



F-18 FDG PET/CT in NK/T-Cell Lymphoma that Progressed from Epstein-Barr Virus-Associated Hemophagocytic Lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome involving an uncontrolled immune response with variable triggers. HLH is rare but highly fatal, even with proper treatment; therefore, early recognition and diagnosis are crucial for management. Although the role of F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in HLH is poorly defined, it can provide valuable information on disease status and possible triggers. Herein, we report an F-18 FDG PET/CT study on a case of NK/T-cell lymphoma that progressed from Epstein-Barr virus-associated HLH.

Keywords F-18 FDG PET/CT · Hemophagocytic lymphohistiocytosis · Epstein-Barr virus · NK/T-cell lymphoma

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome that involves a hyperinflammatory condition due to a disrupted normal immune response. Traditionally, HLH was classified into primary and secondary HLH—the former being a purely genetic disease and the latter being an acquired disease. However, the distinction between primary and secondary HLH is ambiguous. Patients with primary HLH often experience triggering events such as infection, whereas genetic predispositions can be found in patients with secondary HLH [1]. Therefore, it is more favorable to categorize HLH according to its specific etiology. Various malignant and non-malignant conditions, including infection, neoplasm, and autoimmune disease, can trigger HLH. Viral infections are triggering factors in more than one-third of adult HLH cases, Epstein-Barr virus (EBV) infections being the most frequent cause [2]. F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has been used to detect and evaluate a wide range of malignancies by visualizing the metabolic activity

of organs and tissues. Moreover, it has a potential role in the assessment of infectious and inflammatory diseases due to the high F-18 FDG uptake by neutrophils and macrophages [3]. Therefore, F-18 FDG PET/CT can be a valuable tool for the assessment and management of HLH. Herein, we report an F-18 FDG PET/CT study of a case of T-cell lymphoma that progressed from EBV-associated HLH.

Case Report

A 56-year-old woman presented to our institution with persistent fever. The patient's laboratory test results were as follows: red blood cells, $3.72 \times 10^6/\mu\text{L}$; white blood cells, $2000/\mu\text{L}$; hemoglobin, 10.7 g/dL; platelets, $81 \times 10^9/\text{L}$; ferritin, 1902 $\mu\text{g}/\text{L}$; lactate dehydrogenase, 570 U/L; triglycerides, 405 mg/dL; aspartate aminotransferase, 54 U/L; alanine aminotransferase, 15 U/L; C-reactive protein, 4.14 mg/dL; and erythrocyte sedimentation rate, 4 mm/h. Blood culture did not grow any microorganism, and test results for anti-nuclear antibodies and antineutrophil cytoplasmic antibody were negative. The viral load on EBV real-time polymerase chain reaction (PCR) assay was 857,667 copies/mL, and an abdominal CT revealed splenomegaly. The patient met five out of the eight diagnostic criteria in the HLH-2004 guideline [4]: fever, splenomegaly, cytopenias, hypertriglyceridemia, and hyperferritinemia.

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The patient underwent F-18 FDG PET/CT to evaluate the cause of suspected HLH. PET/CT revealed mildly increased FDG uptake in the cervical and retroperitoneal lymph nodes (SUV_{max} = 3.0), and diffuse FDG uptake in the liver and spleen (SUV_{max} = 7.1). Several focal uptakes of FDG in the bones, especially in the periarticular area of the long bones (SUV_{max} = 6.0), were also observed (Fig. 1). When referring to previous reports, underlying hematologic malignancies were suspected [5–7]. Biopsies of the bone marrow and liver were performed to rule out hematologic malignancy. However, there was no evidence of malignancy.

The patient was diagnosed with EBV-associated HLH, and treated with dexamethasone and etoposide. A month later, the patient's symptoms resolved, and the viral load on EBV real-time PCR assay reduced to 2832 copies/mL. The patient was discharged and followed up in an outpatient clinic.

