Primary diffuse large B-cell lymphoma of the central nervous system with rapidly progressing lesions after dimethyl fumarate treatment, showing relapsing and remitting symptoms: A case report

Yuki Kitazaki1,2 | Asako Ueno1,2 | Kenichiro Maeda1,2 | Rei Asano1,2 | Go Aoki3 |
Ayumu Katsuki2 | Norimichi Shirafuji2 | Takahiro Yamauchi4 | Makoto Isozaki4 |
Takahiko Saida5 | Yasunari Nakamoto2 | Tadanori Hamano2,6

1 Department of Neurology, Fukui-ken Saiseikai Hospital, Fukui, Japan
2 Second Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui, Fukui, Japan
3 Department of Hematology, Fukui-ken Saiseikai Hospital, Fukui, Japan
4 Department of Neurosurgery, Faculty of Medical Sciences, University of Fukui, Fukui, Japan
5 Kansai Multiple Sclerosis Center and Kyoto Min-iren Central Hospital, Kyoto, Japan
6 Department of Aging and Dementia, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

Correspondence
Asako Ueno, M.D, Department of Neurology, Fukui-ken Saiseikai Hospital, Fukui, Funabashi 7-1, Wadanaka-cho, Fukui City, Fukui 918-8503 Japan.
Email: maedaa@u-fukui.ac.jp

Abstract

Background: We present a case of B-cell type primary central nervous system lymphoma that rapidly progressed after dimethyl fumarate (DMF) administration.

Case presentation: An asymptomatic white matter lesion of the left frontal lobe was observed in a 56-year-old Japanese man on magnetic resonance imaging during a medical checkup. For the subsequent 5 months, the sporadic white matter lesion showed no change and no contrast effect. He suddenly presented with right upper limb paralysis on day 74. After improvement, he had a recurrence of right upper limb paralysis and diminished vision loss. Based on the 2017 revised McDonald criteria, two attacks, objective clinical evidence of one lesion and cerebrospinal fluid oligoclonal band assay positivity, he was diagnosed with relapsing–remitting multiple sclerosis and administered DMF. Three months after DMF administration, he developed new brain lesions that progressed rapidly; additional immunotherapy was ineffective. He was pathologically diagnosed with B-cell type primary central nervous system lymphoma using brain biopsy on day 301.

Conclusion: Patients with rapidly progressing white matter lesions after DMF administration should be suspected for B-cell type primary central nervous system lymphoma and pathologically diagnosed using brain biopsy.

KEYWORDS
diffuse large B-cell lymphoma, dimethyl fumarate, multiple sclerosis, primary central nervous system lymphoma

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2021 The Authors. Clinical and Experimental Neuroimmunology published by John Wiley & Sons Australia, Ltd on behalf of Japanese Society for Neuroimmunology. [Correction added on 30 July 2021, after first online publication: The copyright line was changed.]
INTRODUCTION

Dimethyl fumarate (DMF) is a first-line disease-modifying therapy (DMT) for treating relapsing–remitting multiple sclerosis (RRMS).\textsuperscript{1} After DMT treatment, the recurrence of RRMS and progression of primary central nervous system lymphoma (PCNSL) cannot be immediately distinguished in patients with progressed white matter lesions. A definitive diagnosis of PCNSL requires pathological diagnosis using brain biopsy, which is invasive.

According to recent reports, B-cell-type PCNSL could develop during the administration of DMTs, such as fingolimod, natalizumab (NTZ) and interferon-\(\beta\).\textsuperscript{2–8} This report presents a case of diffuse large B-cell lymphoma of PCNSL that rapidly progressed after DMF treatment in a patient with white matter lesions.

### 1.1 Case report

An asymptomatic white matter lesion of the left frontal lobe was detected in a 56-year-old Japanese man on magnetic resonance imaging (MRI) at a brain dock examination during a medical checkup (day 1). On day 46, he showed no neurological symptoms, and contrast-enhanced brain MRI on follow up showed no changes (Figure 1A–C). \(^{18}\)F-fluorodeoxyglucose (\(^{18}\)F-FDG)-positron emission tomography showed no \(^{18}\)F-FDG accumulation in the trunk and brain lesion; thus, the lesion showed low probability of a brain tumor (Figure 1D). On day 74, he suddenly presented with right upper limb paralysis and was admitted to Fukui-ken Saiseikai Hospital, Fukui, Japan.

