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ORIGINAL ARTICLE

Fluorine-18 labeled fluorodeoxyglucose positron emission tomography/computed tomography used in diagnosing connective tissue diseases in fever of unknown origin/inflammatory of unknown origin patients

Ziwei Chen[1] · Yuan Li[1] · Qian Wang[1] · Shijia Weng[1] · Yunshan Zhou[2] · Jihong Zhu[3]

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Abstract

Objective To explore the significance of Fluorine-18 labeled fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in diagnosing connective tissue diseases (CTDs) in fever of unknown origin (FUO) or inflammation of unknown origin (IUO) patients.

Methods Clinical and image data of 242 consecutive FUO/IUO patients who underwent PET/CT examination and eventually diagnosed CTDs were retrospectively analyzed, including distribution of diseases, clinical characteristics, and PET/CT imaging findings. The role of FDG PET/CT in differential diagnosis of CTDs was evaluated through clinical questionnaire survey.

Results Patients diagnosed as CTDs accounted for 48.1% of FUO/IUO patients. Among them, adult-onset Still's disease was most frequently diagnosed. Other common diseases included systemic vasculitis, undifferentiated connective tissue disease, rheumatoid arthritis, idiopathic inflammatory myopathy, systemic lupus erythematosus, and polymyalgia rheumatica. On FDG PET/CT examination, 97.9% of the patients had positive findings. Inflammatory lesions were detected in 66.5% and non-specific abnormal uptakes were found in 31.4%. Detected lesions distributed consistently with corresponding susceptible organs and tissues in various diseases. Clinical questionnaire results shown that FDG PET/CT excluded malignant tumors, focal infections, or other typical CTDs in 45.5% of the patients; indicated important diagnostic clues or appropriate biopsy sites in 20.6% of patients; and directly suggested the diagnosis of a CTD in 33.1% of patients.

Conclusion FDG PET/CT could reveal inflammatory lesions in organs and tissues that reflect the clinical characteristics in different CTDs, thus providing an objective evidence for differential diagnosis, classification, and treatment decision of these diseases.

Key Points

- *FDG PET/CT is a useful tool for differential diagnosing connective tissue diseases among patients with fever of unknown origin/inflammatory of unknown origin.*

Keywords Connective tissue diseases · Fever of unknown origin · Fluorodeoxyglucose F18 · Positron emission tomography computed tomography

Fever of unknown origin (FUO) and inflammation of unknown origin (IUO) have always been challenging in clinical practice [1–3]. Connective tissue diseases (CTDs) account for a large proportion of FUO/IUO patients, and their occurrences tend to increase in years [4, 5]. Patients with CTDs who initially present as FUO/IUO often lack characteristic clinical manifestations. Malignancies or infections often need to be excluded during diagnostic process. Even in those patients with a confirmed history of CTDs, it is also necessary to determine whether the primary disease is activated or other conditions are concomitant when fever reemerged, since the long-term use of steroids and immunosuppressive agents increase the risk of concurrent tumor and infection [6–16]. The role of Fluorine-18 labeled

Ziwei Chen and Yuan Li contributed equally.

✉ Qian Wang
wangqian20135@163.com

Extended author information available on the last page of the article

fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in diagnosis of FUO has been confirmed [4, 17–19]. However, its use in differential diagnosis of CTDs in FUO/IUO patients is less reported. To further explore the significance of FDG PET/CT in identifying CTDs in FUO/IUO patients, we conducted a retrospective analysis of the clinical data of a group of FUO/IUO patients who underwent FDG PET/CT examination.

Patients and methods

Study subjects

From January 2013 to December 2019, data of 503 consecutive patients with FUO/IUO who underwent FDG PET/CT examination in Peking University People's Hospital were reviewed. Among them, 242 patients (83 males and 159 females, age 52.8 ± 19.4 years) who were eventually diagnosed as CTDs were included in the study. All patients met the FUO standard [20] (205 cases) or IUO standard [21] (37 cases). Final clinical diagnosis was established by rheumatology specialists based on the clinical manifestation, laboratory, imaging, histopathological examinations, response to treatment, as well as ≥ 6 months' clinical follow-up. The relevant data of patients were obtained through the digital information system of our hospital. Laboratory examination data within 1 week before and after the PET/CT examination could be obtained for all patients.

