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FDG-PET findings of the brain in lymphomatoid granulomatosis

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A 44-year-old man with a history of sudden onset short-term disorientation was admitted to our hospital. T2-weighted fast spin-echo MR images of the head showed increased signal intensity in the bilateral frontal and parietal white matter. Gadolinium-enhanced T1-weighted spin-echo images showed multiple areas with punctate and linear enhancement scattered in the bilateral frontal and parietal white matter. Although ^{18}F-fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) did not display a significant increase in FDG accumulation in the bilateral frontal and parietal white matter, kinetic analysis of this scan showed increased hexokinase activity in the lesions compared to the unaffected occipital white matter. Diagnosis was made by open biopsy of the right frontal lobe and pathologic specimen was positive for lymphomatoid granulomatosis (LYG). The patient received high-dose methotrexate with CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisolone) chemotherapy and follow-up MRI showed improvement of the lesions. [^{18}F]FDG-PET study with kinetic analysis may be useful to diagnose LYG in the central nervous system.

Key words: FDG (fluorodeoxyglucose), lymphomatoid granulomatosis, PET (positron emission tomography)

INTRODUCTION

LYMPHOMATOID GRANULOMATOSIS (LYG) is an uncommon multisystem disease histologically characterized by multifocal "angiocentric and angiodestructive" lymphoreticular proliferative and granulomatous lesions.[1] LYG is currently considered an Epstein-Barr virus (EBV)-associated B-cell lymphoproliferative disorder.[2] LYG most frequently involves the lungs; however the skin and central nervous system (CNS) are also commonly affected.[3] On rare occasions, CNS lesions may be the initial or the only clinical manifestation of the disease.[4–6] The prognosis of LYG is extremely poor. The largest series, of 152 patients, reported a mortality rate of 67% and a median survival time of 14 months,[3] with patients dying of pulmonary complications, infection, and CNS disease. Furthermore, a considerable number of patients with LYG eventually develop non-Hodgkin's lymphoma.[3,7]

We recently encountered a histologically proven LYG patient who showed multiple punctate and linear enhancement in the bilateral frontal and parietal white matter on magnetic resonance imaging (MRI). Although the patient did not display a significant increase in ^{18}F-fluorodeoxyglucose ([^{18}F]FDG) uptake in the bilateral frontal and parietal white matter on positron emission tomography ([^{18}F]FDG-PET), kinetic analysis showed increased hexokinase activity in the lesions. This may indicate malignant characteristics of LYG with an accelerated glycolytic metabolism in the tumor. To our knowledge, this is the first report describing PET findings that may provide biological information on LYG involving the CNS.

