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Case Study

Successful Treatment of Bing-Neel Syndrome Accompanying Waldenström's Macroglobulinemia with R-MPV: A Case Report

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Waldenström's macroglobulinemia (WM) is a neoplasm of lymphoplasmacytic cells that produces monoclonal IgM protein. Although hyperviscosity syndrome is a common feature of WM, central nervous system (CNS) involvement in WM is rare and is known as Bing-Neel syndrome. A 60-year-old woman was referred to our hospital with bed-bound polyneuropathy, edema, splenomegaly, IgM-λ-type monoclonal protein and CD20-positive lymphocyte infiltration in the bone marrow. She was diagnosed with WM accompanying POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) and was treated with rituximab and thalidomide. She achieved partial remission of WM, and thalidomide was continued for POEMS syndrome. She visited our outpatient clinic 6 years later with sudden onset of vertigo and nausea. Magnetic resonance imaging (MRI) revealed a low-density area 4 cm in diameter in her right cerebrum and right mid-brain and she was referred to our hospital. Pathological analysis of brain biopsy samples revealed diffuse large B-cell lymphoma (DLBCL) in the CNS. Nucleic acid sequence analysis of the *VDJ* region using DNA obtained from the original WM tumor cells and brain tissue revealed that the DLBCL cells were derived from the original WM malignant lymphoma cells. She received five cycles of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) therapy and 23.4 Gy of whole-brain irradiation followed by two cycles of high-dose cytarabine, which resolved her neurological symptoms in association with reduction of IgM levels to 367 mg/ dL. MRI and computed tomography of the brain demonstrated complete remission of her CNS lymphoma. 〔*J Clin Exp Hematop 55(2) :* 113-119*, 2015*〕

Keywords: Bing-Neel syndrome, R-MPV, MYD88, Waldenström's macroglobulinemia, POEMS syndrome

INTRODUCTION

Waldenström's macroglobulinemia (WM) is caused by monoclonal proliferation of lymphoplasmacytes. Its clinical manifestations include hyperviscosity syndrome, cytopenia, lymphadenopathy, and splenomegaly. Visual impairment, headaches, peripheral neuropathy symptoms, and other neurological symptoms occur in 25% of WM patients. Most neurological symptoms are caused by hyperviscosity and/ or ischemia,[1] though autoantibodies to nerve antigens may also lead to neurological symptoms.[2] The varied symptoms and lack of specificity mean that a precise diagnosis requires cerebrospinal fluid (CSF) examination, diagnostic imaging and serological tests.[3,4]

Direct invasion of WM cells into the central nervous system (CNS) is rare. However, in 1936, 8 years before the first report of WM, Bing and Neel reported two autopsy cases with CNS symptoms and lymphoplasmacyte infiltration to the CNS, a condition now referred to as Bing-Neel syndrome (BNS).[5] We report a patient in whom a mass lesion was confirmed by brain computed tomography (CT) and magnetic resonance imaging (MRI), but no evidence of malignant cells in the CSF. Craniotomy and biopsy demonstrated transformation of WM to diffuse large B-cell lymphoma (DLBCL) and tumor invasion to the cerebellum. We successfully controlled this disease by combination of rituximab, methotrexate, procarbazine, and vincristine (R-MPV), whole-brain radiation therapy (WBRT) and high-dose cytarabine (Ara-C) therapy.

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CASE REPORT

A 60-year-old woman presented with bed-bound polyneuropathy, edema, splenomegaly, IgM-λ-type monoclonal protein, and infiltration of CD20-positive lymphoplasmacytic cells in the bone marrow in 2008 (Fig. 1). She was diagnosed with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) associated with WM. She was treated with rituximab and thalidomide and her IgM levels decreased and her symptoms were well controlled. Her symptoms recurred in October 2012 and July 2013, but she responded well to retreatment with rituximab and thalidomide maintenance therapy.

