Case Reports in Oncology

Case Rep Oncol 2012;5:339–346
DOI: 10.1159/000339963

Published online:
July 3, 2012

ISSN 1662–6575
www.karger.com/cro

Insufficiency of Positron Emission Tomography and Magnetic Resonance Spectroscopy in the Diagnosis of Intravascular Lymphoma of the Central Nervous System

Nobuyuki Kawai[a] Masaki Okada[a] Reiji Haba[c]
Yuka Yamamoto[b] Takashi Tamiya[a]

Departments of [a]Neurological Surgery and [b]Radiology, Faculty of Medicine, Kagawa University, and [c]Department of Diagnostic Pathology, Kagawa University Hospital, Kagawa, Japan

Key Words
Intravascular lymphoma · Fluorodeoxyglucose · Methionine · Positron emission tomography · Proton magnetic resonance spectroscopy

Abstract
Intravascular large B-cell lymphoma (IVL) is a rare type of extranodal lymphoma with an aggressive clinical course characterized by the proliferation of lymphoma cells within the lumen of small vessels. Diagnosis is often difficult because of marked variability in clinical presentation and nonspecific laboratory and radiological findings, especially when central nervous system (CNS) symptoms are the only manifestation. Modern metabolic imaging techniques such as positron emission tomography (PET) and ^{1}H-magnetic resonance spectroscopy (MRS) have been reported to be useful in the diagnosis of conventional primary CNS lymphoma. We report the case of a 69-year-old man who presented with a progressive leukoencephalopathic syndrome. The patient was examined by ^{18}F-fluorodeoxyglucose and ^{11}C-methionine PET and MRS, but none of these examinations were able to show the presence of a tumor in the lesions or to clarify the tumor characteristics. Brain biopsy was the only way to obtain a definite diagnosis of IVL. The patient was treated intensively with standard immunochemotherapy but died 6 months after the diagnosis. Here, we discuss the insufficiency of modern metabolic imaging techniques, including PET and MRS, and recommend a rapid decision of brain biopsy in the diagnosis of IVL only involving the CNS.

Nobuyuki Kawai, MD

Department of Neurological Surgery
Faculty of Medicine, Kagawa University
1750-1 Miki-cho, Kita-gun, Kagawa 761-0793 (Japan)
Tel. +81 87 891 2207, E-Mail nobu@med.kagawa-u.ac.jp

KARGER

Case Rep Oncol 2012;5:339–346
DOI: 10.1159/000339963
Published online: July 3, 2012

ISSN 1662–6575
www.karger.com/cro

Introduction

Intravascular large B-cell lymphoma (IVL) is a rare type of extranodal lymphoma with an aggressive clinical course characterized by the proliferation of lymphoma cells within the lumen of small vessels with no or only minimal involvement of the parenchyma [1]. The signs and symptoms of the disease are heterogeneous and attributed to vascular occlusion of the small vessel of the involved organ. The central nervous system (CNS) is frequently involved and neurological symptoms were noted in 25% of the patients on initial diagnosis [2], and two-thirds of all cases develop neurological manifestations during the course of the disease [3]. Diagnosis is often difficult because of marked variability in clinical presentation and nonspecific laboratory and radiological findings, especially when neurological symptoms are the only manifestation. Therefore, many of the reported cases were diagnosed postmortem.

