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Differential FDG accumulation associated with GLUT-1 expression in a patient with lymphoma

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We herein report a case of malignant lymphoma that showed differential FDG accumulation associated with the degree of glucose transporter 1 (GLUT-1) expression. For clinical staging purpose, FDG-PET was performed on a 47-year-old male who had been diagnosed to have malignant lymphoma, diffuse medium B-cell type. Although an X-ray CT showed multiple and bulky lymphadenopathy including bilateral submandibular, deep cervical, supraclavicular, axillar, hilar, mesenteric and paraaortic regions, FDG-PET showed a high accumulation only in the bilateral submandibular and deep cervical region. An immunohistochemical analysis demonstrated a high GLUT-1 expression in the right cervical lymph node, which showed a high FDG uptake. On the other hand, a bone marrow specimen with diffuse lymphoma cell involvement indicated showed no FDG accumulation and also revealed a negative GLUT-1 expression. This case suggests that the differential FDG accumulation shown by lesions is associated with the degree of GLUT-1 expression in patients with lymphoma.

Key words: FDG PET, GLUT-1, malignant lymphoma

INTRODUCTION

F-18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) can supply metabolic information different from that obtained by X-ray CT, US, or MRI, because FDG accumulation reflects the tumor glucose metabolism. An increased FDG uptake in lymphoma was first reported by Paul et al.[1] Since then, many reports have demonstrated the clinical usefulness of FDG-PET for the detection,[2,3] staging,[4–11] management,[11–13] and monitoring of the treatment response[14–16] of lymphoma. The degree of FDG accumulation in lymphoma has been reported to correlate with the grade of malignancy[17–20] in classifying the biological behavior. The degree of FDG accumulation has been reported to no only depend on various factors such as the expression and activity of glucose transporter (GLUT),[21–29] also to depend on one of the glycolysis enzymes hexokinase (HK)[24–27] and glucose-6-phosphatase (G6Pase).[30] However, the degree of GLUT and HK expression has not yet been reported in lymphoma in either clinical or experimental studies.

We herein report a case of malignant lymphoma with different accumulations of FDG among the lesions due to different degrees of GLUT-1 expression.

A CASE REPORT

A 47-year-old man was referred to Kyushu University Hospital complaining of a right neck mass. An X-ray CT scan demonstrated multiple lymphadenopathies in the bilateral submandibular, deep cervical, supraclavicular, axillar, mesenteric, and paraaortic regions (Fig. 1). FDG-PET was performed under a fasting state (serum glucose = 109.0 mg/d*l*) using ECAT EXACT HR$^+$ (Siemens, Knoxville, USA) with 4.6 mm of FWHM. Sixty minutes after the administration of 185 MBq FDG, the data acquisition was started in a 3D-mode. Image reconstruction was performed using the filtered back projection

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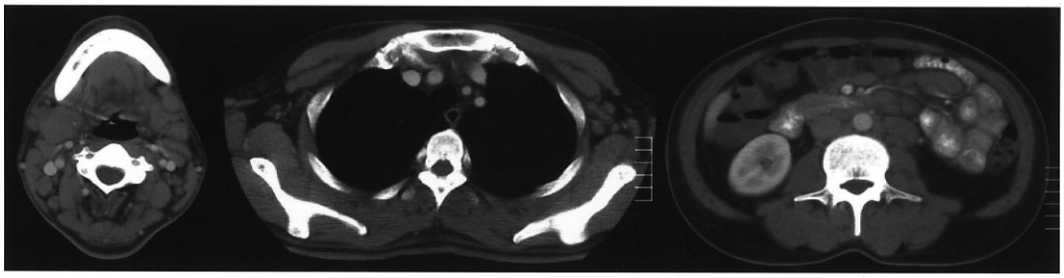

Fig. 1 CT scans demonstrated multiple lymphadenopathy including bilateral submandibular, deep cervical, bilateral axillar, paraaortic and mesenteric regions.

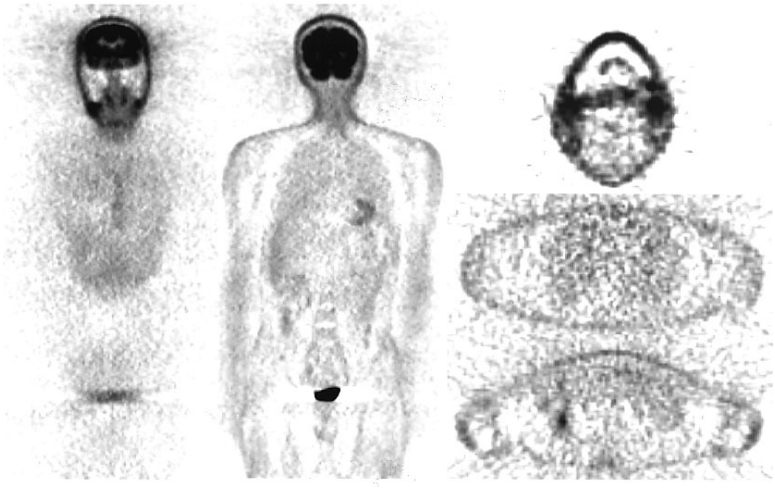

Fig. 2 FDG-PET showed an increased accumulation in the bilateral submandibular and cervical regions, but no accumulation in the other areas of lymphadenopathy including in the supraclavicular, axillar, mesenteric and paraaortic region. Each transaxial FDG-PET image of Figure 2 corresponds to each CT image of Figure 1.

