Original article

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Fluorine-18-fluorodeoxyglucose PET/CT in hematopoietic stem cell transplant patients with fusariosis: initial findings of a case series review

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Background **Fusariosis is an opportunistic fungal infection that affects mostly leukemic and hematopoietic stem cell transplant patients. Locally invasive and disseminated infection may occur. Treatment is challenging, and besides evaluation of immune status, one also needs to take into account organ involvement to predict the duration and prognosis.**

Objective **The aim of this study was to present the findings and clinical follow-up from a series of cases of *Fusarium* spp. infections in patients subjected to hematopoietic stem cell transplant evaluated with one or more fluorine-18-fluorodeoxyglucose (18F-FDG) PET/CT scans, according to the source of clinical culture sample (blood or wound secretion).**

Results **Ten patients were included. In this series, 18F-FDG PET/CT was able to detect osteomyelitis in three patients.**

Conclusion **Although having a small number of patients and lack of standard approach, 18F-FDG PET/CT seemed useful to discriminate uncomplicated cases of primary bloodstream infections and detect occult foci of metastatic infection in patients with positive cutaneous lesions cultures.** ***Nucl Med Commun*** **00:000–000**

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Introduction

Fusariosis (i.e. infections caused by genus *Fusarium*) is an emerging fungal disease that affects mainly immunocompromised hosts with a wide range of clinical manifestations from localized onychomycosis [1] to disseminated infection [2–5] including sinusitis and pneumonia [6]. Portal of entry may be the respiratory tract, cutaneous lesions, especially nail-fold inflammatory lesions of toes, or vascular catheters. Little is known about the pathophysiology and organ involvement in disseminated cases. Neutropenia is a major risk factor for dissemination, and recovery of neutrophil count is crucial for infection resolution [7]. Other risk factors for this invasive fungal disease, in hematopoietic stem cell transplant (HSCT) population, include acute graft-versus-host disease and high dose or prolonged corticosteroid use. In disseminated form, clinical presentation may include presence of multiple subcutaneous nodules, with or without necrosis. Blood culture findings are often positive [8].

Histopathology of *Fusarium* spp. lesions usually shows hyaline, septate hyphae in tissues branching in right and acute angles. These findings are not specific and are similar to *Aspergillus* spp. lesions. Culture from clinical specimens showing typical fusiform hyaline septate macroconidia raises the diagnostic evidence of *Fusarium* spp. Taxonomy is difficult, and most species responsible for opportunistic infections can be grouped into three complexes: *Fusarium solani* species complex, *F. oxysporum* species complex, and *F. fujikuroi* species complex. Correct identification at species level requires DNA-based identification techniques [9] and/or new technologies like MALDI-TOF identification system [10], not available for most mycology laboratories. The management of fusariosis cases is difficult, and disseminated disease is often fatal [11]. Despite improvement in the past decade, survival rates 90 days after diagnosis of fusariosis in leukemic and HSCT patients stay at ~50% [12]. There is no biological marker validated for diagnostic purposes or to guide treatment. Galactomannan test result, an antigen detection-based test commonly used for diagnostic of invasive aspergillosis in neutropenic patients, may be positive in some fusariosis cases, but its role in diagnostic or treatment evaluation remains unclear [13]. *Fusarium* spp. is intrinsically resistant to echinocandins and fluconazole. Main drugs used for therapy are lipid formulations of amphotericin B (L-AMB) and voriconazole (VOR). Antifungal susceptibility profile may show high minimum inhibitory concentrations to VOR and

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L-AMB, although species-specific and strain-specific differences occur. In practice, susceptibility to L-AMB, VOR, and posaconazole is unpredictable, and there is no consensus on what is the best drug for initial or empiric therapy [14]. In general, these are expensive medicines and may cause serious adverse events or significant drug interactions. There is no specific recommendation for duration of therapy, but 12 weeks or longer courses are usual [15].

