ORIGINAL ARTICLE MYCOLOGY

Diagnostic contribution of positron emission tomography with [^{18}F]fluorodeoxyglucose for invasive fungal infections

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Abstract

Optimal staging and evaluation of residual lesions of invasive fungal infections (IFIs) are major challenges in the immunocompromised host. Preliminary data have suggested that [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) uptake may be observed in the course of active invasive fungal infections. The aim of this study was to assess the role of positron emission tomography with [^{18}F]FDG ([^{18}F]FDG-PET) in the diagnosis and staging of IFI. A prospective monocentric study evaluating [^{18}F]FDG-PET in 30 consecutive adults and children with European Organization for Research and Treatment of Cancer/Mycoses Study Group probable or proven IFI was performed. Twenty males and ten females (median age, 45 years (range 6–75 years)) were enrolled. Twenty-six were immunocompromised, as follows: haematological malignancy (18) with allogeneic stem cell transplantation (16/18), solid tumour (three), solid organ transplantation (two), diabetes mellitus (two) and cystic fibrosis (one). IFIs were acute invasive aspergillosis (ten), chronic disseminated candidiasis (ten), zygomycosis (two), black grains eumycetoma (two), pulmonary *Histoplasma capsulatum* var. *capsulatum* histoplasmosis (two), and *Phomopsis* sp. osteoarthritis, *Scedosporium apiospermum* and *Candida krusei* spondylodiscitis, and acute pulmonary coccidioidomycosis in one case each. An increased uptake of [^{18}F]FDG was observed in all areas previously identified by computed tomography and/or magnetic resonance imaging to be involved by IFI. In 4/10 chronic disseminated candidiasis cases, [^{18}F]FDG-PET revealed small splenic abscesses that were unapparent on the corresponding computed tomography scan. [^{18}F]FDG uptake disappeared after 6 months of antifungal therapy in three patients with chronic disseminated candidiasis for whom the [^{18}F]FDG-PET was performed to assess the evolution of the disease. [^{18}F]FDG-PET could potentially be useful for the initial diagnosis and staging of IFI. Whether or not [^{18}F]FDG-PET might be useful for assessing the optimal duration of IFI therapy should now be assessed in a specific prospective study.

Keywords: Aspergillosis, hepatosplenic candidiasis, [^{18}F]FDG positron emission tomography
Original Submission: 12 December 2009; **Revised Submission:** 2 May 2010; **Accepted:** 6 June 2010
Editor: E. Roilides
Article published online: 15 July 2010
Clin Microbiol Infect 2011; **17:** 409–417
10.1111/j.1469-0691.2010.03301.x

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Presented in part at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy; 27–30 September 2006, San Francisco, CA, USA, Abstract M-1307.

Introduction

Invasive fungal infections (IFIs) represent major diagnostic and therapeutic challenges in immunocompromised patients, especially those with haematological malignancy, for whom diagnosis and antifungal treatment are often delayed because of a lack of specific clinical and radiological features [1]. At present, the diagnosis of IFI relies on sophisticated microbiological tools, including culture and molecular identification [2,3],

whereas radiological investigations are still mostly based on conventional computed tomography (CT) [4]. Although pulmonary CT has demonstrated its value for the early diagnosis of invasive pulmonary aspergillosis [5,6], it may miss other foci of infections. In addition, appropriate evaluation of the residual infection has now become a new challenge in immunocompromised patients surviving their initial episode of IFI. In these patients, appropriate duration of antifungal therapy is a key issue for optimal timing of the subsequent specific management of the underlying disease. Preliminary investigations have suggested that classical isotopic methods such as gallium-67 scintigraphy and leukocyte scintigraphy could be useful for the diagnosis of IFI, but so far there is no consensus regarding their use in clinical practice [7].

[^{18}F]2-Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) accumulates in metabolically active cells, including neoplastic and inflammatory cells, and produces a distinct image during positron emission tomography (PET) scanning ([^{18}F]FDG-PET). It is thus useful for detecting malignant and inflammatory processes [8,9]. Similarly, the contribution of [^{18}F]FDG-PET in the diagnosis of infectious diseases will probably be recognized and better codified in the future. Indeed, several groups have demonstrated its contribution in the assessment of osteomyelitis, infected prosthetic devices, fever of unknown origin, and AIDS. Whether or not [^{18}F]FDG-PET represents a useful diagnostic tool during IFI remains unknown. Furthermore, for fungal lesions involving subcutaneous tissues or bones, conventional methods may not be sensitive enough. Finally, [^{18}F]FDG uptake may also constitute a potential marker of residual IFI, which would be particularly useful in helping to reduce the duration of costly systemic antifungal therapies with their inherent side effects in severely immunocompromised hosts.

We thus prospectively assessed the contribution of [^{18}F]FDG-PET in the diagnosis and staging of proven IFI in a monocentric cohort of 30 consecutive patients.

