LETTER TO THE EDITOR

To The Editor

Bing–Neel Syndrome Mimicking Lower Motor Neuron Predominant Amyotrophic Lateral Sclerosis

Waldenström macroglobulinemia (WM) is a rare hematological malignancy, defined as a lymphoplasmacytic lymphoma (LPL) with immunoglobulin M (IgM) paraprotein.[1] Rarely, LPL will infiltrate the central nervous system (CNS), an entity termed Bing–Neel syndrome (BNS). We describe an atypical BNS case, with a lower motor neuron-predominant presentation mimicking amyotrophic lateral sclerosis (ALS).

A 74-year-old male with WM and type I cryoglobulinemia, in remission following bendamustine chemotherapy 4 years prior, and type 2 diabetes mellitus complicated by retinopathy and nephropathy was referred to our center with 24 weeks of slowly progressive, painless lower greater than upper extremity weakness, with subsequent diffuse muscle atrophy and fasciculation, without bulbar involvement. On examination (week 24), facial, palatal, and tongue musculature was preserved, and jaw jerk absent. Atrophy and fasciculations were present throughout all extremities and thoracic and lumbar paraspinals. Tone was reduced in lower extremities. Upper extremities were symmetrically weak proximally and distally (4−/5), as were lower extremities (3/5), save for left iliopsoas (2/5). He was areflexic, with downgoing plantars. There was unchanged, long-standing sensory loss to pinprick to mid-shin bilaterally and reduced vibratory sensation to the ankles, attributed to diabetic polyneuropathy.

Prior investigations by the primary care physician (week 16), including complete blood count and differential, electrolytes, magnesium, calcium, creatinine, urea, creatine kinase, C-reactive protein, liver enzymes, and bilirubin, were normal. Serum protein electrophoresis (SPEP) was normal but had previously identified an IgM kappa peak (7 g/L) with the initial WM presentation that resolved with treatment. Contrast computed tomography (CT) of the head, chest, abdomen, and pelvis was unremarkable. Pre-referral, outpatient nerve conduction studies (week 20, where clinical findings and pattern of weakness were similar to week 24, save for increased strength in the upper and lower extremities at 4+/5 and 4−/5, respectively) demonstrated axonal sensorimotor polyneuropathy. F-response was tested only in left tibial nerve and showed mildly prolonged latency. Electromyography demonstrated active denervation potentials (predominantly fibrillation potentials and/or positive sharp waves with fewer fasciculations) and chronic neurogenic changes in bilateral tibialis anterior, right gastrocnemius, bilateral vastus medialis, and left first dorsal interosseous. Active denervation potentials only without chronic neurogenic changes were observed in left gastrocnemius, deltoid, and triceps. Electromyography of tongue was normal, while thoracic paraspinal muscles demonstrated pervasive motor unit action potentials from incomplete relaxation.

The rapidly progressive weakness, physical examination, and electrodiagnostic findings gave consideration to the diagnosis of lower motor neuron-predominant ALS, among other important mimics. Multifocal motor neuropathy progresses more slowly, motor-predominant chronic inflammatory demyelinating polyradiculoneuropathy typically has a relapsing-remitting course,

and both have demyelinating features on electrophysiology not seen in our patient. The axonal sensorimotor polyneuropathy demonstrated on nerve conduction studies was attributed to diabetes based on a 20-year history of disease; however, the relatively equivalent proximal and distal weakness and presence of active denervation in proximal muscles would argue against a length-dependent axonal polyneuropathy as the sole cause of this presentation. Electromyography of abdominals and other paraspinal levels may have been helpful to distinguish an axonal polyneuropathy or motor neuropathy from a more proximal process, such as diffuse polyradiculopathy or motor neuronopathy, with active denervation being expected in these regions in the latter. However, abdominal or paraspinal studies might not be able to differentiate between polyradiculopathy from leptomeningeal disease and motor neuron disease. Symptomatically, the patient did not report radicular pain. Therefore, in view of the extensively normal pre-referral systemic workup, anterior horn cell disease was initially considered more likely than infiltrative or paraneoplastic polyradicular disease.

