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Successful Treatment of Intracranial Methotrexate-associated Lymphoproliferative Disorder without Epstein-Barr Virus Infection Using Rituximab, Methotrexate, Procarbazine, and Vincristine: A Case Report

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Abstract

Methotrexate-associated lymphoproliferative disorder (MTX-LPD) occurs in patients with rheumatoid arthritis (RA) treated with methotrexate (MTX). MTX-LPD is typically associated with Epstein-Barr virus (EBV) infection and regresses with MTX discontinuation. On the other hand, EBV-negative MTX-LPDs are less common and are more likely to show partial or no regression after MTX discontinuation. There were no standard chemotherapeutic options for refractory MTX-LPD. We present a case of EBV-negative MTX-LPD in the central nervous system (CNS) that was successfully treated with rituximab, methotrexate, procarbazine, and vincristine (R-MPV), followed by reduced-dose whole-brain radiotherapy (rdWBRT), following the same treatment protocol as primary CNS lymphoma. A 59-year-old woman with RA treated with MTX presented with gradually developing staggered gait, memory deficit, and disorientation. Multiple lesions with heterogeneous contrast enhancement were discovered using brain magnetic resonance imaging. The patient was suspected of having MTX-LPD, but discontinuing MTX did not result in regression of the brain lesions. She underwent a biopsy from the left parietal lesion. The tissue was pathologically diagnosed as diffuse large B-cell lymphoma. Furthermore, pathological examination through EBV-encoded ribonucleic acid *in situ* hybridization demonstrated a lack of EBV infection. She was ultimately diagnosed with EBV-negative CNS MTX-LPD. We applied chemotherapy with R-MPV and rdWBRT. The patient achieved a complete response. In the case of CNS MTX-LPD without EBV infection, chemotherapy with R-MPV followed by rdWBRT may be considered.

Keywords: methotrexate-associated lymphoproliferative disorder (MTX-LPD), methotrexate, rituximab, methotrexate, procarbazine, and vincristine (R-MPV), rheumatoid arthritis, primary central nervous system lymphoma (PCNSL)

Introduction

Methotrexate (MTX) has been widely administered to patients with autoimmune diseases, including rheumatoid arthritis (RA). On the other hand, patients receiving MTX have an increased risk of lymphoproliferative disorder (LPD) due to the immunosuppressive state induced by MTX administration.[1,2] The majority of methotrexate-associated lymphoproliferative disorders (MTX-LPDs) are associated with Epstein-Barr virus (EBV) infection and occur in the trunk, including the lymph nodes or extranodal areas such as the epipharynx, lungs, thyroid glands, and skin.[3] Intracranial MTX-LPD can also occur infrequently.[4-13]

Patients with MTX-LPD typically show remission merely upon withdrawal of MTX treatment. As a result, the first step in clinical management of MTX-LPD is close monitoring following MTX discontinuation.

