Image analysis

More than three experienced nuclear medicine physicians read the images together by visual judgment, to determine whether there was abnormal FDG uptake and/or structural changes in the imaging field. Location, number, FDG uptake, and systemic distribution of abnormal lesions were recorded, and their natures were judged in combination with the clinical data. In addition, using the three-dimensional region of interest (3D ROI) technique, the maximum standardized uptake value (SUV_{max}) of the blood pool, liver, spleen and spine were measured and recorded by one fixed physician (Fig. 1). When an abnormal lymph node was found, its SUV_{max} was also measured and recorded.

Data analysis

Clinical features were compared between the patients with AOSD and other CTD. In image analysis, visual judgment was firstly used to analyze the image characteristics for AOSD patients and other CTD patients. Semi-quantitative parameter SUV_{max} was applied to compare the FDG uptake in referred organs in AOSD patients and other CTD patients. The ratios of SUV_{max} in the spleen, bone marrow, and lymph nodes to SUV_{max} in the liver were further used as diagnostic parameters, and the threshold for each parameter was determined by the receiver operating characteristic curve (ROC) analysis, respectively. Then the image diagnostic standard

for AOSD was established based on the visual and quantitative parameters, and its diagnostic efficiency was evaluated.

Statistical analysis

Statistical analysis in this study was carried out by SPSS software (SPSS Inc. Released 2007). Among the different groups, the Student’s *t*-test was used to analyze the difference of ages; Chi-square test was used to analyze the nominal parameters, such as the clinical characteristics; the LSD *t*-test was used to analyze the differences in lesion uptake; ROC curve analysis was used to evaluate the diagnostic threshold of FDG uptake between AOSD and other CTDs group. Difference was considered statistically significant when *P* value was found less than 0.05.

Results

The clinical characteristics of AOSD and other CTDs were listed in Table 3. In this study, the average onset age of AOSD was younger than other CTDs, and AOSD was more likely to occur in women. In AOSD patients, the incidence of rash, arthralgia, sore throat, leukocytosis, elevated neutrophil, and abnormal liver function were significantly higher than in other CTD patients, while more autoantibodies were detected in other CTDs. No significant difference was found in the elevated serum level of C-reactive protein (CPR) and erythrocyte sedimentation rate (ESR) between the two groups.

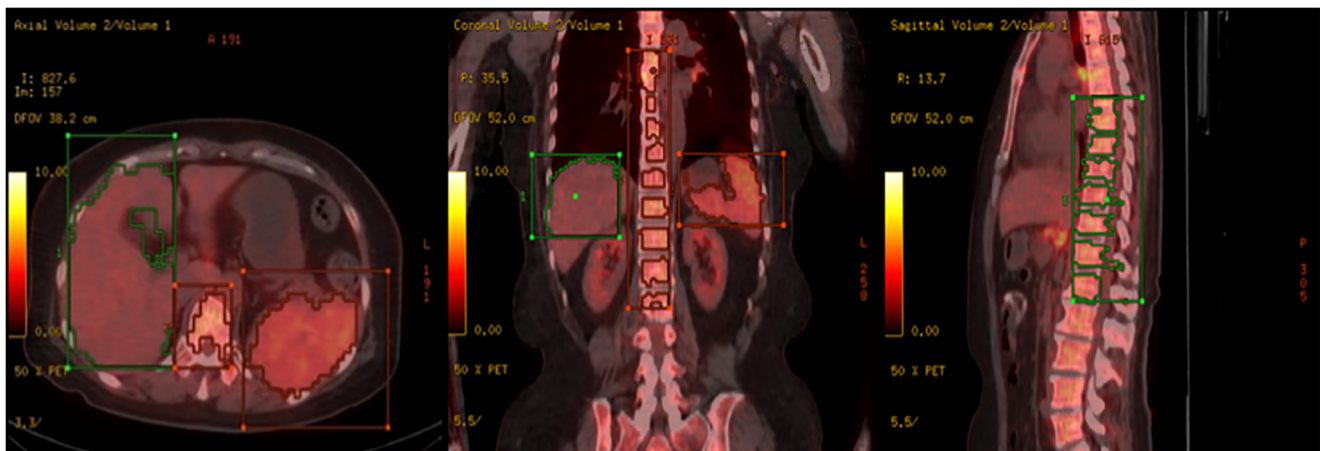


Fig. 1 3D ROI was delineated according to the contours of liver, spleen and spine, and SUV_{max} of corresponding regions was obtained

