Bing-Neel Syndrome Successfully Managed by Ibrutinib: Case Report

Authors:
Awni Alshurafa[1], Anas Alsadi[2], Deena Sideeg Mudawi[1], Mohamed A. Yassin[1]

1. Hematology department, Hamad Medical Corporation, Doha, Qatar.
2. Internal medicine department, Hamad Medical Corporation, Doha, Qatar.

Corresponding author:
Dr. Awni Alshurafa
Hematology fellow
Hamad Medical Corporation
Doha, Qatar.
Contact Number: 0097430827390
E-Mail Address: dr.a.shurafa@gmail.com
Fax Number: 0097444397857
PO Box 3050, Doha, Qatar.

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Abstract:
This abstract describes a case of Waldenström macroglobulinemia and Bing-Neel syndrome in a 33-year-old male patient who initially presented with bleeding diathesis, diffuse lymphadenopathy, and splenomegaly. Subsequently, the patient experienced progressive limb weakness and drowsiness. The diagnosis was confirmed, and the patient showed clinical, biochemical, and radiological responses to treatment with ibrutinib, an oral Bruton tyrosine kinase (BTK) inhibitor. This case highlights the rare occurrence of Bing-Neel syndrome as a complication of Waldenström macroglobulinemia and suggests the potential effectiveness of ibrutinib as a therapeutic option in such cases.

INTRODUCTION:

- Waldenström macroglobulinemia is an uncommon clinical condition characterized by the presence of clonal lymphoplasmacytic cells infiltrating the bone marrow and a monoclonal IgM gammopathy in the bloodstream. Hyperviscosity-related symptoms, including vision problems, headaches, dizziness, and neurological issues, can be present in up to 30% of Waldenström macroglobulinemia patients. It is typically diagnosed in older individuals, with the median age at diagnosis being 70 years, while less than 10 percent of patients are diagnosed under the age of 50 years.

- Bing-Neel syndrome is a rare complication of Waldenström macroglobulinemia where malignant lymphoplasmacytic cells infiltrate the central nervous system. It presents with diverse symptoms such as headaches, cognitive deficits, cranial nerve palsies, paresis, spinal cord dysfunction, and psychiatric symptoms. The optimal treatment for BNS is not standardized due to its rarity and limited literature.

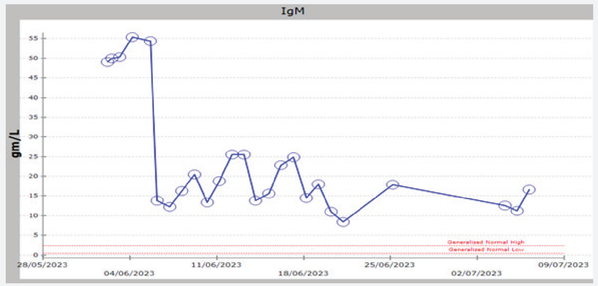
- The choice of systemic treatment should be individualized, considering factors such as patient condition, medical history, patient preference, and the physician's experience. Various treatment options, including intrathecal, intraventricular, targeted therapy, and systemic chemotherapy that has demonstrated or is likely to penetrate the blood-brain barrier, can be considered. However, one notable treatment option is the oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib, which is approved in the United States and Europe for symptomatic Waldenström macroglobulinemia.

- Herein, we report a 33-year-old male patient who presented with bleeding diathesis, diffuse lymphadenopathy and splenomegaly. He developed abrupt progressive limb weakness and drowsiness. He has been diagnosed with Waldenstrom macroglobulinemia and Bing-Neel syndrome and he showed clinical, biochemical and radiological response to ibrutinib.

CASE PRESENTATION:

- Our patient is a 33-year-old Sudanese gentleman with no significant medical and surgical history. He noticed black tarry stool one week before presentation associated with five kilogram weight loss in two months duration, gum bleeding during tooth brush of almost three weeks duration and intermittent dizziness. Physical examination revealed splenomegaly with palpable bilateral axillary and inguinal lymphadenopathy. Initial blood work was remarkable for normocytic anemia with hemoglobin of 7.6 g/dl, MCV of 84.1 fl, INR of 1.6 and a protein gap of 83 g/l with total protein 105 g/l and albumin 22 g/l. Renal function, liver function and aPTT were unremarkable. Esophagogastroduodenoscopy showed evidence of mild gastritis and ultrasound abdomen confirmed hepatosplenomegaly. Peripheral smear showed increased rouleaux formation and serum protein electrophoresis revealed monoclonal IgM kappa in gamma region and IgM level was > 58.5 g/l.

