Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3817-24
Intern Med 64: 1267-1274, 2025
http://internmed.jp

【 CASE REPORT 】

Cognitive Dysfunction as an Initial Manifestation of Rheumatoid Arthritis-associated Intravascular Large B-cell Lymphoma

Junya Kitai[1,2], Ryuichi Minoda Sada[1,3,4], Satoko Yamaguchi[5], Akiyo Shinde[5] and Wataru Maruyama[6]

Abstract:
A 58-year-old Japanese woman with rheumatoid arthritis (RA) presented with the sudden onset of cognitive dysfunction. A random skin biopsy revealed intravascular large B-cell lymphoma (IVLBCL), which resolved spontaneously with methotrexate withdrawal. However, four months later, the disease relapsed with liver injury. After completion of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy, both RA and IVLBCL remained in remission for two years. Among the pathological subtypes of RA-associated lymphoproliferative diseases, reports on IVLBCL are limited, and little is known about its clinical course. Our literature review summarizes the clinical course and mortality of 11 patients with RA-IVLBCL.

Key words: cognitive dysfunction, intravascular large B-cell lymphoma, lymphoproliferative disorder, rheumatoid arthritis, methotrexate

(Intern Med 64: 1267-1274, 2025)
(DOI: 10.2169/internalmedicine.3817-24)

Introduction

Lymphoproliferative disorder (LPD) develops in patients with rheumatoid arthritis (RA). LPD has been reported in 0.8% of patients with RA, and the standardized incidence ratio of malignant lymphoma in patients with RA is 3.48-6.18 times higher than that in the general population (1). Risk factors for the development of RA-associated LPD (RA-LPD) include older age (2), RA disease activity (1), and Epstein-Barr virus infection (3). Methotrexate (MTX), an immunosuppressive drug involved in the development of RA-LPD, also shows a strong association (2). LPDs arising during immunosuppressive therapy are classified as other iatrogenic immunodeficiency-associated LPDs (4), whereas those associated with MTX are termed MTX-LPDs. Some cases regress with withdrawal of MTX, some relapse during the administration of other therapeutic agents after MTX withdrawal, and others do not improve with MTX withdrawal (5). If the LPD does not regress, chemotherapy is required.

Five-year survival rates of 59.2-78.2% have been reported for RA-LPD (2, 6-8). The most common pathological subtype of LPD is diffuse large B-cell lymphoma, followed by classical Hodgkin's lymphoma, Epstein-Barr virus-positive mucocutaneous ulcers, and reactive lymphoid hyperplasia (9). The prognosis of LPD in patients with RA depends on the histopathological type of disease (10). In RA-LPD, both lymph node and extranodal lesions occur at a rate of approximately 50-80% (2, 9, 10). The major extranodal sites of involvement are the lungs and oral or oropharyngeal mucosa (6).

Intravascular large B-cell lymphoma (IVLBCL), first described in 1959 (11), is a rare subtype of lymphoma charac-

[1]Department of General Internal Medicine, Tenri Hospital, Japan, [2]Department of Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Japan, [3]Department of Transformative Protection to Infectious Disease, Graduate School of Medicine, Osaka University, Japan, [4]Department of Infection Control, Graduate School of Medicine, Osaka University, Japan, [5]Department of Neurology, Tenri Hospital, Japan and [6]Department of Hematology, Tenri Hospital, Japan
Received: March 13, 2024; Accepted: July 8, 2024; Advance Publication by J-STAGE: September 4, 2024
Correspondence to Dr. Ryuichi Minoda Sada, sadao@cider.osaka-u.ac.jp

terized by infiltration of large, atypical cells into blood vessels of various diameters (12). The Asian variant of IVLBCL (A-IVL) is generally associated with hemophagocytic syndrome, bone marrow infiltration, respiratory failure, and hepatosplenomegaly, with a few complications, such as lymph node enlargement, mass formation, skin rash, and neuropathy (13). In contrast, variant IVLBCL encountered in Western countries (W-IVL) is often associated with cutaneous and central nervous system (CNS) symptoms (14). Cutaneous variant IVLBCL (C-IVL) is limited to the skin, is seen more frequently in Western countries, and has a better prognosis than other types of IVLBCL (14).

In Japan, IVLBCL accounts for 1% of B-cell lymphomas (15). Survival rates for patients with IVLBCL are better in those treated with rituximab plus chemotherapy than in those treated with chemotherapy alone (16), with 2-year survival rates of 66-92% and complete remission rate of 82-90% in patients with IVLBCL treated with a combination of rituximab and chemotherapy combination (16-18). The incidence of IVLBCL in RA patients has not been explicitly reported in previous studies. Reports of RA-IVLBCL are rare, and the clinical course remains unclear.

