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TOPIC REVIEW

Bing–Neel syndrome: an illustrative case and a comprehensive review of the published literature

Roneil G. Malkani · Martin Tallman · Numa Gottardi-Littell · William Karpus · Laura Marszalek · Daina Variakojis · Bruce Kaden · Matthew Walker · Robert M. Levy · Jeffrey J. Raizer

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Abstract Waldenstrom's macroglobulinemia (WM) is a chronic lymphoproliferative disorder within the spectrum of lymphoplasmacytic lymphoma characterized by proliferation of plasma cells, small lymphocytes, and plasmacytoid lymphocytes. Central nervous system involvement is very rare (Bing–Neel [BN] syndrome). We present the case of a 62-year-old woman previously diagnosed with WM who presented with Bing–Neel syndrome and review the published literature which consists of only case reports. We performed a Medline search using the terms "Waldenstrom's macroglobulinemia and central nervous system" and "Bing–Neel" collecting data on presentation, evaluation, treatment, and outcome and summarizing these findings in the largest pooled series to date. Central nervous system manifestations are localization related. Serum laboratory testing reflects systemic disease. Cerebrospinal fluid analysis may show lymphocytic pleocytosis, elevated protein, and IgM kappa or lambda light chain restriction; cytology results are variable. Imaging is frequently abnormal. Biopsy confirms the diagnosis. Treatment data are limited, but responses are seen with radiation and/or chemotherapy. BN syndrome is a very rare complication of WM that should be considered in patients with neurologic symptoms and a history of WM. Treatment should be initiated as responses do occur that may improve quality of life and extend it when limited or no active systemic disease is present.

Keywords Bing–Neel syndrome · Waldenstrom's macroglobulinemia · Rituximab · Central nervous system · Neurologic complications

R. G. Malkani · J. J. Raizer (✉)
Department of Neurology, Northwestern University, Feinberg School of Medicine, 710 North Lake Shore Dr., Abbott Hall Room 1123, Chicago, IL 60611, USA
e-mail: jraizer@nmff.org

M. Tallman
Section of Hematology/Oncology, Department of Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

N. Gottardi-Littell · W. Karpus · L. Marszalek · D. Variakojis
Department of Pathology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

M. Walker
Department of Radiology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

R. M. Levy
Department of Neurosurgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

B. Kaden
Department of Oncology-Hematology, Advocate Lutheran General Hospital, Park Ridge, IL, USA

Introduction

Waldenstrom's macroglobulinemia (WM), as defined by the World Health Organization, is defined as a lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration [1]. It is characterized by anemia and lymphoplasmacytic infiltration of the bone marrow and often lymph nodes, spleen, and rarely other extranodal sites. Infiltration in the central nervous system (CNS) is very rare and referred to as Bing–Neel (BN) syndrome. To date, only case reports and several very small patient series have been published. We present a case of BN syndrome including diagnosis, evaluation, and treatment. We searched Medline using the search terms

"Waldenstrom's macroglobulinemia and central nervous system" and "Bing–Neel" and reviewed the literature for all cases of CNS involvement to analyze the characteristics of this complication, treatments used and outcomes thus creating the largest pooled series of 32 patients.

Case report

A 62-year-old right-handed woman with a history of WM presented in 2006 with headache, sudden onset aphasia, and a right lower facial droop of 30 min duration. In the week prior, she had malaise, nausea, and headache which all resolved.

She was diagnosed with WM in 1994 with IgM macroglobulinemia and hypercellular bone marrow consisting of small lymphocytes and plasmacytoid lymphocytes. She was monitored for 4 years but then developed worsening anemia and more prominent bone marrow involvement. She was treated with 2-chlorodeoxyadenosine (2-CdA, cladribine) in 1998 with partial remission. After relapsing, she was treated with rituximab in 2000 and again in 2003, but she developed pleurisy with effusion, so rituximab was stopped and 2-CdA was restarted with some response. In 2004 she was treated with bortezomib; during this time, she developed transient word finding difficulty (November 2004) and was diagnosed with a transient ischemic attack related to a newly discovered patent foramen ovale (PFO). Anticoagulation with warfarin was started; bortezomib was discontinued. WM relapsed in 2005 and she was treated with rituximab, cyclophosphamide, vincristine, and dexamethasone for six cycles followed by maintenance rituximab every 3 months. Another transient episode of aphasia occurred 2 months prior to admission and she was continued on warfarin. She also had recurrent pleural effusions, requiring bilateral chest tube thoracostomy placement for drainage and pleurodesis; the etiology of the effusions was unknown but no malignant cells were seen. She also developed paroxysmal supraventricular tachycardia which was treated with metoprolol.

