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SCIENTIFIC ARTICLE

The value of FDG PET/CT in the initial staging and bone marrow involvement of patients with multiple myeloma

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Abstract
Objective The aim of this study was to describe the role of positron emission tomography/computed tomography (PET/CT) with fluorine-18 fluorodeoxyglucose (FDG) in the detection of skeletal and visceral involvement in patients with MM (multiple myeloma) at the initial diagnosis and to evaluate the relation between maximum standardized uptake values (SUVmax) of FDG with bone marrow cellularity and plasma cell ratios.
Materials and methods The study population consisted of 42 patients (15 F, 28 M; mean ± SD age; 47 ± 12 years). Thirty-two patients were referred for initial diagnosis and ten patients were referred for assessment of therapy response. PET/CT scan was obtained 60 min after the administration of 5.4 MBq/kg FDG. The SUVmax of FDG uptake was measured from the region of interest, which was placed at the site of most prominent lesion in bone marrow in PET/CT images.
Results Thirty patients were positive (29 of 32 initially diagnosed, one of ten previously treated) and 12 patients were negative on PET/CT scan. Conventional radiological methods were negative in three of 30 FDG PET/CT-positive patients and these methods did not show any pathological finding in 12 FDG PET/CT-negative patients. The sensitivity of FDG PET in detecting bone marrow involvement at initial diagnosis was 90%. There was a significant correlation between SUVmax values and bone marrow biopsy cellularity and plasma cell ratios, ($r = 0.54$ and $r = 0.74$, $p < 0.01$).
Conclusions The results of this study demonstrated that FDG-PET is a useful technique for the assessment of MM and the correlation between SUVmax and plasma cell ratios in bone marrow biopsy may avoid repeated bone marrow biopsies in the follow-up period.

Keywords Multiple myeloma treatment · FDG PET/CT · Staging · Bone marrow cellularity · Plasma cell ratios

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Introduction

Multiple myeloma (MM) is a malignant hematologic disorder that is characterized by monoclonal proliferation of malignant plasma cells [1]. This malignancy involves the skeleton in more than 80% of patients at the time of initial diagnosis. The extension of bone marrow and extramedullary involvement in patients with MM are important factors in prognosis and clinical management [2]. The Durie-Salmon staging system is the most commonly used staging system for patients with MM [3]. It is based on a combination of clinical factors; amount of M protein, serum hemoglobin level, serum calcium level, number of lytic bone lesions on a skeletal radiographic survey, and renal function [4]. According to the Durie-Salmon staging system, the extent of bone lesions significantly influences therapy. Patients with stage II or III multiple myeloma, with more than one skeletal lesion, require chemotherapy [4].

Bone marrow examination is an important procedure in the diagnosis, staging, and management of MM. It is also essential to confirm complete response of therapy in the

follow-up period. Plasma cell percentages in the bone marrow, based on the examination of aspirate smears, is one of the most important criteria used for the diagnosis of multiple myeloma. A high percentage of plasma cells in the bone marrow has been shown to be a good predictor of relapse in cases of treated multiple myeloma [5]. However, bone marrow biopsy is invasive.

Skeletal radiography is a primary diagnostic study in the detection of bone changes in MM. However, it has limited value for evaluation of stage I and II diseases [6]. Computed tomography (CT) is a sensitive imaging tool for detection of the destructive bone lesions in MM [7]. It has also been proven that CT and magnetic resonance imaging (MRI) are more sensitive than skeletal radiographs in screening and diagnosing multiple myeloma. However, radiological imaging modalities generally can not differentiate treated bone marrow lesions from neoplastic tissue.

Positron emission tomography/computed tomography (PET/CT) with fluorine-18 fluorodeoxyglucose (FDG) is a whole-body imaging technique that provides functional information about the rate of glucose metabolism in the body and is a sensitive method for detecting, staging, and therapy monitoring for various malignant tumors [8]. There is limited information in the literature regarding the diagnostic utility of FDG PET/CT in the assessment of bone marrow involvement of MM. The aim of this study was to evaluate the involvement of bone marrow in the initial diagnosis and follow-up period by using FDG PET/CT and to assess the relationship between maximum standardized uptake value (SUVmax) of FDG with bone marrow cellularity and plasma cell ratios in patients with MM.

Materials and methods

We retrospectively analyzed 42 FDG PET/CT imaging and conventional radiologic studies of patients with MM. Patient population included 15 females and 27 males, with a mean age of 58.5 ± 11.3, range 22-87 years. The local ethics committee approved this investigation. Patients were diagnosed with MM on the basis of the criteria defined by Durie-Salmon (3).

