



Bing-Neel Syndrome – A Challenging Diagnosis: Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. Authors YD and NS drafted and wrote the manuscript. Authors BS and NS developed the therapeutic approach and managed the patient. Authors YD, MG and GB performed the laboratory tests. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Bing-Neel syndrome is a rare neurologic complication of Waldenström's macroglobulinemia, characterized by infiltration of the central nervous system by clonal lymphoplasmacytes. We present a rare clinical case of a patient, who one year after the diagnosis of Waldenström's macroglobulinemia, progressed with diverse neurologic presentation and cerebrospinal fluid involvement. The diagnosis was based on magnetic resonance imaging and flow cytometry detection of clonal B-cells in the cerebrospinal fluid. Bing-Neel syndrome should be considered in patients with neurologic symptoms and a history of Waldenström's macroglobulinemia.

Keywords: *Waldenström's macroglobulinemia; Bing-Neel syndrome; orbital involvement; cerebrospinal fluid.*

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ABBREVIATIONS

LPL/WM: Lymphoplasmocytic Lymphoma/Waldenström's Macroglobulinemia; BNS: Bing-Neel Syndrome; CNS: Central Nervous System; CT: Computer Tomography; MRI: Magnetic Resonance Image; CSF: Cerebrospinal Fluid; BTK: Bruton Tyrosine Kinase.

1. INTRODUCTION

Lymphoplasmacytic lymphoma/ Waldenström's macroglobulinemia (LPL/WM) is a rare indolent B-cell neoplasm which accounts for 2% of non-Hodgkin lymphomas. The clinical presentation is associated either with tumor infiltration or is due to the synthesis of monoclonal IgM. A rare neurological complication of WM with an involvement of the central nervous system (CNS) is the Bing-Neel syndrome (BNS), which is a result of infiltration of CNS by clonal lymphoplasmacytes. The clinical manifestations are various and nonspecific. For the first time in 1937 Jens Bing and Axel Valdemar Neel described a syndrome characterized by anemia and neurological symptoms associated with elevated serum and cerebrospinal fluid immunoglobulins [1]. Eight years later Jan Gösta Waldenström reported that macroglobulinemia was associated with constitutional symptoms, anemia, thrombocytopenia and bone marrow infiltration by lymphocytes and lymphoplasmacytes. The disease is currently defined as WM, named after its discoverer.

We present a rare clinical case of a patient, who one year after WM was diagnosed, progressed with orbital and cerebrospinal fluid involvement.

2. CASE PRESENTATION

A 65-year old-male was admitted to the National Hematology Hospital in October 2017 with complaints of fatigue, weight loss and low-grade fever. The physical exam revealed pallor and palpable peripheral lymphadenomegaly. The patient presented initially with anemic syndrome (hemoglobin - 83 g/l), hyperproteinemia (total protein - 102 g/l), hypoalbuminemia (albumin - 28.9 g/l), while the other parameters were within the reference range. Serum β 2-microglobulin was 6.7 mg/l (normal reference range: 1 – 2.4 mg/l). The peripheral blood smear showed rouleaux formation. Serum protein electrophoresis and immunofixation detected 64.2 g/l monoclonal IgM paraprotein. The value

of the plasma viscosity was elevated – 6.4 mP/s (normal reference range: 1,45 - 1,97 mP/s).

The bone marrow biopsy demonstrated hypercellularity due to diffuse proliferation of mature lymphocytes, lymphoplasmacytes and plasma cells. The additional immunehistochemical staining confirmed the infiltration of CD20 positive B-cells and about 15% of the cell composition were CD138(+) plasma cells. In situ hybridization verified the clonal nature based on kappa light chain restriction in the majority of neoplastic cells. The conventional cytogenetic analysis revealed no clonal chromosome abnormalities. However the molecular biology testing revealed the acquisition of *MYD88 L265P* mutation without the presence of *MMSET-IgH* rearrangements.