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CASE REPORT

A 44-year-old man with a history of sudden onset dementia was admitted to our hospital. One month before the admission, short-term disorientation occurred followed by inactive and gait disturbance. He also presented with a history of dull headache. On neurological examination, he showed memory and intellectual disturbance and ataxic gait. No other neurological deficits including those of the cranial nerves were observed. Neither lymph node swelling nor hepatosplenomegaly was detected. Peripheral blood tests revealed neither an increase in white blood cell counts, nor atypical lymphocytes. Biochemical tests showed raised lymphoma markers including soluble IL-2 receptor (919 U/m*l*, normal range 135–483) and β_2-microglobin (5.8 mg/*l*, normal range 0–2.4). Titers of Epstein-Barr virus at 2 weeks after the admission were as follows: virus capsid antigen (VCA) IgG ×160, VCA IgM < ×10, and Epstein-Barr nuclear antigen (EBNA) ×20. A cerebrospinal fluid (CSF) examination found 57 lymphocytes/mm^3 and an elevated protein concentration (80 mg/d*l*). A cytological examination of the CSF revealed no atypical cells. The chest X-ray taken on admission showed no abnormality. Brain MRI revealed increased signal intensity in the bilateral frontal and parietal white matter on T2-weighted fast spin-echo images (Fig. 1A). These lesions exhibited slightly low signal intensity on T1-weighted spin-echo images. Gadolinium-enhanced T1-weighted spin-echo images showed multiple areas with punctate and linear enhancement scattered in the bilateral frontal and parietal white matter (Fig. 1B). A PET study with [^{18}F]FDG was obtained on the day after hospitalization. Enteral and parenteral sources of glucose were withheld for 6 hours before the PET examination. A 60-minute dynamic PET scan (40 seconds × 1; 20 seconds × 2; 40 seconds × 4; 60 seconds × 4; 180 seconds × 4; 300 seconds × 8) was performed using a Siemens EXACT HR+ PET scanner after an intravenous injection of [^{18}F]FDG at a dose of 216 MBq. Arterial blood samples were withdrawn from the brachial artery at 15-second intervals for the first 3 minutes, followed by increasingly longer intervals to 60 minutes, to measure arterial plasma radioactivity using an auto well gamma counter (ARC-400, Aloka, Tokyo, Japan). The blood sample obtained at 30 minutes after the injection was analyzed for blood glucose concentration and was within the normal range (100 mg/d*l*). The [^{18}F]FDG-PET images did not display a significant increase in FDG uptake in the bilateral frontal and parietal white matter (CMR_{glc}; 44.0 μmol/min/100 g) compared with that observed in the unaffected occipital white matter (CMR_{glc}; 40.5 μmol/min/100 g) (Fig. 2A). Kinetic evaluation of this scan showed decreased FDG transport (K_1; 0.044 m*l*/min) and markedly increased hexokinase activity (k_3; 0.127 min^{-1}) in the lesions compared with that observed in the occipital white matter (K_1; 0.081 m*l*/min, k_3; 0.050 min^{-1}) (Fig. 2B). Open biopsy of the right frontal lobe revealed a perivascular granulomatous infiltrate of small lymphoid cells, plasma cells, and histiocytes (Fig. 3), which is characteristic of LYG. Immuno-histochemistry showed that the infiltrating lym-

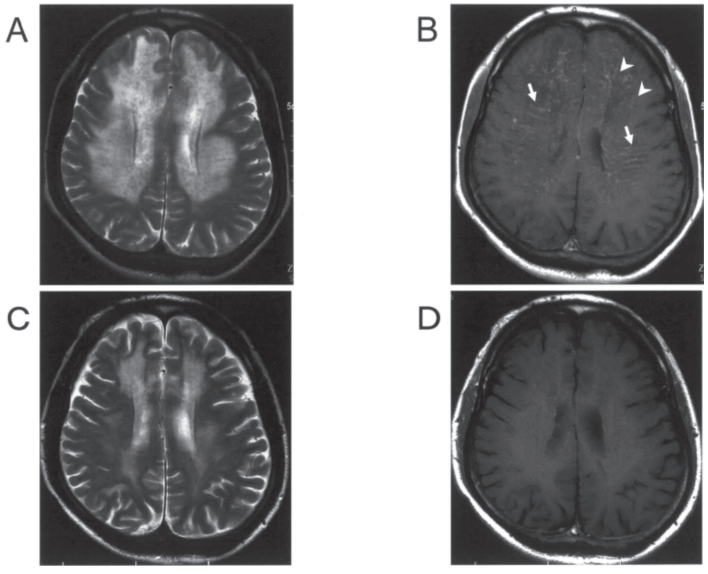

Fig. 1 MR images obtained before (A, B) and after (C, D) chemotherapy. (A) T2-weighted fast spin-echo images show hyper-intense area in the frontal and parietal white matter. (B) Gadolinium-enhanced T1-weighted spin-echo images show multiple areas with punctate (*arrowhead*) and linear (*arrow*) enhancement scattered in the bilateral frontal and parietal white matter. After chemotherapy, MR images show improvement of the lesions on T2-weighted fast spin-echo (C) and gadolinium-enhanced T1-weighted spin-echo images (D).