We herein report a case of RA-IVLBCL in which cognitive dysfunction was the initial presentation and provide a literature review of RA-IVLBCL.

Case Report

A 58-year-old Japanese woman had been diagnosed with RA with negative anti-citrullinated peptide antibodies (ACPAs) and a rheumatoid factor (RF) level of 15.9 IU/mL at the onset and had been taking MTX 8 mg/week for 6 months, with a Simplified Disease Activity Index score of 0.49. She visited our hospital after suddenly losing the ability to operate her smartphone and became disoriented on a path she was accustomed to. Both the incidents occurred on the same day. The patient was treated with folic acid, loxoprofen, and rebamipide.

The patient had no relevant medical histories. On admission, her vital signs were as follows: temperature, 36.6°C; blood pressure, 121/82 mmHg; pulse rate 93/min, and respiratory rate, 18/min; Glasgow coma score, 15; and saturation of percutaneous oxygen, 98% (room air). A physical examination revealed no relevant findings, including joint swelling or lymphadenopathy. A neurological examination revealed no abnormalities in cranial, motor, sensory, reflex, motor coordination, or autonomic nerves. An initial laboratory examination showed a white blood cell count of 4,670 cells/μL (3,544 cells/μL neutrophils; 597 cells/μL lymphocytes), hemoglobin levels of 10.3 g/dL, platelet count of 26.0×10^4/μL, aspartate aminotransferase (AST) level of 38 U/L, alanine aminotransferase (ALT) level of 26 U/L, lactate dehydrogenase (LDH) level of 592 U/L, C-reactive protein level of 1.34 mg/dL, β2- macroglobulin level of 3.31 μg/mL, International Normalized Ratio level of 1.06, Activated partial thromboplastin time level of 27.5 seconds, D-dimer level of 1.1 μg/mL, soluble interleukin-2 receptor (sIL-2R) level of 1,070 U/mL, erythrocyte sedimentation rate (60 min) of 37 mm, EBVCA-IgM <×10, EBVCA-IgG×160, EBNA×40, IgG levels of 1,401 mg/dL, RF level of 13.0 IU/mL, and ACPA levels <0.6 U/mL.

Brain magnetic resonance imaging (MRI) revealed diffuse high-signal areas in the bilateral cerebral hemispheres on diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 1a), leading to the suspicion of subacute cerebral infarction. The details of the cognitive dysfunction were as follows: The Mini-Mental State Examination (MMSE) score was 25 out of 30 (orientation: -1 point/attention and calculation: -1 point/recall: -2 points/visuospatial function: -1 point), the Japanese version of the Montreal Cognitive Assessment score was 20 out of 30 (visuospatial and executive function: -4 points/attention and concentration: -2 points/language -1 point/delayed word recall: -2 points), and the Frontal Assessment Battery (FAB) score was 11 out of 18 (similarities -1 point/lexical fluency: -1 point/motor series: -2 points/conflicting instruction -1 point/go no-go: -2 points). However, it was not possible to explain the association between the MRI findings and cognitive dysfunction. Contrast-enhanced brain MRI was performed to examine the causes of cognitive dysfunction, which showed a subcortical high signal and a linear high signal around the lateral ventricles on post-contrast T2-weighted imaging (T2 WI, Fig. 1b) and contrast effects with a subarachnoid pattern on post-contrast FLAIR imaging (Fig. 1c).

Rheumatoid meningitis was also considered as a differential diagnosis, and a spinal fluid examination was performed, which showed a monocyte count of 96 cells/μL (96% lymphocytes; 4% monocytes) and adenosine deaminase, total protein, albumin, globulin, glucose, sIL-2R, β2-microglobulin, interleukin-6 (IL-6), IgG, RF, and ACPA levels of 5.4 U/L, 283 mg/dL, 147 mg/dL, 136 mg/dL, 66 mg/dL, 87.5 U/mL, 2.71 μg/mL, 4.6 pg/dL, 46.7 mg/dL, <5.0 U/mL, and <0.6 U/mL, respectively. Atypical cells were observed in the spinal fluid.

Thoracic and abdominal computed tomography (CT) revealed splenomegaly with no other mass lesions. A random skin biopsy was performed for IVLBCL; however, no atypical cells were found. Bone marrow aspiration and a biopsy revealed an absence of atypical cells and malignant findings. A second random skin biopsy was performed. One of the four specimens showed large, atypical cells in the small vessels (Fig. 2a), and immunostaining was positive for CD20 (Fig. 2b). MTX was withdrawn from the patient's treatment regimen and was followed up without chemotherapy. We elected not to administer chemotherapy because we expected that the lesion would regress spontaneously (5), given that no progression of cognitive decline had been observed between the time of the initial presentation and the diagnosis, and no other organ or severe organ damage was observed.

