 doi: 10.2176/jns-nmc.2021-0125

NMC Case Report Journal 9, 83-88, 2022

A Case of Lymphomatosis Cerebri Presenting with Rapid Progression of Dementia: A Literature Review

Shoko Merrit YAMADA,[1] Yusuke TOMITA,[1] Mikiko TAKAHASHI,[2] and Masashi KAWAMOTO[2]

[1]*Department of Neurosurgery, Teikyo University Hospital Mizonokuchi, Kawasaki, Kanagawa, Japan*
[2]*Department of Diagnostic Pathology, Teikyo University Hospital Mizonokuchi, Kawasaki, Kanagawa, Japan*

Abstract

Lymphomatosis cerebri is an atypical form of primary central nervous system lymphoma (PCNSL), which frequently causes rapid progression of dementia. A 68-year-old woman exhibited rapidly progressing disorientation and a mini-mental state examination score of 9. The fluid-attenuated inversion recovery of a magnetic resonance image (MRI) demonstrated focal areas of high-signal intensity in the right frontal lobe with a small enhancement, which was histologically diagnosed as diffuse large B-cell type lymphoma. The lesion dramatically shrank, and no enhancements were identified on MRI after treatment with high-dose methotrexate (MTX) and whole-brain radiation (WBR). However, her recovery of cognitive function was poor. The patient visited our clinic every 2 months but succumbed to systemic mycotic sepsis 14 months after the biopsy. Autopsy revealed lymphomatosis cerebri in the patient based on a feature of scattered small clusters of lymphoma cells infiltrating into the brain parenchyma in both cerebral hemispheres. Differentiation of lymphomatosis cerebri from other white matter degenerative diseases is usually challenging because lymphomatosis cerebri seldom forms mass lesions. In lymphomatosis cerebri, the lymphoma cells infiltrate into several regions in the brain tissue, including the basal ganglia, brainstem, and corpus callosum, in addition to periventricular and subcortical white matters. The rapid deterioration of cognitive function in the patient suggests a rapid spread of lymphomatosis cerebri, necessitating early histological diagnosis and prompt treatments. If the diagnosis is obtained, administration of high-dose MTX and WBR followed by rituximab and cytarabine can contribute to a longer survival time, based on our literature review.

Keywords: dementia, malignant lymphoma, MTX, lymphomatosis cerebri, whole brain radiation

Introduction

Lymphomatosis cerebri is considered a diffusely infiltrating form of primary central nervous system lymphoma (PCNSL) without evidence of mass lesions.[1)] Although its definition has not yet been established, Li et al. mentioned that lymphomatosis cerebri can be diagnosed if the following conditions are met: 1) T2-weighted (T2W)/fluid-attenuated inversion recovery (FLAIR) demonstrates abnormal hyperintensity areas involved in at least three cerebral lobes or anatomical regions of the brain, 2) the lesions exhibit nonenhancement or nonmass-like enhancement on the initial MRI, and 3) the lesions are pathologically confirmed as PCNSL.[2)] Several cases of rapidly progressive dementia in lymphomatosis cerebri have been reported.[1,3-15)] In these reports, the duration from the first sign to dementia ranged from 2 weeks to 12 months. The definite diagnosis tends to be delayed when dementia is the only symptom. When a patient demonstrates acute worsening of disorientation with a strange behavior, cerebrovascular diseases, epilepsy, or toxic diseases are suspected rather than brain tumor.[11,12,16)] On the other hand, if cognitive function progressively declines within a few months, degenerative diseases are suspected.[1,4,8,9,13)] In this paper, we reviewed several case reports of lymphomatosis cerebri with rapid deterioration of cognitive function and summa-

Received April 26, 2021; Accepted January 31, 2022

rized the treatments and prognosis of the patients, including our case.