PET with fluorine-18-fluorodeoxyglucose (^{18}F-FDG) combined with low-dose diagnostic computed tomography (CT) can be used to detect foci of infections. Fluorine-18 is a cyclotron-produced radioisotope that undergoes natural positron decay. ^{18}F-FDG is an unspecific marker regularly employed for cancer diagnosis because of high glucose consumption by neoplastic cells, but it also accumulates in infected tissues because of increased uptake of glucose by active inflammatory cells. There is an international guidance about the use of ^{18}F-FDG PET/CT in the diagnosis and follow-up of patients with suspected inflammatory or infectious processes [16,17]. Use of ^{18}F-FDG PET/CT has been demonstrated in evaluation of fever of unknown origin [18] and fever in patients with neutropenia [19,20]. Although lacking of well-controlled studies, there is evidence that ^{18}F-FDG PET/CT can be an interesting tool, providing important information in cases of candidiasis [21,22], cryptococcosis [23,24], histoplasmosis [25,26], aspergillosis [27,28], coccidioidomycosis [29], and mucormycosis [30,31]. PET/CT can measure the amount of ^{18}F-FDG uptake in a standardized and comparable way expressed as standardized uptake value (SUV). Measurable changes in SUV in suspicious or confirmed foci of infection during treatment probably reflect the metabolic activity of the inflammatory cells involved and could be useful to guide therapy, including bacterial osteomyelitis [32] and pulmonary fungal infections [33].

This study describes the results of ^{18}F-FDG PET/CT scans of immunosuppressed HSCT patients with a suspect or confirmed *Fusarium* spp. infection based on a positive mycology culture finding.

Patients and methods

We analyzed retrospectively medical data from patients submitted to HSCT, in a single center, from January 2010 to December 2014, with confirmed *Fusarium* spp. isolation from a clinically significant specimen (blood culture or cutaneous wounds). All patients who were submitted to one or more ^{18}F-FDG PET/CT scans were included. There was no restriction against including patients already on antifungal therapy when PET/CT was performed. There were no specific exclusion criteria, but availability of PET/CT during the study period and clinical condition of patients influenced the inclusion. Follow-up examinations were not regularly scheduled, but some were performed according to medical decision and patient condition. Results of ^{18}F-FDG PET/CT scans were analyzed according to the source of positive *Fusarium* clinical specimen, in correlation to final clinical diagnosis, activity of the infection, and survival 365 days beyond the first positive culture. All PET/CT examinations included in this analysis were personally reviewed by the authors. Despite being a retrospective review of cases, during the study period, all patients were clinically examined by the author, at least monthly, until death or 1 year after last culture. Patients with positive blood cultures were considered disseminated by definition. Patients with ^{18}F-FDG PET/CT suspected foci of infection at any location and any time after positive culture were classified as possible (unspecific findings) or probable (highly suggestive findings) complicated infections according to clinical and radiological follow-up. If microbiologic (culture) or histopathologic examination of the suspicious foci was obtained and positive for *Fusarium* spp., patients were considered proven as having complicated infection.

Microbiological isolation and identification of fungi was done as follows: samples from different clinical specimens from patients were analyzed at local mycology laboratory. All samples were seeded in Sabouraud with chloramphenicol (Difco; Detroit, Michigan, USA) and Mycosel (Difco) agar medium and incubated at 30°C for 5 days. To study the microscopic and macroscopy colony features, the isolates were subcultured on potato dextrose agar medium (Difco) incubated at 30°C for 7 days. Morphological identification of the genus was performed by conventional morphological criteria [33,34]. Virulence test by thermotolerance was performed and confirmed for all isolates by potato dextrose agar medium (Difco) for 7 days at 35° and 37°C.

