Open Access Rheumatology: Research and Reviews

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ORIGINAL RESEARCH

Role of Positron Emission Tomography-Computed Tomography Scan in Reaching Definite Diagnosis in Patients With Fever of Unknown Origin and Inflammation of Unknown Origin in Rheumatology Outpatient Clinic

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Introduction: Patients with fever of unknown origin (FUO) and/or inflammation of unknown origin (IUO) challenge clinicians in daily rheumatology practice. Positron emission tomography-computed tomography (PET/CT) is being used in the diagnostic workup of patients with FUO and/or IUO. This study aims to evaluate the clinical utility and diagnostic performance of PET/CT in the rheumatology outpatient clinic among FUO and IUO patients.

Methods: Patients admitted to Prof. Dr. Cemil Taşcıoğlu City Hospital Internal Medicine Rheumatology Outpatient Clinic between February 2022 and September 2023 with FUO and/or IUO and for whom PET/CT scan was performed were included. Initial acute phase reactants, PET/CT results, definite diagnosis and follow-up of patients without a definite diagnosis were retrospectively evaluated.

Results: Thirty patients were included. Fifteen patients received a final diagnosis. Diagnoses were ankylosing spondylitis (n=4), rheumatoid arthritis (n=1), systemic lupus erythematosus (n=3), giant cell arteritis (n=1), adult onset Still disease (n=1), undifferentiated connective tissue disease (n=1), undifferentiated vasculitis (n=1) and crystal arthropathy (n=1), Hodgkin lymphoma (n=1) and cryptococcosis (n=1). PET/CT's diagnostic accuracy was 66.7%, sensitivity was 100% but specificity was 33%. In 15 patients a definite diagnosis was not reached but in most of these patients, fever did not recur and acute phase reactants regressed either spontaneously or with empiric treatment.

Discussion: PET/CT reliably helps 50% FUO/IUO patients in receiving definite diagnosis. PET/CT's high sensitivity implies that negative results can reliably exclude malignancies in most cases. However, due to its low specificity, positive test may not always imply a serious underlying condition. Majority of the definite diagnoses were rheumatic diseases with a very low proportion of infections and malignancies. This is mainly due to the detailed initial evaluations that are performed in internal medicine clinics. Future studies with more patients will better define the role of PET/CT in FUO/IUO patients in rheumatology clinics.

Keywords: fever of unknown origin, inflammation of unknown origin, PET/CT, rheumatology

Introduction

Patients with fever of unknown origin (FUO) and inflammation of unknown origin (IUO) present unique diagnostic challenges to clinicians, including rheumatologists who try to determine the etiology and treat these groups of patients. There are a wide range of differential diagnoses including infectious, neoplastic or rheumatic diseases.[1] Despite the

Received: 15 October 2024
Accepted: 29 January 2025
Published: 5 February 2025

overall improvements in diagnostic and treatment modalities, 10–50% of patients with FUO do not have a definite diagnosis.[2]

Positron emission tomography-computed tomography (PET/CT) is a hybrid imaging modality that allows scanning the entire body and localizing the area with highest metabolic activity.[3] PET/CT is increasingly being used in rheumatology practice, where it is most commonly used for demonstrating the extent and activity of large vessel vasculitides such as giant cell arteritis and Takayasu arteritis.[4] PET/CT is also useful in rheumatology practice because it can be used in the diagnostic workup of patients with FUO and/or IUO.

Many studies in the literature have evaluated the clinical use and diagnostic performance in FUO and/or IUO in different clinics and among different patient groups, which yielded varying results. In a review of multiple studies, Kouijzer et al report that PET/CT's helpfulness in reaching a final diagnosis in FUO patients varied between from 38% to 75% among different studies which had different definitions for FUO.[5] However, there is less literature exploring PET/CT's diagnostic utility and performance in FUO/IUO patients in rheumatology clinics. The study by Öğüt et al reports that among 58 patients evaluated for FUO/IUO in Rheumatology Clinic, PET/CT helped diagnosis in 52 patients. Twenty-six patients had rheumatic diseases, 20 patients had malignancy, and 6 patients had infectious diseases.[6] This study does not specify how many patients were hospitalized and how many were evaluated in the outpatient clinics. Thus, there is a lack of knowledge in the literature about the diagnostic utility of PET/CT among rheumatology outpatient clinic patients that are being evaluated for FUO/IUO.

The aim of this retrospective study is to determine the clinical utility and diagnostic performance of PET/CT in the rheumatology outpatient clinic, among patients who presented with fever of unknown origin and elevated acute phase reactants for which a definite etiology could not be reached after initial clinical, laboratory and radiographic evaluations.

