Role of ^{18}F-FDG PET in Patients with Infectious Endocarditis

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It was our purpose to evaluate the clinical impact of systematic PET/CT for the diagnosis of infectious embolisms in patients with infectious endocarditis (IE) in comparison with a historic cohort of IE patients managed without this technique. Detection of extracardiac lesions is an essential component of the management and outcome of IE. Studies using PET/CT for the evaluation of patients with IE are scarce, lack a control group, evaluate a small number of patients, or consist of case reports. **Methods:** We performed a prospective cohort study (47 patients with definite IE undergoing PET/CT) with matched controls (94 patients with definite IE not undergoing PET/CT) from January 2012 to July 2013 in a tertiary hospital. The results were compared with those of conventional diagnostic techniques and clinical follow-up. **Results:** PET/CT revealed at least 1 lesion in 35 patients (74.5%): 18 showed an embolic complication, 8 showed pathologic uptake on the valves or cardiac devices, 1 showed both, 5 had incidental noninfectious findings, and the findings for 3 were considered false-positive. The validity values for the efficacy of PET/CT in the diagnosis of septic lesions were as follows: sensitivity, 100%; specificity, 80%; positive predictive value, 90%; and negative predictive value, 100%. PET/CT was the only initially positive imaging technique in 15 true-positive cases (55.5%). The systematic use of PET/CT was associated with a 2-fold reduction in the number of relapses (9.6% vs. 4.2%, $P = 0.25$) and enabled significantly more infectious complications to be diagnosed (18% vs. 57.4%, $P = 0.0001$). **Conclusion:** PET/CT enables the extent of IE to be assessed using a single test. It is fast (<2 h) and comfortable for the patient, gathers whole-body data, and detects significantly more infectious complications.

Key Words: endocarditis; ^{18}F-FDG PET/CT; septic embolism; infectious endocarditis diagnosis

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Infectious endocarditis (IE) is a severe disease that is diagnosed using a combination of clinical, microbiologic, and imaging criteria (*1,2*). Although infrequent, its incidence was shown to be 12.7 cases per 100,000 inhabitants in a study performed in the United States between 1998 and 2009 (*3*). Morbidity and mortality are significant, in part as a result of the high rate of distant embolic complications (23%–45%) (*4,5*).

Failure to identify metastatic complications may lead to early interruption of therapy, thus triggering relapse and an unfavorable outcome. Infectious embolisms can be asymptomatic and difficult to recognize (*6*), with the result that systematic performance of multiple imaging techniques (CT, MR imaging, and ultrasonography) has been recommended for all patients with IE (*7*). However, this approach is time consuming and cumbersome and involves frequent transfer of very ill patients to the radiology department.

^{18}F-FDG PET/CT is widely used on patients with oncohematologic conditions, since it can identify glucose uptake in areas with an increased metabolic rate (*8*). It has a promising role in infectious diseases because of its high sensitivity, anatomic precision, and lack of toxicity (*9,10*). The possibility of scanning the whole body with a single test is particularly appealing for clinicians treating patients with IE.

Studies analyzing PET/CT for the evaluation of patients with IE are scarce, lack a control group, evaluate a small number of patients, or consist of case reports (*11,12*). The field of examination in the recent report by Saby et al. (*13*) was limited to the heart, and a high incidence of false-negative results was detected (33%).

Our purpose was to evaluate the clinical impact of systematic whole-body ^{18}F-FDG PET/CT for the diagnosis of septic embolisms in patients with IE in comparison with a historic cohort of IE patients managed without this technique.

MATERIALS AND METHODS

Design

We performed a prospective cohort study (IE patients undergoing PET) involving matched controls in a 1,500-bed tertiary hospital attending a population of 700,000 inhabitants. Since 2003, all consecutive patients with IE have been prospectively followed by a multidisciplinary team (Group for the Management of Infectious Endocarditis of the Gregorio Marañón Hospital, or GAME). All clinical data are collected prospectively in a preestablished protocol. IE episodes were diagnosed using the modified Duke criteria, which

consist of a combination of clinical, microbiologic, and radiologic findings (*2*).

