Detection of Disseminated Aspergillosis on FDG PET/CT in a Patient with Acute Lymphoblastic Leukemia

Nir Hod MD MHA[1], Reut Anconina MD[1], Daniel Levin MD[1], Ekaterina Tiktinsky MD[1], Dina Ezroh Kazap MD[1], Itai Levi MD[2], Maria Zektser MD[2], Vered Stavi MD[2], Gilbert Sebbag MD[3] and Sophie Lantsberg MD[1]

[1]Institute of Nuclear Medicine and Molecular Imaging and Departments of [2]Hematology and [3]Surgery Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

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Invasive fungal infection (IFI) is an uncommon but serious life-threatening disease, which mostly affects immunosuppressed patients. Recently, due to the increase in the number of immunosuppressed patients, *Aspergillus* has become one of the most common pathogens responsible for fatal IFI [1]. Diagnosis of such infections may be difficult. However, early recognition of disseminated aspergillosis may reduce morbidity and mortality caused by this pathogen, which is more difficult to treat than other fungi, such as *Candida*.

^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) is a well-known useful imaging technique, which is mostly used to detect neoplastic diseases. The technique fuses metabolic imaging of FDG uptake with excellent anatomical resolution of CT. FDG is a glucose analog combined with positron emitting radionuclide, which merely detects glucose metabolism. It is able to concentrate not only in neoplastic diseases but also in cells involved in infection and inflammation, especially in neutrophils and macrophages, which are able to concentrate FDG. The high uptake in activated granulocytes is based on the fact that these cells use glucose as an energy source after activation during the metabolic burst.

FDG PET/CT is becoming more relevant for the diagnosis of several infectious and inflammatory diseases as well as therapy monitoring. Research results describe the usefulness of FDG PET/CT in the diagnosis, management, and follow-up of patients with sarcoidosis, spondylodiscitis, peripheral bone osteomyelitis, fever of unknown origin, and vasculitis [2]. However, for fungal infections, hard evidence is lacking. Preliminary case reports note that FDG PET/CT could be a useful tool.

We present a case of invasive aspergillosis in a young patient presenting with a hematological malignancy that developed disseminated multi-organ involvement, including pulmonary, hepatosplenic, renal, and multiple intramuscular lesions, following chemotherapy. We pay special attention to the potential role of FDG PET/CT in the diagnosis and therapy monitoring of IFI, which supports the results obtained in preliminary studies.

PATIENT DESCRIPTION

A 46 year old man presented with pancytopenia. A bone marrow biopsy was compatible with the diagnosis of B-cell acute lymphoblastic leukemia (B-ALL) with negative Philadelphia chromosome; negative 12, 21 translocation; and with some copies of the *AML-1* gene.

The patient started chemotherapy treatment according to the GMALL protocol. During his chemotherapy treatment, he developed neutropenia and fever, which were not responsive to antibacterial therapy. A contrast-enhanced CT scan showed several nonspecific hypodense lesions in the liver and spleen. The patient was referred for FDG PET/CT to determine more accurately the nature of the lesions and to identify any other lesions not detected by CT.

FDG PET/CT images showed intensely increased FDG uptake in multiple lesions, including the liver and spleen but also in renal, lung (not seen), and multifocal intramuscular lesions [Figure 1]. It is of interest that several hypermetabolic lesions were not demonstrated on the corresponding CT images of the study. Initial percutaneous tissue and microbiological investigations from the liver were not diagnostic and did not confirm infection or malignancy. Therefore, the patient was referred for open liver biopsy guided by FDG PET/CT from the most prominent hypermetabolic lesions seen in the right hepatic lobe. Biopsy ruled out malignant involvement, and microbiological investigation was compatible with the diagnosis of invasive aspergillosis infection. The patient was treated with Amphotericin B antifungal therapy.

Despite antifungal therapy, the patient's clinical condition was not resolved and he underwent a series of follow-up FDG PET/CT scans that revealed persistence of the hepatosplenic fungal infection with some of the lesions showing significantly higher FDG uptake compared with the baseline PET images. The anatomical size of many lesions did not show significant change on the corresponding CT images.

Moreover, the serial scans demonstrated the appearance of new hepatic and splenic hypermetabolic lesions, some of which were not apparent on the corresponding CT images [Figure 1B, Figure 1C]. The results of the scans provided evidence for the progression of the disease indicating that the antifungal therapy was unsatisfactory; therefore, the antifungal therapy was switched and enhanced with the addition of voriconazole. However, the results of the follow-up FDG PET/CT scans clearly showed that the hypermetabolic lesions still persisted, thus indicating that the chronic *Aspergillus* infection was not well-controlled yet and necessitated long-term antifungal treatment. Although repeated bone marrow biopsies revealed hematological remission, stem cell transplantation was postponed due to the persistent IFI, which markedly increases the patient's risk for failure in this condition.

