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【 CASE REPORT 】

# An Autopsy Case of Bing-Neel Syndrome: Discrepancy between the Radiological and Pathological Findings

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**Abstract:**
A 64-year-old man previously diagnosed with Waldenstrom's macroglobulinemia presented to our hospital with confusion. Magnetic resonance imaging (MRI) revealed diffuse meningeal enhancement. The patient was diagnosed with Bing-Neel syndrome (BNS) based on an elevated IgM index and the presence of monoclonal IgM protein, as detected by immunofixation electrophoresis of the cerebrospinal fluid. The patient underwent intrathecal and systemic chemotherapy but ultimately died of pneumonia. An autopsy revealed extensive meningeal and perivascular infiltration by malignant cells throughout the brain and spine. Thus, BNS may cause more extensive malignant infiltration into the central nervous system than is revealed by MRI.

**Key words:** Bing-Neel syndrome, Waldenstrom's macroglobulinemia, central nervous system, neurological complications, IgM index, autopsy

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## Introduction

Bing-Neel syndrome (BNS) is a rare neurologic complication of Waldenstrom's macroglobulinemia (WM) that is caused by infiltration of the central nervous system (CNS) by malignant lymphoplasmacytic cells (LPCs). Recently reported guidelines for BNS (1) have led to greater awareness of this condition. The diagnosis of BNS is based on biopsy histology, magnetic resonance imaging (MRI) findings, a diagnosis of WM based on a bone marrow biopsy, and a cerebrospinal fluid (CSF) examination, including cytology and flow cytometry (1, 2). The rarity and heterogeneity of the symptoms make the diagnosis of BNS challenging. Furthermore, some patients with BNS have very low LPC counts in the CSF (3).

BNS can be categorized based on MRI findings as diffuse or tumoral forms. In the diffuse form, MRI reveals diffuse leptomeningeal contrast enhancement and thickening of the meninges. These findings correspond to the infiltration of malignant cells into the leptomeningeal sheaths and perivascular spaces (1, 4-7). Autopsy cases of BNS in the literature are rare (8-11), and only two such cases have involved MRI findings (10, 11). Both of the reported cases were of the tumoral form, and the radiological-pathological correlation in the diffuse form of BNS remains unknown.

We herein report the autopsy findings of a patient diagnosed with BNS based on the IgM index and the presence of monoclonal IgM protein, as detected by immunofixation electrophoresis of the CSF. The treatment regimen and the radiological findings obtained during treatment are also presented.

## Case Report

A 64-year-old right-handed man with a history of WM who was experiencing confusion and urinary incontinence was admitted to our hospital in late March 2017. In 2010, the patient had experienced a fever and weight loss of approximately 10 kg and had developed anemia. Laboratory tests revealed a white blood cell count of 6,500/μL (67% neutrophils, 17% lymphocytes, 11% monocytes, 1% eosinophils, 3% basophils, and 1% atypical lymphocytes), red blood cell count of 3.73 million/μL, hemoglobin level of 8.6

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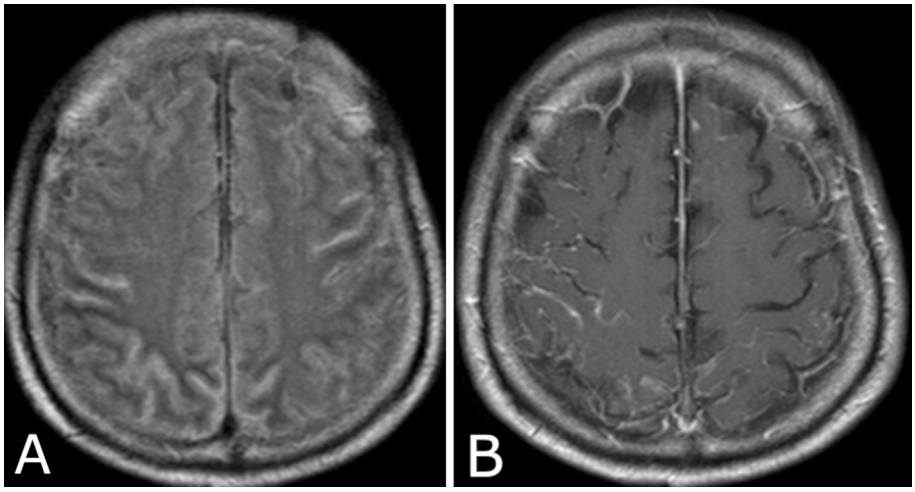