Patients and Methods

Patients

From among 53 patients who presented with IFI during the study period, we selected 30 consecutive patients who were naïve to antifungals. These 30 consecutive patients, 29 adults and one child hospitalized at the Centre d'Infectiologie Necker-Pasteur, Paris for the diagnosis or management of IFI, were prospectively evaluated with [^{18}F]FDG-PET between November 2005 and October 2006. All patients underwent exhaustive, clinical, radiological and microbiological work-ups, and all (or their parents) gave their informed consent to participate. All patients fulfilled the 2002 European Organization for Research and Treatment of Cancer/Mycoses Study Group diagnostic criteria for proven or probable IFI [10]. Exclusion criteria included: (i) any other infection (e.g. bacterial pneumonia or osteomyelitis; (ii) considerable comorbid medical, surgical or psychiatric conditions that were currently uncontrolled or that may have interfered with completion of the study; and (iii) inability to tolerate staying in a PET scanner for the duration of the examination.

Diagnostic work-up for IFI

Conventional diagnostic tests for IFI were routinely performed in all patients prior to the time of [^{18}F]FDG-PET, and included routine laboratory tests (blood cell count, chemistry, C-reactive protein, microbial cultures – blood, urine, sputum, and others as clinically indicated), twice-weekly sequential monitoring of galactomannan in severely neutropenic patients, chest radiography or CT, and magnetic resonance imaging (MRI) when appropriate. The same qualified radiologist (SP) performed all radiological procedures. Additional diagnostic tests, such abdominal CT, bronchoalveolar lavage, endoscopy and/or tissue biopsy, were performed as clinically indicated. CT was used to evaluate all cases of invasive aspergillosis or chronic disseminated candidiasis before the [^{18}F]FDG-PET. CT was performed very early after the suspicion of IFI. [^{18}F]FDG-PET and CT always were performed within 48 h following the initiation of antifungal therapy.

All CT scans were obtained with a four-section CT scanner (MX8000; Philips Medical Systems). CT was performed in 11 patients with 5-mm collimation through the thorax, abdomen and pelvis, and in three patients through the abdomen and pelvis, and included contrast enhancement in all cases. Contiguous 5-mm-thick sections of the entire chest were obtained in nine patients without injection of contrast medium. High-resolution 1-mm-thick images were also obtained in this group of patients. CT scans of the paranasal sinus were obtained in five patients with 3-mm collimation extending from the top of the frontal sinuses down to the maxillary alveolus, without contrast material administration. Four patients underwent MRI, especially for bone infection and spondylitis imaging, with a 1.5-T MRI unit (Signa; GE Medical Systems). T1-weighted and T2-weighted images were obtained, including contrast material enhancement. Lower limbs were explored in two patients, and the spine also in two patients. For the diabetic patients, the blood sugar was controlled with either oral hypoglycaemic agents or insulin before scanning.

[^{18}F]FDG-PET imaging

Every patient fasted for a minimum of 6 h before the intravenous injection of 5 MBq/kg of [^{18}F]FDG. Whole body imaging

was performed on a PET-CT Philips Gemini 16, in accordance with the manufacturer's guidelines, beginning 45–60 min following tracer injection. The [18F]FDG was injected via intravenous catheter. PET acquisition parameters were as follows: whole body scanning from the vertex to the hips, 3 min per step, with no contrast enhancement CT (140 kV, 120 mA to 160 mA, depending on the patient's weight, 2-mm slices, pitch 1.5), and from the hips to the feet (2 min per step), with CT only when clinically required, in order to minimize the dose–length product. Emission data were iteratively reconstructed using a dedicated full three-dimensional row-action maximization-likelihood algorithm, delivered with the [18F]FDG-PET systems by the manufacturer, computing non-corrected and attenuation-corrected data (for segments with corresponding CT slices). Images were analysed on a Brilliance device (Philips), simultaneously displaying non-corrected, attenuation-corrected and CT data.

Image analysis

All PET/CT scans were reviewed by two experienced nuclear medicine physicians (CM and MF), who were not aware of the patient's clinical history and final IFI diagnosis. Images were visually interpreted as normal, equivocal or with pathological uptake, according to standard uptake values (respectively, below 2, between 2 and 3 and above 3 on attenuation-corrected data, or to uptake above lung or soft tissue physiological uptake on non-corrected data).

Results

No adverse effect was observed after injection of the isotope in the 30 patients who were evaluated by [18F]FDG-PET.

Demographic and clinical data are summarized in Table 1.

Demographic and clinical descriptions

Thirty patients (20 males and ten females) were consecutively recruited during the study period. Their median age was 45 years (range: 6–75 years). Eighteen had a haematological malignancy, including 16 with allogeneic stem cell transplantation (eight of whom were grafted with cells from a matched, unrelated donor). Ten of the latter patients received major immunosuppressive therapy for chronic graft-versus-host disease at the time of IFI diagnosis. Eight patients had recently received antineoplastic chemotherapy, and 15 patients high-dose steroid therapy. Among the four immunocompetent patients, one had cystic fibrosis and three had no past medical history. Eight patients had recently experienced profound neutropenia, five of whom were still neutropenic (<500/mm^3) at the time of initial [18F]FDG-PET. IFIs were associated with moulds in 14 cases: eight definite and two probable cases of invasive aspergillosis (isolated pulmonary in four cases, pulmonary and sinus in four cases, sinus and brain in one case, and isolated liver aspergillosis in one case), two cases of zygomycosis, and one case each of *Scedosporium apiospermum* spondylitis and *Phomopsis* sp. osteoarthritis. Yeast infections included chronic disseminated candidiasis (ten) (five definite and five probable) and one case of *Candida krusei* vertebral osteomyelitis. In three cases, [18F]FDG-PET was performed for the evaluation of endemic dimorphic IFI, including two cases of lung *Histoplasma capsulatum* var. *capsulatum* histoplasmosis and one acute pulmonary coccidioidomycosis. In two cases, [18F]FDG-PET was performed during the course of black grains eumycetoma: one was related to *Madurella* spp., and the other to *Leptospheria senegalensis*.

