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ORIGINAL ARTICLE

^{18}F-FDGPET/CT in fever of unknown origin and inflammation of unknown origin: a Chinese multi-center study

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Abstract

Purpose To evaluate the clinical value of ^{18}F-FDG-PET/CT for the diagnosis of fever of unknown origin (FUO) and inflammation of unknown origin (IUO) in Chinese population, as well as the characteristics of PET/CT in different category of etiological disease.

Methods A total of 376 consecutive patients with FUO/IUO who underwent FDG-PET/CT at 12 hospitals were retrospectively studied. FDG uptake was quantitatively and visually evaluated, by using SUV_{max} and a 4-grade scale respectively. A questionnaire survey to the clinicians was used to evaluate the significance of PET/CT in diagnosing of FUO/IUO. Data analysis included the etiological distribution in the study population, image characteristics in different category of diseases, and clinical significance of PET/CT.

Results In 376 studied patients, the infectious diseases accounted for 33.0% of patients, rheumatologic diseases for 32.4%, malignancies for 19.1%, miscellaneous causes for 6.6%, and cause unknown for 8.8%. However, the etiological distribution among hospitals was varied. In addition, the etiological disease composition ratio has changed over time in China. On PET/CT examinations, 358 (95.2%) of the patients had a positive finding. Within them, local high uptake lesion was found in 219 cases, and nonspecific abnormal uptake (NAU) was found in 187 cases. FDG uptake in malignant diseases was significantly higher than in other category diseases both on SUV_{max} and visual scores (t-value range from 4.098 to 5.612, all P value < 0.001). Based on a clinical questionnaire survey, PET/CT provided additional diagnostic information for 77.4% of patients, and 89.6% of patients benefited from PET/CT examination.

Conclusions FDG PET/CT is a valuable tool for clinical diagnosis of FUO/IUO, and it is of great significance in further investigating the usefulness of PET/CT in non-neoplastic diseases.

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Keywords Fever of unknown origin (FUO) · Inflammation of unknown origin (IUO) · Positron emission tomography · Fluorodeoxyglucose

Introduction

Fever of unknown origin (FUO) and inflammation of unknown origin (IUO) are challenging conditions frequently encountered by clinicians. FUO was firstly defined by Petersdorf and Beeson as temperature above 38.3 °C on several occasions, lasting at least 3 weeks, with no ascertainable cause after a week of hospitalization [1]. With advances in medical technology and changes in the medical environment, the definition has undergone several revisions [2, 3]. In recent years, another update criterion has been suggested and defined as IUO to include those with prolonged signs of inflammation but with temperatures below 38.3 °C [4–7]. The clinical presentation of FUO and IUO might differ, but they often reflect similar disease entities [6–8]. In the search for an explanation of FUO or IUO, patients may undergo extensive and expensive investigations and medical treatment. Some of these may be invalid and unnecessarily risky. In contrast to the conventional diagnostic work-up, diagnosis of underlying disease may be improved by ^{18}F-fluorodesoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) [6–22].

However, in previous studies, the image characteristics in different kinds of disease have not been mentioned, image diagnostic criteria used in diagnosis of FUO were inconsistent, and clinical evidence of PET/CT in diagnosing FUO or IUO in Asian populations was still not sufficient. Therefore, we performed a multi-center retrospective study in Chinese population, under the auspices of the Chinese Society of Nuclear Medicine, aimed at further evaluating the clinical significance of PET/CT in diagnosing of FUO/IUO, as well as investigating the characteristics of PET/CT in different category of etiological disease.

Patients and methods

All of the participating units were asked to meet the following conditions: 1) PET/CT equipment is licensed by the Chinese health authorities, 2) quality control data of the device is registered on the nuclear medical network, 3) documents related to the FDG preparation and its safety are complete, 4) informed consent about PET/CT examination (including patient preparation and precautions, radiation exposure, etc.) can be obtained for each patient, and 5) study is approved by the hospital ethics committee. There were 12 institutions who met the above conditions and participated in the study.