Ataxia, nausea, and frequent falling at home developed around June 2014. A brain CT scan revealed a low-attenuation lesion in the cerebellum, and contrast-enhanced MRI showed a 4-cm mass-like lesion extending from the left cerebellum to the pons (Fig. 2). CSF obtained by lumbar puncture showed no malignant cells. A brain tumor biopsy was performed via craniotomy, and histological examination of the biopsy sample revealed infiltration of large atypical lymphocytes accompanied by necrosis. Immunostaining showed positivity for CD20, CD79a, Bcl-2 and MIB-1 in the abnormal cells (Fig. 3), but negativity for CD3, CD5, CD10 and CD138. The patient was therefore diagnosed with DLBCL. Soluble interleukin-2 receptor (221 IU/μL) and lactate dehydrogenase levels were within normal limits. No other primary or metastatic lesions were detected by contrast-enhanced whole-body CT, indicating that the transformed lesion was limited to the CNS. We examined the cerebellum biopsy sample by real-time polymerase chain reaction (PCR) and detected a mutation in myeloid differentiation primary response gene 88 (*MYD88*) L265P in the cerebellum biopsy sample, using OCI-Ly3 (a DLBCL cell line with a homozygous mutation in *MYD88* L265P) as a positive control, and SUDHL4 (a B cell line with no *MYD88* mutation) as a negative control (Fig. 4a). Bone marrow mononuclear cells at onset of WM had the same *MYD88* L265P mutation (Fig. 4b). We also determined that the cerebellum lesion originated from the previous lymphoplasmacyte sample of WM. According to previous reports,[6,7] we amplified part of the variable region (CDR2 and FR-3) and VDJ region (CDR3) of the Ig heavy chain by semi-nested PCR and analyzed its sequence. We then used this sequence to design sequence-specific primers for PCR, using genomic DNA extracted from the cerebellum biopsy specimen and from the bone marrow specimen obtained at the onset of WM. Electrophoresis analysis revealed that the length of these PCR products were identical (Fig. 4c). We sequenced the two PCR products and found that both sequences were almost identical (Fig. 4d). This result strongly suggested that the cerebellum tumor origi-

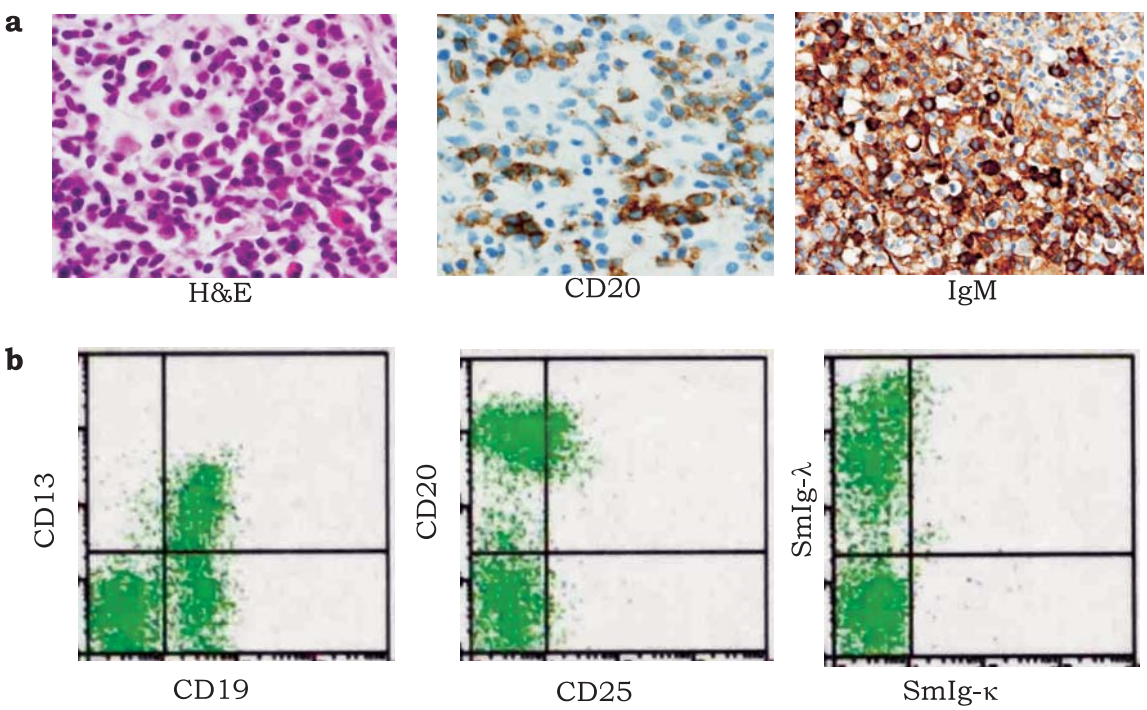

Fig. 1. Histopathology and flow cytometry analysis of bone marrow lesion. (***1a***) Histopathology of bone marrow biopsy sample. Infiltrated atypical lymphocytes were positive for CD20 and IgM in immunohistochemistry. (***1b***) Flow cytometry analysis revealed that CD19- and CD20-positive lymphocytes showed λ light chain restriction. SmIg, surface membrane immunoglobulin