COMMENT

In the past few decades, there has been a considerable increase in both the frequency and importance of IFIs. This increase is directly related to the growing population of immunocompromised individuals, resulting from advances in medical practice such as the use of intensive chemotherapy, immunosuppressive drugs, and growing stem cell transplantation possibilities. Human immunodeficiency virus and other diseases that cause immunosuppression have also contributed to this problem. In the clinical practice, IFI mostly affects patients with hematologic malignancies, such as leukemia or lymphoma. Fungal infections in such patients continue to have a high mortality rate [1]. Despite recent improvement, the therapy for treating IFIs is still disappointing, with high failure rates in both invasive candidiasis and invasive aspergillosis [1]. The mortality rate for invasive aspergillosis is even higher than for invasive candidiasis. Therefore, such infections must be diagnosed as early as possible and appropriate treatment should be initiated immediately. Diagnosis of disseminated fungal infection can be only established via biopsy since CT, ultrasonography, and magnetic resonance imaging (MRI) yield non-specific results. In recent years, the use of FDG PET/CT in inflammatory and infectious diseases is rapidly increasing and is already the gold standard for some indications. However, the application of FDG PET/CT in fungal infection has not yet been well defined in the literature or by the guidelines [2]. The indications are rapidly evolving and these guidelines cannot be seen as definitive.

In our case, CT helped in the initial identification of some of the lesions. However, it lacked both sensitivity and specificity. Metabolic changes precede ana-

