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[18F]FDG-PET/CT for the diagnosis of patients with fever of unknown origin

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Summary

Background and aims: The diagnosis of patients with fever of unknown origin (FUO) remains a challenging medical problem. We aimed to assess the diagnostic contribution of 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/computed tomography (CT) for the evaluation of FUO.
Methods: We performed a 4-year retrospective single-center study of all hospitalized patients that underwent FDG-PET/CT for evaluation of FUO. The final diagnosis of the febrile disease was based on clinical, microbiological, radiological and pathological data available at the final follow-up. Predictors for a contributory exam were sought.
Results: One hundred and twelve patients underwent FDG-PET/CT for the investigation of FUO in the years 2008–2012 and were included in the study. A final diagnosis was determined in 83 patients (74%) and included: infectious disease in 49 patients (43%), non-infectious inflammatory disease in 17 patients (16%), malignancies in 15 patients (14%), other diagnoses in 2 patients (1.7%), FUO resolved with no diagnosis and no evidence of disease during a 6-month follow-up in 23 patients (20%), and death with fever and with no diagnosis in 6 patients (5%). Seventy-four FDG-PET/CT studies (66%) were considered clinically helpful and contributory to diagnosis (46% positive contributory value and 20.5% contributory to exclusion of diagnosis). PET/CT had a sensitivity of 72.2%, a specificity of 57.5%, a positive predictive value (PPV) of 74.2% and a negative predictive value (NPV) of 53.5%. On multivariable analysis, significant predictors of a positive PET/CT contributory to diagnosis were a short duration of fever and male gender.
Conclusions: PET/CT is an important diagnostic tool for patients with FUO.

Background

Fever of unknown origin (FUO) is a condition that presents a diagnostic challenge, despite recent advances in diagnostic techniques.[1–4] The most prevalent causes of FUO are infections, non-infectious inflammatory processes and malignancies.[5,6] The rate of undiagnosed cases had varied widely ranging from 9 to 50%.[2,5,7–9] Conventional anatomic imaging modalities such as ultrasound (US), computed tomography (CT) and magnetic resonance imaging are usually used as the primary diagnostic modality, but have limited sensitivity and specificity, mainly during early stages of the disease. The use of nuclear

medicine techniques in the evaluation of patients with FUO is appealing because they are indicative of functional and metabolic status and may detect focal pathologic changes before morphologic changes may become apparent.[2]

18-Fluoro-2-deoxy-D-glucose positron emission tomography ($^{[18F]}$FDG-PET) is an important aid in the investigation of FUO.[7] $^{[18F]}$FDG is taken up by metabolically active cells with high glucose consumption: neutrophils, lymphocytes and activated macrophages.[10] It accumulates in malignant tissues and at sites of infection and inflammation. When combined with contrast enhanced CT (PET/CT), more precise localization and characterization of the pathological FDG uptake is possible. This can potentially improve diagnostic accuracy.

Aims

Our study aimed to assess the role of FDG-PET/CT as a diagnostic tool for patients with FUO, in a single center retrospective series, and to find predictors for a contributory exam.

Patients and methods

Participants

Study population included all adult hospitalized patients investigated for FUO by FDG PET/CT in the nuclear medicine department at Rabin Medical center, Israel, in the years 2008–2012. The center is a university affiliated, primary and tertiary care center for adult patients (>18 years). Patients were identified as FUO by reviewing all FDG-PET/CT referrals for hospitalized patients. We included patients fulfilling the 'classical FUO' definition by Petersdorf of fever over 38.3°C (101°F) lasting more than 3 weeks without reaching a diagnosis after a 1-week inpatient or outpatient workup,[11] or fulfilling the revised criteria of a diagnostic workup after a 3-day hospital stay or three outpatient visits or 1 week of 'intelligent and invasive' ambulatory investigation.[12] Patients with nosocomial, neutropenic and human immunodeficiency virus-associated fever were excluded.

All patients underwent a basic clinical assessment for fever that included medical history, physical examination, routine laboratory tests (blood count, C-reactive protein, erythrocyte sedimentation rate, blood cultures, infectious serology) and chest X-ray. Further imaging tests such as US, CT, echocardiography, etc. were conducted at the discretion of the treating physician. Data were retrospectively collected by reviewing the electronic patient files. We reviewed patient data from the time of study entry until the latest available follow-up (at least 6 months after discharge) or death. Data included all baseline demographics, comorbidity, clinical, laboratory, microbiological and radiological findings, all antimicrobial treatment and interventions and the final diagnosis given by the treating physician. The study was approved by the local ethics committee.