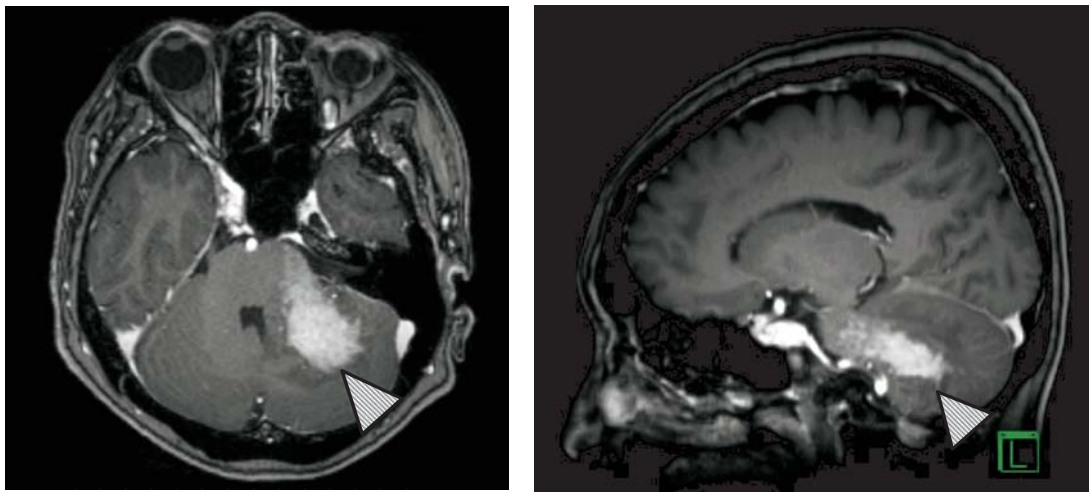

Fig. 2. Brain magnetic resonance imaging (MRI) on admission. Contrast-enhanced MRI showed a 4-cm mass-like lesion extending from the left cerebellum to the pons (*arrowheads*). The distribution of the lesion was consistent with the patient's symptoms and we therefore judged it to be the culprit lesion. Cerebellum biopsy was performed because no malignant cells were detected in the cerebrospinal fluid by lumbar puncture.