Two months after MTX withdrawal, the MMSE and FAB scores were 30/30 and 16/18, respectively, and the cognitive dysfunction had improved. MRI findings had improved as

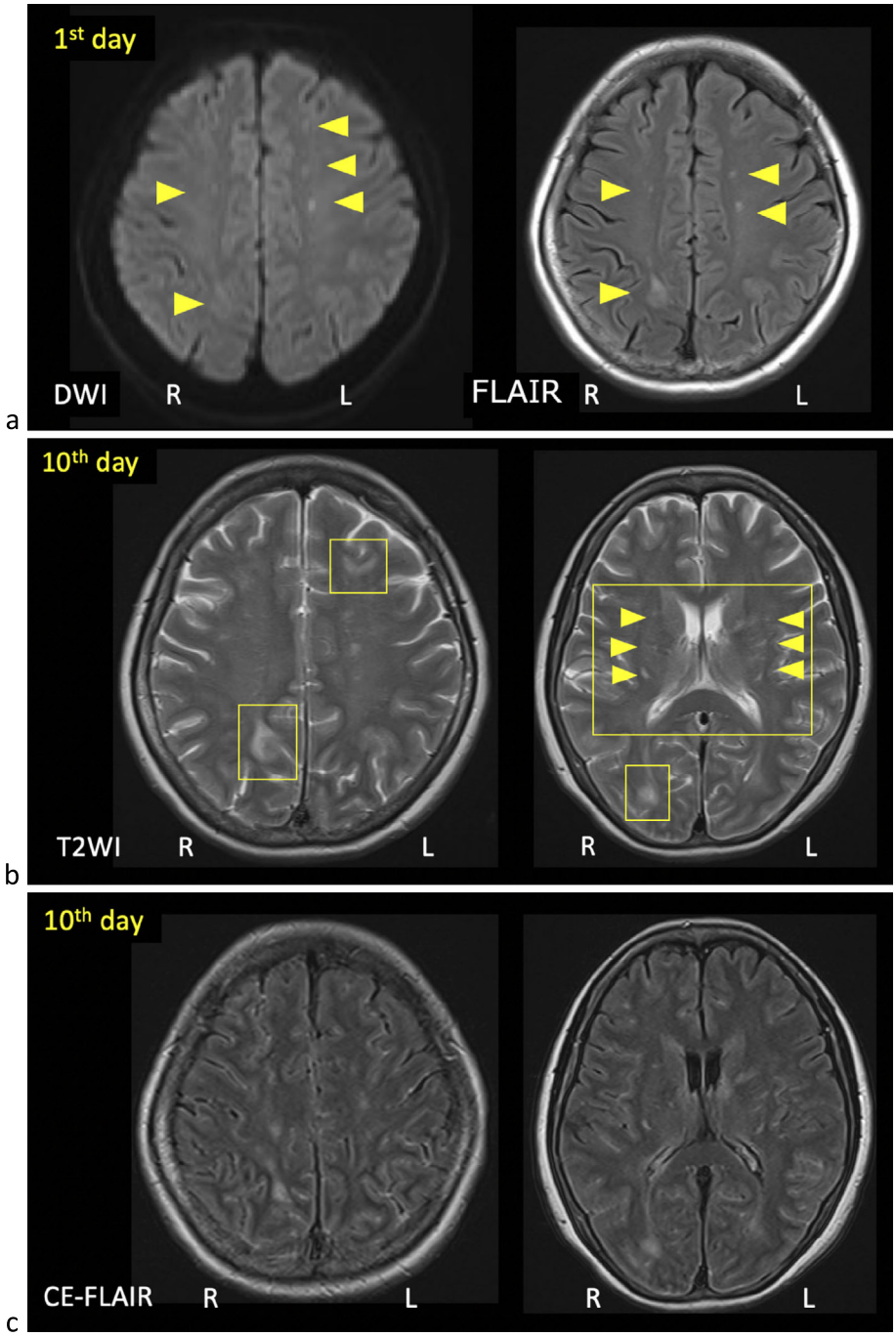

Figure 1. **Initial MRI findings. a) Diffuse high-signal areas in the bilateral cerebral hemispheres on diffusion-weighted and FLAIR images. b) Subcortical high signal and linear high signal around the lateral ventricles on post-contrast T2-weighted images. c) Contrast effects with subarachnoid pattern on post-contrast FLAIR images. Arrowheads indicate high-intensity lesions. CE-FLAIR: contrast-enhanced fluid-attenuated inversion recovery, DWI: diffusion-weighted imaging, L: left, R: right**

well (Fig. 3a, b), LDH levels had decreased, and the lymphocyte count had increased (Fig. 4). After MTX withdrawal, imaging and blood test findings of IVLBCL improved, and the patient was diagnosed with MTX-associated IVLBCL (MTX-IVLBCL).

