Detection of Lymphomatous Marrow Infiltration using F-18 FDG PET at Initial Staging and after chemotherapy

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국문초록

목적 : 악성 림프종 환자에서 골수 침범 여부를 평가하는 데 있어 FDG PET 스캔의 유용성을 장골 골수 생검에 비교하여 평가하고자 한다. **대상 및 방법**: 73명의 림프종 환자(남:녀=43:30, 평균 연령 47세)를 대상으로 하였다. 이 중 69명은 비호지킨성 림프종이었으며 4명은 호지킨성 림프종이었다. FDG PET은53명의 환자에서 병기 결정을 목적으로, 20명에서는 치료후 효과 평가를 위해 시행되었다. 골수 침범에 대한 최종 판정은 두 검사의 일치성으로 판단되었으며 서로 다른 경우엔 장골 골수 생검, 방사선 검사 소견, 그리고 추적 검사에 의해 결정되었다. **결과**: 73명중 54명(74%)에 있어 FDG PET과 장골 골수 검사 결과가 일치하였다. 두 검사 모두 음성인 환자는 54명중 47명이었으며 모두 양성인 환자는 7명이었다. 두 검사가 불일치 하는 경우는 19명이었으며 이 중 6명은 골수 검사는 음성이었으나 FDG PET에서 양성 소견을 보였다. 반대로 12명에서는 FDG PET은 음성이었으나 장골 골수 생검상 골수 침범이 확인되었다. 불일치 결과를 보인 19명 중 마지막 1명의 환자에서는 골수 생검상 음성이었으나 FDG PET에서 위양성 소견을 보였다. **결론** : FDG PET은 림프종 환자의 병기 결정에 있어 장골 골수 검사상 발견되지 않은 골수 침윤을 발견하는 데 도움이 되어 골수 생검에 보조적인 역할이 있었다. PET 검사상 횡격막 상하 림파절 침범과 다수의 골수 병변이 있는 환자에 있어 골수 생검의 필요성에 대해서는 치료 방침이나 예후를 변화시킬 수 있는지의 여부를 보는 연구가 필요하리라 생각된다. 치료후 효과를 판정하는 데 있어 FDG PET은 골수의 현미경학적 잔존 질환을 평가하는 데 있어 골수 생검을 대체하기는 어려울 것으로 사료된다.

Key Words : FDG PET, bone marrow, lymphoma

Introduction

Malignant lymphoma is a heterogeneous group of diseases characterized by a malignant proliferation of cells of the lymphoid system. The pattern and frequency of bone marrow (BM) involvement of the two separate disorders, Hodgkin's disease (HD) and the more common non-Hodgkin's lymphoma (NHL), may vary depending on the cell type of lymphoma. In patients with HD, marrow involvement is rather rare at presentation, and could be seen in 5-32% of patients over the course of the disease progression. A histologic pattern of lymphocyte depletion or mixed cell type may be more frequently associated with marrow involvement at diagnosis. It can be focal, multifocal, or diffuse infiltration and focal lesions are more likely to be seen in the bone marrow distant from the iliac crests.[1-4] With NHL, it is found in about 50-80% of patients with low grade

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and 25-40% with high grade at diagnosis.) Compared to low grade, high grade NHL seems to be more often combined with focal marrow infiltration other than the iliac crest.[4,6)]

Evaluation of bone marrow at presentation has a great importance in staging and subsequently treating the patients with malignant lymphoma.[8)] It is, hence, considered to have a prognostic value. It is also necessary after chemotherapy to confirm complete response in patients with initial marrow involvement or suspected marrow disease. Of various modalities for the detection of lymphomatous marrow involvement, iliac crest biopsy has been served as the standard diagnostic procedure. It reveals the histology of marrow infiltration by lymphoma and assesses the status of normal marrow precursors. In spite of its advantage detecting even microscopic disease, the sensitivity of marrow biopsy suffers from sampling errors and the yield is closely related to the sizes and numbers of the samples.[7)] Accurate staging of the patients with focal marrow involvement other than the iliac crest can be easily missed by iliac crest biopsy since it provides little information on the marrow status outside the iliac crest. F-18 Fluorodeoxyglucose (FDG) Positron emission tomography (PET) is a whole body imaging modality that has successfully detected malignant diseases of various histologic types. Although there is low level of a physiological uptake of FDG in the bone marrow, it is conceivable that PET can differentiate lymphomatous marrow involvement from normal marrow. This study was undertaken to elucidate the potential role of FDG PET in detecting marrow infiltration compared to iliac crest biopsy in patients with lymphoma at staging and follow-up.