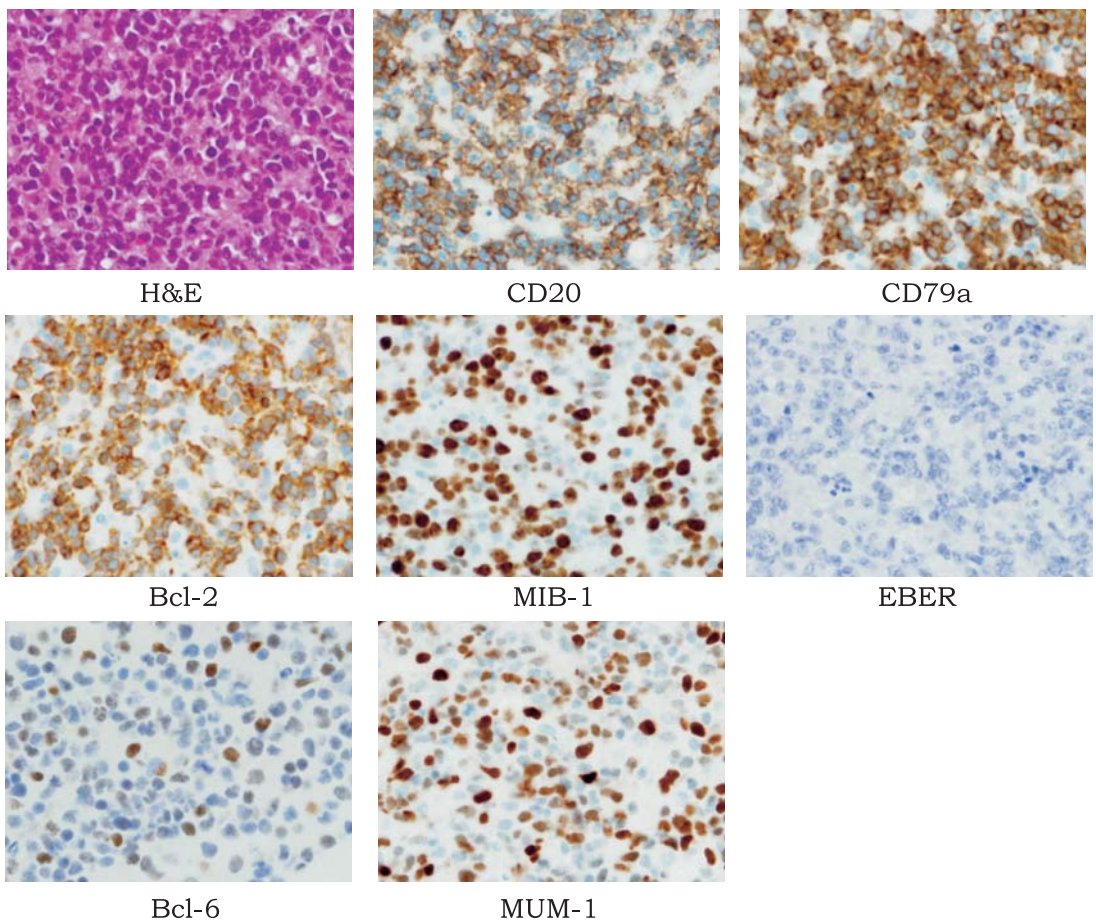

Fig. 3. Histopathology of cerebellum biopsy sample showing infiltration of large atypical lymphocytes accompanied by necrosis. Immunostaining revealed that the abnormal cells were positive for CD20, CD79a, Bcl-2, Bcl-6 (weakly), MUM-1 and MIB-1, and negative for CD3, CD5, CD10 and CD138 (data not shown). EBER, Epstein–Barr virus-encoded small RNA

