



# Bing Neel Syndrome in a Previously Untreated Patient With Waldenström's Macroglobulinemia: Contribution of MYD88 L265P Mutation on Cerebrospinal Fluid

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## Clinical Practice Points

- Bing Neel Syndrome (BNS) is defined as direct central nervous system involvement of Waldenström's macroglobulinemia. BNS is usually a late event, although an incidence of 30% to 36% has been described in large series of previously untreated patients.
- A wide variety of clinical manifestations and radiologic findings for BNS have been reported in published data, depending on the site and type of infiltration.
- In addition to the radiologic findings, the diagnostic approach includes lymphoplasmacytic cell quantitation and flow cytometric analysis of the cerebrospinal fluid (CSF).
- Recently, the evaluation of MYD88 L265P mutation in the CSF has been proposed as a possible diagnostic biomarker for BNS.
- We describe the case of a 58-year-old patient with BNS.
- The detection of MYD88 L265P mutation in the CSF contributed to the diagnosis and to the sequential monitoring of minimal residual disease.
- In the future, the use of CSF sequential molecular monitoring could play an important role in treatment decisions.

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## Introduction

Waldenström's macroglobulinemia (WM) is defined as lymphoplasmacytic lymphoma (LPL) with serum monoclonal IgM secretion.<sup>1</sup> Although clinical manifestations imputable to serum hyperviscosity and peripheral neuropathy represent a common finding in WM, direct infiltration of any part of the central nervous system (CNS) is extremely rare and is classified as Bing-Neel syndrome (BNS).<sup>2</sup> BNS is often diagnosed belatedly and mostly affects patients after multiple lines of therapy have been used. However, in the largest series, its occurrence was reported in 30% to 36% of previously untreated patients.<sup>3-10</sup>

MYD88 L265P is a somatic point mutation detected in approximately 90% of WM cases. The high frequency ( $\leq 87\%$ ) of IgM monoclonal gammopathy of undetermined significance suggests its possible role as an early oncogenic event. Furthermore, MYD88 L265P has become a useful biomarker in distinguishing WM from other lymphomas with IgM secretion.<sup>11</sup> At present, only 1 report investigating the potential contribution of MYD88 L265P mutation for a BNS diagnosis has been published.<sup>6</sup>

We describe the case of a young patient with previously untreated WM, who presented with diplopia as the first BNS symptom. The findings from the diagnostic workup, including the CSF MYD88 evaluation, and treatment options are discussed.

## Case Report

A 58-year-old man without any significant medical history had been diagnosed with WM in August 2011. Because the patient presented with asymptomatic disease, observation was started.

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## BNS, Waldenström's Macroglobulinemia, and MYD88 L265P Mutation

In May 2014, the patient presented with diplopia. No other abnormalities were found in the neurologic evaluation. His visual acuity, color vision, pupillary reflexes, and visual field testing findings were all normal. The complete blood count showed a hemoglobin level of 10.8 g/dL. His hepatic and renal function were adequate. The IgM level was 5942 mg/dL, with a 5.6-g/dL IgM spike. In accordance with the WM international prognostic scoring system, the patient was categorized as having intermediate-risk disease.<sup>12</sup> The findings from the neurologic and ophthalmic clinical evaluations were conclusive for left eye sixth cranial nerve palsy. The brain, orbital, and spinal magnetic resonance imaging (MRI) findings before and after gadolinium enhancement were negative, with no radiologic evidence of nerve infiltration by disease or pathologic tissue.