PET/CT imaging

Patients were fasted at least 6 h before examination, and blood glucose was controlled below 11.2 mmol/L. ^{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, image acquisition was performed using Discovery VCT PET/CT Scanner (GE Healthcare, Milwaukee, Wisconsin, USA). During acquisition, the patients lied in a supine position in the examination bed with both upper limbs placed at the sides of the body. The acquisition field included at least ranging from the base of the skull to the middle of tibia, or extended to the toe, if necessary. Images were reconstructed as three-dimensional PET, CT, and fusion images with a slice thickness of 3.3 mm. More than three experienced nuclear medicine physicians read the images together by visual judgment, observing abnormal uptake of FDG and structural changes in the collection field. Location, number, and systemic distribution of the lesions were recorded, and the nature of the lesions was determined regarding clinical manifestations and laboratory tests. In addition, one fixed nuclear medicine physician measured and recorded the lesion SUV_{max} by using three-dimensional region of interest (3D ROI) technique.

Data analysis

In this group of CTD patients with FUO/IUO, data was analyzed including the distribution of diseases, main clinical manifestations, and their imaging characteristics on FDG PET/CT. In addition, the role of FDG PET/CT in the differential diagnosis of CTDs was evaluated through the course of clinical managements as well as a clinical questionnaire survey, which was obtained from the attending physicians at the end of follow-up. In the questionnaire survey, clinical significance of FDG PET/CT was graded into four levels: G0, FDG PET/CT findings did not help or had an adverse effect on the final diagnosis; G1, FDG PET/CT findings played an important part in ruling out malignancy, focal infection, or typical rheumatologic diseases; G2, FDG PET/CT findings provided additional diagnostic clues (e.g., detecting lesions and suggesting appropriate sites for pathology examinations); and G3, FDG PET/CT revealed the etiological diagnosis directly. It was considered that G0 did not contribute to the differential diagnosis of CTD, while G1–G3 did. The impact of FDG PET/CT on diagnosis of CTD patients was analyzed and compared with that of infection and malignancy patients.

Statistical analysis

Statistical analysis in this study was carried out by SPSS 16.0 software (SPSS Inc. Released 2007). Among the different groups, Student *t* test was used to analyze the difference of mean SUV_{max}. The chi-square test was used to compare the composition ratio between groups. Difference was considered statistically significant when $P < 0.05$.

Results

The 242 patients with CTDs accounted for 48.1% of FUO/IUO patients who received FDG PET/CT examination. Clinical diagnosis of these patients was listed in Table 1. Adult-onset Still's disease was the most common disease. Other diseases included systemic vasculitis, undifferentiated connective tissue disease, rheumatoid arthritis, idiopathic inflammatory myopathy, systemic lupus erythematosus, and polymyalgia rheumatica.

Main clinical manifestations of CTD patients who featured as FUO/IUO, other than fever, were arthralgia, rash, and muscle pain or weakness. Laboratory results generally showed elevated serum C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR). However, clinical

Table 1 Final clinical diagnosis for the 242 FUO/IUO patients

Disease type	Case number	Proportion
Adult-onset Still's disease (AOSD)/juvenile idiopathic arthritis (JIA)	77(74/3)	31.82%
Systemic vasculitis	40	16.53%
Undifferentiated connective tissue disease (UCTD)	29	11.98%
Rheumatoid arthritis (RA)/remitting seronegative symmetrical synovitis with pitting edema (RS3PE)	21(12/9)	8.69%
Idiopathic inflammatory myopathy (IIM)	19	7.85%
Systemic lupus erythematosus (SLE)	17	7.02%
Polymyalgia rheumatica (PMR)	13	5.37%
Panniculitis	5	2.07%
Sjögren's syndrome	5	2.07%
Reactive arthritis	4	1.65%
Relapsing polychondritis	3	1.24%
IgG4-related disease	2	0.83%
Serum negative spinal arthritis	2	0.83%
Mixed connective tissue disease	1	0.41%
Antiphospholipid syndrome	1	0.41%
Primary biliary cholangitis	1	0.41%
SAPHO syndrome	1	0.41%
Gout	1	0.41%

manifestations of different CTDs showed various patterns (Table 2).

