Case report

Successful treatment with tirabrutinib for relapsed Bing-Neel syndrome following high-dose methotrexate and craniospinal irradiation

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A 63-year-old man was diagnosed with Waldenström’s macroglobulinemia (WM). Six courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) resulted in complete remission, but WM relapsed three years after R-CHOP. After six courses of BR (bendamustine, rituximab), the serum IgM level and CRP normalized. Four years after BR, the patient presented with muscle weakness, sensory disturbance, and myoclonus of lower limbs. T2-weighted magnetic resonance imaging (MRI) showed areas of signal hyperintensity with contrast enhancement in the right temporal and parietal lobes in brain parenchyma, medulla, bilateral basal ganglia, white matter of occipital lobe, and thoracic spinal cord at the Th2–11 levels. Open brain biopsy revealed diffuse proliferation of small lymphocytes and plasmacytoid lymphocytes on the brain surface and around cerebral blood vessels, resulting in a diagnosis of Bing-Neel syndrome (BNS). Two courses of R-MPV (rituximab, methotrexate, procarbazine, and vincristine) resulted in progressive disease, but the neurological symptoms and MRI findings improved following craniospinal irradiation of 30.6 Gy. Three years after craniospinal irradiation, T2-weighted MRI showed recurrence of BNS with progression of myoclonus of lower limbs and IgM elevation. Tirabrutinib was started for the second recurrence of WM and progression of BNS. Two months after the initiation of treatment with tirabrutinib, the myoclonus of lower limbs disappeared and the MRI findings showed improvement. Serum IgM levels decreased and no adverse events were observed. Tirabrutinib shows promise as a therapeutic option for relapsed BNS.

Keywords: Bing-Neel syndrome; tirabrutinib; relapse; craniospinal irradiation; high-dose methotrexate

INTRODUCTION

Bing-Neel syndrome (BNS) occurs when lymphoplasmacytic lymphoma (LPL)/Waldenström’s macroglobulinemia (WM) cells infiltrate the central nervous system (CNS) and cause neurological deficits, which is an uncommon presentation of WM that is seen during the course of the disease in about 1%.1-3 The survival rate of BNS has been reported as 60% at 3 years after diagnosis,2 and its prognosis is poor compared with non-BNS WM. Treatment of BNS requires agents that can reach the CNS, which include fludarabine, methotrexate, cytarabine, and the novel Bruton’s tyrosine kinase (BTK) inhibitors.4,5 Tirabrutinib is a second-generation BTK inhibitor that has higher BTK selectivity than ibrutinib, and was approved in Japan for the treatment of LPL/WM in August 2020.5,6 Following approval, there have been few case reports of successful treatment of BNS using tirabrutinib,7,8 due to the rarity of the disease. In addition, there have been no reports regarding its efficacy for relapse of BNS as tirabrutinib was administered early after the diagnosis of BNS in cases reported previously. We report a case of BNS that showed response to tirabrutinib following recurrence after craniospinal irradiation.