Metabolic nuclear imaging with ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-methionine (MET) positron emission tomography (PET) has been used to diagnose primary CNS lymphoma (PCNSL) [4, 5]. The tumor has a very high cellular density with an accelerated metabolism, and typical PCNSL always shows strong accumulation of FDG and MET in the lesions [4, 5]. However, PCNSL with atypical magnetic resonance (MR) findings, such as disseminated or nonenhanced lesions, exhibit obscure or faint FDG and MET uptake in the tumor, and visual or semiquantitative analysis cannot identify the tumor in the lesions [6]. ^{1}H-MR spectroscopy (MRS) provides information on metabolic changes in vivo. The most specific finding for typical PCNSL on MRS is an increase in lipid/lactate peak [7, 8]. PCNSL also demonstrated a raised choline peak relative to creatine and N-acetyl aspartate (NAA), which are nonspecific and also shown in astrocytic tumors. No reports have described the findings in IVL using PET and MRS. Herein, we report a case of histopathologically proven IVL in the CNS presenting with progressive leukoencephalopathic syndrome. The patient was examined by FDG-PET, MET-PET and MRS before brain biopsy. Both PET examinations were unable to show the presence of a tumor in the lesions, and MRS was unable to clarify the characteristics of the tumor. Here, we report the insufficiency of advanced metabolic PET and MRS examinations in the diagnosis of IVL and recommend a rapid decision of brain biopsy when IVL is in the differential diagnosis.

Case Report

A 69-year-old man was admitted with progressive leukoencephalopathic syndrome. Two months prior to admission, he gradually developed gait disturbance, and an initial brain MR image demonstrated multiple subcortical hyperintense lesions on diffusion-weighted images. He was treated as suffering from multiple infarctions using antithrombotic and antiplatelet therapy, but his condition gradually deteriorated and repeat MR images showed progressive leukoencephalopathy in the brain. On admission, the patient was lethargic and bedridden with motor weakness in the extremities. A cytological examination of the cerebrospinal fluid revealed no atypical cells. Brain MRI showed a diffuse high signal intensity area in the white matter on T_2-weighted fast spin-echo images (**fig. 1**a). Gadolinium-enhanced T_1-weighted spin-echo images showed multiple irregular enhancements in the cerebral cortex, the white matter and the basal ganglia as well as in the cerebellum (fig. 1b, c). Some of the cortical lesions were enhanced with a gyriform pattern (fig. 1c).

A Biograph mCT64 scanner (Siemens/CTI, Knoxville, Tenn., USA) was used for PET examination. Enteral and parenteral sources of glucose were withheld for 6 h before the PET examination. For FDG-PET examination, 342 MBq of FDG was injected intravenously. Regional emission images of the brain

Case Rep Oncol 2012;5:339–346
DOI: 10.1159/000339963
Published online: July 3, 2012

ISSN 1662–6575
www.karger.com/cro

were obtained for 10 min, beginning 60 min after FDG administration. The blood sample obtained at FDG injection was analyzed for blood glucose concentration and was within the normal range (122 mg/dl). The FDG-PET images did not display a significant increase in FDG uptake in the lesions and showed glucose hypometabolism in the overlying cerebral cortex (**fig. 2**a). For MET-PET examination, 256 MBq of MET was injected intravenously. The use of MET as a PET tracer was approved by the Human Subjects Ethical Committee of the Kagawa University Faculty of Medicine and informed consent was obtained from the patient's relatives before PET examination. Regional emission images of the brain were obtained for 5 min, beginning 20 min after MET injection. The MET-PET images did not show a significant increase in MET uptake in the lesions (fig. 2b). MRS data were acquired using a 1.5 T whole body MRI system (Achieva; Philips Medical System, Best, The Netherlands) with a circularly polarized head coil. Spectra were obtained with long TE acquisition, a single voxel point-resolved spin-echo sequence for localization (TR/TE 2,000/144 ms) and a three-pulse chemical-shift selective saturation sequence to provide water suppression. MRS showed a lactate/lipid peak, increased choline/creatine and decreased NAA/creatine ratios in the lesion (1.05 and 0.65, respectively) compared to those in the normal brain (0.70 and 1.04, respectively; **fig. 3**a, b).

Stereotactic biopsy of the right frontal lobe lesion was decided and showed large blastic lymphoid tumor cells within the small vessels but not in the brain parenchyma. The tumor cells showed strong immunoreactivity with the pan-B cell marker CD20 but not with the pan-T cell marker CD3, which were diagnostic findings of IVL. Standard immunochemotherapy using rituximab (R; 375 mg/m^2) combined with cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisolone (CHOP) and high-dose methotrexate (MTX; 2.5 mg/m^2) was administrated (R-CHOP + MTX). Neurological improvement was observed after 1 cycle of MTX-CHOP and 3 cycles of R-CHOP + MTX. The patient received five additional treatments of R, but his condition gradually deteriorated after generalized convulsions and he died of pneumonia 6 months after the diagnosis. No autopsy was obtained.