On FDG PET/CT examination, 237/242 (97.9%) of the patients had positive findings. In these CTD patients, tissues and organs with active inflammation showed high uptake of FDG, while some of them did not show significant structural changes. Lesion mean SUV_{max} of CTDs was significantly lower than malignancies, but no significant difference was

Table 2 Main clinical manifestations of different connective tissue diseases

Manifestations	AOSD/JIA ($n=77$)	Systemic vasculitis ($n=40$)	UCTD ($n=29$)	RA/RS3PE ($n=21$)	IIM ($n=19$)	SLE ($n=17$)	PMR ($n=13$)	Others ($n=26$)	Total ($n=242$)
Arthralgia	63	14	16	21	10	8	7	14	153
Muscle pain or weakness	22	25	7	3	16	0	13	2	88
Rash	68	7	16	5	16	7	2	4	125
Sore throat	47	6	2	1	1	2	0	1	60
Dry mouth	0	3	1	2	3	7	3	5	24
Respiratory symptoms	9	14	6	4	4	5	0	5	47
Gastrointestinal symptoms	4	11	3	2	1	6	1	5	33
Emaciation, fatigue	15	14	12	3	5	7	4	7	67
Lymphadenopathy	32	3	5	2	1	5	0	3	51
Anemia	54	32	21	16	11	16	13	17	180
Leukocytosis	51	24	6	5	5	4	6	5	106
Elevated CRP	72	40	27	18	13	13	12	21	216
Elevated ESR	73	40	26	20	15	14	13	22	223
Impaired renal function	9	15	9	8	6	11	1	7	66
Impaired liver function	45	7	13	2	11	9	1	8	96
Positive autoantibodies	14	21	21	9	16	16	7	15	119

AOSD adult-onset Still's disease, *JIA* juvenile idiopathic arthritis, *UCTD* undifferentiated connective tissue disease, *RA* rheumatoid arthritis, *RS3PE* remitting seronegative symmetrical synovitis with pitting edema, *IIM* idiopathic inflammatory myopathy, *SLE* systemic lupus erythematosus, *PMR* polymyalgia rheumatica, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate.

found between that of CTDs and infections or miscellaneous diseases (Table 3).

Inflammatory lesions were detected in 161 (66.5%) patients, and their distribution was consistent with corresponding susceptible organs and tissues in various diseases (Table 4 and Fig. 1). Non-specific abnormal uptake was found in other 76 (31.4%) patients, manifested as increased diffuse FDG uptake in spleen and bone marrow, accompanied by multiple, symmetrical distributed reactive proliferative lymph nodes. Non-specific abnormal uptake was also seen in most of the patients with detected inflammatory lesions. Negative PET/CT was found in 5 cases, including UCTD (2), systemic vasculitis (1), AOSD (1), and RS3PE (1).

Before PET/CT examination, 178 out of 242 (73.6%) patients received experimental treatments including antibiotics (126), glucocorticoid (90), and/or non-steroidal anti-inflammatory drugs (42). Histopathologic biopsies were performed in 102 (42.1%) patients, located in bone marrow 71, skin and soft tissues 25, lymph nodes 14, and other organs 8. None of the biopsy results done before PET/CT had diagnostic significance. However, after PET/CT examination, 40 patients underwent 46 times histopathologic examinations (skin and soft tissues 13, lymph nodes 11, bone marrow 7, and other organs 15), and 10 of them (21.7%) directed to determined diagnosis. In addition, 210 (86.8%) patients changed their therapeutic regimens after the PET/CT scan.

Clinical questionnaire about the role of FDG PET/CT in differential diagnosis of CTDs showed that all but two patients benefited from PET/CT examination in clinical process (Table 5). In 110 (45.5%) patients, FDG PET/CT

Table 3 FDG uptake of different disease types in FUO/IUO patients

Disease type SUV_{max}	CTDs ($n=237$)	Infection ($n=134$)	Malignancy ($n=55$)	Miscellaneous ($n=31$)	Unknown ($n=22$)
Mean ± SD	4.79 ± 2.38	5.17 ± 3.41	12.20 ± 8.13	6.48 ± 4.68	3.98 ± 1.53
Range	1.3–15.9	0.7–21	2.8–43.3	1.5–19.6	1.4–8.9
Student *t* test*	NA	$t=1.133$, $P=0.258$	$t=6.689$, $P<0.001$	$t=1.972$, $P=0.057$	$t=2.258$, $P=0.031$

FDG flurodeoxyglucose, *FUO* fever of unknown origin, *IUO* inflammatory of unknown origin, *CTDs* connective tissue diseases.

*: Compared respectively with CTD patients.

