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Bing–Neel syndrome in a patient with Waldenström Macroglobulinemia. Case Report and Literature Review

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ABSTRACT

Background. In 1936, a condition now known as BNS was first described, it is characterized by the infiltration of LPLs into the CNS, causing neurological symptoms. This rare complication occurs in about 1% of patients with WM. Diagnosing BNS is challenging due to its heterogeneous symptoms and requires specific tests for confirmation. BNS treatment is personalized, often involving high-dose chemotherapy and possibly stem cell transplantation, with early diagnosis being crucial to prevent irreversible damage.

Case Report. A 71-year-old male with a 20-year history of stage IV WM, MYD88 positive, presented in October 2023 with serological disease progression but no CRAB or hyperviscosity syndrome. He had a fever of up to 39°C. Administered antibiotic treatment, improved patient's infectious condition. However, the patient later developed neurological symptoms; MRI and lumbar puncture confirmed the diagnosis of BNS. Ibrutinib was initiated, and the patient's condition improved. Nonetheless the patient's condition worsened, and he was transferred to supportive care.

Conclusions. In conclusion, BNS is a rare but serious complication of WM, requiring early recognition and prompt treatment. In this case, Ibrutinib was crucial in managing BNS symptoms. Despite progress, better treatments and more effective management strategies are still needed.

Keywords: Bing-Neel syndrome, Waldenström Macroglobulinemia, large B cell lymphoma, MYD88 positive.

Abbreviations:

BNS - Bing-Neel syndrome
BTK inhibitor - Bruton Tyrosine Kinase Inhibitor
CNS - Central nervous system
CRAB - Hypercalcemia, renal dysfunction, anemia and bone lesions
CSF - Cerebrospinal fluid
CT - Computed tomography
GAD - Gadolinium
IgM - Immunoglobulin M
LPLs - Lymphoplasmacytic lymphocytes
MRI - Magnetic resonance imaging
WM - Waldenström Macroglobulinemia

INTRODUCTION

In 1936, Jens Bing and Axel Valdemar von Neel were the first to describe two autopsies with notable similarities: both patients had been hyperglobulinemic and exhibited neurological manifestations. During the examination, they identified lymphoplasmacytic lymphocytes (LPLs) within the central nervous system (CNS). Surprisingly, it was only eight years later when Jan Waldenström described a primary disease, now known as Waldenström Macroglobulinemia (WM). The condition first identified in 1936 is now known as Bing–Neel syndrome (BNS), a rare presentation of WM [1].

WM is a lymphoid neoplasm characterized by the uncontrolled proliferation of monoclonal LPLs in the bone marrow that produce immunoglobulin M (IgM) [2]. It accounts for only 1% to 2% of all hematologic malignancies [3]. BNS results are due to CNS infiltration with LPLs, which causes neurological symptoms. This condition is seen in ~1% of patients diagnosed with WM [4].

Usually patients with BNS experience ataxia, balance disorders, cranial nerve involvement, cognitive impairment, paresis, and motor or sensory symptoms [5].

Diagnosing BNS is challenging due to signs being heterogeneous with other etiologies. It is especially difficult to diagnose patients who previously were not diagnosed with WM and to differentiate neurological manifestations from complications

associated with WM, for example, IgM—related neuropathy, hyperviscosity syndrome, or circulatory disturbances [3]. Diagnosing WM is based on finding blood monoclonal IgM protein and LPLs in the bone marrow, as well as the presence of the MYD88 mutation in 90 % of cases. These findings along with clinical symptoms, lead to WM diagnosis [6].

Whereas BNS diagnosis is more complex. The biggest challenge of diagnosing BNS lies in the physician's ability to recognize new or worsening neurological symptoms in patients with known WM. Therefore, the diagnosis of BNS consists of previously mentioned tests for WM and mandatory MRI. Typical findings in the MRI include leptomeningeal enhancement, parenchymal lesions, or diffuse infiltrative patterns. Also, cerebrospinal fluid (CSF) analysis usually shows elevated protein levels, pleocytosis, and the presence of malignant LPLs. Measuring IgM levels in the CSF can also support the diagnosis, especially if they are elevated compared to serum levels [7]. As for molecular testing, it is crucial to test not only MYD88 and L265P but also CXCR4 mutations [7,8]. Early diagnosis of BNS is of utmost importance to prevent irreversible neurological damage.

The treatment of BNS has personalized regimens due to the lack of standardized protocols. BNS treatment mainly consists of high-dose chemotherapy that can penetrate the CNS, such as high-dose Methotrexate, Cytarabine, and Bendamustine. Rituximab is often used adjunctively despite limited CNS penetration [3]. Additionally, a BTK inhibitor - Ibrutinib shows promising results in improving symptoms and survival, but with potential cardiotoxicity side effects [9]. Furthermore, stem cell transplantation is an option: autologous stem cell transplantation shows promising outcomes [10]. Asymptomatic BNS can be managed by observation [3].

The prognosis for BNS varies depending on the extent of CNS involvement. Early detection and timely treatment can improve life expectancy [6].