Discussion

This report highlights the insufficiency of modern metabolic imaging techniques such as PET and MRS in the diagnosis of IVL of the CNS. Both FDG-PET and MET-PET have not been shown to aid localization or diagnosis, and the findings of MRS are nonspecific and cannot differentiate IVL from other tumorous lesions such as gliomatosis cerebri, or nontumorous lesions such as multiple infarctions.

IVL is a rare type of extranodal non-Hodgkin lymphoma. It is generally of B-cell origin and has been classified as a distinct clinicopathological subtype of the diffuse large B-cell lymphoma [1]. The histopathological hallmark of the disease is the presence of neoplastic lymphoma cells in the lumen of small sized vessels [9]. Vascular occlusion results in ischemic, hemorrhagic or necrotic lesions in the involved organs. The most common clinical manifestations involve the CNS and the skin [2], with two-thirds of all cases developing neurological manifestations during the course of the disease [1]. IVL is difficult to diagnose, particularly when neurological symptoms are the only manifestation. Cutaneous involvement is rare in Asian patients [2] but, if present, provides an easy target for biopsy. Our patient presented only with neurological manifestations but did not show cutaneous involvement of IVL. Various imaging findings have been reported but they are all nonspecific. The most common MR finding is abnormal hyperintensity on T_2-weighted and fluid-attenuated inversion recovery images in the deep white matter [10]. Sometimes infarct-like lesions and, less commonly, enhancing parenchymal mass lesions were found [10].

Glucose metabolic imaging with FDG-PET has been used to diagnose PCNSL because the tumor has a very high cellular density with an accelerated glucose metabolism, and

Case Rep Oncol 2012;5:339–346
DOI: 10.1159/000339963
Published online: July 3, 2012

ISSN 1662–6575
www.karger.com/cro

therefore shows a huge uptake of FDG into the tumor [5]. Amino acid metabolic imaging with MET-PET possesses high specificity in tumor detection, tumor delineation and differentiation of benign from malignant lesions in the brain [11]. MET-PET examination in PCNSL is limited and only a few reports demonstrate its diagnostic usefulness and evaluate the therapeutic effect [4, 12]. In our previous reports, PCNSL with typical MR findings showed, without exception, increased FDG and MET uptakes in the tumor before treatment [6]. In these cases, PET examinations can provide valuable information in the primary diagnosis and therapeutic monitoring. However, FDG and MET uptake in the tumor is obscure or faint in some PCNSL patients with atypical MR findings [6]. In particular, FDG-PET barely shows the presence of a tumor in the lesions [6] because of the normally high uptake of FDG in the brain, such as the gray matter, thalamus and basal ganglia. Therefore, PET examinations with FDG and MET in patients with atypical MR findings are not useful in differentiating PCNSL from other tumorous or nontumorous diseases. The overlying cortical gray matter showed glucose hypometabolism in some patients, and our patient also demonstrated glucose hypometabolism in the overlying cerebral cortex. This finding is reported in patients with gliomatosis cerebri due to disconnection of the cortical gray matter by tumor infiltration [13]. Furthermore, nonspecific uptake of FDG and MET has been reported in patients with intracerebral hematoma, cerebral infarction, brain abscess and multiple sclerosis. Tracer uptake in the nontumorous lesions is usually faint, depending on the increased density of inflammatory cells as well as the disruption of the blood-brain barrier. In our IVL case, tracer uptake was not increased, probably due to limited access of tracers to the lesions by vascular occlusion and a small proportion of tumorous cells in the lesions.