**Figure 1. MRI findings. A: Axial FLAIR sequencing demonstrates diffuse T2-hyperintensity along the sulci. B: Axial contrast T1 with gadolinium shows diffuse enhancement of the meninges, predominantly in the right parietal lobe. FLAIR: fluid-attenuated inversion recovery**

g/dL, hematocrit of 28.6%, platelet count of 468,000/μL, and IgM level of 1,831 mg/dL (normal range: 33-190 mg/dL). A blood smear revealed rouleaux formation, and IgM κ-type monoclonal protein was detected in the serum. Enhanced abdominal computed tomography revealed 16-mm lymphadenopathy of the paraaortic lymph node and mild hepatomegaly, but no splenomegaly. A bone marrow biopsy revealed significant infiltration by atypical small lymphocytes, LPCs, and plasmacytes, leading to a diagnosis of WM. The patient partially responded to 6 cycles of therapy with rituximab [375 mg/m$^2$, intravenous (i.v.); on day 1], cyclophosphamide (750 mg/m$^2$, i.v.; on day 2), hydroxy-doxorubicin (50 mg/m$^2$, i.v.; on day 2), and prednisolone (100 mg, oral; on days 2-6). The WM relapsed in 2013. At that time, the patient had an elevated IgM level (1,398 mg/dL) and received 5 cycles of rituximab (375 mg/m$^2$, i.v.; on day 2) and bendamustine (90 mg/m$^2$, i.v.; on days 1 and 2), which led to attenuated serum IgM levels (<1,000 mg/dL).

On admission in 2017, the patient was afebrile, hemodynamically stable, and disoriented. His Glasgow Coma Scale and Mini Mental State Examination scores were E4V4M6 and 20, respectively. In addition, the patient had mild ataxia of the left lower limb and a wide-based gait; the results of other neurological examinations were normal. He had no skin lesions, and the results of ophthalmologic examinations, including a dilated fundus examination, were normal. Laboratory studies showed normal results for serum IgM (97 mg/dL) but decreased values of IgG (236 mg/dL) and IgA (25 mg/dL).

Electroencephalography performed two days after admission revealed no epileptiform discharge, and there were no remarkable cranial computed tomography findings. MRI of the brain (Fig. 1) revealed diffuse high T2/fluid-attenuated inversion recovery (FLAIR) signal intensity along the sulci, with gadolinium leptomeningeal enhancement predominantly in the right parietal lobe. There was no diffusion restriction, and the magnetic resonance angiogram was unremarkable. MRI of the entire spine revealed no abnormal findings.

A CSF examination revealed an opening pressure of 13 cm$H_2O$, 143 white blood cells/mm$^3$ (98% mononuclear leukocytes, 2% polynuclear leukocytes), a glucose level of 40 mg/dL, and a protein level of 256 mg/dL. The IgG index was normal (0.35). The results of tests for infectious diseases in the CSF-including Gram stain, acid-fast bacilli culture, and fungal culture-were negative. The polymerase chain reaction (PCR) results for herpes simplex virus (HSV), varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and *Mycobacterium tuberculosis* were all negative. The results of cytological examinations of the CSF were negative for malignancy. Flow cytometry immunophenotyping of the CSF revealed a non-specific cell lineage pattern with cells positive for CD5, CD38, and human leukocyte antigen-D-related (HLA-DR). Light chain restriction was not detected. Therefore, no clonal B-cell population was observed.

The patient was empirically administered acyclovir (500 mg, i.v.; every 8 hours) until the CSF PCR findings were negative for HSV. Twenty-one days after admission, the patient presented with the acute onset of left hemispatial neglect, failing to recognize objects and people on the left side and deviating the head and eyes to the right. He also exhibited sensory extinction. MRI revealed no significant changes, and focal seizure of the right parietal lobe was suspected. Treatment with levetiracetam was started (1,000 mg/day), and the symptoms resolved in 2 days. Two weeks later, the patient experienced a sensation of crawling, followed by transient bilateral lower limb weakness. Focal seizure recurrence was suspected, and the dose of levetiracetam was increased to 2,000 mg/day. He developed hallucinations and cognitive decline and was treated with i.v. methylprednisolone (1 g/day, for 3 days) without any clinical improvement.