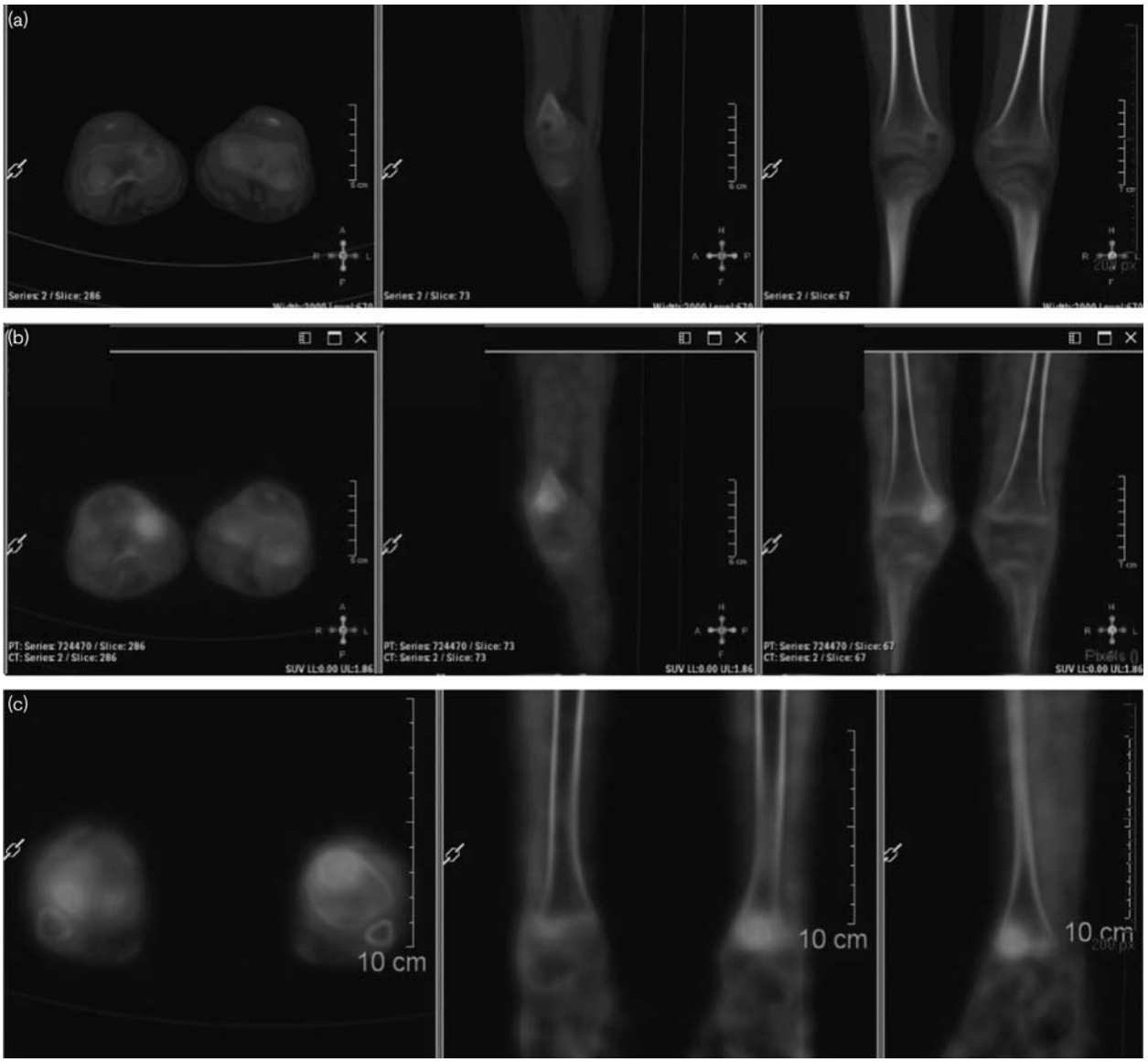
^{18}F-FDG PET/CT protocol was as follows: all patients were instructed to fast for at least 4 h, and serum glucose levels were measured before the injection of ^{18}F-FDG. PET/CT scans were performed on a Phillips Gemini TF (Phillips Healthcare; Cleveland, Ohio, USA) about 60 min after the injection of ^{18}F-FDG (0.12 mCi/kg) with 1-min per bed

Table 1 Demographic and clinical features of HSCT patients with positive culture for *Fusarium* spp.