PET-CT acquisition

$^{[18F]}$-FDG PET/CT was performed using an integrated PET/CT scanner (Discovery STE, GE Medical Systems, Milwaukee WI). $^{[18F]}$FDG dose varied from 370 to 666 MBq (10–18 mCi) according to patient's weight and 800–1000 ml of diluted iodinated contrast material was administered orally for bowel opacification. Chest CT was performed with patients asked to hold their breath with tube voltage of 120 kVp, spiral CT at 0.8 s per rotation, 100 mAs, section thickness of 3.75 mm and 3.75 mm interval with image reconstruction every 2.5 mm. Contrast-enhanced CT was performed from skull base to mid-thigh with tube voltage of 120 kVp, spiral CT at 0.8 s per rotation with modulated 40–300 mAs, section thickness of 3.75 mm and 3.75 mm interval with image reconstruction every 2.5 mm. Iodine contrast media (Ultravist 300; iopromide 0.623 g/ml, Bayer Schering Pharma AG, Berlin, Germany; 1.5 cm^3/kg) was intravenously administered in all examinations, except for patients with iodine hypersensitivity and renal insufficiency. PET emission images were obtained using a weight-based protocol, with 2–3 min of acquisition time per bed position. Five-to-six bed positions from skull base to mid-thigh resulted in an acquisition time of 18–24 min. All PET images were reconstructed using an iterative algorithm, with CT-based attenuation correction applied.

All images were evaluated by a radiology and nuclear medicine expert. PET/CT evaluators were unaware to the patients' final diagnosis.

Interpretation of and analysis of PET/CT results

Studies showing at least one area of pathological FDG uptake were defined as PET positive. Studies showing FDG activity only in areas of the physiologic tracer biodistribution or no sites of increased uptake were considered negative.

Results of PET/CT were evaluated for their diagnostic contribution. A PET/CT study demonstrating a focal, localized disease process further confirmed by additional conventional techniques as representing the cause of FUO was considered as contributory for diagnosis and defined as true-positive (TP).

A PET/CT study showing normal findings was regarded as contributory in excluding focal disease and defined as true-negative (TN) when no localized disease process was further diagnosed, the patient

was discharged from the hospital with no fever; and there was no evidence of disease following 6 months of clinical follow-up. PET/CT was considered non-contributory in the following situations:

A PET/CT study with no suggestive foci was defined as false-negative (FN) when a focal disease process was found within a 6-month interval or the patient died with fever and with no diagnosis.

Abnormal findings in a patient with no final diagnosis of a focal disease process or with pathology identified in a location different from the site demonstrated on PET/CT was defined as non-contributory and false positive (FP).

Final diagnosis

The reference standard was the final diagnosis of FUO at the latest follow-up available, at least 6 months after discharge. The final diagnosis was adjudicated by two specialists in internal medicine that reviewed all clinical, microbiological, radiological data and pathological data available at the final follow-up. Thus, the diagnosis was never based on PET/CT results alone. Final diagnoses were classified as infectious; non-infectious inflammatory; malignancies; other; resolution of FUO without diagnosis (e.g. spontaneous resolution with no further evidence of disease) and no diagnosis with persistence of fever or death.

Statistical analysis

Sensitivity and specificity of PET/CT were calculated per standard definitions, examining whether findings compatible with the diagnosis were observed on examination. We performed univariate and multivariate analyses to identify variables associated with a positive contributory finding on PET/CT (TP results). We compared demographic data, findings on physical examination and laboratory findings between TP results and all other results. Dichotomous variables were examined by chi-square test or Fisher's exact test. Continuous variables were described as means with standard deviation, compared using a T-test (for normally distributed parameters) or as medians and range, compared with the Mann Whitney U test (for other distributions). All of the variables found to be significantly or borderline significantly associated with a TP result on univariate analysis were entered into a forward step logistic regression analysis. Model fit was assessed using the Hosmer and Lemeshow Test and calibration was described by the area under the receiver-operating characteristics curve. Odds ratios (ORs) for TP result with 95% confidence intervals (CIs) are reported. Statistical analysis was performed using PASW Statistics 17 (SPSS Inc., Chicago, IL).