Table 3 Clinical characteristics of AOSD and other CTDs

Clinical manifestation	AOSD (54 cases)	Other CTDs (66 cases)	Statistical parameter
Mean age (years)	40.9 ± 14.9 (18–73)	58.3 ± 17.2 (18–84)	$P < 0.001$
Male to female ratio	9/45 (1:5)	28/38 (1:1.4)	$P = 0.002$
Rash	50 (92.6%)	19 (28.8%)	$P < 0.001$
Arthralgia	42 (77.8%)	27 (40.9%)	$P < 0.001$
Sore throat	36 (66.7%)	3 (4.5%)	$P < 0.001$
Leukocytosis	37 (68.5%)	22 (33.3%)	$P < 0.001$
Elevated neutrophil	40 (74.1%)	34 (51.5%)	$P = 0.009$
Abnormal liver function	52 (96.3%)	22 (33.3%)	$P < 0.001$
Elevated CRP	47 (87.0%)	50 (75.8%)	$P = 0.091$
Elevated ESR	49 (90.7%)	51 (77.2%)	$P = 0.054$
Positive antinuclear antibody or rheumatoid factor	2 (3.7%)	28 (42.4%)	$P < 0.001$

On PET/CT examinations, positive findings were detected in 53/54 (98.1%) of patients with AOSD and 61/66 (92.4%) of patients with other CTD, showing diffuse or focal high uptake of FDG in various organs and tissues (Table 4).

In patients with AOSD, PET/CT showed splenomegaly, diffusely increased FDG uptake in both the spleen and bone marrow, but no significant density or structural changes. Multiple and symmetrically distributed reactive hyperplastic

lymph nodes with increased FDG uptake could be seen throughout the body; most of which were found in the neck and axilla. These lymph nodes were long oval in shape and maintained normal structure, with the maximum short diameter ≤ 1.2 cm. Besides, no involvement of other organs was found in most of the AOSD patients, with the exception of a few patients with articular synovitis and salivary gland inflammatory lesions (Fig. 2).

Table 4 Positive findings of FDG PET/CT in AOSD and other CTDs

Location	AOSD (54 cases)	Other CTDs (66 cases)
Spleen	52 (96.3%)	36 (54.5%) systemic vasculitis (11/16), SLE (8/10), IIM (8/11), RA (3/5), SS (2/2), panniculitis (2/2), IgG4-related diseases (1/2), APS (1/1)
Bone marrow	53 (98.1%)	40 (60.6%) IIM (10/11), systemic vasculitis (9/16), SLE (5/10), RA (5/5), IgG4-related diseases (2/2), panniculitis (2/2), UCTD (2/6), rheumatic polymyalgia (1/5), SS (1/2), recurrent polychondritis (1/2), APS (1/1), autoinflammation syndrome(1/1)
Lymph nodes	41(75.9%)	34 (51.5%) SLE (6/10), IIM (5/11), systemic vasculitis (6/16), RA (2/5), recurrent polychondritis (2/2), UCTD (5/6), panniculitis (2/2), RS3PE (2/2), rheumatic polymyalgia (1/5), SS (1/2), IgG4-related diseases (1/2), APS (1/2)
Articular synovium	5 (9.3%)	16 (24.2%) RA (5/5), rheumatic polymyalgia (5/5), RS3PE (2/2), IIM (2/11), reactive arthritis (1/1), UCTD(1/6),
Salivary glands	1(1.9%)	8 (12.1%) SLE (4/10), RA (2/6), SS (1/2), systemic vasculitis (1/16)
Blood vessels	0	11 (16.7%) systemic vasculitis (7/16), IgG4-relateddiseases (2/2), SLE(1/10), UCTD (1/6)
Lung	0	22 (33.3%) IIM (8/11), SLE (7/10), systemic vasculitis (4/16), SS (1/2), RS3PE (1/2), RA (1/6)
Muscles	0	6 (9.1%) IIM (6/11)
Adipose tissue	0	7 (10.6%) IIM (4/11), panniculitis (2/2), SLE (1/10)
Kidney	0	6 (9.1%) systemic vasculitis (5/16), SLE (1/10)
Cartilage	0	2 (3.0%) recurrent polychondritis (2/2)
Intestine	0	2 (3.0%) APS (1/1), systemic vasculitis (1/16)

