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【 CASE REPORT 】

Bing-Neel Syndrome Successfully Treated with Tirabrutinib

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Abstract:

Bing-Neel syndrome (BNS) is a rare central nervous system manifestation of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM). We herein report a 62-year-old man with LPL/WM after multiple chemotherapies. He had weakness of lower extremities and elevated serum IgM levels. A bone marrow examination showed lymphoplasmacytic cells infiltration. Contrast-enhanced magnetic resonance imaging suggested enhancing lesions in the cauda equina roots. He was diagnosed with BNS and started on treatment with tirabrutinib 480 mg daily. Within three months, he showed clinical and radiologic improvement. Tirabrutinib may have utility as an effective treatment for BNS.

Key words: lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, Bing-Neel syndrome, tirabrutinib, ibrutinib

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Introduction

Lymphoplasmacytic lymphoma (LPL) is a rare mature B-cell lymphoma associated with Waldenström macroglobulinemia (WM), defined as primarily bone marrow involvement and the presence of an IgM monoclonal paraprotein (1). While most neurologic complications of LPL/WM are peripheral neuropathies secondary to IgM-related immunological activity, LPL/WM affecting the central nervous system (CNS), mainly derived from direct CNS infiltration of malignant lymphoplasmacytic cells (LPCs), is recognized as Bing-Neel syndrome (BNS) (2). In BNS, direct LPC infiltration of the CSF is usually detected. However, a wide variety of pathologies are suggested in BNS, some of which are caused by humoral factors, such as IgM deposition in the CNS without LPCs in the CSF (3).

For the treatment for BNS, chemotherapy regimens used in the treatment of primary CNS lymphoma (PCNSL) are commonly used. These treatments include high-dose methotrexate and high-dose cytarabine for several cycles (2). Recently, the efficacy of ibrutinib, an irreversible Bruton's tyrosine kinase (BTK) inhibitor, was reported in a study of LPL/WM (4), but ibrutinib is not approved for the treatment of LPL/WM in Japan as of January 2022.

Tirabrutinib, a selective second-generation BTK inhibitor (5), has been approved for the treatment of LPL/WM and PCNSL, and its efficacy and safety were revealed in previous studies (6, 7). However, there has only been one reported case in which tirabrutinib was used for the treatment of BNS (8).

We herein report a patient who developed BNS secondary to LPL/WM relapse and achieved an excellent response to tirabrutinib.

Case Report

A 51-year-old man presented with anemia. His serum IgM was elevated at 8,364 mg/dL, and a bone marrow examination revealed diffuse infiltration of LPCs. Flow cytometry identified a population of plasma cells (40% of nucleated cells) with the following immunophenotypes: CD10-, CD19+, CD20+, CD38+, and an increased kappa/lambda light chain ratio. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET-CT) demonstrated mild FDG accumulation in the systemic bones and bilateral mandibular, supraclavicular, axillary, paraaortic, and inguinal lymphoid nodules.

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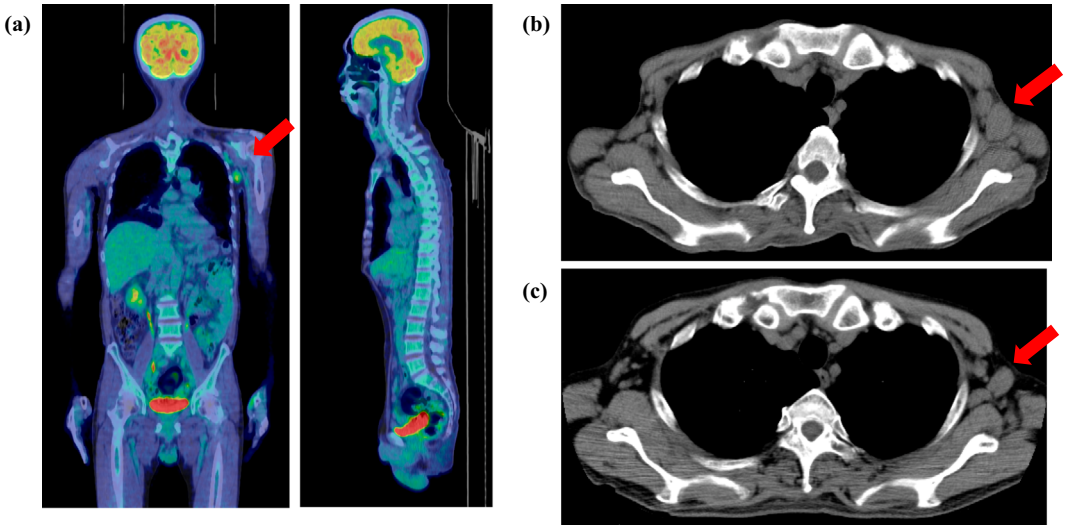

