Int J Clin Exp Pathol 2016;9(8):8017-8026
www.ijcep.com /ISSN:1936-2625/IJCEP0018612

Original Article

Epstein-Barr virus-negative and CD56-positive primary central nervous system lymphoproliferative disorder (diffuse large B-cell lymphoma): a case of report and review of the literature

Yasunobu Sekiguchi[1], Kunimoto Ichikawa[1,6], Haruko Takizawa[1], Mutsumi Wakabayashi[1], Keiji Sugimoto[1], Shigeki Tomita[2], Hiroshi Izumi[2], Noriko Nakamura[3], Tomohiro Sawada[3], Takuya Hirai[4], Iwao Sekikawa[4], Yasunori Ohta[5], Norio Komatsu[6], Masaaki Noguch[1]

Departments of [1]Hematology, [2]Pathology, [3]Clinical Laboratory, [4]Internal Medicine and Rheumatology, Urayasu Hospital of Juntendo University, Japan; [5]Department of Pathology, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan; [6]Department of Hematology, Hospital of Juntendo University, Japan

Received October 27, 2015; Accepted December 26, 2015; Epub August 1, 2016; Published August 15, 2016

Abstract: A 70-year-old man presented with paresis of the right upper and lower extremities and dysarthria. He had been diagnosed with rheumatoid arthritis (RA) in 2006 and started treatment with methotrexate (MTX) at 10 mg/week in 2008. The patient developed MTX-induced pneumonia in April 2011, following which MTX was discontinued (duration of MTX treatment: 4 years and 4 months; total dose received: approximately 1740 mg). The pneumonia subsequently improved. Treatment for RA was then switched to salazosulfapyridine 1000 mg/day and prednisolone 7.5 mg/day, and the clinical course remained favorable. In October 2014, the patient developed paresis of the right upper and lower extremities and dysarthria, and magnetic resonance imaging (MRI) of the brain revealed a mass measuring 3.5 cm in diameter in the left cerebral white matter. Craniotomy and tumor resection were performed, and a diagnosis of primary central nervous system diffuse large B-cell lymphoma was made. The clinical stage was IE. Because of his poor general condition, the patient was initiated on cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy. After completion of two courses, the paresis of the right upper and lower extremities and dysarthria improved; MRI showed marked improvement of the lesion. High-dose MTX therapy and high-dose cytarabine therapy were considered. However, because the patient had a history of MTX pneumonia and did not wish to receive chemotherapy, whole-brain irradiation was performed (total radiation dose, 45 Gy). As of October 2015, the patient's clinical course remains favorable and there is no evidence of recurrence.

Keywords: Rheumatoid arthritis, methotrexate, Epstein-Barr virus, CNS lymphoma, diffuse large B-cell lymphoma

Introduction

The precise causes and mechanisms of "other iatrogenic immunodeficiency-associated lymphoproliferative disorders" (OIIALDs) and methotrexate-related lymphoproliferative disorders (MTX-LPDs) remain unknown. There have been only three reported cases of rheumatoid arthritis (RA) with MTX-LPDs and primary central nervous system lymphoma (RA-MTX-PCNSL), including the patient reported here. In addition, the current case is the only reported case of Epstein-Barr virus-encoded small RNA (EBER)-negative, cluster of differentiation (CD) 56-positive primary central nervous system lymphoma that developed after discontinuation of MTX treatment. We consider that this case will be valuable for elucidating the pathological, molecular-biological, and clinical features of RA-MTX-PCNSL, as well as the prognosis.

Case

A 70-year-old man presented at Juntendo University Urayasu Hospital, Urayasu, Japan, complaining of paresis of the right upper and lower extremities and dysarthria. He had been previously diagnosed with RA and had a history of MTX pneumonia. The patient's family medical history was unremarkable, and the clinical