[18F]FDG-PET for initial staging of IFI

In all patients, [18F]FDG-PET revealed [18F]FDG uptake in the area(s) previously identified by conventional CT scan or MRI as being involved by the IFI. All [18F]FDG-PET scans were performed within 48 h following the initiation of antifungal therapy, in order to avoid false-negative results.

Invasive mould infections. A 6-year-old boy with chronic granulomatous disease was diagnosed with probable invasive pulmonary aspergillosis. [18F]FDG-PET revealed tracer uptake in the area corresponding to the lesions indentified on the corresponding chest CT scan (Fig. 1a,b).

A 33-year-old patient with a past history of refractory Hodgkin's disease was admitted for fever of unknown origin. Three months earlier, he underwent allogeneic stem cell transplantation. He was diagnosed with chronic graft-versus-host disease requiring immunosuppression with cyclosporine and prednisone. He did not receive antifungal prophylaxis, and remained neutropenic. Three months post-transplantation, he was admitted for investigation of probable pulmonary invasive aspergillosis, on the basis of two consecutive positive serum galactomannan detections. [18F]FDG-PET revealed tracer uptake in the right upper lobe (Fig. 1c). Histological study revealed both invasive aspergillosis and Hodgkin's disease relapse.

Yeast infections. Ten patients with chronic disseminated candidiasis were evaluated in our study. In six of them, [18F]FDG-PET revealed lesions undetected by CT scan.

A 27-year-old male patient with testicular cancer presented with multiple hypodense nodular lesions in the liver and the spleen consistent with chronic disseminated candidiasis, occurring during haematopoietic recovery. Although blood cultures were negative for *Candida* spp., the CT-guided liver biopsy

TABLE 1. Major characteristics of 30 patients with invasive fungal infections who underwent [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) positron emission tomography (PET) imaging

Patient	Age (years)	Sex	Underlying disease	Invasive fungal infection and diagnostic modalities	Initial CT findings	Initial PET findings	Follow-up PET findings
1	46	M	Liver transplantation Steroids	Definite liver aspergillosis	Three nodular lesions	[^{18}F]FDG uptake in the liver with three nodular lesions	No
2	48	F	Lymphoma Steroids, chemotherapy, R-CHOP	Probable invasive pulmonary aspergillosis	Lesion in the right upper lobe	[^{18}F]FDG uptake in the right upper lobe	No
3	69	M	Hairy cell leukaemia Cladribine, steroids	Definite invasive pulmonary and sinus aspergillosis	Lesion in the left upper lobe	[^{18}F]FDG uptake in the left upper lobe	No
4	39	F	Acute myeloid leukaemia Allogeneic HSCT, GVHD	Definite pulmonary and sinus aspergillosis	No lesion	[^{18}F]FDG uptake in the left lower lobe	No
5	33	M	Relapsing Hodgkin's disease Allogeneic HSCT, steroids	Definite invasive pulmonary aspergillosis	Lesion in the right upper lobe	[^{18}F]FDG uptake in the right upper lobe	Yes, decrease in [^{18}F]FDG uptake
6	65	M	AIDS HAART Kaposi sarcoma COPD	Definite invasive sinus and pulmonary aspergillosis	No lesion seen in the chest CT scan	[^{18}F]FDG uptake in the right upper lobe	No
7	56	M	Kidney transplantation Tacrolimus and mycophenolate mofetil, steroids	Definite invasive pulmonary aspergillosis	Nodular lesion in the left lower lobe	[^{18}F]FDG uptake in the left lower lobe	No
8	68	M	Diabetes mellitus	Definite sinus and cerebral invasive aspergillosis	Nodular lesion in the left lower lobe	[^{18}F]FDG uptake in the left lower lobe	No
9	6	M	Chronic granulomatous disease Interferon-γ therapy	Probable invasive pulmonary aspergillosis	Nodular lesion in the right upper lobe	[^{18}F]FDG uptake in the right upper lobe	Yes, persistent uptake of [^{18}F]FDG
10	75	F	Giant cell arteritis Steroids	Definite sinus and pulmonary invasive aspergillosis	No lesion	[^{18}F]FDG uptake in the right upper lobe	No
11	22	M	Relapsing acute leukaemia Allogeneic HSCT, GVHD, steroids	Definite hepatosplenic candidiasis	Six nodular lesions seen on the CT scan	[^{18}F]FDG uptake in the liver with six nodular lesions	No
12	56	M	Chronic lymphoid leukaemia Steroids, alemtuzumab	Definite hepatosplenic candidiasis	Four nodular lesions in the same area of the liver	[^{18}F]FDG uptake in the liver with five nodular lesions	No
13	48	F	Chronic myeloid leukaemia Steroids, allogeneic HSCT	Definite hepatosplenic candidiasis	One nodular lesion seen on the liver on the CT scan	[^{18}F]FDG uptake in the liver with four nodular lesions	No
14	27	M	Testicular cancer Antineoplastic chemotherapy, steroids	Probable hepatosplenic candidiasis	Eight lesions seen in the spleen on the CT scan	[^{18}F]FDG uptake in the spleen with ten lesions	Yes, decrease in [^{18}F]FDG uptake
15	24	M	Hodgkin's disease Allogeneic HSCT, steroids, GVHD	Definite hepatosplenic candidiasis	Five lesions seen in the liver on the CT scan and echography	[^{18}F]FDG uptake in the liver and spleen with seven lesions	Yes, persistence of [^{18}F]FDG uptake at 6 and 9 months
16	54	F	Acute leukaemia Antineoplastic chemotherapy	Definite hepatosplenic candidiasis	No lesion seen in the spleen CT	[^{18}F]FDG in the liver and the spleen	No
17	48	F	Acute leukaemia Antineoplastic chemotherapy	Probable hepatosplenic candidiasis	Three nodular lesions seen in the liver and one in the spleen	[^{18}F]FDG uptake in the liver and spleen, three nodular lesions in the liver and two in the spleen	No
18	49	M	Hodgkin's disease relapsed HIV	Probable hepatosplenic candidiasis	Lesions seen in liver and spleen in the same area of the liver	^{18}FDG uptake in the liver and spleen	No
19	25	M	Acute leukaemia Chemotherapy, allogeneic HSCT	Probable hepatosplenic candidiasis	Lesions seen in the liver and spleen in the same area of the liver	[^{18}F]FDG uptake in the liver and spleen	No
20	34	M	Acute leukaemia Chemotherapy	Probable hepatosplenic candidiasis	Lesions seen in the liver and spleen	[^{18}F]FDG uptake in the liver and spleen	No
21	46	F	Acute myeloid leukaemia Allogeneic HSCT, GVHD	Definite pulmonary histoplasmosis	Pulmonary infiltrates	[^{18}F]FDG uptake in both lungs	No
22	46	F	Uterus cancer, past history of lung histoplasmosis	Positive serology, asymptomatic pulmonary nodules	Multiple nodular lesions in both lungs	No [^{18}F]FDG uptake	No

