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【 CASE REPORT 】

Refractory Primary Vitreoretinal Lymphoma Involving the Spinal Cord with a Temporary Complete Response to Tirabrutinib

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Abstract:
Many patients with primary vitreoretinal lymphoma (PVRL) exhibit central nervous system (CNS) involvement either at the diagnosis or during follow-up. The prognosis in the patients of PVRL with relapsed or refractory CNS remains extremely poor. We herein report a patient with refractory PVRL who had recurrence in the spinal cord despite receiving high-dose methotrexate-based chemotherapy and whole-brain radiotherapy. The patient surprisingly responded to tirabrutinib temporarily. We believe that this case suggests the utility of this new target therapy.

Key words: primary vitreoretinal lymphoma, tirabrutinib, spinal cord

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Introduction

Primary vitreoretinal lymphoma (PVRL) is a very rare and classified as a subtype of primary central nervous system lymphoma (PCNSL) (1). PVRL usually presents as diffuse large B-cell lymphoma (DLBCL) with progressive optic nerve and central nervous system (CNS) involvement. The optimal treatment strategy for PVRL remains unknown, and patients with PVRL commonly receive induction treatment with high-dose methotrexate (HD-MTX)-based chemotherapy and whole-brain radiotherapy (WBRT) according to PCNSL (2). However, approximately half of patients with PCNSL treated with conventional HD-MTX-based combination chemotherapy are still at risk of refractory or relapse (3). There is no standard therapy for relapsed or refractory PCNSL at present, and the prognosis in these patients remains extremely poor.

A recent multicenter, open-label, uncontrolled phase I/II study conducted in Japan evaluated the second-generation oral Bruton's tyrosine kinase (BTK) inhibitor tirabrutinib for relapsed/refractory PCNSL (4). More than half of the patients with PCNSL, including those with PVRL, responded to tirabrutinib in the salvage setting. However, the overall complete response (CR) rate was <10%, and the efficacy of tirabrutinib against PVRL remains unknown.

We herein report a patient with primary refractory PVRL who had recurrence in the intramedullary spinal cord and presented with temporary CR to tirabrutinib.

Case Report

A 72-year-old woman had had a history of osteoarthritis and lumbar spondylolisthesis since 45 years old. She had become aware of right visual disturbance more than one year ago and was referred to our hospital for right posterior uveitis of unknown origin. A fundus examination revealed vitritis and a wide yellow subretinal lesion in the right eye. Thus, a vitreous biopsy with cytology, cytokine analysis, and flow cytometry (FCM) were performed.

A vitreous biopsy with cytology revealed large, atypical lymphocytes with clear nucleolus, and multiparameter FCM of vitreous aspirations showed the characteristic phenotype of B-cell lymphoma: κ-chain (+), λ-chain (-), CD19 (+), CD

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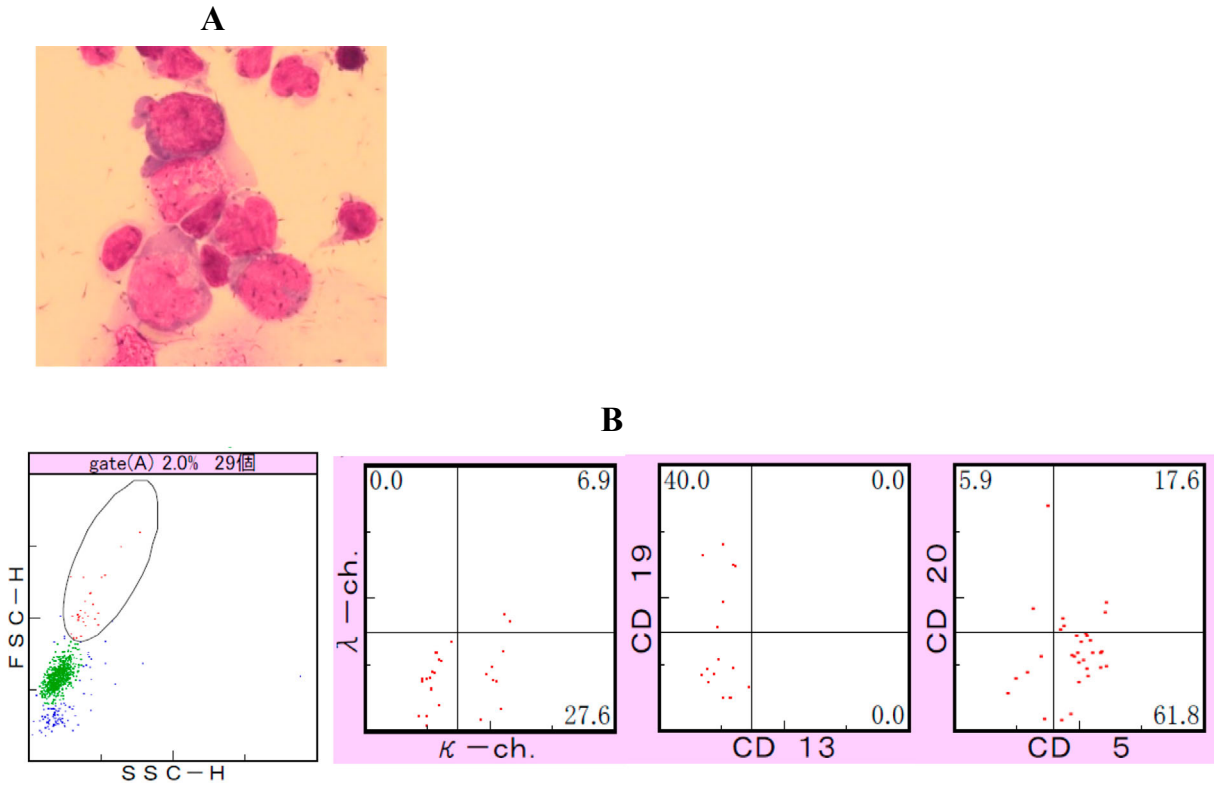