Case Report

A 68-year-old healthy woman had been taking care of her son who was suffering from gastric cancer. One morning, she exhibited bizarre behaviors and a decline in cognitive function; her son took her to our emergency clinic. The patient's blood pressure was 120/70; heart rate, 82 without arrhythmia; and body temperature, 36.3°C. Her mini-mental state examination (MMSE) score was 9; she was not able to focus on the test and rejected to answer some questions. Computed tomography (CT) of the brain revealed subcortical edema at the right frontal lobe, suggesting stroke or tumor (Fig. 1A). The diffusion-weighted image (DWI) of MRI revealed high signals at the cortex in the right frontal lobe, where the gadolinium dimeglumine T1-weighted image (Gd-T1W) showed small enhancements (Fig. 1B). FLAIR revealed multiple high-signal areas in both hemispheres, and arterial spin labeling (ASL) displayed a decrease in cerebral blood flow (CBF) in the right frontal (Fig. 1B). These characteristics were suggestive of venous infarction, encephalitis, multiple sclerosis, sarcoidosis, or malignant lymphoma. Some tumor markers, including soluble interleukin-2 receptor (sIL-R2), were within the normal range, and anti-nuclear antibodies were negative. Cerebrospinal fluid (CSF) examination revealed 1 cell/μL with normal glucose (71 mg/dL) and mildly elevated protein (69.0 mg/dL) levels. The CSF culture and cytology were both negative. Diffuse large B-cell lymphoma (DLBCL) was histologically diagnosed by open biopsy in the enhanced lesion on MRI, where CD20 and CD10 were positive and the MIB-1 index was as high as 50% (Fig. 1C). Under the diagnosis of PCNSL, three courses of high-dose methotrexate (MTX) with dexamethasone administration were performed, followed by whole-brain irradiation of 36 Gy/24 times. The series of treatments were completed 3 months after biopsy. The MMSE score recovered up to 13 in 3 months after the treatments, but the patient was unable to manage her own medication and had difficulty performing activities of daily living without her son's help. The patient visited our clinic every 2 months with her son without any problems. Ten months after the treatment, her MMSE score decreased to 11, and MRI revealed progression of brain atrophy with enlarged ventricle and clearer sulci (Fig. 2A). High signals in the right frontal dramatically shrank on DWI and FLAIR; however, periventricular high intensities remarkably expanded. No enhancement was identified, and an increase in CBF was symmetrically recognized in ASL (Fig. 2A). One month later, the patient was admitted to our hospital in a comatose status with high fever. She died due to systemic mycotic sepsis originating from urinary tract infection 14 months after biopsy. Autopsy was performed, and the brain seemed to be normal macroanatomically (Fig. 2B). However, histological investigation confirmed several small clusters of malignant lymphoma cells scattered in the brain parenchyma (Fig. 2 C).

Discussion

Lymphomatosis cerebi is a rare form of PCNSL. The authors summarized 17 cases of lymphomatosis cerebri, including our case, that first manifested as a dementia-like symptom, as presented in Table 1. The average age of the patients in these cases was 63.6 years, and there was no gender difference in incidence. Among the 17 patients, 6 were diagnosed with lymphomatosis cerebri *via* autopsy, including our case (No. 1, 6, 11, 13, 15, 17), and 6 were diagnosed radiologically and histologically but could not receive appropriate treatments due to delay of the diagnosis and rapid worsening of symptoms (No. 2, 4, 5, 7, 9, 10). Chemotherapy with/without radiation under accurate diagnosis was administered to only five patients (No. 3, 8, 12, 14, 16) who demonstrated better prognosis than others. Therefore, early suspicion of lymphoma and prompt histological diagnosis are crucial for patients with lymphomatosis cerebri. A rapidly progressing dementia is also an important symptom in these patients. It is often difficult to distinguish lymphomatosis cerebri from another disease with periventricular or deep white matter hyperintensities on MRI. However, in most cases of lymphomatosis cerebri, the lesions highly contained basal ganglia, thalamus, brainstem, and corpus callosum, in addition to periventricular and subcortical white matters (Table 1).[1,3-14] In addition, the lesions invade the surrounding tissue concurrently in lymphomatosis cerebri, which might cause rapid deterioration of cognitive function. Early histological investigation is required when high-signal areas are identified in at least three different regions on FLAIR in patients experiencing a rapid decline in cognitive function. When DLBCL is histologically diagnosed in the patient, the diagnosis of lymphomatosis cerebri can be reliable, because most cases of lymphomatosis cerebri have been histologically diagnosed as DLBCL.[1,3-6,8-11,13,15,17]