On presentation in 2006 her examination was unremarkable except for aphasia with poor comprehension and fluency, dysnomia, and a mild right lower facial weakness. Laboratory examination revealed an erythrocyte sedimentation rate of 50 mm/h, INR 3.4, and serum viscosity 1.5 centipoise (normal 1.4–1.8 centipoise). Serum protein electrophoresis and immunofixation revealed a restricted gamma band and monoclonal IgM kappa light chains. Quantitative serum IgM was 393 mg/dl. Cryoglobulin testing was negative.

Electroencephalogram showed mild diffuse cerebral dysfunction and moderate left frontotemporal slowing but no epileptiform discharges. Computed tomography (CT) of the head showed patchy and confluent hypoattenuation in the periventricular and deep subcortical white matter, with some focal predominance involving the anterior limb of the left internal capsule. Magnetic resonance imaging (MRI) of the brain is shown in Fig. 1. There was no diffusion restriction. MR angiogram and venogram were unremarkable. The PFO previously diagnosed was not seen on the current echocardiogram.

Cerebrospinal fluid (CSF) examination revealed an opening pressure of 270 mm H_2O, 11 white blood cells/mm^3, glucose 47 mg/dl (serum glucose 97 mg/dl), and protein 136 mg/dl. IgG index was 0.42. Protein electrophoresis immunofixation of the CSF showed the presence of monoclonal IgM kappa gammopathy. CSF cytology and flow cytometry was negative for malignancy on two occasions; there was T cell predominance in the cells seen. CSF viral studies were negative.

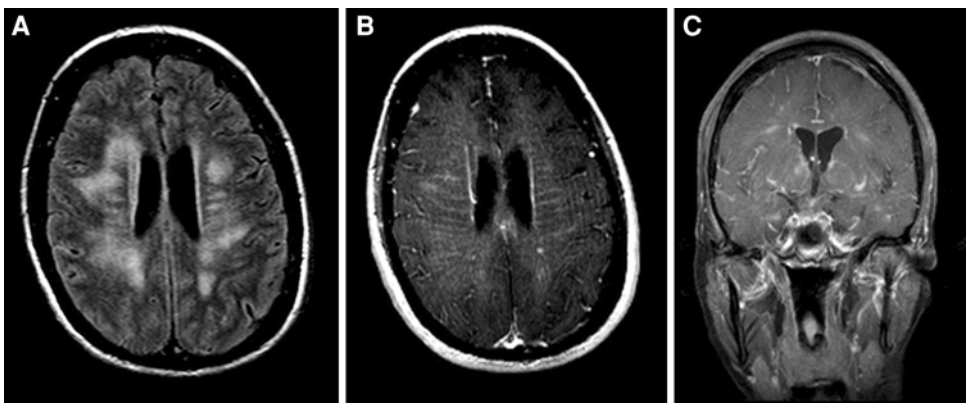

Fig. 1 MRI findings. **a** Axial FLAIR sequence demonstrates abnormal T2-hyperintensity extending from the periventricular to subcortical white matter. The linear and oval configuration of several of the lesions is consistent with a perivascular distribution. **b** Axial T1 image with gadolinium demonstrates linear enhancement corresponding to the T2-hyperintensities. **c** Coronal T1 image with gadolinium demonstrates enhancement with confluent regions

Stereotactic biopsy was performed targeting a small-enhancing lesional component in right corona radiata-internal capsular region (anterior limb). Histopathology is described in Fig. 2 and was consistent with BN syndrome. Conspicuous *kappa* immunoglobulin light-chain restriction was evident by concurrent flow-cytometric immunophenotyping (cell-surface; Fig. 3).