MRS provides in vivo assessment of the metabolism of organs and cells in living tissue with no harm to the human body. Various metabolites in brain tissue, such as NAA, creatine, choline-containing compounds and lactate, can be measured using MRS. Cholines are composed of choline, phosphocholine and glycerolphosphocholine and are considered to be markers for increased membrane turnover or higher cellular density. NAA is regarded as a neuronal marker mainly contained within neurons. The creatine peak is the signal from both creatine and phosphocreatine and represents the tissue energy metabolism. Studies have shown that MRS offers important information on metabolic changes associated with tumor progression and grading [14]. In particular, elevation in choline concentration with NAA depression is an important and reliable indicator of tumor characterization [14]. In PCNSL, the most specific finding is an increase in the lipid/lactate peak [7, 8]. This is a typical characteristic of cell death; however, a lipid/lactate-dominated peak is found in PCNSL that is not morphologically necrotic. This appears to be due to numerous macrophages and the increased turnover of membrane components in transformed lymphoid cells. Harting et al. [7] found a significantly higher lipid/lactate peak in solid PCNSL than in solid low- and high-grade astrocytomas. PCNSL also demonstrated a raised choline peak relative to creatine and NAA, which are nonspecific and also shown in astrocytic tumors [7]. Studies have reported findings of acute ischemic stroke patients at various time points with MRS. Reduced NAA is a consistent finding soon after the stroke. The findings for choline and creatine vary. Lipid/lactate is detected early, then disappears to reappear at about 3 weeks [15]. Our patient showed a small lipid/lactate peak, a relatively increased choline peak and a decreased NAA peak in the lesion. Again, the findings are not diagnostic and cannot differentiate IVL from ischemic lesions. Although the greatest

Case Rep Oncol 2012;5:339–346
DOI: 10.1159/000339963
Published online: July 3, 2012

ISSN 1662–6575
www.karger.com/cro

portion of the voxel for MRS measurement was located in the enhanced lesion, a small proportion of tumorous cells in the lesion may cause this undiagnostic finding.

In conclusion, we report a case of histopathologically proven IVL in the CNS presenting with progressive leukoencephalopathic syndrome. The patient was examined by FDG-PET, MET-PET and MRS, but none of these examinations were able to show the presence of a tumor in the lesions or to clarify the characteristics of the tumor. Due to the absence of a reliable diagnostic method including an advanced metabolic imaging tool and an invasive procedure, commonly a brain biopsy is often required, especially when symptoms in the CNS are the only manifestation of IVL.