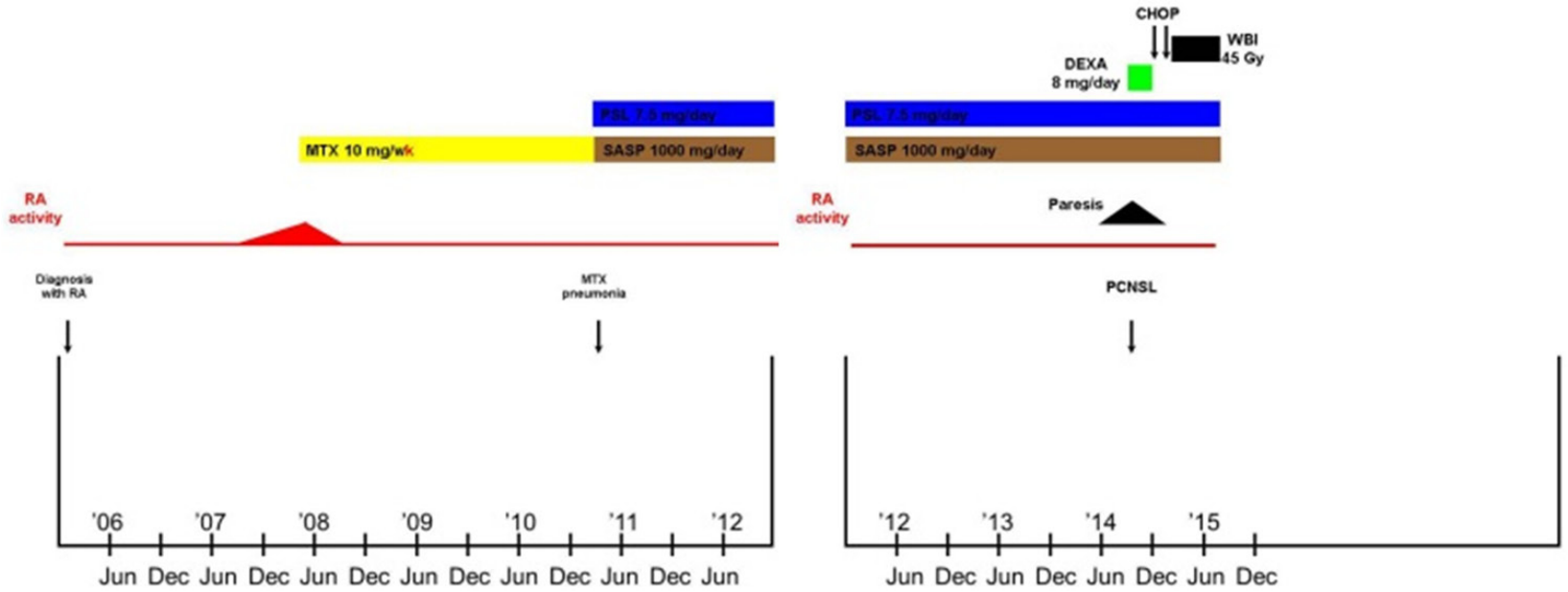


Figure 1. Clinical timeline.The patient was diagnosed as having RA in 2006. Because of increased RA activity, he was started on MTX 10 mg/week in 2008. MTX pneumonia developed in April 2011, and MTX was discontinued; following discontinuation of MTX, the pneumonia improved. At this point, RA treatment was changed to SASP 1000 mg/day and PSL 7.5 mg/day. This regime yielded good control of RA disease activity. PCNSL developed in late October 2014. CHOP therapy was started in early December, and after two courses, both the clinical symptoms and MRI findings improved. WBI was started in late January 2015. As of late August 2015, the patient remains in a favorable clinical condition with no evidence of recurrence. DEXA, dexamethasone.

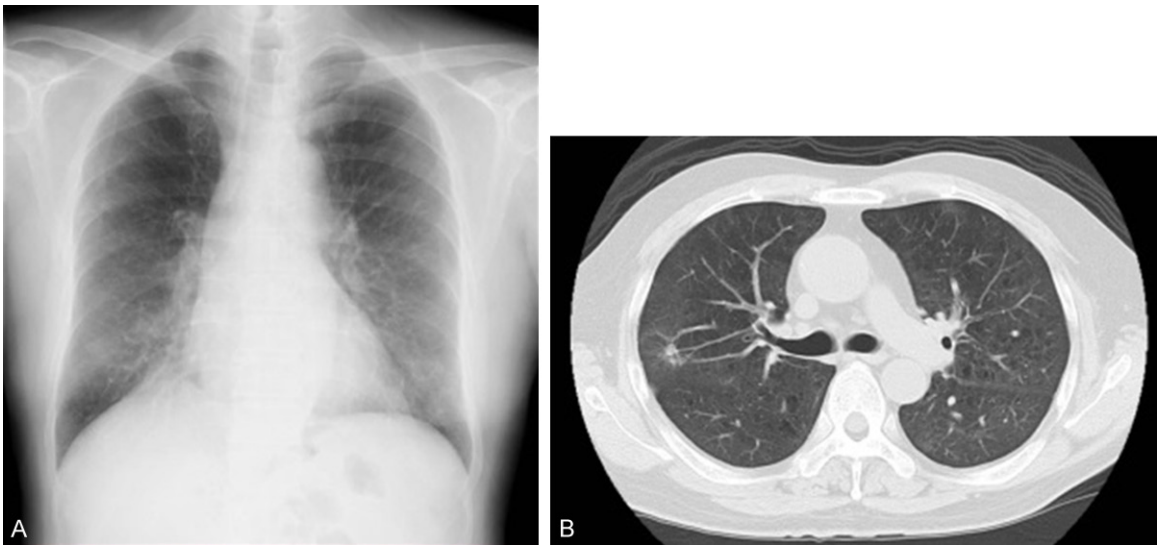


Figure 2. Chest images of MTX pneumonia. A. Radiograph: ground-glass opacities seen in the right middle lobe; B. CT: ground-glass opacities seen in the right middle lobe.