Figure 1. **(A) Cytological examinations of vitreous aspiration revealed large, atypical lymphocytes with clear nucleolus (Giemsa staining: ×600). (B) Multiparameter flow cytometry of vitreous aspiration at the diagnosis shows the characteristic phenotypic profile of κ-chain (+), λ-chain (-), CD19 (+), CD20 (+), and CD5 dim. These findings indicate B-cell lymphoma.**

20 (+), and CD5 dim (Fig. 1). A cytokine analysis of the vitreous humor revealed that interleukin (IL)-6 and IL-10 levels were significantly elevated (IL-6, 484 pg/mL; IL-10, 1,060 μg/mL; and IL-10/IL-6 ratio, 2.19). Brain magnetic resonance imaging (MRI) and a cerebrospinal fluid (CSF) analysis were performed to determine the presence of brain involvement, and there were no abnormal findings. Cytology and FCM were performed for a CSF specimen. Based on the findings of whole-body fluorodeoxyglucose positron emission tomography-computed tomography and bone marrow examinations, the presence of systemic lymphoma was excluded. In addition, she had no abnormal physical symptoms, such as a fever, as is observed with intravascular large B-cell lymphoma. We therefore ultimately diagnosed this patient with PVRL.

Intravitreal methotrexate (MTX) was injected into the affected eye once weekly for 5 weeks. Concurrently, systemic R-MPV (rituximab, MTX, procarbazine, and vincristine) was administered and repeated every four weeks for five cycles. The disappearance of abnormal lymphoid cells was confirmed based on vitreous cytological examination findings, and IL-10 levels returned to the normal range. In addition, the fundus findings were significantly improved (Fig. 2). The patient achieved CR after R-MPV and thereafter received reduced-dose WBRT (23.4 Gy in 1.8-Gy fractions ×13) 3-5 weeks after completing chemotherapy. After radiotherapy, the patient received high-dose cytarabine as consolidation therapy in the first cycle and was temporarily discharged from the hospital.

However, after one week, she required immediate rehospitalization because of subacute bladder, bowel dysfunction, and gait disturbance. Neurological findings revealed lower limb muscle weakness, positive Babinski reflex, and loss of abdominal reflex. Findings of the remaining general and systemic examinations were unremarkable. Spinal cord MRI revealed a gadolinium-enhanced intramedullary tumor that extended longitudinally from thoracic (Th)3 to Th5 (Fig. 3A). CSF cytology and FCM failed to show any malignant cells or immunophenotypic evidence of lymphoma. The patient underwent an intramedullary tumor biopsy; a histological examination of the tumor revealed diffuse proliferation of large atypical centroblast-like cells that were positive for CD20 and CD5 dim and negative for CD3 (Fig. 4). Based on these findings, the patient was diagnosed with intramedullary spinal cord recurrence of PVRL.

