A $^{18}$F-FDG-positive, $^{67}$Ga-negative, and transferrin receptor expression-negative patient with diffuse large B-cell lymphoma

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Abstract We recently experienced a case with uveitis suffering from fever of unknown origin suspected of being caused by sarcoidosis. Chest computed tomography showed right supraclavicular, bilateral mediastinal, and right hilar lymphadenopathy, and intensive abnormal uptake of 2-[$^{18}$F]fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) was observed on positron emission tomography with $^{18}$F-FDG (FDG-PET). On the other hand, $^{67}$Ga scintigraphy showed almost no abnormal findings. Histopathological examination revealed the lesion to be a diffuse large B-cell lymphoma (DLBCL), namely, an aggressive non-Hodgkin lymphoma from a right supraclavicular lymph node biopsy specimen. Additional immunohistochemical analysis showed the negative expression of transferrin receptor (TfR) on the formalin-fixed paraffin-embedded specimen. Although DLBCL is generally considered to be a $^{67}$Ga-avid tumor, it does not always have a large number of TfRs and that leads to a discrepancy between the $^{67}$Ga scintigraphy and FDG-PET findings. FDG-PET should be more appropriate for the initial staging of DLBCL than $^{67}$Ga scintigraphy, whereas $^{67}$Ga scintigraphy might be able to provide additional information including prognostic factors and to support strategies that target TfR for cancer therapy.

Keywords Diffuse large B-cell lymphoma · $^{67}$Ga scintigraphy · Transferrin receptor · FDG-PET

Introduction

$^{67}$Ga and 2-[$^{18}$F]fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) are tumor viability indicators and $^{67}$Ga scintigraphy and positron emission tomography with $^{18}$F-FDG (FDG-PET) have been widely used for the management of lymphomas. The tissue uptake of tracers by malignant tumors is based on different mechanisms. Malignant cells accumulate $^{67}$Ga mainly through an intracellular transferrin (Tf)-related transport mechanism via a $^{67}$Ga–Tf complex [1, 2]. Transferrin receptor (TfR) is a key cell surface molecule that regulates uptake of iron-bound Tf by receptor-mediated endocytosis, and an overexpression of TfR is assumed to be a common feature of malignant tumors. Kiratli et al. [3] showed that rapidly proliferating tumors with a high level of DNA synthesis have high TfR expression for increasing iron uptake and enhance $^{67}$Ga uptake in a flow cytometric analysis in patients with lymphoma. On the other hand, $^{18}$F-FDG is a glucose analogue, which reflects the activity of glucose transport proteins and the intracellular phosphorylation by hexokinase [4, 5]. $^{67}$Ga scintigraphy and FDG-PET have been useful for the initial staging and post-therapeutic follow-up of lymphomas [6].

We report a case of diffuse large B-cell lymphoma (DLBCL), which showed a discrepancy between the $^{67}$Ga scintigraphy and FDG-PET findings, and discuss the advantages of each examination for tumor imaging.
Methods

The FDG-PET scan was performed with a GE ADVANCE (GE Medical Systems, Milwaukee, WI, USA). Before tracer administration, at least a 4-h fasting was required and emission data were collected for 2 min per frame using 2D acquisition at 50 min after the injection of 185 MBq $^{18}$F-FDG. Transmission scan was obtained before emission scan using 68Ge/68Ga rod source for attenuation correction. The acquired data were reconstructed by the iterative reconstruction method selecting 14 subsets, 2 iterations, and $128 \times 128$ matrix.

$^{67}$Ga scintigraphy was performed at 72 h after the injection of 111 MBq $^{67}$Ga-citrate. Imaging was obtained by an E-CAM (Siemens Medical Systems, Hoffman Estates, IL, USA) with medium-energy and a general-purpose collimator. Whole-body imaging was performed with both anterior and posterior view images.

Case report

A 69-year-old man suffering from fever of unknown origin was referred to our hospital. He had been treated for uveitis and received left vitrectomy because of left vitreous hemorrhage. On admission, his right supraclavicular lymph nodes ($10 \text{mm} \times 2$, elastic hard) were palpable. He underwent chest computed tomography (CT), $^{67}$Ga scintigraphy, and whole-body FDG-PET scan. Chest CT showed right supraclavicular, bilateral mediastinal, and right hilar lymphadenopathy (Fig. 1), and his physician considered him to have sarcoidosis on the basis of the clinical course (uveitis and lymphadenopathy). Intensive $^{18}$F-FDG accumulations of the lymphadenopathy and an incidental nodular uptake of $^{18}$F-FDG in the left pelvis were observed on FDG-PET (Fig. 2). In contrast, $^{67}$Ga scintigraphy showed almost no abnormal findings except for slightly increased left hilar $^{67}$Ga uptake (Fig. 3). The left hilar accumulation of $^{67}$Ga was regarded as a non-specific physiological one because of the absence of left hilar lymphadenopathy on chest CT. Histopathological examination from a right...