The CSF examination was repeated. A quantitative IgM analysis of the CSF revealed a significantly elevated IgM level (40.9 mg/dL: normal range: 0.001-0.092 mg/dL). The

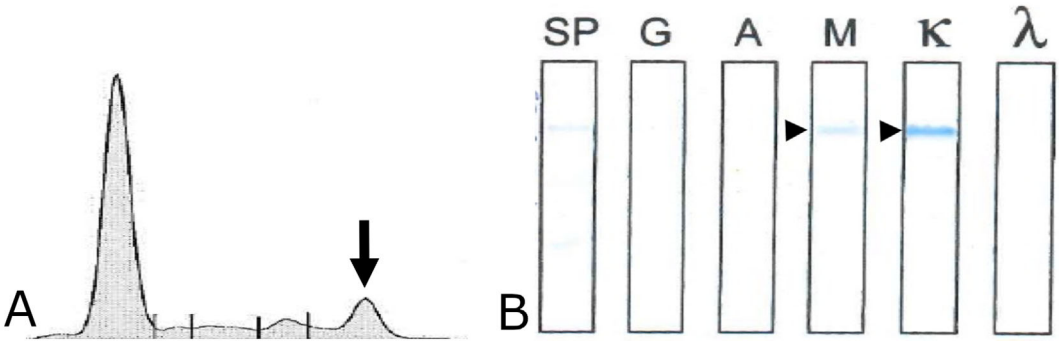


**Figure 2. Protein electrophoresis of the cerebrospinal fluid. A: Protein fraction showing an M peak in the γ fraction (arrow). B: Immunofixation electrophoresis demonstrating a monoclonal IgM κ band (arrow head). A: IgA, G: IgG, M: IgM, SP: serum protein**

IgM index, defined as [CSF IgM (mg/L) /serum IgM (g/L]) / [CSF albumin (mg/L) / serum albumin (g/L)], was also significantly elevated at 7.09 (normal reference range: <0.045-0.06) (6, 12). CSF protein fractionation showed the M peak in the γ fraction (Fig. 2A). Immunofixation electrophoresis revealed a monoclonal IgM κ band (Fig. 2B). These findings led to the diagnosis of BNS.

The patient was treated twice weekly with intrathecal methotrexate (15 mg), cytarabine (30 mg), and dexamethasone (5 mg) for 1 week. In addition, systemic chemotherapy was started with an 80% dose of high-dose methotrexate/cytarabine therapy (13) (methotrexate 800 mg/m$^2$, i.v.; on day 1; cytarabine 2.4 g/m$^2$/day, i.v.; on days 2 and 3).

A subsequent CSF examination suggested a progressive decline in the number of leukocytes and in the protein level. MRI of the brain revealed the resolution of the T2/FLAIR high intensity along the sulci and of meningeal enhancement. However, the patient developed a fever, confusion, and respiratory failure on day 19 of methotrexate/cytarabine therapy despite the improvements in his CSF and MRI findings. He did not report any headaches throughout the clinical course. Blood tests revealed a significant decline in the white blood cell (300/μL) and neutrophil (0/μL) counts. Febrile neutropenia was suspected, and numerous anti-infectives were administered without any clinical improvement. The patient expired four months after hospitalization.

An autopsy was performed 11 hours after death. The patient's brain weighed 1,410 g. Gross pathology revealed yellow deposits on the brain surface, predominantly on the right parietal lobe. A microscopic tissue examination revealed that the malignant cells had massively infiltrated into the pia mater (Fig. 3A) and arachnoid membrane. Extensive perivascular infiltration by malignant cells into the white matter, basal ganglia, and brainstem was also observed (Fig. 3B). Low perivascular infiltration by malignant cells was observed in the cerebral cortex. Malignant cell infiltration into ventricular wall was not observed. In the lumbar spine, infiltration of malignant cells into the pia mater and perivascular spaces was observed (Fig. 3C). The malignant cells were positive for CD20, CD79a, κ chain, and IgM; partially positive for CD138; and negative for CD3 and λ chain (Fig. 3D and E). IgM deposits were not observed in the meninges or parenchyma (Fig. 3F). Klüver-Barrera staining indicated an absence of demyelination in the white matter. In the bone marrow, the proliferation of small- to medium-sized atypical lymphocytes and plasma cells was observed. These findings were consistent with the diagnosis of BNS. Of note, there was no evidence of infiltration by malignant cells into other organs apart from the CNS. Importantly, bronchopneumonia was observed in the diffuse area of the inferior lobes of both lungs and was likely the direct cause of the patient's death.