From January 2012 to July 2013, all patients with proven IE underwent PET/CT. The exclusion criteria for PET/CT were hemodynamic instability, pregnancy, surgery during the previous month, clinical intolerance to the test, and known active malignancy. Patients (cases) were matched by affected valve and etiology of definite IE with patients from our cohort who were diagnosed before the PET/CT study was initiated (controls).

Ethics

The study was approved by the Institutional Review Board (356/11), and all patients gave their written consent.

Imaging Protocol

Our hospital protocol for detecting septic embolism in patients with IE includes systematic CT of the chest and abdomen or abdominal ultrasound and, if central nervous system symptoms are present, cranial CT or MR imaging. PET/CT was performed simultaneously with these conventional diagnostic techniques.

Patients fasted for at least 6 h before the PET/CT study (i.e., with respect to time of injection of ^{18}F-FDG). If present, hyperglycemia was corrected according to our hospital protocol. PET was not performed if glucose levels were greater than 160 mg/dL in nondiabetic patients or greater than 200 mg/dL in diabetic patients at the time that ^{18}F-FDG was to be injected. The injection and uptake phase lasted 45 min.

According to our hospital protocol, diagnostic craniocervicothoracoabdominal CT with an intravenous contrast agent (Optiray UltraJect, 300 mg/mL; Mallinckrodt) was performed in all cases, except those with documented allergy or compromised renal function or taking concomitant medication (metformin). The intravenous contrast agent was administered when the patient was already lying on the hybrid PET/CT device, allowing us to avoid the time lapse between explorations. An oral contrast agent (barium sulphate, 5%, 150 mL; Rovi Laboratorios) was administered in all cases to improve evaluation of the alimentary tract, unless poor tolerance was observed or anticipated. A 4 MBq/kg dose of ^{18}F FDG (350–400 MBq) was administered intravenously 60 min before imaging, with a subsequent rest period of 45 min. Afterward, PET/CT images were acquired with a Biograph 6-4R truePoint PET/CT (Siemens) device with a true PET/CT device from the vertex to the mid thigh. Images were reconstructed in axial slices using iterative reconstruction. Attenuation correction was performed with PET/CT fusion in 3 planes and revised using Leonardo software (e.soft PET/CT Platinum workstation; Siemens). All images were evaluated visually and quantitatively by a nuclear physician with PET/CT experience. In doubtful cases, the PET/CT scan was evaluated by at least 2 nuclear medicine specialists. The CT part of the examination was evaluated independently by an expert radiologist. In the PET/CT scan, the presence or absence of an abnormal accumulation of ^{18}F-FDG, especially focal accumulation, was evaluated, as was its size and intensity. Qualitative and semiquantitative values (maximum standardized uptake value [SUV_{max}] and mean SUV) were recorded for each lesion. Any nonphysiologic focus of uptake greater than uptake by healthy surrounding tissue (for lesions smaller than approximately 2 cm) or uptake greater than reference parenchymal uptake by the mediastinal blood pool or liver (for larger lesions) was considered suggestive of pathologically increased metabolic activity. Noninfectious incidental focal hypermetabolic lesions were classified as neoplasms or inflammation according to radiologic, clinical, and histologic findings, independently of SUVs. Response was assessed by reviewing the images using the same color scale range, and mean liver SUVs were recorded for both examinations. Images were considered to be comparable in the case of an overlap of ×2 SDs of the mean liver SUV. Both uncorrected and attenuation-corrected images were assessed in order to identify any artifacts caused by contrast agents, metallic implants, or patient motion.

Definitions and Evaluation Criteria

A true-positive PET/CT result was defined as abnormal ^{18}F-FDG uptake by any organ or tissue that was later confirmed as a pathologic lesion through clinical, microbiologic, or standard imaging findings. A false-positive PET/CT result was defined as abnormal ^{18}F-FDG uptake in the absence of clinical or microbiologic findings, with negative standard imaging results and no relapse during follow-up. Noninfectious incidental PET/CT findings were excluded from the efficacy analysis.