Table 4 Inflammatory lesions detected by FDG PET/CT in patients with connective tissue diseases

Disease type (cases)	Lesion locations (cases)	SUV_{max}
AOSD /JIA(77)	Joint (14), salivary gland (5), lung (1)	1.2–3.8
Systemic vasculitis(40)	Blood vessel (18), kidney (13), muscle (10), joint(6), lung(3), intestinal tract (2)	1.4–6.4
UCTD(29)	Joint (6), lung (3), salivary gland (3), muscle (2), kidney (2), serosa (2)	1.3–3.1
RA/RS3PE(21)	Joint (16), lung (3), muscle (1), salivary gland (1)	2.2–11.9
IIM(19)	Lung (13), muscles (8), skin (4), joint (4), salivary glands (1)	1.3–4.3
SLE(17)	Serosa (9), lung (4), salivary gland (4), kidney (1), join t(1), skin (1), muscle (1)	1.3–7.2
PMR(13)	Joint (13), blood vessel (3)	1.9–7.1
Panniculitis(5)	Panniculus adiposus(5), joint(2), serosa(1)	1.8–5.0
Sjögren's syndrome(5)	Salivary gland(2), lung(2)	1.3–3.5
Reactive arthritis(4)	Synovial joint(4)	2.8–3.7
Relapsing polychondritis(3)	Trachea(3), costicartilage(2), ear and nasal cartilage(2), joint(1)	3.2–7.5
IgG4-related disease(2)	Retroperitoneal soft tissue(2), joint(1)	3.8–5.4
Serum negative spinal Arthritis(2)	Synovium (1), joint surface(1)	4.0–6.9
Mixed connective tissue Disease(1)	Lung(1), skin(1)	2.8
Antiphospholipid syndrome(1)	Serous fluid(1)	0.8
Primary biliary cholangitis(1)	Salivary gland(1)	3.2
SAPHO syndrome(1)	Joint surface(1)	7.1
Gout(1)	Synovium(1)	5.3

AOSD adult-onset Still's disease, *JIA* juvenile idiopathic arthritis, *UCTD* undifferentiated connective tissue disease, *RA* rheumatoid arthritis, *RS3PE* remitting seronegative symmetrical synovitis with pitting edema, *IIM* idiopathic inflammatory myopathy, *SLE* systemic lupus erythematosus, *PMR* polymyalgia rheumatica, SUV_{max} maximum standard uptake value.

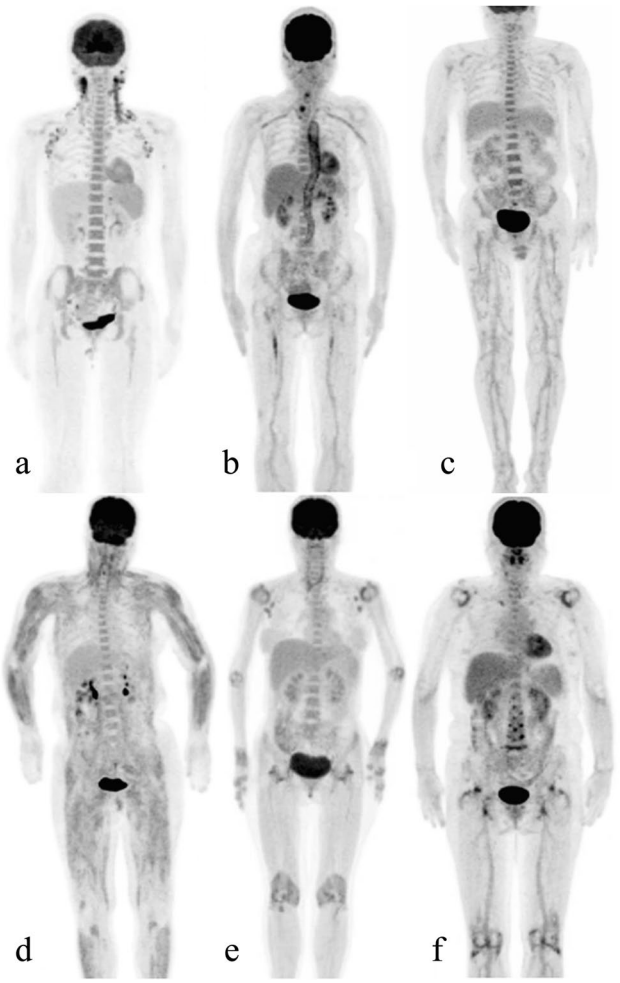

Fig. 1 FDG PET/CT images in patients diagnosed with different CTDs. A. adult-onset Still's disease, B. giant cell arteritis, C. polyarteritis nodosa, D. idiopathic inflammatory myopathy, E. rheumatoid arthritis, and F. polymyalgia rheumatica. Lesion distribution was consistent with the corresponding susceptible organs and tissues for each disease

excluded malignancies, focal infections, or other typical CTDs, and thus helped to establish a certain diagnosis. This was commonly seen in AOSD, UCTD, SLE, and Sjögren's syndrome. In 50 (20.6%) patients, PET/CT findings suggested important diagnostic clues or appropriate biopsy sites that contribute to diagnosis. In 80 (33.1%) patients, PET/CT findings could directly prompt a specific CTD, which was commonly seen in systemic vasculitis, RA, IIM, panniculitis, relapsing polychondritis, etc.