TABLE 1. (Continued)

Patient	Age (years)	Sex	Underlying disease	Invasive fungal infection and diagnostic modalities	Initial CT findings	Initial PET findings	Follow-up PET findings
23	61	F	No underlying disease	Acute pulmonary coccidioidomycosis	Nodular lesion in the right upper lobe, mediastinal adenopathy	[^{18}F]FDG uptake in the mediastinum and right upper lobe	Yes, decrease in [^{18}F]FDG uptake
24	42	M	No, African man	Mycetoma, *Leptospheria senegalensis*	Osteoarthritis of the lower limb seen on technetium bone scan	[^{18}F]FDG uptake in the right lower limb and right fibula	Yes, decrease in [^{18}F]FDG uptake
25	55	M	No, African man	Mycetoma, *Madurella* spp.	Osteoarthritis of the lower limb seen on technetium bone scan	[^{18}F]FDG uptake in the left lower limb and right tibia	No
26	59	M	Diabetes mellitus African man	*Phomopsis* sp. osteoarthritis	Osteoarthritis seen on technetium bone scan	^{18}FDG uptake in the ankle and tibia	Yes, decrease of the FDG uptake
27	32	M	Cystic fibrosis, chronic liver disease	Definite *Scedosporium apiospermum* spondylitis	High-intensity signal in T10, T11 and T12 on MRI, but not in L2 and L3	[^{18}F]FDG uptake in T10, T11, T12, L2, and L3	Yes, persistence of [^{18}F]FDG uptake, despite antifungal therapy
28	58	F	Non-Hodgkin's malignant lymphoma, rheumatoid arthritis	Probable sinus and pulmonary zygomycosis	Lung infiltrates, sinusitis	No [^{18}F]FDG uptake in the sinus area, [^{18}F]FDG uptake in the lungs	No
29	59	F	Diabetes mellitus	Definite sinus and pulmonary zygomycosis	Multiple nodular lesions in both lungs	[^{18}F]FDG uptake in both lungs and in the mediastinum	No
30	70	M	Chronic lymphoid leukaemia	Definite *Candida krusei* spondylodiscitis	Spondylodiscitis seen in L3 on MRI	[^{18}F]FDG uptake in the L3 spine	No

COPD, chronic obstructive pulmonary disease; CT, computed tomography; F, female; GVHD, graft-versus-host disease; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplantation; M, male; MRI, magnetic resonance imaging; R-CHOP, rituximab + cyclophosphamide + doxorubicin + viucristine + preduisone.

showed a polymorphonuclear infiltrate and hyphae. [^{18}F]FDG-PET revealed at least ten focal areas of increased uptake in the spleen and six in the liver. It is of note that two of these lesions were not detectable on the corresponding CT scan (Fig. 2a). A second [^{18}F]FDG-PET scan was performed 3 months after the first, and showed no uptake (Fig. 2b).

Dimorphic fungal infections. Three patients were evaluated for initial staging of dimorphic fungal infections. Two of them were followed for histoplasmosis and one of them for acute pulmonary coccidioidomycosis.