A year later, the patient visited our institution because of nasal discomfort. Nasal endoscopy and CT revealed a mass in the right nasal cavity. A biopsy was performed to evaluate the nasal mass, and histopathologic results confirmed a case of NK/T-cell lymphoma. The patient underwent PET/CT to assess the extent of the disease, which revealed a mass with intense FDG uptake (SUV_{max} = 32.8) in the nasal cavity, suggesting lymphoma involvement (Fig. 2). Chemotherapy with dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) regimen was initiated immediately after the diagnosis. The patient tolerated the treatment well, without significant events. Two months later, PET/CT

was performed to evaluate the patient's response to therapy. The metabolic activity in the nasal cavity had disappeared, and there was no abnormal FDG uptake (Fig. 3).

Discussion

HLH is a fatal disease with high morbidity, even with proper treatment, and prompt diagnosis is crucial for patient management. However, diagnosis can be difficult because symptoms (fever and hepatosplenomegaly) and laboratory results (cytopenias, hypertriglyceridemia, and hypofibrinogenemia) of HLH are non-specific. Furthermore, anatomic imaging techniques, such as CT and magnetic resonance imaging (MRI), provide little information on this disease. Only brain MRI is recommended for cases in which central nervous system disease is suspected [4]. On the other hand, PET/CT can provide valuable clinical clues on the extent and possible causes of the disease.

Currently, there is no consensus on the role of PET/CT in the HLH-2004 guidelines [4]. However, there are a few studies on the clinical value of PET/CT in HLH. Kim et al. [8] reported that six of fourteen HLH patients in their study had malignancy, and that PET/CT detected malignancy in five out of these six patients. Yuan et al. [9] evaluated the clinical value of F-18 FDG PET/CT in patients with secondary HLH. PET/CT identified 22 possible triggers from 45 HLH patients: 5 infections, 1 lupus, 2 rheumatic arthritis, 1 adult-onset Still's disease, and 13 lymphomas. Zheng

Fig. 1 F-18 FDG PET/CT at initial diagnosis. PET/CT shows diffuse FDG uptake in the liver and enlarged spleen (SUV_{max} = 7.1), several hypermetabolic lymph nodes in the neck and retroperitoneum (SUV_{max} = 3.0), and multiple bone marrow uptakes (SUV_{max} = 6.0)