The episodic aphasia and facial droop was felt to be focal seizures rather than transient ischemic events, the patient was started on levetiracetam 500 mg twice daily and warfarin was discontinued. The patient was treated with four monthly cycles of methotrexate 3.5 mg/m^2 (day 1), vincristine 1.4 mg/m^2 (day 1), and procarbazine 100 mg/m^2 daily for 7 days with no improvement in MRI brain. The patient developed painful palpable mass in her right humerus; bone marrow replacement was found on MRI, which was consistent with WM or plasmacytoma and treated with 30 Gy of radiation therapy resulting in

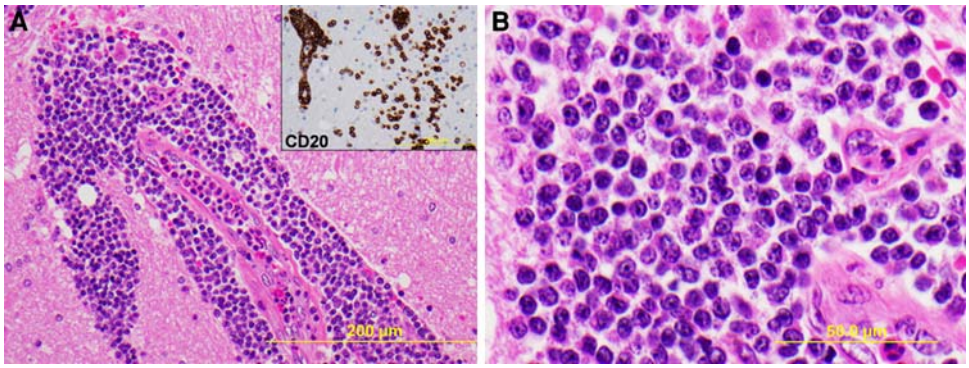

Fig. 2 Histologic findings. **a** Histomicrograph, stereotactic biopsy right frontal deep-white matter lesion: The enlarged illustration (*left*) depicts enlarged area of perivascular infiltrate by small lymphocytes with mostly round nuclei and clumped chromatin. The *inset* shows multiple dense perivascular infiltrates with a loose scattering of single cells in surrounding areas. Immunohistochemistry confirms their B-cell nature (CD20+). **b** The larger picture shows that the infiltrating cells are smaller than endothelial cells, are mature appearing lymphocytes with an admixture of plasmacytoid lymphocytes and rare plasma cells

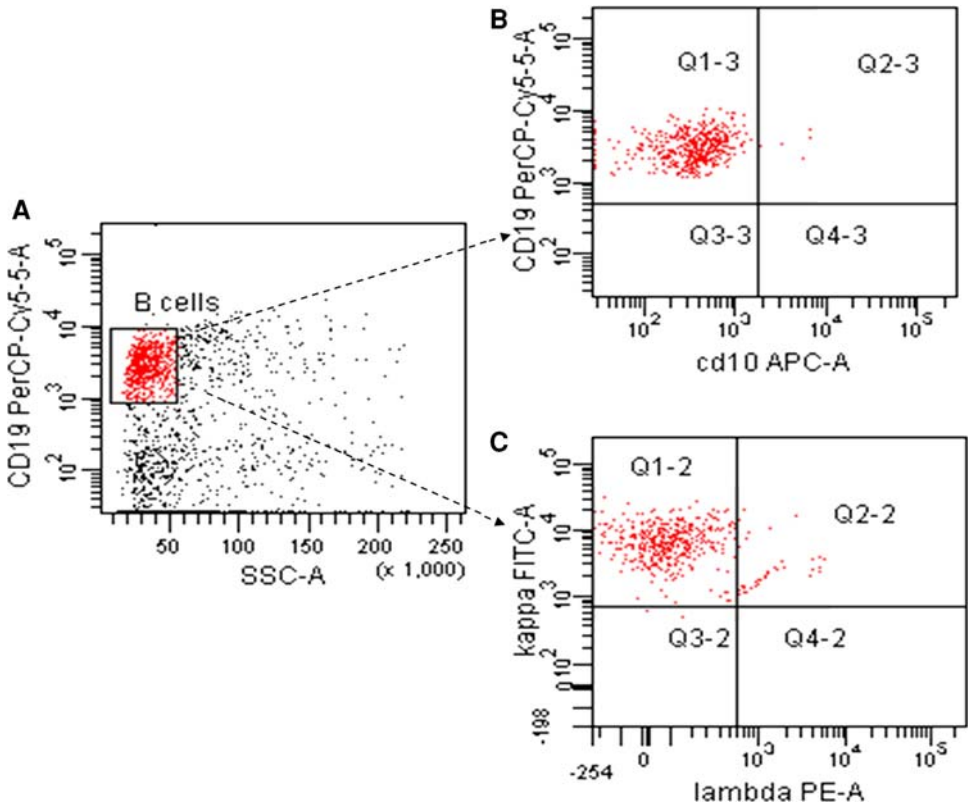

Fig. 3 Flow cytometric findings. (**a**, *left*) Flow-cytometric analysis detects the presence of CD45+ lymphocytes, which comprise CD19+ B-cells. (**b**, *upper right*, and **c**, *lower right*) Specific gating on this CD19 population (*arrows*) indicates a population of CD10-B-cells with conspicuous *kappa* light-chain restriction. These data are consistent with a monoclonal B-cell population, based on restriction for cell-surface immunoglobulin light chain