However, even after discontinuing MTX, some MTX-LPD

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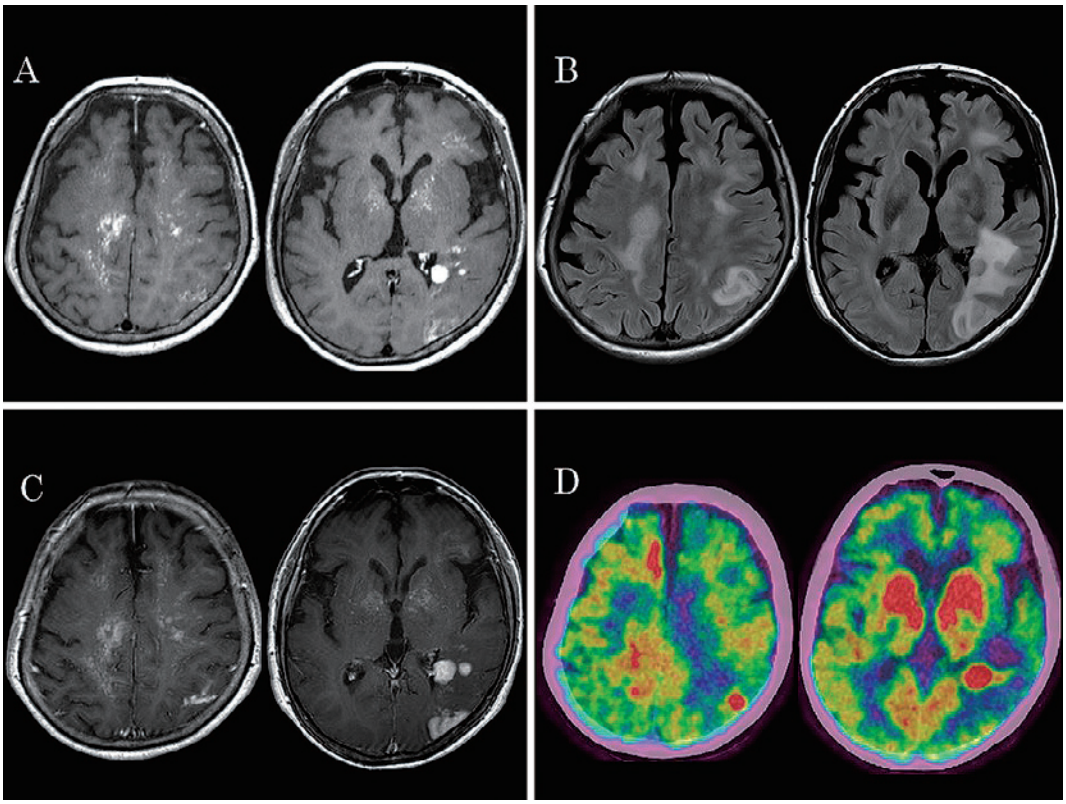

Fig. 1 Brain MRI upon admission and after MTX withdrawal and FDG-PET findings after MTX withdrawal.
A: Gd-T1WI upon admission showing multiple lesions in the bilateral cerebral hemisphere and basal ganglia.
B: FLAIR images upon admission showing hyperintensity surrounding lesions.
C: Gd-T1WI after MTX withdrawal showing no regression.
D: FDG-PET after MTX withdrawal showing increased FDG uptake in the lesion.

cases were unable to achieve regression.[14,15] These patients require further treatment. Unfortunately, there are no standard treatment options for MTX-LPD beyond MTX cessation. We present a case of EBV-negative MTX-LPD in the central nervous system (CNS) that was successfully treated with rituximab, methotrexate, procarbazine, and vincristine (R-MPV) chemotherapy, followed by low-dose whole-brain radiotherapy (rdWBRT).

Case Report

This case report was prepared after informed consent was obtained from the patient. A 59-year-old woman presented with a 6-week history of gradually developing staggering gait and a 4-week history of slowly progressive memory deficit. She was diagnosed with RA 9 years prior and had been receiving MTX (8 mg/week) therapy for 7 years. Neurological examination revealed impaired orientation (Glasgow Coma Scale 14/15; E4V4M6) and staggering gait with bilateral lower extremity weakness.

In gadolinium-enhanced T1-weighted images (Gd-T1WI), brain magnetic resonance imaging (MRI) revealed multiple lesions with heterogeneous enhancement (Fig. 1A). On fluid-attenuated inversion recovery (FLAIR), perifocal edema was also observed (Fig. 1B). Spinal MRI revealed no abnormalities, and contrast-enhanced whole-body computed tomography revealed no apparent lymphadenopathies or other lesions suspected of malignancy. Laboratory results showed elevated serum soluble interleukin-2 receptor levels (926 U/mL). Serum antigen tests for EBV were as follows: virus capsid antigen (VCA) IgG, 40 IU/mL; VCA IgM, <10 IU/mL; EBV nuclear antigen, 20 IU/mL; and early antigen-diffuse-type and restricted-type IgG, <10 IU/mL, which discredits the possibility of a previous infection. EBV-DNA was undetectable in her whole blood. Because CNS MTX-LPD was suspected, MTX administration was stopped based on her drug history and brain MRI findings.