Finally, the diagnosis of WM was established. The computer tomography scan (CT) displayed generalized lymphadenomegaly and hepatomegaly without osteolytic lesions. The enlarged lymph nodes were located bilaterally in the cervical and supraclavicular region (up to 35/20 mm), in the mediastinum (up to 35/23 mm), in the axillary (up to 20/20 mm), para-aortic and para-caval, iliac and inguinal regions (up to 25/20 mm). Therefore, the patient was stratified in the intermediate risk group according to ISSWM. Monotherapy with alkylating agent bendamustine was initiated in a dose of 90 mg/m². Therapeutic response was determined after the sixth course. A 50% reduction of the paraprotein level (19.7 g/l) was detected and the CT findings showed only residual iliac lymph nodes up to 20/20 mm. According to the IWWM-6 criteria the therapeutic response was assessed as partial [2]. No maintenance therapy was applied. The patient was monitored monthly, and laboratory parameters showed no changes.

One year after diagnosis and 6 months after the cessation of therapy, the patient was admitted with complaints of progressive bilateral deafness, vertigo, coordination and low grade right lagophthalmos. The neurologic examination revealed static and locomotor ataxia, right lower monoparesis, deafness, sensory syndrome of the left lower limb with no data for diplopia or nystagmus. The additional laboratory tests revealed only paraproteinemia of 10.2 g/l without hyperviscosity syndrome. Magnetic resonance imaging (MRI) detected signal hyperintensity on T2 FLAIR sequence in the right orbit and in the left maxillary sinus without focal lesions in the

brain parenchyma, brainstem, cervical and lumbar segment of the spinal cord (Fig. 1).

The cerebrospinal fluid (CSF) biochemistry study detected elevated protein level (7406 mg/l, reference range: 150 - 450 mg/l) and hypoglycorachia (0.59 mmol/l, reference range:

2.2 - 4.4 mmol/l). The morphological analysis of the CSF demonstrated pleiocytosis (164 cells / μ L) of atypical lymphocytes with plasmacytic differentiation, expressing B-cell antigens CD19(+), CD79b(+), CD20(+) and CD38(+), detected by multiparametric flow cytometry (Fig. 2).

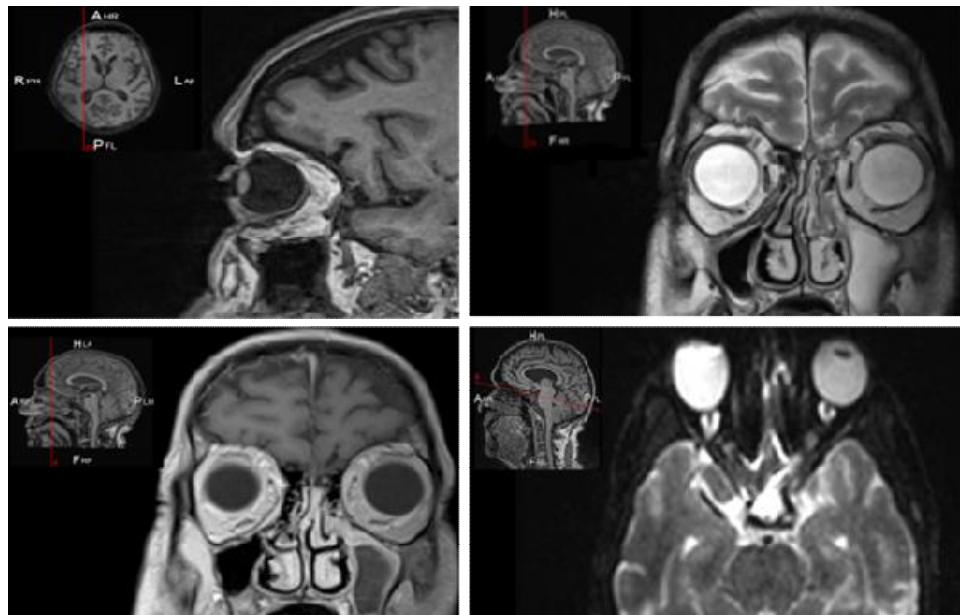


Fig. 1. MRI imaging of the brain of the patient demonstrated changes in the right orbit and left maxillary sinus