Statistical Analysis

The analyses were performed using SPSS, version 18.0 (SPSS Inc.). All tests were 2-sided. A P value of less than 0.05 was considered significant. For classification of the PET/CT results, we used a discrepancy analysis (*14*), which is recommended for the evaluation of new, highly sensitive imaging tests.

RESULTS

Patient Characteristics

During the study period there were 70 endocarditis episodes, but 23 patients had to be excluded from the study. The reasons for exclusion were early surgery (8 cases), early death (5 cases), discharge (5 cases), admission to the intensive care unit (2 cases), active malignancy (2 cases), and intolerance of the test (1 case). Among the excluded patients, IE was due to *Staphylococcus aureus* (9 cases), *Staphylococcus epidermidis* (4 cases), an unknown cause (4 cases), *Enterococcus faecalis* (3 cases), *Streptococcus viridans* (2 cases), and *Streptococcus pneumoniae* (1 case). Overall mortality during the study period was 29%.

The study population thus included 47 patients from the 70 sequential cases of IE (67.1%). The epidemiologic and clinical characteristics of the study patients are shown in Table 1. Mean age was 61.3 y (±19 [SD]), and 30 were male. Infection was caused by Gram-positive microorganisms in 33 cases (70.2%), Gram-negative microorganisms in 4 (8.5%), anaerobes in 5 (10.6%), fungi in 2 (4.2%; *Aspergillus fumigatus* in one and *Candida parapsilosis* in the other), and unknown microorganisms in 2 (4.2%). In one case, infection was polymicrobial (2.1%). IE was left-sided in 38 of 47 cases (80.8%), prosthetic valves or cardiac devices were affected in 48.9%, and 24 (51.1%) of the patients had native valve IE. The median length of treatment was 43 d (interquartile range, 34–53 d). Thirty patients (63.8%) underwent valve replacement. The 2 study patients who died were a heart recipient with *A. fumigatus* IE and a massive pulmonary embolism and a patient with *S. epidermidis* IE who had septic shock. Finally, 1 patient with very extensive *Clostridium perfringens* IE is on the waiting list for heart transplantation.

PET/CT Results

PET/CT showed 42 lesions in 35 of 47 patients (74.5%). The 42 affected sites were as follows: lung, 10 (23.8%); bone, 6 (14.3%); sigmoid, rectum, and anus, 6 (14.3%); extracardiac prosthetic material, 5 (11.9%); prosthetic valve, 4 (9.5%); soft tissue, 3 (7.1%); spleen, 3 (7.1%); brain, 3 (7.1%); right atrium and diaphragm, 1 each (4.8%). The classification of PET/CT results according to our definitions is shown in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org).

TABLE 1
Epidemiologic and Clinical Characteristics of Patients with IE: Assessment of Extent of Infection Using PET/CT (Cases) or Conventional Imaging Methods (Controls)