Results

Study population and final diagnosis

Between January 2008 and December 2012, 722 hospitalized patients underwent PET/CT. We reviewed 146 referrals due to fever and excluded 34 exams that did not fulfill inclusion criteria (of them: 6 neutropenic fever, 13 nosocomial fever, 12 no fever and 3 patients in which the source of fever was known).

Thus, 112 patients that underwent PET/CT for classic FUO were included in the analysis. Sixty-two patients underwent a contrast-enhanced CT, compared with 50 in whom contrast was not injected. Reasons for not receiving contrast included renal failure or hypersensitivity to iodine. Characteristics of patients are depicted in Table 1.

A final diagnosis was determined in 83 patients (74%). Infectious disease was diagnosed in 49 patients (43%), non-infectious inflammatory disease in 17 patients (16%), malignancies in 15 patients (14%), other diagnoses in 2 patients (1.7%), FUO resolved with no diagnosis and no evidence of disease during a 6-month follow-up in 23 patients (20%), and death with fever and with no diagnosis in six patients (5%).

PET/CT results

A total of 69 PET/CT studies demonstrated pathological FDG uptake and were considered abnormal. In 52 patients PET/CT results were abnormal, established the cause of FUO and were thus considered TP. In 17 patients, they were abnormal and considered FP. PET/CT showed no pathological FDG uptake in 43 cases (23 of them were considered TN and 20 were considered FN). This yielded a sensitivity of 72.2%, a specificity of 57.5%, a PPV of 74.2% and a NPV of 53.5%.

Seventy-four studies (66%) were considered clinically helpful and contributory to diagnosis. The 52 cases of TP had positive contributory value (46%) and the 23 cases (20.5%) of TN were contributory to exclusion of diagnosis. Table 2 depicts the PET/CT results according to the final diagnoses.

Of note, in the 62 patients who underwent contrast-enhanced CT, the TP rate was 51% (32/62) and the FP rate was 13% (8/62). In the 50 patients in whom contrast was not injected, the TP rate was 40% (20/50) and the FP rate was 18% (9/50).

Positive contributory PET/CT studies (TP)

Fifty-two studies were TP. There were 31 cases of infections (60% of all TP). These included seven

cases of pneumonia, 11 cases of infective endocarditis or other endovascular infections (endocarditis 4, aortitis 1, infected aortic graft 2, infected femoral graft 2, infected pacemaker 2, infected stent in pulmonary artery 1), four cases of infected transplanted kidney and one case of pyelonephritis in a native kidney, two cases of septic arthritis and one case of osteomyelitis, one case of liver abscesses, one epidural abscess, one cytomegalovirus (CMV) colitis, one case of tuberculosis and one case of multiple nocardial abscesses. PET/CT results of four of these cases are presented in Figures 1–4.

There were 14 cases of malignancies (27% of all TP). Because there were 15 cases of malignancies, this showed that PET/CT was contributory to diagnosis of malignancies in 93% (14/15) of the cases. Of them, nine were non-Hodgkin's lymphoma, two were Hodgkin's lymphoma, two were lung carcinoma and one was a sarcoma. In nine of them, the FUO was the initial presentation of malignancy and in six cases the FUO represented a relapse. Notably, the four non-infectious inflammatory diseases included acute pericarditis, two exacerbations of Crohn's disease and one case of hemophagocytic syndrome. In the two cases of Crohn's disease, the pathological FDG uptake led to a colonoscopy that revealed active inflammation on biopsy, consistent with Crohn's disease. CT was performed in 23 of 51 cases of a TP PET/CT. The PET/CT contributed more than the total body CT in 12/23 of cases (52%).

Table 1 Baseline characteristics of included patients with FUO

Characteristic	*N* (%)
Number of patients	112
Age, median (range)	60 (19–94)
Gender (M/F)	57/55
Underlying diseases and medications	
Diabetes mellitus	28 (25%)
Renal failure	29 (26%)
Solid organ transplant	21 (18.7%)
Collagen disease	2 (1.7%)
Malignancy	23 (20.5%)
Previous chemotherapy	9 (8%)
Previous steroids	30 (27%)
Data regarding the febrile episode	
Median duration of fever before hospitalization (range)	26 days (4–210)
Maximal fever	39°C (37.5 –40.5°C)
Other diagnostic tests performed	
CT	60 (54%)
Echocardiogram	70 (62.5%)
Abdominal US	82 (73%)
Infectious serology	85 (75%).
Bone scan	4 (3.5%)
Gallium scan	2 (1.7%)