Effective treatments for lymphomatosis cerebri have not yet been established. Even high-dose MTX can provide lymphomatosis cerebri patients overall survival of 13.8 months,[18] which is much shorter than that in PCNSL patients.[19] Younger age (<56 years old), higher Karnofsky Performance Status, therapy with MTX, and B-cell type are independent better prognostic factors.[19] As presented in Table 1, the overall survival time is very short in lymphomatosis cerebri patients with rapidly progressing dementia. Performing WBR on patients with lymphomatosis cerebri accompanied by dementia might be controversial considering the risk of dementia worsening by leukoencephalopathy; moreover, a high dose of MTX without radiation can contribute to good prognosis and lowers the risk of leu-

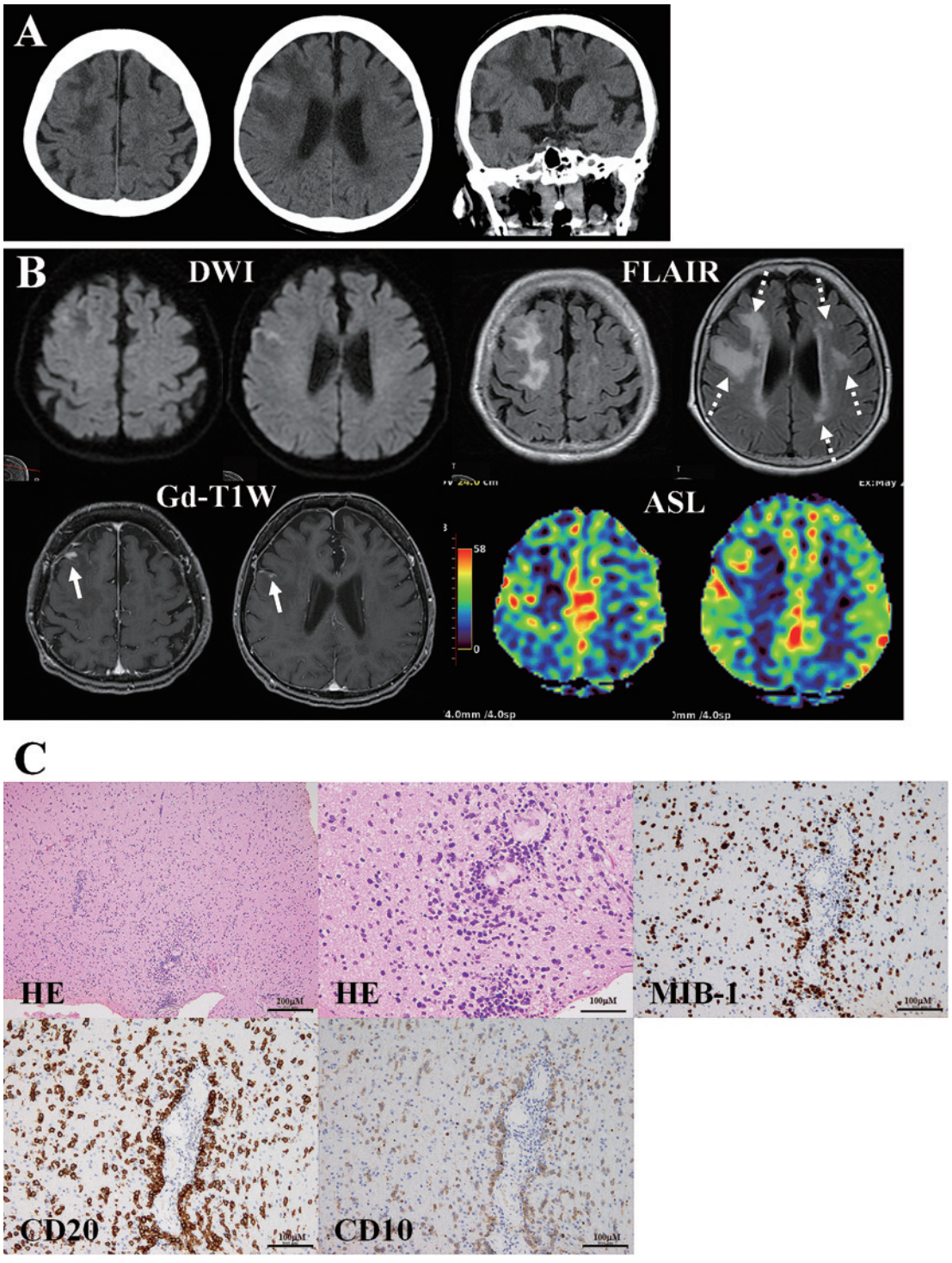

Fig. 1 Preoperative imaging studies and pathology.
A: Computed tomography scan upon admission shows focal brain edema in the right frontal lobe.
B: DWI of MRI demonstrates cortical and subcortical small high-signal lesions, and small enhanced-portions in Gd-T1W are identified (white arrows) corresponding to the high-signal lesions on DWI. High-signal areas are much wider on FLAIR, which are identified in multiple regions (white dotted arrows), including the right frontal lobe, right supplementary motor area, left central semiovale, and periventricular areas. ASL reveals low CBF in the right frontal lobe matching the high-signal areas on FLAIR.
MRI: magnetic resonance image, DWI: diffusion-weighted image, FLAIR: fluid-attenuated inversion recovery, Gd-T1W: gadolinium-dimeglumin-T1-weighted image, ASL: arterial spin labeling.
C: Histological investigations demonstrate cluster of large lymphocytes with CD20 strongly positive and CD10 weakly positive features. The MIB-1 index is higher than 50%.