However, four months after MTX withdrawal, she presented with a week history of a fever and malaise without neurological findings or cognitive dysfunction. Laboratory examinations revealed increased LDH, AST, ALT, and sIL-2R levels and decreased lymphocyte counts. Abdominal CT showed hepatosplenomegaly but no other findings of febrile origin. The patient was diagnosed with recurrent IVLBCL with liver injury and treated with six courses of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy. After consultation with hematologists, intrathecal administration of MTX was not performed. This decision was made due to the absence of CNS symptoms at the time of relapse and the consideration that the

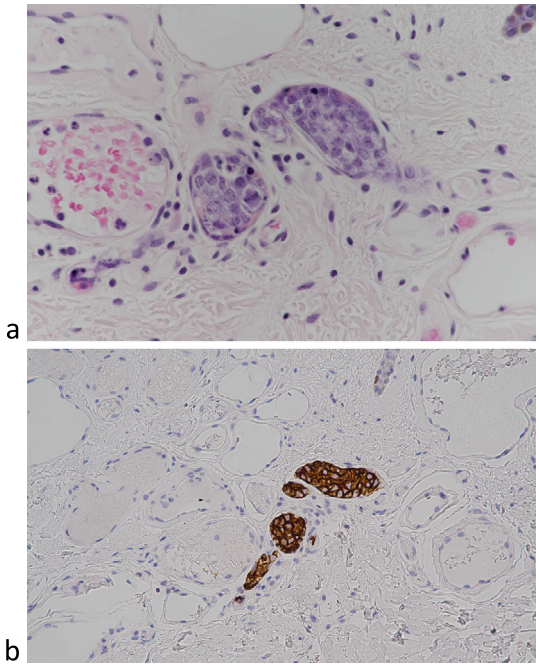

Figure 2. Biopsy findings. a) A skin biopsy shows large, atypical cells in the small vessels. Hematoxylin and Eosin (H&E) staining ×400. b) Positive immunostaining for CD20. H&E staining ×200.

disease was MTX-IVLBCL. After the completion of chemotherapy, IVLBCL and RA remained in remission for two years without any disease-modifying antirheumatic drugs.

Discussion

We encountered a case of RA-IVLBCL with signs and symptoms of both A-IVL and W-IVL. In this patient, splenomegaly was consistent with the typical findings of A-IVL and cognitive dysfunction, with typical findings of W-IVL. Although IVLBCL spontaneously regressed with MTX withdrawal alone, the disease relapsed in a different organ from the initial presentation. Both IVLBCL and RA were in complete remission with chemotherapy and remained in drug-free remission for two years. As with other RA-LPDs, LDH levels and lymphocyte counts were useful predictors of recurrence (19). CNS symptoms were observed in 42% of IVLBCL cases. The most common CNS complications identified were cognitive impairment and dementia (60.9%) (20). IVLBCL is frequently present in the CNS but is rarely limited to this system, as in this case (12), with such cases accounting for 5% of IVLBCL cases (14). Head MRI findings in patients with IVLBCL include hyperintense lesions in the pons on T2WI, nonspecific white matter lesions, infarct-like lesions, and meningeal thickening and/or enhancement, with abnormal signals disappearing when the patient responds to chemotherapy (21). The present case showed three of these features: nonspecific white matter lesions, infarct-like lesions, and meningeal thickening and/or enhancement. The symptoms and MRI findings in this case were consistent with distinctive MRI findings typical of IVLBCL. In addition, although untreated, the abnormal MRI findings improved with symptom improvement, which is consistent with the course of the CNS findings in patients with IVLBCL. Sudden onset of cognitive dysfunction in patients with RA should also be considered in the differential diagnosis of IVLBCL.

There are no reports on the prevalence of IVLBCL in patients with RA, and only a few such case reports are available in the literature. Therefore, we conducted an extensive search of case reports of IVLBCL in patients with RA by searching PubMed on January 15, 2024, for the terms [“arthritis, rheumatoid”(MeSH Terms) OR “rheumatoid arthritis” (Title/Abstract)] AND [“intravascular”(Title/Abstract) AND (“lymphoma”(MeSH Terms) OR “lymphoma”(Title/Abstract))]. Nine case reports from 1993 to 2022 were identified (22-31), but no case series were found. The citations of the identified literature were reviewed, and 11 cases of IVLBCL in patients with RA were identified, including our case (Table). A case of RA-IVLBCL was first reported in 1987 (22). In 2015, the first case of MTX-IVLBCL in a patient with RA receiving MTX was reported in Japan (23). The median age of onset was 63 years old (range 50-76 years old; man:woman ratio, 0.22). Epstein-Barr virus-encoded RNA *in situ* hybridization was positive in one of the six stained cases. RA-LPD has been shown to be significantly associated with Epstein-Barr virus infection (3); however, the association between IVLBCL and Epstein-Barr virus is unknown.