Predictors of positive contributory PET/CT findings

Of all variables entered into the univariate analysis, the only variables found to be significantly correlated with positive contributory PET/CT results were male sex, presence of a rash and number of days of fever before the PET/CT, with a median of 19 days (4–90) for a positive contributory PET/CT vs. a median of 30 days (7–210) for all other results (Table 3). There was a trend towards a difference in lymphadenopathy (four patients with a positive contributory vs. 10 with all other results). These four variables were entered into the forward regression analysis, and the only two that remained predictive of a positive contributory result were male sex and number of days of fever the PET/CT (Table 4).

Table 2 Results of PET/CT according to final diagnoses

Diagnostic Category	PET/CT abnormal		PET/CT normal		No. of patients
	TP, contributory to diagnosis	FP, non-contributory	TN, contributory to exclusion	FN, non-contributory	
Infection	31	4	6	8	49 (43%)
Non-infectious inflammatory diseases	4	5	1	7	17 (16%)
Malignancies	14	0	0	1	15 (14%)
Miscellaneous	2	0	0	0	2 (1.7%)
FUO resolved, no diagnosis	1	6	16	0	23 (20%)
Patient died with no diagnosis	0	2	0	4	6 (5%)
Total (%)	52 (46.4%)	17 (15%)	23 (20.5%)	20 (18%)	112

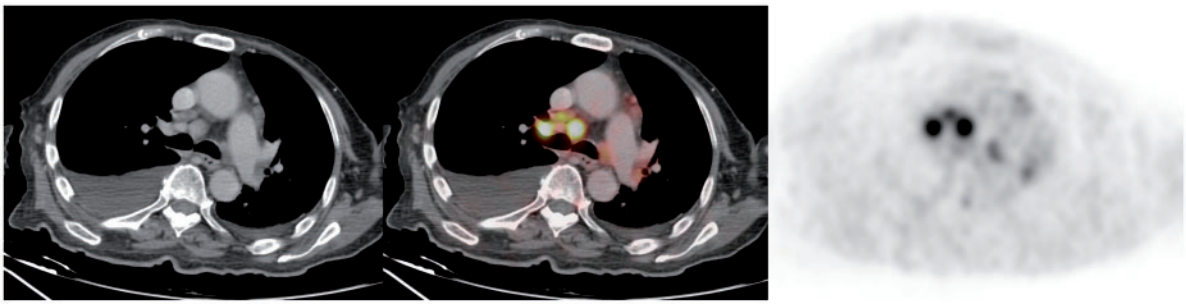

Figure 1. An 80-year-old man, who was diagnosed with chronic lymphocytic leukemia (CLL) 13 years earlier, was admitted due to 2 months of fever, weight loss and night sweats. PET/CT demonstrated mediastinal and hilar lymphadenopathy up to 2.5 cm with pathological FDG uptake. A mediastinoscopy and lymph node biopsy demonstrated caseating granulomas and Ziehl Neelsen staining showed acid fast bacilli and no evidence of CLL. A diagnosis of tuberculosis was confirmed and antituberculosis therapy was commenced.

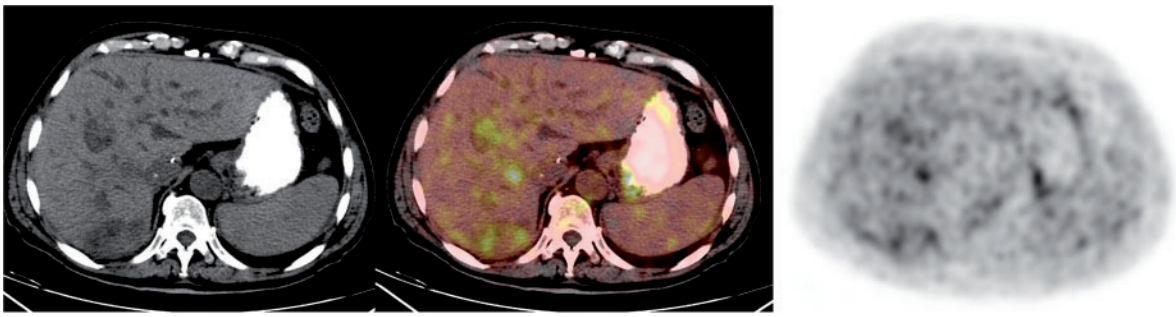

Figure 2. A 65-year-old man, who underwent liver transplant 8 months earlier, was admitted due to 3 weeks of fever. Abdominal US demonstrated multiple hypodensic lesions, which were found to have high FDG uptake on PET/CT. A diagnosis of liver abscesses was made, and broad spectrum antibiotics were administered for a prolonged duration.