Materials and Methods

We reviewed retrospectively medical records of our hospital from June 2002 to March 2003 and selected those patients who were diagnosed with malignant lymphoma. The study population was limited only to those patients with FDG PET study for either staging or evaluation of treatment response one or upto 2 months after a standard course of chemotherapy. Seventy-three patients (30 females and 43 males, a mean age of 47 years old, 4 Hodgkin's disease, HD and 69 Non-Hodgkin's lymphoma, NHL) were finally included in this study. Of the 69 patients with NHL, there were 17 low grade NHL, 32 intermediate grade NHL, and 20 high grade NHL. FDG PET was performed for the purpose of staging in 53 patients as well as for the assessment of treatment response after the completion of a standard course of chemotherapy in 20 of the 73 patients. Of the 20 patients, 9 were known to have marrow disease at initial presentation. Bilateral iliac crest biopsies were obtained within 4 weeks following FDG PET imaging from all patients. Final conclusions regarding bone marrow involvement were based on concordance between BM biopsy and FDG PET. Among cases of discordant results, it was considered positive for marrow lymphoma if BM biopsy is positive. When FDG PET is positive with a negative BM result, other imaging or follow up imaging was used to make a final conclusion.

FDG PET imaging was performed using a PET scanner (GE advance, Milwaukee, WI) that acquires data in 2-dimensional mode. The intrinsic spatial resolution of the system is 5 mm (FWHM) in the center of the FOV. All patients fasted for at least 4 hours and the serum glucose level was less than 140 mg/dl in all patients. The PET scanning was initiated 60 minutes after intravenous administration of 370 MBq of FDG. Sequential scans were acquired to cover the neck, chest, abdomen, pelvis, and proximal thighs. Transmission scans using Ge-68 point sources were obtained after the completion of the emission scans, in order to correct for non-uniform attenuation correction. The images were reconstructed using ordered subset expectation maximization algorithm (OSEM), an iterative reconstruction algorithm.

FDG PET images were qualitatively assessed on a computer screen by two nuclear medicine physicians blinded to other clinical or imaging information. FDG uptake in the bone marrow was visually evaluated with special caution. The scan was considered negative for infiltration if FDG uptake in the bone marrow was uniform without focally increased uptake. Conversely, it was considered positive if there was a focal lesion of increased FDG uptake compared to the surrounding normal marrow. Those who were on bone marrow stimulatory factors at the time of FDG PET showed diffusely increased FDG uptake in the bone marrow. Although it was difficult to exclude the possibility of focal marrow disease because of underlying increased marrow FDG uptake, uniform distribution of FDG throughout the marrow was read as negative and non-uniform FDG uptake as positive for marrow involvement in this study. The imaging analysis was based upon considering the patient as a whole and not by individual lesions, i.e. the study was assumed to be positive if there was one or more marrow involvement detected and negative if there was none noted. In cases of disagreement, a final decision was made by consensus.

Results

There were 54 (74%) of the 73 patients in whom FDG PET and iliac crest biopsy were concordant. In 47 of these 54 patients, both FDG and iliac crest biopsy were concordantly negative whereas the remaining 7 patients at staging, concordantly positive. In 4 of the 7 patients with positive results, the location of marrow lesions on FDG PET was not the iliac crest (Fig. 1).

Of 19 patients with discordant results between the two

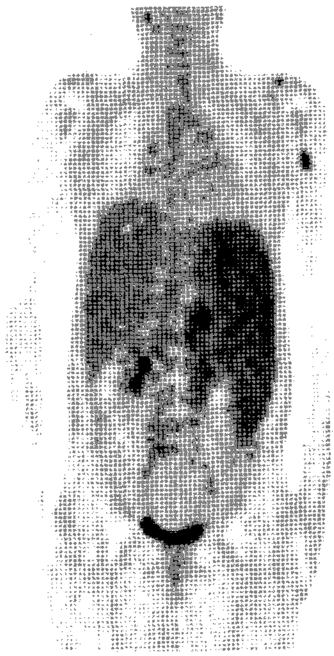

Fig. 1. A 38-year-old female with low grade lymphoma. A coronal view of FDG PET shows a focus of increased uptake in the left humerus, not in the iliac crest. However, iliac crest biopsy was positive for lymphomatous marrow involvement.