IIM: idiopathic inflammatory myopathy, SLE: systemic lupus erythematosus, RA: rheumatoid arthritis, SS: Sjogren's syndrome, RS3PE: remitting seronegative symmetrical synovitis with pitting edema syndrome, APS: antiphospholipid syndrome, UCTD: undifferentiated connective tissue disease

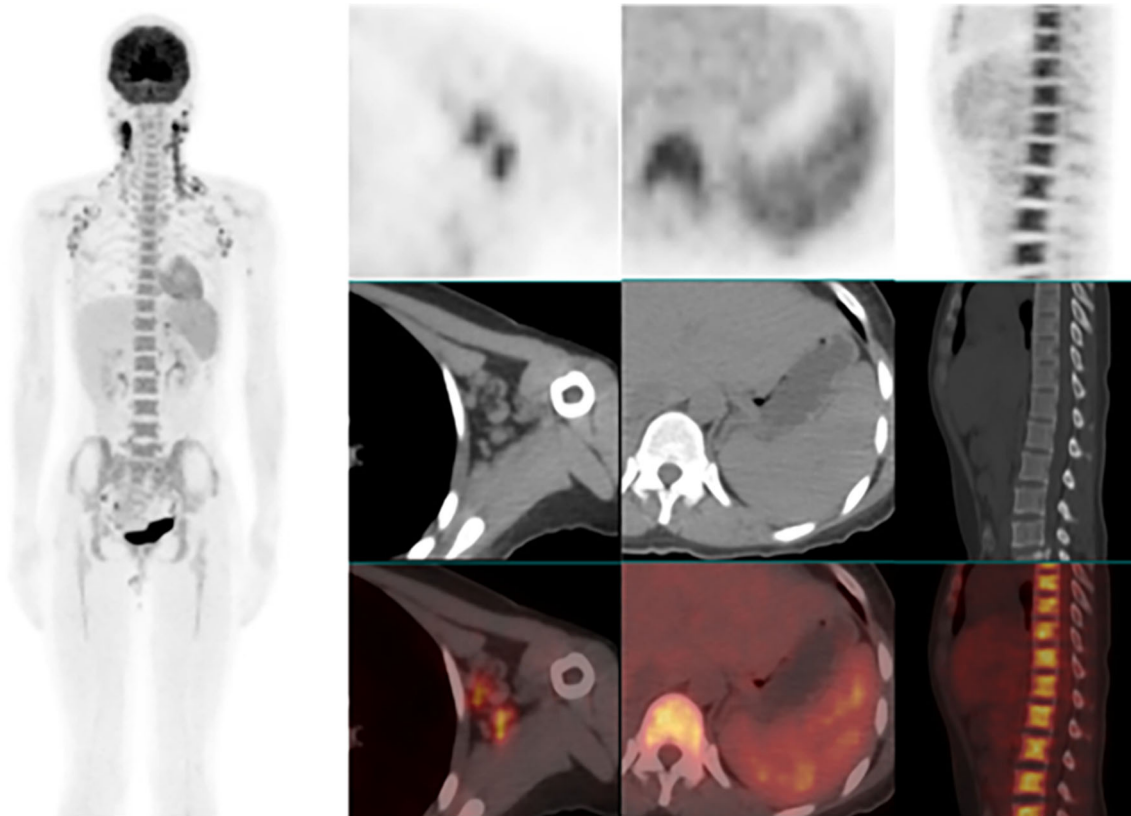


Fig. 2 FDG PET/CT images in a 32-year-old female who manifested clinically as FUO. PET/CT showed splenomegaly, diffusely increased FDG uptake in both the spleen and bone marrow, reactive hyperplastic

lymph nodes symmetrically distributed in the bilateral neck and axilla, and no other positive findings were found throughout the body. Final clinical diagnosis for the patient was AOSD

In patients with other CTD, although diffuse uptake in the spleen and bone marrow could also be seen, the incidence was significantly lower than in patients with AOSD ($P < 0.001$). Reactive hyperplastic lymph nodes were also found, but the distribution patterns as in the neck and axilla were less common. While the