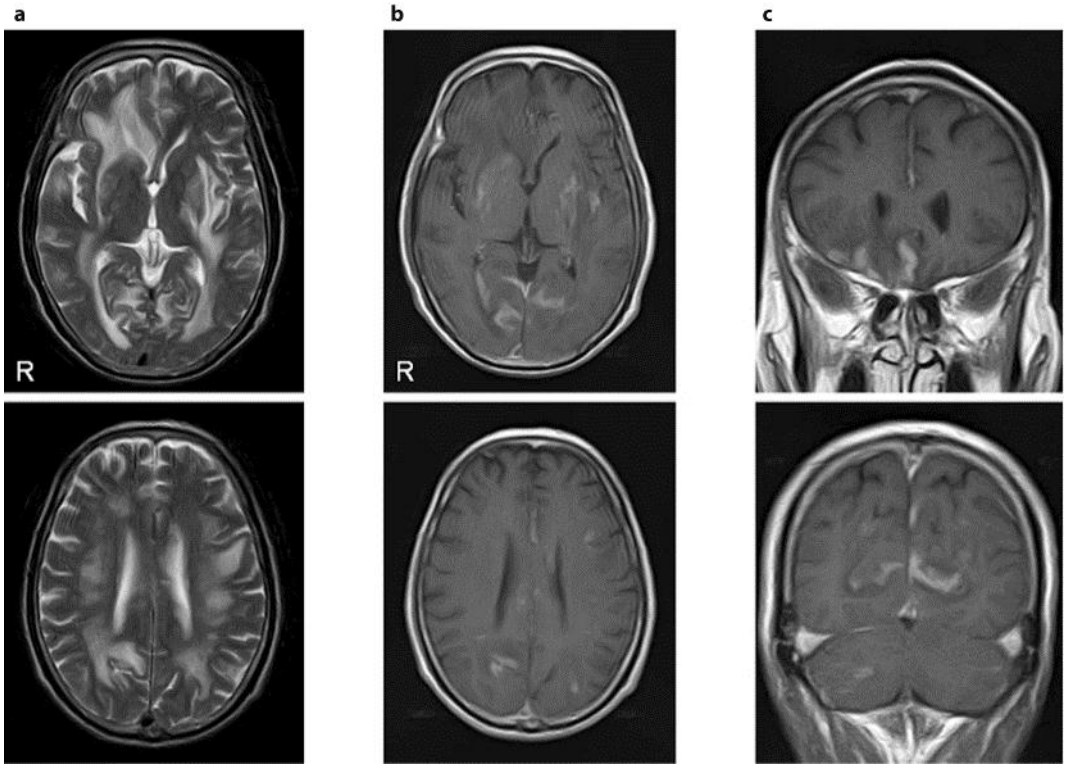

Fig. 1. T_2-weighted axial MR images showing diffuse high intensities in the white matter (**a**). Contrast-enhanced T_1-weighted axial MR images showing multiple irregular enhancement in the cerebral cortex, white matter and basal ganglia (**b**). Contrast-enhanced T_1-weighted coronal and sagittal MR images showing gyriform enhancement in the cerebral cortex and patchy enhancement in the cerebellum (**c**).

Case Rep Oncol 2012;5:339–346
DOI: 10.1159/000339963
Published online: July 3, 2012

ISSN 1662–6575
www.karger.com/cro

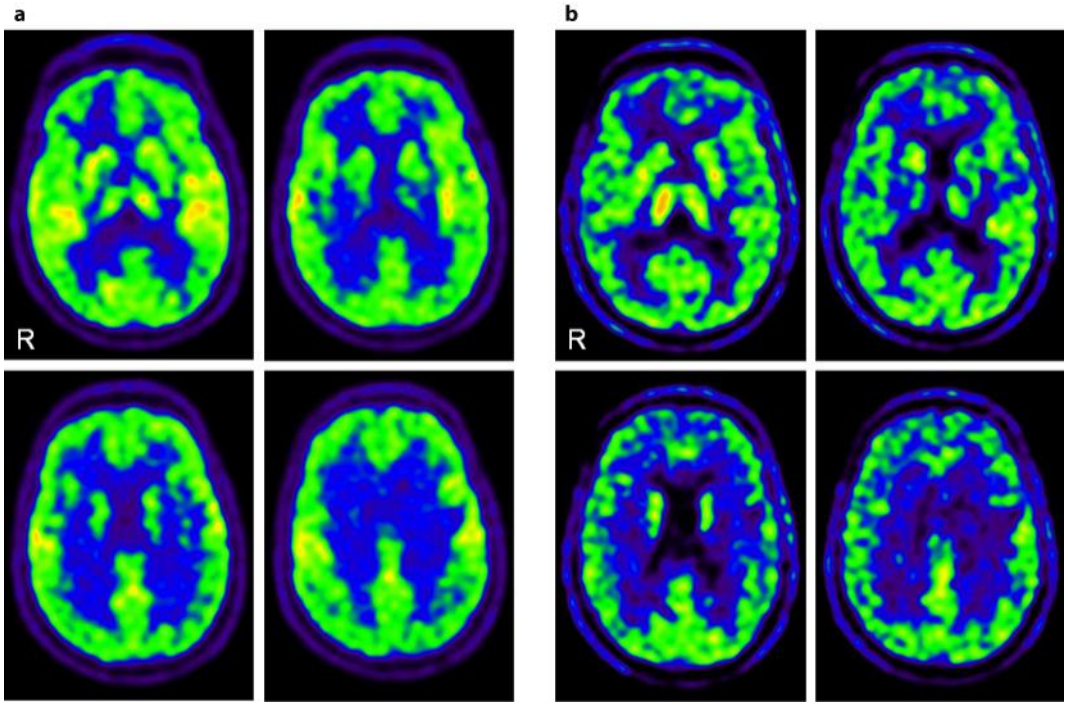

Fig. 2. FDG-PET images showing no focally increased FDG uptake corresponding to the enhanced lesions and diffuse glucose hypometabolism in the cerebral cortex (**a**). MET-PET images showing no focally increased MET uptake corresponding to the enhanced lesions (**b**).

