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Review article

# Bing–Neel syndrome: Two unexpected cases and a review of the literature

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ABSTRACT

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by the proliferation of small B-lymphocytes in the bone marrow that produce monoclonal immunoglobulin M (IgM). We describe two patients with WM who presented with neurological symptoms due to infiltration of lymphoplasmacytoid tumor cells in the central nervous system, a condition known as Bing–Neel syndrome. A literature review revealed that this syndrome is rare and commonly missed in clinical practice due to its variable presentation and a lack of awareness or knowledge. Brain and spinal magnetic resonance imaging may show a focal mass or diffuse infiltration. The diagnosis of Bing–Neel syndrome requires proof of IgM or lymphoplasmacytoid cells in cerebrospinal fluid or in a brain biopsy. Treatment with intravenous and/or intrathecal chemotherapy and cranial radiotherapy is described in literature with generally poor outcome, although a combination of these therapies seems to improve outcome. Nevertheless, insufficient data are currently available to make general treatment recommendations.



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## 1. Introduction

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by the proliferation of small B-lymphocytes in the bone marrow, which produce monoclonal immunoglobulin M (IgM) paraprotein [1,2]. This rare disease has an incidence of 3 in $10^6$ persons per year in Western populations, with male and Caucasian preponderance [3,4]. Patients may develop symptoms due to infiltration of hematopoietic tissue or the presence of monoclonal antibodies in the circulation. Neurological symptoms occur in 25–50% of the patients either as a consequence of peripheral nerve infiltration (10–15% of WM patients), typically leading to a distal symmetric slowly progressive

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sensorimotor neuropathy, or as a result of hyperviscosity (10–30% of WM patients), leading to a clinical spectrum of reduced vision, headache, hearing loss, dizziness, vertigo, eye movement disturbance, ataxia, stroke and subarachnoid hemorrhage [5]. Infiltration of the central nervous system by small lymphocytes, lymphoplasmacytoid and plasma cells, or paraprotein is extremely rare (<50 cases described) and referred to as Bing–Neel syndrome. We report two cases of Bing–Neel syndrome and review the literature with an emphasis on diagnostic and therapeutic considerations.

## 2. Materials and methods

### 2.1. Patients

We prospectively studied two patients with established WM who were diagnosed with Bing–Neel syndrome in 2013 at the Sint-Jan Hospital Bruges. The patients received no treatment for WM at the time of Bing–Neel syndrome diagnosis.

### 2.2. Imaging

Cerebral imaging was performed by magnetic resonance imaging (MRI) with T1 before and after gadolinium contrast, T2, T2-star, flair and diffusion weighted sequences in patient one and with computed tomography scanning (CT) before and after iodine contrast in patient two.

### 2.3. Flow cytometry

Flow cytometry on cerebrospinal fluid (CSF) in both patients and on bone marrow in patient one at the time of BNS diagnosis was performed with a FACSCanto II flow cytometer with 8-color reagent panels (Becton Dickinson, San Jose, California, USA). First, a screening panel consisting of CD3, CD4, CD8, CD16, CD19, CD20, CD34, CD38, CD45, CD56, kappa and lambda was run to investigate the presence of a monoclonal B-cell population. If the screening panel indicated the presence of a clonal population, two extensive panels of antibodies directed against B-lymphocyte antigen markers were run to further characterize and identify the malignant population. The first panel consisted of CD10, CD19, CD20, CD23, CD43, CD45, CD79b, CD200. The second panel consisted of CD5, CD19, CD45, CD81, IgD, IgM, FMC7. Flow cytometry of the bone marrow of patient two (in 2009) was performed on a FACSCalibur flow cytometer with 2-color reagent panels including CD2, CD5,CD4, CD8, CD10, CD11c, CD19, CD20, CD22, CD23, CD24, CD25, CD33, CD34, CD38, CD79a, CD79b, IgA, IgD, IgG, IgM, HLA-DR, FMC7, kappa and lambda.

### 2.4. Genetic analysis

Clonality was investigated in both patients by molecular analysis of rearrangements of the heavy chain immunoglobulin (IgH) gene and light chain kappa immunoglobulin (IgK) gene. Polymerase chain reaction (PCR) fragments were generated with consensus forward primers which bind to the framework 1 (FR1) and FR3 region, and consensus JH exon reverse primers. Primer sequences are described by Aubin et al. [6] and Diss et al. [7] respectively. Rearrangements of IgK were detected using two primer sets designated IgKa and IgKb, as described by the European BioMED-2 collaborative study (Van Dongen et al.) [8]. Amplified PCR products were analyzed by capillary electrophoresis (ABI 3130 Genetic Analyzer, Life Technologies, Paisley, UK). The MYD88 L265P point mutation analysis was performed with primer sequences previously published by Treon et al. [9], by allele-specific PCR (AS-PCR) as described by Mori et al. [10]. The assay was validated to have a sensitivity of 0.1% mutant allele. PCR products were detected by classical 2% agarose gel electrophoresis.

