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Bing-Neel syndrome: a rare neurological complication of Waldenström macroglobulinaemia

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SUMMARY
Bing-Neel syndrome (BNS) is a very rare manifestation of Waldenström macroglobulinaemia (WM), in which lymphoplasmacytic cells invade the central nervous system. The clinical presentation includes symptoms of headaches, visual floaters, neuropathy, seizures and gait abnormalities. Here, we describe an elderly woman, who presented with complaints of visual floaters, progressive neuropathy and cognitive changes. Workup including a bone marrow biopsy confirmed the diagnosis of WM. Shortly afterwards, the patient experienced a seizure leading to hospitalisation, which revealed a right frontal lobe lesion on brain MRI. A biopsy of the lesion showed a small B cell lymphoma positive for an MYD88 mutation, confirming BNS. The patient was initially treated with ibrutinib, before transitioning to zanubrutinib. However, bevacizumab was discontinued later due to the development of proteinuria. Since then, the patient has been maintained on ibrutinib alone, taking a daily dose of 150 mg. She also has a medical history significant for glaucoma. She presented to the ophthalmology clinic with a complaint of ‘floaters’ in her right eye that had been present for the past year. She also complained of progressively worsening neuropathy in her fingers and toes, as well as worsening memory loss. Physical examination was significant for slowed responses to commands, but there were no focal neurological deficits and fundoscopic exam showed no abnormalities. She denied any family history of cognitive disorders, malignancy or severe visual deficits.

BACKGROUND
Waldenström macroglobulinaemia (WM) is an uncommon haematological malignancy characterised by IgM monoclonal gammopathy in the blood with the invasion of lymphoplasmacytic lymphoma (LPL) into the bone marrow. About 1000–1500 new cases are diagnosed annually in the USA. The manifestations of WM are usually related to the build-up of IgM paraprotein in the serum including hyperviscosity, peripheral neuropathy and cold agglutinin haemolytic anaemia. Rarely, the LPL infiltration can be extramedullary. Bing-Neel syndrome (BNS) is a very rare extramedullary manifestation of WM, in which LPL invades the central nervous system (CNS), resulting in neurological symptoms, such as cognitive deficits, visual disturbances, headaches or gait disorders. The true incidence of BNS is unknown, but at least 150 cases have been described in the literature, and it is estimated to complicate 1% of WM patients. Due to the heterogeneity of the presentation and the rarity of the disease, Bing-Neel syndrome remains a diagnostic challenge with emerging efforts to establish a consensus on diagnosis and treatment methods. Here, we present the case of a woman in her early 80s with BNS, who initially presented with visual floaters, cognitive changes and neuropathies in her extremities, followed by a seizure. This case highlights the need for adding BNS to the differentials whenever a patient with BNS presents with neurological symptoms and sheds light on BNS diagnosis and management.

CASE PRESENTATION
The patient is a woman in her early 80s with a history of non-small cell lung cancer diagnosed 14 years ago. The lung cancer showed a positive EXON 21 mutation and an absence of the T790M mutation. Her initial treatment included thoracotomy followed by 5 cycles of carboplatin/docetaxel. After the initial treatment, the patient was given maintenance therapy with erlotinib/bevacizumab. However, bevacizumab was discontinued later due to the development of proteinuria. Since then, the patient has been maintained on erlotinib alone, taking a daily dose of 150 mg. She also has a medical history significant for glaucoma. She presented to the ophthalmology clinic with a complaint of ‘floaters’ in her right eye that had been present for the past year. She also complained of progressively worsening neuropathy in her fingers and toes, as well as worsening memory loss. She denied decreased appetite, fevers, chills, weight loss or fatigue. Physical examination was significant for slowed responses to commands, but there were no focal neurological deficits and fundoscopic exam showed no abnormalities. She denied any family history of cognitive disorders, malignancy or severe visual deficits.