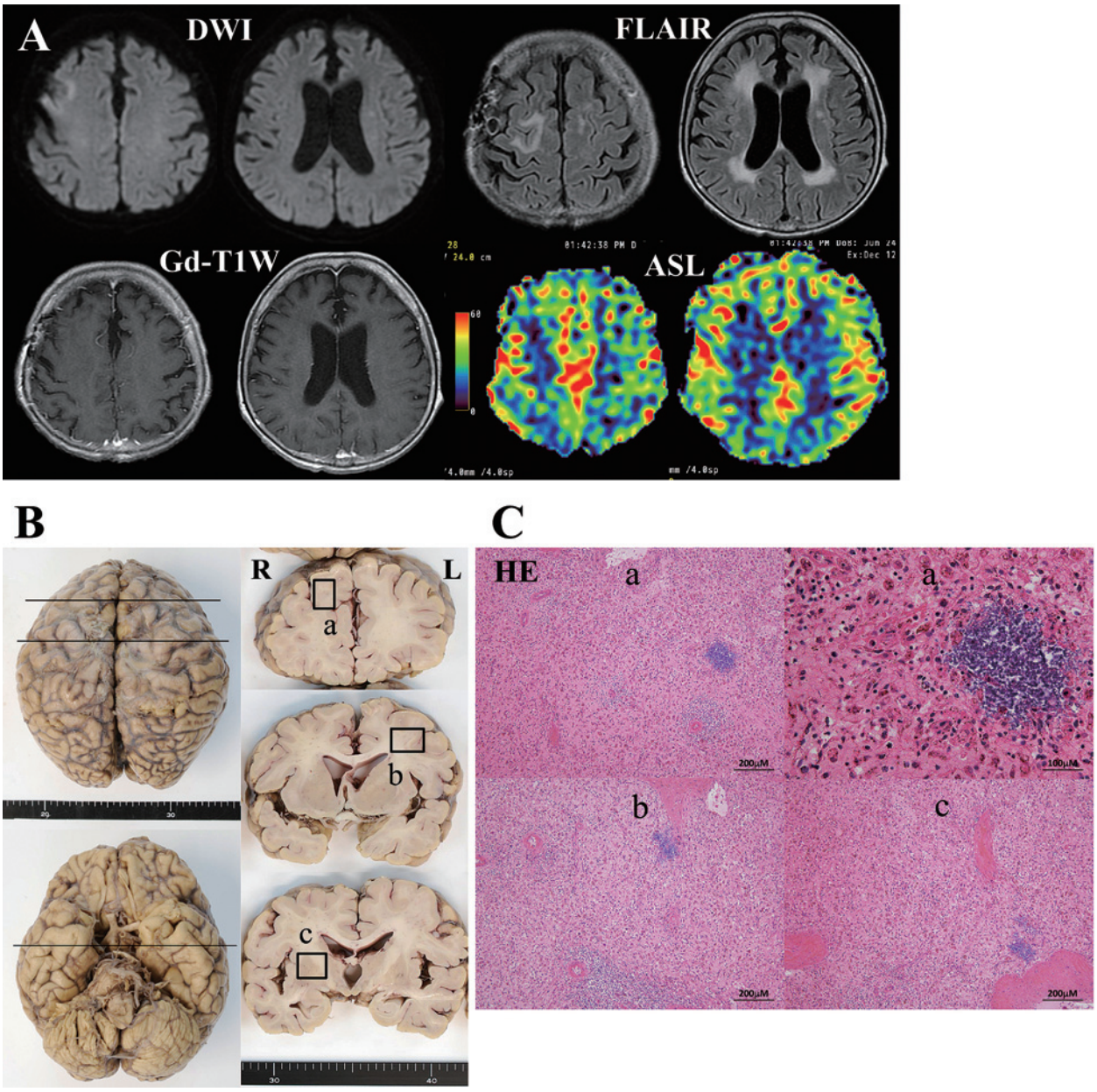

Fig. 2 Follow-up MRI and histology in autopsy.
A: MRI was performed 10 months after the treatment completion. High-signal areas in the right frontal lobe dramatically shrink on DWI and FLAIR, but periventricular high intensities enlarge on FLAIR with more obvious sulci, suggesting brain atrophy. There are no enhanced lesions on Gd-T1W, and ASL shows an increase in CBF without right-left difference.
B: The brain tissue in autopsy displays no abnormalities macroanatomically, and the brain is incised in a coronal section along the black lines. The deep white matter in the right and left frontal lobes (a, b black squares) and right basal ganglia (c black square) are focally excised for histological staining.
C: Histologically, scattered small clusters of lymphoma cells are found to be infiltrating into the brain parenchyma of both cerebral hemispheres and the right basal ganglia: (a) from the right frontal, (b) from the left frontal, (c) from the right putamen.

koencephalopathy, especially in elders with PCNSL lymphoma.[20,21] However, four patients who had undergone WBR (No. 8, 12, 14, 17) survived longer than those who did not (Table 1). Fortunately, under the diagnosis of PCNSL, high-dose MTX and WBR were achieved in our case, which might have contributed to the survival time of 14 months. The survival time can be increased by administrating high-dose MTX with WBR therapy; however, it has been reported that dementia in patients with lymphomatosis cerebri progressively worsens with poor prognosis despite the treatments.[15,22] Worsening of dementia after the treatments suggests progression of lymphomatosis cerebri, necessitat-

Table 1 Cases of lymphomatosis cerebri with dementia as the initial symptom

No.	Author, Year	Age	Sex	Symptoms	Period	Location	Enhance	Biopsy	Tx	Prognosis
1	Bakshi R, 1999[3]	41	M	forgetfulness disorientation	2 M	bilateral periventricular white matter, pons, corpus callosum	(–)	(–) autopsy	steroid	7 months Dead
2		75	F	cognitive decline	3 M	periventricular white matter	(–)	(+)	/	/