## Discussion

To our knowledge, this is the first autopsy case report describing the diffuse form of BNS. We report two important clinical findings: 1) pathological involvement of the CNS can be more extensive in BNS than is suggested by MRI, and 2) the IgM index and immunofixation electrophoresis of the CSF are useful as screening tools in the diagnosis of BNS.

Reports of autopsy cases of BNS in the literature are rare, and only two such papers have reported MRI findings (10, 11). In both cases, MRI revealed tumoral lesions, and autopsy histology revealed malignant cell infiltration of the tumoral lesion and other parts of the brain. In our case, BNS manifested as the diffuse form on MRI. Although the abnormalities detected by MRI were localized along the sulci and meninges, autopsy findings revealed prominent perivascular infiltration by LPCs throughout the brain and lumbar spine. Fintelmann et al. reported that some patients with BNS have very low LPC counts in the CSF and suggested that IgM deposits, rather than infiltration by malignant cells, may cause the neurological symptoms (1, 3, 14). In our case, we initially suspected that IgM deposition was responsible for the symptoms because LPCs were not detected in the CSF with either cytology or flow cytometry. However, an autopsy revealed prominent perivascular infiltration by malignant cells in the brain without any obvious IgM deposits. Importantly, malignant cell infiltration was observed in the meninges and perivascular spaces in the

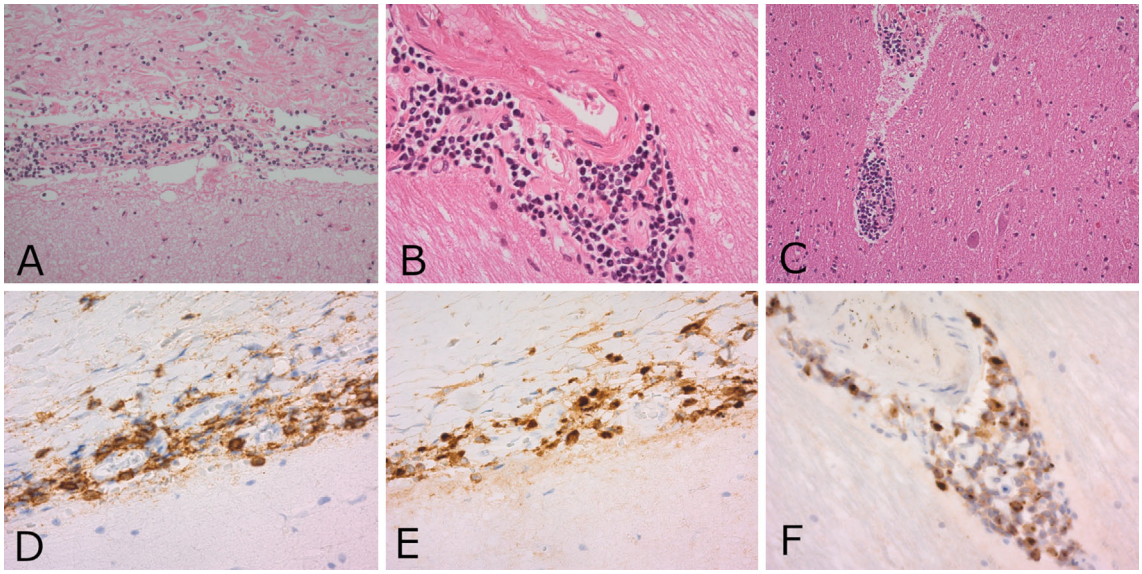


**Figure 3.** **Microscopic pathological findings in the brain. LPC infiltration into the pia mater. (A) H&E staining, 200×. Perivascular infiltration by LPCs in the cerebral white matter (B) and lumbar spine (C). H&E staining, 400× and 200×. Immunohistochemical study revealing CD20 and IgM positivity in the LPCs in the pia mater. (D) CD20 staining, (E) IgM staining, 400×. IgM positivity in the perivascular LPCs in the cerebral white matter. No obvious IgM deposition was detected in the parenchyma. (F) IgM staining, 400×. LPC: lymphoplasmacytic cell, H&E: Hematoxylin and Eosin**

brain and lumbar spine. Thus, there may be a discrepancy between the extent of the lesion observed on MRI and the histological infiltration by malignant cells in BNS.

