

A Possible Case of Diffuse Bing-Neel Syndrome in Waldenström's Macroglobulinaemia



Jonathan Mackenney MBChB BSc (hons)

is an SHO currently practising Emergency Medicine at the Northern Hospital in Melbourne, Australia. He attended Bristol University, UK and worked in Frenchay Hospital's department of neurology during his foundation years. He has just completed a visiting fellowship in Biomedical Ethics and Biolaw at the National University of Singapore, where his research included stem cell ethics and consent in embryo research.

Correspondence to:

Jonathan Mackenney,
Unit 5,
160 Easey Street,
Collingwood, VIC,
Australia 3066.
Email: jonathanmackenney@
hotmail.com

Acknowledgement:

I would like to acknowledge Dr Belinda Austen, Consultant Haematologist, Frenchay Hospital for her time and kind suggestions.

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Bing-Neel syndrome is a rare neurological complication of Waldenström's macroglobulinaemia. We present this case to illustrate the diagnostic difficulties entailed in its diagnosis, and the high index of suspicion required in Waldenström's patients with non-specific neuropsychiatric symptoms.

A 68-year-old man was referred by his GP to the medical assessment unit with a fall and increasing confusion.

He had been diagnosed with Waldenström's macroglobulinaemia three months prior to admission and was under the care of haematologists. He was known to have a persistent IgM paraprotein band (measured at 17g/l two months previously) with normal LDH and no Bence-Jones protein in his urine. Plasma viscosity was elevated at 2.25. As he was found to be asymptomatic at that time and had no clinical lymphadenopathy, active monitoring had been commenced.

He also had a long history of COPD, requiring intermittent home oxygen. He was maintained on 7.5mg prednisolone.

He had been admitted to hospital eighteen months prior to this presentation with presumed bacterial meningitis. Cerebrospinal fluid (CSF) analysis at that time had revealed elevated protein (1.3g/dl), 54 white cells (WC) per mm³ (80% polymorphs) but no organisms were seen or grown. A year later, his respiratory consultant had performed a CT brain to investigate two episodes of confusion, which were felt to be unrelated to infection or hypoxia. The scan was reported as normal.

On this admission, twelve months of cognitive decline and reduced mobility was described without explanation. His GP had tentatively suggested a diagnosis of Alzheimer's Disease. Over the preceding week, he had become slightly more short of breath and had a non-productive cough. He was noted to have global muscle wasting with an unsteady, narrow based gait, but further neurological examination failed to elicit any focal signs. He had no hepatosplenomegaly and no palpable lymphadenopathy. His temperature was 37.5 degrees Celsius.

He was found to be confused with a mini mental-state examination score of 25/30. There were deficits in recall and orientation indicating a possible delirium. The preliminary serology was unremarkable except for a CRP of 35, plasma viscosity of 1.9 and a white cell count of 13 000/microlitre with a slight neutrophilia. LDH was within normal ranges.

Neuro-imaging included a CT head and later an MRI brain. Both scans were unremarkable. A

lumbar puncture was performed for CSF analysis and to evaluate pressure-related phenomena. The opening pressure was 11cm water. CSF microscopy yielded two white cells/mm³ with laboratory CSF analysis revealing 3.1mmol glucose, and a raised protein (2.6g/dl). Oligoclonal bands (OCB) were positive (with no correlates on serum electrophoresis) but no organisms were seen or cultured. A ZN stain revealed no acid-fast bacilli and TB PCR was later reported as negative. Pre and post lumbar puncture cognitive testing were identical.

A CT of chest, abdomen and pelvis was unremarkable; VDRL serology, Lyme serology and viral serology including HIV and viral hepatitis were negative. Sputum culture and microscopy remained negative throughout and atypical chest infections were felt to be unlikely based on negative imaging, serology, urine antigen tests and sputum/blood cultures. An ELISPOT test for tuberculosis was also negative.

After a week of treatment for infective exacerbation of COPD, he continued to decline. He exhibited marked delirium and worsening mobility despite improvement of his respiratory symptoms and no evidence of ongoing infection. Steroids had been tailed down and stopped after his antibiotic course was completed.

Lumbar puncture was repeated two weeks after the admitting one. This time CSF microscopy results were as follows: white cells-140/mm³ red cells-20/mm³, protein 2.2g/dl. The white cells comprised predominantly abnormal lymphocytes. Immunophenotyping performed on this CSF sample confirmed a malignant non-Hodgkin's lymphoma (NHL) -type clone, positive for CD79A surface antigen.

Bone marrow biopsy correlated with the CSF findings, showing the same clone of NHL cells.

He was treated with a short course of high dose dexamethasone but made no significant improvement. During this time, he continued to decline, becoming more confused and frail. MRI spine showed no lesions suggestive of Central Nervous System (CNS) lymphoma and he was unable to tolerate MRI brain with gadolinium.

He sustained a fracture to his right hip after falling out of bed and died some weeks later in a terminal care placement. Post-mortem was not performed.