Subsequent MRI of the other CNS regions and a fundus examination showed no abnormalities. Two additional cycles of high-dose cytarabine plus rituximab were administered; however, the intramedullary tumor expanded, and paraplegia progressed (Fig. 3B). At this point, her performance status was 4; however, she strongly hoped to be discharged even after several weeks. Therefore, the oral drug tirabrutinib was

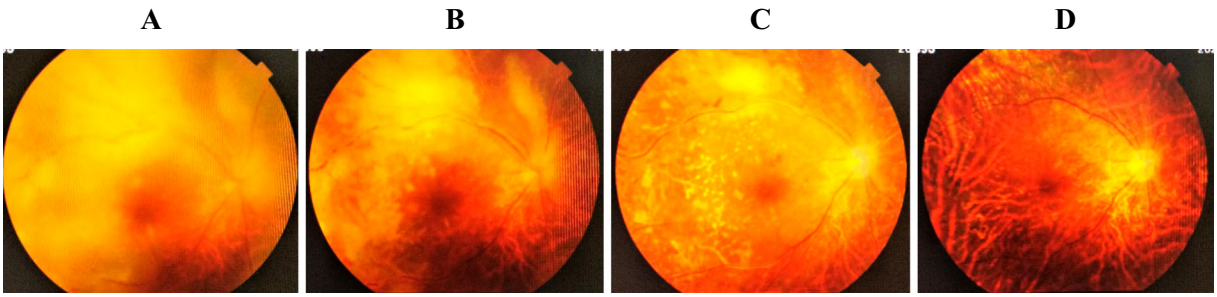

Figure 2. **Fundus photographs showing a subretinal yellowish infiltrate and overlying haziness caused by lymphoma at the diagnosis (A). Photograph after treatment (fundus findings are quite clear), (B) photograph after the first intravitreal methotrexate injection, (C) photograph after all courses of intravenous HD-MT combination chemotherapy and intravitreal methotrexate injection, and (D) photograph after whole-brain radiotherapy.**

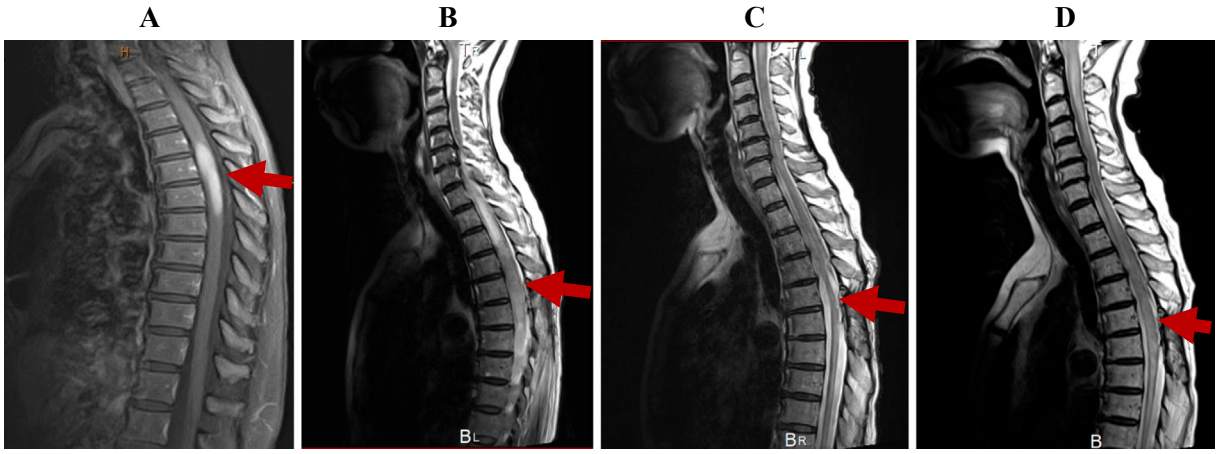

Figure 3. **Spinal cord MRI showing a gadolinium-enhanced intramedullary tumor (A). The intramedullary tumor expanded despite being treated with two cycles of high-dose cytarabine plus rituximab (B). MRI taken two weeks after initiating tirabrutinib shows complete response (C). However, two months after initiating tirabrutinib, MRI shows re-growth of the intramedullary tumor (D).**

selected as salvage treatment, after obtaining consent from the patient and her family.