A 60-year-old female developed acute pulmonary coccidioidomycosis after returning from a 5-week vacation in Irvine, CA, USA. Chest X-ray and CT scanning revealed infiltrates in the upper left lobe. Bronchoalveolar lavage fluid grew *Coccidioides immitis*. [^{18}F]FDG-PET revealed high uptake of [^{18}F]FDG in the left upper lobe. In addition, it also revealed two other foci of [^{18}F]FDG uptake that were not detectable on the CT scan (Fig. 3).

Fungal osteomyelitis. Five patients with musculoskeletal fungal infections were enrolled in this study.

A 56-year-old West African man was admitted for a painless leg ulcer with osteomyelitis. A deep subcutaneous biopsy sample grew *Phomopsis* sp., and [^{18}F]FDG-PET showed uptake in the left ankle (Fig. 4a). The MRI scan had shown the same.

A 55-year-old West African man was admitted for the evaluation and treatment of *Madurella* spp. mycetoma of the left foot (Fig. 4b).

Evaluation of residual IFI with [^{18}F]FDG-PET

[^{18}F]FDG-PET was performed to assess residual IFI in eight cases. In four cases of invasive aspergillosis, uptake of [^{18}F]FDG either decreased or disappeared 4 months after the beginning of antifungal therapy (data not shown). For two patients with chronic disseminated candidiasis, lesions disappeared at 3 and 16 months after antifungal therapy initiation, respectively (sequential follow-up of one representative patient is presented in Fig. 2. These observations, in combination with the normalization of clinical status and biological test results, led us to stop the antifungal therapy, and allowed a new antineoplastic chemotherapy course to be started.

In the last patients, [^{18}F]FDG-PET was performed to assess the evolution of disease identified by conventional tools (Fig. 3b). For instance, a 46-year-old female with a past history of lung histoplasmosis was admitted for evaluation of pulmonary nodules revealed by chest CT while she was receiving chemotherapy and radiotherapy for uterine carcinoma. [^{18}F]FDG-PET was performed and did not show any uptake in the lungs, thereby confirming inactive nodular lesions rather than active infection or malignancy (data not shown).

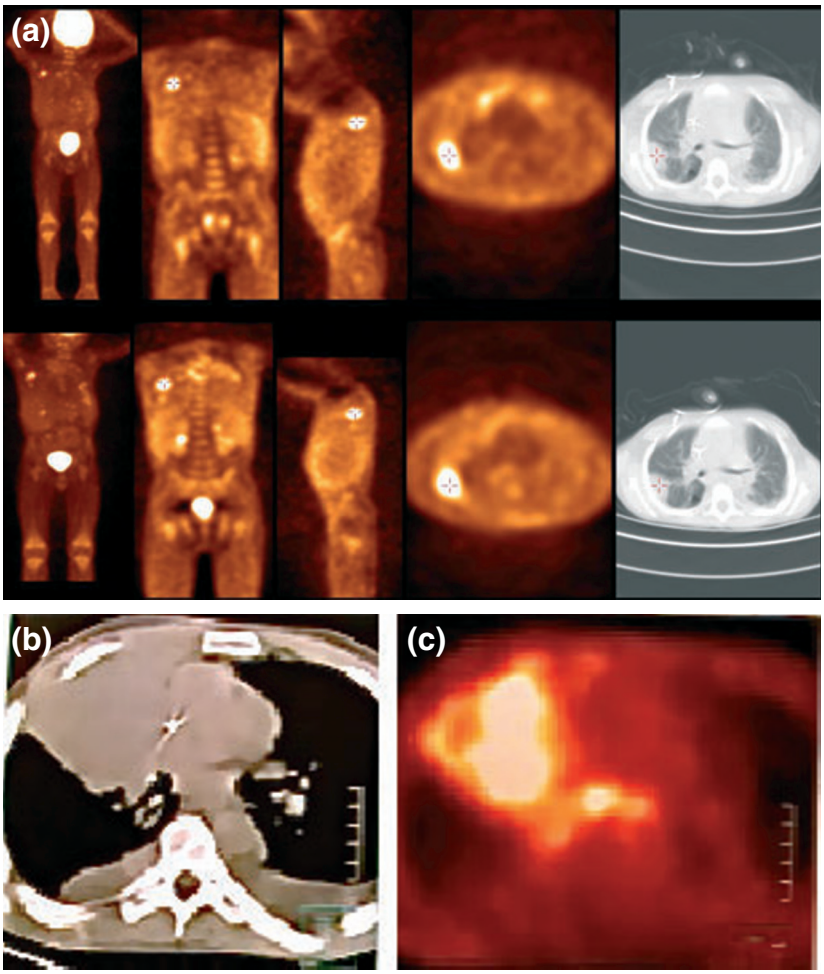

FIG. 1. (a) Coronal emission. Positron emission tomography (PET) with [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG-PET) shows an inflammatory lesion in the right lower lobe. Both PET and computed tomography (CT) gave abnormal findings in the context of invasive pulmonary aspergillosis. (b) Coronal emission. [^{18}F]FDG-PET scan 3 months after bone marrow transplant (BMT). Hypermetabolic lesions have disappeared. (c) [^{18}F]FDG-PET scan shows uptake in the right upper lobe, in accordance with what was observed on the corresponding CT scan. The final diagnosis was, in fact, invasive aspergillosis and relapsing Hodgkin's disease.