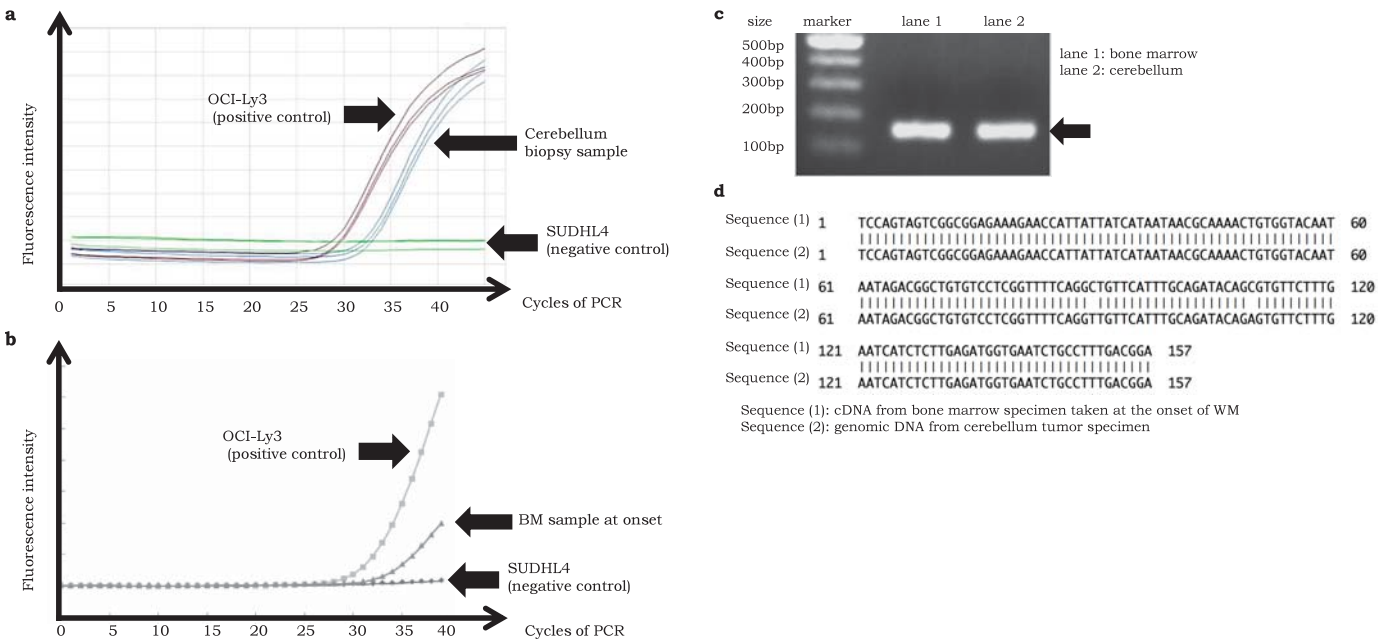

Fig. 4. The cerebellum diffuse large B-cell lymphoma (DLBCL) cells originated from the lymphoplasmacytic cells of Waldenström's macroglobulinemia (WM) at onset. (***4a***) We analyzed *MYD88* L265P by real-time polymerase chain reaction (PCR) using genomic DNA from the cerebellum biopsy specimen, with OCI-Ly3 (DLBCL cell line with homozygous mutation in *MYD88* L265P) as a positive control, and SUDHL4 (B cell line without *MYD88* mutation) as a negative control. Fluorescence intensity was increased in the biopsy specimen and COI-Ly3, but not in SUDHL4. The tests were performed in triplicate. (***4b***) We also identified the *MYD88* L265P mutation in a cDNA sample of bone marrow cells at onset of WM by real-time PCR method. (***4c***) Sequence-specific PCR of immunoglobulin variable region. We amplified the immunoglobulin variable region with cDNA from the bone marrow cells at the onset of WM and genomic DNA from the cerebellum DLBCL cells. Both PCR products were the same size. (***4d***) The DNA sequences of both the immunoglobulin variable region between the bone marrow cells at the onset of WM and the cerebellum DLBCL cells were almost identical.

nated from the same clonal B lymphocytes in the bone marrow at the onset of WM.

The patient's nausea and vomiting disappeared after treatment with glycerol and betamethasone. R-MPV therapy[8] was administered based on a diagnosis of WM transformation to DLBCL (Fig. 5). R-MPV therapy included rituximab 610 mg on day 1, methotrexate 5,700 mg on day 2, vincristine 2 mg on day 2, and procarbazine 100 mg/ day on days 1-7 (odd cycles only). Folinic acid (leucovorin) was given appropriately, based on the blood concentration of methotrexate. Vomiting reappeared on day 2. Brain CT showed no signs of new lesions, or hemorrhage, and the symptoms disappeared immediately with antiemetic drugs and betamethasone to prevent brain edema. By the end of the first cycle of R-MPV, the patient's nausea, vomiting, and double vision had disappeared, and there was significant improvement of her subjective symptoms (Fig. 5).

All chemotherapy-related adverse events (grade 2 nausea, grade 3 neutropenia) were manageable. MRI after the first treatment cycle confirmed significant reduction of the tumor (Fig. 6), which supported continuation of the same treatment. Complete remission was confirmed by brain MRI after five cycles of therapy. Reduced-dose WBRT (23.4 Gy) and two cycles of high-dose Ara-C were given as consolidation therapy (Fig. 5). The patient's disease was well controlled and progression-free survival was demonstrated after 6 months' observation.

DISCUSSION

WM is associated with various neurological symptoms involving both peripheral and central nerve symptoms. Most CNS symptoms are caused by hyperviscosity or ischemia, though lymphoplasmacyte infiltration into the CNS has also been reported.[9] Plasma exchange may improve symptoms associated with hyperviscosity syndrome,[10] but symptoms caused by malignant-cell infiltration into the CNS, namely BNS, require chemotherapy or radiotherapy. It is therefore important to distinguish between hyperviscosity syndrome and tumor-cell infiltration, though making this distinction is often difficult.[11]

In a review of 36 cases of BNS by Ly *et al.*,[11] only 30 were proven by CSF study, suggesting that the sensitivity of this method alone is insufficient. Invasion of malignant lym-