FDG PET/CT scan showed hypermetabolic lymphadenopathy in the neck, axillae, chest, abdomen and pelvis along with splenomegaly with increased distal uptake, moderately hyperplastic bone marrow and small right lung nodule that is suggestive of lymphoproliferative disorder and lymphoma.(see image)
The patient underwent axillary lymph node and bone marrow biopsy. Next day he developed drowsiness, quadriplegia and urinary retention. Provisional diagnosis of hyperviscosity syndrome was made and he was started on pulse steroid and plasmapheresis. MRI head and spinal cord revealed an abnormal T2/FLAIR signal intensity involving bilateral cerebral deep white matter extending throughout basal ganglia and internal capsules to the brainstem and upper cervical cord up to C4-5 level (Image 1). Postcontrast images show diffuse supra/infratentorial sulcal and basal ganglia perivascular and pattern of enhancement involving the leptomeninges. Suspected perivascular enhancement also along the upper cervical cord (see image).
Weakness improved with repeated sessions of plasmapheresis. Meanwhile, axillary lymph node biopsy revealed malignant plasma cell proliferation (further details are needed from pathology report) and bone marrow biopsy confirmed involvement of bone marrow by a lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia. (further details are needed from pathology report). Patient was diagnosed with Waldenstrom macroglobulinemia along with Bing-Neel syndrome. CNS involvement which has been suggested by MRI findings was planned to be confirmed by lumbar puncture. However, it was difficult initially as patient was not cooperative and has bleeding diathesis. It was done few weeks after hospital admission and result showed 11 WBCs, 93% of them are lymphocytes and CSF protein of 0.85 gm/l. Patient was started on ibrutinib 560 mg daily and he showed clinical, biochemical and radiological improvement. Figure 1 showed level of IgM and its response to treatment.



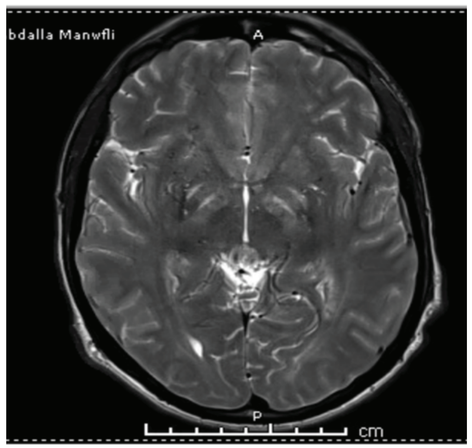


Image 1: Abnormal T2/FLAIR signal intensity involving bilateral cerebral deep white matter extending throughout basal ganglia and internal capsules to the brainstem and upper cervical cord up to C4-5 level.

He regained his functional status and follow up FDG PET/CT one month later showed improvement and resolution of hypermetabolic lymph nodes and regression of splenomegaly. His hospital course was complicated by central-line infection that treated effectively with antibiotics and then he was discharged and planned to continue ibrutinib along with rituximab as outpatient.

DISCUSSION:

- Bing-Neel syndrome can occur in individuals with Waldenström macroglobulinemia, even without systemic progression, and it can also be the first indication of both Bing-Neel syndrome and Waldenström macroglobulinemia, leading to a simultaneous diagnosis of both conditions. The exact incidence of Bing-Neel syndrome is uncertain; however, based on a retrospective cohort study involving 1,523 individuals diagnosed with Waldenström macroglobulinemia, only 13 patients (0.8%) were identified with Bing-Neel syndrome, indicating a very low prevalence.

- Treatment becomes more complex when Bing-Neel syndrome is diagnosed with Waldenström macroglobulinemia, as it necessitates addressing both systemic disease and the central nervous system involvement by selecting medications that can effectively penetrate the blood-brain barrier and target the underlying pathology. A multidisciplinary approach involving hematologists, neurologists, radiologists, pathologists, and other specialists is crucial for the optimal management of Bing-Neel syndrome. The optimal treatment for BNS is not standardized due to its rarity and limited literature. Several treatment options are available for Bing-Neel syndrome (BNS), including high-dose methotrexate (MTX), high-dose cytarabine, fludarabine, cladribine, bendamustine, and radiation therapy. Bruton's tyrosine kinase inhibitors such as ibrutinib, and acalabrutinib, are being used in the treatment of Waldenström macroglobulinemia.

- Multiple studies have shown that ibrutinib has the ability to cross the blood-brain barrier in patients with different B-cell malignancies, including Waldenström macroglobulinemia (WM). These studies have demonstrated that ibrutinib can have an impact on central nervous system (CNS) disease in lymphomas that are responsive to ibrutinib treatment. It is administered at a daily dose of 420 mg, which has shown effectiveness in treating WM. Furthermore, recent reports indicate that a dose of 560 mg, similar to the dosage used in Mantle cell lymphoma, is also effective in treating WM and possesses the ability to cross the blood-brain barrier. However, the optimal dosage and treatment schedule of ibrutinib for CNS disease are still not fully understood and require further clarification. A multicenter study investigated the effectiveness of ibrutinib in treating Bing-Neel syndrome. Twenty-eight BNS patients received ibrutinib monotherapy, with doses of 420 mg or 560 mg administered orally once daily. Within three months of therapy, 85% of patients experienced symptomatic improvements, 60% showed radiologic improvements, and 47% achieved clearance of the disease in the cerebrospinal fluid. The study reported promising survival rates, including a 2-year event-free survival rate of 80%, a 2-year ibrutinib survival rate of 81%, and a 5-year BNS survival rate of 86%.

- In our patient, using of ibrutinib at a daily dose of 560 mg resulted in clinical improvement of neurological symptoms and radiological improvement of lymphadenopathy and splenomegaly. This may provide additional evidence about the effectiveness of treatment for WM and Bing-Neel syndrome using Bruton's tyrosine kinase inhibitors.

DECLARATION:

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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ETHICAL DISCLOSURE:

The case approved by Hamad Medical Corporation Medical Research Center and the patient signed written informed consent for the publication of any potentially identifiable images or data included in this article.

AUTHORSHIP CONTRIBUTION:

The authors contributed equally to the manuscript.