In these eight cases, [^{18}F]FDG-PET was performed every 3 months for 1 year, and for two patients, [^{18}F]FDG-PET was performed every 6 months for the following 2 years.

Discussion

We report here the results of the first prospective study evaluating [^{18}F]FDG-PET for the initial and residual staging of a wide range of consecutive IFIs. Our aim was to evaluate this technique and address the challenges of early diagnosis and precise localization of IFI in both immunocompromised [10,11] and immunocompetent patients. Conventional imaging techniques such as CT and MRI provide excellent structural resolution for visualizing advanced disease [5]. However, these modalities may give false-negative results for the detection of early disease, especially in neutropenic patients [12,13]. Preliminary use of [^{18}F]FDG-PET in the oncology setting has revealed cases of false-positive uptake corresponding to a wide range of infections, usually opportunistic in the context of immunosuppression [14]. Here, we show the power of [^{18}F]FDG-PET to detect IFI, with at least the same sensitivity as conventional imaging. In addition, we were also able to detect infectious foci that had not been identified with conventional methods.

Indeed, all areas of infection, whatever the fungal pathogen involved, observed with conventional imaging techniques such as MRI and CT scan were detected by [^{18}F]FDG-PET. It is of note that [^{18}F]FDG-PET was able to detect infected areas of lung, sinus as well as subcutaneous, and bone fungal infections. These results support those obtained in preliminary studies that suggested the clinical usefulness of [^{18}F]FDG-PET for the diagnosis of IFIs in a limited number of patients. Ho *et al.* [15] were the first to demonstrate [^{18}F]FDG uptake, in four cases of lung and hepatosplenic candidiasis. In addition, [^{18}F]FDG uptake was observed in invasive mould infections, involving the lung and brain [16]. Finally, one case of lung cryptococcosis was also associated with [^{18}F]FDG uptake [17].

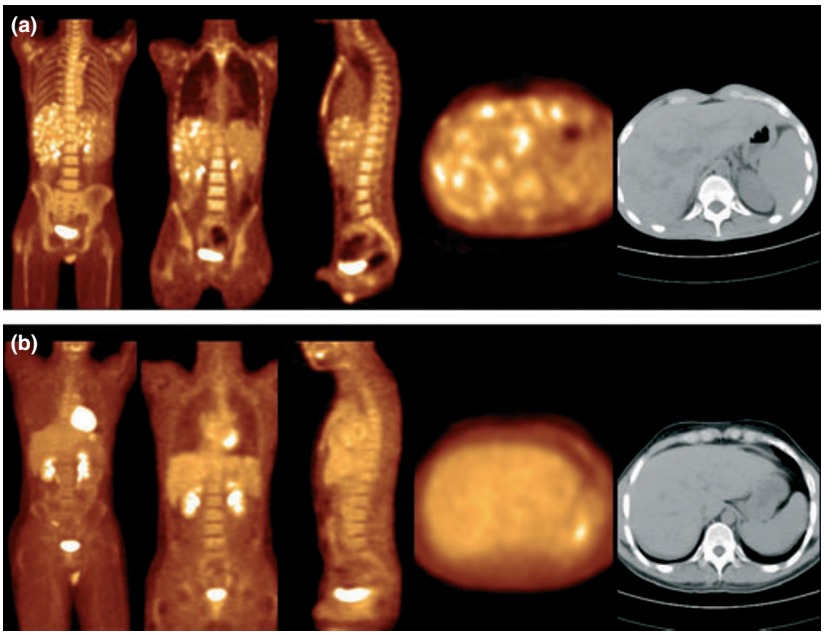

FIG. 2. (a) Accumulation of [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) in the liver before antifungal treatment in a patient with hepatosplenic candidiasis. (b) Three months after the beginning of antifungal therapy, [18F]FDG uptake has disappeared.