Figure 1. **^{18}F-FDG PET-CT and plane CT obtained before and after the initiation of tirabrutinib. (a) PET-CT showing mild FDG accumulation in the left axilla (arrow) but no accumulation in CNS six months before tirabrutinib initiation. (b) Plane CT findings showing enlarged left axillary lymph nodes (arrow) on day -9. (c) Plane CT findings showing diminished left axillary lymphadenopathy (arrow) on day 158.**

The patient was diagnosed with LPL/WM and received rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine, and prednisone (R-CHOP) chemotherapy for six courses, achieving complete remission (CR) according to PET-CT. However, the serum level of IgM re-increased at 56 years old, and re-enlargement and mild accumulation of FDG in the right cervical, bilateral axillary, and paraaortic lymphoid nodules was detected. Rituximab and bendamustine (R-Benda) chemotherapy was initiated at 57 years old, and CR was confirmed by PET-CT after six courses of R-Benda. A bone marrow examination at the same time revealed no LPC infiltration.

CR was successively confirmed on subsequent CT. However, PET-CT at 62 years old showed mild FDG accumulations in the left axilla with no accumulation in the CNS (Fig. 1a). The IgM level had increased, and anemia had worsened gradually over the past half a year. During the same period, numbness and weakness of the lower extremities appeared and gradually became exacerbated. Plane CT also showed enlarged left axillary lymph nodes (Fig. 1b). The patient was admitted to our department under suspicion of a relapse of LPL/WM and CNS invasion of LPCs.

At the time of admission, the patient was anemic, with a hemoglobin level of 11.7 g/dL, white blood cell count of 9.8 $\times 10^9$/L, and platelet count of 79.6$\times 10^9$/L. His IgM level was elevated at 2,056 mg/dL, soluble interleukin 2 receptor (sIL-2R) 7,527 U/mL, C-reactive protein (CRP) 7.21 mg/dL, and beta-2 microglobulin 2.7 mg/dL (Table). Serum protein electrophoresis and immunofixation electrophoresis (IFE) revealed IgM kappa monoclonal protein (M-protein) of 1.1 g/dL, kappa light chain of 54.3 mg/L, lambda light chain of 10.3 mg/L, and kappa lambda light chain ratio of 5.22. A bone marrow examination showed diffuse infiltration of LPCs (Fig. 2). The predominant B-cell phenotype on flow cytometry was CD10-, CD19+, CD20+, and CD38+ with an increased kappa/lambda light chain ratio. Molecular testing using reverse transcription quantitative polymerase chain reaction (RT-qPCR) of the bone marrow detected an *MYD88*^{L265P} mutation.

Contrast-enhanced magnetic resonance imaging (MRI) for the whole spine revealed multiple thickened, enhanced lesions in the spinal leptomeninges and cauda equina roots (Fig. 3a, b). Contrast-enhanced MRI findings for the brain were normal, and an eye examination revealed no evidence of ocular involvement. A cerebrospinal fluid (CSF) analysis showed that the protein levels were elevated at 88 mg/dL and 3 lymphocytes/mm^3, with no evidence of malignant lymphocytes on cytology or a flow cytometry analysis. An *MYD88*^{L265P} mutation was not detected in the CSF by droplet digital PCR. However, based on the obvious systemic relapse of LPL/WM, neurological symptoms consistent with direct tumor infiltration, and the MRI findings, we clinically diagnosed the patient with BNS accompanied by the second relapse of LPL/WM at 62 years old, 11 years after the first diagnosis.

Once the diagnosis was established, we selected tirabrutinib 480 mg daily for the treatment of BNS, due to its proven efficacy against LPL/WM (6) and PCNSL (7) and the lack of pharmaceutical approval to administer ibrutinib for LPL/WM in Japan. Within a week of starting treatment with tirabrutinib, the patient noticed clinical improvement with the resolution of his mild fever and recovery of numbness and weakness of the lower extremities. Laboratory data, including IgM, sIL-2, and CRP levels, improved within a month (Fig. 4). On follow-up after 3 months of tirabrutinib therapy, hemoglobin recovered to 14.9 g/dL, and IgM, sIL-2 R, and CRP improved to 211 mg/dL, 1,243 U/mL, and 0.08 mg/dL, respectively (Table). Serum M-protein was detected

Table. Laboratory Data Comparison by before and 3 Months after the Initiation of Tirabrutinib.