However, neurological symptoms did not improve, and brain MRI did not reveal any regression of these lesions.

One week after MTX discontinuation (Fig. 1C), fluorine-18-fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed uptake in brain lesions without evidence for systemic lesions (Fig. 1D). The patient underwent biopsy on the left parietal lesion. Histopathological examination of the tumor specimen showed proliferation of large atypical lymphoid cells (Fig. 2A-B). These cells ex-

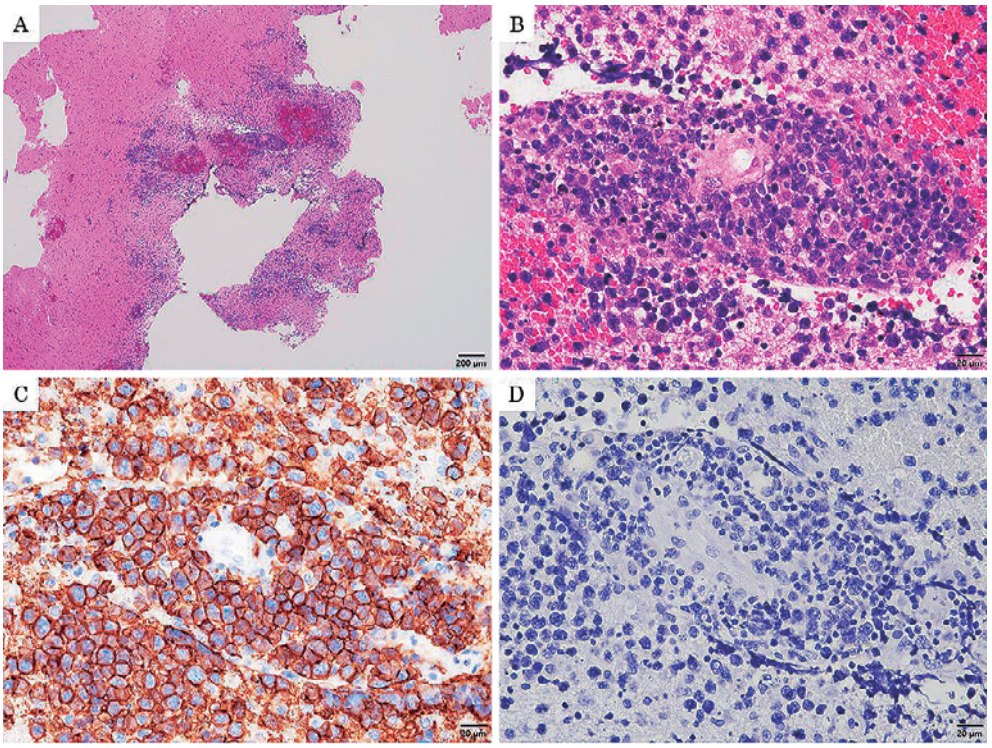

Fig. 2 The pathological findings of the left parietal lesion.
A: Hematoxylin and eosin (H&E) staining (original magnification ×40) showing lymphocytic cells, some of which show perivascular cuffing.
B: H&E staining (original magnification ×400) showing diffuse and perivascular infiltration of large atypical lymphoid cells.
C: Immunostaining for CD20 (original magnification ×400) demonstrating a positive result.
D: *In situ* hybridization (original magnification ×400) showing no evidence of EBER.