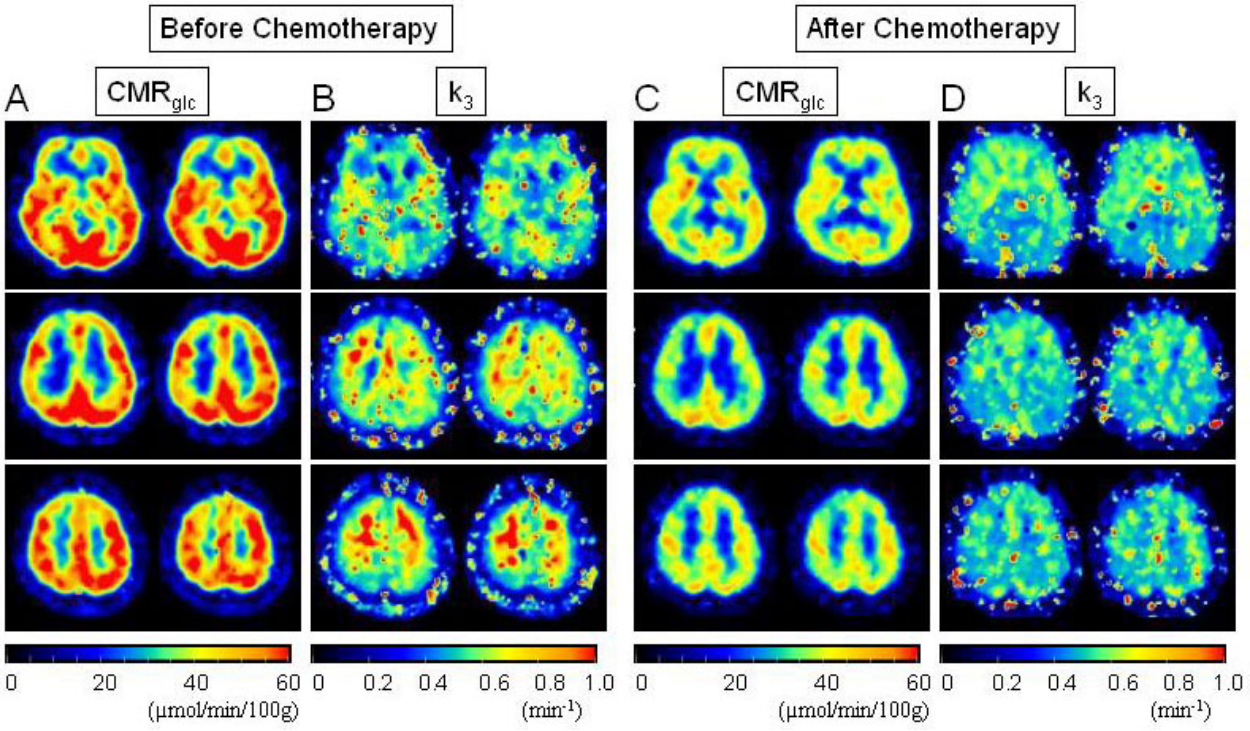

Fig. 2 [^{18}F]FDG-PET images with kinetic analysis obtained before (A, B) and after (C, D) chemotherapy. (A) The images do not display a significant increase in FDG uptake (CMR_{glc}) in the bilateral frontal and parietal white matter. (B) Kinetic analysis of this scan shows markedly increased hexokinase activity (k_3) in the lesions compared with the unaffected occipital white matter. After chemotherapy, FDG uptake in the cortex is reduced globally compared with that observed in the initial [^{18}F]FDG-PET images (C) and kinetic analysis of this scan shows decreased hexokinase activity (k_3) in the lesions (D).