On neurological examination, the patient presented with only right upper limb paralysis. Routine blood analysis showed a normal white...
cell count of 5900/µL (lymphocytes, 1416/µL), and normal lactate dehydrogenase, soluble interleukin-2 receptor and β2-microglobulin levels. Serological test results, including tests for HIV and Epstein–Barr virus, and autoantibodies to myelin oligodendrocyte glycoprotein and aquaporin 4, were negative. Cerebrospinal fluid (CSF) analysis showed normal cell count, protein and β2-microglobulin levels (2.2 mg/L; normal range, <3.3). CSF myelin basic protein level was not elevated. The oligoclonal band (OCB) assay detected more than two unique immunoglobulin G (IgG) bands. The CSF immunoglobulin G index was normal (0.36). CSF cytology was negative when carried out three times. Brain contrast MRI showed no changes in the initial lesion and remained non-contrast-enhancing on day 76 (Figure 1E–H).

On a tentative diagnosis of clinically isolated syndrome, the patient was treated with methylprednisolone (1 g/day) for 3 days beginning on day 76; the patient’s neurological symptoms improved after immunotherapy. On day 170, he had a relapse of motor paralysis in the right upper limb and developed vision loss in his right eye. On ophthalmic examination, he had vision loss in his right eye without optic neuritis or uveitis. Optical coherence tomography did not provide supporting data for the origin of vision loss associated with optic neuritis. His neurological symptoms recovered gradually without treatment. Brain contrast MRI showed no white matter changes, no optic neuritis and no contrast-enhancing effects in the initial lesion. Furthermore, contrast effects of MRI and 18F-FDG accumulation in the right basal ganglia, which might have differed from typical RRMS, such as dissemination in space and dissemination in time. No lesions were observed in specific regions of RRMS, including the periventricular, juxtacortical and infratentorial regions, and the spinal cord. The clinical course of the onset of paralysis in the right upper extremity 1 month after lesion development was also inconsistent with RRMS.

Initially, the present patient was excluded from the diagnosis of PCNSL owing to relatively specific findings of RRMS, such as a positive result for CSF-OCB; therefore, he was diagnosed with RRMS based on the 2017-revised McDonald criteria. His brain and spine MRI, however, did not satisfy typical RRMS, such as dissemination in space and dissemination in time. No lesions were observed in specific regions of RRMS, including the periventricular, juxtacortical and infratentorial regions, and the spinal cord. The clinical course of the onset of paralysis in the right upper extremity 1 month after lesion development was also inconsistent with RRMS.

DISCUSSION

We present a case of B-cell-type PCNSL that progressed during DMF treatment. Key considerations were: (i) whether the patient had initially developed PCNSL; and (ii) whether DMF administration promoted the pathological progression of B-cell-type PCNSL.

Our patient presented with two acute neurological attacks, an atypical white matter lesion and a positive result for CSF-OCB; therefore, he was diagnosed with RRMS based on the 2017-revised McDonald criteria. His brain and spine MRI, however, did not satisfy typical RRMS, such as dissemination in space and dissemination in time. No lesions were observed in specific regions of RRMS, including the periventricular, juxtacortical and infratentorial regions, and the spinal cord. The clinical course of the onset of paralysis in the right upper extremity 1 month after lesion development was also inconsistent with RRMS.

Initially, the present patient was excluded from the diagnosis of PCNSL owing to relatively specific findings of RRMS, such as a positive result for CSF-OCB and spontaneously improved neurological symptoms. Furthermore, contrast effects of MRI and 18F-FDG accumulation in the right basal ganglia, which might have differed from the initial lesion without contrast effects and 18F-FDG accumulation in the left frontal lobe. Ultimately, the initial lesion could not be confirmed as a lesion of RRMS, suggesting that the present patient could have initially developed PCNSL. In any case, PCNSL should not be overlooked in patients with white matter lesions, with or without contrast effects.

Our patient presented with white matter lesions without progression and the absence of contrast-enhanced effects for 3 months initially. Nevertheless, after a few months of DMF administration, new PCNSL lesions developed and progressed with contrast enhancement. Other DMTs for RRMS, such as fingolimod, NTZ and interferon-β, led to B-cell-type PCNSL during each treatment alone (Table 1). No causal relationship between DMT and the development of PCNSL has been determined; however, in the absence of Epstein–Barr virus or HIV infection, immunomodulation caused by DMT could contribute to the development of PCNSL (Table 1). In immunocompromised patients, PCNSL results from the uncontrolled proliferation of immortalized B cells in the nervous system. In particular, it was reported that four
patients with multiple sclerosis developed B-cell-type PCNSL during NTZ therapy.\textsuperscript{4–7} The mechanism considered to cause B-cell-type PCNSL after NTZ administration was as follows. NTZ affected the immune system, reducing the number of lymphocytes that entered the central nervous system.\textsuperscript{16} As a result, after NTZ administration, the number of immune cells playing a monitoring role decreased, thereby allowing malignant cells to potentially increase in the central nervous system.\textsuperscript{7}