Table 1. Laboratory findings of the present case on admission

Peripheral blood			
WBC	10,400/μl↑	Hb	13.4 g/dl
Neut	72.5%↑	Ht	42.7%
Ly	17.6%↓	MCV	92.1 fl
Mono	7.8%↑	MCH	28.8 pg
Eo	0.4%	Plt	24.6×10^4/μl
Ba	0.2%	Reti	1.9%
RBC	464×10^4/μl		
Biochemistry			
T.P.	7.2 g/dl	γ-GTP	18 IU/l
Alb	3.7 g/dl↓	T-Bil	0.4 mg/dl
AST	30 IU/l	BUN	19 mg/dl
ALT	16 IU/l	Cr	0.91 mg/dl↓
LDH	260 IU/l↑	Uric acid	3.0 mg/dl
ALP	215 IU/l	CRP	4.5 mg/dl↑
Immunoserological analysis			
HBs Ag	Negative	CA-RF	638 AU/ml↑
HCV Ab	Negative	anti-CCP	13.3 U/ml↑
IgG	1080 mg/dl	HIV antibody	Negative
IgA	221 mg/dl	HTLV-1 antibody	Negative
IgM	149 mg/dl	EBV VCA IgG	×40↑
Serum β2MG	2.5 mg/dl↑	EBV VCA IgM	<×10
ANA	<×40	EBV EBNA	×20↑
RF	614 IU/ml↑	EBV DNA	Negative
MMP-3	573 ng/ml↑		
Flow cytometry of brain tumor biopsy specimens			
CD2	17.1%	CD20	83.5%↑
CD3	14.4%	CD22	80.0%↑

course is shown in **Figure 1**. The patient was diagnosed as having RA at a neighborhood hospital in 2006 and was subsequently kept under observation without treatment. However, in 2008, because RA activity was diagnosed, he was started on MTX treatment at a dose of 10 mg/week. The RA activity reduced in response to this treatment and the clinical course appeared favorable.

In April 2011, the patient developed MTX pneumonia (**Figure 2A**, **2B**), following which MTX was discontinued (the MTX treatment duration was 4 years and 4 months and the total dose received was approximately 1740 mg). The pneumonia improved, and the treatment for RA was switched to salazosulfapyridine (SASP) 1000 mg/day and prednisolone (PSL) 7.5 mg/day; this treatment regime yielded good control of RA disease activity.

In late October 2014, the patient presented with paresis of the right upper and lower extremities and dysarthria, and was admitted to the Department of Neurosurgery of Juntendo University Urayasu Hospital. The laboratory findings on admission are shown in **Table 1**. Brain magnetic resonance imaging (MRI) (T1-fluid-attenuated inversion re-

CD4	15.9%	κ	67.8%↑
CD5	12.7%	λ	20.7%
CD7	17.6%	CD13	5.4%
CD8	9.7%	CD30	2.4%
CD10	1.2%	CD45	100.0%↑
CD19	77.4 %↑	CD56	40.0%
Tumor markers			
AFP	3.9 ng/ml	SCC	0.8 ng/ml
CEA	2.3 ng/ml	CYFRA	1.2 ng/m
CA 19-9	4.7 U/ml	PRO-GRP	32.8 pg/ml
PSA	0.856 ng/ml	sIL-2R	317 U/ml

Urinalysis revealed no abnormality.Chromosomes in brain tumor biopsy specimens G-banding: poor.↑, ☒; ↓, ☒; WBC, white blood; Neut, neutrophil; Ly, lymphocyte; Mono, monocyte; Eo, eosinocyte; Ba, basophile; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular cell volume; MCH, mean corpuscular cell hemoglobin; Plt, plate; Reti, reticulocyte; T.P., total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-guanosine triphosphate; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; β2MG, β2-microglobulin; ANA, antinuclear antibody; RF, rheumatoid factor; MMP-3, matrix metalloproteinase-3; CA-RF, anti-galactose-deficient immunoglobulin G antibody; anti-CCP, anti-cyclic citrullinated peptide antibody; HIV, human immunodeficiency virus; HTLV-1, human T-cell leukemia virus; EBV VCA IgG, Epstein-Barr virus-viral capsid antigen antibody, immunoglobulin G; EBV VCA IgM, Epstein-Barr virus-viral capsid antigen antibody, immunoglobulin M; EBNA, Epstein-Barr virus nuclear antigen; CD, cluster of differentiation; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PSA, prostate-specific antigen; SCC, squamous cell carcinoma; CYFRA, cytokeratin fragment; PRO-GRP, progastrin-releasing peptide; sIL-2R, soluble interleukin-2 receptor.