3	Rollins KE, 2005[4]	65	M	memory loss	6 M	periventricle, corpus callosum, midbrain	/	(+)	MTX	14 months Dead
4		80	F	confusion, apathy	6 M	periventricle pons	(–)	(–) CSF	steroid	1 month Dead
5	Lewerenz J, 2007[5]	65	F	personality change forgetfulness	Several months	periventricle thalamus, hypothalamus	(+)	(+)	steroid Azathioprine	7 months Dead
6	Vital A, 2007[6]	64	F	cognitive deterioration	1 M	periventricle white matter	(–)	(–) autopsy	None	3 months Dead
7	Weaver JD, 2007[7]	77	M	confusion disorientation	1 M	white matter (temporal pole, left insula, central semiovale)	/	(+)	None	1 month Dead
8	Kanai R, 2008[8]	53	M	personality change forgetfulness	2 M	bilateral frontal and temporal white matter	(–)	(+)	steroid WBR 36 Gy	11 months Alive
9	Pandit L, 2010[9]	49	M	Irritability moodiness	6 M	bilateral white matter in parietal, temporal, frontal, corpus callosum	/	(+)	No Tx	Dead shortly
10	Raz E, 2011[10]	72	M	inattentiveness flat affect	2 M	bilateral thalamus, midbrain, pons, dentate nuclei	(–)	(+)	/	/
11	Leschziner G, 2011[11]	67	M	disorientation somnolence	10 W	corpus callosum, bilateral thalamus, midbrain	(+)	(–) autopsy	steroid	1 month Dead
12	Kitai R, 2012[1]	56	F	personality change forgetfulness	4 M	lt. insula, thalamus, rt. frontal, temporal deep white matter	(+)	(+)	steroid WBR 36 Gy	19 months Bedridden
13	Rivero Sanz E, 2014[12]	60	F	personality change cognitive decline mutism	2 W	bilateral frontal white matter, caudate nuclei, thalamus	/	(–) autopsy	Chlorpromazine Phenytoin	2 months Dead
14	Samani A, 2015[13]	50	F	personality change amnesia	3 W	bilateral cerebral peduncle	(+)	(+)	MTX Cytarabine Rituximab WBR 40 Gy	10 months Alive
15	Lee PJ, 2016[14]	66	F	cognitive decline	6 M	lt. precentral gyrus, pons, thalamus, midbrain	(+)	(–) autopsy	steroid	Dead
16	Kerbauy MN, 2019[15]	74	M	cognitive decline progressive dementia	12 M	lt. frontal white matter	(+)	(+)	MTX, TMZ, Rituximab	18 months Alive
17	*Our case*	68	F	strange behavior cognitive decline	One day	rt. frontal, supplemental motor area, lt. central semiovale	(+)	(+) autopsy	steroid, MTX WBR 36 Gy	14 months Dead