Characteristics	*N*
Sex (male/female)	5/5
Average age at transplantation (range) (years)	22.5 (5.8–47.2)
Type of HSCT	
Autologous	5
Allogeneic related donor	5
Mean number of days between first culture and HSCT (range)	−17 (−117 to +26)
Source of culture	
Blood	5
Cutaneous lesions	5
Neutropenia between culture and first PET/CT (days)	
<7	5
>7	5
Mean number of days between first culture and first PET/CT (range)	34 (6–105)

Evaluated with one or more ^{18}F-FDG PET/CT scans.
CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; HSCT, hematopoietic stem cell transplant.

Fig. 1



Computed tomography (CT) and PET/CT images in a child with Burkett's lymphoma submitted to autologous bone marrow transplant 46 days before. Images obtained 35 days after the first positive blood culture result for *Fusarium* spp. (a) Low-resolution CT shows round lytic lesion at medial condyle of right femur. (b) Combined image PET/CT shows local high fluorine-18-fluorodeoxyglucose uptake (standardized uptake value = 1.72). (c) Combined image PET/CT displaying hypermetabolic nodules at distal epiphysis of both tibias (standardized uptake value = 1.25 left and standardized uptake value = 1.12 right).

position. The CT parameters were 90 mAs and 120 kV. CT scans were not of diagnostic quality and were used for anatomic registration and for attenuation correction. Emission data were corrected for dead time and random and scatter coincidences. Iterative reconstruction method was applied. All examinations were visually and semiquantitatively analyzed by two experienced nuclear medicine physicians. Maximum standardized uptake value (SUV_{max}) (corrected for total injected activity and patient weight) analysis was performed.

This study was approved by our institutional review board, with a waiver of informed consent.

Results

During the study period, 15 patients undergoing HSCT had at least one clinical significant cutaneous lesion culture (five patients) or blood culture-positive (10 patients) for *Fusarium* spp. Five could not be evaluated with ^{18}F-FDG PET/CT scans mostly because of severity of disease and clinical instability (all five were bloodstream infections,

and mean survival time after blood culture was 49 days; all died of uncontrolled infection), but 10 of them could be evaluated by one or more ^{18}F-FDG PET/CT scans ($n = 20$). Some demographic and clinical features of these patients are shown on Table 1.