The cerebrospinal fluid (CSF) analysis showed slightly increased CSF protein, a normal glucose level, and the presence of lymphoplasmacytic cells on cytologic examination. An elevated CSF IgM value of 0.612 mg/dL (range, 0.001-0.092 mg/dL) was found, and immunofixation demonstrated a monoclonal IgM  $\kappa$  band. The IgM index<sup>13</sup>  $([\text{CSF} - \text{IgM} (\text{mg/dL})/\text{serum} - \text{IgM} (\text{g/L})]/[\text{CSF} - \text{albumin} (\text{mg/dL})/\text{serum} - \text{albumin} (\text{g/L})])$  was 0.103 (normal reference range,  $< .06$ ). The findings from flow cytometry (FC) of the peripheral blood samples were negative. Examination of the CSF confirmed the presence of a malignant B-cell clone (CD5<sup>-</sup>, CD10<sup>-</sup>, CD19<sup>+</sup>, CD20<sup>+</sup>, CD22<sup>+</sup>, FMC7<sup>-</sup>, and CD23<sup>-</sup>, with kappa light chain restriction in 3345 cells). The detection of a monoclonal IgH rearrangement using polymerase chain reaction (PCR) confirmed B-cell clonality. Furthermore, the MYD88 L265P mutation was positive on CSF examination. All these findings were consistent with the diagnosis of BNS. Considering the absence of hyperintense lesions on MRI, a tissue biopsy was not performed. Concomitantly, disease restaging was performed. Examination of the bone marrow biopsy specimen revealed a massive (80%) LPL infiltration, with a detectable MYD88 L265P mutation. The computed tomography scan did not show lymphadenopathy and/or organomegaly.

From June to August 2014, the patient was treated with 3 monthly courses of R-DHAP (rituximab 375 mg/m<sup>2</sup> on day 1, cisplatin 50 mg/m<sup>2</sup> on days 1 and 2, cytarabine 2 g/m<sup>2</sup> on days 2 and 3, and dexamethasone 20 mg/m<sup>2</sup> on days 1-4). Without waiting for the achievement of a chemotherapy nadir, the patient received 7 intrathecal chemotherapy injections with cytarabine, methotrexate, and methylprednisolone (total dose, 40 mg, 12 mg, and 20 mg, respectively) to achieve CSF cytology and FC negativity. The intrathecal treatments were administered on days 1, 4, and 8 during the first R-DHAP session and thereafter on day 1 and at bone marrow recovery after the second and third course.

After the second lumbar puncture, despite clinical improvement, the cytologic and FC examinations both revealed CD20<sup>+</sup> cells and MYD88 L265P mutation. After the third lumbar puncture, the cytology and FC findings were negative. Nevertheless, the MYD88 L265P mutation was present on qualitative PCR. This was considered significant for the persistence of molecular disease. Finally, at the fourth intrathecal injection, molecular eradication was demonstrated, with the PCR results for MYD88 L265P were indeterminate. The neurologic symptoms showed progressive improvement during high-dose and intrathecal chemotherapy, with complete resolution of diplopia documented after the third

R-DHAP course and 7 lumbar punctures. The treatment was well tolerated overall.

Regarding WM, a partial response in the IgM levels and IgM spike (2241 mg/dL and 2.1 g/dL, respectively) was obtained. To achieve a better quality of response to allow for the performance of stem cell harvesting, additional treatment with 5 weekly cycles of BDR (bortezomib, rituximab and dexamethasone)<sup>14</sup> was given from August to February 2015. Concomitantly, 7 additional intrathecal chemotherapy injections were administered monthly. Grade 2 paresthesia after the third BRD course was the only adverse event reported. At treatment completion, the patient had obtained a very good partial response with an IgM spike reduction of  $> 90\%$ , full hematologic recovery, and 10% residual LPL marrow infiltration.

At 4 months after the end of BDR, peripheral stem cell harvesting was performed. A total of  $6.4 \times 10^6/\text{kg}$  CD34<sup>+</sup> cells was collected. However, with the achievement of a successful response, stem cell transplantation was not performed. At the last follow-up visit, 17 months after the BNS diagnosis, our patient was alive and free of progression.

### Discussion

A wide variety of clinical situations with BNS have been described, depending on the infiltration site and type. Patients with a "pseudotumor" MRI detectable form often develop seizure or focal neurologic signs. In the "diffuse" form, leptomeningeal space and periventricular white matter infiltration will result in confusion, headache, cognitive decline, and psychiatric manifestations.<sup>15-19</sup> In a recent series of 44 patients analyzed by the French Innovative Leukemia Organization, 36% of patients had presented with cranial nerve involvement with predominance of facial or oculomotor nerve palsy.<sup>9</sup> However visual impairment without other CNS manifestations has rarely been described.<sup>5,20</sup> After 3 years of asymptomatic disease, our patient presented with only diplopia, resulting from sixth cranial nerve palsy, showing the onset of BNS. This confirms that BNS should be suspected in the case of visual impairment as an isolated symptom.

