Bing-Neel Syndrome: Literature Review and Case Report

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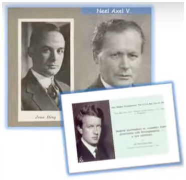

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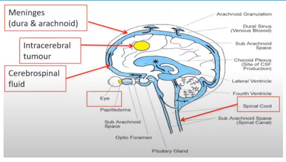
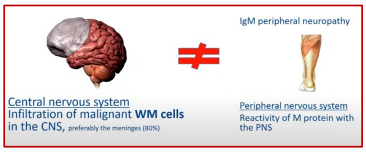

Meninges (dura & arachnoid)
Intracerebral tumour
Cerebrospinal fluid
Eye
Papilloedema
Arachnoid Granulation
Dural Sinus (Venous Blood)
Sub Arachnoid Space
Choroid Plexus (Site of CSF Production)
Lateral Ventricle
Fourth Ventricle
Spinal Cord
Sub Arachnoid Space (Spinal Canal)
Optic Foramen
Pituitary Gland

Background

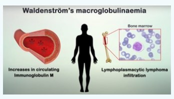
- Waldenström macroglobulinemia (WM) is a rare, indolent B-cell lymphoproliferative disorder, classified as lymphoplasmacytic lymphoma in the 2016 World Health Organization (WHO) classification.
- It has a wide spectrum of complications, mostly related to the monoclonal M-component (e.g. hyperviscosity syndrome, IgM-related neuropathies or tissue deposition).
- Bing–Neel syndrome (BNS) is an uncommon extramedullary manifestation of WM resulting from an unexplained migration and homing of clonal lymphoplasmacytic cells (LPCs) to the central nervous system (CNS), and rarely the peripheral nervous system (PNS) resulting in neurological symptoms

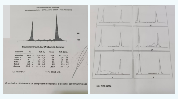


- It should be suspected if unexplained neurological signs appear in WM, even without systemic progression.
- BNS presents with a widely heterogeneous clinical presentation, with no pathognomonic symptom, often leading to a delay in diagnosis.
- The neurologic presentation tends to develop over a period of weeks to months and can be extremely variable, depending on the location and extension of the lesion.
- There is currently no consensus on the diagnostic criteria, treatment strategies and evaluation of response.
- The diagnostic approach should be based on cerebrospinal fluid analysis and magnetic resonance imaging of the brain and spinal axis
- Survival may reach years under proper therapy.
- We report the case of a patient presenting lymphoplasmacytic infiltration of the central nervous system suggestive of Bing-Neel syndrome (BNS) after 12 years of progression of WM
- This case sheds light on the pathophysiology, diagnostic characteristics, and management of a very rare complication of a rare disease.

Case Presentation

- **Case history**
- A 68-year-old man was followed up in our department since September 2002 for a typical WM. A first complete remission was obtained with CHOP.

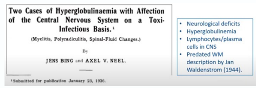




- In March 2007, he relapsed, and a second complete remission was obtained with chlorambucil.
- FCR therapy regimen (fludarabine, cyclophosphamide and rituximab) was used on July 2011.
- **Diagnosis and investigations**
- In March 2014, the patient admitted to hematology department. He had a progressive neurological symptoms with persistant headaches, episods of convulsion, blurry vision and disorders of memory.
- On physical examination, his vital signs were stable, and neither lymphadenopathy nor organomegaly was present. The motor and sensory examinations were normal, and there were no pathologic reflexes.
- The Laboratory examination showed no abnormalities in all parameters.
- Brain scan revealed a multifocal supratentorial edematous process of secondary appearance (several isodense formations ranging from 5 to 22 mm). The patient did not undergo biopsy.
- Brain magnetic resonance imaging (MRI) showed multiple areas of hypersignal in T2/FLAIR sequence, pseudonodular, iso signal in T1, enhancing after gadolinium injection, some following the morphology of the furrows producing neuromeningeal infiltration above and below symetrical bilateral fronto-temporo-parietal and left tentorial cerebellar peduncular.
- Examination of the cerebrospinal fluid (CSF) showed a lymphocytic meningitis with an increase of the CSF protein, and a normal CSF glucose.
- The diagnostic work-up for WM was in favor of a stable disease: full body CT-scan normal, bone marrow aspiration 8% infiltration WM, IgM lambda 18 gr/l, β2 µglobulin: 2.3 mg/l, LDH 200 U/L
- **Treatment**
- Our patient underwent successful treatment with MPV-A regimen chemotherapy of Methotrexate 3,5 g/m² D1, Vincristine 1,4 mg/m² max 2 mg D1, Procarbazine 100 mg/m² D1 to D7 cycles 1, 3, & 5 - 5 cycles repeated every 15 days, at final a closing course with AraC 3 g/m² D1 and D2 without radiation therapy.
- Patient fully recovered, the evolution was favorable characterized by a disparition of clinical signs, a remarkable regression of lesions on MRI and normalization of cerebrospinal fluid. The patient is lost to follow-up after a 36-month follow-up

Literature Review

- BNS is an extremely rare neurologic complication of WM, in which malignant lymphoplasmacytic cells invade the CNS, named after two physicians, Jens Bing and Axel Neel in 1936, this was reported 8 years before Jan Waldenström described the disease we currently know as WM.