Clinical and radiological classification according to source of culture

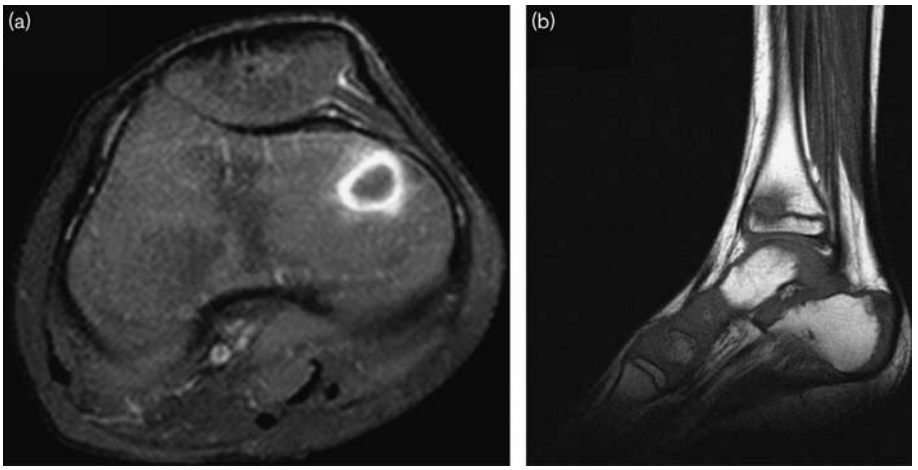
Blood

Five patients had one or more positive blood cultures for *Fusarium* spp. Among them, two were considered uncomplicated bloodstream infections, as they showed no signs of abnormal ^{18}F-FDG uptake. The other three were considered complicated disseminated infection with probable secondary osteomyelitis in one patient (Figs 1 and 2) and possible disseminated infection with deep muscular and subcutaneous hypermetabolic nodules in two patients (two nodules each patient, culture was not obtained). One patient died 63 days after first positive blood culture, with active infection (osteomyelitis). The other four were alive and free of infection at 1-year follow-up.

Skin lesion

Five patients had *Fusarium* spp. isolated in secretions from cutaneous wounds (two intertrigo, one paronychia, and two biopsies of nodules in the subcutaneous tissue). Three of them had disseminated disease with secondary osteomyelitis (two cases) and striated muscle and subcutaneous tissue involvement. Clinical, radiological, and laboratory follow-up confirmed the diagnosis of disseminated fusariosis. In two patients, infection was confirmed by subsequent culture of suspected foci (proven complicated disseminated), and one patient (see Table 3) was considered probable complicated disseminated according to clinical and radiological follow-up (no biopsy for culture was attempted). One case had clinically localized *Fusarium* spp. infection (interdigital intertrigo between second/third left toes) diagnosed before autologous transplant. The ^{18}F-FDG PET/CT showed a hypermetabolic large lesion at left lumbar paravertebral musculature, but biopsy revealed neoplastic infiltration, not infection. Clinical and laboratory follow-up confirmed the diagnosis of uncomplicated localized infection. Other patient developed intertrigo lesion 4 days after autologous HSCT. PET/CT done 35 days after culture and

Fig. 2



Nuclear magnetic resonance of the same patient performed 3 days after the PET/CT revealed images highly suggestive of bone abscess (osteomyelitis). (a) Right knee and (b) right ankle. Patient died of metabolic complications during treatment before any other procedure could be performed.

Table 2 Number of patients by clinical form of fusariosis according to ^{18}F-FDG PET/CT scans findings and source of positive culture and 1-year survival status

	Blood	Cutaneous lesion	One-year survivors	Total
Uncomplicated bloodstream infection	2	0	2	2
Disseminated infection with bone involvement	1	2	1	3[a]
Disseminated infection without bone involvement	2	1[b]	3	3
Localized infection	0	2	2	2
Total	5	5	8	10

CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose.
[a]One patient bone involvement was confirmed by culture, and in the other two, osteomyelitis was diagnosed by radiological and clinical evolution.
[b]Confirmed by histopathology of subcutaneous lesion detected by PET/CT.

with antifungal therapy did not reveal suspicious foci of distant infection and showed almost resolution of primary lesion. This was considered localized uncomplicated infection (resolved).

Clinical and radiological features in complicated disseminated disease

Among those 10 patients, six were considered possible complicated disseminated infections, with or without osteomyelitis, on the basis of the findings of ^{18}F-FDG PET/CT (Table 2).

^{18}F-FDG PET/CT scans in possible disseminated fusariosis cases (six patients) showed multiple foci (mean count = 4; range = 2–8 foci per patient) of increased glucose uptake, with a mean SUV_{max} of 3.31 (range = 1.5–8.7). These foci were localized in muscles, subcutaneous tissue and bone. The great majority of these high glucose uptake focal areas in the connective tissue were localized in lower limbs (22 out of 24), one in temporal muscle and one in the forearm. In two patients with disseminated disease, ^{18}F-FDG PET/CT also revealed hypermetabolic lesions in lungs (one patient) and esophagus mucosa (one patient). No involvement of the liver, spleen or adrenal glands was noted in any case. Six patients had profound neutropenia (< 100 neutrophils/mm^3) and four were neutropenic for more than 7 days after the isolation of *Fusarium* spp. and before the first PET/CT examination. Bone impairment was noted only in patients with more than 7 days of profound neutropenia.

