Unusual association of multiple sclerosis with monoclonal gammopathy of undetermined significance (MGUS): two case reports

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Summary

We present two patients with demyelinating disease meeting the diagnostic criteria for multiple sclerosis. Both patients had IgG λ monoclonal gammopathy in serum and cerebrospinal fluid associated with intrathecal antibody synthesis. This association is very unusual and it is not certain whether the co-occurrence of these disorders might be the result of a causal link between multiple sclerosis and monoclonal gammopathy or a fortuitous phenomenon.

KEY WORDS: monoclonal gammopathy, multiple sclerosis, unusual association.

Introduction

Patients with monoclonal gammopathy of undetermined significance (MGUS) occasionally have associated neurological disorders like peripheral neuropathy and motor neuron disease. The neuropathies are usually demyelinating sensorimotor neuropathies and in many of them monoclonal immunoglobulins act as autoantibodies against nerve glycoconjugates, like myelin-associated glycoprotein (MAG) or sulfate-3-glucuronyl paragloboside (SGPG) (1,2). Central nervous system demyelination was suggested in chronic inflammatory demyelinating polyneuropathy (CIDP) (3-5) and in polyneuropathy associated with benign IgM monoclonal gammopathy (6). Multiple sclerosis (MS) is a typical demyelinating disease of the central nervous system (CNS). Its association with MGUS might suggest the existence of a causal link between dysglobulinemia and MS.

Case 1

A sailor, 56 years old, was admitted to our clinic presenting postural instability and gait disequilibrium. His symptoms had presented acutely 4 months earlier and deteriorated slowly ever since. The patient reported a history of episodic diplopia (fifteen years ago), and thirteen years ago presented a further episode of instability that lasted a few weeks before completely remitting. He also reported two episodes of dizziness, instability and malaise, occurring four and three years ago respectively, which remitted completely after a few weeks.

Clinical features. The patient had an ataxic gait associated with dysmetria and dysdiadochokinesia. There was no muscular weakness and tendon and plantar reflexes were normal. There were no abnormal sensory signs or symptoms.

Laboratory studies. Magnetic resonance imaging (MRI) of the brain revealed many focal lesions of high signal intensity on T2-weighted images, located in the subcortical area, the periventricular area, and the left cerebellar peduncle. These lesions were not enhanced following intravenous infusion of contrast agent GdTPA (Fig. 1a, 1b). Increased latency of visual-evoked potentials (VEPs) was found after stimulation both of the right and of the left eye. Serum protein electrophoresis revealed a peak in
γ-globulin area. Serum immunoglobulin levels were as follows (normal range given in brackets): IgG, 1040 mg/dl (700-1600 mg/dl), IgM, 28.5 mg/dl (40-230 mg/dl), IgA, 142 mg/dl (70-400 mg/dl). Cerebrospinal fluid (CSF) examination showed albumin index 6.3 (normal values<10), IgG index 0.52 (normal values<0.65), no pleocytosis and no elevated protein level. Agarose isoelectric focusing demonstrated oligoclonal IgG bands (OCB) in CSF and monoclonal bands in CSF and serum (Fig. 1c). Serum and CSF immunofixation (IFx) with anti IgG, anti IgA, anti IgM, anti k and λ chain antibodies revealed an IgG λ monoclonal band. Urine analysis with IFx was negative for Bence-Jones protein. A bone marrow aspirate and biopsy showed the presence of a monoclonal plasmacytic population (3-5%) producing IgG λ chains. Thorax and abdomen CT scanning did not reveal enlarged lymph nodes or lymphomatous organ diffusions. Radionuclide bone scanning did not reveal any osteolytic lesions.

**Case 2**

A carpenter, 52 years old, three years ago presented distal causalgia and numbness of the upper and lower limbs. A few months later he also presented mild gait disequilibrium. The above symptoms had a progressive course until his admission to our clinic, in October 2002.

**Clinical features.** The patient had a mild sensory ataxia. His tendon reflexes were brisk with mild left prevalence. He also had an extensor left plantar reflex.