Characteristic	Cases (n = 47)	Controls (n = 94)	P
Epidemiology			
Mean age ± SD	61.3 ± 19 y	64.6 ± 21 y	0.34
Sex			0.8
Male	30 (63.8%)	62 (65.9%)	
Female	17 (36.2%)	32 (34.1%)	
Immunosuppression	6 (12.8%)	13 (13.8%)	0.62
HIV infection	0	3	0.21
Transplantation	2	5	0.78
Charlson comorbidity index	4.09 (±2.7)	5.05 (±2.6)	0.13
Previous prosthetic valve	15 (31.9%)	40 (42.5%)	0.22
Aortic	9 (19.1%)	31 (32.9%)	
Mitral	6 (12.7%)	7 (7.4%)	
Pulmonary	0	2 (2.1%)	
Cardiac device	11 (28.5%)	21 (12.85%)	0.88
Pacemaker	8 (17.0%)	18 (19.1%)	
Defibrillator	3 (6.4%)	3 (3.2%)	
Intravascular device	10 (21.2%)	7 (7.4%)	0.01
Central vein catheter	8 (17.0%)	6 (6.4%)	
Other prosthetic material	2 (4.2%)	1(1.0%)	
IE Episode			
Etiology			0.13
Gram-positive	33 (70.2%)*	70 (74.5%)	
Gram-negative	4 (8.5%)†	7 (7.4%)	
Anaerobes	5 (10.6%)‡	1 (1%)	
Fungi	2 (4.2%)	4 (4.2%)	
Unknown	2 (4.2%)	10 (10.6%)	
Polymicrobial	1 (2.1%)	2 (2.1%)	
Anatomic distribution of IE			
Prosthetic IE	15(48.6%)	40 (45.7%)	0.22
Aortic	8	20	
Mitral	7	19	
Native IE	24 (51.4%)	50 (54.3%)	0.81
Aortic	12	19	
Mitral	11	25	
Tricuspid	1	6	
Cardiac device	8 (17.0%)	4 (4.2%)	
Outcome			
Treatment-related			
Days of treatment	43 d (IQR, 34–53)	34 d (IQR, 17–42)	0.1
Time to effective treatment	3.67 d (±7.8)	13.1 d (±43)	0.15
Persistent BSI	3 (6.4%)	16 (17.0%)	0.08
Valve surgery replacement	30 (63.8%)	39 (41.5%)	0.01
Clinical			
Hospital stay	39 d (IQR, 23–56)	29 d (IQR, 17–54)	0.82
Infectious complications	27 (57.4%)	17 (18%)	0.0001
Readmission	5 (10.6%)	7 (7.4%)	0.5
Relapse	2 (4.2%)	9 (9.6%)	0.26

*_E. faecalis,_ 11; _S. aureus,_ 5; _S. viridans,_ 4; _Streptococcus gallolyticus,_ 3; _S. epidermidis,_ 2; _S. anginosus,_ 2; _Staphylococcus lugdunensis,_ 1; _Streptococcus gordonii,_ 1; _S. pneumoniae,_ 1; group C _Streptococcus,_ 1; _Abiotrophia defectiva,_ 1; group G _Streptococcus,_ 1.

†_P. aeruginosa,_ 2; _H. aphrophillus,_ 1; coagulase-negative _Staphylococcus,_ 1.

‡_Aggregatibacter actinomycetemcomitans,_ 1; _Bacteroides thetaiotaomicron,_ 1; _C. perfringens,_ 1; _Lactobacillus paracasei,_ 1; and _P. acnes,_ 1.

IQR = interquartile range; BSI = bloodstream infection.

Five patients (10.6%) had a noninfectious PET/CT finding (lung cancer, colonic adenocarcinoma, lymphocytic interstitial pneumonia, diverticulosis, and solitary lung nodule). None of the findings were identified by the conventional radiologic extension study. These incidental findings were excluded from the efficacy analysis.

The validity values for efficacy of PET/CT for the diagnosis of infectious embolism were as follows: sensitivity, 100%; specificity, 80%; positive predictive value, 90%; and negative predictive value, 100%. Overall, 27 patients (57.4%) were classified as true-positive. Only 12 of the 27 true-positive results (44.4%) were

initially identified in the conventional extension study, as follows: lung, 3; spleen, 2; brain, 2; rectal wall, 3; and aortic prosthetic valve and pleura (1 each). In the remaining 15 true-positive cases (55.5%), PET/CT was the only initially positive imaging technique: 5 cases of spondylodiskitis (Fig. 1) (SUV_{max}, 5.39); 3 cases of intravascular or endovascular prosthetic material infection (SUV_{max}, 7.39); 3 cases of septic pulmonary embolism (SUV_{max}, 3.75); 2 sigmoid, rectum, and anus lesions (SUV_{max}, 7.53); 1 case of septic spleen embolism (Fig. 2) (SUV_{max}, 5.60); 1 case of brain embolism (SUV_{max}, 7.8); 1 pulmonary valve graft (SUV_{max} 4.33); and 1 case of soft tissue around the pacemaker (SUV_{max}, 3.74) (Supplemental Table 1). These findings resulted in prolongation of antibiotic treatment for a mean of 52 d (SD, 49 d).