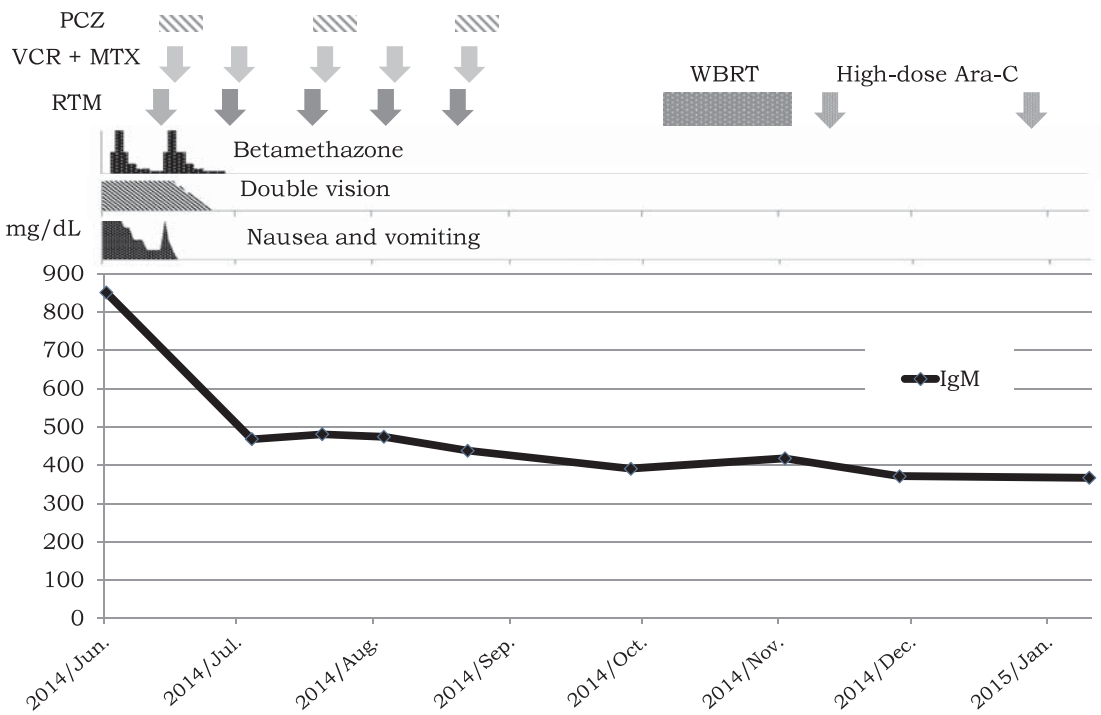

Fig. 5. Clinical course. Treatment of cerebral edema was initiated immediately after admission and biopsy was performed. Nausea and vomiting occurred transiently during the first cycle of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) (*upper column*), though the other symptoms improved. All the patient's symptoms had disappeared by the beginning of the second cycle. Five cycles of R-MPV therapy with whole-brain radiation therapy and high-dose cytarabine were administered with no severe adverse events. Serum IgM levels initially fell rapidly, followed by a slower decline. PCZ, procarbazine; VCR, vincristine; MTX, methotrexate; RTM, rituximab; WBRT, whole-brain radiation therapy; Ara-C, cytarabine

