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

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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 noneenhancement 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.3-5 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.6-10 On the other hand, if cognitive function progressively declines within a few months, degenerative diseases are suspected.11,12,15 In this paper, we reviewed several case reports of lymphomatosis cerebri with rapid deterioration of cognitive function and summa-
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, 36.5°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 (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. Decrease in cerebral blood flow (CBF) in the right frontal lobe was identified, and an increase in CBF was symmetrically shown 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. However, histological investigation confirmed several small clusters of malignant lymphoma cells scattered in the brain parenchyma (Fig. 2C).

Discussion

Lymphomatosis cerebri 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). 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. 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, which is much shorter than that in PCNSL patients. Younger age (<56 years old), higher Karnofsky Performance Status, therapy with MTX, and B-cell type are independent better prognostic factors. 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.
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%.

MRI: magnetic resonance image, DWI: diffusion-weighted image, FLAIR: fluid-attenuated inversion recovery, Gd-T1W: gadolinium-dimeglumin-T1-weighted image, ASL: arterial spin labeling.

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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-
Rapidly Progressing Dementia in PCNSL

| No. | Author, Year  | Age | Sex | Symptoms                      | Period | Location                          | Enhance         | Biopsy | Tx                  | Prognosis  |
|-----|---------------|-----|-----|--------------------------------|-------|----------------------------------|-----------------|--------|---------------------|------------|
| 1   | Bakshi R, 1999 | 41  | M   | forgetfulness, disorientation  | 2 M    | bilateral periventricular white matter, pons, corpus callosum | (−)             | (−)    | steroid, autopsy    | 7 months Dead |
| 2   | Rollins KE, 2005 | 75  | F   | cognitive decline             | 3 M    | periventricular white matter     | (−)             | (−)    | /                  | /          |
| 3   | Lewerenz J, 2007 | 65  | M   | memory loss                   | 6 M    | periventricule, corpus callosum, midbrain | /               | (+)    | MTX                 | 14 months Dead |
| 4   | Vital A, 2007  | 64  | F   | cognitive deterioration       | 1 M    | periventricule white matter      | (−)             | (−)    | None                | 3 months Dead |
| 5   | Weaver JD, 2007 | 77  | M   | confusion, apathy             | 1 M    | white matter (temporal pole, left insula, central semiovale) | /               | (+)    | None                | 1 month Dead |
| 6   | Kitai R, 2012  | 56  | F   | personality change, forgetfulness | 4 M    | lt. insula, thalamus, rt. frontal, temporal deep white matter | (+)             | (+)    | steroid, WBR 36 Gy | 11 months Alive |
| 7   | Rivera Sanz E, 2014 | 60  | F   | personality change, moodiness | 2 W    | bilateral frontal white matter, caudate nuclei, thalamus | /               | (−)    | Chlorpromazine, Phenytoin | 2 months Dead |
| 8   | Samani A, 2015 | 50  | F   | personality change, amnesia    | 3 W    | bilateral cerebral peduncle      | (+)             | (+)    | MTX                  | 10 months Alive |
| 9   | Lee PJ, 2016   | 66  | F   | cognitive decline             | 6 M    | lt. precentral gyrus, pons, thalamus, midbrain | (+)             | (+)    | Cytarabine, Rituximab, WBR 40 Gy | Dead |
| 10  | Kerbauy MN, 2019 | 74  | M   | cognitive decline, progressive dementia | 12 M  | lt. frontal white matter        | (+)             | (+)    | MTX, TMZ, Rituximab, steroid, WBR 36 Gy | 18 months Alive |
| 11  | Our case       | 68  | F   | strange behavior, cognitive decline | One day | rt. frontal, supplemenal motor area, lt. central semiovale | (+)             | (+)    | WBR 36 Gy            | 14 months Dead |

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

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).

Administration of the combination of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) followed by reduced dose of WBR 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. Temozolomide (TMZ) treatment or immunotherapy might be one of the selections for lymphomatosis cerebri as an adjuvant treatment following MTX therapy, 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.

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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.

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