Table 1 Cases reported on Bing–Neel syndrome

Reference	Age/sex	Neurological symptoms and exam	CSF WBC/protein[a]	Other tests and imaging	CNS pathology (autopsy or biopsy)	Treatment	Response
[3]	36/F	Back pain Quadraparesis Bilateral ptosis Aphonia Optic neuropathy	nl/↑	NA	Endothelial swelling w/ plasmacytic perivascular infiltrate. Glial proliferation in meninges of neuro-axis	NA	
	59/F	Vomiting Dizziness Paresthesias	NA/NA	NA	Vascular endothelium swollen w/o distinct inflammation. Glial proliferation. Round cell infiltrate in the medulla	NA	
[27]	64/M	Back pain Confusion Focal weakness and atrophy Focal ↑ reflexes	nl/nl	NA	NA	NA	
	58/F	None	NA/NA	NA	Multifocal areas of plasmacytes in tumor arrangement. Round cell perivascular infiltrate	NA	
	57/F	Back pain Focal weakness Bilateral Babinski Focal decreased proprioception	↑/↑	NA	Perivascular plasmacytic infiltrates along neuro-axis	NA	
[6]	51/M	SAH Bilateral sciatica Hemiparesis/paraparesis Urinary retention Saddle anesthesia ↓ Ankle reflexes Focal seizure Aphasia	NA/NA	NA	Diffuse vascular congestion. Perivascular infiltrates in pons. Softening and myelomalacia of lumbosacral spinal cord	Blood transfusion for anemia and seizure medications	NA

Table 1 continued

Reference	Age/sex	Neurological symptoms and exam	CSF WBC/protein[a]	Other tests and imaging	CNS pathology (autopsy or biopsy)	Treatment	Response
[7]	60/F	Headache Lethargy Confusion Vomiting Hemiparesis with hyperreflexia and Babinski Aphasia	NA/nl	EEG: diffuse and focal slowing. Ventriculogram: massive L to R shift	Poorly demarcated yellow-gray tumor in L hemisphere. Globular tumor R frontal cortex w/ cellular infiltrate, plasmacytes, PAS + material, mitoses and multinucleated cells. Additional microscopic tumor nodules	NA	
[28]	54/F	Asthenia Drowsiness Coma	NA/NA	NA	Mononuclear perivascular infiltrate in leptomeninges, brainstem, and protuberance	NA	
[29]	56/M	Hemiplegia Hemianesthesia HH	NA/NA	Myelogram: L4/L5 herniated disc	NA	Chlorambucil High dose testosterone Vitamin C and D2, calcium	Not reported
[4]	48/M	Dementia Disorientation CN3 palsy Dysdiadochokinesia Nuchal rigidity Focal myoclonus	↑/↑	EEG: generalized slowing	Cerebral edema. Perivascular infiltrates. Proliferation of reticular cells, microglia, PAS+ deposits. Plasmacytes w/ peripheral nuclei	NA	
[19]	49/M	Weakness CN8 deficit L5/S1 radiculopathy	↑/NA	NA	NA	NA	
[9]	69/F	Weakness Encephalopathy	↑/↑	CSF IF: IgM kappa light chain	Meningeal plasmacytic infiltration and IgM kappa light chains	BCNU IV + prednisone PO → IT chemotherapy → BCNU IV + prednisone	Significant improvement w/ IT therapy
[16]	56/M	Acral dysesthesia Hemiparesis w/ myoclonic tremor and Babinski Cognitive decline Dysphagia	NA/↑	EEG: bicerebral dysfunction	Mildly congested leptomeninges. Plaque-like foci of gray granular softening in subcortical white matter, centrum semiovale, and temporal lobes. Scanty lymphoplasmacytic infiltrates and mild perivascular fibrosis	CTX, prednisone, and VCR prior to neurological dysfunction	Unknown but died

