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LETTER TO THE EDITORS

Progressive gait ataxia and intention tremor in a case of Bing–Neel syndrome

Stephan Kolbaske · Annette Grossmann · Reiner Benecke · Matthias Wittstock

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Sirs,

Waldenstrom's macroglobulinemia (WM) is caused by neoplastic proliferation of plasmocytoid lymphocytes and production of monoclonal immunoglobulin M (IgM) [1–3]. A few years ago, Bing and Neel reported CNS symptoms associated with hyperglobulinemia and intracerebral infiltration of plasma cells and lymphocytes in two patients [4].

Usually, neurological symptoms are due to blood hyperviscosity and subsequent ischaemic brain lesions. Fatigue, headache, dizziness and blurred vision are the most common symptoms of hyperviscosity syndrome [5]. Neurological symptoms like typical focal deficits (paresis, increased tendon reflexes), seizures and nonfocal deficits (disorders in memory or personality, changes in level of alertness) may also be due to infiltration of the central nervous system (CNS) by malignant lymphoid cells [6]. This rare condition is termed Bing–Neel syndrome (BNS) presenting in a tumoral form or a diffuse infiltration of pons, medulla, periventricular white matter or leptomeningeal spaces [7–9]. In cerebral manifestation of WM in the CSF lymphocytic pleocytosis and blood-brain barrier dysfunction comparable to chronic meningoencephalitis can be observed. Cytologic differentiation may show inflammatory activation like lymphoid, plasmacytoid cells or other activated B-lymphocytes. Also atypical or malignant cells may be seen. Furthermore, intrathecal synthesis of IgM and detection of monoclonal IgM paraprotein of light chain type is typical. Here we describe a patient with ataxia and tremor as a consequence of a diffuse form of BNS.

A 60-year-old man was admitted with progressive gait ataxia, seizure-like events and intention tremor of upper limbs beginning four months previously. He was unable to walk without help. WM was diagnosed 14 years before with five relapses since then and was treated successfully with different therapeutic regimes including prednisolone, chlorambucil, fludarabine and bendamustine. The last course of bendamustine treatment ended 6 months before admission. When neurological symptoms started the patient was off medication.

At admission there was no suggestion of active WM or other types of B-cell lymphoma in hematologic laboratory, thoracic and abdominal computertomographic images or bone-marrow biopsy. A cerebral magnetic resonance imaging (MRI) done one month before revealed no abnormalities. There was no evidence of a relation to a hyperviscosity syndrome or blood dyselectrolytaemia leading to central pontine myelinolysis.

Two CSF analyses showed lymphocytic pleocytosis with 50 and 75 Mpt/l leucocytes, respectively, with dominance of about 80% lymphocytes and a few lymphoid, plasmacytoid, activated B-lymphocytes and IgM producing atypical cells, increased protein (3,500 mg/l, and 1,800 mg/l albumin) IgM level of 72 mg/l and intrathecal synthesis of IgM. There was no evidence for oligoclonal IgG in CSF or serological evidence for acute inflammation of CNS or systemic infection. In immunofixation electrophoresis in serum and CSF, identical IgM kappa paraproteins were detectable. The immunophenotypical analysis of CNS identified IgM-producing cells with CD19 and CD22 positivity. An actual MRI-study displayed a diffuse irregular infiltration of pons in T2-weighted and

S. Kolbaske · R. Benecke · M. Wittstock (✉)
Department of Neurology, University of Rostock,
Gehlsheimer Str. 20, 18147 Rostock, Germany
e-mail: matthias.wittstock@med.uni-rostock.de