Twelve patients (25.5%) were classified as true-negative, since both PET/CT and conventional imaging techniques excluded the presence of complications (Supplemental Table 1). The median length of therapy in these patients was 34.5 d (interquartile range, 12.25–46.5), and all patients remained asymptomatic during follow-up.

There were 3 false-positive PET results (6.4%) in patients with abnormal uptake on their initial PET/CT scan that was not subsequently confirmed (Supplemental Table 1). The sites included left radius (SUV_{max}, 3.80), diaphragm (SUV_{max}, 7.56), and soft tissue (SUV_{max}, 2.15) (Supplemental Table 1). None of them had associated clinical signs or symptoms, follow-up by conventional imaging was negative, treatment was not modified (median of 45 d), and all patients remained asymptomatic during follow-up. No false-negative results were detected.

Comparison of Cases and Controls

To assess the clinical impact of PET/CT in patients with IE, we compared the study cases with a historic control cohort (1:2) from our database matched for etiology and site of IE. The epidemiologic and clinical characteristics of cases and controls were similar (Table 1). Systematic use of PET/CT led to a statistically significant increase in the diagnosis of infectious complications (57.4% vs. 18.0%, $P = 0.0001$). Although the difference did not reach statistical significance because of the low number of cases, PET/CT was associated with a 2-fold reduction in the number of relapses (4.2% vs. 9.6%, $P = 0.25$). Hospital stay remained stable, mainly because of the support of the outpatient parental antibiotic therapy program.

DISCUSSION

Our study showed that PET/CT is a more effective way of assessing the extent of infection in patients with IE. PET/CT was the only initially positive diagnostic imaging test in 55.5% of patients and reduced by 2-fold the incidence of relapses.

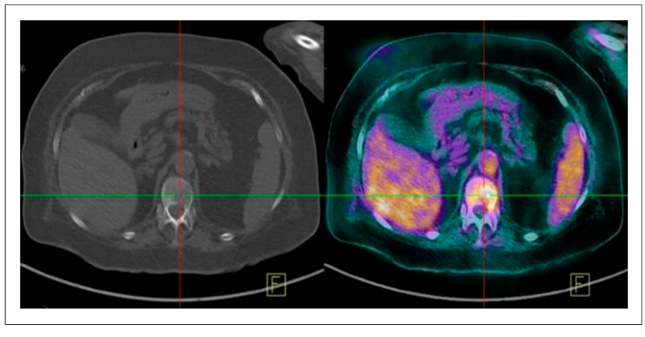

FIGURE 1. PET/CT images of case of spondylodiskitis.

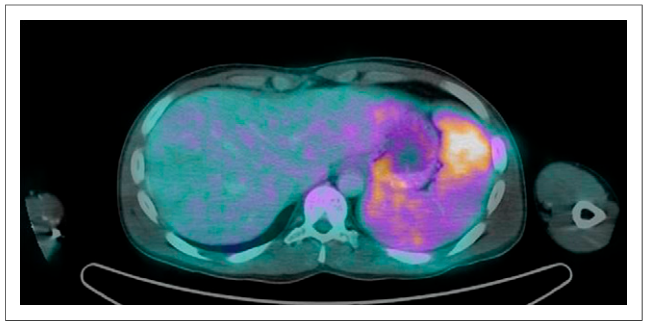

FIGURE 2. PET/CT image of male patient with spleen embolism.

The outcome of IE is closely associated with the extent of systemic embolization and extracardiac infection; most relapses are due to an insufficient duration of original treatment or a persistent focus of infection (*7*). However, a diagnosis of peripheral septic embolism is often challenging. Current guidelines (*7*) agree that embolic events can be totally silent in 20% of cases, especially those affecting the spleen or cerebral blood flow, and can be detected only by imaging techniques (abdominal and cerebral CT). To date, no clear consensus has been reached on which imaging technique should be performed or whether imaging should be performed systematically or only in symptomatic patients. In many cases, the extension study requires multiple tests that are not only time consuming but also expensive and troublesome for the patient.