A patient entering the study should meet the standard of FUO or IUO. In the current study, FUO was defined as [5]: 1) an illness of more than 3 weeks in duration, 2) temperature exceeding 38.3 °C on more than three occasions, 3) diagnosis uncertain despite appropriate investigations, after at least three outpatient visits or at least 3 days in hospital. IUO was defined as [6]: 1) an illness of at least 3 weeks' duration, 2) temperature not exceeding 38.3 °C on more than three occasions, but with a raised inflammatory marker (C-reactive protein and/or erythrocyte sedimentation rate) on more than three occasions, 3) diagnosis uncertain despite appropriate investigations, after at least three outpatient visits or at least 3 days in hospital. Between July 2016 and December 2017, a total of 376 consecutive patients were included in the study, who met the criteria of FUO or IUO and underwent FDG PET/CT examinations.

PET/CT scanners used in the study were Discovery ST/VCT (two) that were manufactured by GE Healthcare, and Biograph 16/64 (four), Biograph mCT (four) and Biograph mCT flow (two) manufactured by Siemens Healthineers. PET/CT scans were performed with a standard technique, based on the guidelines issued by Chinese Society of Nuclear Medicine (at least 4 h of fasting, blood glucose levels below 11.1 mmol/l, imaging performed 1 h after the injection of 2.96–7.77 MBq/kg of FDG) [23]. The imaging field included at least from the base of the skull to the middle of the thigh. At each hospital, PET/CT images were evaluated by two experienced nuclear medicine physicians, according to the diagnostic criteria set by the research group after discussion. It was considered as positive when any abnormal FDG uptake found on PET imaging. Lesion SUV_{max} was measured by using 3D ROI technique. If a homogeneous high uptake was found in liver or spleen, a spheroid ROI with diameter of 3.0 cm was drawn in liver or spleen parenchyma; and if a homogeneous high uptake found in spine, a cuboid ROI was drawn containing lumbar vertebraes 3 to 5. Visual evaluation with a 4-grade scale (grade 0: FDG uptake lower than the background; grade 1, equivalent to the background; grade 2, higher than background; and grade 3, very strong uptake) [24] was also used for evaluation of lesion uptake. The CT images were used to assist the reading of the PET images.

Final clinical diagnosis for each patient was established based on the laboratory examination, imaging examination, histopathologic examination, and clinical course. It was classified into five categories: infections, rheumatologic diseases, malignancies, miscellaneous causes, and cause unknown. Data analysis included the etiological distribution in the study population, image characteristics in different category of

diseases, and clinical significance of PET/CT. The significance of PET/CT in diagnosis of FUO/IUO was evaluated through a questionnaire survey to the clinicians: 1) did PET/CT provide additional new information? (yes or no), 2) did PET imaging have a clinical impact on clinical decisions? (grade 0, PET/CT findings was wrong and caused confusion; grade 1, PET/CT findings did not affect clinical decisions; grade 2, PET/CT findings did not change but increased the certainty of clinical decisions; and grade 3, PET/CT findings changed the clinical decision) [24].

With regard to the interinstitutional PET/CT system performance harmonization [25, 26], SUV measurements generated by different devices were normalized after data collection. Using a NEMA image quality control phantom, six simulated lesion spheres (diameters: 10 mm; 13 mm; 17 mm; 22 mm; 28 mm; 37 mm) with 2, 4, 8, and 16 times of background activity (background activity concentration equals 2 kBq/ml) were prepared. Images of the phantom were acquired in each participating unit with its own routine scan protocols. Correction coefficients for SUV in each lesion size and uptake concentration were obtained through this phantom study and used to standardize the SUV values to those measured with GE discovery VCT.

Statistical analysis was performed using the SPSS 16.0 software (SPSS Inc., released in 2007). Between-groups comparison of continuity variables was analyzed by Student's *t*-test. Linear correlation analysis was used to analyze the correlation between continuity variables. The chi-square test was used to compare the composition ratio between groups. Difference was considered statistically significant when $P < 0.05$.

Results

In the 376 patients, there were 195 males and 181 females; their age ranged from 4 to 91 years, with a mean age of 51.6 ± 20.1 years. Among them, 346 met the FUO standard and 30 met the IUO standard. Their course of illness ranged from 3 weeks to 416 weeks. Final clinical diagnosis and etiological classification for the 376 patients are listed in Table 1. Table 2 shows the distributions of disease category among different hospitals. It was demonstrated that infection and rheumatologic disease are the most commen causes for FUO/IUO, but the distribution of disease category among different hospitals is variable.

