Bing–Neel Syndrome in a Patient with Waldenstrom's Macroglobulinemia: A Challenging Diagnosis in the Face of Normal Brain Imaging

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Waldenstrom's macroglobulinemia (WM) is a clinicopathological entity defined by lymphoplasmacytic lymphoma in bone marrow with an immunoglobulin M (IgM) monoclonal gammopathy in blood [1]. Central nervous system (CNS) manifestations in patients with WM are usually a result of serum hyperviscosity [2]. In some patients, central neurological symptoms can be caused by direct infiltration of CNS by malignant cells, also known as Bing–Neel syndrome (BNS) [3,4]. Diagnosis of BNS is usually suspected in patients with WM who exhibit CNS symptoms and abnormal brain magnetic resonance imaging (MRI) findings, which can then be confirmed with cerebrospinal fluid (CSF) analysis and/or biopsy [5,6]. We report a case of WM with recurrent neurological symptoms and normal brain MRI where CSF flow cytometry and immunofixation electrophoresis clinched the diagnosis of BNS.

A 67-year-old female developed progressive anemia and was diagnosed with WM. She achieved partial response with five cycles of rituximab and bendamustine. Eighteen months later, she developed fatigue, pancytopenia, and cognitive decline. Bone marrow biopsy showed lymphoplasmacytic (LPL) infiltration of marrow space and recurrence of WM, following which she received two cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Posttreatment marrow showed minimal residual disease and normalization of M-spike. Over a period of next 11 months, she continued to have progressive cognitive decline. Blood work showed increased levels of serum IgM, and computed tomography (CT) scan of torso showed diffuse lymphadenopathy. Given the rapidly progressive decline in cognition, brain MRI was performed, and it did not reveal any abnormality. However, subsequent comprehensive panel of CSF studies showed evidence of direct CNS LPL infiltration. Differential

cell count of CSF revealed predominant lymphocytosis, flow cytometry analysis detected CD45, CD19, and lambda light chains, and CSF immunofixation electrophoresis unveiled IgM monoclonal protein. A paraneoplastic auto-antibody (PNA) panel including anti-Hu, anti-Yo, and anti-Ri antibodies was negative. Diagnosis of BNS was made based on the above findings. Thereafter, patient received salvage treatment with intravenous rituximab, dexamethasone, high-dose cytarabine, carboplatin (R-DHAC) and intrathecal methotrexate, cytarabine, and hydrocortisone. With the use of intrathecal chemotherapy, significant decrease in cognitive deficit and fatigue was noted. Mini-mental state examination (Folstein Test) score improved from 14/30 to 26/30, and 9-item fatigue severity scale (FSS) score improved from 50 to 28. In addition, CSF abnormalities resolved completely, and positron emission tomography (PET) scan after two cycles of salvage chemotherapy showed complete metabolic response with resolution of lymphadenopathy. Bone marrow biopsy after three cycles of salvage R-DHAC revealed no plasmacytic involvement, and patient underwent autologous stem cell transplant (Table 1).

Our patient was recognized to have central neurological symptoms from direct tumor infiltration of the CNS, and not merely due to hyperviscosity of the CNS blood vessels, making it a case of BNS. Paraneoplastic syndrome is unlikely to be a cause of this patient's CNS symptoms despite the evidence of increased IgM monoclonal protein in CSF. This is because (1) the plasma PNA panel (involving known PNAs) was negative, and (2) the fact that IgM auto-antibodies in plasma, if any, would lack capacity to cross blood–brain barrier. Presence of IgM in the CSF almost always occurs as a result of direct tumor infiltration of CNS. Even though our patient's CSF was tested positive for both lymphoplasmacytic

Table 1 Comparison of clinical and investigational parameters in the patient before and after treatment with intrathecal chemotherapy

Parameter	Before treatment with ITC (Patient received only SC)	After treatment with ITC (Patient received ITC along with SC)
Cognition	Poor cognition (MMSE 14/30)	Improved cognition (MMSE 26/30)
Fatigue	Fatigue (FSS 50)	Improved fatigue (FSS 28)
S. Protein electrophoresis	Elevated serum IgM	No abnormality
CSF differential cell count	Predominant lymphocytosis	No abnormality
CSF flow cytometry	CD45+, CD19+, λ light chains	No abnormality
CSF immunoelectrophoresis	IgM monoclonal protein	No abnormality
PET-CT scan of torso	Hypermetabolic activity	Complete metabolic response
Bone marrow biopsy	LPI infiltration	Resolution of LPI infiltration
Brain MRI	No abnormality	No abnormality

ITC, Intrathecal chemotherapy; SC, Systemic chemotherapy; MMSE, Mini-mental state examination; FSS, Fatigue Severity Scale; S. Protein, Serum protein; IgM, Immunoglobulin M; CSF, Cerebrospinal fluid; PET-CT, Positron emission tomography-computed tomography; MRI, Magnetic resonance imaging; LPI, Lymphoplasmacytic.

cells and monoclonal antibodies, the latter finding is not a prerequisite to confirm the diagnosis of BNS. Less than 50 cases of BNS have been described in the literature so far. Our patient was unique in having normal brain imaging findings despite the diagnosis of BNS. Authors believe that one is more likely to have normal brain imaging in the setting of diffuse form of BNS, as opposed to tumoral form of BNS. In diffuse form, lymphoplasmacytoid cells are localized to leptomeninges, which may be missed by brain MRI in rare circumstances. This case underscores the importance of performing CSF flow cytometry and immunofixation electrophoresis in diagnosing BNS, especially in patients

with WM with persistent central neurological symptoms. These patients require intrathecal chemotherapy in addition to systemic treatment. Alternatively, cranial irradiation can be considered along with systemic treatment. Failure to identify this subset of patients with WM (who have BNS with normal brain MRI) will inevitably result in disease progression, which can be fatal.

Conflict of Interest

The authors declare no conflict of interest.

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