Results and interpretation of follow-up PET/CT exams

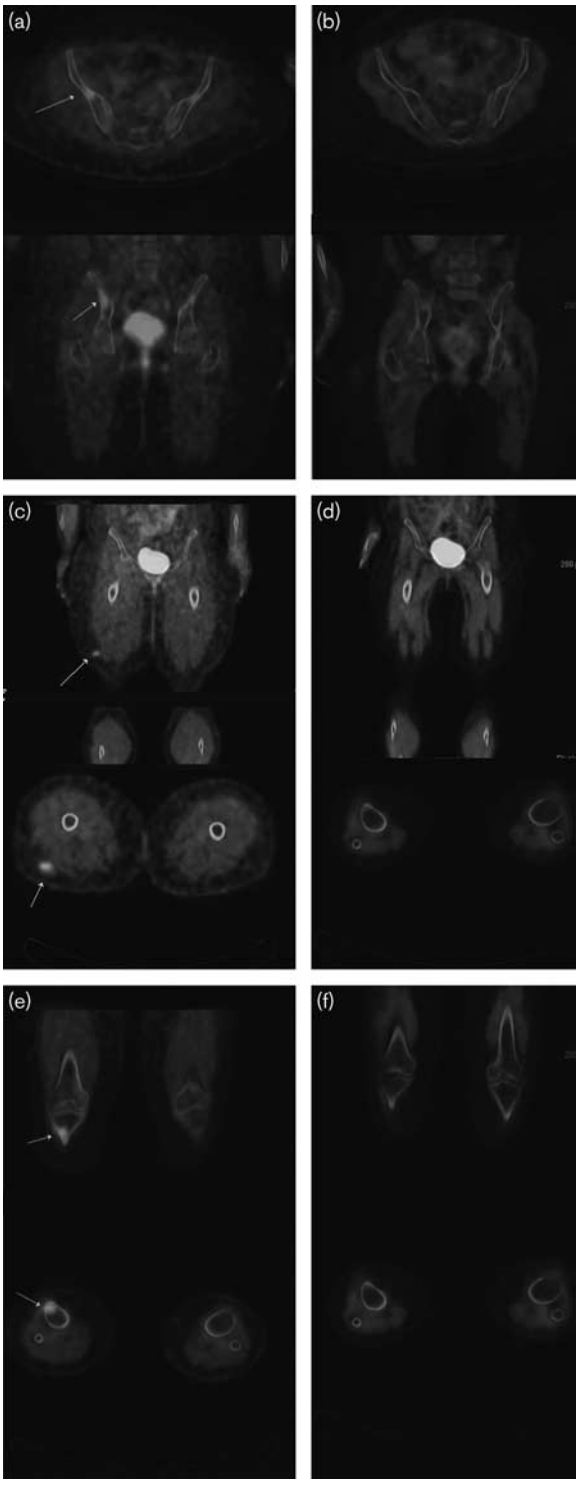
Four patients with probable/possible disseminated disease were subjected to two or more PET/CT scans. Table 3 shows the results of six sequential examinations performed in a patient with aplastic anemia presenting with paronychia of the left first toe before HSCT. In this patient, first PET/CT was done 6 weeks after the positive culture finding (wound secretion from nail-fold) and 74 days before the transplant. Before the first PET/CT,

Table 3 Distribution and SUV_{max} of ^{18}F-FDG hypermetabolism foci observed over time with sequential PET/CT scans in a patient with aplastic anemia and disseminated fusariosis

Local	SUV_{max}					
Right ilium	3.3	2.6	2.2	0	0	0
Right femur (diaphysis)	4.4	3.9	3.0	3.0	2.5	1.7
Right tibia (epiphysis)	3.6	2.6	2.4	1.8	2.2	0
Rigth tibia (diaphysis)	3.5	2.6	2.4	2.2	2.9	1.9
Left tibia (diaphysis) A	3.3	2.8	2.1	2.1	2.7	1.7
Left tibia (diaphysis) B	4.4	3.3	2.5	2.4	3.0	2.4
Distal phalange first left foot	2.4	2.1	0	0	0	0
Subcutaneous tissue right tight	3.4	0	0	0	0	0
Timing of PET/CT						
Days since culture	43	82	118	172	201	278
Days since HSCT	−74	−35	1	55	84	161

CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; HSCT, hematopoietic stem cell transplant; SUV_{max}, maximum standardized uptake value.