MTX is the most commonly used immunosuppressive drug, and 9 (81.8%) patients with IVLBCL with a history of MTX use have been reported. Of these, seven cases occurred when MTX was administered. No cases of spontaneous resolution of IVLBCL have been reported, but five cases of MTX-IVLBCL regressed without treatment, and three cases of untreated MTX-IVLBCL, including the present case, relapsed within four to eight months. In cases of RA-IVLBCL, factors associated with IVLBCL development, such as MTX, should be eliminated, and R-CHOP should be considered in case of deterioration. Nine patients (81.8%) had symptoms of A-IVL, 4 (36.3%) had W-IVL, 3 (27.2%) had symptoms of both A-IVL and W-IVL, and 2 (18.1%) had C-IVL. Cases with symptoms of only W-IVL and those with symptoms of only C-IVL have been reported in countries other than Japan, while cases with symptoms of A-IVL have been reported in Japan. Therefore, A-IVL is likely the most common type of RA-IVLBCL. Although follow-up times varied, the survival was confirmed in 9 (81.8%) RA-IVLBCL cases, and 8 of those 9 (88.9%) were in complete remission with chemotherapy.

Few reports have described the symptoms of RA after the completion of chemotherapy. Two patients, including this case, were reported to have maintained RA remission after the completion of chemotherapy for two years, and one patient had relapse of RA after the completion of chemotherapy. However, when R-CHOP is administered for malignant lymphomas that develop into autoimmune diseases, includ-

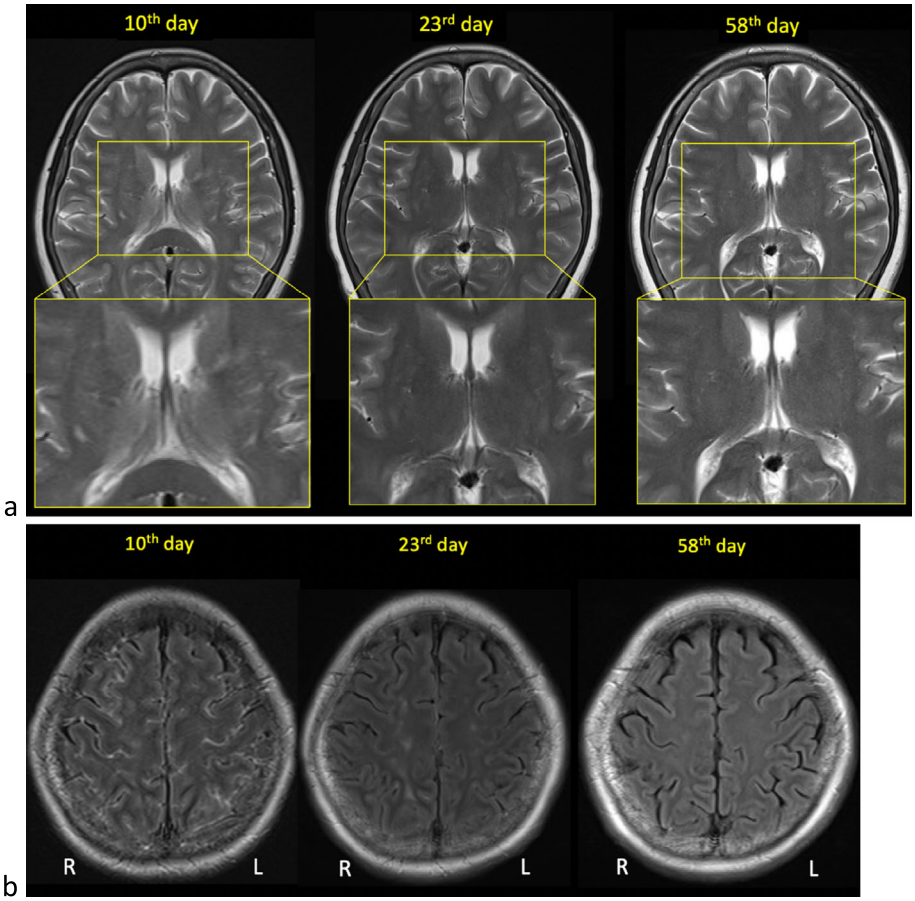

Figure 3. **MRI findings after MTX withdrawal. a) The subcortical high signal and periventricular linear high signal in the lateral ventricles seen on post-contrast T2-weighted MRI are improved. b) The subarachnoid pattern seen on post-contrast FLAIR MRI is improved. L: left, MRI: magnetic resonance imaging, MTX: methotrexate, R: right, FLAIR: fluid attenuated inversion recovery**