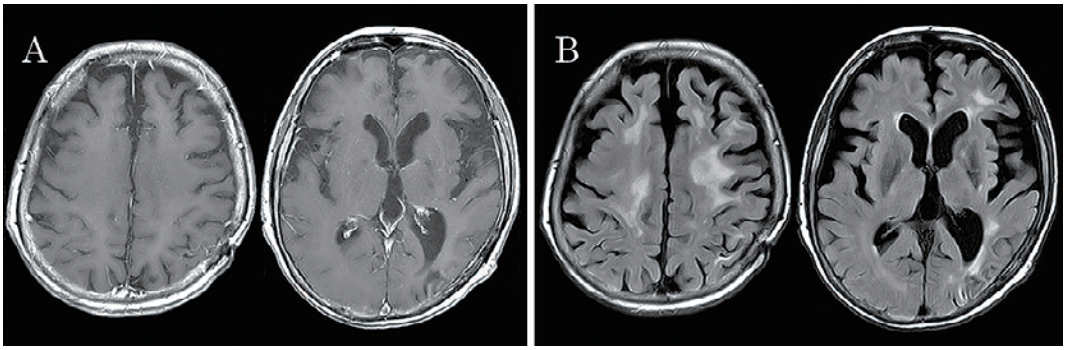

Fig. 3 Brain MRI findings after 7 cycles of chemotherapy with R-MPV and rdWBRT.
A and B: Gd-T1WI (A) and FLAIR (B) showing no evidence of lesions.

pressed CD 20 (Fig. 2C) and CD 10, were partially positive for BCL6 and MUM1, and were negative for CD 5 and CD 3. When these findings were combined, they led to the diagnosis of diffuse large B-cell lymphoma, germinal center B-cell like subtype. *In situ* hybridization of EBV-encoded small RNA (EBER) was negative (Fig. 2D). Thus, on the basis of drug history and pathology results, she was diagnosed with EBV-negative CNS MTX-LPD.

Considering her disease progression despite MTX cessation, we started chemotherapy with R-MPV. Her neurological symptoms gradually improved after she started chemotherapy, and her intracranial lesion decreased in size. After 7 cycles of R-MPV chemotherapy, she achieved a complete response (CR). She received rdWBRT [23.40 Gy in 1.8-Gy fractions × 13] as consolidation treatment and was discharged from the hospital without disease (Fig. 3). She has remained in remission for 16 months after completion of chemo-radiotherapy.

Table 1 Summary of reported EBV-negative CNS MTX-LPD cases

Study	Age (years)/ sex	Underlying disease	LPD site	Histopathology	Spontaneous regression	Additional treatment	Out-come	Follow-up duration
Liu et al., 2015[9]	58/M	RA	Cerebrum	DLBCL	Not available	Radiotherapy	Good	1 year
Kikuchi et al., 2016[4]	50/F	RA	Dura mater	IVLBCL	Not available	R-CHOP + intrathecal chemotherapy (PSL+ MTX + Ara-C)	CR	2 years
Uchida et al., 2018[5]	52/F	RA	Cerebrum	DLBCL	No	Rituximab + high-dose MTX + Ara-C, radiotherapy	Died	17 months
This study	59/F	RA	Cerebrum	DLBCL	No	R-MPV, radiotherapy	CR	10 months

Abbreviations
Ara-C = cytarabine; CR = complete response; DLBCL = diffuse large B-cell lymphoma; IVLBCL = intravascular large B-cell lymphoma; MTX = methotrexate; PSL = prednisolone; RA = rheumatoid arthritis; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-MPV = rituximab, methotrexate, procarbazine, and vincristine

Discussion

CNS MTX-LPD is exceptionally rare. To the best of our knowledge, only 10 cases have been reported.[4-13] Out of 11 cases, including the case presented here, 4 were negative for EBV infection and all of the required additional treatment (Table 1).[4,5,9]

LPDs are caused by several types of immunodeficiency or drugs. The World Health Organization classified immunodeficiency-related LPDs into four categories: LPD associated with primary immune disorders, lymphomas associated with human immunodeficiency virus infection, post-transplant LPD, and other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPD).[16] OIIA-LPD includes lymphoid proliferations or lymphomas that develop in patients treated with anti-RA drugs, including MTX, tacrolimus, and anti-tumor necrosis factor α drugs.[16] Most OIIA-LPD cases develop in patients with RA who are treated with MTX, and the median duration of MTX administration is 54 months.[3] On the other hand, the OIIA-LPD category remains contentious due to the difficulty in distinguishing the direct effect of immunosuppressive drugs from the effect of autoimmune diseases themselves.[17] Some studies have shown that patients with RA are more likely to develop LPD, regardless of the history of MTX use.[18,19] As a result, MTX-LPD could be divided into two pathogeneses. One is truly caused by MTX, whereas the other is caused by RA or other factors other than MTX. Withdrawal from MTX may be ineffective in cases of MTX-LPD caused by RA.