(FBP) method with a Hann 0.4 filter without attenuation correction. FDG-PET showed an increased accumulation in the bilateral submandibular and deep cervical region, but no accumulation in any other lesions including those in the supraclavicular, axillar, mesenteric and paraaortic regions or in any areas of the bone (Fig. 2). A lymph node biopsy was performed on the right cervical lymph node which showed a strong FDG accumulation and proved to be malignant lymphoma diffuse medium B-cell type. A bone marrow biopsy obtained from the sternum revealed diffuse lymphoma cell involvement, but no abnormal FDG accumulation was observed in any bone marrow. Finally, the patient was diagnosed malignant lymphoma diffuse medium B-cell type stage IV. He was treated with high dose chemotherapy combined with PBSCT and thereafter attained a complete remission.

To elucidate the cause of differential FDG accumulation, we investigated expression of GLUT-1, GLUT-4 and HK-I in the right cervical lymph node and bone marrow by an immunohistochemical analysis. Immunohistochemical staining was performed using the streptavidin-biotin-peroxidase complex method (Histofine SAB kit, Nichirei, Tokyo, Japan). The expressions of GLUT-1 and GLUT-4 were evaluated using polyclonal rabbit antibodies against GLUT-1 (AB1353) and against GLUT-4 (AB1346) purchased from CHEMICON International Inc. (USA). The expression of HK-I was evaluated using specific mouse monoclonal antibody against HK-I (MAB1534: CHEMICON International Inc., USA). The labeling indices of lymphoma cells in each specimen were estimated by counting the number of lymphoma cells with positive-staining among at least 200 lymphoma cells. The tumors were considered to be positive if the labeling indices were 10% or more. In the right cervical lymph node, the labeling index of GLUT-1 was 11.8%, but GLUT-4 and HK-I were 3.3% and 1.5%, respectively (Fig. 3). On the other hand, in the bone marrow, the labeling index of GLUT-1 was 1.0%, but those of GLUT-4 and HK-I were 10.7% and 10.7%, respectively (Fig. 4).

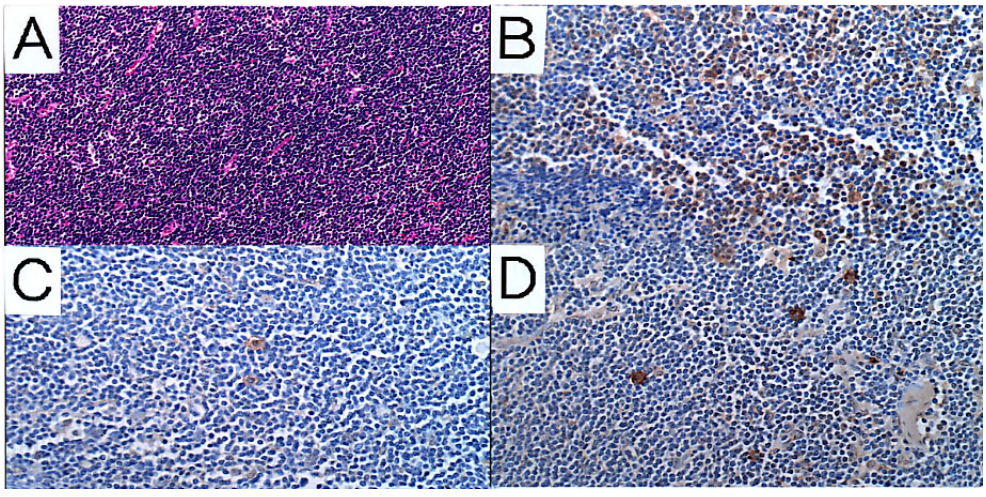

Fig. 3 Hematoxylin-Eosin staining of the right cervical lymph node specimen demonstrated that medium sized atypical lymphoid cells proliferated diffusely (A). An immunohistochemical analysis showed a positive GLUT-1 expression in 11.8% of lymphoma cells (B), while GLUT-4 (C) and HK-I (D) were expressed only in 3.3 and 1.5% of cells, respectively.