Method

Patient Selection Criteria and Data Collection

Institutional ethical approval was obtained from Prof. Dr. Cemil Taşcıoğlu City Hospital Non-Interventional Clinical Research Ethical Committee. Decision number was E-48670771-514.99-228765388. This study complied with the declaration of Helsinki.

Patients who were admitted to Prof. Dr. Cemil Taşcıoğlu City Hospital Internal Medicine Rheumatology Outpatient Clinic between February 2022 and September 2023 with fever of unknown origin and/or inflammation of unknown origin and for whom PET/CT scan was performed for diagnosis were included in the study. Informed consent of the study participants was obtained prior to the commencement of the study.

Inclusion criteria of the study were as follows: Patients with fever of unknown origin and/or inflammation of unknown origin who are 18–80 years old at the time of admission, where rheumatologic examinations failed to diagnose any cause for fever or elevated acute phase reactants, such as arthritis. Exclusion criteria were as follows: Patients younger than 18 years old or older than 80 years old, patients with a medical history for previous malignancy or autoimmune disease, patients with active infectious diseases, pregnant or lactating patients, patients that had a recent history of trauma, operation or serious hemorrhage.

Medical records of the patients were retrospectively assessed for the following: Age, sex, fever at the time of the presentation, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at the time of presentation. PET/CT results of these patients were retrospectively analyzed for largest maximum standardized uptake value (SUV_{max}) and the interpretation of the findings of the PET/CT report by the nuclear medicine specialist (described as "normal", "inflammatory", and "suspicious for neoplasia"). After PET/CT patients underwent further diagnostic studies such as histopathological examinations, other imaging modalities or serological tests, which were guided by the PET/CT results. The final diagnoses that were received after these studies were also recorded and classified as the following: Infectious causes, autoimmune causes, neoplasias, and no definite diagnosis). Follow-up of the patients who did not have a definite diagnosis, empirical treatment modalities these patients received and the final status of the fever and acute phase reactants of these patients were also recorded.

Positron Emission Tomography/Computed Tomography Protocol

All PET/CT scans were performed in the Prof. Dr. Cemil Taşcıoğlu City Hospital Nuclear Medicine Clinic.

Before the PET/CT scan, patients completed 4–6 hours of fasting. According to the routine protocol, 6 hours before the imaging, patients started to drink the oral contrast (Iohexol 350 mgI/mL) after mixing it with 1.5 liters of water. After checking that the patients' blood glucose was less than 200 mg/dl, intravenous injection of F-18 FDG with 0.09–0.14 mCi activity was performed. After injection, patients were kept in a calm environment that preserved their body temperature for a waiting period of 60 minutes. Then the imaging was initiated. Imaging was performed in supine position and the imaging area included the levels between vertex and upper thigh levels. Low dose non-diagnostic CT was performed for anatomical correlation and for use in attenuation correction. After that, PET was performed for the same anatomical area. Images were obtained with General Electric Discovery MI 3 Ring PET/CT (GE Healthcare, Milwaukee, USA) device. All PET images were obtained in 3B mode. In reconstruction algorithm, Ordered Subset Expectation Maximization (OSEM) and Block Sequential Regularized Expectation Maximization (Bayesian factor: 700) (BSREM) and point spread function (PSF) methods were used. The images obtained were transferred to the system. Then, different nuclear medicine specialists who were not blinded to the clinical data reported the results.

Statistical Analysis

For statistical analysis Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) was utilized. While assessing the data, descriptive statistical methods (mean, standard deviation, median, frequency, percent, minimum, maximum) were used. Quantitative data's normal distribution was tested according to Shapiro–Wilk test and graphical analysis.

When comparing quantitative variables of two groups with non-normal distribution, Mann Whitney *U*-test was used. When comparing three or more groups with non-normal distribution Kruskal Wallis test and post hoc Bonferroni–Dunn test were used.

When comparing qualitative variables Fisher-Freeman-Halton test was used. While assessing the diagnostic performance of PET/CT sensitivity, specificity, positive predictive value, negative predictive value, McNemar test and Cohen's kappa coefficient of interrater reliability were used. When assessing the relationships of the quantitative variables, Spearman correlation analysis was used. While assessing statistical significance, $p<0.05$ was utilized.

Results

Demographic Variables, Fever, Acute Phase Reactants at the Time of Diagnosis

In the given time interval, 18667 outpatient clinic visits were performed. PET/CT was used in 101 cases. Thirty of the patients had PET/CT performed for fever of unknown origin and/or inflammation of unknown origin. Twenty patients were female and ten patients were male. Mean age of the patients was 51.23 ±13.89 and median age was 52 (26–78). Mean fever at the time of presentation was 37.85 ± 0.18 °C and median fever was 37.8 (37.5–38.3) °C. ESR at the time of presentation was 70.2 ±25.1 mm/hour and median ESR was 67.5 (25–120) mm/hour. CRP at the time of presentation was 53.1 ± 38.9 mg/l and median CRP was 52.5 (2–142).