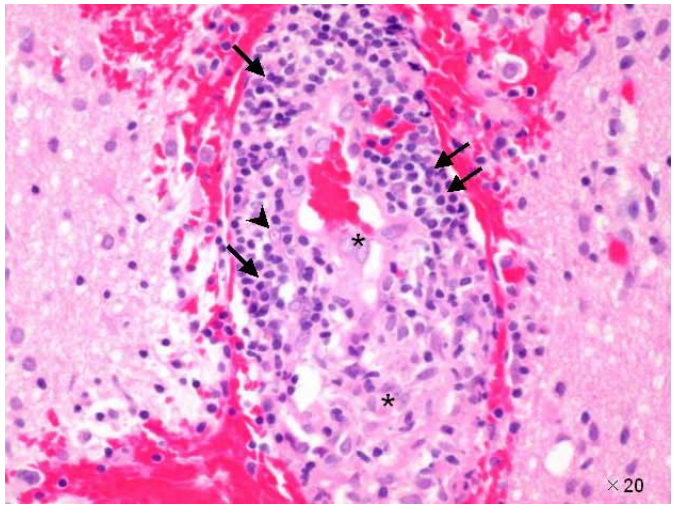

Fig. 3 Histopathological examination of specimens from the right frontal lobe by open biopsy. Hematoxylin and eosin staining shows granulomatous infiltration of small lymphoid cells (*arrow*), plasma cells *(arrowhead*), and histiocytes (*asterisk*), which are predominant in the perivascular space (original magnification, ×20).

phoid cells predominantly consisted of T cells (CD3+) scattered with B cells (CD20+). *In situ* hybridization for EBV-encoded RNA (EBER) and EBV-encoded product, latent membrane protein-1 (LMP-1), in the lesion were negative. A high-dose of methotrexate (2.0 g/m^2) in combination with CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisolone) chemotherapy was administrated. His neurological findings gradually improved after the chemotherapy and follow-up MRI showed improvement of the lesions on T2-weighted fast spin-echo and gadolinium-enhanced T1-weighted spin-echo images (Fig. 1C and 1D). Follow-up [^{18}F]FDG-PET images showed globally decreased FDG uptake in the cortex compared with that observed in

the initial [^{18}F]FDG-PET images (Fig. 2C). Kinetic analysis of this scan revealed a decrease in hexokinase activity in the lesions (k_3; 0.054 min^{-1}) (Fig. 2D).

DISCUSSION

Lymphomatoid granulomatosis (LYG) was first described in 1972 as an angiocentric, angiodestructive lymphoproliferative, and granulomatous disease predominantly affecting the lung.[1] Central nervous system (CNS) involvement in LYG is seen in approximately 30% of cases,[3] with a clinical picture similar to that of vasculitis and/or lymphoma. There are a few reports of exclusive CNS involvement,[4–6] like in our case. The presence of CNS involvement is a grave prognostic factor, associated with a mortality rate of 86% after 14 months compared with 66% for patients without CNS involvement.[3] Lack of typical neurological manifestations and radiological features often results in a delay in the correct diagnosis of this disease.[4,6] The definitive diagnosis of LYG is based on histopathology.[1] Neurological symptoms frequently are nonspecific and may consist of headache, seizures, hemiparesis, ataxia, blindness, deafness, cranial-nerve paralysis, altered consciousness, and dementia.[3,6,8,9] Our patient presented with short-term disorientation without specific neurological signs. Diagnosis of this disease using imaging techniques has also been difficult.[6,8] Recently, Patsalides et al. summarized the MRI features of 13 CNS-involved LYG cases and reported that multiple focal intraparenchymal lesions, which exhibited T2 prolongation and commonly punctate or linear enhancement, were the most frequent abnormalities.[10] Our patient also presented with increased signal intensity on T2-weighted fast spin-echo images and typical punctate and linear enhancement scattered in the white matter on gadolinium-enhanced T1-weighted spin-echo images.