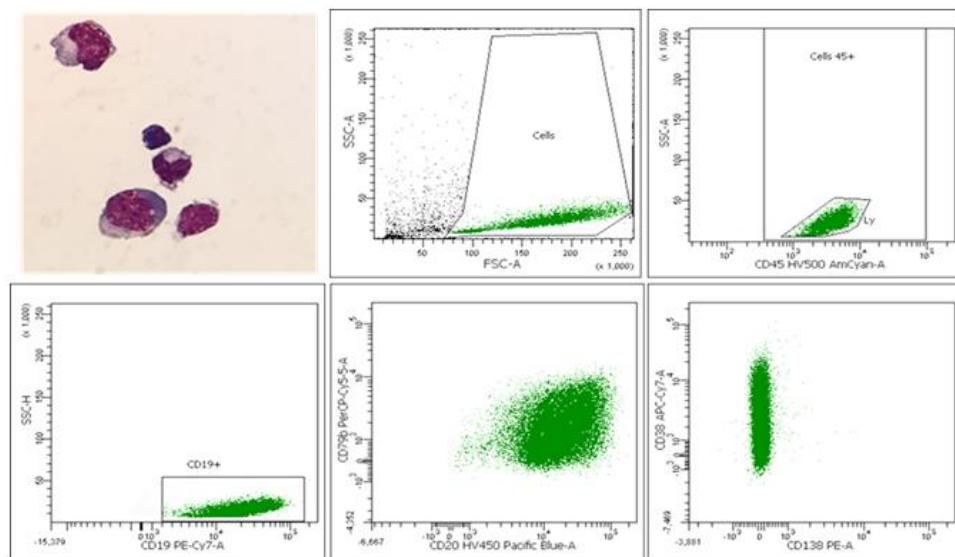


Fig. 2. Morphological features of the lymphoplasmacytic cells in CSF (Giemsa staining, magnification x100). The multiparametric flow cytometry analysis of the CSF demonstrated B-cells (dot plots stained in green), which expressed CD45(^{high}) CD19(+) CD20(+) CD79b(+) CD38(+) CD138(-). 40 000 cells were acquired

Intrathecal therapy with combination of methotrexate 15 mg i.t. and cytarabine 40 mg i.t. was given. However, the patient refused any systemic chemotherapy and one month later died at home.

3. DISCUSSION

LPL/WM is an incurable indolent B-cell neoplasm with overall survival of around 10-years [3]. However complications may occur that may worsen the prognosis, BNS being one of the rare options. The prevalence of BNS in LPL/WM has been estimated as less than 1% [4], however, it is largely unknown and because of the rarity of the disease it might be underdiagnosed. The clinical symptoms are both diverse and non-specific as the neurologic status may be due to hyperviscosity syndrome or by a direct tumor infiltration. Here we present a clinical case that raised specific questions and was the subject of important discussions about the need to follow the recommendations for diagnosis and treatment.

Some of the patient's characteristics corresponded to the commonly reported. We presented a 65-year-old male, which falls into the most common category according to Simon et al. who described a series with 80% male prevalence at a median age at the time of BNS of 63 years (range: 47-84) [5]. Despite that research papers in the recent years have demonstrated that BNS may be the first manifestation of the disease in 15-36% of the patients without any previous history of WM [1], most commonly it occurs secondary during the clinical course of the disease with the median time from WM diagnosis to BNS of 3 years (range 0-16) [6] and the longest reported period is 25 years [7]. Our clinical case was diagnosed with BNS only one year after WM without any signs of systemic progression of the disease as described in other publications [1,8]. Therefore, BNS should be considered in any patient with WM and neurologic complains.

Our patient presented with diverse neurological symptoms that would suggest meningeal and/or cranial nerves involvement, including deafness, vertigo, coordination and unilateral lagophthalmos. In addition, the neurologic examination revealed ataxia, motor and sensory disturbances of lower limbs suggesting parenchymal lesions. In BNS, clinical manifestations are a consequence of LPL cells invading the CNS, which should be