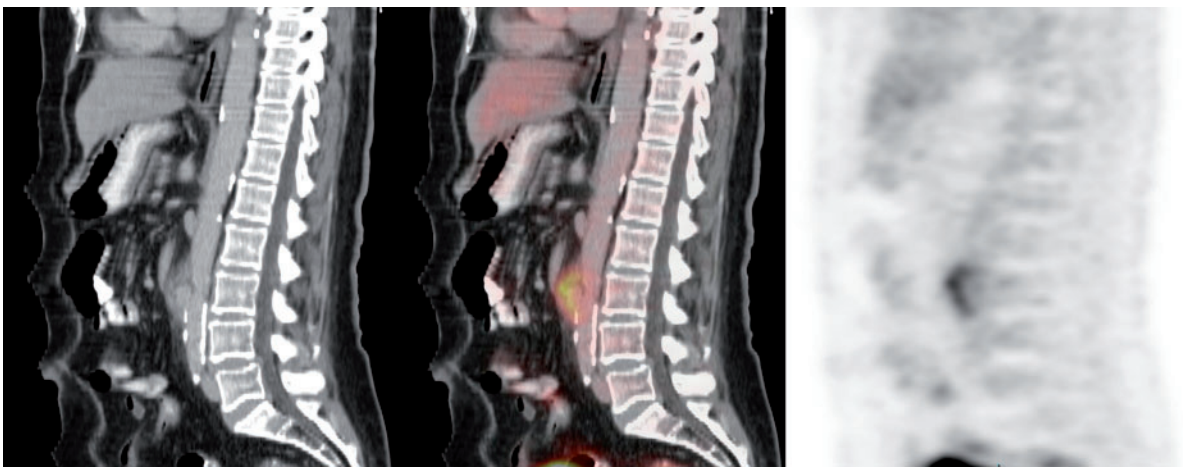

Figure 3. A 69-year-old woman was evaluated for abdominal pain and 3 weeks of fever. An abdominal CT scan showed an infra-renal abdominal aortic aneurysm with a dissection of ~3 cm long. PET/CT demonstrated thickening of the aortic wall and increased FDG uptake. A diagnosis of suspected infectious aortitis/mycotic aneurysm was made. Broad spectrum antibiotics were administered, and the patient underwent aortic aneurysm repair the following day.

TN results

Twenty-three studies were TN (Table 2). In 16 cases, the FUO resolved spontaneously with no evidence of disease. There were six cases of infections. These included three cases of Q-fever infection (without endocarditis), two cases of Epstein-Barr viral infection, which were diagnosed by serology and one case of urosepsis which was diagnosed by urinalysis