### 2.5. Literature review

A literature search was performed by systemic searches in the PubMed database from its inception to December 2014. We applied the search terms “Bing–Neel syndrome”, “lymphoplasmacytic lymphoma and central nervous system” and “Waldenström and central nervous system”. Language was limited to English, French, German and Dutch. Animal studies were excluded. References in relevant papers were reviewed for additional cases.

## 3. Case presentation

### 3.1. Case one

A 65 year-old woman with a medical history of WM since 17 years (previously treated with chlorambucil and prednisolone, considered in remission) underwent an open discectomy for a cervical intervertebral disk displacement. The intubation was complicated by a recurrent laryngeal nerve palsy. Two weeks after discharge, she developed progressive headache, nausea and vomiting. Over the course of days she progressively developed vertigo, gait instability and loss of visual acquity, followed by visual hallucinations and delirium four weeks later. Clinical investigation revealed an agitated hallucinating patient with a hoarse voice and no other neurological signs. Body temperature was normal. Blood analysis showed anemia with hemoglobin 8.9 g/dl (ref. value 12.6 –17.4 g/dl), red blood cells (RBC) $2.89 \times 10^{12}$/l(ref. value 4.5–6.5x10125 × 1012/l), leucopenia with white blood cells (WBC) $1.300 \times 10^{9}$/l), elevated sedimentation rate (103 mm/h) and C-reactive protein (CRP) 85.4 mg/l (ref. value <5.0 mg/l). Serum protein electrophoresis and immunofixation revealed monoclonal IgM lambda protein with elevated serum IgM 209.0 g/dl (ref. value 4.0–23.0 g/l) and IgG 41.0 g/dl (ref. value 70.0–160.0 g/dl). Brain MRI showed multiple small vasculo-ischemic white matter lesions bifrontal and periventricular, without diffusion restriction or contrast enhancement (Fig. 1A-B). Iatrogenic meningitis was suspected, and the patient was empirically started on acyclovir, vancomycin and ceftazidime. A lumbar puncture provided clear CSF containing 107 WBC per μl (100% lymphocytic), 5 RBC per μl, and protein 67 mg/dl (ref. <40 mg/dl) with normal IgG index (0.44, ref. value 0.23–0.64). Viral, bacterial and fungal CSF cultures including cryptococcus, acid-fast bacilli and PCR for the herpes, varicella and enteroviridae were negative. CSF cytology identified small lymphocytes, often with a lymphoplasmacytic character, intermediate nucleocytoplasmic ratio, rather irregular nuclei containing condensed chromatin without nucleoli and a relatively small amount of unilateral, strongly basophilic cytoplasm with perinuclear halo (Fig. 2A). Flow cytometry revealed a predominant B-cell population (98% CD19+ cells, negative for CD5, CD10, CD23, CD38, CD43, CD81, and positive for CD20, CD79b, CD200, FMC7) expressing lambda light chains (Ig lambda 97%, Ig kappa/lambda ratio < 0.1) and surface IgM. A clear and strong clonal pattern, without a polyclonal background, was observed for the IgH FR3-JH, IgKa and IgKb primer sets. A MYD88 L265P mutation was observed in CSF cells. A bone marrow sample taken three days before the CSF sample also showed an IgKb monoclonal fragment of the same length, but no clonal fragments in the IgH FR3-JH, IgKa reactions, probably due to an insufficient number of malignant cells in this sample (Fig. 2B). The MYD88 L265P mutation was clearly observed in DNA isolated from this bone marrow sample. Bing–Neel syndrome was diagnosed, and treatment was initiated with intrathecal chemotherapy (cytarabin 30 mg, methotrexate 15 mg and dexamethasone 5 mg twice weekly for 4 weeks to a total of 7 cycles). Subsequent CFS sampling during therapy showed a progressive decline in the number of leukocytes. The delirium responded within two weeks to high oral doses of olanzapine and trazodone. Because of persistent loss of visual acuity in the left eye one month after the treatment, brain MRI was repeated now showing meningeal thickening and contrast enhancement around the left anterior clinioid process, suggestive