^{18}F-fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) has proven very effective for the diagnosis of primary central nervous system lymphoma (PCNSL) because the tumor has high cellular density with an increased glycolytic metabolism in the tumor cells, and therefore shows a huge accumulation of FDG.[11,12] With human [^{18}F]FDG-PET studies, dynamic image acquisition separates regional FDG uptake into FDG transport and hexokinase activity. The benefits and limitations to apply this method to human brain tumor were discussed previously.[13,14] The measured values for FDG metabolism require careful interpretation in primary brain tumor. Although our patient did not display a significant increase in FDG uptake in the lesions, markedly increased hexokinase activity was revealed by kinetic analysis of this scan. These are different from the findings commonly observed in typical PCNSL which shows markedly increased FDG uptake in the tumor with accelerated hexokinase activity.[13] The hexokinase activity observed in our LYG patient (k_3; 0.127 min^{-1}) was higher than that observed in PCNSL patients (k_3; 0.093 ± 0.026 min^{-1}).[13] However, the transport activity in our LYG patient (K_1; 0.044 m*l*/min) was apparently lower than that in PCNSL patients (K_1; 0.079 ± 0.015 m*l*/min).[13] The number of glucose transporters on the tumor cells might be lower or glucose transport to the tumor might be inhibited due to angiocentric and angiodestructive proliferation of the tumor cells in LYG patients. Further examinations including immunostaining of glucose transporter are necessary to define the exact reason for this result. We recently reported similar findings to those observed in our LYG patient in a patient with histologically proven non-enhancing PCNSL.[14] The patient also had decreased FDG transport and increased hexokinase activity in the tumor.[14]

LYG may remain static or persistently progressive and its natural course is extremely variable.[3,7,15,16] Grades of the disease are assigned with a scale of I to III, on the basis of the number of atypical EBV-positive B cells and the amount of necrosis.[17,18] Grade III lesion has sheets of large atypical EBV-positive cells and is histologically considered a diffuse large B cell malignant lymphoma. In our patient, pathological specimen revealed a perivascular granulomatous infiltrate of small lymphoid cells, plasma cells, and histiocytes, which is characteristic of LYG and was assigned to grade I because of the low number of EBV-positive atypical large B cells without necrosis in the cellular infiltrate. Treatment in LYG and especially in cerebral LYG remains controversial. There is no specific therapy and most cases reported in the literature to date are anecdotal.[4,6,9,19] In the case of progressive disease (grade III LYG), conventional chemotherapy should be attempted first.[16,18] It has been considered that treatment with interferon or observation alone may be reasonable for grade I or grade II pulmonary LYG.[18] Considerable debate exists concerning whether LYG is a true inflammatory process or merely a variant of malignant lymphoma. Although some authors might regard all cases of LYG as lymphoma,[16] it is believed that grade I and grade II lesions should not be regarded as lymphomas because some cases may regress spontaneously.[3,15] Clinically, LYG acts like a malignancy with its aggressive characteristics and high mortality rate.[3] Furthermore, patients with LYG may eventually develop lymphoma of the large B-cell type, with an incidence ranging from 10% to 15%.[3,7] Fauci et al. suggested that early recognition and prompt treatment during the LYG phase of the disease may not only lead to complete remission, but also decrease the possibility of the development of a lymphoid neoplasm.[7]

In conclusions, the enhanced hexokinase activity observed in our patient might indicate malignant characteristics of LYG. We treated the patient aggressively with combined chemotherapy and radiotherapy even in grade I LYG. A long-term follow-up of this patient and further experience are necessary to define the absolute value of [^{18}F]FDG-PET study in patients with LYG involving the CNS. [^{18}F]FDG-PET study with kinetic analysis may be

useful to diagnose LYG in the central nervous system.