The introduction of PET/CT to the investigation of tumor extent in oncology revolutionized the practice of medicine (*8*); assessment of hypermetabolic lesions in the field of infectious diseases is more recent (*6*). In 2010, Vos et al. (*10*) used PET/CT technology to assess distant infectious lesions in 115 nonneutropenic patients with Gram-positive bloodstream infections. Metastatic infectious foci were detected in 35% of patients; in half, the diagnosis was not previously suspected. Subsequently, the use of PET/CT to investigate high-uptake lesions in the heart or in intracardiac devices has been evaluated (*13,15*).

Studies evaluating the role of PET/CT in ruling out extracardiac involvement in patients with endocarditis are mainly case reports (*12*). Van Riet et al. studied 25 patients with IE and found infectious septic embolisms in about 44% of patients (*11*); however, the study did not have a control group, nor did it attempt to evaluate the clinical impact of these findings. Our study showed that 57.4% of patients were eventually diagnosed with an infectious complication and that more than half (60%) were asymptomatic. PET/CT makes it possible to detect infectious embolism throughout the body in a single easily performed test (<2 h) that is comfortable for the patient and provides the clinician with whole-body data. Although the purpose of this study was not to evaluate heart valve lesions with PET/CT but to evaluate extracardiac involvement, PET/CT detected 7 of 8 cases of IE related to extracardiac prosthetic material: 3 defibrillators (2 with septic pulmonary embolisms and 1 with a subcutaneous abscess), 1 aortic graft infection, 1 extracardiac Fontan tube infection (Fig. 3), 1 aortic graft infection (Fig. 4), and 1 central vein catheter (pulmonary septic embolism) (Fig. 5). These findings agree with those of Sarrazin et al (*15*), who also found that PET/CT was a useful tool for the diagnosis and determination of the extent of infections from cardiovascular implantable electronic devices. Gated studies of the heart, a previous diet preparation for the patient, and

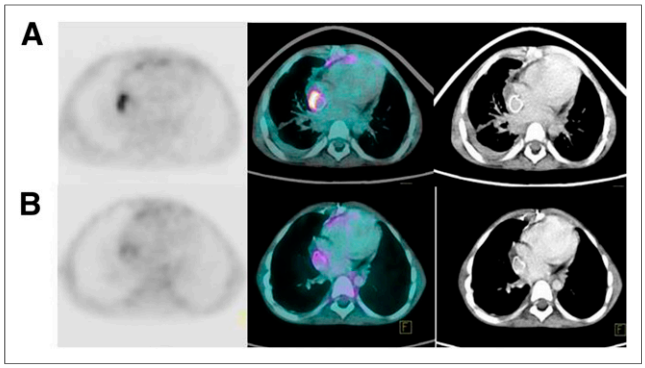

FIGURE 3. PET (left), PET/CT (middle), and CT (right) images of female patient with cardiac Fontan tube and group C *Streptococcus* IE. (A) Initial images. (B) Images after 6 wk of antibiotic treatment.

a longer acquisition time would definitely increase the detection of heart valve lesions, but more information is needed on this aspect.

The systematic performance of PET/CT made it possible to detect other diseases, such as cancer, that could be involved in the pathogenesis of endocarditis. Although the pathophysiologic relationship between endocarditis and neoplasm remains unclear, the simultaneous finding of both entities is not rare (*16*). Thomsen et al. (*17*) recently proposed that endocarditis is a substantial clinical marker for the presence of occult cancer, with a standardized incidence rate of 1.61 (confidence interval, 1.5–1.71). In this series, cancer risk in endocarditis patients was highly elevated during the first 3 mo of follow up (standardized incidence rate, 8.03; 95% confidence interval, 6.92–9.26). In our series, PET/CT enabled early detection of 2 tumors (1 lung and 1 colon) in patients with *Propionibacterium acnes* and *Streptococcus anginosus* IE.