Histopathologic examinations were obtained in 372 of the patients (98.9%), including lymph node (217 cases), bone marrow (169 cases) and other tissues (105 cases). None of them received spleen biopsy. Among these patients, 165 underwent histopathologic examination before the PET/CT, through none obtained direct diagnostic clues. However, 105/242 of patients (43.4%) achieved etiological diagnosis through histopathologic examination performed after PET/CT, including 21 infections, six rheumatologic diseases, 65 malignancies and 13 miscellaneous diseases. Within the 217 patients underwent lymph node biopsies, nonspecific reactive hyperplasia was found in 118 (54.3%), and their etiologic diagnosis were infections (31), rheumatologic diseases (69), malignancy (three), miscellaneous (six) and unknown cause (nine). Other positive results included lymphoma (46), histiocytic necrotizing lymphadenitis (four), Castleman disease (two), Rosai–Dorfman disease (one) and lung cancer (one);

Table 1 Clinical diagnosis and etiological classification in 376 patients with FUO/IUO

Etiology classification	Case number	Proportion	Clinical diagnosis
Infection	124	33.0%	Pathogen: tubercle bacillus (19), Epstein–Barr virus (14), bacterium burgeri (8), Burkholderia cepacia (2), Salmonella gallinarum (1), spirochaeta (1), Penicillium Marneffei (1), Escherichia coli (1), Klebsiella pneumoniae (1), mycoplasma pneumoniae (1), uncertain (75)
			Infection site: lung (31), urinary tract (11), periprosthesis (7), lymphnode (4), peritoneum (3), bone (2), intestinal tract (2), ovary or uterus (2), pericardiac (1), liver (1), muscle (1), spleen (1), kidney (1), meninges (1), epididymis (1), multiple sites (17), uncertain (38)
Rheumatologic disease	122	32.4%	Adult-onset Still's disease (39), undifferentiated connective tissue disease (19), systemic vasculitis (16), idiopathic inflammatory myopathy (10), systemic lupus erythematosus (9), polymyalgia rheumatic (7), relapsing polychondritis (4), rheumatoid arthritis (3), Sjogren's syndrome (3), panniculitis (3), juvenile idiopathic arthritis (3), IgG4-related disease (2), reactive arthritis (2), ankylosing spondylitis (1), antiphospholipid syndrome (1)
Malignancy	72	19.1%	Lymphoma (56), leukemia (9), lung cancer (2), myelodysplastic syndrome (2), colon cancer (1), gastric cancer (1), hepatic cellular cancer (1)
Miscellaneous	25	6.6%	Drug allergy (11), histiocytic necrotizing lymphadenitis (4), Castleman disease (3), primary hemophagocytic syndrome (2), inflammatory bowel disease (2), Rosai–Dorfman disease (1), limbic encephalitis (1), hyperthyroidism (1)
Unknown	33	8.8%	Uncertain (33)

Table 2 Distribution of etiological diseases in different hospitals

	Cases provided	Infection	Rheumatologic disease	Malignancy	Miscellaneous	Unknown
Peking University People's Hospital	170	47 (27.6%)	78 (45.9%)	22 (12.9%)	14 (8.2%)	9 (5.3%)
Huashan Hospital	38	17 (44.7%)	12 (31.6%)	4 (10.5%)	3 (7.9%)	2 (5.3%)
Nanfang Hospital	38	9 (23.7%)	10 (26.3%)	14 (36.8%)	4 (10.5%)	1 (2.6%)
Beijing Anzhen Hospital	25	23 (92.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)
The First Hospital of China Medical University	20	5 (25.0%)	6 (30.0%)	4 (20.0%)	1 (5.0%)	4 (20.0%)
Other hospitals	85	23 (27.1%)	16 (18.8%)	27 (31.8%)	3 (3.5%)	16 (18.8%)
Total	376	124	122	72	25	33

The remaining 45 had no significant findings. In the 169 patients who underwent bone marrow smear and biopsy, 46 cases manifested as bone marrow abnormal proliferation, hemophagocytosis, or indeterminate abnormal cells, and these nonspecific findings were seen in infections (15), rheumatologic diseases (11), malignancies (12), miscellaneous diseases (three) and unknown reason (five); Other positive results included lymphoma (16), leukemia (nine) and myelodysplastic syndrome (two); the remaining 96 cases had no significant findings.