INVESTIGATIONS
The patient had an unremarkable complete blood count and kappa/lambda light chain ratio. However, quantitative serum immunoglobulin tests showed an isolated increase in IgM of 1039 mg/dL (normal range is 40–230 mg/dL). Also, serum protein electrophoresis with serum immunofixation showed a dense band of monoclonal IgM in the gamma area, raising suspicion for WM. A bone marrow biopsy showed a lymphoplasmaclastic non-Hodgkin’s lymphoma that was positive for an MYD88 mutation consistent with WM. At the time of diagnosis, the platelet count was 243 10^9/L, haemoglobin count was 12.1 g/L and beta 2 microglobulin count was 1.23 mg/L. Shortly thereafter, she developed a seizure and was admitted to the hospital. She underwent brain MRI, which showed a right frontal lobe lesion with surrounding perifocal oedema (figure 1). A stereotactic brain biopsy was performed, which showed a small B cell lymphoma positive for an MYD88 mutation (figure 2). The status of the CXCR4 mutation in our patient was not tested.

DIFFERENTIAL DIAGNOSIS
As the patient had evidence of monoclonal IgM gammopathy, evidence of WM on bone marrow...
1. Lymphoma. (A) Low power. (B) High power.

2. Bone marrow biopsy showing ≤10% infiltration by small lymphocytes with plasmacytoid or plasma cell differentiation, demonstrating lymphoplasmacytic features or lymphoplasmacytic lymphoma with an intertrabecular pattern. This criterion helps differentiate WM from IgM monoclonal gammopathy of undetermined significance, which has a benign prognosis. It is also consistent with the International Multiple Myeloma Working Group definitions, but it differs from the second international workshop on WM criteria, which considers any percentage of bone marrow infiltration sufficient to diagnose WM.12

The clinical presentation of BNS encompasses a wide variety of neurological symptoms, such as gait disorders, cognitive changes, focal neurological deficits and visual disturbances. Our patient presented initially with visual floaters followed shortly by a seizure episode. The diagnosis of BNS should be considered when a patient with WM develops CNS symptoms. The current gold standard for diagnosis is histological biopsy of neural tissue identifying a lymphoma with an MYD88 L265P mutation, such as in our patient. According to current diagnostic guidelines, the definitive diagnosis of BNS can be established through histological biopsy of the meninges or neural tissue when applicable. Alternatively, a thorough examination of cerebrospinal fluid (CSF) is essential, confirming the presence of LPL without evidence of transformation, along with B cell monoclonality determined by molecular analysis or flow cytometry. Radiological evidence may provide support, but it is considered insufficient for diagnosing BNS. Unfortunately, the status of the CXCR4 mutation in our patient was not determined. The CXCR4 receptor is a chemokine receptor that binds to the CXCL12 (SDF-1a) ligand, which promotes the migration of lymphoplasmacytic cells to the bone marrow stroma, promoting their survival and proliferation.14 In a prospective study of three patients with BNS, CXCR4 mutation was tested in the CSF of these patients and was negative.14 Interestingly, a CXCR4 mutation has been shown to confer intrinsic resistance to ibrutinib therapy in some patients with WM.15

In terms of brain imaging, patients with BNS may have either leptomeningeal involvement or a tumorous growth of single or multiple lesions. In our patient, a brain MRI showed a solitary brain mass with surrounding vasogenic oedema. As reported in the literature, leptomeningeal diffuse involvement form is more common than tumorous involvement in BNS.16

Current guidelines recommend treatment in symptomatic patients and monitoring in asymptomatic patients. There are currently no standardised treatment regimens, but therapeutic options have traditionally included intrathecal chemotherapy, brain radiation or high-dose systemic chemotherapy with methotrexate, cytarabine, bendamustine and fludarabine. When combined with bendamustine, rituximab achieved remission in a case reported in 2015,17 which subsequently encouraged its use in other cases.18 Rituximab monotherapy is not advised for BNS due to its limited penetration into the CNS.18 We considered trying a combination of lenalidomide and rituximab for our patient as this combination has been previously shown to have a 50% response rate for patients with WM.19 Notably, our patient did not experience the commonly associated side effect of aggravation anaemia with lenalidomide therapy.20 In Bing-Neel syndrome, which is characterised by CNS involvement of lymphoplasmacytic cells, we used lenalidomide/rituximab combination therapy to target both the systemic and CNS disease manifestations. However, it is important to emphasise that further studies and clinical trials are needed to establish the efficacy and safety of lenalidomide/rituximab combination therapy specifically
for Bing-Neel syndrome, as the available evidence is limited to only two cases now. The inclusion of our case in the discussion provides a valuable contribution to the existing literature, but caution should be exercised in extrapolating the findings to a broader population. Additionally, it is worth highlighting that it is difficult to differentiate single-agent versus double-agent responses.