covery) revealed a mass measuring 3.5 cm in diameter and edema in the left cerebral white matter at the level of the centrum semiovale. Edema was also found in the white matter of the right occipital lobe (**Figure 3A**). Craniotomy and tumor resection were performed in early November, and histopathological examination of the resected specimen led to a diagnosis of diffuse large B-cell lymphoma (DLBCL) (3 years and 6 months after discontinuation of MTX) (**Figure 4**).

The patient was referred to the ☒ department in late November 2014. Treatment with dexamethasone was initiated at a dose of 8 mg/day, with gradual tapering of the dose and eventual discontinuation of the drug. Whole-body computed tomography (CT) imaging showed no abnormalities (**Figure 5A**, **5B**), and bone marrow and cerebrospinal fluid examinations revealed no infiltration of ☒. The clinical stage of the ☒ was IE. According to the ☒ prognostic scoring system for PCNSL, the patient was classified as high risk, with four risk factors: advanced age, elevated serum lactase dehydrogenase, performance status 3, and deep subcortical lesions. Because of his poor general condition, the patient was started on CHOP therapy (each cycle consisting of cyclophosphamide [1000 mg], vincristine [1.5 mg], doxorubicin [60 mg], and PSL [60 mg] for 5 days) from early December 2014. With this treatment, the paresis of the right upper and lower extremities and dysarthria improved. The second course of CHOP therapy was started in late December. A repeat brain MRI in mid-January 2015 showed marked improvement in ☒ (**Figure 3B**), and the paresis of the right upper and lower extremities and dysarthria had disappeared.

High-dose MTX therapy and high-dose cytarabine therapy were considered as treatment for ☒. However, because of the history of MTX pneumonia, neither the patient nor his family desired any treatment that would require continued hospitalization (such as high-dose MTX therapy or high-dose cytarabine therapy). Outpatient chemotherapy was also rejected by the patient. Consequently, whole-brain irradiation (WBI) was selected and was started in late January 2015. The patient was discharged in late February after he had received a total radiation dose of 45 Gy. As of October 2015, the patient remained in a good general condition with no evidence of recurrence.

Discussion

The present patient developed PCNSL after he had received MTX treatment for RA; OIIALD or MTX-LPD were considered likely etiologies [1]. The World Health Organization (WHO) has not defined whether MTX-LPDs are limited to those occurring during MTX treatment or whether the entity may also include LPDs developing after discontinuation of MTX [1].

Tokuhira et al. classified 23 MTX-LPD patients into three groups: LPDs occurring during MTX treatment and regressing after MTX withdrawal

