Peripheral neuropathy associated with IgM monoclonal gammopathy of unknown significance is a common disorder, while the association of paraproteinaemic neuropathies with haematological malignancies is far less frequent. We report a 76-year-old patient with a subacute and rapidly progressive sensorimotor demyelinating polyneuropathy causing sensory ataxia, painful paraesthesias and marked motor and sensory deficit in four limbs. Monoclonal gammopathy of IgM type associated with a rectal low-grade B-cell non-Hodgkin lymphoma was detected. Research for anti-MAG and antiganglioside autoantibodies including anti-GM1 and anti-GQ1b evidenced a high titre of IgM antibodies against the disialosyl group of GD1b. This is the first report on a paraproteinaemic polyneuropathy with IgM autoantibodies against glycolipid GD1b associated with B-cell lymphoma. The IgM type of these autoantibodies suggests that they represent all or part of the paraprotein produced by lymphoma cells.

Key words Paraproteinaemic neuropathies • Gangliosides • GD1b • Monoclonal gammopathy • B-cell lymphoma

Introduction

The occurrence of peripheral neuropathy associated with IgM monoclonal gammopathy of unknown significance (MGUS) is quite common and suggests a pathogenic role of monoclonal proteins in peripheral nervous system damage [1, 2]. About one half of patients with paraproteinaemic neuropathy show IgM monoclonal antibodies reacting with myelin-associated glycoprotein (MAG) [3]. Paraproteinaemic neuropathies caused by haematologic malignancies are far less frequent and the associated autoantibody pattern is variable. We report a patient with a subacute and rapidly progressive sensorimotor demyelinating polyneuropathy, monoclonal gammopathy and selective positivity of IgM autoantibodies against glycolipid GD1b associated to B-cell lymphoma.

Case report

A 76-year-old woman presented with a one-month history of weight loss and painful paraesthesias at the distal extremities of the four limbs followed by progressive and diffuse motor weakness. Anamnesis did not reveal significant antecedents. Neurological examination showed sensory ataxia, marked motor deficit with 4 on the Medical Research Council scale in proximal and distal muscle districts of four limbs, superficial and proprioceptive sensory deficit with a stocking-glove distribution and areflexia in the lower limbs. Electroneurography documented absent sensory action potentials, prolonged distal latencies of motor action potentials (longest distal latency=8.7 ms) and markedly slowed motor conduction velocities (lowest conduction velocity=22 m/s). There was further evidence of conduction block or temporal dispersion of motor action potentials in both ulnar, tibial and peroneal nerves in other than known entrapment sites demonstrating patchy and
focal demyelination. Electromyography showed fibrillations and positive waves in approximately 4–6/10 needle positions in all explored muscle districts documenting acute neurogenic damage. Cerebrospinal fluid examination evidenced a slight increase in protein concentration. Diagnosis of subacute demyelinating sensorimotor polyradiculoneuropathy was established. Haematologic screening revealed a monoclonal gammopathy with high serum IgM (1151 mg/dl), light chain kappa proteinuria and slightly elevated levels of beta-2-microglobulin. A total body CT scan documented a pelvic mass identified as an intramural submucosal rectal tumour by colonoscopy. Microscopic diagnosis was low-grade B-cell non-Hodgkin lymphoma. Bone marrow biopsies obtained by sternal and ischial puncture did not reveal lymphoplasmacellular infiltrates. Research for antiganglioside autoantibodies using a dot blot anti-ganglioside profile (Euroimmun, Luebeck, Germany) evidenced a high titre (1:3200) of IgM antibodies against the disialosyl group of GD1b. Anti-GM1, anti-GQ1b and anti-MAG antibodies were not detected. Anti-Hu, anti-Yo and anti-Ri autoantibodies were absent.

The patient underwent a 5-day course of high-dose intravenous immunoglobulin treatment (0.4 g/kg/day) followed by corticosteroid therapy with a daily oral dose of 1 mg/kg of prednisone without clinical improvement. The course of the illness was rapidly progressive leading to pharmacoresistant severe pain of four limbs and tetraplegia. The patient was transferred to the haematological unit in order to undergo chemotherapy for lymphoma. However, intestinal pseudo-obstruction occurred, probably as a result of severe autonomic impairment, and led to death within 2 months from the initial symptoms.

Discussion

MAG is the main target of IgM monoclonal antibodies in paraproteinaemic neuropathies. The clinical presentation in these patients is usually a chronic, symmetric, sensorimotor, demyelinating neuropathy, with a predominance of ataxia over motor signs [3, 4]. The haematological condition mainly associated with this entity is MGUS, but malignancies may also occur. Features which suggest lymphoproliferative disorders include weight loss, rapid progression of the neuropathy, higher levels of paraprotein (>1 g/l), elevated levels of beta-2-microglobulin and light chain proteinuria [5]. These findings were all present in our patient.

This is the first report on a paraproteinaemic polyneuropathy with IgM autoantibodies against glycolipid GD1b associated to B-cell lymphoma. Two other case reports on polyneuropathies and IgM monoclonal gammopathy with GD1b antibodies have been described. In the first one, a sensory axonal neuropathy with GD1b antibodies cross-reacting toward GQ1b was detected [6]. In the second one, a sensorimotor axonal neuropathy was documented and GQ1b antibodies were not tested [7]. Therefore, the clinical and electrophysiological patterns of polyneuropathies with IgM antibodies against GD1b ganglioside are heterogeneous. The occurrence of serum IgG autoantibodies cross-reacting with glycolipid GD1b and other gangliosides has been reported in about 20% of a large series of patients with Guillain-Barré syndrome [8]. In a few patients these antibodies were monospecific to GD1b, and this finding correlated with the presence of sensory disturbances and demyelination [8]. In MGUS neuropathy, anti-GD1b and anti-GQ1b antibodies were reported to be consistently related to sensory ataxic signs [9]. Indeed, GD1b is shown to be abundant in large neurons of human dorsal root ganglia, in sympathetic ganglia as well as in the paranodal myelin of motor and sensory peripheral nerves [10]. The pathogenic role of anti-GD1b antibodies has been experimentally proven by the induction of sensory neuropathy in rabbits [11].

Serum autoantibodies recognising more than one ganglioside are found relatively frequently, probably because of the antigenic similarities of these molecules. Monoclonal IgM autoantibodies showing affinity for the terminal Gal(β1–3)GalNAc residue, which is shared by GM1 and GD1b [12], have been recently reported in a patient with a multifocal motor neuropathy associated with a B-cell lymphoma [13]. However, the selective involvement of motor fibres in that case suggests that nerve fibre damage was mediated by anti-GM1 activity.

In our patient, a subacute sensorimotor demyelinating neuropathy is associated with antibodies directed against the NeuNAc(α2–8)NeuNAc residue (the disialosyl group), which is present in GD1b but not in GM1. The IgM type of these autoantibodies suggests that they represent all or part of the paraprotein produced by lymphoma cells.

References

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