The gold standard for the diagnosis of BNS is a histological biopsy of the cerebrum or meninges (1). However, the invasive histological biopsy procedure is difficult in some situations, such as in elderly patients or those with a poor general condition. Since Poulain et al. reported that the presence of the *MYD88* L265P mutation in the CSF contributes to a diagnosis of BNS (4), there have been cases in which BNS has been diagnosed based on the presence of this mutation in the CSF (15-18). However, detection of the *MYD88* mutation requires specific techniques, such as an allele-specific PCR assay or real-time quantitative PCR. Furthermore, it is often difficult to detect clonality in the CSF by cytology or flow cytometry because of the low rate of cell infiltration into the CSF (19, 20). Elevation of the IgM index indicates that the concentration of IgM in the CSF is higher than expected due to passive leakage across the blood-CSF barrier (6, 12, 21). A monoclonal band detected by immunofixation electrophoresis indicates the clonality of elevated protein. Thus, elevation of the IgM index and the presence of a monoclonal IgM band as detected by electrophoresis indicate the local synthesis of monoclonal IgM in the CSF. The local synthesis of monoclonal IgM may be evidence for the infiltration and proliferation of malignant LPCs into the CSF. Our case findings suggest that the IgM index and immunofixation electrophoresis of the CSF can be used as screening tools for BNS since the diagnosis was confirmed by an autopsy.

Most CNS symptoms are caused by hyperviscosity syndrome in WM patients (22). To distinguish BNS from hyperviscosity syndrome, it is important to determine the serum IgM level. The serum IgM level is related to the risk of hyperviscosity syndrome but not to BNS (23). Hyperviscosity syndrome usually occurs with a serum IgM level ≥3,000 mg/dL (24). In our case, the serum IgM level was normal when neurological symptoms were observed. Furthermore, the patient did not exhibit findings that would indicate hyperviscosity syndrome, including abnormal findings in the fundus, skin lesions, or cerebrovascular disease as observed on MRI. Therefore, we excluded a diagnosis of hyperviscosity syndrome. The IgM index and immunofixation electrophoresis of the CSF are also useful for distinguishing BNS from hyperviscosity syndrome.

In conclusion, malignant LPC infiltration may be more extensive than is suggested by MRI findings. In addition, the IgM index and immunofixation electrophoresis of the CSF are useful for the diagnosis of BNS. Physicians should be aware that malignant cell infiltration may be present when a patient has a history of a malignant disease or exhibits neurological symptoms inconsistent with MRI findings, or when protein levels in the CSF are elevated for an unknown reason. BNS cases may be undiagnosed and underreported, and the IgM index and immunofixation electrophoresis should be more widely employed to identify cases of BNS. More cases of BNS diagnosed using this approach should be reported in the literature.