In recent years, BTK inhibitors, such as ibrutinib and zanubrutinib, have been used as they have shown to improve efficacy in WM, it was shown that ibrutinib penetrates the blood-brain barrier and is also effective in BNS. Our patient was initially treated with ibrutinib but was subsequently switched to zanubrutinib due to a lower side-effect profile and superior CNS penetration. However, the patient had disease progression on a follow-up MRI of the brain 6 months later, for which whole-brain radiation therapy was initiated along with rituximab and lenalidomide maintenance therapy. Remission was achieved eventually despite the complicated course of treatment. The 3-year overall survival rate is 59%, and poor prognostic factors include older age (>65 years), thrombocytopenia and previous treatment for WM. Our patient was shown to be at intermediate risk according to the ISSWM scoring system, known for its utility in guiding treatment decisions and predicting 5-year survival rates in patients with WM.7

Data regarding the prognosis of BNS are scarce, and most of the existing evidence about treatment outcomes was prior to the introduction of BTK inhibitors.24 One retrospective case series reported a 5-year survival rate of 86% in BNS patients treated with ibrutinib.26 Prior to the introduction of ibrutinib, Simon et al reported a 5-year survival of 71% in their case series.20 BNS is a very rare, yet increasingly well-recognised, extramedullary manifestation of WM. Recent advances in treatment, such as the use of BTK inhibitors, have been reported to improve outcomes. However, BTK inhibitors failed to achieve remission in our patient and they were not well tolerated. Eventually, the initiation of whole-brain radiation and chemoimmunotherapy in our patient was successful in halting the disease progression.

Learning points

► Bing-Neel syndrome (BNS) should be considered in the differential diagnosis whenever a patient with Waldenström macroglobulinaemia presents focalising neurological symptoms or a seizure.
► Brain MRI in BNS might show either leptomeningeal enhancement or tumorous growth. Our patient was found to have a right frontal lobe mass, which was biopsied and the pathology was positive for MYD88 mutation.
► Bruton’s tyrosine kinase inhibitors were reported to be linked to improved outcomes in patients with BNS. However, our patient did not tolerate ibrutinib and developed disease progression on zanubrutinib.
► Whole-brain radiation and chemoimmunotherapy with lenalidomide and rituximab achieved disease remission in our patient; since this is only a single case, future clinical trials are needed to study this combination as a potential option. Caution should be exercised before using this option until more evidence is available.

Patient’s perspective

► As a long-time lung cancer survivor, I had been on alert for years to the possibility of brain metastases. But the ‘spot’ showing on my brain scans was not behaving like mets; they seemed to change size and shape, waxing and waning. My eyesight was deteriorating—seemingly beyond what would be expected due to my glaucoma. Rather, we suspected the brain lesion was interfering with my ability to see. My doctors urged close monitoring with non-invasive scans. They had concerns about possible lymphoma. I visited a top-notch neurosurgeon; he urged that a brain biopsy to secure tissue for conclusive analysis would be so invasive and potentially damaging that the risk-benefit did not make sense. He suggested I consider him a last resort. And then I had a seizure. It was terrifying. I thought I was screaming for help, but my family said I was rigid and huffing a bit, but otherwise silent. I went ahead with the brain biopsy, which confirmed an unusual syndrome that is the subject of this article. When the syndrome did not respond well to chemotherapy, I consulted with a trusted radiation oncologist, who advised whole-brain radiation (WBR). While the WBR positively affected the lesions, the cumulative impacts of my cancers and all of my anticancer treatments have been tough to bear, and of course, it is hard to figure out which progression or treatment causes which symptoms. Those symptoms, which I am living with now, include challenges to balance and movement, difficulties with short-term memory, digestive upset and skin breakdown—to name just a few. I have innate optimism and have developed a core of strength throughout my life. I credit those characteristics, combined with excellent medical professionals, for my survival today.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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