	Day -11	Day 88	
WBC	9.8 (H)	8.4	/μL
Hb	11.7 (L)	14.9	g/dL
Plt	79.6 (H)	35.9 (H)	$\times 10^3$/μL
TP	6.8	6.3 (L)	g/dL
Alb	2.7 (L)	4.4	g/dL
A/G	0.66 (L)	2.32 (H)	
IgA	35 (L)	24 (L)	mg/dL
IgG	456 (L)	459 (L)	mg/dL
IgM	2,056 (H)	211 (H)	mg/dL
CRP	7.21 (H)	0.08	mg/dL
LD (IFCC)	174	124	IU/L
AST (GOT)	11 (L)	13	IU/L
ALT (GPT)	20	7 (L)	IU/L
T-Bil	0.8	1.1	mg/dL
Ca	8.7 (L)	9.5	mg/dL
IP	2.8	3.8	mg/dL
BUN	8.4	13.8	mg/dL
Cre	0.38 (L)	0.55 (L)	mg/dL
eGFR	171	171	mL/min/1.73m^2
Na	128 (L)	142.0	mmol/L
K	4.7	5.0 (H)	mmol/L
Cl	94 (L)	104.0	mmol/L
APTT	28.5	25.0	s
PT	85.8	117.2	%
sIL-2R	7,527 (H)	1,243 (H)	U/mL
beta-2 microglobulin	2.7 (H)	2.5 (H)	mg/dL
Free light chain assay			
κ	54.3 (H)	20.6 (H)	mg/L
λ	10.4	7.6	mg/L
κ/λ ratio	5.22 (H)	2.71 (H)	
Electrophoresis of protein			
Alb	43.4	65.7	%
α1-globulin	6.1	3.8	%
α2-globulin	15.6	9.5	%
β-globulin	10.3	11.6	%
γ-globulin	24.6	9.4	%
M protein (IgM-κ)	16	Detected only by IFE	%
	1.1		mg/dL

only by IFE. Contrast-enhanced MRI revealed significant interval resolution of previously enhancing lesions (Fig. 3c, d). Plane CT five months later revealed diminished left axillary lymphadenopathies (Fig. 1c), which indicated the efficacy of tirabrutinib against systemic lesions in addition to CNS involvement. The patient continued taking tirabrutinib 480 mg daily without any adverse events.

Discussion

In the present case, BNS secondary to refractory LPL/WM was successfully treated with a single agent in tirabrutinib, a second-generation BTK inhibitor (5). BNS is a rare CNS manifestation of LPL/WM and can present at any course of the disease. The median time from the WM to BNS diagnosis is 3 years, and 70% of WM patients receive systemic therapy for WM before the diagnosis of BNS (9). The clinical manifestations of BNS are diverse and nonspecific, accompanying focal complaints, such as gait disturbances, visual and auditory defects, or global manifestations, such as seizures or reduced consciousness (10). The diagnosis of BNS is generally suggested by the presence of radiological abnormalities and supported by the presence of LPCs in a biopsy of the lesion or a CSF analysis via cytology, flow cytometry, or molecular testing for *MYD88*^{L265P} mutations (2, 11, 12).

Notably, BNS also has a non-cellular form, in which other mechanisms aside from direct LPC infiltration, such as local deposition of IgM, induce neurologic symptoms without pleocytosis in the CSF (3). This current case with obvious radiological CNS abnormalities and non-cellular CSF might have been one of BNS involving non-cellular, humoral factors. The most common MRI abnormality in BNS is a leptomeningeal enhancement, seen in about 80% of BNS patients with MRI abnormalities, and 6 out of 7 patients with medullary contrast-enhanced MRI had cauda equina enhancement in a previous study (10). These findings were also observed in the present case, and these findings may have supported the diagnosis of BNS.