high uptake lesions in other tissues became the major positive findings on PET/CT, with or without structural changes. Various tissue involvements were observed, corresponding to disease characteristics, respectively, such as joints, blood vessels, muscles, lungs, and subcutaneous soft tissues (Fig. 3).

The results of semi-quantitative analysis showed that the average SUV_{max} of the spleen and bone marrow were significantly higher in both AOSD patients and other CTD patients comparing with the control group, and the SUV_{max} of the liver was significantly lower. Meantime, AOSD patients showed higher uptake of FDG in the spleen, bone marrow, and positive lymph nodes than other CTD patients (Table 5).

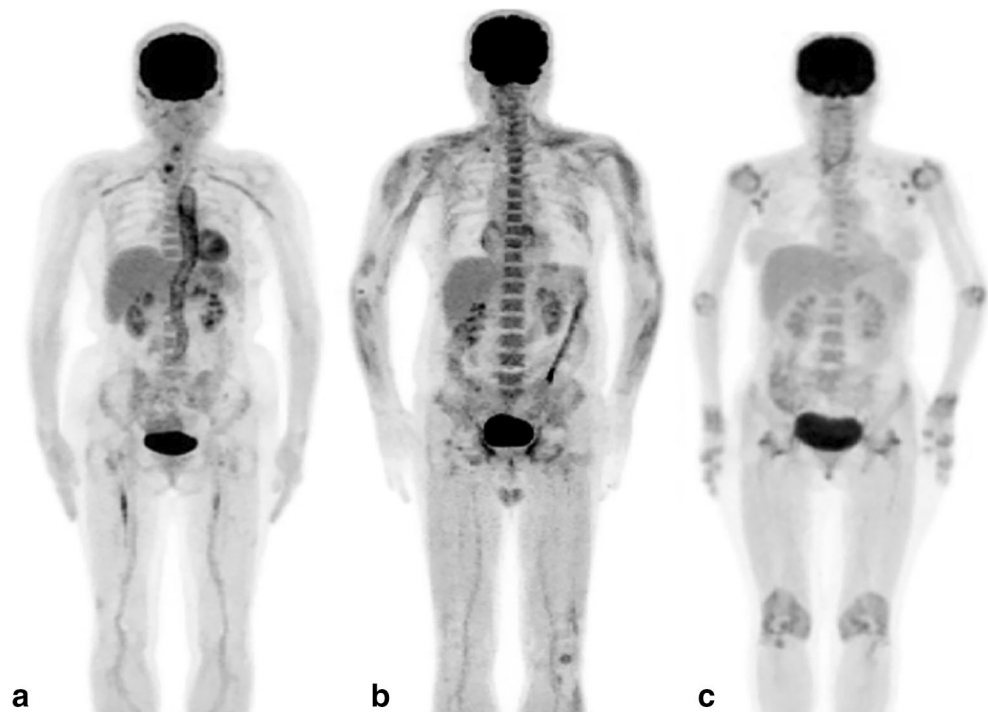
In our study, the following imaging findings were considered to be associated with the presence of AOSD: ① spleen $SUV_{max}/liver\ SUV_{max} \geq 1.2$ and/or bone marrow $SUV_{max}/liver\ SUV_{max} \geq 1.4$; ② symmetrically distributed reactive hyperplastic lymph nodes that