demonstrated by detection of clonal B-cells in a biopsy or CSF and/or by imaging of the CNS according to the recently developed guidelines [1]. In our case at least some of the symptoms were associated with meningeal involvement by clonal lymphoplasmacytes confirmed by microscopic and immunophenotypic examination of CSF. Morphology on cytopspin slides allowed us to detect lymphoplasmacytic morphology and the potential deficits of the diagnostic yield were overcome by the ancillary flow cytometry which revealed the same immunophenotype profile of the malignant cells in the CSF as in the initial bone marrow examination [9]. Although the CNS involvement was not detected by a histological biopsy, which is regarded as the golden standard for the diagnosis of BNS [1], the case can be assigned to the cellular category of patients with CNS involvement by WM, defined as group A, which accounts for 75% of the cases in whom clonal B-cells in CSF can be detected. In the remaining 25%, defined as a "non-cellular" category - group B, other mechanisms, such as IgM deposition, might produce the neurologic symptoms and can be considered as an earlier stage of the disease [10]. Demonstration of group B cases is performed by detecting M-protein in cerebrospinal fluid by electrophoresis and immunofixation. Molecular testing is strongly advised. The detection of *MYD88 L265P* mutation in the CSF could provide additional evidence for the diagnosis of BNS, however, it could not be performed due to technical reasons [1].

The MRI findings were most probably responsible for the lagophthalmos which was the only eye manifestation in our patient. The orbital infiltration in WM occur rarely [11-13] and even more rarely occurs simultaneously with CSF involvement. We found single publications in the literature similar to our report with orbital infiltration preceding meningeal and cerebrospinal fluid infiltration who firstly complained of decreased eye movements bilaterally [14], or with optical neuritis and CNS infiltration [15]. Of interest is a patient with initial manifestation of BNS, who presented with WM and orbital involvement 3 years later [10]. No meningeal involvement, neither focal lesions in the brain parenchyma, brainstem, cervical and lumbar segment of the spinal cord were revealed that could be associated with the remaining clinical symptoms. MRI is a highly sensitive technique to diagnose diffuse or focal involvement of CNS but even when the tumor formation is not found, BNS should still be

considered [16]. Several reports present similar diagnostic challenges due to the discrepancy between the diverse clinical presentation of the disease and scarce or missing MRI findings. Interestingly, an autopsy case report concluded that the pathological involvement of CNS can be even more extensive than the MRI suggested [17]. Thus when even minor neurologic symptoms occur in a patient with known WM history, extensive examinations should be initiated to exclude BNS.

Unfortunately, we were not able to actively treat and to follow our patient since he refused systemic therapy, deteriorated rapidly and died within a month after diagnosis at home. Although it was difficult to predict the clinical outcome since there are still no established prognostic factors due to the rarity of the entity, we could speculate that there were at least two out of the three unfavourable parameters, defined by Castillo *et al.* in an univariate analysis, i.e. age above 65 years and previous treatment for WM [3]. Most data on BNS come either from case reports or from small series with a short follow-up period, therefore, the prognosis of BNS needs further clarification. However, long-term outcome of WM with BNS seems favorable in a considerable proportion of patients in some cohorts [8,18].

There is still no consensus on the treatment of BNS, because of the rarity of the disease. The therapy for BNS includes cytotoxic agents that have a good CNS penetration and methotrexate and/or cytarabine intrathecally are generally used [1]. Systemic chemotherapy and radiotherapy are considered in group A patients in comparison to those in group B with low cellular infiltration and accompanying symptoms of IgM deposition, where the therapeutic approach may include plasmapheresis. Autologous transplantation of hematopoietic stem cells has been applied in selected patients [19]. Novel agents such as ibrutinib – an inhibitor of Bruton tyrosine kinase (BTK), has demonstrated high response rates [20]. Despite of the lack of specific guidelines, treatment should be initiated as responses do occur that may improve quality of life and extend it when limited or no active systemic disease is present.

4. CONCLUSION

In the current case report we present a male patient with a cellular variant of BNS with diverse clinical manifestations and orbital and maxillary

involvement by MRI, which occurred one year after the diagnosis of WM and 6 months after the cessation of the initial therapy. BNS should be considered in patients with neurologic symptoms and a history of Waldenström's macroglobulinemia because it is a rare complication, which may occur at any time in the course of the disease and may be associated with poor outcome if not treated.

CONSENT

Informed consent was obtained from the patient to allow data on his condition to be included in scientific publications.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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