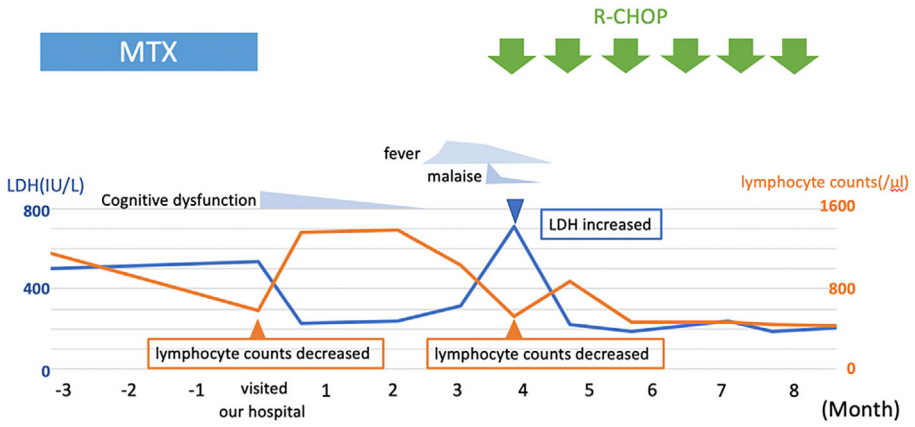

Figure 4. **Clinical course of the patient. LDH: lactate dehydrogenase, MTX: methotrexate, R-CHOP: rituximab, doxorubicin, cyclophosphamide, vincristine, prednisolone**

ing RA, autoimmune disease symptoms often improve during chemotherapy, but relapse occurs at a median of seven weeks after the end of chemotherapy (32). The proportion of patients with RA for whom rituximab is effective is reported to be 40-80% (32-35). Long-term follow-up is required for patients with RA and RA-IVLBCL, as RA can increase disease activity once in remission.

Conclusion

This clinical vignette described a case of RA-IVLBCL with cognitive dysfunction as the only initial presentation, with symptoms of both A-IVL and W-IVL. The completion of R-CHOP therapy maintained the remission of the symptoms and signs of both RA-IVLBCL and RA. Long-term

Table. Cases of RA-IVLBCL in the Literature.

Case	Age (years)	Sex	Symptom and organ involvement at initial presentation	Symptom and organ involvement at relapse	IVLBCL variant	Biopsy site	Immunosuppressant used at initial presentation	Concomitant MTX use at IVL diagnosis	Interval from MTX to IVLBCL
1	50	F	Fever/rash Meninges	-	A-IVL W-IVL	Rash	MTX, ETN	Yes	+3 y
2	75	F	Fever/malaise	-	A-IVL	RSB	MTX, SSZ	Yes	+2 m
3	76	M	Fever/dyspnea	Fever/dyspnea	A-IVL	RSB	MTX	Yes	+10 y
4	70	F	Fever/dyspnea	-	A-IVL	Lung	MTX	Yes	+7 y
5	56	F	Dyspnea/ dizziness	Mesenteric lymphadenopathy	A-IVL	RSB	MTX	Yes	+6 y
6	67	F	Fever/rash Gut	-	W-IVL	Autopsy	PSL, gold	Yes	-1 y
7	59	M	Fever/ dyspnea/rash	-	A-IVL W-IVL	RSB	PSL, CPA, and Tac	Yes	-13 y
8	63	F	Rash	-	C-IVL	Rash	PSL	No	-
9	65	F	Rash	-	C-IVL	Rash	NSAIDs	No	-
10	62	F	Fever/red eyes	Fever/red eyes Lungs	A-IVL	Lung	MTX	Yes	NI
11	58	F	Cognitive dysfunction meninges	Fever Liver injury	A-IVL W-IVL	RSB	MTX	Yes	+6 m

Case	Progress after MTX discontinuation	Interval from regression to relapse	EBER	Chemotherapy	Response to chemotherapy	Maintenance of remission	Outcome	Ref
1	Regression	-	-	R-CHOP IT	CR	2 y	Survival	(23)
2	Persist	-	-	R-Hyper-CVAD/MA	CR	1 y	Survival	(24)
3	Regression →relapse	8 m	-	R-THP-COP IT HD-MTX	CR	2 m	Survival	(25)
4	Regression	-	-	-	-	1 m	Survival	(26)
5	Regression →relapse	4 m	-	R-CHOP R-HDMTX IT	CR	1 y	Survival	(27)
6	-	-	NI	-	-	-	Dead	(28)
7	-	-	+	R-CHOP	PD	-	Dead	(29)
8	-	-	NI	CPA, vincristine, and PSL	CR	ND	Survival	(22)
9	-	-	NI	CHOP	CR	4 y	Survival	(30)
10	Progress after MTX discontinuation	-	NI	R-CHOP	CR	1.5 y	Survival	(31)
11	Regression	4 m	NI	R-CHOP	CR	2 y	Survival	This case