A. Grossmann
Department of Diagnostic and Interventional Radiology,
University of Rostock, Rostock, Germany

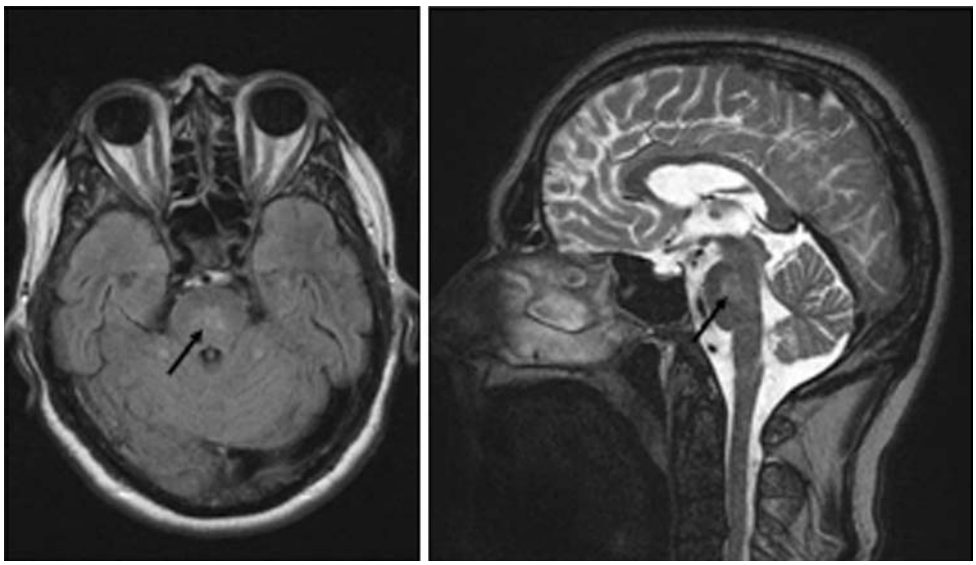

Fig. 1 Cerebral MRI of the 60 year-old patient with BNS (Impect, Siemens; 1.0 Tesla). Sagital (T2-weighted) and horizontal plain (FLAIR)

Table 1 Diagnostic findings in Bing–Neel syndrome (according to Delgado et al. 2002 [10])

History of Waldenström macroglobilinaemia
Encephalopathy
Neuropathy
Stroke
CSF
moderate lymphocytic pleoytosis
intrathecal immunoglobulin synthesis
MRI
hyperintense lesions in FLAIR-weighted images
only slight contrast enhancement
Facultative dural biopsy
plasmacytoid lymphocyte infiltration

FLAIR images (Fig. 1). There was no evidence for pathologic enhancement or a displacing effect.

Because of diffuse infiltration and localization in pons, as in our case, stereotactic biopsy, surgery or radiation is not practicable because of the high risk of secondary damage and worsening of neurological deficits. Therefore, in our case the diagnosis of BNS was based on ongoing focal neurologic deficits caused by diffuse pontine infiltration, typical pleocytosis in CSF with detectable atypical B-cells, dysfunction of blood-brain barrier, intrathecal IgM production and detectable IgM Kappa paraproteins in serum and CSF. As our case also showed, the beginning of BNS must not be connected with active systemic WM. In our case there was no evidence for active WM outside the CNS, as shown by regular hematologic laboratory, thoracic and abdominal computertomographic images and bone-marrow biopsy. The diffuse infiltration of pons was detectable for the first time 3 months after the beginning of neurological symptoms and 4 weeks after proof of pathologic CSF. The clinical presentation of our case with gait ataxia and intention tremor pointed to an affection of cerebello-pontine pathways.

Chemotherapy with systemic application of fludarabine (25 mg/m^2 body surface area; 49 mg absolute) in combination with cyclophosphamid (300 mg/m^2 body surface area; 585 mg absolute) and intrathecal application of rituximab in a total dose of 10 mg was initiated. After this, pathologies in CSF and MRI vanished and were not detectable anymore. In contrast to this fast regression, the patient recovered very slowly from clinical symptoms. At discharge, intention tremor had disappeared but gait ataxia was still present, and walking assistance was required.

There are no consensus criteria for diagnosis or treatment of this rare condition. Clinical findings in BNS are summarized in Table 1. Treatment of BNS is based on a very low evidence level. Usually a chemotherapeutic approach alone, as in our case, or in combination with radiation therapy is performed [10].

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