In contrast, the mechanism of lymphoma development during the DMF treatment was considered as follows. DMF primarily had immunomodulatory effects on the peripheral immune system in patients with multiple sclerosis.\textsuperscript{17} In particular, CD8\textsuperscript{+} T cells, which play a major role in tumor immunity, were suppressed in patients with RRMS during DMF treatment.\textsuperscript{18} DMF induces apoptosis in human T cells \textit{in vitro}, and T cells suppress the growth of this potential B-cell population.\textsuperscript{19} Actually, in the BG00012 Monotherapy Safety and Efficacy Extension Study in Multiple Sclerosis (ENDORSE) trial, the overall incidence of malignancies was 2\% among patients treated with DMF; however, no cases of malignant lymphoma were observed.\textsuperscript{1} Therefore, the loss of T-cell regulation owing to DMF immunomodulation did not prove to have caused the increased incidence of PCNSL in the present patient. The risk of malignancy was not increased among patients treated with DMF compared with the incidence of cancer in the general RRMS population.\textsuperscript{1} Recently, DMF was found to show anti-tumor effects.\textsuperscript{20} DMF induced apoptosis of hematopoietic tumor cells by inhibition of nuclear factor-kB p65 nuclear translocation.\textsuperscript{20} Therefore, DMF might have the potential to combine therapy with other anticancer drugs to treat hematopoietic tumors. Long-term data are thus required to determine the risk of DMF-related malignancies.

Our patient presented with a short period of 3 months until the diagnosis of PCNSL after DMF administration. In past reports of PCNSL that developed after the administration of DMTs (Table 1),\textsuperscript{2–8} NTZ administration, which plays a vital role in reducing central lymphocytes,\textsuperscript{18} promoted the development of B-cell-type PCNSL in patients with multiple sclerosis within 2–21 months.\textsuperscript{4–7} DMF administration, which mainly suppresses the peripheral lymphocytes,\textsuperscript{17} requires a more extended administration period to develop B-cell-type PCNSL than NTZ administration. Therefore, B-cell-type PCNSL was considered to have developed in the present patient in the initial stages. In addition, the lymphocyte count of our patient was maintained at >900/\(\mu\)L in the blood analysis for 3 months after DMF administration. Although the maintenance of lymphocyte count >900/\(\mu\)L is important for reducing the risk of progressive multifocal leukoencephalopathy, this number might not be directly related to the prevention or promotion of PCNSL.\textsuperscript{17}

In conclusion, even for patients with white matter lesions, including isolated lesions with no contrast effect, the possibility of B-cell-type PCNSL should not be excluded. In the absence of a clear-cut typical clinically isolated syndrome, caution should be exercised in making the diagnosis of RRMS, and the diagnosis should be confirmed by further clinical and radiological follow up. In such cases, the clinician should consider postponing a definitive diagnosis and initiation of long-term disease-modifying therapies, pending longer
TABLE 1  Clinical findings of seven previously reported cases of B-cell-type primary central nervous system lymphoma that occurred during treatment with a single disease-modifying therapy,\textsuperscript{2–8}, including comparisons with the present case

| DMT          | Yang et al.\textsuperscript{2} | Chiang et al.\textsuperscript{3} | Schiwekert et al.\textsuperscript{4} | Phan-Ba et al.\textsuperscript{5} | Matze et al.\textsuperscript{6} | Na et al.\textsuperscript{7} | Saida et al.\textsuperscript{8} | Present case |
|--------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|--------------|
| Age (years)  | IFN-\(\beta\)                   | IFN-\(\beta\)                   | NTZ                             | NTZ                             | NTZ                             | NTZ                             | FTY                             | DMF          |
| Sex          | Male                             | Female                          | Male                            | Male                            | Female                          | Male                            | Female                          | Male         |
| Period between the diagnosis of MS and PCNSL | 36 months                       | 240 months                      | 36 months                       | 240 months                      | 43 months                       | 36 months                       | NA                              | 4 months     |
| Treatment period for DMT | 13 months                       | 240 months                      | 21 months                       | 2 months                        | 3 months                        | 7 months                        | 38.5 months                    | 3 months     |
| EBV infection | NA                             | -                              | -                               | -                               | -                               | -                               | NA                              | -            |
| HIV infection | -                              | NA                             | NA                             | NA                              | NA                             | NA                             | -                               | -            |
| Brain lesions with MRI contrast | +                              | +                              | +                               | +                               | +                               | +                               | +                               | Initial lesion – New lesions + |
| Brain lesions with PET accumulation | NA                             | NA                             | NA                             | NA                              | NA                             | NA                             | NA                              | Initial lesion – New lesions + |
| Pleocytosis  | 2/\(\mu\)L                      | 7/\(\mu\)L                      | 6/\(\mu\)L                      | NA                              | 20/\(\mu\)L                     | NA                              | NA                              | 7/\(\mu\)L |
| CSF-cytodiagnosis | -                              | -                              | NA                             | NA                              | -                               | NA                              | NA                              | -            |
| CSF-OCB      | NA                              | NA                             | +                               | NA                              | +                               | NA                              | NA                              | +            |
| CSF-\(\beta\)-MG | NA                             | NA                             | NA                             | NA                              | NA                             | NA                              | NA                              | 2.2          |
| Pathological findings | DLBCL                           | DLBCL                           | DLBCL and Burkitt lymphoma     | High-grade B-cell lymphoma      | DLBCL                           | DLBCL                           | B-cell lymphoma                 | DLBCL        |