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REFERENCES

1. Liebow AA, Carrington CRB, Friedma PJ. Lymphomatoid granulomatosis. *Hum Pathol* 1972; 3: 457–558.
2. Taniere P, Thivolet-Bejui F, Vitrey D, Isaac S, Loire R, Cordier JF, et al. Lymphomatoid granulomatosis—a report on four cases: evidence for B phenotype of the tumoral cells. *Eur Respir J* 1998; 12: 102–106.
3. Katzenstein AL, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: a clinicopathological study of 152 cases. *Cancer* 1979; 43: 360–373.
4. Hamilton MG, Demetrick DJ, Tranmer BI, Curry B. Isolated cerebellar lymphomatoid granulomatosis progressing to malignant lymphoma. Case report. *J Neurosurg* 1994; 80: 314–320.
5. Paspala AB, Sundaram C, Purohit AK, Immaneni D. Exclusive CNS involvement by lymphomatoid granulomatosis in a 12-year-old boy: a case report. *Surg Neurol* 1999; 51: 258–260.
6. Tateishi U, Terae S, Ogata A, Sawamura Y, Suzuki Y, Abe S, et al. MR imaging of the brain in lymphomatoid granulomatosis. *AJNR Am J Neuroradiol* 2001; 22: 1283–1290.
7. Fauci AS, Haynes BF, Costa J, Katz P, Wolff SM. Lymphomatoid granulomatosis. Prospective clinical and therapeutic experience over 10 years. *N Engl J Med* 1982; 306: 68–74.
8. Kerslake R, Rowe D, Worthington BS. CT and MR imaging of CNS lymphomatoid granulomatosis. *Neuroradiology* 1991; 33: 269–271.
9. Kleinschmidt-DeMasters BK, Filley CM, Bitter MA. Central nervous system angiocentric, angiodestructive T-cell lymphoma (lymphomatoid granulomatosis). *Surg Neurol* 1992; 37: 130–137.
10. Patsalides AD, Atac G, Hedge U, Janik J, Grant N, Jaffe ES, et al. Lymphomatoid granulomatosis: abnormalities of the brain at MR imaging. *Radiology* 2005; 237: 265–273.
11. Rosenfeld SS, Hoffman JM, Coleman RE, Glantz MJ, Hanson MW, Schold SC. Studies of primary central nervous system lymphoma with fluorine-18-fluorodeoxyglucose positron emission tomography. *J Nucl Med* 1992; 33: 532–536.
12. Roelcke U, Leenders KL. Positron emission tomography in patients with primary CNS lymphomas. *J Neuro-Oncol* 1999; 43: 231–236.
13. Kawai N, Nishiyama Y, Miyake K, Tamiya T, Nagao S. Evaluation of tumor FDG transport and metabolism in primary central nervous system lymphoma using [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) kinetic analysis. *Ann Nucl Med* 2005; 19: 685–690.
14. Kawai N, Kawanishi M, Tamiya T, Nagao S. Usefulness of [^{18}F]FDG-PET kinetic analysis in non-enhancing central nervous system lymphoma: case report. *Ann Nucl Med* 2005; 19: 415–419.
15. Koss MN, Hochholzer L, Langloss JM, Wehunt WD, Lazarus AA, Nichols PW. Lymphomatoid granulomatosis: a clinicopathological study of 42 patients. *Pathology* 1986; 18: 283–288.
16. Jaffe ES, Wilson WH. Lymphomatoid granulomatosis: pathogenesis, pathology and clinical implications. *Cancer Surv* 1997; 30: 233–248.
17. Lipford EH Jr, Margolick JB, Longo DL, Fauci AS, Jaffe ES. Angiocentric immunoproliferative lesions: a clinicopathological spectrum of post-thymic T-cell proliferations. *Blood* 1988; 72: 1674–1681.
18. Guinee DG, Perkins SL, Travis WD, Holden JA, Tripp SR, Koss MN. Proliferation and cellular phenotype in lymphomatoid granulomatosis: implications of a higher proliferation index in B cells. *Am J Surg Pathol* 1998; 22: 1093–1100.
19. Petrella TM, Walker IR, Jones GW, Leber B. Radiotherapy to control CNS lymphomatoid granulomatosis: a case report and review of the literature. *Am J Hematol* 1999; 62: 239–241.