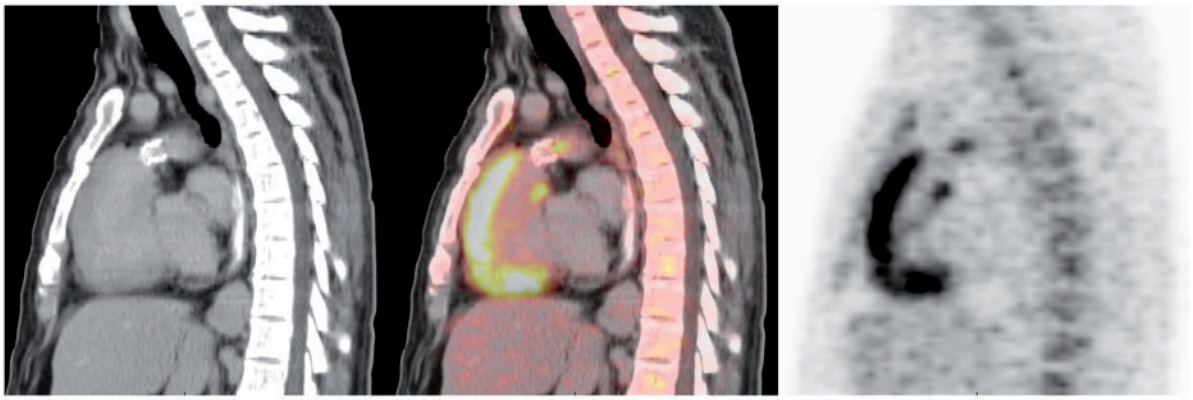

Figure 4. A 20-year-old man underwent a correction of transposition of great arteries during childhood with stent insertion in the pulmonary artery. He was hospitalized due to 4 weeks of fever. Methicillin-sensitive *Staphylococcus aureus* was cultured from the blood, antibiotic was strated and trans-esophageal echocardiogram demonstrated pulmonary trunk stenosis with a suspicious echogenic mass within the pulmonary stent. PET/CT demonstrated pathological FDG uptake surrounding the pulmonary artery stent. In addition to 6 weeks of intravenous antibiotics, he underwent surgery with removal of the infected stent.

Table 3 Baseline characteristics of patients with FUO according to PET/CT findings (positive contributory findings vs. all others)

	n **(%)**		
	PET/CT with positive contributory findings (TP), *N* = 52	**All other PET/CT findings, *N* = 60**	***P*-value**
Demography, comorbidity			
Age (years), median (range)	60 (19–85)	60 (20–93)	0.728
Male sex	33 (63.5)	24 (40)	0.013
Diabetes mellitus	12 (23.1)	16 (26.7)	0.662
Insulin	4 (7.7)	6 (10)	0.669
Renal failure	16 (30.8)	13 (21.7)	0.273
Malignancy	13 (25)	10 (16.7)	0.276
Previous chemotherapy	5 (9.6)	4 (6.7)	0.567
Steroid use	15 (28.8)	15 (25)	0.647
Solid organ transplant	12 (23.1)	9 (15)	0.275
Weight loss	15 (28.8)	19 (31.7)	0.405
Number of fever days before PET, median (range)	19 (4–90)	30 (7–210)	0.01
Findings on physical examination			
Heart murmur	18 (34.6)	18 (30)	0.602
Lymphadenopathy	4 (7.7)	10 (16.7)	0.119
Rash	2 (3.8)	12 (20)	0.01
Maximal fever (°C)	39 (38–40)	39 (38–41)	0.657
Laboratory findings			
Proteinuria	22 (45.8)	33 (57.9)	0.218
Hematuria	34 (70.8)	42 (73.7)	0.745
Leukocyturia	19 (39.6)	22 (38.6)	0.918
Maximal leukocyte count/μl	13 140 (1850–184 900)	12 500 (3190–283 700)	0.935
Maximal platelet count/μl	311 500 (20 000–804 000)	273 000 (27 000–804 000)	0.843
Minimal Hb level (g/dl)	9.3 (5.9–16)	9.15 (6–16.4)	0.956
Maximal ESR (mm/h)	70 (13–120)	100 (3–120)	0.173
Maximal CRP	15.2 (2.2–23)	11.6 (0.1–15)	0.692

Table 4 Multivariate logistic regression analysis for predictors for positive contributory PET/CT findings

	OR (95% CI), $N=52$	*P* value
Male sex	3.321 (1.423–7.747)	0.005
Lymphadenopathy	0.548 (0.14–2.139)	0.386
Rash	0.221 (0.041–1.179)	0.077
Number of fever days before PET	0.983 (0.967–1)	0.05
Hosmer Lemeshow test	Chi-square 3.88, df=7	0.793
Area under receiver operating curve	0.736 (0.642–0.831)	<0.001

and urine culture (without pyelonephritis). There was one case that was diagnosed as an exacerbation of lupus erythematosus according to clinical criteria. All of these were regarded as TN, because they were not expected to present with focal findings on PET/CT.

FP and FN

The FP cases included 17 cases (Table 2). In six of them, the FUO resolved spontaneously. There was increased FDG uptake in lymphadenopathy in four of these cases. This led to lymph node biopsy in three cases that demonstrated no pathological process. In the fourth case, fever resolved and a biopsy was not taken. In the other two cases, the uptake was in the aorta and sternum, and no biopsy was performed. Five cases were diagnosed as non-infectious inflammatory diseases. Three of them were diagnosed as systemic lupus erythematosus exacerbation: in one, pathological uptake in the stomach led a gastroscopy which was normal, in the second, uptake in lymph nodes led to lymph node biopsy which was normal and in the third there was increased uptake in the axial skeleton. Two cases of vasculitis demonstrated uptake in pulmonary nodules which were unrelated to the disease. The four cases of infection included three viral infections (H1N1 influenza, CMV infection and coxsackie) with pathological uptake in kidney, gluteus and stomach respectively, which were irrelevant to the diagnosis. The fourth infection was a urinary tract infection in a transplanted kidney, with uptake in the lungs.