Intrathecal chemotherapy with or without intravenous high-dose methotrexate or cytarabine and systemic chemo-

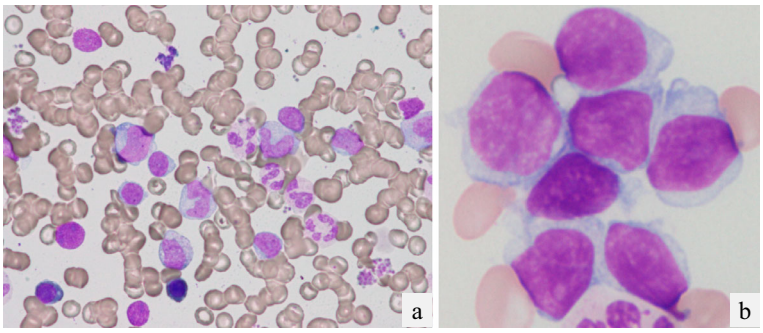

Figure 2. Bone marrow aspirate at the admission. Small lymphocytes, plasmacytoid lymphocytes, and plasma cells are shown (a). Plasmacytoid lymphocytes were characterized by relatively coarse chromatin and indented nuclei (b).

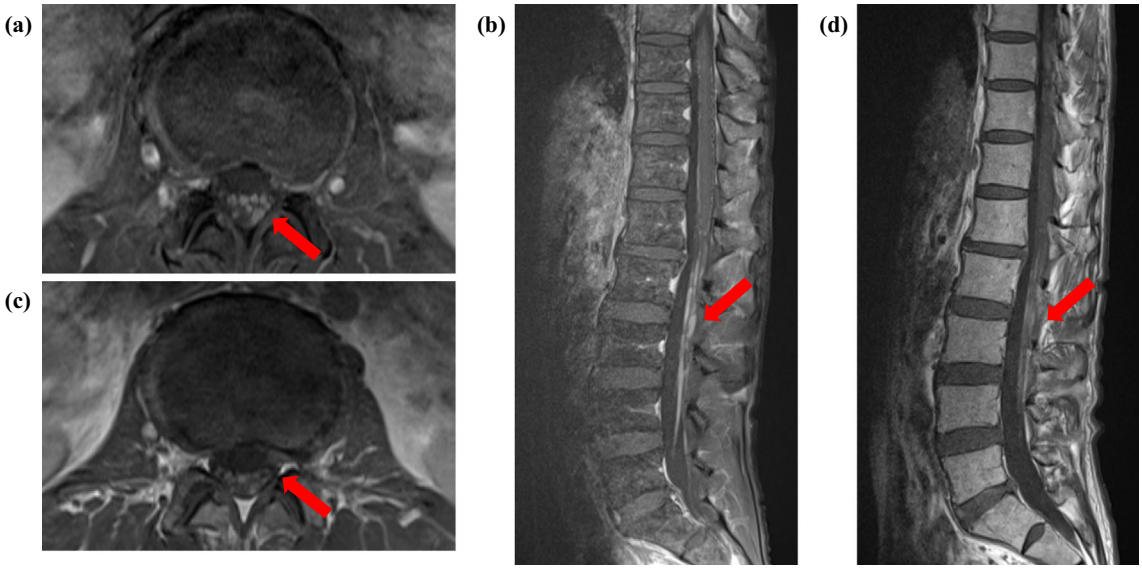

Figure 3. **Contrast-enhanced MRI of the patient's cauda equina roots (T1 post-contrast) obtained before and after the initiation of tirabrutinib. (a) Axial-enhanced image of L2/L3 Level on day -10. (b) Sagittal-enhanced image on day -10. Arrows show lesions. (c) Axial image at the L2/L3 Level showing resolution of the enhancing lesion (arrow) on day 79. (d) Sagittal image showing resolution of the enhancing lesion (arrow) on day 79.**