\(\beta\)-MG, \(\beta\)-microglobulin; CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; DMF, dimethyl fumarate; DMT, disease-modifying therapy; EBV, Epstein–Barr virus; FTY, fingolimod; HIV, human immunodeficiency virus; IFN-\(\beta\), interferon-\(\beta\); MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, unavailable; NTZ, natalizumab; OCB, oligoclonal band; PCNSL, primary central nervous system lymphoma; PET, positron emission tomography; RRMS, relapsing–remitting multiple sclerosis.
follow up to accumulate additional evidence supporting the diagnosis. For patients with rapidly progressing white matter lesions after DMF administration, B-cell-type PCNSL should be suspected and pathologically diagnosed using brain biopsy.

DISCLOSURE
Conflict of interest: The authors declare no conflict of interest.

REFERENCES
1. Gold R, Arnold DL, Bar-Or A, Hutchinson M, Kappos L, Havrdova E, et al. Long-term effects of delayed-release dimethyl fumarate in multiple sclerosis: interim analysis of ENDORSE, a randomized extension study. Mult Scler. 2017;23:253–65.
2. Yang J, Wu S. Multiple sclerosis preceding CNS lymphoma: a case report. Acta Neurol Taiwan. 2007;16:92.
3. Chiang S, Kesari NK, Bradshaw A, Chen W, Samudralwar R, Alobaidy AM, et al. Pearls & Oysters: CNS lymphoma in a patient with relapsing-remitting multiple sclerosis treated with interferon. Neurology. 2017;89:e210–3.
4. Schweikert A, Kremer M, Ringel F, Liebig T, Duyster J, Stüve O, et al. Primary central nervous system lymphoma in a patient treated with natalizumab. Ann Neurol. 2009;66:403–6.
5. Phan-Ba R, Bisig B, Deprez M, De Prijck B, Delrue G, Herens C, et al. Central nervous system lymphoma associated with natalizumab: another patient. Mult Scler. 2012;18:1653–4.
6. Na A, Hall N, Kavar B, King J. Central nervous system lymphoma associated with natalizumab. J Clin Neurosci. 2014;21:1068–70.
7. Saida T, Itoyama Y, Kikuchi S, Hao Qi, Kurosawa T, Ueda K, et al. Long-term efficacy and safety of fingolimod in Japanese patients with relapsing multiple sclerosis: 3-year results of the phase 2 extension study. BMC Neurol. 2017;17:17.
8. Bjerrum OW, Lage S, Hansen OE. Measurement of beta-2-microglobulin in human cerebrospinal fluid by ELISA technique. Acta Neurol Scand. 1986;74:177–80.
9. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162–73.
10. Ikeguchi R, Shimizu Y, Shimizu S, Kitagawa K. CSF and clinical data are useful in differentiating CNS inflammatory demyelinating disease from CNS lymphoma. Mult Scler. 2018;24:1212–23.
11. Zou Y, Tong J, Leng H, Jiang J, Pan M, Chen Z. Diagnostic value of 18F-FDG PET and PET/CT in immunocompetent patients with primary central nervous system lymphoma: a systematic review and meta-analysis. Oncotarget. 2017;8:41518–28.
12. Davies G, Keir G, Thompson EJ, Giovannoni G. The clinical significance of an intrathecal monoclonal immunoglobulin band: a follow-up study. Neurology. 2003;60:1163–6.
13. Yang J, Wu S. Multiple sclerosis preceding CNS lymphoma: a case report. Acta Neurol Taiwan. 2007;16:92.
14. Chiang S, Kesari NK, Bradshaw A, Chen W, Samudralwar R, Alobaidy AM, et al. Pearls & Oysters: CNS lymphoma in a patient with relapsing-remitting multiple sclerosis treated with interferon. Neurology. 2017;89:e210–3.
15. Schweikert A, Kremer M, Ringel F, Liebig T, Duyster J, Stüve O, et al. Primary central nervous system lymphoma in a patient treated with natalizumab. Ann Neurol. 2009;66:403–6.
16. Phan-Ba R, Bisig B, Deprez M, De Prijck B, Delrue G, Herens C, et al. Central nervous system lymphoma associated with natalizumab: another patient. Mult Scler. 2012;18:1653–4.
17. Na A, Hall N, Kavar B, King J. Central nervous system lymphoma associated with natalizumab. J Clin Neurosci. 2014;21:1068–70.