**Laboratory studies.** Brain MRI revealed many focal lesions of high signal intensity in T2- and proton density (Pd)-weighted images and of low signal intensity in T1-weighted images located in the periventricular and supraventricular area, the basal ganglia and internal capsule area, and the right pontine area. Some of these lesions were enhanced following intravenous infusion of GdTPA. There was mild generalized atrophy especially of the corpus callosum (Fig.s 2a, 2b). There was no VEP response following right eye stimulation, whereas stimulation of the left eye produced an increased latency response. Serum protein electrophoresis revealed a peak in γ-globulin area. Serum immunoglobulin levels were as follows (normal ranges are given in brackets): IgG, 1000 mg/dl (700-1600 mg/dl), IgA, 128 mg/dl (70-400 mg/dl), IgM, 118 mg/dl (40-230 mg/dl). CSF exami
nation showed IgG 7.62 (0.50-6.10), IgG index 0.82 (normal <0.65), albumin index 14 (normal <10), protein 51 mg/dl, and no pleocytosis. Agarose isoelectric focusing demonstrated monoclonal bands and identical IgG OCB in serum and CSF (Fig. 2c). Serum and CSF IFx with anti IgG, anti IgA, anti IgM, anti k and λ chain antibodies revealed an IgG λ protein. Urine analysis with IFx was negative for Bence-Jones protein. A bone marrow aspirate and biopsy showed the presence of a monoclonic plasmocytic population (3%) and a marked prevalence of IgG λ chains. Ultrasound scanning of both patients’ heart and neck arteries was negative for vascular atheromatosis and embolicogenic heart lesion. Serum and CSF fluorescent treponema antibody (FTA) and venereal disease research laboratory (VDRL) test, serum vitamin E, C3, C4, C-reactive protein (CRP), rheumatoid antigen (RA), anti-nuclear antibodies (ANA), anti-DNA, anti-extractable nuclear antibodies (ENA) were normal, excluding CNS syphilis, avitaminosis E or collagen disease. Subcutaneous abdomen tissue biopsy did not detect amyloid.

Figure 2c - Case 2, isoelectric focusing pattern showing serum and CSF monoclonal bands and identical serum and CSF oligoclonal bands.

Discussion

According to recommended diagnostic criteria for MS (7), our first patient had definite relapsing-remitting MS and our second patient definite primary progressive MS. Multiple sclerosis is an inflammatory demyelinating disease of the CNS in which many immunological disturbances have been reported, like the presence of OCB in CSF, activation of CD4, and decrease of T-suppressor lymphocytes. The existence of oligoclonal antibodies (80-90% of MS patients), which are potentially able to act against myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), myelin associated glycoprotein (MAG) and other components, provides evidence of intrathecal B-cell activation. According to CSF and serum isoelectric focusing patterns (Fig. 1c), our first patient showed intrathecal OCB production plus monoclonal bands. Consequently we have, in accordance with a European consensus report (8), a mixed pattern of intrathecal synthesis plus monoclonal gammopathy (type 2 plus type 5). The second patient had monoclonal and identical OCB in CSF and serum (type 4 plus type 5) (8). This is evidence of systemic immune activation and passive movement of oligoclonal antibodies from the serum into the CSF across the blood-CSF barrier. The IgG index is the ratio of CSF/serum quotient for IgG to albumin. High IgG index values are a quantitative indication of intrathecal OCB synthesis. In our patient with an elevated IgG index (0.82), we probably have both systemic and intrathecal immune responses. MS is one of the most common causes of this mixed response and the presence of serum bands might be the result of infections triggering relapses of the disease (9). Disorders triggering systematic only responses, such as inflammatory conditions (sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, primary anti-phospholipid syndrome), neoplastic diseases, and neuropathies, were excluded.

Patients with IgM peripheral neuropathy occasionally present CNS demyelination (6,10). In some of these, with or without MRI evidence of demyelination, antibodies reacting against CNS white matter glycolipids were present (10,11). These glycolipids remain to be characterized. IgM paraprotein from cases presenting polyneuropathy have been found to bind to specific neurons of the rodent brain (12). What is the role of these antibodies? Do they have any involvement in the pathogenetic mechanisms of CNS demyelination?

Tsung reported a patient with MS and monoclonal gammapathy associated with multiple myeloma (13). His conclusion was that this association may not be coincidental. Conceivably, in conditions of abnormal cell-mediated and humoral immune responses, like MS, if an antigenic stimulus persists for a long time, one of the plasma cell clones might escape the normal control mechanisms and produce a homogenous monoclonal immunoglobulin.

In another study (14), the authors tried to correlate the late onset of the disease in four MS patients with paraproteinemia with a general immune dysregulation causing production of nonspecific monoclonal immunoglobulins.

The question of the potential causative role of monoclonal proteins in MS and in CNS demyelination generally cannot be answered today. It is necessary to establish whether these proteins bind to some known or unknown neural antigens and if they do, to investigate whether this binding plays a causative role in the disease or is a result of a general immune disequilibrium. That said, no one has excluded the possibility that this association may be coincidental.

References


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