studies, FDG PET of 6 patients accurately detected bone marrow infiltration while iliac crest biopsy was negative. For these 6 patients, there were 2 with mixed cellularity HD, 2 with intermediate grade lymphoma, and 2 with high grade lymphoma. The patterns of marrow involvement were multifocal and extensive in 5 patients and a focal uptake in the right proximal femur in 1 patient (Fig. 2). However, in one of the 19 patients, iliac crest was truly negative but FDG PET was falsely positive. There was a focus of mildly increased FDG uptake in the thoracic spine. An MRI of the spine was performed to evaluate the lesion on PET and showed the absence of marrow disease. Meanwhile, iliac crest biopsy accurately detected the presence of marrow infiltration in 12 of the 19 patients with discordant results. All the 12 patients had NHL; 3 with low grade, 5 with intermediate grade, and 4 with high grade.

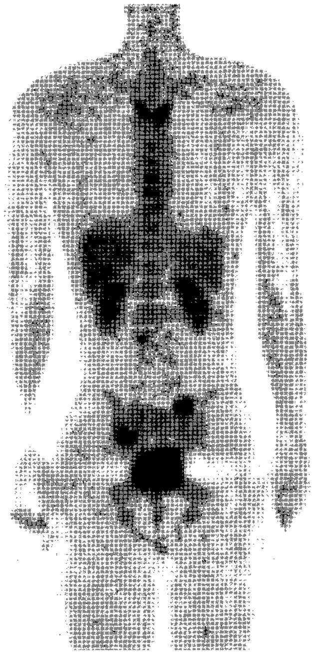

Fig. 2. A 22-year-old male with mixed cellularity of HD. A coronal view of FDG PET demonstrates multifocal bone marrow involvement in the T-spine, L3, and the regions of both sacroiliac joints. Iliac crest biopsy failed to reveal marrow infiltration in this patient.

When the patient population was divided into two groups, one group at staging (n=53) and the other group for the evaluation of treatment response after chemotherapy (n=20), the results of the individual modality in assessing marrow lymphoma are shown on Table 1. Among 53 patients at staging, there were 20 patients with marrow disease. Both PET and BM biopsy detected marrow disease in 7 patients while marrow infiltration only on PET in 5 patients and only on BM biopsy in 8 patients. No abnormal FDG uptake of the iliac crest was noted in 2 of the 5 patients with marrow lymphoma on PET. There was increased uptake of the iliac crest in the remaining 3 patients which could have been detected on BM biopsy. Of 20 patients who were evaluated for treatment response, 11 had had no marrow disease at staging and developed no marrow lymphoma after the end of treatment as well. Of the 9 patients with initial marrow disease, there were 5 patients with residual marrow disease. In all but one patient, residual marrow disease were found only by iliac crest biopsy.

All 3 patients whose PET scans showed diffusely and uniformly increased FDG uptake throughout the skeleton were on colony stimulatory factors to support marrow suppression by chemotherapy. Although their PET scans were interpreted as negative because of the uniform FDG uptake in the marrow, a residual marrow disease were revealed by iliac crest biopsy in one of the 3 patients. This validates the delay of PET scan in patients who were recently on growth factor to minimize the possibility of missing residual disease in the marrow.

Discussion

Random bone marrow biopsy of the iliac crest is prone to sampling error, and a negative biopsy does not exclude tumor involvement especially in the presence of positive findings on other imaging.[4,6,8,9] Various imaging modalities have been used as an adjunct to blind biopsy for the complete assessment of the bone marrow outside the iliac crest.

Although Tc-99m bone scintigraphy has been used to evaluate bone involvement of malignant lymphoma, it has a limited value for the detection of infiltrative marrow disease.[10] Bone marrow scan with antigranulocyte monoclonal antibody has improved the sensitivity and diagnostic accuracy of bone marrow scan for the assessment of marrow involvement.[11,13] When the diagnostic accuracy of bone marrow scan with monoclonal antibody and MRI was compared to that of iliac crest biopsy in 32 patients with malignant lymphoma, a low sensitivity of blind iliac crest biopsies was shown to identify marrow infiltration in high grade NHL and HD.) Both imaging techniques demonstrated a high rate of detection of marrow infiltration in patients with negative biopsies. The sensitivity of bone marrow scan with monoclonal antibody for the detection of lymphomatous marrow was comparable to that of MRI. Although MRI using special pulse sequences such as STIR can offer a high tissue contrast to detect marrow infiltration, evaluation of the whole marrow by MR imaging may not be clinically practical at this point.