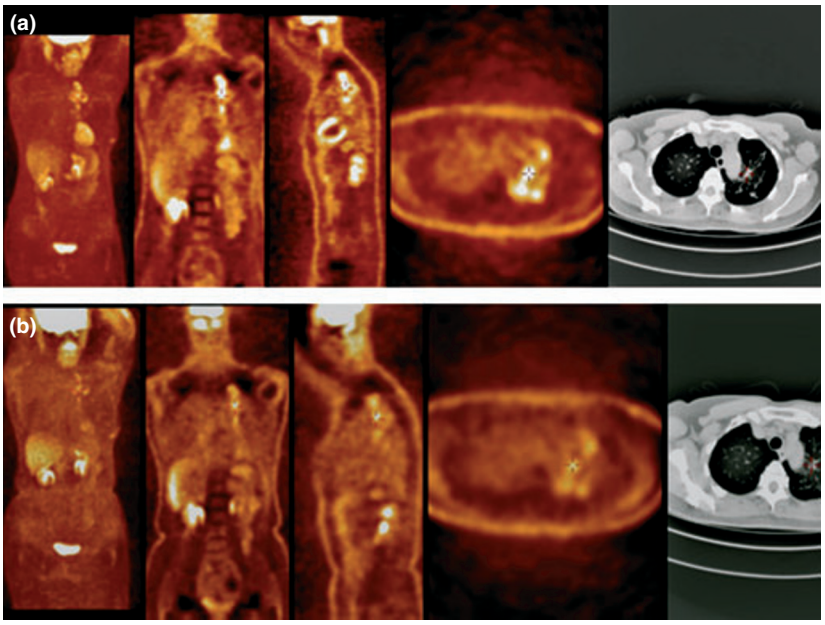

FIG. 3. (a) Chest computed tomography shows a single nodular shadow with an irregular margin, spiculation, convergence of peripheral vessels and pleural indentation, and positron emission tomography with [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) ([18F]FDG-PET) demonstrated accumulation in the left lower lobe and uptake in a mediastinal adenopathy. (b) Three months later, [18F]FDG-PET shows decreased uptake of [18F]FDG in the same area. The diagnosis of coccidioidomycosis was confirmed by bronchoalveolar lavage, which grew *Coccidioides immitis*.

Importantly, [18F]FDG-PET also revealed occult foci of IFI in ten cases, notably new foci in the liver in six cases of chronic disseminated candidiasis, and unidentified foci of infection in two cases of mould sinusitis. Some bone lesions, which had been detected in the two patients with fungal spondylitis, had not been previously detected by the conventional techniques. Together, these results suggest that [18F]FDG-PET is able to detect active functional/metabolic changes reflecting inflammatory cell activity before the onset of anatomical abnormalities as assessed with conventional radiological tools. This is in line with data from Bleeker-Rovers *et al.* [18], who described patients with invasive candidiasis in whom [18F]FDG-PET showed multiple foci of [18F]FDG uptake, contrasting with the lack of abnormality detected with conventional radiological tools.

Although the sensitivity of this new imaging procedure is valuable for assessing various types of IFI, its specificity remains to be determined, especially for discriminating infection from malignancy and inflammatory disease (e.g. in the particular setting of chronic granulomatous disease) [7].

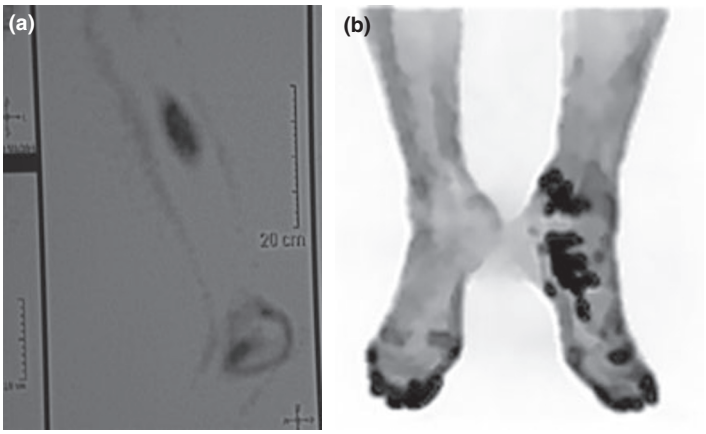

FIG. 4. (a) This patient presented with [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) uptake in the left limb, and this accumulation was caused by a *Phomopsis* sp. post-traumatic infection. (b) Positron emission tomography with [^{18}F]FDG shows accumulation of the isotope in the left foot, corresponding to a proven Madurella foot.

Physicians should consider the potential alternative diagnosis of IFI when discovering pulmonary or hepatic nodules or bone lysis in the oncological setting. Even though high-intensity uptake in patients with central nervous system aspergillosis without evidence of suggestive lesions on CT imaging has been reported [16], we do not recommend the use of [^{18}F]FDG-PET in cases of cerebral IFI, as the cerebral cortex, which uses glucose as a substrate, exhibits spontaneous high uptake of [^{18}F]FDG. During exploration of the thorax, it is desirable that normal organs do not interfere with the interpretation of images. Normal areas in the lungs and mediastinum are not problematic, but the heart may show relatively high uptake of [^{18}F]FDG, especially if the patients has had meals. Indeed, myocardial glucose kinetics are related to feeding state, insulin and free fatty acid levels, and heart work.

Finally, regarding the decision to stop antifungal therapy [19], our data suggest that [^{18}F]FDG-PET might be useful for monitoring the response to antifungal therapy, as shown in six cases of our series. In our experience, the finding of decreased uptake of [^{18}F]FDG at the site of infection could result in a shortened duration of systemic antifungal treatment, without evidence of IFI relapse on subsequent follow-up imaging studies. In the latter six patients, resolution of the infection noted on corresponding CT or MRI was associated with scarring, and occurred several weeks after the decrease or disappearance of [^{18}F]FDG uptake. Furthermore, [^{18}F]FDG-PET providing whole body imaging, may also be a useful tool for the assessment of the overall therapeutic response [19]: preliminary experience in a few patients has suggested that [^{18}F]FDG uptake actually decreases during antifungal therapy [16,20]. However, these results raise questions about the cause of [^{18}F]FDG uptake in IFI. Indeed, in some cases, the [^{18}F]FDG-PET activity persists for a surprisingly long time. This is probably linked to the inflammation that may still surround non-viable fungal elements. The best paradigm remains chronic disseminated candidiasis, in which liver biopsy most often shows inflammatory cells, despite the absence of viable yeasts, and for which uptake of [^{18}F]FDG may persist. This clearly suggests that uptake of [^{18}F]FDG reflects acute inflammation rather than microbiologically active infection as such. We might speculate that experimental animal models could help to identify new imaging tools for distinguishing between active infection and residual local inflammation.