CASE REPORT

A 63-year-old man presented with anemia and multiple lymphadenopathies. His serum immunoglobulin (Ig)M level was elevated (6606 mg/dl; reference range, 35–220 mg/dl), and serum protein electrophoresis demonstrated an M spike...
in the γ-fraction with M protein of the IgM-κ type according to serum immunoelctrophoresis. Ophthalmologic examination revealed retinal hemorrhages and retinal vessel engorgement associated with hyperviscosity. Pathological examination of a biopsied axillary lymph node showed diffuse proliferation of small, abnormal lymphocytes with plasmacytoid differentiation. Immunohistochemically, abnormal lymphocytes were positive for CD20, IgM, and κ; and negative for CD5, CD10, CD23, and λ (Figure 1). Examination of bone marrow aspirates revealed increases in plasmacytoid lymphocytes (62.9%) with May-Giemsa staining. Flow cytometry of bone marrow showed clusters of lymphocytes that were positive for CD19, CD20, and κ; and negative for CD5, CD10, CD23, and λ, and WM was diagnosed. Plasma exchange was performed twice until the serum IgM protein concentration decreased, and complete remission was achieved after administration of six courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). WM relapsed three years after R-CHOP, with elevation of serum IgM level and C-reactive protein (CRP). The serum IgM level and CRP normalized after 6 courses of BR (bendamustine, rituximab). Four years after BR, the patient presented with muscle weakness, sensory disturbance, and myoclonus of lower limbs. T2-weighted magnetic resonance imaging (MRI) revealed areas of hyperintensity that showed contrast enhancement in the right temporal and parietal lobes in brain parenchyma, medulla, bilateral basal ganglia, white matter of occipital lobe, and thoracic spinal cord at the Th2–11 levels. 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography also showed abnormal FDG accumulation in the medulla and thoracic spinal cord at the Th5–8 levels (Figure 2a). The cerebrospinal fluid (CSF) cell count was 14/μl, all of which were mononuclear cells. Morphologically, the cells were mature lymphocytes, but B-cell phenotype assessment by flow cytometry was not performed. Biochemical and immunological examination of CSF showed an elevated protein level (372 mg/dl), glucose at the lower limit of normal (57 mg/dl), and a slight increase in soluble interleukin (IL)-2 receptor (592 U/ml). No Mycobacterium or Cryptococcus infections were identified, and serum aquaporin 4 antibody was negative. Serum IgM and soluble IL-2 receptor levels were within normal ranges (123 mg/dl and 493 U/ml, respectively). Open brain biopsy of the right temporal lobe revealed diffuse proliferation of small lymphocytes and plasmacytoid lymphocytes on the surface of the brain and around blood vessels. Immunohistochemically, abnormal lymphocytes were positive for CD20, IgM, and κ; and negative for CD10, CD23, and λ (Figure 3). Although identification of immunoglobulin heavy chain (IGH) rearrangement and MYD88 L265P mutation analysis of the specimen of cerebrum were not performed, the patient was diagnosed with BNS based on cerebral infiltration of tumor cells having identical morphology and surface markers to those identified in the lymph node and bone marrow at initial diagnosis of WM. Two courses of R-MPV (rituximab, methotrexate, procarbazine, and vincristine) resulted in progressive disease. Craniospinal irradiation of 30.6 Gy improved the neurological symptoms and MRI findings (Figure 2b). The patient’s neurological symptoms of gait abnormalities and involuntary movements of lower limbs gradually progressed, with anemia, elevation of serum IgM levels, CRP, and soluble IL-2 receptor two years after craniospinal irradiation. Three years after craniospinal irradiation, serum IgM level, CRP, and soluble IL-2 receptor increased to 1032 mg/dl, 18.5 mg/dl, and 2354 U/ml, respectively, and T2-weighted MRI showed recurrence of the areas of hyperintensity that exhibited contrast enhancement in the medulla and bilateral basal ganglia.

Fig. 1. Histological findings of an axillary lymph node (hematoxylin and eosin staining and immunostaining) at diagnosis of lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia. There is diffuse proliferation of small abnormal lymphocytes with plasmacytoid differentiation. Immunohistochemically, abnormal lymphocytes were positive for CD20, IgM, and κ; and negative for CD5, CD10, CD23, and λ.
Fig. 2. Magnetic resonance imaging (MRI) and $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography images.

a) T2-weighted MRI reveals areas of hyperintensity that show contrast enhancement in the medulla, surface of the right temporal lobe, bilateral basal ganglia, parietal cortex, and spinal cord at the Th2–11 levels, suggesting a diagnosis of Bing-Neel syndrome.

$^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography shows abnormal $^{18}$F-fluorodeoxyglucose accumulation in the medulla and spinal cord at the Th5–8 levels.

b) The areas of signal hyperintensity show improvement after craniospinal irradiation.

c) There is progression of the areas of hyperintensity and contrast enhancement in the medulla and bilateral basal ganglia at two years after craniospinal irradiation.

d) Areas of signal hyperintensity appear indistinct at two months of treatment with tirabrutinib.