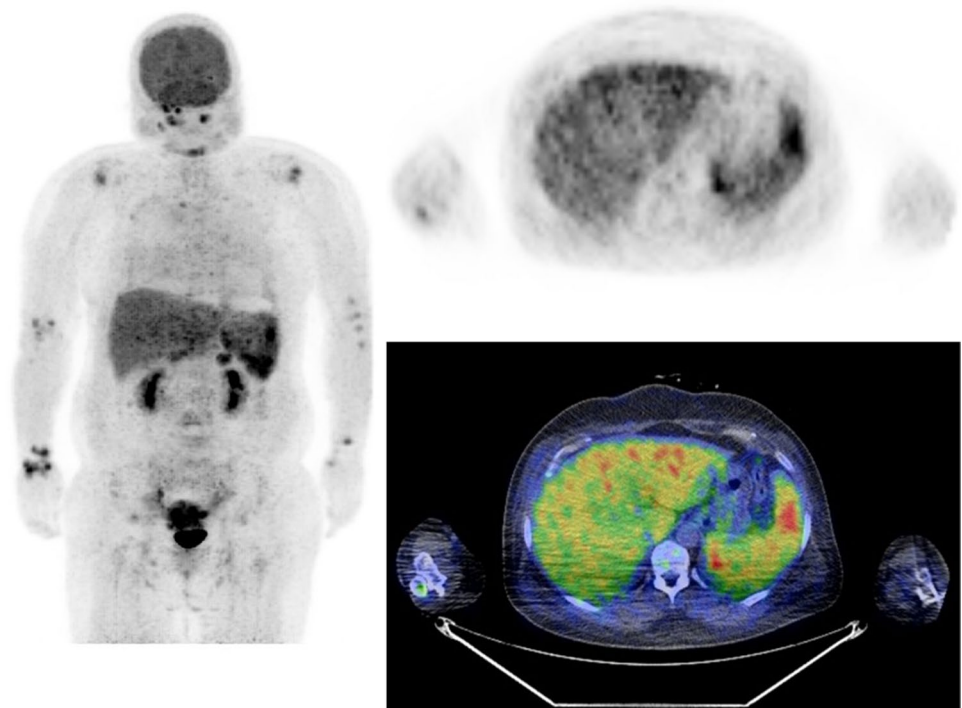


Fig. 2 F-18 FDG PET/CT was performed to evaluate the extent of NK/T-cell lymphoma. A mass with intense FDG uptake ($SUV_{max} = 32.8$) is seen in the right nasal cavity. Multiple, focal, mild FDG uptake suggestive of inflammatory change is also seen in both the lungs

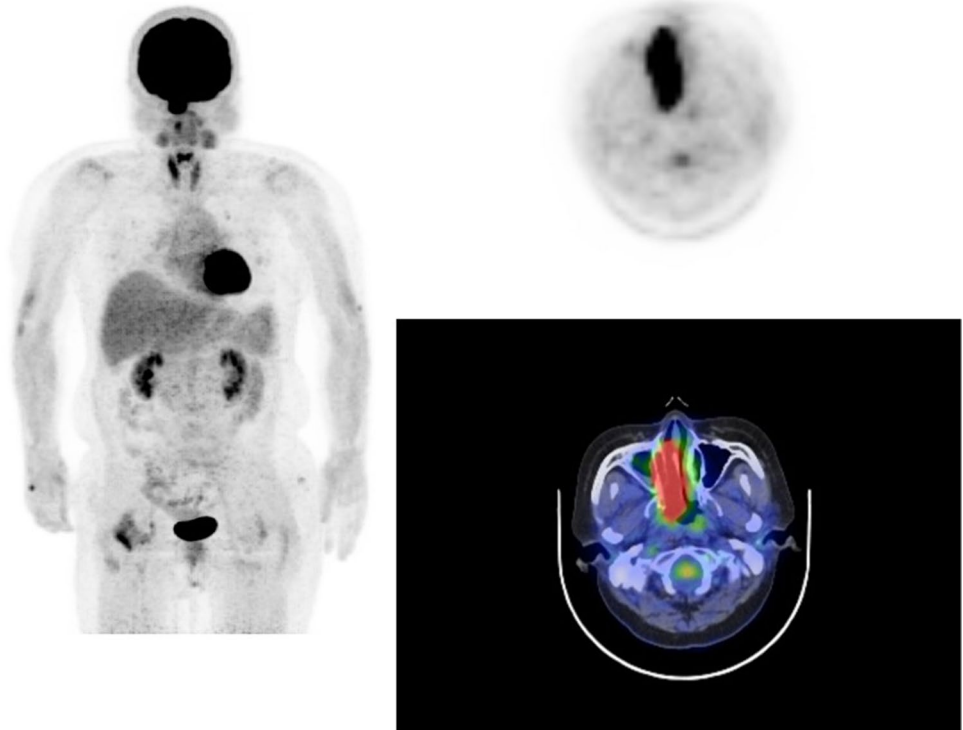
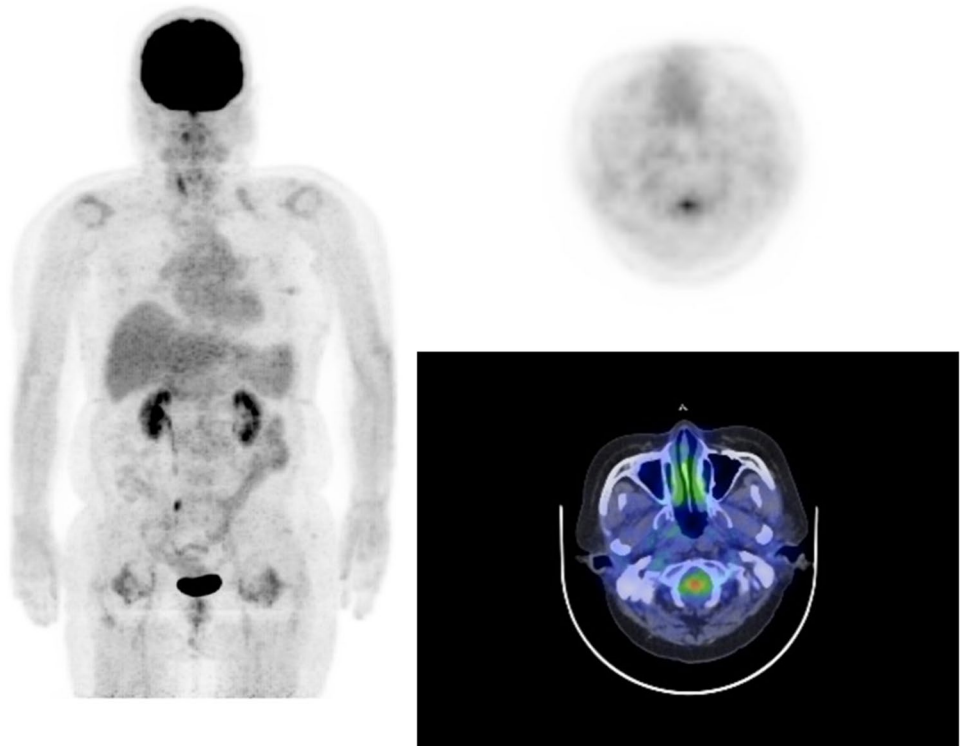