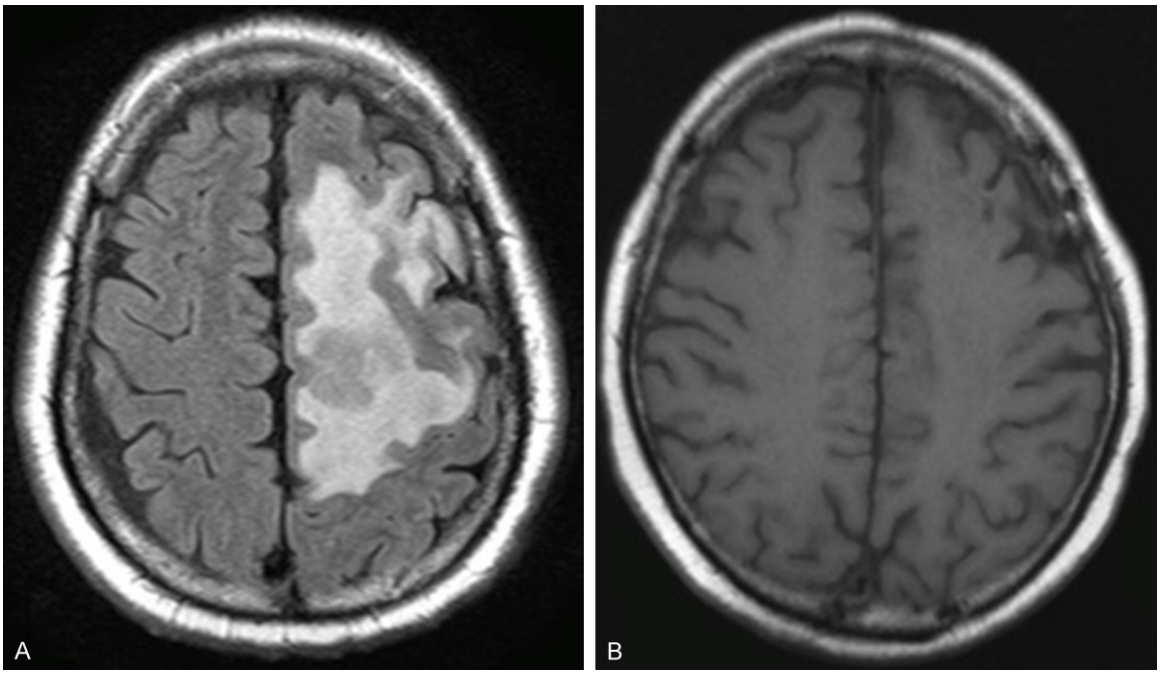


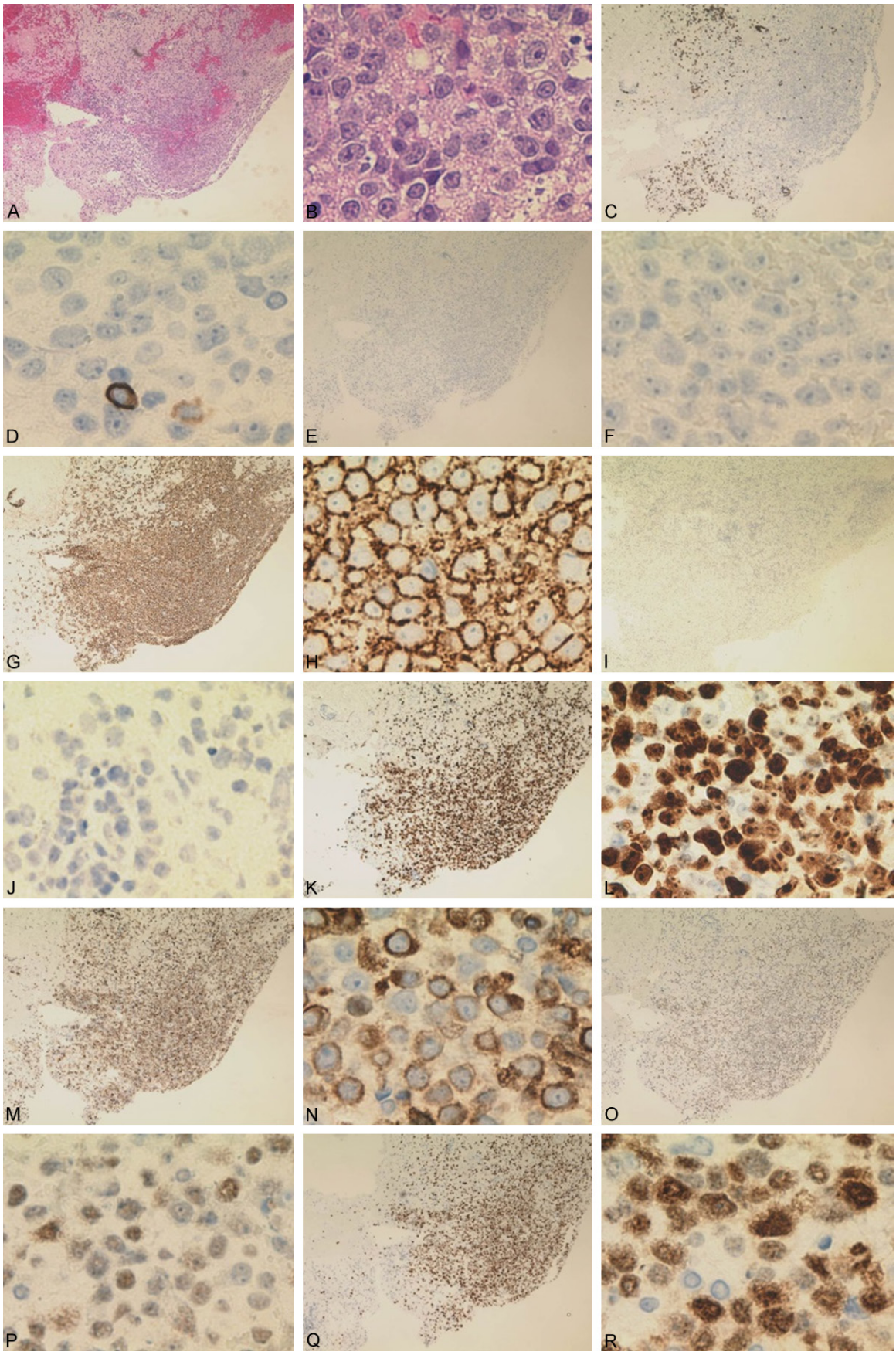
Figure 3. Brain MRI (T1 FLAIR). A. Before treatment: a mass measuring 3.5 cm in diameter and edema were seen in the left cerebral white matter at the level of the centrum semiovale. B. After resection of the tumor and the completion of two courses of CHOP therapy: the mass has decreased in size and the edema in the left cerebral white matter at the centrum semiovale level has improved.