Table 1 continued

Reference	Age/sex	Neurological symptoms and exam	CSF WBC/protein[a]	Other tests and imaging	CNS pathology (autopsy or biopsy)	Treatment	Response
[30]	58/F	Hypomania Spatial disorientation Headache Facial droop, hemiparesis, and HH Dysmetria Mydriasis	nl/nl	EEG: dysrhythmic R polymorphic delta CT head: posterior R hemispheric mass MRI brain: T2 hyperintensities in the R superior frontal gyrus, frontal PVWM, and posterior cingulate gyrus	Tumoral formation R frontal horn and splenium extending to R occipital region surrounded by edema. Perivascular malignant lymphoplasmacytoid infiltration	Chlorambucil prior to neurological dysfunction. Then chlorambucil and tetracosactide IV	Significant improvement but relapse in 2 months. Died due to increased ICP
[31]	65/M	Memory difficulty Gait difficulty Sphincter abnormalities Coma Hyperthermia and death	↑/↑	CT head: marked supratentorial hydrocephalus	Lymphocytic infiltrate in meninges and parenchyma	MTX IT	No response
[10]	40/M	Hemiplegia ↓ Visual acuity Seizure Confusion Cerebellar ataxia	NA/NA	CT head: Enhancing heterogeneous hypodensities in the R frontorolandic region and L temporal region with mass effect	NA	Methylprednisolone and RT. When mass developed: VCR, melphalan, CTX, BCNU, and prednisolone	Remission for 2 years after first cycle, then developed mass L of 3rd ventricle, died after first cycle of subsequent chemotherapy
	52/M	HH Aphasia Facial droop	NA/NA	CT head: L temporoparietal mass	NA	Prednisolone, VCR, melphalan, CTX, and BCNU.	Significant improvement after third cycle, sustained at 3 years
	70/M	Deafness Facial neuralgia with loss of corneal reflex	nl/↑	CT head: perimeningeal infiltration of R cerebellopontine angle and periventricular infiltration in L occipital horn	NA	BCNU IV, CTX IV, and VCR IV, melphalan PO, and prednisone.	Rapid improvement but developed headache and ataxia after 7th cycle, multiple new lesions on CT, and patient died
[13]	68/F	Memory difficulty Headache	↑/↑	CSF IF: IgM kappa CT head: butterfly-shaped hyperdensity of splenium of corpus callosum and hydrocephalus MRI: T2 hyperintensity	NA	Chlorambucil, prednisone, MTX IT, and whole brain RT	Improved but symptoms recurred 2 years later and patient died

Table 1 continued

Reference	Age/sex	Neurological symptoms and exam	CSF WBC/protein[a]	Other tests and imaging	CNS pathology (autopsy or biopsy)	Treatment	Response
[32]	68/F	Confusion Impaired attention Aphasia	NA/NA	MRI brain: enhancing T1 hyperintensity in the L frontal lobe	Perivascular infiltrate of lymphocytes, lymphoplasmacytic cells, and mature plasmacytes w/ glial proliferation in and around the Virchow Robin spaces, stain (+) for IgM lambda light chain	Local RT 30 Gy in 3 weeks	Significant improvement
[5]	65/F	Weakness Confusion Cognitive decline	NA/NA	CT head: enhancing L frontal hypodensity in genu of corpus callosum MRI brain: T2 hyperintensity and enhancement	Perivascular infiltrate w/ immature lymphocytes in Virchow Robin spaces and mature IgM lambda plasmacytoid cells in parenchyma	Focal RT 40 Gy in 5 weeks	Significant improvement
[22]	56/M	Facial weakness Seizure	NA/NA	MRI brain: enhancing thickened L hemispheric dura and leptomeninges	Lymphocytes, plasma cells, plasmacytoid lymphocytes, +IgM kappa	Cladribine	Resolution on MRI, no recurrence of neurological symptoms
[33]	70/F	Focal seizure	NA/NA	CT head: R rolandic tumor involving vault, dura, and cortex	Lymphoplasmacytoma, monoclonal kappa and lambda light chain	Resection, RT × 2 months, and chloraminophene	No recurrence on MRI
[15]	82/M	Weakness Decreased fine motor control Lower motor neuron findings	nl/↑	MRI brain: multiple enhancing white matter lesions with edema FDG-PET: hypometabolic lesions	Prominent perivascular infiltrates, CD20+, CD3−, and CD68−. Kappa light chains diffusely	Rituximab	After treatment, patient developed cognitive impairment and confusion
[11]	72/F	Headache Dizziness Weakness Post chemotherapy hemiparesis	NA/NA	MRI brain: R basal ganglia mass	Diffuse lymphocytic infiltration of cerebral parenchyma	CTX PO, VCR IV, prednisone. After recurrence: RT 45 Gy whole brain and 15 Gy tumor boost, cladribine IV, CTX IV, and prednisolone	After CVP, but developed L hemiparesis (no response) After RT and further chemotherapy, there was near complete resolution of tumor
[34]	68/M	Cognitive impairment Gait apraxia Incontinence Dysarthria Babinski bilaterally	↑/↑	EEG: anterior slowing MRI brain: numerous T2 and diffusion hyperintensities in various arterial distributions	NA	None	
[8]	61/F	Hemiparesis Numbness Dysarthria Encephalopathy Bilateral CN6 palsies	↑/↑	CSF IF: IgM kappa MRI brain: atrophy, mild hydrocephalus	NA	IT MTX	Resolution in 1 week, but patient died 6 months later