On PET/CT examinations, 358 (95.2%) patients had a positive finding. Within these patients, local high uptake lesion was found in 219 cases, including 74 of infectious diseases, 63 of rheumatologic diseases, 67 of malignancies, ten of miscellaneous causes and five of cause unknown. And nonspecific abnormal uptake (NAU) was found in 187 patients, which manifested as spleen and bone marrow diffuse high uptake and multiple reactive hyperplasia lymph nodes with high uptake and symmetrical distribution. NAU more commonly occurred in the rheumatologic disease, followed by cause unknown and miscellaneous causes (Table 3). In 74.3% (139/187) of these patients, NAU was the only positive finding on PET/CT. In patients showed NAU, multiple high uptake lymph nodes were found in 84.5% (158/187) of cases, and histopathologic evidence of nonspecific reactive hyperplasia was obtained in 82.7% (105/127) of these patients.

Table 4 shows FDG uptake in different category diseases. The FDG uptake in malignant diseases was significantly higher than in other category of diseases both on SUV_{max} and visual scores (t-value range from 4.098 to 5.612, all P value < 0.001).

Based on the clinical questionnaire survey, PET/CT provided additional diagnostic information for 291 patients (77.4%). The impact of PET/CT for the clinical decision in FUO/IUO is listed in Table 5. If G2 and G3 were considered as helpful, 89.6% of patients in the study benefited from the PET/CT examination. And PET/CT examination tended to provide more help in the diagnostic process for rheumatic disease and malignancies.

Through at least 3 months of follow-up, patients' clinical outcome was assessed as complete remission, partial remission, no change, progression of disease, or died. Complete remission rate was highest in the cause unknown group, and partial remission rate was highest in the rheumatologic disease group (Table 6).

Discussion

Establishing an etiologic diagnosis for FUO or IUO is challenging for the clinician, because they may be caused by as many as 200 potential different diseases, and most of the patients present with unspecific symptoms and few diagnostic clues. The high sensitivity and wide field imaging of PET/CT are helpful in detecting the lesions that were clinically unknown or undetected with conventional imaging techniques, and simultaneously in obtaining a multi-systematic observation. Therefore, in recent years, the diagnostic role of PET/CT in relation to FUO/IUO has been widely recognised [6–22]. ^{18}F-FDG is an indicator of increased intracellular glucose metabolism, and therefore taken up not only by malignant cells but also by those involved in infectious and inflammatory processes [8, 10]. It has been reported that FDG-PET/CT could provide clinically important information with regard to the underlying pathologic condition for between 42% and 92% of patients with FUO/IUO [19]. However, the evaluation of PET/CT diagnostic efficacy in related studies did not take into account the impact of different disease types and image interpretation criteria.

Table 3 Nonspecific abnormal uptake in different category diseases

	Infection	Rheumatologic disease	Malignancy	Miscellaneous	Unknown	Total
Case number	41	99	5	17	25	187
Proportion	33.1%	81.1%	6.9%	68.0%	75.8%	49.7%

Table 4 FDG uptake in different etiological diseases

FDG uptake		Infection	Rheumatologic disease	Malignancy	Miscellaneous	Unknown
SUV_{max}	Mean ± SD	5.4 ± 3.6	4.5 ± 3.0	9.4 ± 7.0	5.0 ± 3.3	4.3 ± 2.6
	Range	0.5~18.9	1.3~27.1	2.8~47.3	1.3~13.0	1.2~11.2
Visual score	Mean ± SD	2.3 ± 0.7	2.3 ± 0.5	2.8 ± 0.4	2.4 ± 0.8	2.1 ± 0.7
	Range	0–3	0–3	1–3	0–3	0–3

A Chinese survey has reported that in 10,201 FUO patients, the cause was infectious diseases (53.5%), rheumatologic diseases (20.1%), malignancies (12.0%), miscellaneous causes (6.4%) and cause unknown (8.2%). And it also found that the proportion of infectious diseases was decreasing and that of rheumatologic diseases and others was increasing between 1979 and 2012 [27]. However, our study showed that infection and rheumatologic disease accounted for 33.0 and 32.4% of patients respectively; this indicates that the proportion of rheumatologic diseases in Chinese FUO patients is on the rise over time. Our study also revealed a difference in the etiological distribution among hospitals due to the different medical characteristics of each hospital. In view of the fact that 95.2% of patients had a positive PET/CT, this may suggest that it is necessary to analyze the diagnostic role of PET/CT in FUO/IUO from different perspectives, especially in non-neoplastic diseases.