Case Rep Oncol 2012;5:339–346
DOI: 10.1159/000339963
Published online: July 3, 2012

ISSN 1662–6575
www.karger.com/cro

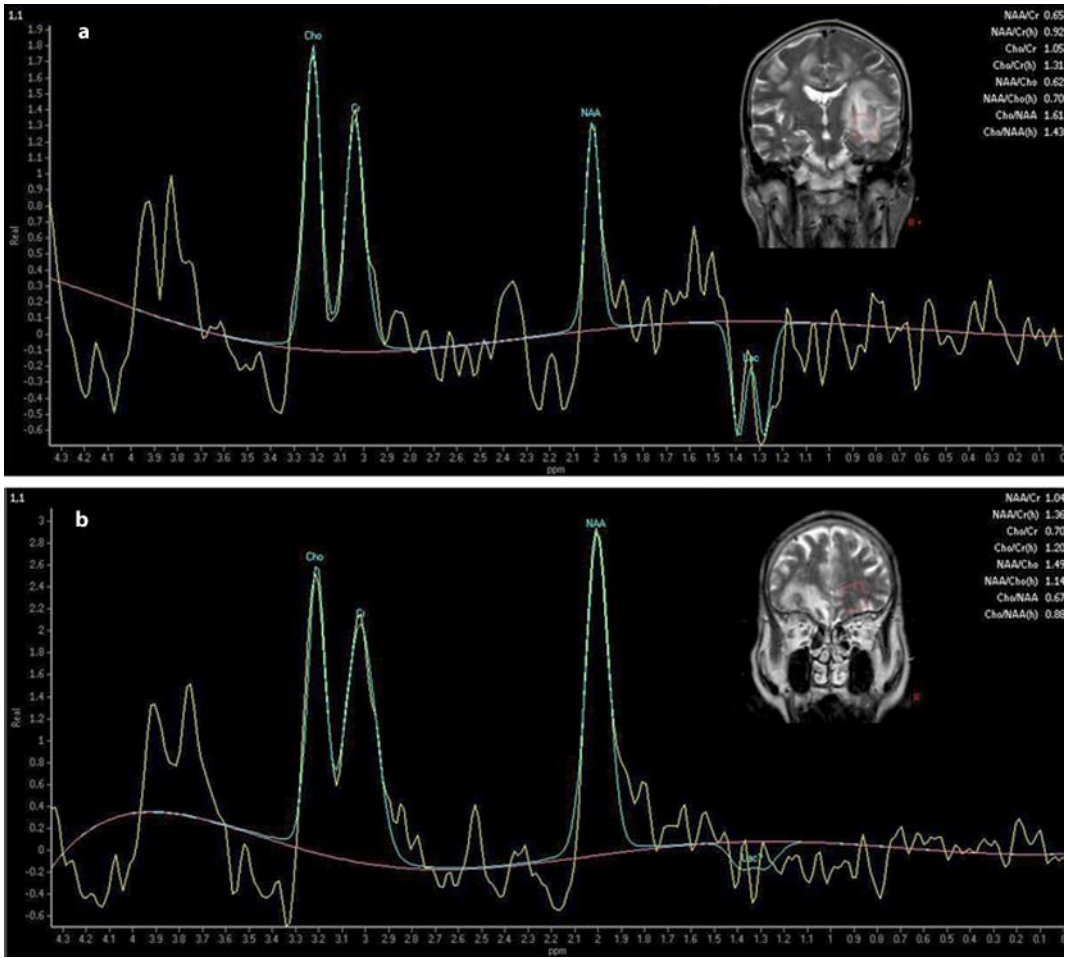

Fig. 3. MRS in lesion (**a**) showing a small lactate peak, an increased choline peak and a decreased NAA peak relative to creatine compared to the normal cortex (**b**). The choline/creatine ratio was higher in the lesion (1.05) than in the normal brain (0.70). The NAA/creatine ratio was lower in the lesion (0.65) than in the normal brain (1.04).