Table 1 continued

Reference	Age/sex	Neurological symptoms and exam	CSF WBC/protein[a]	Other tests and imaging	CNS pathology (autopsy or biopsy)	Treatment	Response
[14]	80/M	Dizziness Weakness Encephalopathy	↑/↑	CSF IF: IgM kappa MRI brain: multiple enhancing periventricular nodular T2 hyperintensities and a suprasellar mass	Diffuse tumor-like infiltrate in ventricular walls and CD20+ perivascular infiltrate. Large B cells in interchiasmatic hypothalamic region	NA	
[12]	54/M	Aphasia Impaired cognition	↑/↑	MRI brain: numerous increased T2 signals in L > R centrum semiovale without atrophy FDG-PET: hypometabolism in L > R frontotemporal areas and L basal ganglia	NA	NA	
[35]	51/F	Headache	↑/↑	CT head: multifocal extra-axial masses along the dura MRI brain: extra-axial soft tissue tumor along the L cavernous sinus, R frontal convexity, tentorium, and falx	Diffuse infiltration with atypical cells, plasmacytoid lymphocytes, CD20(+), LCA(+), CD3(−), VS38a(+)	Whole brain RT 1980 cGy, fludarabine	Headache improved with RT MRI improved with fludarabine
[36]	64/M	Headache Aphasia-transient	nl/↑	MRI brain: enhancing R PVWM T2 hyperintensity	NA	Temozolamide	NA
Malkani et al.	62/F	Headache Episodic aphasia Facial droop	↑/↑	MRI brain: sulcal T2 hyperintensities with patchy nodular enhancement	Patchy diffuse deep white matter perivascular lymphoproliferative process with some gray matter involvement. Neoplastic B cells were CD28+, CD19+, and CD10− with monoclonal kappa light chains	MTX, VCR, and procarbazine. Then rituximab, fludarabine	Improvement clinically and in MRI

All patients listed had a diagnosis of WM or hypergammaglobulinemia with elevated erythrocyte sedimentation rate

Abbreviations: *WM* Waldenstrom's macroglobulinemia; *MM* multiple myeloma; *WBC* white blood cell; *OP* opening pressure; *CSF* cerebrospinal fluid; *CT* computed tomography; *MRI* magnetic resonance imaging; *FDG-PET* fluorodeoxyglucose positron emission tomography; *EEG* electroencephalogram; *CVP* cyclophosphamide, vincristine, prednisone; *SAH* subarachnoid hemorrhage; *R* right; *L* left; *PAS* periodic acid-Schiff; *PEP* protein electrophoresis; *IF* immunofixation; *ICP* intracranial pressure; *PVWM* periventricular white matter; *HH* homonymous hemianopsia; *w/* with; *w/o* without; *RT* radiation therapy; *CTX* cyclophosphamide; *MTX* methotrexate; *IT* intrathecal; *BCNU* carmustine; *VCR* vincristine

[a] Elevated CSF WBC range: 5–460 WBC/hpf; elevated CSF protein range: 40–1,810 mg/dl

