The Use of FDG PET/CT in the Diagnosis and Monitoring of Disseminated Aspergillosis

Ora Shovman MD[1,2]

[1]Zabludowitz Center for Autoimmune Diseases, Department of Internal Medicine 'B' and Rheumatology Unit, Sheba Medical Center, Tel Hashomer, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

The prevalence of life-threatening fungal infections in immunocompromised patients has been gradually increasing in the last decades. This high-risk population includes patients with prolonged neutropenia, allogeneic hematopoietic stem cell transplant, solid organ transplant, inherited or acquired immunodeficiencies, corticosteroid use, and other conditions. Aspergillosis is one of the most common fungal infections, and may involve the eyes, ears, larynx, lungs, and sinuses in its localized form [1]. Immunocompromised patients are prone to develop disseminated multisite disease, with the lung being the most common site of invasive aspergillosis, reflecting the usual portal of entry. The dissemination to other organ systems, including the central nervous system, heart, kidney, and liver, usually occurs by a hematogenous dissemination. Culture of *Aspergillus* species in combination with the histopathologic demonstration of tissue invasion by hyphae provides ultimate evidence of invasive aspergillosis.

In such cases, early diagnosis and evaluation of response to antifungal treatments is of high importance. Although definitive diagnosis is made by histopathologic analysis, several technologies may raise the suspicion of an aspergillosis infection.

Currently, computed tomography (CT) and magnetic resonance imaging (MRI) may provide excellent structural resolution for visualizing advanced diseases but they generally have limited value in detecting early disease. ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) is a metabolic imaging technique that may be used to identify lesions associated with early fungal infection, reveal the extent of the infection, and monitor the treatment response to antifungal therapy [2,3].

In this issue of the *Israel Medical Association Journal* (*IMAJ*), an interesting case report by Hod and colleagues [4] illustrates the application of FDG-PET/CT in an immunocompromised patient with acute lymphoblastic leukemia who developed invasive disseminated aspergillosis. Following chemotherapy treatment, the patient presented with fever and neutropenia and underwent a CT that revealed only liver lesions. In contrast, a FDG-PET/CT that was performed shortly afterward demonstrated widespread disease involving the liver, spleen, kidneys, lungs, and muscles. Moreover, FDG-PET/CT was useful in guiding an open liver biopsy from the most prominent hypermetabolic lesions that revealed a fungal infection, whereas a previous percutaneous biopsy from the liver was inconclusive. FDG-PET/CT was also used to monitor the progression of the disease and the appearance of new lesions despite different antifungal therapies. The scan revealed that the treatment was unsatisfactory. Due to these findings, it was decided that bone marrow transplantation is necessary, despite hematological remission in bone marrow biopsy [4].

This case provides additional evidence regarding the potential role of FDG-PET/CT in the diagnosing, monitoring of disease activity, guiding of biopsy, and making of clinical decisions in patients with invasive aspergillosis. A different study investigated additional applications of FDG PET/CT in patients with aspergillosis and reported that FDG PET/CT may help in differentiating between invasive and non-invasive aspergillosis [5]. While invasive aspergillosis usually presents with multiple hypermetabolic nodules, non-invasive aspergillosis presents with solitary isometabolic nodules with a halo pattern.

It should be noted that in some cases, pulmonary aspergillosis can mimic a lung malignancy with regard to clinical manifestations and radiological signs on FDG PET/CT [6,7]. Therefore, histopathologic evaluation is necessary for definitive diagnosis before deciding about further treatment strategy.

CONCLUSIONS

FDG PET/CT may be used for the diagnosis and management of aspergillosis in immunocompromised patients. However, only limited research results exist regarding this application of FDG PET/CT, and additional studies are required.

Correspondence
Dr. O. Shovman
Dept. of Internal Medicine B, Sheba Medical Center, Tel Hashomer 5265601, Israel
email: orashovman@walla.co.il

References

1. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; 63: 1-60.

2. Sharma P, Mukherjee A, Karunanithi S, et al. Potential role of 18F-FDG PET/CT in patients with fungal infections. *AJR Am J Roentgenol* 2014; 203: 180-9.