Discussion

Waldenström's macroglobulinaemia is an indolent lymphoplasmacytic lymphoma that primarily affects males with an average age of 60. The neoplastic clone produces IgM which is detectable as a paraprotein band on serum electrophoresis.¹

CNS symptoms in Waldenström's macroglobulinaemia are not uncommon and usually explained by hyperviscosity phenomena. Bing-Neel syndrome refers to malignant infiltration of the CNS by lymphoplasmacytic cells. It was named after Jens Bing and Axel Valdemar Neel, two Danish physicians working in the early twentieth century. The syndrome encompasses two pathological presentations dubbed "tumoural" and "diffuse." The tumoural presentation usually presents with seizures or focal neurological defects whereas the diffuse form of the disease is characterised by non-focal neuro-psychiatric dysfunction such as cognitive decline, personality change or depression of consciousness.²

Most reported cases of Bing-Neel Syndrome are tumoural, involving focal neurological signs with correlative imaging representing CNS infiltration of lymphoplasmacytic cells. However, a minority of cases present with the diffuse form of the disease. Some cases have been diagnosed on the basis of cerebrospinal fluid infiltration with normal imaging.³ In cases with normal neuro-imaging, the presumed pathophysiology is leptomeningeal infiltration with or without neoplastic obstruction of microvascular structures.

The case described above demonstrates the diagnostic challenge in a patient presenting with non-specific neurological deterioration. Despite negative neuro-imaging, a diagnosis of Bing-Neel was suggested when CSF analysis revealed malignant infiltration of the CNS.

It is interesting that initial CSF analysis revealed a normal white cell count despite being temporally removed from the second by only two weeks. The dramatic increase in abnormal CSF lymphocytes did, however, reflect his equally dramatic acute-on-chronic cognitive decline. It was postulated that cessation of his long-term steroid therapy may have allowed malignant proliferation of the abnormal lymphocytes.

Several issues remain unanswered in this case. The link between his cognitive decline over one year and the malignant CNS infiltration remains unclear. It may be that he was suf-

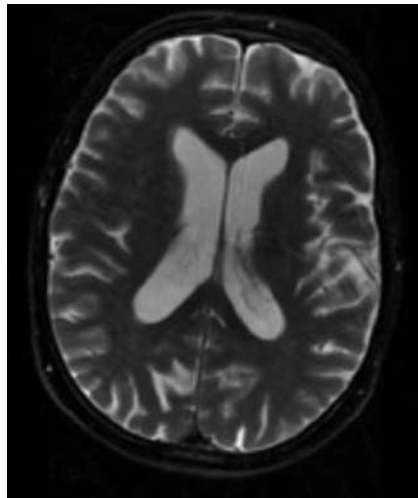


Figure 1: T2 weighted MRI brain: No mass lesions or lymphomatous infiltrates were seen in this scan. The patient was unfortunately unable to tolerate a second scan with gadolinium.

fering from a concurrent, second neurodegenerative process. The most likely process was thought to be Alzheimers disease but fluctuating delirium during his hospital stay made further neuropsychiatric evaluation difficult. Other causes of raised CSF protein and positive OCB include neurosyphilis and neuro-sarcoid. A diagnosis of neurosyphilis was refuted as he was at low risk and VDRL screening was negative. Neuro-sarcoid was not considered as he had no peri-hilar lymphadenopathy, normal neuro-imaging and normal serum ACE levels. Subacute Sclerosing Panencephalitis also causes raised CSF protein and positive OCB. However, he had no history of measles infection and this syndrome primarily affects children and young adults. Positive OCB and raised CSF protein have been reported in CNS lymphoma.⁴

Treatment of Bing-Neel syndrome is largely dependent on whether the presentation is tumoural or diffuse. Standard chemotherapy for Waldenström's macroglobulinaemia is often indicated; current therapies include high

dose steroids and chlorambucil. Tumoural presentations amenable to surgery and targeted radiotherapy have the greatest overall survival figures.² Diffuse presentations may benefit from cranial irradiation and chemotherapy but because of the small number of recorded cases, evidence for treatment is limited. The role of purine nucleoside analogues in the condition remains unclear despite promising evidence in other indolent lymphoproliferative disorders.⁵ Five-year mortality in treated or untreated Bing-Neel sufferers is high.

The patient described here was too frail to undergo chemotherapy; his response to high dose dexamethasone was poor. Whole brain irradiation was not offered due to continuing diagnostic uncertainty and lack of any evidence of leptomeningeal infiltration; he was not a candidate for meningeal biopsy.

Conclusion

Bing-Neel syndrome is a rare complication of Waldenström's macroglobulinaemia. A high index of suspicion should, however, be maintained when working-up the Waldenström's patient presenting with a non-specific history of cognitive decline; Bing-Neel syndrome is a potentially treatable disorder. ♦

REFERENCES

1. Cheson BD (2006). "Chronic Lymphoid Leukemias and Plasma Cell Disorders", in Dale DD, Federman DD: *ACP Medicine*. New York, NY: WebMD Professional Publishing.
2. Delgado J, Canales MA, Garcia B, Alvarez-Ferreira J, Garcia-Grande A, Hernandez-Navarro F. *Radiation Therapy and Combination of Cladribine, Cyclophosphamide, and Prednisone as Treatment of Bing-Neel Syndrome: Case Report and Review of the Literature*. American Journal of Haematology, 2002;69:127-31.
3. Donix M, Beuthien-Baumann B, von Kummer R, Gahn G, Thomas F, Holthoff V. *Nonfluent aphasia in a patient with Waldenström's macroglobulinemia*. Journal of Clinical Neuroscience, 2007;14(6):601-3.
4. Davies G, Keir G, Thompson EJ, Giovannoni G. *The clinical significance of an intrathecal monoclonal immunoglobulin band: A follow-up study*. Neurology 2003;60:1163-6.
5. Tellman MS, Hakimian D. *Purine nucleoside analogues: emerging roles in indolent lymphoproliferative disorders*. Blood 1995;86:2463-74.