decreased size of lesion and resolved pain. Rituximab 750 mg/m^2 was started twice weekly for five cycles. Brain MRI after the rituximab showed a minor improvement in enhanced and FLAIR sequences. Two courses of fludarabine 20 mg/m^2 day 1–4 once a month were added to rituximab without further improvement on MRI, so it was discontinued due to myelotoxicity and lack of additive response. At this time the patient was re-staged. Fluorodeoxyglucose positron emission tomography (FDG-PET) of the brain did not show any areas of uptake. FDG-PET of the body showed nonspecific uptake in the left anterior neck, over the apex of the right lung, posteromedial chest wall, right paraspinal muscles, right anterior abdominal wall, and left iliac and femur. Bone marrow biopsies of the iliac crests in April and October 2007 showed hypocellularity with no morphologic evidence of disease. The samples were insufficient for B-cell studies by flow cytometry to assess clonality. MRI of her left thigh showed bone marrow replacement and necrosis in the proximal two-thirds of the femur. Since the findings on follow-up right arm, left leg, and brain MRI were stable and the serum IgM remained low, rituximab was tapered to a monthly schedule and then every 6 weeks, on which she continues currently. There has been no recurrence of neurological symptoms or progression of her systemic and CNS disease based on neurological examination and brain MRI.

Discussion

In 1944, discovery of macroglobulinemia associated with constitutional symptoms, anemia, thrombocytopenia, and lymphocytic and lymphoplasmacytic infiltration of bone marrow was reported by Waldenstrom [2]. Eight years prior, Bing and Neel described a syndrome of anemia with neurological dysfunction associated with increased blood and CSF globulins [3]. The neurological patterns they encountered included paralysis, headache, and vomiting, and they were associated with perivascular lymphoplasmacytoid infiltrates in the CNS, bone marrow, lymph nodes, spleen, and liver on pathology. Bing–Neel syndrome is currently defined as WM with CNS involvement of perivascular infiltration of small lymphocytes, lymphoplasmacytoid cells, and plasma cells [4]. The areas of infiltrate can be small and numerous and can coalesce to be more solid and tumorous [5]. We reviewed all published cases reviewing presentation, laboratory, pathology and imaging findings as well as treatments and outcomes since no large series exist. Thirty-two cases of BN syndrome have been published and are summarized in Table 1 with a summary of most common findings in Table 2.

CNS manifestations of WM include strokes, other focal or multifocal brain syndromes, diffuse encephalopathies, subarachnoid hemorrhage, or a combination of these; BN syndrome refers specifically to the involvement of perivascular infiltrates rather than stroke or hemorrhage due to hyperviscosity [6]. Symptoms commonly include seizures, confusion, cognitive decline, headache, blurry or cloudy vision, psychiatric manifestations, pain, numbness, paresthesias, hearing loss, and weakness [7]. Such manifestations result directly from the locus of the involvement by infiltration or indirectly by hyperviscosity.

Serum laboratory tests associated with BN syndrome only reflect WM. At least 5% macroglobulinemia, serum protein electrophoresis with a monoclonal IgM kappa or lambda light chain restriction, and bone marrow lymphoplasmacytic infiltrate are necessary to diagnose WM. The erythrocyte sedimentation rate may be >100 mm/s and there is often a normocytic, normochromic anemia. Variable findings include elevated serum viscosity, elevated transaminases, cryoglobulins, and rarely Bence Jones proteinuria [7–9]. It is interesting that in our patient, other than the right humeral and asymptomatic left femoral involvement noted on imaging, her disease was stable and IgM remained <425 mg/dl.

Computed tomography of the brain may reveal a hypodensity due to mass effect or infarction, or hyperdensity from subarachnoid hemorrhage [5, 6, 10]. MRI often illustrates T2 and FLAIR hyperintensities with edema, which is isointense on T1 and may enhance, in the area or areas of involvement but can be normal [5, 8, 11–15]. FDG-PET demonstrates areas of hypometabolism that correspond to areas of involvement on MRI [12, 15]. Electroencephalography may show generalized slowing, indicative of cerebral dysfunction, or focal epileptiform activity [4, 8, 16].

Cerebrospinal fluid findings include an elevated opening pressure, lymphocytosis with WBC between 100 and 500 cells/mm^3, total protein >100 mg/dl, and normal or decreased glucose [7–9]. IgM kappa or lambda band restriction can be seen with immunofixation; more commonly in diffuse rather than in coalescent CNS disease. Cytology and flow cytometry may reveal small lymphoplasmacytoid cells that are CD20 positive, as well as CD19, CD22, CD38, and/or CD45 positive, CD5 positive or negative, and CD10 negative [8, 11, 14]. While a positive test substantiates the diagnosis, negative results do not exclude it as in our case, given the low sensitivity of cytological testing due to the paucity or absence of neoplastic cells.