PET/CT Results

Mean largest SUV_{max} of PET/CT reports was 5.33 ± 4.96 and median SUV_{max} was 3.9 (0–21.1). PET/CT findings were classified as the following: "normal" in 5 patients (16.7%), "inflammatory" in 19 patients (63.3%) and "suspicious for neoplasia" in 6 patients (20%).

There was no difference between patients whose PET/CT results were interpreted as "normal", "inflammatory" and "suspicious for neoplasia" in terms of the fever, CRP and ESR at the time of presentation ($p=0.922$ for fever, $p=0.566$ for CRP and $p=0.981$ for ESR). Largest SUV_{max} value differed significantly between the three groups (0.37±0.82 for "normal group", 5.09 ± 3.71 for "inflammatory group" and 10.23 ± 6.22 for "suspicious for neoplasia" group, $p=0.001$).

Further Diagnostic Tests and Final Diagnoses

Further diagnostic tests performed after PET/CT were as follows: Further clinical evaluation in 12 patients, ultrasound in 3 patients, magnetic resonance imaging (MRI) in 6 patients, biopsy in 6 patients, serological tests in 2 patients and no further diagnostic test in 1 patient (who was diagnosed giant cell arteritis after initial clinical evaluation and typical PET/CT findings without a further workup).

Final diagnosis was reached in 15 patients (50%) and in the remaining 15 patients (50%) a definite diagnosis was not reached. Thirteen of the 19 patients whose PET/CT findings were interpreted as "inflammatory" received a definite diagnosis: Ankylosing spondylitis in 4 patients, systemic lupus erythematosus in 3 patients, rheumatoid arthritis in 1 patient, adult onset Still disease in 1 patient, giant cell arteritis in 1 patient, undifferentiated connective tissue disease in 1 patient, unclassified rheumatoid factor positive vasculitis (without rheumatoid arthritis) in 1 patient and degenerative joint pathology secondary to crystal arthropathy in 1 patient. Two of the six patients whose PET/CT was "suspicious for neoplasia" received diagnosis: Hodgkin lymphoma in 1 patients and cryptococcosis in 1 patient whose clinical and PET/CT findings were highly suspicious for lung neoplasm. None of the 5 patients with "normal" PET/CT had a definite diagnosis after further workup. There was significant difference between the groups in terms of the percent of patients that receive a final diagnosis (0% in "normal group", 68.4% in "inflammatory group" and 33.3% in "suspicious for neoplasia group", p=0.016).

Correlation Between Largest SUV_{max} and Acute Phase Reactants

There was not a statistically significant correlation between largest SUV_{max} values and CRP or ESR values in all patients (p=0.228 for CRP and p=0.610 for ESR) or when patients were classified as "normal" (p=0.182 for CRP and p=0.182 for ESR), "inflammatory" (p=0.386 for CRP and p=0.342 for ESR) or "suspicious for neoplasia" (p=0.787 for CRP and p=0.623) according to their PET/CT report.

Diagnostic Performance of PET/CT

Diagnostic performance of the PET/CT in patients that have reached a final diagnosis is demonstrated in Table 1. In Table 1, PET/CT results were summarized as being "normal" or "abnormal".

According to Table 1, sensitivity of PET/CT was 100%, specificity was 33.3%, positive predictive value was 60%, negative predictive value was 100% and accuracy was 66.7%. Cohen's kappa coefficient was 0.333, meaning there was a fair agreement between PET/CT and definitive diagnostic tests.

Follow-up of Patients That Did Not Receive Diagnosis

During the follow-up of 5 patients with "normal" PET/CT, fever did not recur. In 2 of the 5 patients CRP and ESR spontaneously normalized, and in 2 patients these parameters regressed to normal under empirical colchicine therapy. In 1 patient acute-phase reactants remained elevated but no new clinical findings emerged.

Table 1 Diagnostic Performance of PET/CT

	PET/CT					
	Abnormal		**Normal**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Final diagnosis(+)	15	50.0	0	0	**15**	**50.0**
No final diagnosis	10	33.3	5	16.7	**15**	**50.0**
Total	**25**	**83.3**	**5**	**16.7**	**30**	**100**

Notes: Bolded values: This study includes a total of 30 patients. In 15 patients a final diagnosis was reached and in the remaining 15 patients, there was no final diagnosis. PET/CT demonstrated abnormal fluorodeoxyglucose uptake in 25 patients which included all 15 patients with a final diagnosis (true positives) and 10 patients without a final diagnosis (false positives). PET/CT was normal in 5 patients without a final diagnosis (true negatives).
Abbreviation: N, Number.