The FN included 20 studies. There were eight cases of infectious diagnoses, seven of which were endocarditis. These were diagnosed according to accepted clinical criteria or transesophageal echocardiography. There was one case of myelitis. Non-infectious inflammatory diseases included granulomatous hepatitis (per liver biopsy) (2), polymyalgia rheumatica (1), temporal arteritis (1), polyarteritis nodosa (1), sarcoidosis (1) and hemophagocytic syndrome (1). The one malignancy that demonstrated a FN PET result was a case of marginal zone lymphoma diagnosed per bone marrow biopsy. Four patients died with no diagnosis.

Discussion

In our large retrospective study of 112 patients, we identified a potential role of PET/CT for the diagnosis of FUO. PET/CT was found to contribute clinically to diagnosis or exclusion of diagnosis in 66% of cases. A final diagnosis was reached in 74% of patients (83/112). This is consistent with results of previous studies of PET/CT for the evaluation of FUO that ranged from 50% to 91%.[2,7,13–16]

The spectrum of etiologies in our study and their distribution are consistent with previous reported data, derived from other studies of PET/CT for evaluation of FUO[2,13,14,16] as well as studies of other modalities for diagnosis of FUO.[5,17]

Our study lends further support to the ability of PET/CT, rather than PET only, to contribute to the diagnosis in patients with FUO. Our study shows that PET/CT was contributory to diagnosis in 66% of the cases. These results of PET/CT are better than those of earlier studies of stand-alone FDG-PET (without CT) that ranged from 16% to 68.8%[2,13,18–20] and comparable to more recently reported studies, with a contributory PET/CT performance that ranged from 45.8% to 90%.[15,16,21–24] This is probably due to the fact that FDG-PET is limited by the anatomic information it provides and suggests that the additional information provided by the CT scan improves the diagnostic potential of this modality.

The sensitivity of 72% calculated in our study is in accordance with previous studies. Two meta-analyses were recently published. One included nine studies and assessed both FDG-PET alone and PET/CT.[7] The pooled sensitivity reported for FDG-PET alone was 82.6% (95% CI: 72.9–89.9) and for

PET/CT it was much higher 98.2% (95% CI: 93.6%–99.8%). In this meta-analysis, only 32.2% of PET studies were contributory to the final diagnosis, while for FDG-PET/CT the number was considerably higher, 62.1%. The other meta-analysis included 15 studies of PET/CT and demonstrated a sensitivity of 85% (95% CI: 81–88%).[25] These results, as well as ours, are also consistent with recent publications from this year. In a retrospective study of 57 patients with FUO, PET/CT was found to be contributory to diagnosis in 75% of the cases,[24] and in an another study of 50 patients with FUO, it was able to detect the cause of fever in 60%.[26] Another study of 31 pediatric patients with FUO that underwent PET/CT demonstrated a sensitivity of 80%.[23] Therefore, it appears that PET/CT, more than PET alone, is a valuable modality for evaluation of FUO.

In 15 patients in our study, malignancy was found to be the cause for FUO, lymphoma being the most common. Notably, in 14 of them (93%), the PET/CT was contributory and led to biopsies that confirmed the diagnosis. This is in accordance with a recent retrospective study of 73 patients with FUO who underwent PET/CT due to the suspicion of lymphoma,[27] in which PET/CT was positive in 88% of the patients with confirmed lymphoma.

Another finding in our study is the spontaneous resolution of FUO in 20% of patients without a diagnosis. The proportion of undiagnosed patients is in accordance with previous studies, which show that in 10–50% of patients the underlying disease remains undiagnosed.[2,7,10,13–16] The results of all of the studies emphasize the fact that despite advances in imaging studies, there is still a significant proportion of undiagnosed cases.