All patients underwent whole-body FDG PET using a Siemens Biograph LSO HI-REZ integrated PET/CT camera (Siemens Medical Solutions, Biograph 6, IL, Chicago, USA). PET/CT scans were obtained 60-80 min after the administration of 5.4 MBq/kg FDG. The patients fasted for at least 6 h and serum glucose levels were less than 120 mg/dl in all patients. Two nuclear medicine physicians analyzed the data together for this study. There was no inter-observer variability. The SUVmax of FDG uptake was measured from region of interest (ROI), which was placed at the most prominent lesion in bone marrow. A SUVmax higher than background bone marrow activity was considered to indicate the site of active disease. In FDG PET-negative patients, SUVmax values were obtained from right iliac bone as a background activity. The standard uptake value (SUV) was calculated using the following formula: SUV = Tissue concentration (MBq/g)/Injected dose (MBq)/Body weight (g). PET/CT imaging and other conventional radiological modalities such as radiographs, CT, or MRI were performed within 2 weeks after the bone marrow biopsy. Three weeks after the therapy period, PET/CT imaging was performed to evaluate the therapy response. For myeloma therapy, melphalan and prednisone or high-dose dexamethasone combination with vincristine and adriamycin (VAD regimen) were given.

Bone marrow biopsy samples were examined by an experienced hematopathologist, measured for bone marrow cellularity and plasma cell infiltration. For routine histopathological evaluation, Tru-Cut biopsy needle samples were collected in Holland fixation and after decalcification in formic acid, four aspiration cytology samples were added to MGG (May-Grunwald-Giemsa) dye and one aspiration cytology sample was added to Prussian Blue stain. The biopsies were studied for percentage of bone marrow cellularity and plasma cell infiltration.

Statistical Analysis

The mean and standard deviation (SD) were calculated on SUVmax by using descriptive statistics. Pearson's test was used to calculate the correlation between PET/CT and histopathological results. p values less than 0.05 were considered statistically significant.

Results

Forty patients were diagnosed with MM and the remaining two patients were diagnosed with plasmocytoma according to histopathology and cytopathology results. FDG-PET/CT images of patients with MM showed focal, diffuse, or focal and diffuse uptake on axial-peripheral skeleton especially in the spine and pelvis. It was found that ten of 30 FDG PET/CT-positive patients' FDG uptakes were focal, ten patients' uptakes were diffuse, and the remaining ten patients' uptakes were focal and diffuse. For the initial evaluation of MM, 32 patients had FDG PET/CT examination and bone marrow biopsy results. In these 32 patients, 20 of them had MRI imaging and 22 of them had CT imaging. PET/CT examinations for the initial diagnosis showed increased FDG uptake at single or multiple lesions on bone marrow in 29 of 32 patients (Figs. 1 and 2), while conventional techniques were positive for malignancy in 27 and were negative in five patients. Maximum standardized uptake values ranged from 1.0 to 14.2 in 32 newly

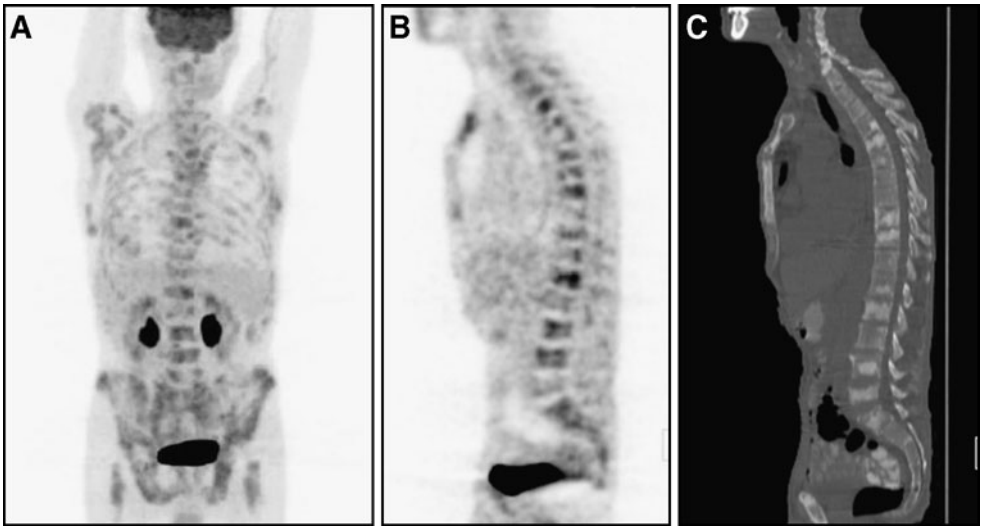

Fig. 1 A 57-year-old male patient with newly diagnosed multiple myeloma was evaluated before therapy. Whole-body FDG PET MIP (**a**) and sagittal PET slice (**b**) show multiple foci of increased FDG uptake in bone marrow throughout the body, consistent with myelomatous involvement. Standardized uptake values of lesions ranged from 3.5 to 6.5. Sagittal CT image (**c**) shows multiple lytic and sclerotic lesions in vertebral column