The conventional extension study comprised 76 imaging techniques (1.61 tests per patient), including CT (27), echography (25), radiography (13), MR imaging (5), scintigraphy (5), and angio-CT (1). PET/CT is clearly more expensive than conventional CT or MR imaging (€658 [~$908] per patient vs. €326.42 [~$451] per patient), although it has considerably improved the diagnosis of infectious complications. In 15 of 27 cases (55.5%), PET/CT was the only initially positive imaging technique that revealed an infectious complication. On the basis of data from Spanish health authorities (*18*), the mean extra cost of a major complication from a systemic infection is €20,241 (~$27,940); therefore, early diagnosis of infectious complications with PET/CT is cost-effective. Vos et al. (*9*) evaluated the cost-effectiveness of routine PET/CT in 115 high-risk patients with Gram-positive bacteremia and found that the cost-effectiveness ratio was $72,487 per prevented death.

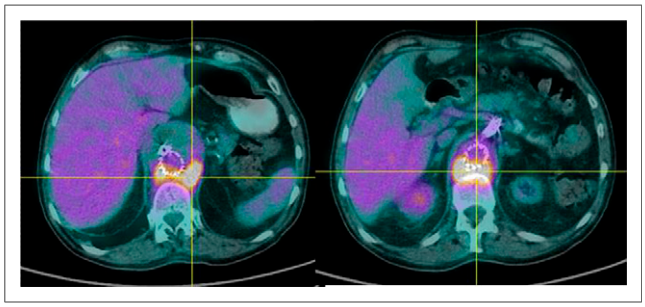

FIGURE 4. PET/CT images of male patient with aortic graft prosthetic material infection.

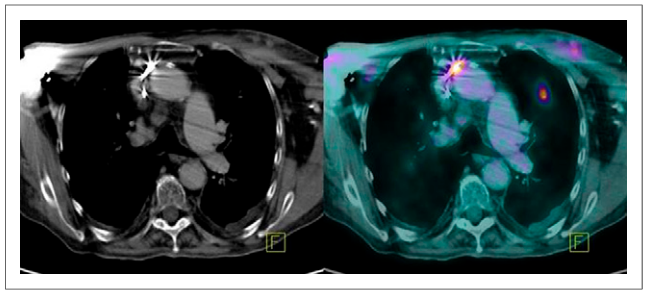

FIGURE 5. PET/CT images of case of pulmonary septic embolism.

Our study was subject to a series of limitations. First, it was performed in a single center, thus reducing the number of patients who could be included. Second, early PET/CT could be performed in only 66% of patients with IE, mainly because of emergency surgery and hemodynamic instability, which probably excluded patients with the most severe complications. Because of inflammatory changes and hemodynamic instability after cardiac surgery, we decided not to perform the test immediately on patients who had recently undergone surgery. This problem could be resolved as experience with the technique increases. Furthermore, our institution has only 1 PET/CT device, and cancer patients are given preference on the waiting list. Therefore, scheduling was problematic in some cases; however, given increasing evidence of the usefulness of PET/CT in patients with infectious diseases, we expect this situation to change. Third, PET/CT is a highly sensitive test for localizing abnormalities, since the results are a measure of inflammatory cell activity (*19*); therefore, the results could increase the risk of false-positive findings. To minimize this effect, we performed a discrepancy analysis and compared PET/CT results with clinical and microbiologic data and the results of conventional imaging techniques. The most problematic discrepant results were those for the 3 patients in whom PET/CT findings could not be confirmed by clinical, microbiologic, or radiologic findings during the course of their disease. For the sake of this study, we considered these results to be false-positive. Fourth, to assess the impact of PET/CT on mortality or relapse in patients with IE, a prospective randomized study with a larger number of subjects should be performed.

CONCLUSION

PET/CT is an effective way of accomplishing the extension study in a single test in patients with IE. It is quickly performed (<2 h) and comfortable for the patient and provides the clinician with whole-body data. PET/CT enables the diagnosis of a significantly higher percentage of infectious complications (18.0% vs. 57.4%, $P = 0.0001$), and its use procured a trend toward a reduced number of relapses (9.6% vs. 4.2%, $P = 0.25$) in patients with IE.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. No potential conflict of interest relevant to this article was reported.

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