Many previous studies defined the focal FDG uptake as a positive PET/CT, and NAU was not given much discussion. In some literatures [8, 13–16], NAU has been considered as false-positive or non-contributing to diagnosis. However, in our study, about half of patients showed NAU on PET/CT, although this phenomenon is not present in the "EANM/SNMMI guideline for ^{18}F-FDG use in inflammation and infection" [12]. A meta-analysis showed that PET/CT had a higher diagnostic rate in the studies with a higher proportion of neoplasms and infections, but for those non-neoplastic causes, such as adult-onset Still's disease and polymyalgia rheumatica, its value was limited [28]. In the current study, we regard NAU as the positive finding for PET/CT, and the results not only have a high positive rate, but also have a positive impact on the clinical management of 89.6% of patients compared with the previous studies [24], especially for those patients with rheumatologic disease.

NAU was more commonly occurred in the rheumatologic diseases, such as adult-onset Still's disease (Fig. 1) [29, 30]. Hepatomegaly, splenomegaly, diffuse high uptake of FDG in the spine and spleen, as well as multiple reactive hyperplasia lymph nodes symmetrically distributed in the neck, axillary, and groin, just reflect the activation of the immune system and the secretion of cytokines in the procedure of inflammation [10, 31]. For FUO/IUO patients, establishing an etiologic diagnosis is often difficult when simply relying on clinical manifestation, laboratory examination, conventional imaging, and sometimes even invasive histopathological examination. Comprehensive judgment of various information is important. In this process, the role of PET/CT can be quite complex. It can help to detect or exclude malignant tumors in the initial stage, which will contribute to the etiological diagnosis or the decision of experimental treatment [32]; for certain diseases, PET/CT can also reveal the characteristic manifestations of the disease through observing lesion site and distribution, which probably may lead to final clinical diagnosis [33, 34]. Therefore, a negative or NAU on PET/CT is not always unhelpful in clinical procedure [15–17]. In fact, diagnosis of FUO/IUO in most hospitals in China involves multidisciplinary joint consultation, and this may also be the reason for the higher diagnostic rate using PET/CT obtained in this study. According to the above, we recommend NAU as a new standard of interpretation for PET/CT in diagnosis of FUO/IUO. Of course, detailed studies about the significance and presentation pattern of NAU in different types of disease are still needed.

The pathological examination results of the patients in this group show that, during the diagnostic process of FUO, pathological diagnosis has significant value for the detection of malignant lesions, but the value is limited in non-neoplastic diseases, which highlights the significance of PET/CT. Since

Table 5 Impact of FDG PET/CT for the clinical decision in FUO/IUO

Category	G0	G1	G2	G3	Total
Infection	2 (1.6%)	20 (16.1%)	80 (64.5%)	22 (17.7%)	124
Rheumatologic disease	2 (1.6%)	4 (3.3%)	96 (78.7%)	20 (16.4%)	122
Malignancy	3 (4.2%)	1 (1.4%)	35 (48.6%)	33 (45.8%)	72
Miscellaneous	0	4 (16.0%)	16 (64.0%)	5 (20.0%)	25
Unknown	1 (3.0%)	2 (6.1%)	28 (84.8%)	2 (6.1%)	33
Total	8 (2.1%)	31 (8.2%)	255 (67.8%)	82 (21.8%)	376

Table 6 Clinical outcome of patients with fever of unknown origin or inflammation or unknown origin

Clinical outcome	Infection ($n = 124$)	Rheumatologic disease ($n = 122$)	Malignancy ($n = 72$)	Miscellaneous ($n = 25$)	Unknown ($n = 33$)	Total ($n = 376$)
CR	31 (25.0%)	24 (19.7%)	5 (6.9%)	5 (20.0%)	13 (39.4%)	78 (20.7%)
PR	77 (62.1%)	86 (70.5%)	32 (44.4%)	17 (68.0%)	13 (39.4%)	225 (59.8%)
NC	4 (3.2%)	6 (4.9%)	16 (22.2%)	2 (8.0%)	7 (21.2%)	35 (9.3%)
PD	5 (4.0%)	2 (1.6%)	3 (4.2%)	–	–	10 (2.7%)
Death	7 (5.7%)	4 (3.3%)	16 (22.6%)	1 (4.0%)	–	28 (7.5%)