diagnosed myeloma patients. The ratio of the bone marrow cellularity and plasma cells were lower (range of 10-50%) in three FDG PET-negative myeloma patients who were newly diagnosed. The sensitivity of FDG PET in detecting bone marrow involvement at initial diagnosis was 90%. In the follow-up period, patients' FDG PET/CT results were negative but one of ten patients' pathological findings was positive for active disease, and nine patients' results were negative. One of nine patients' results was false-negative. Computed tomography and MRI did not show any pathological findings in FDG PET-negative patients. Ten patients were followed-up clinically for at least 6 months and eight of them were confirmed as being in remission. There were 30 true-positive, four false-negative, and eight true-negative results on FDG PET. Of four false-negative patient's, three of them were newly diagnosed and one patient was in the follow-up period. These patient's radiologic findings, such as radiographs, CT, and MRI imaging, were considered to be normal. Sensitivity, specificity, positive predictive value, and negative predictive value of FDG PET imaging were calculated as 88%, 100%, 100%, and 66%, recpectively.

All patients' bone marrow mean SUVmax value was calculated as 5.21 with a range of 1.0-14.5. However, there was not adequate data for determination of the cut-off value to differentiate active and inactive disease. All patients' average bone marrow cellularity and plasma cell infiltration were calculated 72.6 and 69.0%, respectively. There was a significant positive correlation between SUVmax of FDG and plasma cell ratios ($r = 0.54$ and $r = 0.74$, $p < 0.01$). Similarly, in false-negative patients, SUVmax values of bone marrow were not increased and their plasma cell ratios

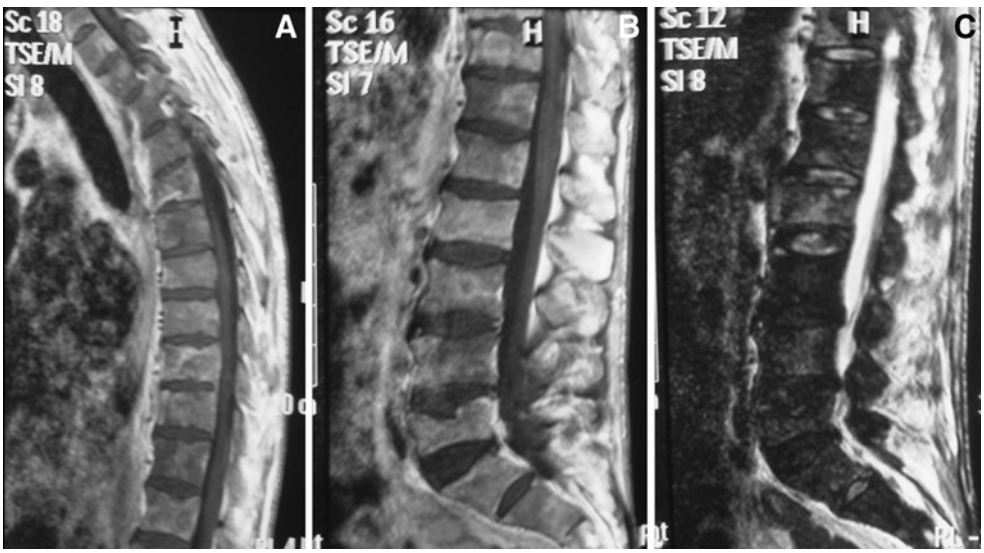

Fig. 2 The same patient's T1-weighted sagittal dorsal (**a**) and lumbar (**b**) MRI images show multifocal hypointense lesions and T2-weighted MRI image (**c**) shows multifocal hyperintense lesions

were also lower than PET-positive patients. There were no extraskeletal abnormal findings in FDG PET/CT scans of any patients in the study group.

Discussion

Multiple myeloma is characterized by uncontrolled proliferation of a clone of plasma cells within the bone marrow. The presence of bone marrow involvement and extent of extramedullary tissues in patients with MM are important factors influencing prognosis and clinical management [4, 8]. The clinical manifestations of myeloma disease result from the uncontrolled and progressive proliferation of a plasma cell clone, the effect of normal bone marrow replacement and the overproduction of monoclonal proteins. The diagnosis of MM is based on specific criteria that include plasma cell infiltration of bone marrow, paraproteinemia, and osteolytic bone lesions [9]. Microscopic examination of the bone marrow plays a crucial role in the diagnosis of MM and monitoring therapy. The percentage of plasma cells in the bone marrow is important for the diagnosis of MM [2, 10].