In this study, the contribution of FDG PET/CT for all of 503 FUO/IUO patients was listed in Table 6. The contribution of PET/CT with a role of G1-G3 for CTDs was higher than that for infections ($\chi^2 = 7.507$, $P = 0.006$) and similar to that for malignancies ($\chi^2 = 3.439$, $P = 0.064$).

Discussion

In recent years, incidence of CTDs in population is rising. Differential diagnosis and treatment are related to prognosis of patients [22–24]. Studies have shown that FDG PET/CT has advantages over conventional imaging techniques in detecting inflammatory lesions [18, 19, 25–31], but its significance in diagnosis of various CTDs has rarely been reported. Meanwhile, FUO/IUO is a clinically challenging diagnostic problem. Etiological diseases can be classified into infections, CTDs, malignancies, and other miscellaneous diseases. Current studies demonstrated that CTDs were main etiological reasons for FUO/IUO. Revealing the role of FDG PET/CT in CTD patients manifest as FUO/IUO is not only helpful for differential diagnosis but also of importance in treatment monitoring and prognosis assessment.

The study of FDG PET/CT imaging features in CTD patients manifested as FUO/IUO was valuable for differential diagnosis. In the current study, patients with CTDs underwent PET/CT examination mostly because lack of diagnostic clues or need to exclude malignancy, infection, and other CTDs. Usually the incidence and disease type distribution in FUO/IUO patients are related to age, sex, region, environment, and other factors [4, 17]. In our study, CTDs accounted for 48.1% of FUO patients, which is higher than previously reported [5], and more rare diseases are included. Considering this group of data were obtained from large general hospitals and had a large sample size, we believed that our results provide credible reference for those CTD patients with fever as the main clinical manifestation. In addition, as the diagnostic value of FDG PET/CT in CTDs being gradually recognized by clinicians, the number of FDG PET/CT examinations used for the differential diagnosis for FUO/IUO patient has been increasing year by year. This may also be a reason for the higher proportion of CTDs.

For now, FDG PET/CT is mainly used in diagnosis of malignant tumors. Its diagnostic value for various CTDs remains to be understood. Our study showed that in CTD patients who initially presented as FUO/IUO and underwent PET/CT examination, AOSD was the most common disease, accounting for 31.82% of the patients, followed by systemic vasculitis, UCTD, RA, IIM, SLE, PMR, etc. In FDG PET/CT images, the inflammatory lesions could be observed in the forms of high uptake of FDG, before significant structural changes could be seen. The overall distribution and pattern of the lesions usually corresponded with the clinical characteristics of respective diseases, which were also obviously different from the image manifestations of malignant tumors or infectious diseases [25, 27, 28, 30]. The SUV might contribute to differentiate

Table 5 Role of FDG PET/CT in differential diagnosis of different types of connective tissue diseases

Diseases (cases)	G0 Cases (%)	G1 Cases (%)	G2 Cases (%)	G3 Cases (%)
AOSD/JIA(77)	1(1.3)	67(87.0)	6(7.8)	3(3.9)
Systemic vasculitis(40)	1(2.5)	4(10.0)	7(17.5)	28(70.0)
UCTD(29)	0(0.0)	18(62.1)	9(31.0)	2(6.9)
RA/RS3PE(21)	0(0.0)	2(9.5)	9(42.9)	10(47.6)
IIM(19)	0(0.0)	3(15.8)	8(42.1)	8(42.1)
SLE(17)	0(0.0)	10(58.8)	2(11.8)	5(29.4)
PMR(13)	0(0.0)	0(0.0)	3(23.1)	10(76.9)
Systemic panniculitis(5)	0(0.0)	0(0.0)	0(0.0)	5(100.0)
Sjögren's syndrome(5)	0(0.0)	4(80.0)	1(20.0)	0(0.0)
Reactive arthritis(4)	0(0.0)	0(0.0)	2(50.0)	2(50.0)
Relapsing polychondritis(3)	0(0.0)	0(0.0)	0(0.0)	3(100.0)
IgG4-related disease(2)	0(0.0)	0(0.0)	1(50.0)	1(50.0)
Serum negative spinal arthritis(2)	0(0.0)	0(0.0)	1(50.0)	1(50.0)
Mixed connective tissue disease(1)	0(0.0)	0(0.0)	1(100.0)	0(0.0)
Antiphospholipid syndrome(1)	0(0.0)	1(100.0)	0(0.0)	0(0.0)
Primary biliary cholangitis(1)	0(0.0)	1(100.0)	0(0.0)	0(0.0)
SAPHO syndrome(1)	0(0.0)	0(0.0)	0(0.0)	1(100.0)
Gout(1)	0(0.0)	0(0.0)	0(0.0)	1(100.0)
Total	2(0.8)	110(45.5)	50(20.6)	80(33.1)