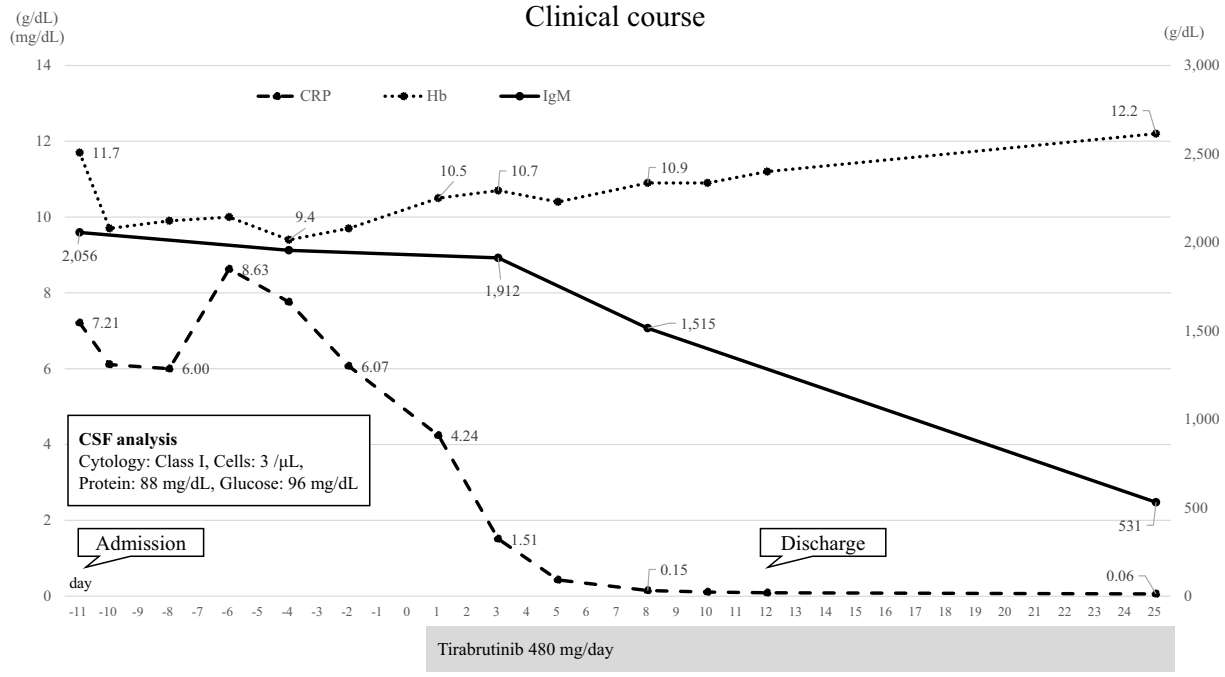

Figure 4. **Changes in the laboratory data around the initiation of tirabrutinib.**

immunotherapies, including fludarabine, cyclophosphamide, rituximab, and bendamustine, has historically been used to treat BNS (12). However, recent studies have shown that, in LPL/WM, a mutation in *MYD88*^{L265P} serves to support the survival of lymphoplasmacytic cells via BTK activation (13, 14). Ibrutinib, an irreversible BTK inhibitor, proved effective against LPL/WM in a prospective, multicenter study (3). Even in the treatment of BNS, a small-scale multicenter study revealed that 85% of BNS patients treated with ibrutinib monotherapy showed improvement or resolution of BNS symptoms as the best response, and the estimated 2-year survival rate from ibrutinib initiation was 81% (15). Ibrutinib appeared as a new treatment option for LPL/WM and BNS.

However, some adverse events caused by off-target effects of ibrutinib, such as atrial fibrillation, bleeding events, and hypertension, were reported as reasons for treatment discontinuation (4). Tirabrutinib hydrochloride (ONO/GS-4059),

herein referred to as tirabrutinib, is a second-generation BTK inhibitor designed to have fewer off-target effects than ibrutinib, with the goal of improving efficacy and reducing toxicity (5). Tirabrutinib was recently approved for the treatment of LPL/WM (6) and PCNSL (7) in Japan. A multicenter, phase II study of tirabrutinib in patients with treatment-naïve or with relapsed/refractory WM revealed a high overall response rate of 96.3% and 100%, respectively, with fewer adverse events than with ibrutinib (6). In the treatment of PCNSL, the CSF/plasma concentration ratio with tirabrutinib was approximately 13-18%, which was higher than the ratio with ibrutinib (1-7%) (7). Fewer adverse events and a higher CSF penetration ratio support the efficacy of tirabrutinib over ibrutinib in LPL/WM with CNS involvement.

This case report is extremely valuable in that tirabrutinib was shown to be effective against BNS. Within three months after tirabrutinib initiation, the patient's neurological symptoms and radiological findings had improved dramatically, supporting the rapid and strong efficacy of tirabrutinib for BNS. A previous case report also suggested the efficacy of tirabrutinib for relapsed LPL/WM with BNS in the short term of treatment (8).

We suggest tirabrutinib be considered for the treatment of BNS, especially in patients with comorbidities such as atrial fibrillation, bleeding factors, and other conditions that can be expected to worsen with ibrutinib, although no large-scale study on this topic has yet been conducted.

As the follow-up period in our study was limited to three months after tirabrutinib initiation in this single case, a long-term evaluation of the treatment responses and further accumulation of cases are warranted to establish a treatment option with tirabrutinib for BNS.

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

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