References

1 Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD: World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835–3849.

2 Shimada K, Kinoshita T, Naoe T, Nakamura S: Presentation and management of intravascular large B-cell lymphoma. Lancet Oncol 2009;10:895–902.

3 Aznar AO, Montero MA, Rovira R, Vidal FR: Intravascular large B-cell lymphoma presenting with neurological syndromes: clinicopathologic study. Clin Neuropathol 2007;26:180–186.

4 Ogawa T, Kanno I, Hatazawa J, Inugami A, Fujita H, Shimosegawa E, Murakami M, Okudera T, Uemura K, Yasui N, Mineura K: Methionine PET for follow-up of radiation therapy of primary lymphoma of the brain. Radiographics 1994;14:101–110.

5 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.

Case Rep Oncol 2012;5:339–346
DOI: 10.1159/000339963
Published online: July 3, 2012

ISSN 1662–6575
www.karger.com/cro

6 Kawai N, Okubo S, Miyake K, Maeda Y, Yamamoto Y, Nishiyama Y, Tamiya T: Use of PET in the diagnosis of primary CNS lymphoma in patients with atypical MR findings. Ann Nucl Med 2010;24:335–343.

7 Harting I, Hartmann M, Jost G, Sommer C, Ahmadi R, Heiland S, Sartor K: Differentiating primary central nervous system lymphoma from glioma in humans using localised proton magnetic resonance spectroscopy. Neurosci Lett 2003;22:163–166.

8 Taillibert S, Guillevin R, Menuel C, Sanson M, Hoang-Xuan K, Chiras J, Duffau H: Brain lymphoma: usefulness of the magnetic resonance spectroscopy. J Neurooncol 2008;86:225–229.

9 Nakamura S, Ponzoni M, Campo E: Intravascular large B-cell lymphoma; in Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, ed 4, Lyon, IARC Press, 2008, pp 252–253.

10 Williams RL, Meltzer CC, Smirniotopoulos JG, Fukui MB, Inman M: Cerebral MR imaging in intravascular lymphomatosis. AJNR Am J Neuroradiol 1998;19:427–431.

11 Herholz K, Hölzer T, Bauer B, Schröder R, Voges J, Ernestus RI, Mendoza G, Weber-Luxenburger G, Löttgen J, Thiel A, Wienhard K, Heiss WD: 11C-methionine PET for differential diagnosis of low-grade gliomas. Neurology 1998;50:1316–1322.

12 Kawase Y, Yamamoto Y, Kameyama R, Kawai N, Kudomi N, Nishiyama Y: Comparison of 11C-methionine PET and 18F-FDG PET in patients with primary central nervous system lymphoma. Mol Imaging Biol 2011;13:1284–1289.

13 Plowman PN, Saunders CA, Maisey MN: Gliomatosis cerebri: disconnection of the cortical grey matter, demonstrated on PET scan. Br J Neurosurg 1998;12:240–244.

14 Möller-Hartmann W, Herminghaus S, Krings T, Marguardt G, Lanfermann H, Pilatus U, Zanella FE: Clinical application of proton magnetic resonance spectroscopy in the diagnosis of intracranial mass lesions. Neuroradiology 2002;44:371–381.

15 Wardlaw JM, Marshall I, Wild J, Dennis MS, Cannon J, Lewis SC: Studies of acute ischemic stroke with proton magnetic resonance spectroscopy: relation between time from onset, neurological deficit, metabolic abnormalities in the infarct, blood flow, and clinical outcome. Stroke 1998;29:1618–1624.