CASE REPORT

A 71-year-old Caucasian male, with a 20-year history of chronic stage IV lymphoproliferative disorder (WM) and a positive MYD88 mutation presented for consultation.

From documentation it was known, that the patient in 2018 experienced severe headaches and underwent therapeutic plasmapheresis for hyperviscosity syndrome. Due to disease progression, manifesting as hyperviscosity syndrome, anemia, and thrombocytopenia, he was treated at the oncohematology department with eight courses of RCD chemotherapy. This resulted in a reduction of the IgM gradient from 49,8g/l to 32g/l, and a 53% response rate after six courses, as well as normalization of hemoglobin

and coagulation parameters. Following completion of the treatment partial remission was achieved.

In February 2022, the patient experienced recurrent epistaxis, rising concern for a relapse of hyperviscosity syndrome. Diagnostic testing subsequently confirmed the progression of the disease. After careful evaluation of the patient's general condition, age, and disease activity, treatment with glucocorticoids was initiated. In the event of inadequate response, it was planned to initiate imunochemotherapy according to the RCD regimen. Ultimately, eight courses were administered, achieving partial remission and granting 69% disease reduction. Over the subsequent six months no evidence of CRAB or hyperviscosity syndrome was observed. The patient remained in remission and asymptomatic until the time of this consultation.

Presently, the patient was admitted for further consultation due to fever up to 39°C lasting several days. Administered lab tests showed serological progression of the disease IgM gradient dynamics rose from 10,3 g/l to 33,8 g/l. No CRAB or hyperviscosity syndrome was present, for which the patient was previously treated.

On examination, skin and mucous membranes were slightly pale, peripheral lymph nodes exhibited no abnormalities, heart rate was rhythmic and tachycardic, blood pressure and respiratory rate were slightly elevated. Lung auscultation revealed coarse wheezing with occasional clear rales on both sides. Abdominal palpation showed a tender liver with no palpable spleen. No edemas were present. The patient was hospitalized for infection assessment and treatment.

A chest x-ray, abdominal ultrasound, blood tests, and blood culture were ordered and treatment with Fluconazole and Piperacillin/Tazobactam was initiated. The chest x-ray showed enlarged lymph nodes in the mediastinum and right lung root, along with fibrous scarring changes in the same lung and interstitial-perivascular changes in both lungs. Abdominal ultrasound revealed an enlarged spleen and small concernment in the left kidney.

After three days blood culture showed no growth, however, the patient’s condition remained severe, with daily fevers above 38°C, Vancomycin was added to the treatment. Subsequent lab tests revealed increasing C-reactive protein and creatinine levels, the glomerular filtration rate of 37ml/min, led to reduction of Vancomycin dose. Piperacillin/Tazobactam was changed to Meropenem. Additionally, a chest x-ray was ordered, revealing signs of hydrothorax, leading to prescription of intravenous Furosemide. Follow-up blood tests showed increase in creatinine levels and decrease in glomerular filtration rate, this was attributed to Vancomycin. Consequently, Vancomycin was replaced by Linezolid. 10-days after hospitalization the patient’s fever subsided,

however, 4 days later a subfebrile fever appeared due to the patient's refusal of treatment, C-protein remained at 175mg/l.

The following day, a neurologist was consulted, given the patient woke up with left facial droop and involuntary urination, the speech remained coherent. After examination neurologist diagnosed left facial nerve neuropathy and to clarify the etiology of the condition referred the patient for head CT to exclude cerebrovascular accident, lumbar puncture for possible neuroleukaemia, and head MRI for volumetric masses. Head CT showed no abnormalities. MRI findings revealed slight diffuse atrophic lesions and grade II internal hydrocephalus. Additionally, single foci of vascular origin in both cerebral hemispheres were found, as well as pronounced ferrodeposits in the globus pallidus and substantia nigra areas, indicating possible extrapyramidal lesions. The lumbar puncture uncovered the presence of LPLs in the spinal fluid, raising suspicion of BNS, therefore Ibrutinib was prescribed with flow cytometry later confirming the diagnosis.

Five days later blood tests showed pancytopenia and decreasing C-reactive protein levels, with the fever resolved, the patient's general condition improved. On the 34^{th} hospitalization day, the patient was discharged with a significantly improved condition.

Three months later the patient was hospitalized to neurological department due to significant symptom progression, primarily presenting with difficulty swallowing. A neurological consultation revealed severe hyperreflexic dysphagia without overt neuro-mediated symptoms. Pharyngography was prescribed to assess the stage of dysphagia, but the procedure could not be performed as the patient was unable to swallow contrast material. A repeat MRI showed previously noted changes. An otorhinolaryngologist was consulted, and examination revealed that the vocal folds exhibited minimal mobility, were fixed in a paramedial position, and the vocal cleft is narrowed but still patent for breathing. A diagnosis of bilateral partial paralysis of the vocal cords and larynx was concluded and a nasogastric probe for feeding was inserted.