Repeat SPEP (week 24) demonstrated recurrence of a monoclonal IgM kappa peak (2 g/L). Type I cryoglobulinemia was detected. Cerebrospinal fluid (CSF) analysis revealed 260 white blood cells/mm^3, protein 172 mg/dL, and glucose 4.7 mmol/L. Fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT demonstrated hypermetabolism in biparietotemporal cerebral cortex (considered nonspecific, but compatible with CNS lymphoma [Figure 1(A)]), along the right parotid gland corresponding to right facial nerve perineural thickening and enhancement on magnetic resonance imaging (MRI) [Figure 1(B)], and along the brachial and lumbosacral plexi and sciatic nerves bilaterally [Figure 1(C–D)]. Contrast-enhanced MRI of brain and cervical, thoracic, and lumbosacral spine revealed enhancement along the conus medullaris with thickening and enhancement of the cauda equina [Figure 1(D)]. CSF flow cytometry subsequently demonstrated a monoclonal population of small lymphoid cells with plasmacytoid features and kappa restriction, confirming relapsed LPL in CSF and a diagnosis of BNS. While awaiting chemotherapy, the patient developed acute hypoxemic respiratory failure and digital ischemia secondary to hyperviscosity and cryoglobulinemia. Palliative measures were pursued and he passed away 2 days later.