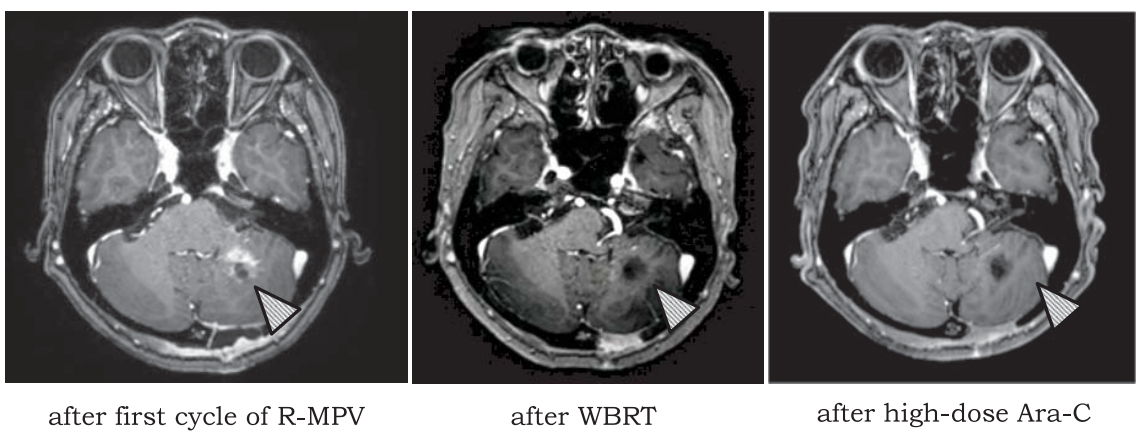

Fig. 6. Response evaluation with brain magnetic resonance imaging (MRI). MRI scans after the first cycle of treatment revealed decreases in tumor volume and midline shift (*left panel*). After the completion of all treatments (*middle panel*: after whole-brain radiation therapy; *right panel*: after cytarabine), the contrast-enhanced area had completely disappeared and complete remission was achieved. R-MPV, rituximab, methotrexate, procarbazine, and vincristine; WBRT, whole-brain radiation therapy; Ara-C, cytarabine

phoid cells into the CNS is generally associated with a poor prognosis. According to a comprehensive review by Malkani *et al*.,[9] the therapeutic regimen and patient response differed among individuals. The rarity of BNS makes the possibility of a prospective clinical trial unlikely. There is currently no evidence to suggest that transformed aggressive and indolent lymphomas with intracranial invasion should be treated with the same strategies. However, some case reports of treatment with purine nucleotide analogs and rituximab have been published recently.[9,12] Compared with conventional alkylating agents (e.g., cyclophosphamide and chlorambucil), purine nucleotide analogs are effective at various cell-cycle stages, and may thus be more appropriate for the nature of indolent tumors. No other lesions were detected by whole-body CT in the current case, and the treatment strategy used was therefore the same as for primary CNS lymphoma.[13,14]

In addition to methotrexate and Ara-C, which can permeate the CSF, WBRT is often carried out in these cases. Dose-reduction trials for brain radiation have recently been conducted in light of post-radiation toxicities, such as loss of cognitive function in elderly patients. With a view to reducing the dosage of WBRT in CNS lymphoma, Morris *et al*. conducted a study in 52 patients with a mean age of 60 years, among whom 31 (60%) achieved complete remission with R-MPV therapy followed by dose-reduced WBRT. We therefore adopted this regimen on the basis of these promising results (77% 2-year progression-free survival (PFS) and 7.7-year median PFS).[8]

The *MYD88* L265P mutation was detected by real-time PCR in the cerebellum biopsy sample. MYD88 plays a part in toll-like receptor and interleukin-1 receptor signaling leading to enhanced B cell survival.[15] The *MYD88* L265P mutation is detectable in some (～30%) DLBCLs originating from activated B cells, and most (～95%) cases of WM, but not in multiple myeloma.[15] It was therefore not possible to conclude that the cerebellum biopsy sample had the same clonal origin as the previous WM sample on the basis of the *MYD88* L265P mutation alone. To distinguish the transformation of WM from *de-novo* DLBCL, we therefore developed a variable-region-specific PCR primer and applied it to both the bone marrow WM cells at diagnosis and the cerebellum biopsy sample, as described previously.[6,7] The sequences of both PCR products were almost identical, strongly suggesting that they contained the same variable regions and thus arose from the same clonal B lymphocytes.

Although rare, POEMS syndrome may be complicated with WM.[16] POEMS syndrome is characterized by five clinical manifestations: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormalities. Accordingly, polyneuropathy, M-proteinemia, hepatosplenomegaly, edema and hypertrichosis, and elevation of plasma vascular endothelial growth factor (265 pg/mL) were confirmed at the onset of the current case in 2008, as previously reported in detail.[16]

Thalidomide maintenance therapy was given for POEMS syndrome, which controlled the progress of the peripheral nerve symptoms. However, IgM levels increased slowly, implying that the tumor burden was increasing slowly. Given that soluble interleukin-2 receptor and lactate dehydrogenase were not elevated, and the mass lesion was only detected in the cerebellum, it was concluded that the transformed lesion was localized to the CNS.

Complete response and PFS were achieved with R-MPV therapy and dose-reduced WBRT in the current case of WM accompanied by BNS, with no apparent deterioration of cognitive function. R-MPV with dose-reduced WBRT followed by high-dose Ara-C may thus represent a promising therapeutic approach for BNS.

CONFLICT OF INTEREST: The authors declare that they have no conflicts of interest in relation to this paper.

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