MTX-LPD is typically associated with EBV infection. The EBV positivity rate in patients with MTX-LPD is approximately 60% in Japan, which is higher than that reported in Western studies.[14,20] Previous research on all-site MTX-LPD has shown that spontaneous regression after MTX withdrawal occurs more frequently in EBV-positive patients than in EBV-negative patients.[14,21] EBV infection is related to the pathogenetic mechanism of MTX-LPD through DNA methylation that can interrupt the expression of tumor suppressor genes.[22] EBV infection has been linked to a lower incidence of CpG island methylator phenotype, apoptosis-related gene hypermethylation, and BCL2 expression in patients with RA with MTX-LPD, implying spontaneous regression after MTX withdrawal and better prognoses in patients with EBV-positive MTX-LPD. As a result, EBV-negative MTX-LPD cases are more likely to demonstrate partial or no regression after MTX withdrawal, requiring further intervention.[22]

Of the many reported approaches, no standard chemotherapy regimen has been established for MTX-LPD cases, including CNS.[3-5] Cyclophosphamide, vincristine, doxorubicin, prednisolone, MTX, bleomycin, mitomycin C, mercaptopurine, melphalan, and rituximab are all chemotherapeutic agents that have been tried.[3] Each chemotherapy regimen was essentially selected according to the histopathological appearance of tumor cells. For example, for non-Hodgkin lymphoma cases, the most commonly used chemotherapy regimens were rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone and rituximab, cyclophosphamide, pirarubicin, vincristine, and prednisolone.[14,20] However, these regimens may be ineffective in the treatment of CNS MTX-LPD due to low penetration of the CNS.[23]

R-MPV followed by rdWBRT is an effective treatment for primary CNS lymphoma (PCNSL).[24] Those who achieved CR after 5-7 cycles of induction chemotherapy with R-MPV

receive rdWBRT (23.4 Gy). Aside from that, standard WBRT (45 Gy) is available. We used R-MPV in this case, as we did in the case of ordinary PCNSL, and achieved CR. Although the use of MTX is controversial for patients with MTX-LPD,[25] regimens that included MTX have been effective in some cases.[4,5,7] Our findings suggest that an R-MPV regimen could be a viable treatment option for patients with CNS MTX-LPD when MTX withdrawal is ineffective, particularly in EBV-negative cases.

Conclusion

R-MPV followed by rdWBRT may be considered for patients with CNS MTX-LPD without EBV infection.

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Abbreviations in this paper

MTX = methotrexate; RA = rheumatoid arthritis; LPD = lymphoproliferative disorder; MTX-LPD = methotrexate-associated lymphoproliferative disorder; CNS = central nervous system; R-MPV = rituximab, methotrexate, procarbazine, and vincristine; rdWBRT = reduced-dose whole-brain radiotherapy; MRI = magnetic resonance imaging; Gd-T1WI = gadolinium-enhanced T1-weighted images; FLAIR = fluid-attenuated inversion recovery; EBV = Epstein-Barr virus; VCA = virus capsid antigen; FDG-PET = fluorine-18-fluorodeoxyglucose-positron emission tomography; EBER = Epstein-Barr virus-encoded small RNA; CR = complete response; OIIA-LPD = other iatrogenic immunodeficiency-associated lymphoproliferative disorders; PCNSL = primary central nervous system lymphoma; H&E = hematoxylin and eosin

Conflicts of Interest Disclosure

All authors have no conflict of interest.

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