In the absence of a primary neurological pathology to explain the dysphagia, the condition was attributed to progression of the oncohematological disease. The patient was subsequently transferred to the oncohematology department. Ibrutinib was initiated, however, the therapeutic response was insufficient. Consequently, treatment was escalated to high-dose methotrexate (3 – 6 g/m^2) and Rituximab (375 – 750 mg/m^2) administered intravenously, following the R-HDMtx chemotherapy protocol, given treatments ability to penetrate the hematoencephalic barrier.

Despite these interventions, no substantial clinical improvement was achieved. After exhausting specific treatment options, the patient was referred for further supportive care.

DISCUSSION

Although our understanding of BNS is more advanced than ever, significant uncertainties remain. Firstly, prompt diagnosis of this syndrome remains problematic. BNS is very heterogeneous, and has a wide spectrum of clinical presentation, with no specific symptomatology, therefore, it can be mistaken for various other illnesses [11]. However, in 74%-93% of cases the central nervous system is affected typically in diffuse manner [12]. Besides, BNS patients can remain asymptomatic even when their brain parenchyma or cerebrospinal fluid is infiltrated [11]. Furthermore, diagnosing BNS usually involves brain and spine MRI with intravenous Gadolinium (GAD), especially in T1, to exclude the other possible diagnoses. Abnormalities on MRI are found in up to 80% of BNS patients. Nevertheless, a normal MRI cannot eliminate BNS diagnosis. Also, CSF analysis is beneficial for the identification of this condition. The key element of BNS diagnosis is finding LPCs in CSF cytology or brain tissue biopsy. Regardless, the brain tissue biopsy is not considered a routine procedure [3,9].

Additionally, physicians find it difficult to differentiate BNS from WM complications, especially - hyperviscosity syndrome and polyneuropathy. Hyperviscosity syndrome is characterized by elevated levels of IgM (greater than 4 g/dL) and can present with nonspecific central nervous system symptoms, in comparison, BNS usually presents less than 1 g/dL in CSF, but not always. Polyneuropathy typically manifests as a symmetrical, ascending, progressive sensory polyneuropathy, often associated with IgM. The main aspect of the difference is that it can be linked to anti-myelin-associated glycoprotein (MAG) antibodies [13,14].

Another factor to consider is markers used for WM and BNS illnesses, for example, MYD88 mutations, can be found in other lymphoproliferative disorders, such as chronic lymphocytic leukemia or marginal zone lymphoma [15,16].

The main goal of BNS treatment is to alleviate symptoms and prolong the progression-free survival of the patients. We still do not have standard treatment guidelines. However, high-dose methotrexate, cytarabine, purine analogs, and bendamustine have all shown efficacy and are commonly used in practice. Nonetheless, due to their adverse effects, treatment should be individualized [2].

In this case, BKT inhibitor — ibrutinib was selected. From 2015 it has gained widespread use among clinicians. This medication showed markable efficacy in treating

WM with MYD88 and L265P mutations. It has been proven to penetrate the blood-brain barrier and induce a response in some CNS lymphoid tumor infiltrations [17-19]. In a study involving 28 patients with BNS who were treated with ibrutinib, 85% of them experienced symptomatic improvement [9].

Another treatment option is autologous stem cell transplant. This type of treatment showed remarkable results in small case series. 11 out of 14 patients with BNS had a positive response to the treatment, and 10 out of 14 remained in remission after three years [10].

The prognosis of BNS patients remains unclear. One study with 34 patients estimated a three-year survival rate of 59% [20], while another study involving 44 patients estimated a five-year survival rate of 71% [12]. We believe, that there is a lack of information about the etiology of WM and its complication, BNS. It's not fully understood why this syndrome occurs or why certain medications are effective. Furthermore, physicians lack clear patient treatment guidelines and still rely on personalized approaches to seek illness remission. Lastly, it is unknown if infectious diseases can trigger or accelerate BNS.

CONCLUSION

In conclusion, BNS is a rare but serious complication of WM. The most important aspects of treating BNS are early recognition and prompt treatment. For this specific case, first-line medication ibrutinib played the utmost role in managing symptoms of BNS, however as the disease progressed such treatment became insufficient. Despite our advanced understanding of BNS, there remains a substantial need for enhanced medications and more effective symptom management strategies. A deeper understanding is needed to create effective treatment protocols for BNS and discover new treatment options.

PATIENT CONSENT

Informed consent was obtained from the participant prior to his inclusion in the study.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

AUTHOR'S CONTRIBUTIONS

Conceptualization, Margarita. Gimbutytė., Sofija. Mančinskaja., Gertrūda. Dagytė.; investigation, Margarita. Gimbutytė., Sofija. Mančinskaja., Gertrūda. Dagytė.; resources,

Margarita. Gimbutytė.; writing—original draft preparation, Sofija. Mančinskaja., Gertrūda. Dagytė.; writing—review and editing, Margarita. Gimbutytė.; supervision, Margarita. Gimbutytė.; project administration, Margarita. Gimbutytė. All authors have read and agreed to the published version of the manuscript.

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