Fig. 3



Comparison between first (a, c, and e) and last (b, d, and f) PET/CT fusion images in a patient with aplastic anemia, who presented with left toe paronychia before allogenic hematopoietic stem cell transplant. Hypermetabolic nodular lesions shown at right ilium (a), right thigh subcutaneous tissue (c), and right tibia epiphysis (e). Last control examination performed 235 days apart and after 260 days of liposomal amphotericin B shows complete resolution with no abnormal standardized uptake value at corresponding sites (b, d, and f, respectively). See also Table 3.

patient received 8 days of liposomal amphotericin and 1 day of VOR intravenous therapy. Last scan was realized 18 days after suspension of systemic antifungals from a total time of therapy of 143 days of VOR and 260 days of L-AMB. Figure 3 shows the comparison of images from first and last PET/CT. This patient was alive and considered free of infection at 1-year follow-up.

Two cases of disseminated fusariosis, in deeply immunosuppressed allogeneic recipients were followed with three (from 19 days until 140 days after first *Fusarium* spp. isolation) and with two (8 and 40 days after first *Fusarium* spp. isolation) ^{18}F-FDG PET/CTs. These examinations showed multiple hypermetabolic focal areas involvement of bones, muscles, and lymph nodes. On both cases, there was appearance of new focal areas of increased marked glucose uptake and variation in SUV_{max} with increase in some previous observed areas and decrease uptake in others. Both patients died of fusariosis, 256 and 73 days after the microbiological diagnostic, despite combination therapy with VOR and L-AMB.

One recipient of autologous HSCT was followed with two PET/CT scans, 6 and 214 days after the isolation of *Fusarium* spp. from a blood culture. This patient had less than 7 days of neutropenia, and after bone marrow recovery, was considered only mildly immunosuppressed. First examination was not suggestive of complicated infection with normal physiologic distribution of ^{18}F-FDG except by some activity ($SUV_{max} = 2.5$) in subcutaneous tissue at site of recent central venous catheter puncture. On the second examination, two new focal areas of high ^{18}F-FDG uptake were noted, on subcutaneous tissue and muscles at right gluteal region ($SUV_{max} = 2.8$), despite previous therapy with VOR (69 days) and L-AMB (21 days). As the patient was asymptomatic and baseline diseased was under remission, no other therapy was added. At 1-year follow-up, patient was alive and the infection was considered clinically cured.

Discussion

Evaluation for extension of disease in an immunocompromised host with a positive result from a mycology culture of a skin lesions is often a challenge [35,36]. This study offers the contribution of ^{18}F-FDG PET/CT in helping the evaluation of immunocompromised patients with a suspicion of fusariosis, on the basis of mycological isolation of *Fusarium* spp. in clinical specimens. Although the number of cases is very small, in our experience, it seemed useful to differentiate disseminated versus locally invasive infection in patients with positive cultures from cutaneous lesions. In this series, three cases of disseminated infection were identified among five patients with *Fusarium* spp. positive cultures from a cutaneous lesion. In two cases, suspicion of disseminated disease was high as the source of culture was a biopsy of subcutaneous nodule. In these two patients, PET/CT revealed other clinically undetected foci of infection (one case of proven culture periarticular abscess). In a patient with paronychia, the lesion seems to be the portal of entry, and multiple clinically silent bone lesions were detected (Table 3). As culture of suspicious lesions was not obtained, the case was classified as probable on the basis of clinical and radiological follow-up. Dissemination was ruled out in two patients with *Fusarium* intertrigo.