AOSD adult-onset Still's disease, *JIA* juvenile idiopathic arthritis, *UCTD* undifferentiated connective tissue disease, *RA* rheumatoid arthritis, *RS3PE* remitting seronegative symmetrical synovitis with pitting edema, *IIM* idiopathic inflammatory myopathy, *SLE* systemic lupus erythematosus, *PMR* polymyalgia rheumatica.

Table 6 Role of FDG PET/CT in differential diagnosis of FUO/IUO

Category (cases)	G0 Cases (%)	G1 Cases (%)	G2 Cases (%)	G3 Cases (%)
CTDs (242)	2(0.8)	110(45.5)	50(20.6)	80(33.1)
Malignancies (54)	3(5.6)	0(0.0)	16(29.6)	35(64.8)
Infections (147)	9(6.1)	48(32.7)	54(36.7)	36(24.5)
Other (60)	6(10.0)	25(41.7)	23(38.3)	6(10.0)
Total (503)	20(4.0)	183(36.4)	143(28.4)	157(31.2)

CTDs from malignancies. However, within inflammatory lesions, such as infectious diseases, miscellaneous diseases, and various kinds of CTDs, the SUV of lesions overlaps greatly. Although the diagnostic value of FDG PET/CT in specific CTDs remains to be confirmed, it can be seen from this study that different image patterns could be found in PET/CT for different CTDs. In some patients, active inflammatory lesions detected by FDG PET/CT were asymptomatic and hard to detect by routine imaging; thus FDG PET/CT provided more evidence for diagnosis and clinical classification of CTDs. With the help of FDG PET/CT combined with clinical data, many difficult cases could be diagnosed correctly. Previous studies have also shown that FDG PET/CT had multi-level significance in diagnosis of inflammatory diseases, including detecting or excluding malignant tumors, revealing lesions that indicated diagnostic clues and appropriate biopsy sites, and providing evidence for experimental treatment [4, 17, 32–34]. And this multi-level diagnostic significance highlights its advantages in the diagnosis of CTDs.

In the study, the value of FDG PET/CT in differential diagnosis of CTDs was confirmed by the course of management and clinical questionnaire survey. Although histopathologic biopsies yielded relatively low diagnostic capacity in CTDs [4], PET/CT suggested more non-routine biopsy sites and improved the diagnostic significance of biopsies. Meanwhile, it played an important role on tailoring the treatment strategies. By the clinical questionnaire survey, FDG PET/CT detected inflammatory lesions that indicated important diagnostic clues or appropriate biopsy sites in 20.6% of patients and directly suggested a specific diagnose in 33.1% of patients. Even non-specific abnormal uptake on FDG PET/CT which was once considered to be of no diagnostic significance [33–37] actually played a diagnostic role in excluding other diseases. In our study, 45.5% of patients benefited this way, therefore receiving proper diagnosis and treatment. The contribution of FDG PET/CT in clinical diagnosis of CTD patients was significantly better than infection patients and was not inferior to malignancy patients. This implied that FDG PET/CT could be as helpful for rheumatologists as oncologists. In fact, as physicians started to

realize the important role of FDG PET/CT in clinical practice, its use in diagnosis of CTDs had been increasing and is no longer limited to the differential diagnosis of FUO/IUO.

In our study, it was demonstrated that FDG PET/CT could reveal the inflammatory lesions in organs and tissues that reflect the clinical characteristics of different CTDs, thus providing an objective evidence for differential diagnosis, classification, and treatment decision in CTDs. We believe that the combination of clinical and imaging features may provide diagnostic criteria with higher performance. However, this work is difficult to fully explain in this study because of the inclusion of multiple types of CTDs, and this is also the inadequacy of this research. Future studies on different types of CTD need to be carried out.