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

## References


1. Minnema MC, Kimby E, D'Sa S, et al. Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome. Haematologica **102**: 43-51, 2017.
2. Vos JM, Kersten MJ, Kraan W, et al. Effective treatment of Bing-Neel Syndrome with oral fludarabine: a case series of four consecutive patients. Br J Haematol **172**: 461-464, 2016.
3. Fintelmann F, Forghani R, Schaefer PW, Hochberg EP, Hochberg FH. Bing-Neel Syndrome revisited. Clin Lymphoma Myeloma **9**: 104-106, 2009.
4. Poulain S, Boyle EM, Roumier C, et al. *MYD88* L265P mutation contributes to the diagnosis of Bing Neel syndrome. Br J Haematol **167**: 506-513, 2014.
5. Simon L, Fitsiori A, Lemal R, et al. Bing-Neel syndrome, a rare complication of Waldenström macroglobulinemia: analysis of 44 cases and review of the literature. A study on behalf of the French Innovative Leukemia Organization (FILO). Haematologica **100**: 1587-1594, 2015.
6. Frustaci AM, Rusconi C, Picardi P, et al. Bing Neel syndrome in a previously untreated patient with Waldenström's macroglobulinemia: contribution of MYD88 L265P mutation on cerebrospinal fluid. Clin Lymphoma Myeloma Leuk **16**: e7-e9, 2016.
7. Malkani RG, Tallman M, Gottardi-Littell N, et al. Bing-Neel syndrome: an illustrative case and a comprehensive review of the published literature. J Neurooncol **96**: 301-312, 2010.
8. Logothetis J, Silverstein P, Coe J. Neurologic aspects of Waldenström's macroglobulinemia. Arch Neurol **3**: 564-573, 1960.
9. Scheithauer BW, Rubinstein LJ, Herman MM. Leukoencephalopathy in Waldenström's macroglobulinemia. Immunohistochemical and electron microscopic obesrvations. J Neuropathol Exp Neurol **43**: 408-425, 1984.
10. Welch D, Whetsell WO Jr, Weil RJ. Pathologic quiz case: a man with long-standing monoclonal gammopathy and new onset of confusion. Arch Pathol Lab Med **126**: 1243-1244, 2002.
11. Garderet L, Baudel JL, Cervera P, et al. 'Indolent' Waldenström's macroglobulinemia and a cerebrospinal fluid protein level of 16 g/L. Eur J Haematol **77**: 80-82, 2006.
12. Blennow K, Skoog I, Wallin A, Wikkelsö C, Fredman P. Immunoglobulin M in cerebrospinal fluid: reference values derived from healthy individuals 18-88 years of age. Eur Neurol **36**: 201-205, 1996.
13. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: an active regimen for aggressive mantle-cell lymphoma. J Clin Oncol **16**: 3803-3809, 1998.
14. Nagayama S, Minato N, Nakata M, et al. A case of Waldenström macroglobulinemia initially manifested as consciousness disturbance: Bing-Neel syndrome. Nihon Shinkei Kyukyu Gakkai Zasshi (Journal of Japanese Congress on Neurological Emergencies) **25**: 29-32, 2013 (in Japanese, Abstract in English).
15. Cabannes-Hamy A, Lemal R, Goldwirt L, et al. Efficacy of ibrutinib in the treatment of Bing-Neel syndrome. Am J Hematol **91**: E17-E19, 2016.
16. Van Cauwenberge MG, Depreter B, Dumoulin EN, Emmerechts J, Nollet F, Vanopdenbosch LJ. Bing-Neel syndrome: two unexpected cases and a review of the literature. J Neurol Sci **356**: 19-26, 2015.
17. Kopińska AJ, Helbig G, Koclęga A, Kyrcz-Krzemienń S. Bing-Neel syndrome with detectable MYD88 L265P gene mutation as a late relapse following autologous hematopoietic stem cell transplantation for Waldenström's macroglobulinemia. Turk J Hematol **34**: 186-187, 2017.
18. Castillo JJ, D'Sa S, Lunn MP, et al. Central nervous system involvement by Waldenström macroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study. Br J Haematol **172**: 709-715, 2016.
19. Vargas A, Dixit KS, Quigley JG, Testai FD. Spinal cord and cranial Bing-Neel Syndrome complicated by cerebral ischemia: a case report. J Neurol Sci **366**: 44-46, 2016.
20. Bacquet JL, Weiss N, Meyniel C, et al. Neither the patient nor the physician could see anything: atypical Bing-Neel syndrome. Am J Hematol **91**: 858-859, 2016.
21. Zetterberg H. Pathognomonic cerebrospinal fluid findings in Bing-Neel syndrome. J Neurooncol **104**: 615, 2011.
22. Kikukawa Y, Yamamura-Fujimoto A, Endo S, et al. Successful treatment of Bing-Neel Syndrome accompanying Waldenström's macroglobulinemia with R-MPV: a case report. J Clin Exp Hematop **55**: 113-119, 2015.
23. Halperin D, Hallam S, Haroon A, Butler T, Agrawal S. Bing-Neel Syndrome case report: a previously undocumented IgG variant with MRI, PET/CT, and PET/MRI imaging. Case Rep Hematol **2016**: 2016.
24. Vijay A, Gertz MA. Waldenström macroglobulinemia. Blood **109**: 5096-5103, 2007.