ing maintenance treatments. Recently, new effective chemotherapies for PCNSL have been reported. Administration of rituximab and cytarabine seems to be effective for lymphomatosis cerebri as an adjuvant therapy (No. 14, 16 in Table 1).[13,15] Administration of the combination of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) followed by reduced dose of WBR[23] might be appropriate for lymphomatosis cerebri patients with dementia. Bruton tyrosine kinase inhibitor ibrutinib was introduced as a novel effective agent to PCNSL, especially to B-cell type lymphoma.[24] Temozolomide (TMZ) treatment or immunotherapy might be one of the selections for lymphomatosis cerebri as an adjuvant treatment following MTX therapy,[15,25-27] although the effect of TMZ on PCNSL has not yet been proven. When an effective treatment for lymphomatosis cerebri is established, improvement of the patient's cognitive function can be expected.

Acknowledgments

The author expresses gratitude to Edanz Group Japan for editing this manuscript.

Consent from the Participants

The consent from all the participants were obtained.

Conflicts of Interest Disclosure

There are no conflicts of interest in this report.

References

1) Kitai R, Hashimoto N, Yamate K, et al.: Lymphomatosis cerebri: clinical characteristics, neuroimaging, and pathological findings. *Brain Tumor Pathol* 29: 47-53, 2012
2) Li L, Rong JH, Feng J: Neuroradiological features of lymphomatosis cerebri: a systematic review of the English literature with a new case report. *Oncol Lett* 16: 1463-1474, 2018
3) Bakshi R, Mazziotta JC, Mischel PS, Jahan R, Seligson DB, Vinters HV: Lymphomatosis cerebri presenting as a rapidly progressive dementia: clinical, neuroimaging and pathologic findings. *Dement Geriatr Cogn Disord* 10: 152-157, 1999
4) Rollins KE, Kleinschmidt-DeMasters BK, Corboy JR, Damek DM, Filley CM: Lymphomatosis cerebri as a cause of white matter dementia. *Hum Pathol* 36: 282-290, 2005
5) Lewerenz J, Ding X, Matschke J, et al.: Dementia and leukoencephalopathy due to lymphomatosis cerebri. *J Neurol Neurosurg Psychiatry* 78: 777-778, 2007
6) Vital A, Sibon I: A 64-year-old woman with progressive dementia and leukoencephalopathy. *Brain Pathol* 17: 117-118, 2007
7) Weaver JD, Vinters HV, Koretz B, Xiong Z, Mischel P, Kado D: Lymphomatosis cerebri presenting as rapidly progressive dementia. *Neurologist* 13: 150-153, 2007
8) Kanai R, Shibuya M, Hata T, et al.: A case of 'lymphomatosis cerebri' diagnosed in an early phase and treated by whole brain radiation: case report and literature review. *J Neurooncol* 86: 83-88, 2008
9) Pandit L, Chickabasaviah Y, Raghothaman A, Mustafa S, Vasudevan A: Lymhomatosis cerebri--a rare cause of leukoencephalopathy. *J Neurol Sci* 293: 122-124, 2010
10) Raz E, Tinelli E, Antonelli M, et al.: MRI findings in lymphomatosis cerebri: description of a case and revision of the literature. *J Neuroimaging* 21: e183-e186, 2011
11) Leschziner G, Rudge P, Lucas S, Andrews T: Lymphomatosis cerebri presenting as a rapidly progressive dementia with a high methylmalonic acid. *J Neurol* 258: 1489-1493, 2011
12) Rivero Sanz E, Torralba Cabeza MÁ, Sanjuán Portugal F, García-Bragado F: Lymphomatosis cerebri mimicking iatrogenic Creutzfeldt-Jakob disease. *BMJ Case Rep* 2014: bcr2013201246, 2014