Two Cases of Hyperglobulinaemia with Affection of the Central Nervous System on a Toxi-Infectious Basis.[1]

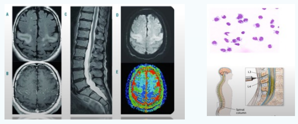
(Myelitis, Polyradiculitis, Spinal-Fluid Changes.)

By

JENS BING and AXEL V. NEEL.

[1] Submitted for publication January 23, 1936.

- = 1% of all WM patients, no prospective studies (>180 cases reported in literature : 2 publications with 34 & 44 pts)
- The median age is 63 years, and BNS is more often seen in males.
- BNS can occur at any moment in the disease course of WM. Typically, it occurs at time of WM relapse. The median time between the diagnosis of WM and BNS is 3 to 4 years (our case report). Can present even if systemic disease is stable or may occur as initial presentation of WM (15-36% of pts)
- Median time from first symptom and diagnosis of BNS was 4 months but > 1 year in 20% of pts
- The clinical presentation of BNS encompasses a wide variety of neurological symptoms,, such as gait disorders, cognitive changes, focal neurological deficits and visual disturbances.
- **Diagnostic testing**
- MRI with contrast (intravenous Gadolinium, GAD), especially in T1 to exclude the other possible) brain (abnormal in 78% of cases) and whole spine MRI. It should be performed before the CSF is collected if possible.
- Cerebral spine fluid (CSF) analysis (standard analysis : cell count, glucose and total protein, cytology, flow-cytometry). Recently, the mutation of *MYD88*^{L265P} gene and immunoglobulin gene rearrangement (IgH) have emerged as promising diagnostic techniques for BNS
- Biopsy of Brain or meninges (lining around the brain and spinal cord) : is not usually necessary



- Two distinct forms have been described: tumoral (our case) and diffuse infiltrative.

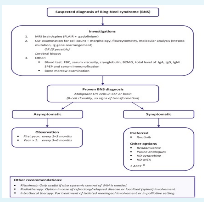
	meningeal	tumor
Incidence	91-94%	6-9%
Symptoms	Headache Nausea and vomiting Visual disturbances, Hearing loss Cranial neuropathies (facial or oculomotor nerves)	Paresis Seizures Aphasia Psychiatric symptoms Cerebellar dysfunction Impairment of consciousness including coma
MRI	Contrast enhancement and/or thickening of meningeal sheaths	Unifocal or multifocal Usually located in the deep subcortical hemispheric regions

- CNS invasion is a site of disease that is very difficult to treat across all lymphoma subtypes. Historically, BNS has been treated with chemotherapeutic agents that enter into the CNS. The therapeutic regimens were adapted from the current treatment options for primary CNS lymphomas (PCNSL) with systemic high-dose methotrexate being preferred.
- Ibrutinib, a Bruton kinase inhibitor approved for WM, has been recently added to the therapeutic armamentarium of BNS due to its ability to pass the blood-brain barrier.
- **Based on a retrospective case series of 28 pts, Ibrutinib improved or resolved symptoms in 85% of patients. Moreover, 83% had a decrease or resolution of radiologic abnormalities and in 47%, the disease was no longer detectable in the CSF. The 2-year event-free survival was 80% and the 5-year survival rate 86%.**

Conclusion

- Bing-Neel syndrome is a very rare complication of WM that should be considered in patients with neurologic symptoms and a history of WM.
- A brain MRI and histologic analysis may be a good supportive tool to diagnose Bing-Neel syndrome.
- Despite recommendations recently published, there is still no clear consensus on treatment of BNS, which includes systemic immunochemotherapy, intrathecal chemotherapy and brain irradiation as possible options.
- Recently, the introduction of a new class of drugs, the Bruton tyrosine kinase inhibitors (BTKi), including ibrutinib, has shown promising efficacy in both disease and BNS management, leading to a rapid shift in treatment paradigms for this disease.

Diagnostic Workup and Treatment of Bing–Neel Syndrome


Suspected diagnosis of Bing-Neel syndrome (BNS)
Investigations
1. MRI brain/spine (FLAIR + gadolinium)
2. CSF examination for cell count + morphology, flowcytometry, molecular analysis (MYD88 mutation, Ig gene rearrangement)
OR (if possible)
Cerebral biopsy
3. Other:
Blood test: FBC, serum viscosity, cryoglobulin, B2MG, total level of IgA, IgG, IgM SPEP and serum immunofixation
Bone marrow examination
Proven BNS diagnosis
Malignant LPL cells in CSF or brain
(B-cell clonality, so signs of transformation)
Asymptomatic
Symptomatic
Observation
First year: every 2–3 months
Year > 1: every 3–6 months
Preferred
Ibrutinib
Other options
Bendamustine
Purine analogues
HD-cytarabine
HD-MTX
± ASCT
Other recommendations:
Rituximab: Only useful if also systemic control of WM is needed.
Radiotherapy: Option in case of refractory/relapsed disease or localized (spinal) involvement.
Intrathecal therapy: For treatment of isolated meningeal involvement or in palliative setting.

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