BNS is a rare complication of WM and likely underrecognized, owing to protean clinical manifestations dependent on site of tumoral infiltration.[2] Diagnostic delay of several months was common in cohort studies.[2,3] Epidemiological data are lacking, and prevalence is unknown; however, a retrospective study of patients with WM, which has an age- and sex-adjusted incidence of 0.57 per 100,000 person-years,[1] demonstrated only 0.8% progressed to BNS.[4] Up to one-third of BNS patients present without preceding WM diagnosis.[2] Two disease forms are recognized: a diffuse form defined by leptomeningeal infiltration and a tumoral form whereby lymphomatous cells form clusters within CNS parenchyma.[5] Diagnostic criteria were recently defined: biopsy of the CNS parenchyma or meninges demonstrating LPL is the gold standard; however, where biopsy is unattainable, CSF evidence of LPL by flow cytometry is accepted as evidence of leptomeningeal disease.[5] Contrast-enhanced MRI of brain and spinal cord is recommended for supportive evidence of leptomeningeal disease,
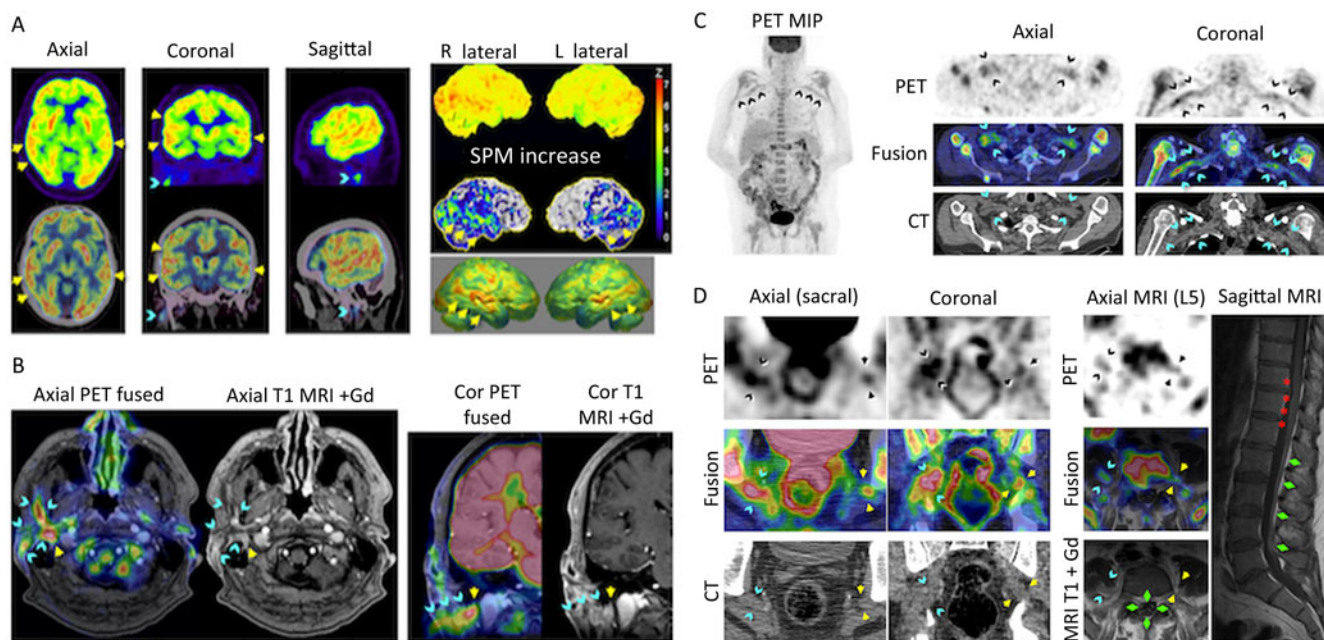
Figure 1: Leptomeningeal infiltration in Bing–Neel syndrome. (A) Left paired panels with PET only (top row) and PET fused to CT (bottom row): axial, coronal, and sagittal reformats from brain FDG-PET/CT demonstrating hypermetabolism (▶ yellow arrowheads) in biparietal and temporal regions, right greater than left; also, right parotid hypermetabolism (❯ blue chevrons). Right panels: right lateral and left lateral views showing hypermetabolism on surface projection map (SPM) (top row); corresponding hypermetabolism on statistical parametric mapping to age- and gender-matched normal control population database (middle row); hypermetabolism in bilateral parietotemporal regions on 3D surface renderings (bottom row). (B) Axial (left pair) and coronal (right pair) FDG-PET fused to 3D T1 MRI with gadolinium enhancement, showing hypermetabolism (❯ blue chevrons) corresponding to heterogeneous branching enhancement tracking along right facial nerve branches within right parotid gland, and extending medially and superiorly into stylomastoid foramen (▶ yellow arrowheads). (C) Hypermetabolism along bilateral brachial plexus distribution, tracking paralleling the subclavian and axillary arteries and veins, but without continuation of hypermetabolism medially into the mediastinum, as expected for brachial plexus (❯/❯ black/blue chevrons). Left panel showing MIP from whole-body PET. Right set of panels showing supraclavicular/shoulder region with axial (left) and coronal (right) reformats from FDG-PET/CT, with PET only (top), PET fused to CT (middle), and CT only (bottom). (D) Left pair of panels from whole-body FDG-PET/CT with axial (left) and coronal (right) reformats; PET only (top row), PET to CT fusion (middle row), and CT only (bottom row). Severe right sciatic nerve hypermetabolism on FDG-PET/CT (❯/❯ black/blue chevrons), with much milder left sciatic nerve hypermetabolism (▶ yellow arrowheads), with associated asymmetric thickening of right sciatic nerve on CT (bottom panels, ❯ blue chevrons). Second from right-hand panels from whole body FDG-PET fused to axial T1 MRI with gadolinium enhancement, showing right (❯ blue chevrons) greater than left (▶ yellow arrowheads) lumbosacral plexus thickening and enhancement with associated hypermetabolism, as well as enhancement of nerve roots along cauda equina (♦ green diamond). Right-most panel with post-gadolinium T1-weighted sagittal MRI of lumbosacral spine demonstrating diffuse thickening and enhancement of cauda equina (♦ green diamonds) with associated enhancement along conus medullaris and ventral spinal cord (★ red stars). MIP, maximum intensity projection.

however, may be normal. FDG-PET/CT findings of neurolymphomatosis in BNS have not been previously reported, and our report adds to literature suggesting that FDG-PET/CT may identify sites of neurolymphomatosis not detected by contrast-enhanced MRI.[6] Enhanced detection of nervous system infiltration in cases of hematologic malignancies may be a valuable tool in differentiating direct invasion, such as in neurolymphomatosis, from paraneoplastic syndromes, of which motor neuron presentations have been described in hematologic malignancies and solid organ tumors.[7] FDG-PET/CT is a useful adjunct, as many cases of paraneoplastic syndromes do not have associated onconeural antibodies, and paraneoplastic syndromes can be the index presentation of malignancy. A recent consensus statement on therapy recommends short courses of steroids to achieve a rapid clinical response with subsequent systemic therapy with methotrexate, cytarabine, fludarabine, cladribine, or bendamustine recommended based on protocols for WM.[1] Rituximab may complement the aforementioned chemotherapeutics, while intrathecal therapy may be used for disease confined to leptomeninges.