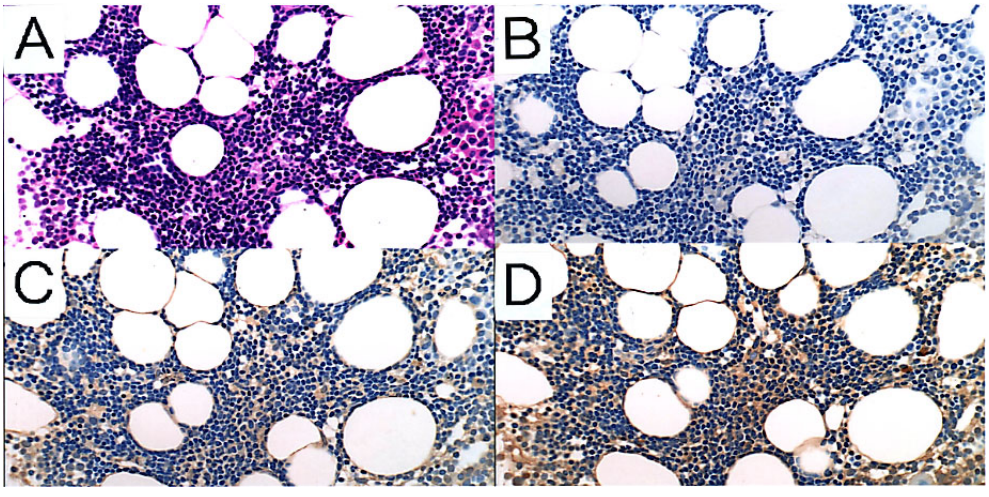

Fig. 4 Hematoxylin-Eosin staining of the bone marrow specimen demonstrated small to medium sized lymphocytes to infiltrate through the bone marrow (A). An immunohistochemical analysis showed a positive GLUT-1 expression in only 1.03% of lymphoma cells (B), while GLUT-4 (C) and HK-I (D) expression was observed in 10.7 and 10.7% of the lymphoma cells, respectively.

DISCUSSION

FDG-PET showed a high sensitivity for detecting lymphoma, while either a slight degree of FDG accumulation or none at all has been reported in low grade or MALT type lymphomas[20] as well as in indolent lymphoma.[31] A negative FDG accumulation was also reported in some patients with intermediate grade lymphoma.[11]

In this study, we encountered a patient with diffuse medium type lymphoma (intermediate grade) who showed different accumulations of FDG in various lesions. Although our case was not either low grade or MALT type lymphoma, FDG accumulation was only seen in the bilateral submandibular and deep cervical regions while none was observed in the supraclavicular, axillar, mesenteric, and paraaortic regions or the bone marrow.

The degree of FDG accumulation in various tumors is considered to depend on the activity of GLUTs and HKs in the cells based on the findings of experimental and clinical studies.[21–29] In experimental studies, a predominant expression of GLUT-1 has been demonstrated in malignant tumor cells.[25–27] In clinical studies, Brown et al. reported that an increased FDG uptake was associated with increased GLUT-1 expression in breast cancer.[28] Higashi et al. reported that FDG accumulation showed a positive correlation with the GLUT-1 expression in

pancreatic cancer.[29] In our case, an immunohistochemical analysis revealed that a higher expression of GLUT-1 was observed in the right cervical lymph node with an intense FDG accumulation, but a lower expression of GLUT-1 was seen in the bone marrow with no FDG accumulation. Our results correlated with those of previous studies which demonstrated that the degree of FDG accumulation was associated with the GLUT-1 expression.[28,29] The GLUT-1 expression is thus considered to play an important role in the FDG accumulation in malignant lymphoma.

In our case, GLUT-4 expression did not show any relationship with the FDG accumulation, and our findings were consistent with those from previous reports.[29,32] Because GLUT-4 activity is modulated by translocation from the *trans*-Golgi reticulum to the plasma membrane depending on the insulin stimulation,[33] GLUT-4 is considered not to play an important role for FDG accumulation under a fasting state. Although we did not examine the expression of any other GLUT isoforms, including GLUT-2, GLUT-3, and GLUT-5, no relationship with FDG accumulation has so far been reported.[21,29,32] In this study, the degree of HK-I expression did not show any relationship with the FDG accumulation. Adams et al. found that dominant expression of HK-I in normal human kidney cells, while HK-II expression was dominant in renal cell carcinomas.[34] Some previous experimental studies demonstrated a predominant expression of HK-II in malignant tumor cells.[25–27] Although we did not examine the HK-II expression, the relationship between the FDG uptake and the degree of HK-II expression has not yet been observed in clinical study.[28] Thus, it is possible that HK-I may not play crucial role in FDG accumulation.

Recently, FDG-PET has also been introduced to assess the response in the treatment of various malignant tumors and to detect recurrent tumors. Our case suggests the importance of a baseline study to confirm that the tumor is an FDG positive one before starting chemotherapy. In patients with FDG negative lymphoma, as in our case, baseline studies before starting chemotherapy are therefore important to avoid misinterpretation.

In summary, we herein described a case of malignant lymphoma with different FDG accumulations in various lesions. An immunohistological analysis showed different GLUT-1 expression associated with different accumulations of FDG. We thus found that different expression of GLUT-1 results different accumulations of FDG in the lesions of patients with malignant lymphoma.

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