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Data transparency All data and materials of this study support the published claims and comply with field standards.

Declarations

Ethics approval The study has been approved by the ethics committee of Peking University People's Hospital and havs therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate All participants provided written informed consent to be included in the study and their aggregated data to be used for scientific publications.

Consent for publication All authors have previously given their agreement for publication of the article with an agreement form to the Clinical Rheumatology Journal.

Conflict of interest The authors declare no competing interests.

References

1. Mourad O, Palda V, Detsky AS (2003) A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med 163(5):545–551
2. Cunha BA (2007) Fever of unknown origin: focused diagnostic approach based on clinical clues from the history, physical examination, and laboratory tests. Infect Dis Clin North Am 21(4):1137–1187
3. Fusco FM, Pisapia R, Nardiello S, Cicala SD, Gaeta GB, Brancaccio G (2019) Fever of unknown origin (FUO): which are the factors influencing the final diagnosis? A 2005–2015 systematic review. BMC Infect Dis 19(1):653
4. Wang Q, Li YM, Li Y, Hua FC, Wang QS, Zhang XL et al (2019) (18)F-FDG PET/CT in fever of unknown origin and inflammation of unknown origin: a Chinese multi-center study. Eur J Nucl Med Mol Imaging 46(1):159–165
5. Tan X-y, He Q-y. [Chinese literature review of etiology distribution of adult patients with fever of unknown origin from 1979 to 2012]. [article in Chinese] Zhonghua Nei Ke Za Zhi 2013;52(12):1013–7.
6. Zhou WJ, Yang C-D (2009) The causes and clinical significance of fever in systemic lupus erythematosus: a retrospective study of 487 hospitalised patients. Lupus 18(9):807–812
7. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P et al (2003) Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine 82(5):299–308
8. Jallouli M, Frigui M, Marzouk S, Mâaloul I, Kaddour N, Bahloul Z (2008) Infectious complications in systemic lupus erythematosus: a series of 146 patients. Rev Med Interne 29(8):626–631
9. De Cock D, Hyrich K (2018) Malignancy and rheumatoid arthritis: Epidemiology, risk factors and management. Best Pract Res Clin Rheumatol 32(6):869–886
10. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE (2002) Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis rheum 46(9):2287–2293
11. Turesson C (2016) Comorbidity in rheumatoid arthritis. Swiss Med Wkly 146:w14290
12. Partington R, Helliwell T, Muller S, Abdul Sultan A, Mallen C (2018) Comorbidities in polymyalgia rheumatica: a systematic review. Arthritis Res Ther 20(1):258
13. Tiniakou E, Mammen AL (2017) Idiopathic inflammatory myopathies and malignancy: a comprehensive review. Clin Rev Allergy Immunol 52(1):20–33
14. Turesson C, Matteson EL (2013) Malignancy as a comorbidity in rheumatic diseases. Rheumatology (Oxford) 52(1):5–14
15. Di Franco M, Lucchino B, Spaziante M, Iannuccelli C, Valesini G, Iaiani G (2017) Lung Infections in systemic rheumatic disease: focus on opportunistic infections. Int J Mol Sci 18(2):293
16. Bernatsky S, Boivin JF, Joseph L, Rajan R, Zoma A, Manzi S et al (2005) An international cohort study of cancer in systemic lupus erythematosus. Arthritis Rheum 52(5):1481–1490
17. Kubota K, Nakamoto Y, Tamaki N, Kanegae K, Fukuda H, Kaneda T et al (2011) FDG-PET for the diagnosis of fever of unknown origin: a Japanese multi-center study. Ann Nucl Med 25(5):355–364
18. Li Y, Wang Q, Wang X, Li X, Wu H, Wang Q et al (2020) Expert Consensus on clinical application of FDG PET/CT in infection and inflammation. Ann Nucl Med 34(5):369–376
19. Jamar F, Buscombe J, Chiti A, Christian PE, Delbeke D, Donohoe KJ et al (2013) EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. J Nucl Med 54(4):647–658
20. Knockaert DC, Vanderschueren S, Blockmans D (2003) Fever of unknown origin in adults: 40 years on. J Intern Med 253(3):263–275
21. Vanderschueren S, Del Biondo E, Ruttens D, Van Boxelaer I, Wauters E, Knockaert DD (2009) Inflammation of unknown origin versus fever of unknown origin: two of a kind. Eur J Intern Med 20(4):415–418
22. Witte T (2018) Sjögren's Syndrome: Early diagnosis and effective treatment. Dtsch Med Wochenschr 143(24):1778–1782
23. Doria A, Zen M, Canova M, Bettio S, Bassi N, Nalotto L et al (2010) SLE diagnosis and treatment: when early is early. Autoimmun Rev 10(1):55–60
24. Schneider M, Krüger K (2013) Rheumatoid arthritis–early diagnosis and disease management. Dtsch Arztebl Int 110(27–28):477–484
25. Kubota K, Yamashita H, Mimori A (2017) Clinical value of FDG-PET/CT for the evaluation of rheumatic diseases: rheumatoid arthritis, polymyalgia rheumatica, and relapsing polychondritis. Semin Nucl Med 47(4):408–424