Our patient's clinical presentation and electromyographic evidence of active and chronic denervation in cervical and lumbosacral segments and clinically observed atrophy and fasciculations in thoracic segments chiefly raised concern for lower motor neuron-predominant ALS and would have met both revised 2015 El Escorial and Awaji diagnostic criteria for ALS, had the alternative diagnosis of BNS not been made, underscoring the importance of ruling out other etiologies of the presentation.[8] This highlights the lower specificity of the revised 2015 El Escorial criteria, which was created to facilitate earlier diagnosis and expedited specialist referral, relative to earlier, more stringent criteria. This case also highlights the variable presentation of BNS and the diagnostic challenge it presents. BNS may be the index presentation of WM or there may be no evidence of progression of WM prior to the development of BNS.[1] In our case, neurological symptoms were apparent before recurrent elevation of IgM paraprotein was detected by SPEP.

Our patient's weakness was likely multifactorial; the subacute decline with associated diffuse FDG-PET/CT abnormalities consistent with neurolymphomatosis involving the brachial/lumbosacral plexi and cauda equina suggests that infiltrative axonal radiculoplexus neuropathy was primarily responsible,

with relatively lesser contribution from less extensive leptomeningeal lymphomatosis involving the ventral lumbosacral spinal cord. Contribution from a paraneoplastic neuropathy cannot be excluded, and premorbid, stable diabetic axonal polyneuropathy is also acknowledged.

Ultimately, the neurologist's recognition of BNS in the differential diagnosis of lower motor neuron disease is paramount, as treatment of BNS and associated paraproteinemic complications, including hyperviscosity, can prevent accrual of further disability.[5]

DISCLOSURES

GB, BNP, ANW, RH, CP, and SK have nothing to disclose.

STATEMENT OF AUTHORSHIP

GB was responsible for the study concept and writing of the manuscript. BNP and ANW were responsible for writing of the manuscript. RH was responsible for figure preparation and writing of the manuscript. CP and SK were responsible for study supervision and critical revision of the manuscript for intellectual content.

Grayson Beecher iD
Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Alberta, Canada

Brendan Nicholas Putko
Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Alberta, Canada

Amanda Nicole Wagner
Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Alberta, Canada

Ryan Hung iD
Department of Radiology and Diagnostic Imaging, University of Alberta, Edmonton, Alberta, Canada

Cecile Phan
Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Alberta, Canada

Sanjay Kalra
Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Alberta, Canada

Correspondence to: Grayson Beecher, Department of Medicine, Division of Neurology, University of Alberta, 7-132F Clinical Sciences Building, 11350 - 83 Ave., Edmonton, Alberta T6G 2G3, Canada. Email: beecher@ualberta.ca

REFERENCES

1. Gertz MA. Waldenstrom macroglobulinemia: 2019 update on diagnosis, risk stratification, and management. Am J Hematol. 2019; 94(2):266–76.
2. Simon L, Fitsiori A, Lemal R, et al. Bing-Neel syndrome, a rare complication of Waldenstrom macroglobulinemia: analysis of 44 cases and review of the literature. A study on behalf of the French Innovative Leukemia Organization (FILO). Haematologica. 2015;100(12):1587–94.
3. Castillo JJ, D'Sa S, Lunn MP, et al. Central nervous system involvement by Waldenstrom macroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study. Br J Haematol. 2016; 172(5):709–15.
4. Kulkarni T, Treon SP, Manning R, et al. Clinical characteristics and treatment outcome of CNS involvement (Bing-Neel syndrome) in Waldenstrom's macroglobulinemia. Blood. 2013;122(21):5090.
5. Minnema MC, Kimby E, D'Sa S, et al. Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome. Haematologica. 2017;102(1):43–51.
6. Grisold W, Grisold A, Marosi C, et al. Neuropathies associated with lymphoma(dagger). Neurooncol Pract. 2015;2(4):167–78.
7. Mele N, Berzero G, Maisonobe T, et al. Motor neuron disease of paraneoplastic origin: a rare but treatable condition. J Neurol. 2018;265(7):1590–9.
8. Ludolph A, Drory V, Hardiman O, et al. A revision of the El Escorial criteria - 2015. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(5–6):291–2.