3. Franzius C, Biermann M, Hülskamp G, et al. Therapy monitoring in aspergillosis using F-18 FDG positron emission tomography. *Clin Nucl Med* 2001; 26: 232-3.

4. Hod N, Anconina R, Levin D, Tiktinsky E, Ezroh Kazap D, Levi I, Zektser M, Stavi V, Sebbag G, Lantsberg S. Detection of disseminated aspergillosis on FDG PET-CT in a patient with acute lymphoblastic leukemia. *IMAJ* 2018; 20: 717-9.

5. Kim JY, Yoo JW, Oh M, et al. 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography findings are different between invasive and noninvasive pulmonary aspergillosis. *J Comput Assist Tomogr* 2013; 37: 596-601.

6. Wilkinson MD, Fulham MJ, McCaughan BC, Constable CJ. Invasive aspergillosis mimicking stage IIIA non-small-cell lung cancer on FDG positron emission tomography. *Clin Nucl Med* 2003; 28: 234-5.

7. Baxter CG, Bishop P, Low SE, Baiden-Amissah K, Denning DW. Pulmonary aspergillosis: an alternative diagnosis to lung cancer after positive [18F]FDG positron emission tomography. *Thorax* 2011; 66: 638-40.

Capsule

Role of stem cell-like memory t cells in systemic lupus erythematosus

Stem cell-like memory T (Tscm) cells are long-lived memory T cells that have multipotent capacity to differentiate into different subsets. However, the role of Tscm cells in autoimmune diseases remains unclear. **Lee** et al. performed phenotypic studies to identify Tscm cells in patients experiencing systemic lupus erythematosus (SLE). CD4+ and CD8+ Tscm cells were identified in SLE patients and healthy controls (HCs). In in vitro culture systems, CD4+ Tscm cells were induced to differentiate into subsets of T cells, including follicular helper T (Tfh) cells, and cytokine production patterns were assessed after stimulation. After confirming induction of transcription factors for Tfh cells, the capacity of CD4+ Tscm-derived Tfh cells to help B cells was analyzed by measuring antibody secretion. The percentages of CD4+ and CD8+ Tscm cells among the naive CD4+/CD8+ or total CD4+ T cell populations were significantly higher in SLE patients than in HCs. Stimulated Tscm cells from SLE patients could replenish themselves and differentiate into other T lymphocyte subsets, including Tfh cells upon stimulation with T cell receptor. Production of T cell factor 1, which is an inducer of Tfh, was also increased. The differentiated Tfh cells increased antibody production by autologous B cells.

Arthritis Rheumatol 2018; 70: 1459

Eitan Israeli

Capsule

PD-1+ T cells prompt pulmonary fibrosis

Although immunological T cells expressing programmed cell death 1 (PD-1) are sometimes described as exhausted, they are not too exhausted to wreak havoc in a variety of settings. **Celada** and colleagues examined cells from patients with sarcoidosis or idiopathic pulmonary fibrosis and saw an increase in PD-1+ CD4+ T cells relative to healthy controls. These cells were mostly T helper 17 cells and were able to induce fibroblasts to produce collagen in vitro. Blocking PD-1 in the co-culture system prevented this induction and associated cytokine production from the T cells. Furthermore, blocking PD-1 in a mouse model of pulmonary fibrosis reduced fibrosis symptoms.

Sci Transl Med 2018; 10: eaar8356

Eitan Israeli

Capsule

Waking up in a trap

Cancer patients who have undergone successful treatment can experience a relapse of their disease years, or even decades, later. This is because cancer cells that have disseminated beyond the primary tumor site enter a state of dormancy, where they remain viable but and not proliferating. Eventually, by mechanisms that are poorly understood, these clinically undetectable cells "wake up" and form actively growing metastases. Studying mouse models, **Albrengues** and co-authors found that sustained lung inflammation and the accompanying formation of neutrophil extracellular traps (NETs) could convert dormant cancer cells to aggressive lung metastases. Awakening of these cells was associated with NET-mediated remodeling of the extracellular matrix and could be prevented by an antibody against the remodeled version of a matrix protein called laminin-111.

Science 2018; 361: eaao4227

Eitan Israeli