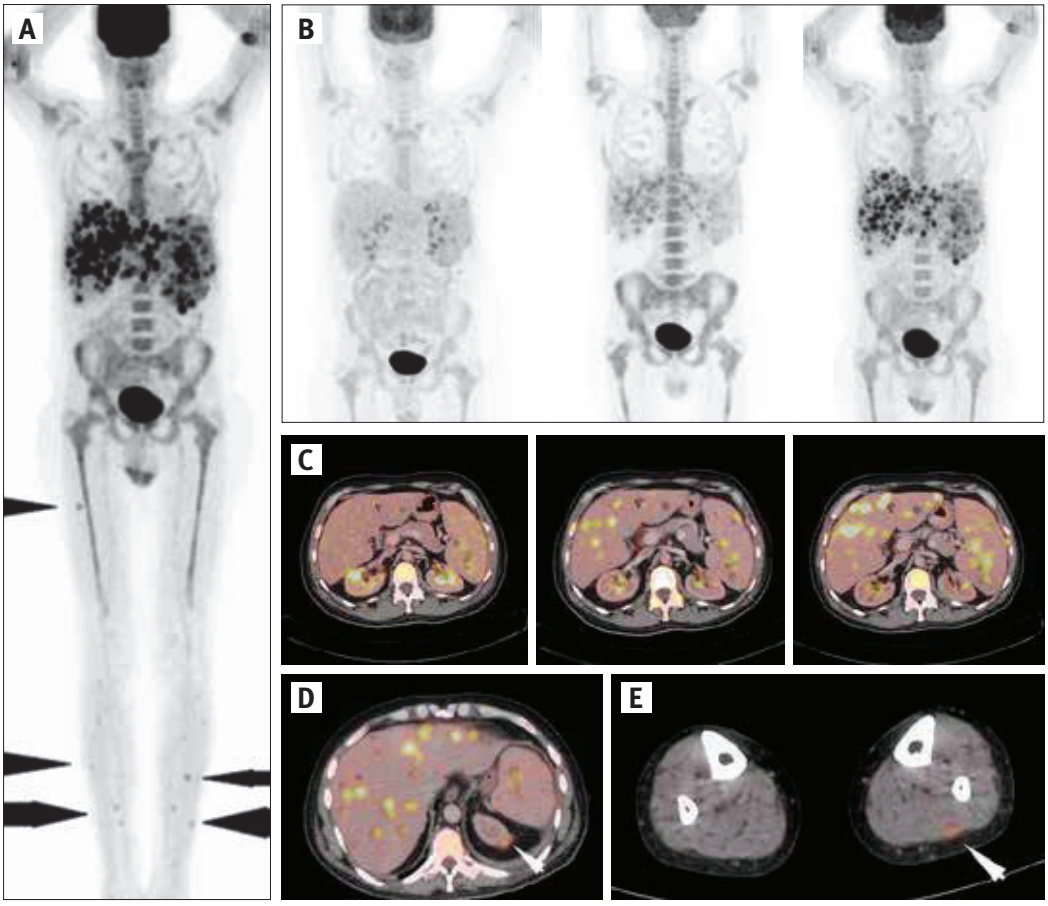

Figure 1. ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) images. **[A]** Whole body maximum intensity projection image shows multifocal lesions in the liver and spleen with intensely increased FDG uptake. In addition, numerous hypermetabolic lesions were seen in the muscles of the lower extremities (arrows). **[B]** Serial follow-up scans (chronologically performed from left to right) revealed that the uptake of the lesions in the liver and spleen increased despite enhancement of antifungal therapy with appearance of multiple new hypermetabolic lesions, many of them were unrecognized on CT components of the study, indicating progression of the disease and unsuccessful therapy. **[C]** Serial axial fusion PET/CT scans (chronologically from left to right) showed the appearance of new lesions. **[D]** Left kidney involvement is demonstrated (arrow). **[E]** One of the intramuscular lesions is demonstrated in the left leg (arrow). Many of the lesions were initially unapparent on the CT component of the study

tomical changes so modern hybrid imaging of PET/CT, which integrates high anatomical resolution with metabolic changes, are likely to detect these infections at an earlier stage with higher diagnostic accuracy rates. Research results have highlighted the advantages of PET/CT in imaging fungal infections [3-5]. FDG PET/CT frequently found occult lesions that were not found with other imaging techniques, and the results helped to determine treatment length.

Clearly it is of invaluable importance to have a noninvasive whole-body technique to localize all fungal lesions (even in the presence of severe neutropenia) and to have a way to monitor disease activity to decide whether therapy can be stopped, should be prolonged, or should be switched.

Disseminated fungal lesions seen on ultrasound, CT, or MRI have been found to persist for a long time after successful antifungal treatment due to conditions such as fibrosis; therefore, these imaging modalities may have limitations in assessing therapeutic effect and guiding therapy. In contrast, FDG PET/CT provides more accurate information on therapeutic response, especially for residual metabolically active focal deposits in IFIs. FDG PET/CT allows whole body imaging, which may detect any uptake throughout the body in one imaging session and thus is likely to pick up infectious foci that may not yet have become clinically apparent and were not detected by other imaging studies. This phenomenon was consistently demonstrated in a number of papers. In a literature review article [5], FDG PET/CT correctly predicted disease progression, whereas MRI findings suggested improvement. In another study, after completion of antifungal therapy for hepatosplenic and renal abscess before restarting chemotherapy, FDG PET/CT detected lesions in the skeletal and cardiac muscles, and in the lungs, that showed antifungal treatment failure; hence, a different antifungal therapy was given and lesions resolved. The preliminary papers, however, usually involved a limited number of patients [3-5].

CT and MRI depend on structural resolution for visualizing disease but nuclear medicine techniques can detect in vivo pathophysiological changes before anatomical changes are observed. Modern hybrid imaging modality of PET/CT provides a unique opportunity to combine the excellent anatomical resolution with metabolic functional information to diagnose, localize, and stage IFIs at a very early stage. The overall agreement of the studies is that FDG PET/CT is useful in staging IFIs [3-5]. It is helpful to know the extent of the infection and the organs involved before the onset of therapy, not only to correctly stage it during infection, but also to decide later if the infection disappeared after completion of the therapy to exclude recurrence. However, histological confirmation must always be performed for a final diagnosis, as well as for distinguishing between active infection and residual local inflammation. FDG PET/CT is able to define the sites of active infection where biopsy is likely to provide the correct diagnosis.

CONCLUSIONS

This case demonstrated the diagnostic potential of FDG PET/CT in detecting invasive aspergillosis, including guidance for the most appropriate site for biopsy, detection of the true extension of the disease and evidence for fungal infection activity, and monitoring the antifungal treatment effectiveness by a series of FDG PET/CT scans. Further investigation with a larger patient cohort is warranted.

Correspondence
Dr. N. Hod
Institute of Nuclear Medicine and Molecular Imaging, Soroka University Medical Center, Beer Sheva 84101, Israel
Phone: (972-8) 640-0754
Fax: (972-8) 638-3695
email: hod_n@yahoo.com

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Capsule

Giving antibodies a boost

Persistent immune activation during chronic infections is often associated with increased generation and deposition of immune complexes. The actions of antibody-based drugs can thus be severely impaired in individuals with chronic infections. Using lymphocytic choriomeningitis virus (LCMV) as a model of chronic infection, **Wieland** and colleagues examined how to enhance antibody functions in this setting. The ability of antibodies to deplete target cells was dependent on antigen expression levels. Furthermore, afucosylation of antibodies directed against CD4 and CD8α enhanced their ability to deplete $CD4^+$ and $CD8^+$ T cells in mice persistently infected with LCMV. Whether afucosylation can be universally used to enhance antibody functions during chronic infections remains to be seen.

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