FDG PET imaging has gained popularity in the staging of patients with malignant lymphoma. Many previous studies have shown the value of FDG PET in evaluating not only nodal disease, but also extranodal involvement of lymphoma such as hepatic, splenic, or bone marrow infiltration.[14,17] It has been proposed as a new approach for the evaluation of almost entire bone marrow in patients with malignant lymphoma.[8,10,15] The FDG PET and unilateral iliac crest biopsies were compared in 50 lymphoma patients and agreed in 39 patients (78%), being concordant positive in 13 and concordant negative in 26 patients.[15] The study suggested a potential of FDG PET to reduce the need for staging marrow biopsy. In another prospective study of 78 patients with untreated lymphoma, FDG PET provided additional information in some patients with high grade NHL and HD.[8] Complimentary results of both FDG PET and bone marrow biopsy were found in the group of patients with lower grade NHL. False negative findings on FDG PET occurred in patients with a low density of marrow infiltration or involvement by some low grade NHL with low or absent FDG uptake in their primary disease.[8,15]

Despite these results, the role of FDG PET is yet controversial in evaluating lymphomatous marrow and needs to be further validated.[18,20] FDG PET may be of limited value in patients who have cytokine induced diffusely increased bone marrow uptake simulating diffuse marrow infiltration or masking focal marrow involvement.[21,22] We also missed residual marrow lymphoma in one of the 3 patients who were on colony stimulatory drug on FDG PET. Therefore, it should be postponed to perform a FDG PET scan in these patients and BM biopsy could be done instead. Moreover, a recent report documented less promising results regarding the role of FDG PET in evaluating marrow disease in patients with lymphoma.) FDG PET showed the higher overall negative predictive value than the positive predictive value (83.8% vs 66.6%) in detecting marrow involvement of lymphoma. Another disadvantage of FDG PET would be the absence of information on the status of normal marrow precursors. Finally, it could not provide information on discordant marrow lymphoma that has a different histology from nodal lymphoma.

In this study, there were 20 patients with marrow involvement at staging. Both PET and BM biopsy detected marrow disease in 7 patients while only PET or BM biopsy detected infiltration in 5 and 8 patients, respectively. FDG PET seems to be useful in detecting additional marrow infiltration that may not be revealed by iliac crest marrow biopsy alone. In these patients, it can also guide the location to be histologically evaluated. However, it is difficult to replace the need for staging BM biopsy based on our results. Blind BM biopsy should be still performed in patients whose PET scans revealed no evidence of marrow involvement of lymphoma. Only with those cases showing involvement of lymph nodes above and below the diaphragm and multiple marrow diseases on FDG PET, the rationale for blind BM biopsy can be reevaluated in term of affecting further treatment plans or giving prognostic significance. Overall, FDG PET may play a complimentary role to biopsy in the evaluation of marrow lymphoma at staging and can be done before BM biopsy to guide it.

Marrow biopsy appears to be more sensitive to detect microscopic residual disease than FDG PET in the assessment of therapeutic responsiveness of marrow lymphoma. Among 5 patients with residual marrow disease, 4 could be revealed only by BM biopsy in this study. The role of FDG PET for residual lymphoma was less clear than that for staging. At present, follow-up BM biopsy appears to be mandatory for the exclusion of residual marrow disease in those patients with initial marrow involvement.

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PURPOSE: To assess the ability of FDG PET for the detection of bone marrow infiltration compared to iliac crest biopsy in patients with lymphoma. MATERIALS AND METHODS: Seventy-three patients (30 females and 43 males, mean age of 47 years old) with malignant lymphoma (4 Hodgkin's disease, HD and 69 Non-Hodgkin's lymphoma, NHL) were included. FDG PET was performed for staging in 53 patients and to assess treatment response after the completion of chemotherapy in 20 patients. Final conclusions were based on biopsy, other imaging studies, or clinical follow-up. RESULTS : There were 54 (74%) of the 73 patients in whom FDG PET and iliac crest biopsy were concordant. Forty-seven of the 54 patients showed concordant negative results while the remaining 7 patients had concordant positive results. Of 19 patients with discordant results, FDG PET accurately detected bone marrow infiltration in 6 patients with negative iliac crest biopsy. On the contrary, iliac crest biopsy identified bone marrow infiltration in 12 of the 19 patients. In remaining one of the 19 patients with discordant results, iliac crest biopsy was true negative but FDG PET was falsely positive. CONCLUSION : FDG PET seems to be an adjunct in detecting marrow infiltration that may not be revealed by iliac crest biopsy at staging. For the assessment of treatment response, it may be less helpful than biopsy in detecting microscopic residual disease in the bone marrow.

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