Surprisingly, after two weeks, MRI showed total tumor removal and complete disappearance of the peritumoral signal abnormality (Fig. 3C). The patient's neurological deficits subsequently improved, and she was able to move from the bed to the wheelchair. She was discharged home to spend time with her family while continuing tirabrutinib treatment. Two months after initiating tirabrutinib, lower limb muscle weakness appeared, and MRI showed re-growth of the intramedullary tumor (Fig. 3D). After two weeks, dysarthria and dysphagia appeared, and she required immediate hospitalization because of aspiration pneumonia. The patient's neurological deficits subsequently worsened, and her level of consciousness declined. She developed mandibular breathing and died three months after initiating tirabrutinib.

Informed consent was obtained from the patient's family for the publication of this case report and any accompanying images. This case report was approved by the hospital's institutional review board.

Discussion

In our case, tirabrutinib was effective, although temporarily, for PVRL refractory to intensive multidisciplinary treatment.

In a previous report, the combined treatment protocols of intravitreal MTX injections, MTX-based systemic induction chemotherapy and consolidation high-dose cytarabine, and reduced dose of WBRT for PVRL showed potential utility for reducing the CNS relapse rate (5). Our patient received combined R-MPV and intravitreal MTX injection with WBRT; however, unfortunately, PVRL relapsed in the intramedullary spinal cord, despite the absence of intraocular relapse. Intravitreal MTX injections and WBRT as local therapy for PCNSL, including PVRL, were temporarily effective for intraocular and intracranial tumor suppression. However, our patient's lymphoma cells, which are resistant to systemic and local MTX therapy and radiotherapy, proliferated into the spinal cord to escape such intensive therapies.

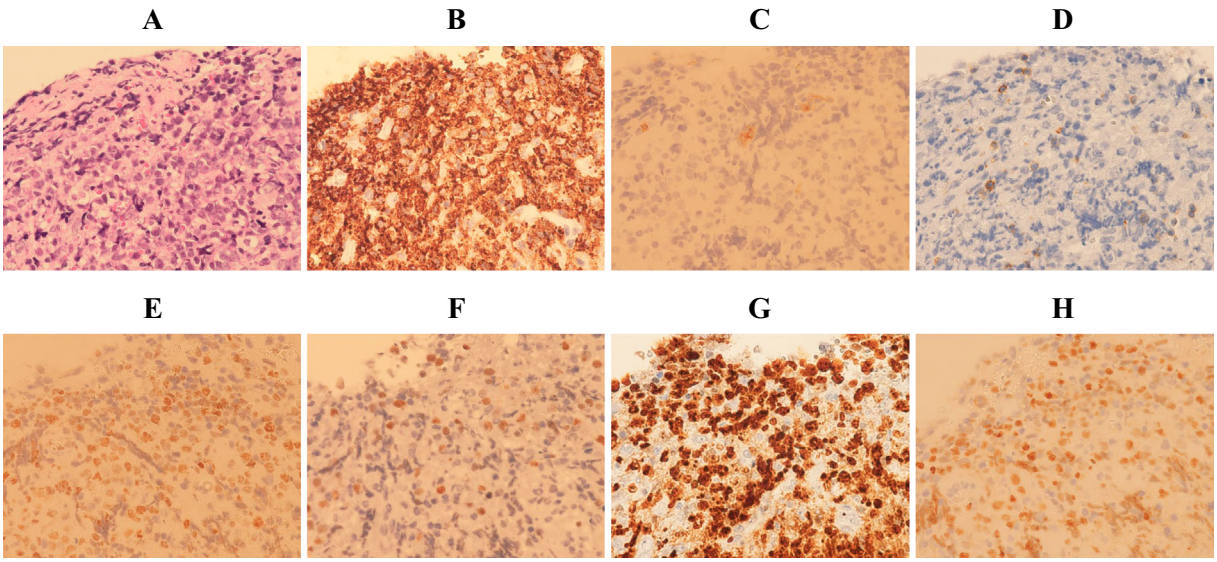

Figure 4. Immunohistochemistry of relapsed PVRL of the intramedullary tumor. Diffuse proliferation of large, atypical lymphocytes (A, Hematoxylin and Eosin staining, ×600). Tumor cells are CD20-positive (B, ×600), CD10-negative (C, ×600), weakly CD5-positive (D, ×600), BCL6-positive (E, ×600), and weakly MUM1-positive (F, ×600). Ki-67 staining shows a proliferation index of approximately 80% (G, ×600). MYC staining shows approximately 30% expression (H, ×600). PVRL: primary vitreoretinal lymphoma