mainly distributed in the neck and axilla, with a lymph node $SUV_{max}/liver\ SUV_{max}$ ratio ≥ 1.8 ; and ③ no other abnormal uptake found in other organs. When two or more standards above were met, the diagnostic sensitivity, specificity, and accuracy for AOSD reached 90.7%, 92.4%, and 91.7%, respectively. According to this image diagnosis standard, there were 5 false positives and 5 false negatives. Three of the false negative patients had recently received glucocorticoid therapy. False positive patients were eventually diagnosed with undifferentiated CTD (2), idiopathic inflammatory myopathy (2), or systemic lupus erythematosus (1).

Discussion

AOSD is predisposed to middle-aged and young people [18], and its pathogenesis is not completely clear. It is generally believed that it is related to the immune mechanism triggered by inflammatory factors. Overexpression of macrophage colony-stimulating factors induces macrophage differentiation and promotes the expression of sequential pro-inflammatory factors, including IL-1b, IL-6, IL-8, IL-18, tumor necrosis

Fig. 3 FDG PET/CT images in patients with other connective tissue diseases. A abnormal uptake of FDG in large and middle blood vessels in a patient with giant cell arteritis; B abnormal muscle uptake in a patient with idiopathic inflammatory myopathy; and C abnormal synovial uptake of multiple joints in a patient with rheumatoid arthritis



factor- α (TNF- α), and interferon- γ (IFN- γ) [19, 20]. Early diagnosis of AOSD is important because treatment in time can ameliorate patients' prognosis efficiently [21]. Although Yamaguchi classification criteria could be used in the diagnosis of AOSD, malignancies, infections, and other CTDs must be excluded first in the diagnostic process. It is well-known that FDG PET/CT plays an important role in detecting malignant tumors, and it is also promising in detecting infectious lesions [13, 14]. Therefore, during the diagnosis of AOSD, FDG PET/CT could help detect or exclude malignant tumors and infectious lesions and suggest reasonable biopsy site, thus further establish the diagnosis [9–12]. Some researchers demonstrated that the FDG uptake was correlated with disease activity and could also be used to evaluate the progress of disease and therapeutic effects [9, 12, 22].

When FDG is used for inflammatory imaging, the lesion uptake of FDG is correlated with capillary dilatation and inflammatory cell infiltration [23, 24]. Previous studies suggested that patients with AOSD mainly showed multiple enlarged lymph nodes on FDG PET/CT, as well as increased diffuse FDG uptake in the spleen and bone marrow [9–11]. On the other hand, Dr. Yamashita et al. reported additional abnormal uptake in the joints, salivary glands, pericardium, and pleura in AOSD [12]. However, these studies did not clarify the morphological and distribution characteristics of lymph nodes, nor did they compare the abnormal uptake of AOSD patients with other CTD patients. Our study showed that the reported PET/CT manifestations in AOSD could also be seen in other CTDs. But AOSD usually has the following features: diffuse uptake of FDG in the spleen and bone