A-IVL: Asian variant IVLBCL, C-IVL: cutaneous variant IVLBCL, CPA: cyclophosphamide, CR: complete remission, CVA/MA: cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate and cytarabine, EBER: Epstein-Barr virus-encoded RNA, ETN: etanercept, F: female, HDMTX: high-dose methotrexate, IT: intrathecal injection of anticancer drugs, IVLBCL: intravascular large B-cell lymphoma, M: male, m: month, MTX: methotrexate, NI: no information, PD: progression disease, PSL: prednisolone, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, Ref: reference, RSB: random skin biopsy, SSZ: salazosulfapyridine, Tac: tacrolimus, R-THP-COP: rituximab, pirarubicin, cyclophosphamide, vincristine, and prednisolone, W-IVL: Western countries variant IVL, y: year

"-" indicates the period between MTX being withdrawn and the onset of IVLBCL.

"+" indicates the period between MTX being initiated and the onset of IVLBCL.

follow-up after remission is necessary in patients with RA-IVLBCL.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

This research was conducted as part of the All-Osaka U Research in "The Nippon Foundation-Osaka University Infectious Disease Response Project."

References

1. Shimizu Y, Nakajima A, Inoue E, et al. Characteristics and risk factors of lymphoproliferative disorders among patients with rheu-