Fig. 3 F-18 FDG PET/CT after the chemotherapy for NK/T-cell lymphoma. Disappearance of the metabolic activity in the nasal cavity mass. Mild FDG uptake is seen in both the lungs, without any significant change



et al. [10] also investigated the role of F-18 FDG PET/CT in secondary HLH. PET/CT was helpful in determining the

potential causes of HLH in 65.1% (28/43, 25 lymphomas) of the patients in their study.

Unfortunately, most studies have focused on the usefulness of PET/CT at initial diagnosis, and there are few studies on the role of PET/CT in the monitoring of disease status in HLH patients. Given that a subsequent proportion of EBV-associated HLH can progress to T-cell lymphoproliferative disease after initial treatment of HLH [11, 12], utilizing PET/CT as a disease monitoring tool in EBV-associated HLH seems reasonable.

In this case, NK/T-cell lymphoma developed after initial treatment in a patient with EBV-associated HLH. PET/CT was performed at the initial diagnosis, and underlying hematologic malignancies were suspected. Follow-up PET/CT was performed after the histologic diagnosis of lymphoma, which showed the occurrence and extent of the disease. The third PET/CT was useful for evaluating the response to chemotherapy for lymphoma. Based on these serial PET/CT findings, we propose the use of PET/CT as a disease monitoring tool in the management of EBV-associated HLH.

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Author Contribution The study was designed by Il-Hyun Kim. Material preparation and data collection were performed by Il-Hyun Kim and Joon-Kee Yoon. The image interpretation was performed by Il-Hyun Kim, Su Jin Lee, Young-Sil An, and Joon-Kee Yoon. The first draft of the manuscript was written by Il-Hyun Kim and Joon-Kee Yoon, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of Data and Material Please contact author for data requests.

Declarations

Competing Interests Il-Hyun Kim, Young-Sil An, Su Jin Lee, and Joon-Kee Yoon declare that they have no competing interests.

Ethics Approval and Consent to Participate This study was approved by the Institutional Review Board (AJIRB-MED-EXP-21) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The institutional review board waived the need to obtain informed consent.

Consent for Publication The institutional review board waived the need to obtain informed consent because of the anonymity and the retrospective nature of the study.

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