(MTX-Regressive-LPDs, ☒ patients); LPDs occurring during MTX treatment, but not regressing after MTX withdrawal and requiring chemotherapy (MTX-Persistent-LPDs, ☒ patients); and LPDs developing during treatment with other antirheumatic drugs in patients with a history of MTX treatment (MTX-Other-LPDs, ☒ patients) [2]. Analysis of data from the five patients with MTX-Other-LPDs suggested the possibility that LPDs occur as a result of a prolonged immunodeficient state induced by MTX treatment, and in four of the five patients, LPD occurred 4-27 months after discontinuation of MTX [2]. The present case is considered to be an MTX-Other-LPD, despite the onset of LPD being 3 years and 6 months after discontinuation of MTX, which is longer than that for MTX-Other-LPD patients reported by Tokuhira et al.

To date, there have been only three reported cases of PCNSL that developed after MTX treatment for RA (RA-MTX-PCNSL), including the current case (**Table 2**). In the three known cases of RA-MTX-PCNSL, the duration of RA was 7-9 years (long-standing and unknown in one case), which was somewhat shorter than the median of 11 years (3-360 months) in previously reported cases of MTX-LPD [5]. According to Tokuhira et al., the average duration of RA was 9.7 years for MTX-Regressive-LPD patients, 10.0 years for MTX-Persistent-LPD patients, and 11.9 years for MTX-Other-LPD patients [2].

In the three known RA-MTX-PCNSL cases, the MTX treatment duration varied from 1 to ≥10 years. According to a WHO report, LPDs occur an average of 3 (0.5-5) years after the start of MTX treatment [1]. The reported mean MTX treatment durations were 4.8, 4.3, and 3.9 years in MTX-Regressive-LPD, MTX-Persistent-LPD, and MTX-Other-LPD patients, respectively [2]. The median MTX treatment durations before the onset of LPD reported in other studies are 4.5 years (2-131 months) [5] and 5.8 years (1-13 years) [6].

The total MTX dose was 417.1-1740 mg in the three RA-MTX-PCNSL patients, which was comparable with that in a previous report on lymphoproliferative disorders in rheumatoid arthritis patients (940 [24-4785] mg) [5] and tended to be higher than the average of 372.4 mg reported for MTX-Regressive-LPD patients, 338.2 mg for MTX-Persistent-LPD patients, and 278.4 mg for MTX-Other-LPD patients [2].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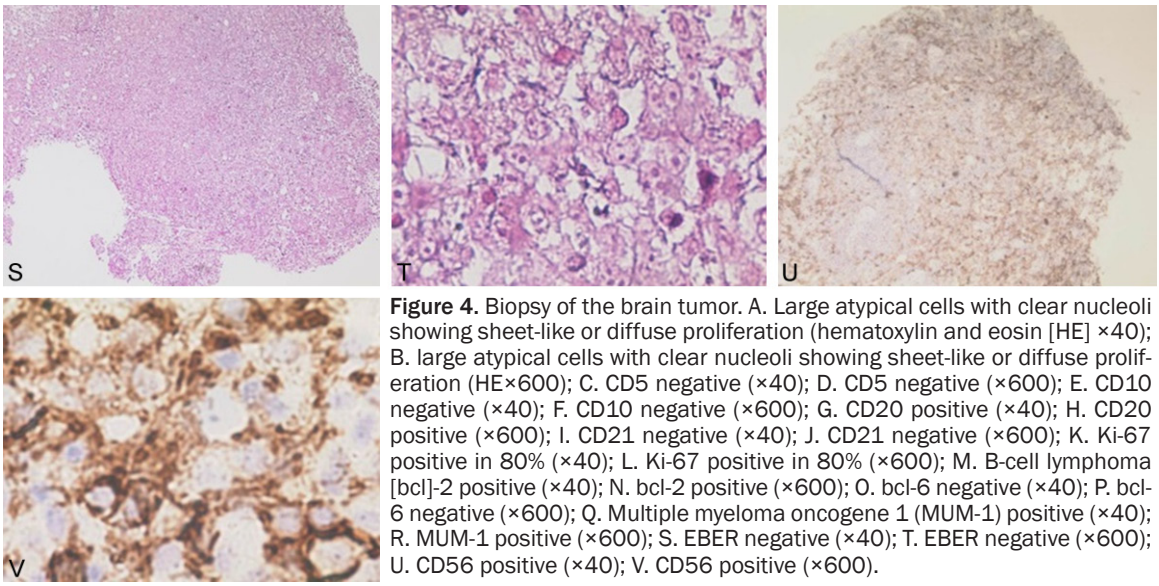