Positive blood cultures are often associated with serious disease and prolonged courses of antifungals. According to our analysis, PET/CT was able to discriminate patients with infectious metastatic complications from those with bloodstream infection only. Two out of three patients with positive blood cultures and PET/CT signs of muscular and skeleton involvement died versus none (1-year survival) of the two with uncomplicated bloodstream infections. It is important to note that in one patient with bloodstream infection, a first examination performed less than 1 week after culture did not show metastatic infection, but a second PET/CT more than 6 months later was suggestive of resolving deep muscle abscess (possible infection, other causes not ruled out). Results must be interpreted with caution. Among main limitations are the small number of patients and variation in time of PET/CT acquisition after first positive culture finding.

Owing to low number of patients and lack of standard approach, the value of negative examinations to rule out complication (metastatic infection) cannot be determined.

In our case series, most of suspected *Fusarium* spp. lesions on disseminated cases occurred in bone, muscle, subcutaneous tissue and lymph nodes. The number and localization of lesions were very similar among our cases. Owing to low number of patients and lack of identification of *Fusarium* at species level, we could not assert that these are typical of disease.

Areas of elevated SUV_{max} were noted in esophagus and lung in two cases of disseminated disease. These could also represent inflammatory reaction at the portal of entry for the fungus or another concomitant infection with unidentified etiology.

Follow-up with a second or more PET/CT scans was possible in four the disseminated cases. Despite low number of cases, and different times of follow-up, there seems to have a relation between appearance of new lesions and a poor prognosis, as two of three patients with new lesions at follow-up examinations died compared with a patient with no new lesion who survived. There are no specific examinations or laboratory parameters to evaluate the effect of antifungal treatment in fusariosis. Although there are no standards to define cure or resolution using ^{18}F-FDG PET/CT in infectious lesions, ^{18}F-FDG PET/CT progressive reduction of SUV, disappearance of previous lesion, and no appearing of new lesions could be considered indicators to evaluate efficacy of antifungal therapy. More structured approach, with a great number of patients to evaluate the utility of

sequential examinations, in defining treatment of complicated cases might be interesting. In our cases, the follow-up PET/CTs were not previously programed, and ideal schedule for examinations could not be determined.

Lipid formulations of amphotericin B (lipid complex or liposomal) and VOR are highcost medications in many parts of the world. It is plausible that in most cases, a few days of antifungal treatment expenses overload the cost of a PET/CT examination [37]. In our opinion, it is probably cost-effective to evaluate with one or more ^{18}F-FDG PET/CTs to avoid undertreating patients with extensive disease (osteomyelitis) or treating patients with no signs of complications for too long.

A revision paper about uses of PET/CT in fungal infections has been published but did not include any cases of fusariosis [38]. Utility of ^{18}F-FDG PET/CT to detect a mycotic aneurism in acute myeloid leukemia with disseminated fusariosis case was reported [39]. Use of serial ^{18}F-FDG PET/CT examinations (at baseline and at 2 and 4 months) in a child with B-cell acute lymphoblastic leukemia, who developed multiple widespread subcutaneous nodules caused by *Fusarium* spp., was considered useful for early evaluation to antifungal therapy response [40].

To our knowledge, this is the first study about the use of ^{18}F-FDG PET/CT in a series of patients with fusariosis. This series of cases represents the experience of a single reference tertiary hospital in a subset of patients submitted to HSCT over a 5-year period. More studies are necessary to assess the full potential of this technology in the management of fusariosis cases.

Conclusion

In this case series, ^{18}F-FDG PET/CT helped to evaluate the extent of *Fusarium* spp. infections in some patients submitted to HSCT. Complicated infections involved mainly bone, muscle, and subcutaneous tissue. A more structured approach could be useful for monitoring the response to antifungal treatment in complicated cases.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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