matoid arthritis concurrently treated with methotrexate: a nested case-control study of the IORRA cohort. Clin Rheumatol **36**: 1237-1245, 2017.
2. Honda S, Sakai R, Inoue E, et al. Association of methotrexate use and lymphoproliferative disorder in patients with rheumatoid arthritis: results from a Japanese multi-institutional retrospective study. Mod Rheumatol **32**: 16-23, 2022.
3. Banko A, Miljanovic D, Lazarevic I, et al. New evidence of significant association between EBV presence and lymphoproliferative disorders susceptibility in patients with rheumatoid arthritis: a systematic review with meta-analysis. Viruses **14**: 115, 2022.
4. Gaulard P, Swerdlow SH, Harris NL, Sundstrom C, Jaffe ES. Other iatrogenic immunodeficiency-associated lymphoproliferative disorders. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Swerdlow SH, Campo E, Harris NL, et al., Eds. IARC Press, Lyon, 2017: 462-464.
5. Tokuhira M, Tamaru JI, Kizaki M. Clinical management for other iatrogenic immunodeficiency-associated lymphoproliferative disorders. J Clin Exp Hematop **59**: 72-92, 2019.
6. Hoshida Y, Xu JX, Fujita S, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol **34**: 322-331, 2007.
7. Saito R, Tanaka M, Ito H, et al. Overall survival and post-spontaneous regression relapse-free survival of patients with lymphoproliferative disorders associated with rheumatoid arthritis: a multi-center retrospective cohort study. Mod Rheumatol **32**: 50-58, 2022.
8. Tokuhira M, Watanabe R, Nemoto T, et al. Clinicopathological analyses in patients with other iatrogenic immunodeficiency-associated lymphoproliferative diseases and rheumatoid arthritis. Leuk Lymphoma **53**: 616-623, 2012.
9. Takada H, Kaneko Y, Nakano K, et al. Clinicopathological characteristics of lymphoproliferative disorders in 232 patients with rheumatoid arthritis in Japan: a retrospective, multicenter, descriptive study. Mod Rheumatol **32**: 32-40, 2022.
10. Kurita D, Miyoshi H, Ichikawa A, et al. Methotrexate-associated lymphoproliferative disorders in patients with rheumatoid arthritis: clinicopathologic features and prognostic factors. Am J Surg Pathol **43**: 869-884, 2019.
11. Pfleger L, Tappeiner J. [On the recognition of systematized endotheliomatosis of the cutaneous blood vessels (reticuloendotheliosis?]. Hautarzt **10**: 359-363, 1959 (in German).
12. Ponzoni M, Campo E, Nakamura S. Intravascular large B-cell lymphoma: a chameleon with multiple faces and many masks. Blood **132**: 1561-1567, 2018.
13. Murase T, Nakamura S, Kawauchi K, et al. An Asian variant of intravascular large B-cell lymphoma: clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haemophagocytic syndrome. Br J Haematol **111**: 826-834, 2000.
14. Ferreri AJ, Campo E, Seymour JF, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. Br J Haematol **127**: 173-183, 2004.
15. Shimada K, Kiyoi H. Current progress and future perspectives of research on intravascular large B-cell lymphoma. Cancer Sci **112**: 3953-3961, 2021.
16. Shimada K, Matsue K, Yamamoto K, et al. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. J Clin Oncol **26**: 3189-3195, 2008.
17. Ferreri AJ, Dognini GP, Bairey O, et al. The addition of rituximab to anthracycline-based chemotherapy significantly improves outcome in 'Western' patients with intravascular large B-cell lymphoma. Br J Haematol **143**: 253-257, 2008.
18. Shimada K, Yamaguchi M, Atsuta Y, et al. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone combined with high-dose methotrexate plus intrathecal chemotherapy for newly diagnosed intravascular large B-cell lymphoma (PRIMEUR-IVL): a multicentre, single-arm, phase 2 trial. Lancet Oncol **21**: 593-602, 2020.
19. Kuramoto N, Saito S, Fujii T, et al. Characteristics of rheumatoid arthritis with immunodeficiency-associated lymphoproliferative disorders to regress spontaneously by the withdrawal of methotrexate and their clinical course: a retrospective, multicenter, case-control study. Mod Rheumatol **32**: 24-31, 2022.
20. Fonkem E, Dayawansa S, Stroberg E, et al. Neurological presentations of intravascular lymphoma (IVL): meta-analysis of 654 patients. BMC Neurol **16**: 9, 2016.
21. Abe Y, Narita K, Kobayashi H, et al. Clinical value of abnormal findings on brain magnetic resonance imaging in patients with intravascular large B-cell lymphoma. Ann Hematol **97**: 2345-2352, 2018.
22. Willemze R, Kruyswijk MR, De Bruin CD, Meijer CJ, Van Berkel W. Angiotropic (intravascular) large cell lymphoma of the skin previously classified as malignant angioendotheliomatosis. Br J Dermatol **116**: 393-399, 1987.
23. Kikuchi J, Kaneko Y, Kasahara H, et al. Methotrexate-associated intravascular large B-cell lymphoma in a patient with rheumatoid arthritis. Intern Med **55**: 1661-1665, 2016.
24. Kida T, Kohno M, Chinen Y, et al. Intravascular lymphoma in a rheumatoid arthritis patient following short-term methotrexate treatment. Rheumatology (Oxford) **56**: 318-320, 2017.
25. Hagihara M, Mese T, Ohara S, Hua J, Ide S, Inoue M. Methotrexate-associated intravascular large B-cell lymphoma in a patient with rheumatoid arthritis: a very rare case. Intern Med **57**: 3001-3005, 2018.
26. Iwami E, Ito F, Sasahara K, et al. Pulmonary intravascular large B-cell lymphoma in a patient administered methotrexate for rheumatoid arthritis. Intern Med **59**: 429-433, 2020.
27. Tabuchi T, Inoue H, Obama K. Development of intravascular large B-cell lymphoma during methotrexate treatment for rheumatoid arthritis. Intern Med **61**: 87-90, 2022.
28. Bogomolski-Yahalom V, Lossos IS, Okun E, Sherman Y, Lossos A, Polliack A. Intravascular lymphomatosis - an indolent or aggressive entity? Leuk Lymphoma **29**: 585-593, 1998.
29. Komeno Y, Akiyama M, Okochi Y, et al. Hemophagocytic syndrome-associated intravascular large B-cell lymphoma in a rheumatoid arthritis patient. Case Rep Hematol **2019**: 8947616, 2019.
30. Chakravarty K, Goyal M, Scott DG, McCann BG. Malignant 'angioendotheliomatosis'- (intravascular lymphomatosis) an unusual cutaneous lymphoma in rheumatoid arthritis. Br J Rheumatol **32**: 932-934, 1993.
31. Winegarner A, Hashida N, Koh S, Nishida K. Hemorrhagic hypopyon as presenting feature of intravascular lymphoma, a case report. BMC Ophthalmol **17**: 195, 2017.
32. Wöhrer S, Troch M, Zwerina J, et al. Influence of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone on serologic parameters and clinical course in lymphoma patients with autoimmune diseases. Ann Oncol **18**: 647-651, 2007.
33. Wang KC, Liao HT, Chen WS, et al. Real-world effectiveness and safety of rituximab in the treatment of rheumatoid arthritis: a single-center experience in Taiwan. Int. J. Rheum. Dis **22**: 860-868, 2019.
34. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med **350**: 2572-2581, 2004.
35. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Ar-

thritis Rheum **54**: 1390-1400, 2006.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).

© 2025 The Japanese Society of Internal Medicine