Table 5 FDG uptakes in patients with AOSD and patients with other CTDs

SUVmax	AOSD(54 cases)		Other CTDs(66 cases)		Control group(40 cases)	
	Range	Mean value \pm SD	Range	Mean value \pm SD	Range	Mean value \pm SD
Blood pool	0.9–1.9	1.4 \pm 0.2 ^{#*}	0.9–2.5	1.6 \pm 0.3	0.9–3.0	1.6 \pm 0.4
Liver	1.8–3.6	2.3 \pm 0.4 [#]	1.5–3.9	2.4 \pm 0.5 [#]	1.6–3.7	2.7 \pm 0.4
Spleen	1.8–6.5	3.2 \pm 1.0 ^{**}	1.1–5.0	2.3 \pm 0.7 [#]	1.0–2.5	1.8 \pm 0.3
Bone marrow	2.1–8.1	4.4 \pm 1.4 ^{**}	1.4–4.5	2.8 \pm 0.7 [#]	1.6–3.2	2.3 \pm 0.5
Lymph node ^{&}	1.6–11.1	5.1 \pm 2.6 [*]	1.3–6.7	3.0 \pm 1.3	–	–

#: There is a significant difference compared with the control group (all $P < 0.005$)

*: There is a statistical difference between AOSD patients and other CTDs patients (all $P < 0.001$)

&: This was calculated from the patients with hyperplastic lymph nodes, including 41 with AOSD and 34 with other CTDs. SUV_{max} was measured in the largest lymph node in each patient

marrow is more common and higher than other CTDs, suggesting the inflammatory responses in the above-mentioned organs were more active [25, 26]. Multiple reactive hyperplastic lymph nodes are symmetrically distributed in various lymph node regions of the body but mainly in the neck and axilla; and other organs seldomly involved. When these imaging features were used in the diagnosis of AOSD, a satisfactory diagnostic efficiency could be obtained. In fact, combining the imaging findings with the patients' clinical manifestations (such as fever, rash, sore throat, leukocytosis, elevated neutrophils, and liver dysfunction) would yield a more confident diagnosis.

The etiology of FUO includes infections, CTDs, malignancies, and some miscellaneous diseases. When PET/CT is introduced to the diagnosis process, it appears to be easy for nuclear medicine physicians to detect or exclude malignancies, since malignant tumors often showed occupying effect of malignant growth and higher FDG uptake compared with benign lesions [7]. The value of PET/CT in detecting infectious lesions has also been recognized [13, 15]. However, in CTDs, although PET/CT is positive in most of the cases, some non-focal uptake were often overlooked, or regarded as “non-specific uptake” with no diagnostic significance [27–31], such as diffuse high uptake on spleen and bone marrow. Therefore, it remains controversial whether PET/CT can be helpful for the classification of CTDs in FUO patients. Although the use of FDG PET/CT in various CTDs have been reported, such as vasculitis [8], idiopathic inflammatory myopathy [5], rheumatoid arthritis, and systemic lupus erythematosus [6], cohort studies on image characteristics and its diagnostic significance are still rare. Considering that the 32.4% of FUO patients are caused by CTDs, AOSD is the most common disease within the CTDs [7]. we investigated the significance of FDG PET/CT in early differential diagnosis of AOSD from other CTDs. Results of our study suggested that FDG PET/CT is an effective technique for early diagnosing of AOSD, and the distribution status of inflammatory lesions could provide a basis for CTDs classification. Of course, PET/CT image characteristics in other CTDs still require to be confirmed.

For AOSD patients, differential diagnosis with lymphoma should be considered. It was thought by some scholars that the radiologic findings of AOSD on FDG PET/CT were similar to lymphoma [11, 12]. However, it has been suggested from our current study that AOSD image features displayed on FDG PET/CT can be used not only to differentiate other CTDs but also to differentiate lymphoma, although the relevant analysis data was not included in the study. Based on our clinical experience, enlarged lymph nodes with different morphologic findings from reactive hyperplasia were usually found in lymphoma. In our opinion, if a FUO patient who met the Yamaguchi criteria and manifested multiple, symmetrically distributed lymph nodes with increased FDG uptake and normal structure on PET/CT, especially when a reactive

hyperplasia lymph node was demonstrated by biopsy, lymphoma should be excluded. Otherwise, it might delay the proper treatment and waste medical resources.

Compliance with ethical standards

Disclosures None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent does not apply as this is a review manuscript.

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