During the follow-up of 6 patients who had "inflammatory" PET/CT, but did not receive a definitive diagnosis, fever did not recur. In 3 patients acute phase reactants normalized spontaneously, in 2 patients these parameters regressed with empirical glucocorticoid treatment and in 1 patient acute phase reactants remained elevated with no new clinical findings.

During the follow-up of 4 patients who had PET/CT results that were reported as "suspicious for neoplasia", 1 patient was lost to follow-up. Fever of the remaining three patients did not recur. In one of these patients acute phase reactants spontaneously normalized, in 1 patient they normalized with empirical colchicine and in 1 patient acute phase reactants remained elevated with no new clinical findings.

Discussion

PET/CT enabled us to reach a final diagnosis in 15 of the 30 patients. Thus, it was diagnostic in 50% of the patients. In the review by Bharucha et al where the authors analyzed 18 studies that evaluated PET/CT's role in FUO, the pooled diagnostic yield was 56%.[7] In their review exploring the role of PET/CT in diagnosis of fever of unknown origin, Singh et al report that in two series by Tsuzuki and Singh, PET/CT helped 48% and 53.2% of FUO patients in reaching a definite diagnosis respectively.[8–10] These percentages are similar to the 50% of cases with diagnostic PET/CT that we hereby report.

Thirteen patients were diagnosed with rheumatic diseases, 1 patient was diagnosed with Hodgkin lymphoma and in one patient where PET/CT revealed a lung mass, which was highly suspicious for lung cancer, histopathological evaluation demonstrated cryptococcosis. In the literature there are similar cases where this fungal infection mimicked lung neoplasms.[11]

The ratio of infectious diseases and malignancies is low in comparison to studies of Ferda et al and Sheng et al.[12,13] In the study by Ferda et al, PET/CT was performed in an internal medicine clinic in 48 patients with FUO. Eighteen patients had infectious causes, 8 had malignancies and 13 patients had autoimmune or non-infectious granulomatous etiologies.[12] In the study by Sheng et al which was performed in an infectious diseases clinic, PET/CT was performed in 48 patients with FUO. Fifteen patients were diagnosed with infectious diseases, 12 patients had malignancies and 9 patients had inflammatory diseases.[13] The predominance of rheumatic diseases is due to the different population in which our study was performed. This difference is due to the "referral chain" that the patients go through in Turkish healthcare system, where patients undergo initial diagnostic evaluations and therapeutic interventions in internal medicine clinics before being referred to rheumatology clinics. Thus, the initial workup excludes infectious causes and neoplastic etiologies in most of the patients.

Despite its own cost seeming as a potential disadvantage for PET/CT, studies have demonstrated that early use of PET/CT in FUO or IUO patients shortens the hospital stays and reduces medical costs by helping clinicians in reaching a definite diagnosis earlier and preventing clinicians from using other potentially costly diagnostic modalities.[5] PET/CT's role in diagnostic algorithms of FUO and IUO patients needs to be defined with larger and better designed studies that evaluate its role in different clinical settings.

In our study, PET/CT demonstrated 100% sensitivity and %100 negative predictive value as it demonstrated abnormal SUV_{max} uptake in all 15 patients where a definite diagnosis was reached. However, PET/CT was normal in only 5 of the 15 patients without a definite diagnosis and therefore had a very high false positivity. A negative PET/CT seems to reliably rule out infectious, neoplastic or rheumatic diseases but a positive PET/CT may not necessarily predict a serious underlying pathology since the positive predictive value of PET/CT is only 60%. These results are similar to the study by Garcia-Vicente et al, where the sensitivity of PET/CT was 84%, lower than our study's 100% sensitivity.[14] Specificity was 31% and the accuracy was 61%, similar to our study's 33% specificity and 66.7% accuracy.[14]

The rheumatic diseases diagnosed in this study were ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, undifferentiated connective tissue disease, giant cell arteritis, adult onset Still disease and crystal arthropathy and unclassified vasculitis. PET/CT's role in diagnosis and follow-up of large vessel vasculitides is well established.[15] In our patient with giant cell arteritis, when combined with initial clinical evaluation, PET/CT was sufficient in reaching diagnosis without using any further diagnostic modalities. PET/CT's role is also expanding to the diagnosis and follow-up of other rheumatic diseases such as ankylosing spondylitis,[16] rheumatoid arthritis,[17] crystal arthropathies,[18] adult onset Still disease,[19] systemic lupus erythematosus[20] and other connective tissue diseases.[21] It is

important to note that PET/CT is not being routinely used in the diagnosis of the rheumatic diseases other than large cell vasculitides for the diagnoses listed above. However in atypical presentations of these rheumatic diseases with FUO and elevated acute phase reactants, PET/CT had an important role both in helping clinicians reach these diagnoses and rule out malignancies.