13) Samani A, Davagnanam I, Cockerell OC, Ramsay A, Patani R, Chataway J: Lymphomatosis cerebri: a treatable cause of rapidly progressive dementia. *J Neurol Neurosurg Psychiatr* 86: 238-240, 2015
14) Lee PJ, Berrios I, Ionete C, Smith T: Lymphomatosis cerebri: diagnostic challenges and review of the literature. *BMJ Case Rep* 2016: bcr2016216591, 2016
15) Kerbauy MN, Pasqualin DDC, Smid J, et al.: Diffuse large B-cell lymphoma of the central nervous system presenting as "lymphomatosis cerebri" and dementia in elderly man: case report and review of the literature. *Medicine* 98: e14367, 2019
16) Cordonnier C, Hénon H, Derambure P, Pasquier F, Leys D: Influence of pre-existing dementia on the risk of post-stroke epileptic seizures. *J Neurol Neurosurg Psychiatry* 76: 1649-1653, 2005
17) Sugie M, Ishihara K, Kato H, Nakano I, Kawamura M: Primary central nervous system lymphoma initially mimicking lymphomatosis cerebri: an autopsy case report. *Neuropathology* 29: 704-707, 2009
18) Izquierdo C, Velasco R, Vidal N, et al.: Lymphomatosis cerebri: a rare form of primary central nervous system lymphoma. Analysis of 7 cases and systematic review of the literature. *Neuro Oncol* 18: 707-715, 2016
19) Kobayashi H, Yamaguchi S, Motegi H, et al.: Long-term evaluation of combination treatment of single agent HD-MTX chemotherapy up to three cycles and moderate dose whole brain irradiation for primary CNS lymphoma. *J Chemother* 31: 35-41, 2019
20) Freilich RJ, Delattre JY, Monjour A, DeAngelis LM: Chemotherapy without radiation therapy as initial treatment for primary CNS lymphoma in older patients. *Neurology* 46: 435-439, 1996
21) Thiel E, Korfel A, Martus P, et al.: High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol* 11: 1036-1047, 2010
22) Murakami T, Yoshida K, Segawa M, et al.: A case of lymphomatosis cerebri mimicking inflammatory diseases. *BMC Neurol* 16: 128, 2016
23) Hattori K, Sakata-Yanagimoto M, Okoshi Y, et al.: A single institutional retrospective evaluation for younger patients with primary central nervous lymphomas on a modified R-MPV regimen followed by radiotherapy and high dose cytarabine. *J Clin Exp Hematop* 57: 41-46, 2017
24) Grommes C, Nayak L, Tun HW, Batchelor TT: Introduction of novel agents in the treatment of primary CNS lymphoma. *Neuro Oncol* 21: 306-313, 2019
25) Faivre G, Butler MJ, Le I, Brenner A: Temozolomide as a single agent maintenance therapy in elderly patients with primary CNS lymphoma. *Clin Lymphoma Myeloma Leuk* 19: 665-669, 2019
26) Makino K, Nakamura H, Kudo M, Takeshima H, Kuratsu J: Complete response to temozolomide treatment in an elderly patient with recurrent primary central nervous system lymphoma--case report. *Neurol Med Chir (Tokyo)* 47: 229-232, 2007
27) Furuse M, Nonoguchi N, Omura N, et al.: Immunotherapy of nivolumab with dendritic cell vaccination is effective against intractable recurrent primary central nervous system lymphoma: a case report. *Neurol Med Chir (Tokyo)* 57: 191-197, 2017

Corresponding author: Shoko M. Yamada, MD, PhD
Department of Neurosurgery, Teikyo University Hospital Mizonokuchi, 5-1-1 Futago, Takatsu-ku, Kawasaki, Kanagawa 213-8507, Japan.
e-mail: smyamada@med.teikyo-u.ac.jp