Finally, in these types of patient, especially immunocompromised hosts, an emerging question is the increased risk of cancer. Indeed PET/CT examinations, especially those that include diagnostic CT, result in increased patient radiation exposure as compared with stand-alone CT or PET examinations, as the effective dose is a combination of that from PET and that from CT. Indeed, a recent study demonstrated that whole body PET/CT scanning was accompanied by a substantial radiation dose, with its subsequent cancer risk, especially in young patients. The induced cancer risk was estimated to be 5.5–20.9% higher in the Hong Kong population than in the US population for 20-year-old individuals [21].

In conclusion, [^{18}F]FDG-PET constitutes a valuable and sensitive tool for the initial staging of non-central nervous system IFI, when compared with conventional radiological methods. In addition, our work also suggests that [^{18}F]FDG-PET may be valuable for the assessment of residual IFI. The value of [^{18}F]FDG-PET for determining the optimal duration of antifungal therapy in immunocompromised hosts with IFI now deserves investigation in a prospective study.

Transparency Declaration

The authors declare they do not have any conflict of interest.

References

1. Barnes PD, Marr KA. Risks, diagnosis and outcomes of invasive fungal infections in haematopoietic stem cell transplant recipients. *Br J Haematol* 2007; 139: 519–531.
2. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. *Lancet Infect Dis* 2005; 5: 609–622.
3. Yeo SF, Wong B. Current status of nonculture methods for diagnosis of invasive fungal infections. *Clin Microbiol Rev* 2002; 15: 465–484.
4. Caillot D, Couaillier JF, Bernard A *et al.* Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol* 2001; 19: 253–259.
5. Greene RE, Schlamm HT, Oestmann JW *et al.* Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. *Clin Infect Dis* 2007; 44: 373–379.
6. Legrand F, Lecuit M, Dupont B *et al.* Adjuvant corticosteroid therapy for chronic disseminated candidiasis. *Clin Infect Dis* 2008; 46: 696–702.
7. Kumar R, Basu S, Torigian D, Anand V, Zhuang H, Alavi A. Role of modern imaging techniques for diagnosis of infection in the era of 18F-fluorodeoxyglucose positron emission tomography. *Clin Microbiol Rev* 2008; 21: 209–224.
8. Nakamoto Y, Eisbruch A, Achtyes ED *et al.* Prognostic value of positron emission tomography using F-18-fluorodeoxyglucose in patients with cervical cancer undergoing radiotherapy. *Gynecol Oncol* 2002; 84: 289–295.
9. De Winter F, Vogelaers D, Gemmel F, Dierckx RA. Promising role of 18-F-fluoro-D-deoxyglucose positron emission tomography in clinical infectious diseases. *Eur J Clin Microbiol Infect Dis* 2002; 21: 247–257.
10. Ascioglu S, Rex JH, de Pauw B *et al.* Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; 34: 7–14.
11. Nucci M, Marr KA. Emerging fungal diseases. *Clin Infect Dis* 2005; 41: 521–526.
12. Maertens J, Theunissen K, Verhoef G *et al.* Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis* 2005; 1: 1242–1250.
13. Mahfouz T, Miceli MH, Saghafifar F *et al.* 18F-fluorodeoxyglucose positron emission tomography contributes to the diagnosis and management of infections in patients with multiple myeloma: a study of 165 infectious episodes. *J Clin Oncol* 2005; 23: 7857–7863.
14. Bakheet SM, Powe J. Benign causes of 18-FDG uptake on whole body imaging. *Semin Nucl Med* 1998; 28: 352–358.
15. Ho AY, Pagliuca A, Maisey MN, Mufti GJ. Positron emission scanning with 18-FDG in the diagnosis of deep fungal infections. *Br J Haematol* 1998; 101: 392–393.
16. Chamilos G, Macapinlac HA, Kontoyiannis DP. The use of 18F-fluorodeoxyglucose positron emission tomography for the diagnosis and management of invasive mould infections. *Med Mycol* 2008; 46: 23–29.
17. Igai H, Gotoh M, Yokomise H. Computed tomography (CT) and positron emission tomography with [18F]fluoro-2-deoxy-D-glucose (FDG-PET) images of pulmonary cryptococcosis mimicking lung cancer. *Eur J Cardiothorac Surg* 2006; 30: 837–839.
18. Bleeker-Rovers CP, Warris A, Drenth JP, Corstens FH, Oyen WJ, Kullberg BJ. Diagnosis of *Candida* lung abscesses by 18F-fluorodeoxyglucose positron emission tomography. *Clin Microbiol Infect* 2005; 11: 493–495.
19. Ichiya Y, Kuwabara Y, Sasaki M *et al.* FDG-PET in infectious lesions: the detection and assessment of lesion activity. *Ann Nucl Med* 1996; 10: 185–191.
20. Franzius C, Biermann M, Hulskamp G *et al.* Therapy monitoring in aspergillosis using F-18 FDG positron emission tomography. *Clin Nucl Med* 2001; 26: 232–233.
21. Huang B, Wai-Ming Law M, Khong P-L. Whole-body PET/CT scanning: estimation of radiation dose and cancer risk. *Radiology* 2009; 251: 166–174.