Interestingly, the group of patients who underwent contrast-enhanced PET/CT showed better results than patients who did not receive contrast. This is in concert with a recent study that showed that standardized uptake values were significantly elevated in liver tissue when using PET images corrected for attenuation with contrast-enhanced high-dose CT compared with PET images corrected with unenhanced low-dose CT.[28] Another study demonstrated that the diagnostic accuracy of distant metastasis, scalene node metastasis and peritoneal dissemination with contrast-enhanced PET/CT was significantly higher than that of non-contrast PET/CT in 95 patients with pancreatic cancer.[29] This may suggest that contrast-enhanced PET/CT has added value for evaluation of FUO.

Our study evaluated PET/CT only for patients with classical FUO. Nowadays, PET/CT has a role in diagnosing other infectious and inflammatory conditions. In a previous prospective study of 79 patients, conducted by our group, we have shown that PET/CT also has a potential role in diagnosing infections in patients with hematological malignancies (mainly acute leukemia) and persistent febrile neutropenia.[30] The recent study of pediatric patients included a group of patients who were immune-suppressed. PET/CT was contributory to diagnosis in this population as well.[23] Notably, a recent case report confirmed the ability to diagnose leukemia, according to diffuse FDG uptake in bone marrow.[31] Moreover, PET/CT has recently been shown to be valuable in the diagnosis and treatment monitoring of non-malignant pulmonary disorders, many of which present with FUO[32] including diagnosing tuberculosis[33] and monitoring response to treatment according to FDG uptake in lymph nodes.[34]

Our main findings were predictors for a contributory PET/CT results. A shorter duration of days of fever before the PET/CT was associated with achieving a positive contributory diagnosis (TP). This is similar to results by Bleeker Rovers *et al.*,[2] which demonstrated in a prospective study of 73 patients with FUO that fever that persisted for <180 days was associated with a higher likelihood of achieving a diagnosis. An older prospective study of 167 patients with FUO also showed that the chance of reaching a diagnosis for fever lasting longer than 6 months was significantly lower.[5] Patients with FUO without a diagnosis do fairly well according to a cohort study of 61 patients discharged from the hospital with no diagnosis and followed up for 5 years, with a mortality rate of only 3.2%.[35]

The other predictive factor for a TP PET/CT was male gender. This was also found in the study by Crouzet *et al.*,[14] although only on univariate analysis. A possible explanation may be that non-infectious inflammatory conditions are less prevalent in male patients. In our study, only 7/17 in this group were male. Because PET/CT may have a lower diagnostic yield in these conditions, its overall diagnostic yield in males, in whom their relative proportion is low, may be higher than in females.

A major strength of our study is the fact that to the best of our knowledge it is the largest retrospective series reported thus far. Furthermore, it included PET/CT studies performed in the years 2008–2012, and thus the results represent the distribution of FUO etiologies in recent years and may be applicable to clinical practice nowadays.

The main limitation of our study is its retrospective design. However, clinically relevant data were obtained for all patients at a follow-up of 6 months. None of the patients in which FUO resolved with no diagnosis presented with another febrile episode due to infection or any other cause. Due to the retrospective nature, there was no formal diagnostic algorithm and the timing for performance of PET/CT

was at the discretion of the physician. Moreover, only 54% of patients underwent a CT scan before PET/CT. Therefore, we could not assess the added value of PET/CT to patients who had undergone CT or the role of PET/CT as a substitute to CT. Nevertheless, the PET/CT contributed more than the total body CT in 12/23 (52%) of TP cases.

Another important limitation of our study, as with previous studies examining the role of PET/CT for diagnosis of FUO, is incorporation bias. There is no gold standard for diagnosis of FUO, it is usually a clinical diagnosis that takes into account all laboratory and imaging results. PET/CT may have influenced the management of patients, resulted in further diagnostic evaluation and ultimately determined the final diagnosis, thus, possibly falsely increasing both sensitivity and specificity.

Our study provides additional support to the use of PET/CT as an important diagnostic tool in FUO. It may even be cost effective because an accurate and possibly early diagnosis may limit the need for additional non-contributory tests. A randomized controlled trial comparing between total body CT and PET/CT, conducted as a first line diagnostic tool may help resolve this question. Future studies with long-term follow-up are needed to assess whether PET/CT improves outcomes in FUO.

Conclusions

In our retrospective study of PET/CT for evaluation of FUO in 112 patients, we show that 66% of studies are contributory to diagnosis. On the basis of these results we support PET/CT as the most important imaging technique for FUO. We emphasize the importance of predictive factors as male gender and length of fever for achieving a positive contributory result.

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