FDG PET/CT is a useful imaging tool to evaluate disease activity of the skeletal system, to detect extraosseous involvement, to assess patients with nonsecretory myeloma, and to evaluate therapy response visually and semi-quantitatively [11, 12]. The Durie-Salmon staging system includes has indicated that FDG PET or PET/CT is necessary to confirm the staging of MM [13, 14]. Major advantages of FDG PET/CT over other imaging techniques are the ability to detect medullary and extramedullary lesions in a single examination and the possibility to distinguish disease from necrotic tiisue and radiation changes [15]. Nanni et al. compared FDG PET/CT with whole-body X-ray (WBXR) and MRI results in 28 patients with newly diagnosed symptomatic MM. They found that the number of lesions in the skeleton with FDG PET/CT was higher than WBXR in 16 patients (57%), and in 12 patients they found similar findings (25%) [16]. When comparing FDG PET/CT with MRI, they found that FDG PET/CT detected more lytic bone lesions than MRI in seven patients (25%). In 14 patients, FDG PET/CT and MRI detected the same number of lesions in the spine and pelvis [16]. Fonti et al. showed that FDG PET/CT performs better than both 99mTc-MIBI and MRI in the detection of focal lesions [17]. However, they showed that FDG PET/CT and MRI were comparable and both methods performed better than 99mTc-MIBI in the spinal and pelvic areas [17]. Bredella et al. showed that the sensitivity of FDG PET/CT in detecting myelomatous involvement was 85% and specificity was 92% [18]. In this study group, the sensitivity and specificity of FDG PET was found 90% and 100% in detecting bone marrow involvement at initial diagnosis.

Zamagni et al. showed that in 65% of patients, PET/CT scans were found negative following autologous transplantation in their preliminary results of the study and this finding closely followed the achievement of a marked (≥90%) degree of tumor response [19]. In this study, nine of ten follow-up patients FDG PET/CT results were found negative. One of nine patients' FDG PET result was false-negative. Eight of ten patients' bone marrow biopsy results were negative as a response to therapy and two patients' biopsy results were positive as a Nux disease. It is suggested that these patients' FDG PET studies will be negative if they are in remission or relapse in the follow-up period and bone marrow biopsy is necessary. More patients and longer follow-up is necessary for a better definition of the role of FDG PET/CT in monitoring of therapy response. Durie et al. claimed that negative FDG PET/CT findings strongly support the diagnosis of monoclonal gammopathy of undetermined significance (MGUS). They also showed that residual disease after stem cell transplantation and extramedullary myeloma detected by FDG PET/CT were indicators of high-risk myeloma and of poor prognosis [13]. False-positive FDG PET/CT findings may also occur in the setting of infection and inflammation, inflammatory changes from radiation therapy, or post-surgery, which also demonstrate hypermetabolism, and thereby reduce specificity. In this study, there were no false-positive results found.

Fonti et al. demonstrated that FDG-PET/CT images of patients with MM have shown focal, diffuse or focal and diffuse uptake especially on spine and pelvis [17]. In this study, ten of 30 FDG PET/CT-positive patients results showed focal, ten patients showed diffuse and the remaining ten patients showed focal and diffuse uptake.

Bone marrow examination continues to be the cornerstone for establishing the diagnosis of MM in association with other clinical and laboratory parameters. Plasma cell morphology has a significant correlation with clinical stage and survival [20]. The current definition of complete response in MM requires a bone marrow examination showing less than 5% plasma cells and negative serum and urine immunofixation [21]. Subramanian et al. observed that the infiltration pattern and percentage in the bone marrow were significantly correlated with the clinical stage of the disease [20]. Similarly, significant correlation between FDG SUVmax on PET/CT and bone marrow cellularity and plasma cell ratios on biopsy samples were found in this study. According to these results, it is suggested that if FDG PET/CT is positive and SUVmax values are high at the time of initial diagnosis, these patients can be followed by FDG PET/CT scans or MRI imaging together. Therefore, bone marrow biopsy may not be necessary in the follow-up period, because, if there is a relapse or refractory disease, these patients' bone morrow SUVmax values will be higher as in the initial imaging. Also, false-

positive results can be excluded with lower SUVmax values or correlating with radiological imaging methods.

Conclusions

The results of this study demonstrated that FDG-PET is a useful technique for the assessment of MM and the correlation between SUVmax and plasma cell ratios in bone marrow biopsy may avoid repeated bone marrow biopsies in the follow-up period.

Conflict of Interest The authors declare that they have no conflict of interest.

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