Figure 4. Biopsy of the brain tumor. A. Large atypical cells with clear nucleoli showing sheet-like or diffuse proliferation (hematoxylin and eosin [HE] ×40); B. large atypical cells with clear nucleoli showing sheet-like or diffuse proliferation (HE×600); C. CD5 negative (×40); D. CD5 negative (×600); E. CD10 negative (×40); F. CD10 negative (×600); G. CD20 positive (×40); H. CD20 positive (×600); I. CD21 negative (×40); J. CD21 negative (×600); K. Ki-67 positive in 80% (×40); L. Ki-67 positive in 80% (×600); M. B-cell lymphoma [bcl]-2 positive (×40); N. bcl-2 positive (×600); O. bcl-6 negative (×40); P. bcl-6 negative (×600); Q. Multiple myeloma oncogene 1 (MUM-1) positive (×40); R. MUM-1 positive (×600); S. EBER negative (×40); T. EBER negative (×600); U. CD56 positive (×40); V. CD56 positive (×600).

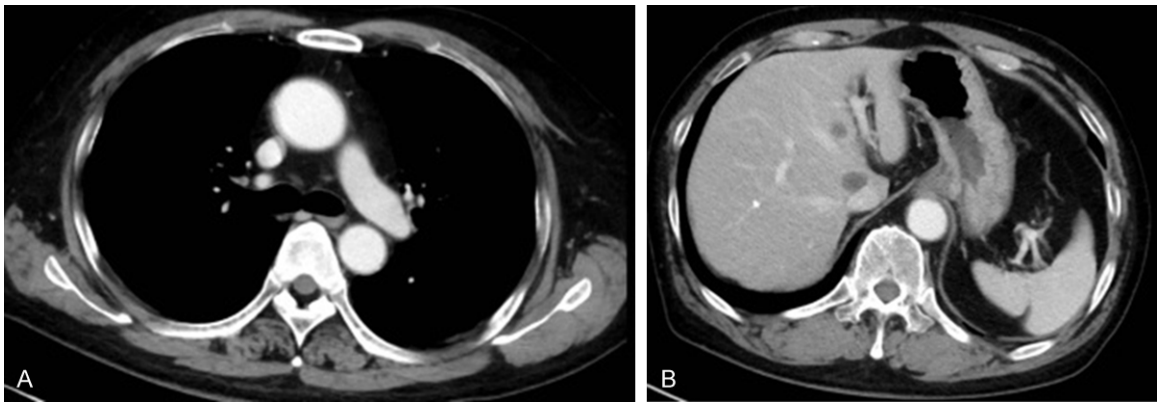

Figure 5. Whole-body CT. A. Chest: no abnormalities; B. Abdomen: no abnormalities.

Although the two previously reported cases of RA-MTX-PCNSL were EBERpositive [3, 4], the present case was EBER-negative (**Figure 4S**, **4T**). CD21 serves as the Epstein-Barr virus (EBV) receptor [7], and it is possible that the present case was EBER-negative because the tumor was CD21-negative (**Figure 4I**, **4J**). In addition, in the two previously reported cases of RA-MTX-PCNSL, the onset of the LPD was during the course of MTX treatment, whereas, in the present case, it developed 3 years and 6 months after the discontinuation of MTX. In the present case, the onset of PCNSL occurred 9 years after the diagnosis of RA and 7 years and 10 months after the start of MTX.

The onset of PCNSL 3 years and 6 months after the discontinuation of MTX and the EBER negativity are unique features of the current case. According to the WHO, the EBER-positive rate is as low as 25% in DLBCL patients with RA and MTX-LPD [1]. The EBER-positive rate of ☒ varies among reports from 16% to 44% [2, 5, 6, 8-11].