In their study, Kim et al demonstrated that FUO patients in which PET/CT was non diagnostic, prognosis was more favorable.[22] In another study, Eynath et al report that among FUO patients that were investigated with PET/CT, FUO spontaneously resolved in 28% of patients. Lack of anemia, lack of hypoalbuminemia and lack of pathological FDG uptake were associated with spontaneous resolution.[23] In 5 of our patients, PET/CT was "normal". Fever did not recur in any of these patients. In 2 patients acute phase reactants spontaneously regressed, in two patients they regressed with empirical colchicine treatment and in one patient they remained elevated without any new clinical signs or symptoms. In 10 patients with FUO and IUO, even though PET/CT revealed increased SUV_{max} uptake, further diagnostic studies failed to reach any definite diagnosis. Fever did not recur in any of the patients. In 4 of these patients acute phase reactants spontaneously regressed, in 2 patients acute phase reactants normalized with empirical steroid treatment and in 1 patient the acute phase reactants regressed with empirical colchicine treatment. In 2 patients acute phase reactants remained elevated without any new clinical signs or symptoms and 1 patient was lost to follow-up. Thus among these 15 patients where PET/CT was "normal" or a definite diagnosis was not reached. Fever resolved in all 15 patients, acute phase reactants spontaneously resolved in 6 patients. Acute phase reactants resolved with empirical colchicine treatment in 3 patients and with empirical glucocorticoids in 2 patients. In 3 patients acute phase reactants remained elevated. Thus, our results in patients with "non diagnostic" PET/CTs demonstrate that this group of patients mostly had a favorable prognosis similar to the studies mentioned above.

Limitations of our study include its retrospective design, the relatively low number of patients that were enrolled, lack of a control group and the fact that the PET/CT results were reported by different nuclear medicine specialists.

In conclusion, in a well-defined population that underwent initial diagnostic evaluation in internal medicine clinics, where most infectious diseases and malignancies were ruled out, PET/CT was useful in reaching a final diagnosis in 50% of the patients in the rheumatology outpatient clinic with FUO or IUO. PET/CT had a 100% sensitivity and despite its high false-positive results had a diagnostic accuracy of 66.7%. In 13 of these patients, final diagnoses were rheumatic diseases, most of which were atypical clinical presentations of some of the common rheumatic diseases such as ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, undifferentiated connective tissue disease and crystal arthropathies. In one patient where PET/CT and clinical findings were characteristic, diagnosis of giant cell arteritis was finalized without any further diagnostic workup. In one patient with adult onset still disease, PET/CT helped ruling out infections and neoplastic diseases. In the remaining 15 patients where PET/CT was not helpful for diagnosis, most of the patients had a good prognosis with signs and symptoms of inflammation resolving either spontaneously or with empirical use of glucocorticoids or colchicine.

It seems that PET/CT will continue to play an important role in daily rheumatology practice in the differential diagnosis of patients with FUO and IUO. Future research on use of PET/CT in this setting in rheumatology clinic should focus on technical improvements in PET/CT imaging that can reduce the rate of false-positive results, technical parameters other than SUV_{max} that can distinguish increased "inflammatory" FDG uptake from increased "neoplastic" FDG uptake, development of composite scores that incorporate demographical, laboratory and PET/CT parameters that can reliably predict malignancy without need of invasive biopsies and future studies with larger number of patients that better define the place and role of PET/CT in FUO/IUO setting in rheumatology outpatient clinics.

Key Points

-In a well-defined population that underwent initial diagnostic evaluation in Internal Medicine clinics, PET/CT was useful in reaching a final diagnosis in 50% of the patients in the Rheumatology Outpatient Clinic with FUO or IUO. PET/CT had a 100% sensitivity and despite its high false-positive results had a diagnostic accuracy of 66.7%.

-In 13 of these patients, final diagnoses were rheumatic diseases, most of which were atypical clinical presentations of some of the common rheumatic diseases.

-In the remaining 15 patients where PET/CT was not helpful for diagnosis, most of the patients had a good prognosis with signs and symptoms of inflammation resolving either spontaneously or with empirical treatment.

Disclosure

The authors declare that they have no conflicts of interest.

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