It is well known that when BNS is suspected, the results from serum laboratory tests will not be helpful, because they will only reflect the WM disease status. Variable findings have been reported in association with BNS such as a high erythrocyte sedimentation rate, elevated serum viscosity, elevated cryoglobulin levels, and Bence-Jones proteinuria.<sup>21</sup> In our patient, the disease status and laboratory test results were similar to those 6 months earlier; thus, the CSF findings were crucial for the BNS diagnosis.

The presence of a high concentration of LPL cells in the CSF categorized our patient to group A according to the Fintelmann classification.<sup>22</sup> Despite the high number of CSF LPL cells and palsy of the sixth cranial nerve, our patient had normal MRI findings, which is an atypical finding in group A patients.<sup>23</sup>

We suggest that in patients with WM and cranial nerve impairment, CNS localization should always be suspected, because a similar BNS presentation, characterized by bilateral abducens nerve paresis with negative MRI findings, was reported by Bhatti et al.<sup>24</sup> Furthermore, normal MRI findings have been reported in 22% of cases in the largest series published to date.<sup>9</sup>

Although cytologic CSF evidence of LPL cells, combined with characteristic FC findings, is highly suggestive for BNS, the finding

of a monoclonal IgM band in the CSF of patients with MW generally cannot be considered, per se, diagnostic. The IgM level in the CSF can be elevated because of passive leakage of proteins across the blood–brain barrier.<sup>13</sup> The value obtained using the IgM index allowed us to speculate the presence of primitive intrathecal IgM production.

Recently, and for the first time, Poulain et al<sup>6</sup> reported the importance of the diagnostic support of MYD88 L265P mutation detection in the CSF from 3 patients with BNS.<sup>6</sup> Sequential measurements of the mutation with quantitative PCR were used to monitor the treatment response. In our patient, a MYD88 L265P mutation was present in the CSF at diagnosis. Subsequent monitoring was useful to detect minimal residual disease, even in the absence of CSF cells at cytology and FC analysis. This supports the importance of MYD88 L265P mutation detection, not only in the diagnostic evaluation, but also in monitoring the treatment response. Although 2 large retrospective series have recently been reported,<sup>9,10</sup> the best treatment strategy for BNS has not yet been defined.

Despite the evidence of a response to intrathecal chemotherapy or radiotherapy, systemic treatment is usually needed to achieve sustained remission and disease control in the bone marrow.<sup>9,10,15,20,25</sup> In the retrospective series by Simon et al<sup>9</sup> and Castillo et al,<sup>10</sup> in addition to intrathecal treatment, most patients had received high-dose chemotherapy (52% and 41%, respectively). The remission of neurologic symptoms and clearance of LPL cells have been described in several cases after combination treatment with rituximab and fludarabine, as well as 2-chlorodeoxyadenosine, suggesting the possible ability of purine analogs (PAs) to penetrate into the CNS compartment.<sup>4,26–28</sup> To our knowledge, data concerning the ability of PAs to cross the blood–brain barrier have been mainly based on animal models. It has been speculated that the success of PAs treatment might be related to an increased barrier permeability in meningeal disease and slower clearance from the CSF.<sup>27</sup>

Considering this possible individual behavior and the young age of our patient, we opted for an aggressive approach with high-dose chemotherapy. Both high-dose methotrexate (MTX) and the R-DHAP regimen combined with intrathecal MTX have been successfully used in published studies.<sup>8,17,21,29,30</sup> However, in the series by Simon et al,<sup>9</sup> the use of high-dose chemotherapy did not affect progression-free survival and overall survival. In our patient, a rapid clinical response was observed after 2 lumbar punctures and R-DHAP initiation. Considering our patient's young age and disease prognosis, we chose to administer 2 additional courses of high-dose chemotherapy. Despite the favorable outcome, we speculate regarding the correct treatment intensity that should be administered for BNS. In our patient, we obtained early complete CSF molecular eradication. Even if no current data are available regarding the value of the achievement of CSF-negative molecular disease, it is reasonable to assume that a fewer number of R-DHAP courses could also lead to the same results in CNS disease.

## Conclusion

In the present study, we have confirmed the high sensibility of PCR in detecting minimal molecular residual disease in the CSF in our patient. We suggest that its sequential use for CNS disease monitoring could allow clinicians to choose the correct

amount and type of chemotherapy agents and, furthermore, avoid unnecessary toxicity.

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