Relapsed BNS treated with tirabrutinib
Examination of bone marrow aspirates showed a few mature or plasmacytoid lymphocytes (3.6%) with May-Giemsa staining, and the CSF cell count was 3/μl, all of which were mononuclear cells. Morphologically, the cells were mature lymphocytes, and almost all the cells showed nonspecific T-cell phenotype by flow cytometry. Tirabrutinib was started at 480 mg/day for the second recurrence of WM and progression of BNS (Figure 4). Serum IgM levels, CRP, and soluble IL-2 receptor had decreased at one month after initiation. The areas of hyperintensity in the medulla and bilateral basal ganglia on MRI became indistinct (Figure 2d) at two months, with disappearance of the myoclonus of lower limbs due to basal ganglion lesions, and improvement in the Manual Muscle Test (MMT) of lower limbs from MMT 4 to MMT 5. No tirabrutinib-associated adverse events were observed. The patient has continued taking tirabrutinib with a sustained clinical response at the latest follow-up.

**DISCUSSION**

In the present case, relapsed BNS after craniospinal irradiation was successfully treated with tirabrutinib. LPL/WM is an indolent B-cell lymphoma characterized by bone marrow involvement of lymphoplasmacytic lymphocytes with serum M protein of IgM type.9 CNS infiltration in LPL/WM is characteristic of BNS and is reportedly seen in approximately 1% of patients with LPL/WM.10 In the diagnosis of BNS, clonality assessment using IGH rearrangement is recommended in CSF or in a specimen of cerebrum.1,4 In the present case, the diagnosis of BNS was based on tumor cell infiltration of cerebrum with similar morphology and surface markers as tumor cells in the lymph node and bone marrow at initial diagnosis of WM. It is a limitation in the present diagnosis of BNS that assessment of IGH rearrangement was not performed, given that it is a strong diagnostic proof for BNS.

The CNS penetration of drugs is the most important aspect in the treatment of BNS. Chemotherapy based on intrathecal chemotherapy or high-dose methotrexate has been the only treatment option until the recent addition of BTK inhibitors.1,4 In LPL/WM, BTK activation has been found to be associated with activation of Toll-like receptor 4/IL-1 receptor signaling pathway as well as B-cell receptor signaling pathway, resulting in tumor progression.11,12 BTK is considered an ideal molecular target in LPL/WM and efficacy has been shown in several clinical trials.13,14 In addition, BTK inhibitors have been reported to penetrate the CNS;1,5,16 thus, BTK inhibitors may become ideal drugs for treatment of BNS. A multicenter retrospective study of treatment of BNS with ibrutinib, a first-generation BTK inhibitor, showed symptomatic, radiographic, and cytologic responses in 28 patients with untreated or relapsed/refractory BNS.17 The event-free survival rate and overall survival rate at two years was 80% (95% CI, 58%–91%) and 81% (95% CI, 49%–94%), respectively. In contrast, there are several case reports of second-generation BTK inhibitors such as zanubrutinib and tirabrutinib for treatment of BNS.7,8,18 In two previous case reports, tirabrutinib was administered as an initial treatment after the diagnosis of BNS.7,8 The current case is the first report of tirabrutinib for relapse of BNS after R-MPV and craniospinal irradiation, and a rapid response was observed without any adverse events. The current case
was not indicated for high-dose methotrexate therapy as the patient was clinically refractory to R-MPV. In general, whole-brain radiation therapy (WBRT) carries a risk of late-onset neurotoxicity in patients who achieve long-term disease control, which is why we hesitated to use systemic intensive chemotherapies and retreatment of WBRT in the current case. In a phase 2 study of tirabrutinib for relapsed/refractory primary central nervous system lymphoma (PCNSL), all patients received methotrexate and 65.9% received WBRT at enrollment, and there were few patients with the complication of seizure after tirabrutinib. This result suggests that tirabrutinib may be tolerable for patients with relapsed refractory BNS treated with methotrexate or WBRT. In addition, this study showed a high response rate of tirabrutinib for relapsed/refractory PCNSL, and the present data may assist in evaluating its usefulness for CNS lesions in WM. A serious limitation of the current case report should be acknowledged. The observation period after symptomatic and imaging improvements with tirabrutinib was very short, and further long-term observation is therefore necessary for evaluation of sustained response.

BNS is an extremely rare disease with no established treatment strategy. Long-term follow-up will be needed to assess the durability of response and safety with BTK in BNS. Tirabrutinib may be one of the most promising therapeutic options for BNS, as a second- or later-line therapy as well as a first-line therapy.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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