Biopsy is often required for definitive diagnosis. Multiple reports have demonstrated the same pathology in the CNS as in the bone marrow, spleen, lymph nodes, and liver. Bone marrow analysis shows nodular, diffuse, and/or interstitial infiltrates of small lymphocytes, plasmacytoid lymphocytes, and plasma cells with or without paratrabecular

Table 2 Findings in Bing–Neel syndrome [1, 3–16, 19, 25–36]

Signs and symptoms	Seizure
	Encephalopathy
	Cognitive decline
	Blurry vision
	Diplopia
	Psychiatric manifestations
	Numbness and paresthesias
	Weakness
	Headache
Laboratory testing	Macroglobulinemia
	IgM kappa or lambda light chain restriction
	Elevated erythrocyte sedimentation rate
	Normocytic anemia
Cerebrospinal fluid analysis	Elevated opening pressure
	Lymphocytic pleocytosis 100–500 cells/mm^3
	Elevated protein 40–2,000 mg/dl
	IgM kappa or lambda band restriction
	CD20+ lymphoplasmacytoid cells in cytology and flow cytometry
Magnetic resonance imaging	T2/FLAIR hyperintensity in area of involvement
	May be small or large lesions
	May enhance with gadolinium
Bone marrow pathology	Nodular, diffuse, and/or interstitial infiltrate of lymphocytes, plasmacytoid lymphocytes, and plasma cells
	May include paratrabecular aggregates
CNS pathology	Soft, circumscribed, gray-yellow or gray-red areas
	Perivascular lymphoplasmacytic infiltration in Virchow Robin spaces
	Demyelination with axonal loss

aggregates are seen [1]. On autopsy, gross examination of brain tissue reveals softened, circumscribed, and grayish-yellow or grayish-red areas [4, 6, 16]. Microscopically, there is a lymphoplasmacytic infiltrate surrounding the Virchow-Robin spaces. Mature plasma cells penetrate into the parenchyma and produce IgM kappa or lambda light chains. Intranuclear periodic acid-Schiff (PAS) positive material can be seen. As stated above, these cells have variable cell marker expression. Once present, the plasma cells cause reactive changes, such as proliferation of reticulum cells within Virchow Robin spaces, as well as foamy histiocytes, astrocytes, and microglia. Demyelination with axonal loss may occur in irregular patches. Mural PAS positive fluid may be found in the blood vessel walls and permeating the surrounding white matter [4–6, 11, 15, 16]. Electron microscopy demonstrates cytoplasmic inclusions in pericytes and macrophages and membrane bound inclusions consisting of microtubules in gently curved arrays singly or in small groups [16].

Weiss et al. [17] and Frantzen et al. [18] proposed that the CSF concentration of paraprotein has no correlation with neurological dysfunction since several patients had CSF monoclonal paraprotein without neurological disease. Hansotia et al. [19] confirmed these findings but speculated that when the CSF paraprotein concentration increases out of proportion to the albumin, there is usually neoplastic lymphoplasmacytoid cell proliferation beyond the blood brain barrier.

The prognosis of Bing–Neel syndrome had historically been poor. Various chemotherapeutic agents have been used though no clinical trials have been performed due to the rarity of the syndrome (Table 1). Remission has been reported with the use of intrathecal methotrexate alone, and improvement has been noted with carmustine intrathecally and intravenously, or with radiation therapy (20–40 Gy of whole brain radiation therapy) [5, 8, 9]. 2-Chlorodeoxyadenosine, a purine analog, has been reported to have an 85% efficacy alone in previously untreated WM without CNS involvement ($N = 26$) [20]. When 2-chlorodeoxyadenosine was combined with cyclophosphamide and prednisone and given in 6 courses to 19 patients with lymphoproliferative disorders (3 patients had WM), the overall response rate was 88%, but none of those patients had CNS disease [21]. Richards successfully used 2-chlorodeoxyadenosine to treat a patient with leptomeningeal involvement of WM, and he suggested its success may be

due to increased blood brain barrier penetration in meningeal disease and slower clearance from the CSF [22]. Rituximab has also been used with good success in systemic WM and was moderately effective in our patient but not in a case reported by Welch et al. [15, 23–26].

Conclusion

We present a case of BN syndrome and compiled the largest series to date of 32 patients with this entity based on a comprehensive review of the published literature. Bing–Neel syndrome is a rare complication of WM that varies in neurologic presentation with focal, multifocal, or diffuse symptoms. Imaging and CSF are often abnormal, though the latter may not be. While prognosis has historically been poor, this complication appears more amenable to treatment with responses or disease stabilization using the latest chemotherapeutic agents with or without radiation therapy.

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