Approximately 65-90% of patients with PVRL eventually progress to PCNSL, an aggressive lymphoma that confers a high mortality rate (6). Furthermore, a Japanese multicenter retrospective study of patients with PVRL revealed that 132 of 217 patients (60.8%) manifested both ocular and CNS lesions (7). A pathologic analysis revealed that most (95%) PCNSLs were DLBCL. In their pioneering study, Alizadeh et al. used gene expression profiling to identify three DLBCL molecular subtypes: namely activated B-like DLBCL (ABC), germinal center B-cell (GCB), and primary mediastinal DLBCL (8). In that report, the ABC immunoprofile was associated with significantly poorer outcomes than the GCB immunoprofile. Based on this stratification according to molecular signatures, PCNSL was subsequently classified as ABC DLBCL, and >80% of PVRL cases belong to this subtype (9). The poor outcomes may reflect an exceptionally aggressive biological behavior of tumor cells with its ABC immunoprofile. Our patient was subclassified according to the expression of GCB and ABC markers using the methods published by Hans et al. (10). Using a decision tree, the Hans classification distinguishes two subgroups based on the following three immunohistochemical staining markers: CD10, BCL-6, and MUM1. The present patient was assigned to the ABC group based on the CD10-BCL-6+ MUM1+immunophenotype. However, the classification of DLBCL based on gene expression profiling and immunohistochemical findings was developed almost two decades ago. Therefore, the development of new classifications based on data from genetic markers is required.

There are challenges associated with making a diagnosis based on the genetic profile of PVRL, because of the low volumes of samples available in the form of vitreous aspirate/subretinal aspirate. Furthermore, it is difficult to elucidate the molecular pathogenesis of PVRL. To address these unmet needs, several emerging molecular techniques, including high-resolution single-cell-based analyses and gene expression profiling analyses, have been developed. These techniques can identify actionable genomic alterations from small-volume, intraocular liquid biopsies and determine the biological characteristics of PVRL (11, 12). *MYD88* mutations, especially L265P, are very frequent in PVRL, and their detection allows a definitive diagnosis of lymphoma to be made, even with poor-quality samples (13). In addition, *CD79B* mutations, which affect the B-cell receptor (BCR) of antigen signaling activation similar to *MYD88*, may serve as prognostic markers for CNS progression (12). Driver genes of PVRL, such as *MYD88* and *CD79B*, can also be therapeutic targets.

BTK inhibitors target BCR signaling and are particularly active in lymphomas, with mutations altering the BCR subunits *CD79B* and *MYD88*. Tirabrutinib is a second-generation, potent, highly selective, irreversible oral BTK inhibitor (14). The pivotal clinical trial for tirabrutinib approval in Japan for relapsed/refractory PCNSL revealed that the overall response rate was 64% and that all patients with concurrent intraocular lymphoma (3/3 patients) achieved a partial response (4). However, the overall CR rate was only 9.1%. Furthermore, PVRL relapsed in the spinal cord, as in the present case, and temporarily achieved CR via tirabrutinib treatment. Since tirabrutinib was effective, we predicted that BTK was constantly activated in this case. Unfortunately, we were unable to perform gene mutation analyses

of *MYD88* and *CD79B*, so the relationship between mutational status and responses to BTK inhibitors involving tirabrutinib remains unknown.

A recent study (15) focused on IL-10, as it is well known to activate signal transducer and activator of transcription (STAT) 3 *in vitro* in DLBCL cases. Furthermore, high serum levels of IL-10 are strongly correlated with a poor survival (16). In that report, the BTK inhibitor ibrutinib effectively blocked tumor cell-intrinsic IL-10 expression and tumor growth *in vivo*. Patients with DLBCL cells with a high IL-10 expression, such as those with PVRL, may show a particularly strong response to BTK inhibitor. In the future, we hope to clarify the genetic abnormalities and cytokine expression associated with patients with PCNSL, including those with PVRL, in order to predict a response to tirabrutinib.

In conclusion, we report the first case in which PVRL recurred only in the spinal cord. Although there is no established treatment for relapsed/refractory PVRL, the new therapeutic agent tirabrutinib seems to be effective, albeit temporarily, considering the molecular pathogenesis of PVRL. Successful treatment with tirabrutinib made it possible for our patient to spend the end of life at home with her family, which was the greatest benefit in this case.

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

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