MTX reactivates EBV, thereby causing lymphoma in some cases [12], although some patients who are EBV-negative also develop lymphoma, e.g., the present case; the precise mechanism of the development of lymphoma in EBV-negative the latter cases remain unknown. LPDs disappear or diminish after discontinuation of MTX in some cases, and in these cases, MTX is considered to be the likely cause of the LPD [2, 8, 11, 13, 14].

Niitsu et al. reported that 6 of 29 MTX-LPD patients achieved remission after discontinuation of MTX, and that of these, 4 were EBER

Table 2. The three known cases of PCNSL that developed after MTX treatment for RA

Case	Age (y)/ sex	Duration of RA before the onset of PCNSL	RA treatment before the onset of PCNSL	MTX treatment duration before the onset of PCNSL (total dose)	RA activity at the onset of PCNSL	Histological type of PCNSL	EBER	Treatment of lymphoma	Response	Outcome	Ref
1	53/F	7 y	Bucillamine (200 mg/day) PSL (5-10 mg/day) MTX (8 mg/wk)	1 y (417.1 mg)	Good control	DLBCL CD56?	+	Discontinuation of MTX	CR	CR maintained for 8 y, surviving	3
2	78/F	Long-standing	Standard dose MTX	≥10 y (n.a.)	n.a.	n.a. CD56?	+	Discontinuation of MTX	CR	Died of RA 3 m later	4
3	70/M	9 y	MTX (10 mg/wk) SASP (1000 mg/day) PSL (7.5 mg/day)	3 y 4 m (1740 mg)	Good control	DLBCL CD56-positive CD21-negative	-	CHOP WB	CR	CR maintained for 6 m, surviving	Present case

y, year; M, male; F, female; PCNSL, primary central nervous system lymphoma; RA, rheumatoid arthritis; PSL, prednisolone; MTX, methotrexate; wk, week; SASP, salazosulfapyridine; m, months; n.a., not available; DLBCL, diffuse large B-cell lymphoma; EBER, Epstein-Barr virus-encoded small RNA; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; WBI, whole-brain irradiation; CR, complete remission.

positive and achieved complete remission. However, no significant difference in the survival times has been reported between EBER-positive and EBER-negative patients [8]. Similarly, Tokuhira et al. reported finding no significant difference in the prognosis between EBER-positive and EBER-negative groups of MTX-LPD patients [2]. Involvement of the EBV and its influence on the prognosis are unknown in patients with RA-MTX-PCNSL, including the present case.

It has been reported that RA patients, even those not receiving MTX treatment, are at a 2- to 20-fold higher risk of developing LPD than those without RA [2, 15]. Increased RA activity is thought to be one of the causes of LPD [16]. In the present case, RA activity was suppressed by MTX, and after discontinuation of MTX, RA activity was suppressed by the combination of PSL and SASP (**Table 1**). Therefore, increased RA activity is unlikely to have been the cause of LPD in the present case. Another possible mechanism is that a large number of EBV-positive B cells are present in RA patients, and that stimulation of these cells leads to LPD [8]. This possibility is also unlikely in the present case because our patient was EBV negative.

In the case of OIIALDs, it is difficult to assess to what extent iatrogenic immunodeficiency, primary disease, and concomitant drugs are related to the development of LPD, and the exact mechanism of development remains unclear. Thus, it remains unclear to what extent MTX is involved in the development of LPDs [2, 17]. If the LPD regresses after discontinuation of MTX, MTX is highly likely to be involved. However, inEBER-negative cases, cases with the onset of LPD after the discontinuation of MTX, cases where the LPD does not regress after the discontinuation of MTX, and cases with no RA disease activity it is difficult to assess the contribution of MTX. However, even in cases where the onset of LPD occurs after the discontinuation of MTX and the test for EBER is negative, as in the present case, the possibility of MTX-LPD cannot be ruled out.

The present case was CD56 positive. It has been reported that 1.2%-7% of all DLBCL cases are CD56 positive [18-20], but this is the only reported case of CD56-positive PCNSL.

There have been only three reported cases of PCNSL after MTX treatment for RA, including the present case. The prognosis and the pathological, molecular-biological, and clinical features of this condition remain unknown, and further studies are required with a larger number of cases.

Disclosure of conflict of interest

None.

Address correspondence to: Yasunobu Sekiguchi, Department of Hematology, Urayasu Hospital of Juntendo University, 2-1-1 Tomioka, Urayasu, Chiba, Japan. Tel: +81-47-353-3111; Fax: +81-47-381-5054; E-mail: yasu_sek@juntendo-urayasu.j

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