26. Hess S, Hansson SH, Pedersen KT, Basu S, Hoilund-Carlsen PF. FDG-PET/CT in infectious and inflammatory diseases. PET Clin 2014;9(4):497–519, vi-vii.
27. Bosnic D, Baresic M, Padjen I, Balenovic A, Zarkovic K, Anic B (2013) Fever of unknown origin: large vessel vasculitis diagnosed by PET/CT. Rheumatol Int 33(9):2417–2421
28. Li Y, Zhou Y, Wang Q (2017) Multiple values of (18)F-FDG PET/CT in idiopathic inflammatory myopathy. Clin Rheumatol 36(10):2297–2305
29. Kubota K, Ito K, Morooka M, Minamimoto R, Miyata Y, Yamashita H et al (2011) FDG PET for rheumatoid arthritis: basic considerations and whole-body PET/CT. Ann N Y Acad Sci 1228(1):29–38
30. Zhou X, Li Y, Wang Q (2020) FDG PET/CT used in identifying adult-onset Still's disease in connective tissue diseases. Clin Rheumatol 39(9):2735–2742
31. Lei W, Zeng H, Zeng D-X, Zhang B, Zhu Y-H, Jiang J-H et al (2016) (18)F-FDG PET-CT: a powerful tool for the diagnosis and treatment of relapsing polychondritis. Br J Radiol 89(1057):20150695
32. Sheng JF, Sheng ZK, Shen XM, Bi S, Li JJ, Sheng GP et al (2011) Diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with fever of unknown origin. Eur J Intern Med 22(1):112–116
33. Gafter-Gvili A, Raibman S, Grossman A, Avni T, Paul M, Leibovici L et al (2015) [18F]FDG-PET/CT for the diagnosis of patients with fever of unknown origin. QJM 108(4):289–298
34. Tokmak H, Ergonul O, Demirkol O, Cetiner M, Ferhanoglu B (2014) Diagnostic contribution of (18)F-FDG-PET/CT in fever of unknown origin. Intern J Infect Dis 19:53–58
35. Schonau V, Vogel K, Englbrecht M, Wacker J, Schmidt D, Manger B et al (2018) The value of (18)F-FDG-PET/CT in identifying the cause of fever of unknown origin (FUO) and inflammation of unknown origin (IUO): data from a prospective study. Ann Rheum Dis 77(1):70–77
36. Keidar Z, Gurman-Balbir A, Gaitini D, Israel O (2008) Fever of unknown origin: the role of 18F-FDG PET/CT. J Nucl Med 49(12):1980–1985
37. Ergül N, Halac M, Cermik TF, Ozaras R, Sager S, Onsel C et al (2011) The diagnostic role of FDG PET/CT in patients with fever of unknown origin. Mol Imaging Radionucl Ther 20(1):19–25

Authors and Affiliations

Ziwei Chen[1] · Yuan Li[1] · Qian Wang[1] · Shijia Weng[1] · Yunshan Zhou[2] · Jihong Zhu[3]

Ziwei Chen
chenziwei@bjmu.edu.cn

Yuan Li
liyuan0007@163.com

Shijia Weng
scarrita@163.com

Yunshan Zhou
yunshanzhou17@163.com

Jihong Zhu
zhujihong64@sina.com

[1] Department of Nuclear Medicine, Peking University People's Hospital, No.11 Xizhimen South Street, Xicheng District, Beijing 100044, China

[2] Department of Rheumatology and Immunology, Peking University People's Hospital, No.11 Xizhimen South Street, Xicheng District, Beijing 100044, China

[3] Department of Emergency, Peking University People's Hospital, No.11 Xizhimen South Street, Xicheng District, Beijing 100044, China