



Bone Marrow Involvement as the Initial Presentation of Hodgkin's Lymphoma Is Undetectable by ^{18}F -Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

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We report a 28-year-old male who presented with fever and bone pain without peripheral lymphadenopathy observed during initial physical examination. Subsequent bone marrow examination revealed the presence of Reed-Sternberg (RS) cells, which led to a diagnosis of mixed cellularity subtype of Hodgkin's lymphoma (HL). However, the initial ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan did not show any detectable marrow or nodal lesions, with the exception of FDG uptake in an extranodal lesion over the right adrenal gland. Two weeks later, a 2-cm enlarged lymph node over the left submandibular region appeared. Excisional biopsy revealed HL. Mixed cellularity subtype of stage IV HL with initial bone marrow and unilateral adrenal gland involvement followed by submandibular lymphadenopathy was diagnosed, according to clinical, imaging, and histological manifestations. This patient received six cycles of chemotherapy with regimen of doxorubicin, bleomycin, vinblastine, and decabazine (ABVD). The subsequent FDG-PET/CT scan revealed complete remission after chemotherapy.

Key words: Hodgkin's lymphoma, ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography, bone marrow

INTRODUCTION

Hodgkin's lymphoma (HL) is a curable malignancy characterized by initial nodal lesion. Extranodal involvement as the initial presentation is rare. Bone marrow (BM) is the major extranodal area involved and BM examination is a necessary diagnostic procedure to assess the accurate pathological staging. Recently, ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan has been reported to be a useful tool to stage HL with great accuracy and to ascertain HL correctly in treatment monitoring under suspicion of recurrence. FDG-PET/CT scan also has the advantage of

detecting BM involvement in a noninvasive way, compared with the currently used diagnostic procedure of BM biopsy. A previous study reported that FDG-PET/CT scan has a high potential to detect BM involvement in HL^{1,2,3}.

We report a case of HL characterized by initial extranodal bone marrow and adrenal gland involvement, followed by submandibular lymphadenopathy. The initial staging by FDG-PET/CT scan failed to detect BM involvement. The role of FDG-PET/CT scan in staging BM involvement is discussed.

CASE REPORT

A 28-year-old male presented at an outside hospital with spiking fever, nonproductive cough, sore throat, and bone pain, which had started three weeks prior to examination. He was admitted to the hospital under a diagnosis of fever of unknown origin. After exclusion of infectious and autoimmune disease, BM examination over the right superior iliac crest was performed and histological examination revealed scattered Reed-Sternberg (RS) cells. Thus, a diagnosis of stage IV HL was suggested, as initial BM involvement was detected. He was referred to

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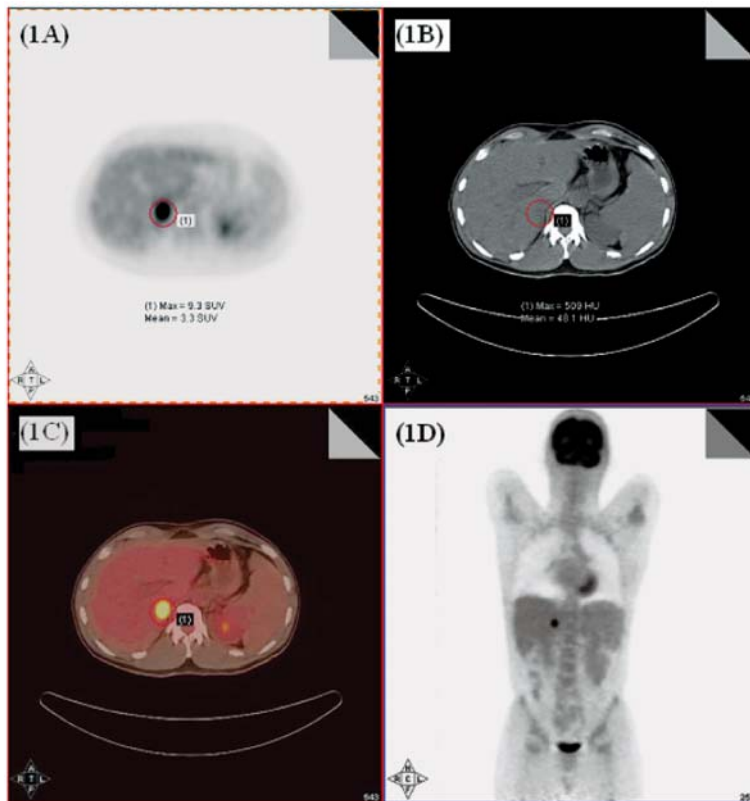


Fig. 1 Pre-chemotherapy stage: transaxial slices of FDG-PET scan (1A), non-contrast CT scan (1B), fused FDG-PET/CT scan (1C), and MIP view of FDG-PET scan (1D) of the initial FDG-PET/CT scan showed a focal FDG-avid lesion (about 1.8 cm in diameter) over the right adrenal region, with SUVmax of 9.5.