CR: complete remission

PR: partial remission

NC: no change

PD: progressed disease

FDG PET/CT has multiple functions in the diagnostic procedure, especially in non-neoplastic diseases, its diagnostic value in FUO/IUO cannot be fully demonstrated by simply evaluating its role in detecting malignant tumors or infectious lesions. In order to avoid non-objective judgment caused by the lack of understanding of the clinical situation by radiologists, in this study we evaluated the significance of PET/CT in FUO /IUO by using a questionnaire to the clinician according to Kubota's method [24]. Our study shows that PET/CT provided additional information for 77.4% of patients with FUO/IUO, and 89.6% patients benefited from the examination in the clinical procedure.This indicates that FDG PET/CT is a valuable tool in the diagnosis of FUO/IUO.

The PET/CT image characteristics for different categories of diseases related to the FUO/IUO have rarely been mentioned in previous studies. Our study showed that the lesion uptake of FDG in the malignancies was higher than in the other types of disease, although there were some overlaps between different types of disease. The lesion uptake of FDG combined with the structural information provided by CT may be helpful in differential diagnosis. In addition, according to the clinical follow-up, complete remission rate was highest in the patients whose etiological diagnosis was unknown, and partial remission rate was highest in the patients with rheumatologic disease. This suggested that the patients with better outcome tend to have a relative lower lesion uptake, and PET/CT may also have a potential value on the prognosis of diseases.

In conclusion, FDG PET/CT is a valuable tool for diagnosing FUO/IUO. From the current study results obtained in FUO or IUO patients, it is suggested that it is of great importance to

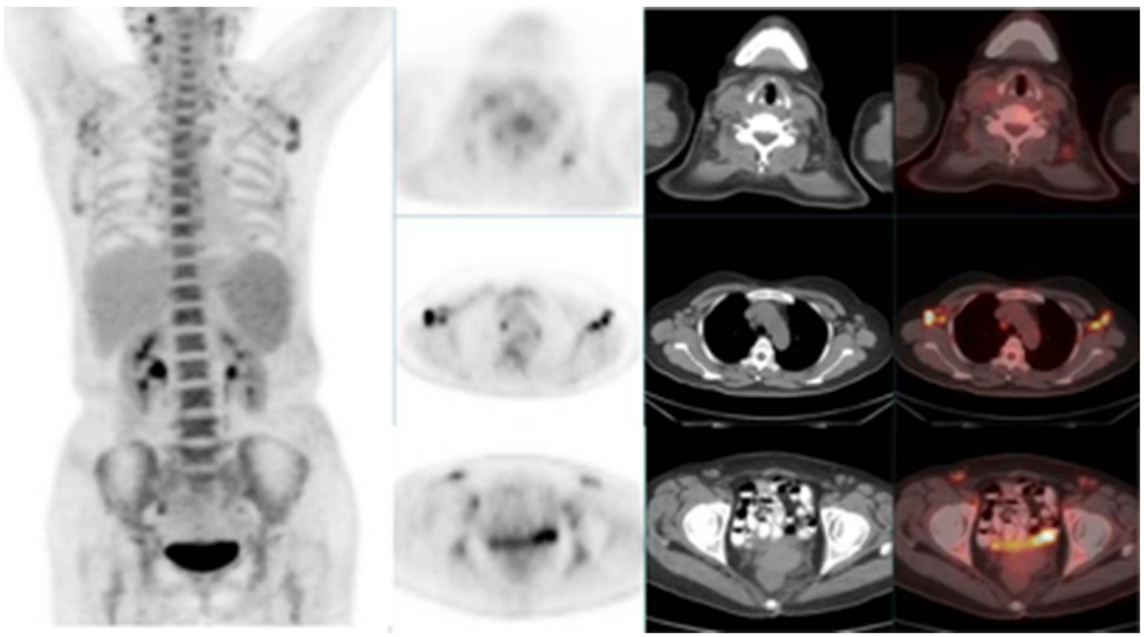

Fig. 1 FDG PET/CT images of a 28-year-old woman with FUO. FDG PET/CT show diffuse high uptake in spleen and bone marrow, and multiple reactive hyperplasia lymph nodes symmetrically distributed in bilateral neck, axillary and groin. The final clinical diagnosis is adult-onset Still's disease

further investigate the usefulness of PET/CT in non-neoplastic diseases.

Compliance with ethical standards

Conflict of interest 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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