our institution for treatment. Upon admission, the body temperature was 37.4 °C; the blood pressure was 112/80 mmHg; and the respiratory rate was 20/min. Physical examination revealed pale conjunctiva and no obvious peripheral lymphadenopathy. A complete blood cell count revealed a white blood cell count of $4.22 \times 10^9/L$, a platelet count of $152 \times 10^9/L$, and a hemoglobin level of 12.6 g/dL. Serum biochemistry showed a lactate dehydrogenase level of 351 U/L (normal reference range 135–225 U/L) and an albumin level of 4.7 g/dL. Viral screening revealed no specific abnormalities. FDG-PET/CT scan was performed for initial staging, which demonstrated a focal FDG-avid lesion of 1.8 cm in diameter over the right adrenal gland with a standardized uptake value (SUV) of 9.5, increasing to 13.1 on delayed imaging. Otherwise, no other abnormal ^{18}F -FDG uptakes emerged elsewhere in the patient's body, including the BM and lymphatic areas (Fig. 1). CT scan of the abdomen showed splenomegaly with a longitudinal axis of 14.8 cm and a 1.8-cm low-density tumor over the right adrenal gland. Stage IV HL with extranodal BM and

unilateral adrenal gland involvement was diagnosed. Two weeks later, a fixed and non-tender lymph node of 1 cm in diameter appeared in the left submandibular region, which grew to 2 cm in five days. The patient received excisional biopsy of the lymph node and histological examination revealed a mixed cellularity subtype of HL. International Prognostic Factors Project (IPFP) score evaluation revealed a score of 2 for this subject. Because of advanced stage IV HL, the patient received six cycles of chemotherapy with doxorubicin (25 mg/m²), bleomycin (10 mg/m²), vinblastine (6 mg/m²), and decabazine (375 mg/m²) (ABVD protocol administered at day 1 and day 15 every month). Total remission of HL was noted according to normal appearance of FDG-PET/CT scan and no evidence of Reed-Sternberg (RS) cells in BM biopsy after chemotherapy.

DISCUSSION

Classical HL always arises and disseminates in lymph nodes and metastasizes to extranodal regions, such as BM, as disease progresses⁴. In this patient, initial exclusive BM involvement suggested stage IV HL, which is infrequent in the literature. Approximately 5% of HL present with BM infiltration as the only manifestation⁵. Most patients diagnosed as HL with only BM involvement are concordant with HIV infection⁶; however, BM biopsy is still essential in the staging of HL, especially for patients presenting with cytopenia and fever of unknown origin⁵.

What is the definite role of FDG-PET/CT scan in the staging of HL? Can FDG-PET/CT scan detect all involved nodal and extranodal lesions, including BM? Can FDG-PET/CT scan replace conventional imaging methods, such as gallium and computed tomography (CT) scan, or invasive procedures, such as BM biopsy? Positive BM involvement indicates stage IV disease, which would lead to therapeutic aggressiveness and poor prognostic consequences. In recent retrospective studies, BM biopsy was compared with FDG-PET scan in detecting BM involvement in lymphoma. These authors concluded that visual interpretation of FDG uptake on BM FDG-PET scan correctly assesses scattered BM lesions and has the potential to subrogate invasive BM biopsy, with 80% sensitivity and 100% specificity in upgrading the stage of patients up to 10%^{7,8}. A recent study also declared that FDG-PET/CT

fusion scan when applied to the restaging of treated HL had a sensitivity of 100% and a specificity of 90.7%⁹. FDG-PET/CT scan, which combines the advantages of anatomic identification via CT scan with the biological appearance through FDG-PET scan, could thus more exactly detect nodal and extranodal lesions in staging of HL, when compared with FDG-PET scan or CT scan alone. In addition, CT scan has limitations in detecting pathological changes of normal-sized LNs of HL. Thus, FDG-PET/CT scan has the potential to play a powerful role in staging accuracy, compared with FDG-PET scan or CT scan^{8,10,11,12}. Nevertheless, the case reported here presented with BM involvement, which is traditionally detected by BM biopsy, rather than FDG-PET/CT scan. Another study claimed that FDG-PET scan should only be used to complement BM biopsy in detecting BM involvement in any lymphoma subtype, instead of completely replacing the invasive method^{13,14}. FDG-PET/CT scan did not increase the sensitivity of detection of BM involvement in lymphoma. Thus, the current paradoxical conclusions from a series of FDG-PET studies and the inability of this technique to detect BM involvement may explain the uncertain role of FDG-PET/CT scan in detecting BM involvement of HL. It is possible that BM examination remains the gold standard procedure in the staging of HL.

According to the Ann Arbor staging system and the International Prognostic Factors Project (IPFP) score¹⁵, this patient was defined as having advanced stage IV HL with an IPFP score of 2. Because of the low IPFP score, we could expect a good prognosis for this patient, even if the subject initially presented with advanced stage disease. As predicted, the subsequent FDG-PET/CT scan and BM biopsy examinations showed complete remission of HL after six cycles of chemotherapy. According to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for HL, surveillance PET should not be carried out routinely, because of the risk for false positives¹⁶. A combined analysis of the clinical, imaging, and pathological reports could therefore be crucial for management decisions regarding follow-up and monitoring of patients after completion of treatment.

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