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Case Report

Intractable axonal neuropathy with multifocal peripheral nerve swelling in neuromyelitis optica spectrum disorders: A case report

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ABSTRACT

We report a patient with neuromyelitis optica spectrum disorders (NMOSD) with anti-aquaporin 4 (AQP4) antibodies, who developed intractable axonal neuropathy presenting with multifocal peripheral nerve swelling by magnetic resonance (MR) neurography. A 52-year-old woman with a 12-year history of polymyositis and rheumatoid arthritis had been treated with prednisolone, tacrolimus, and abatacept (CTLA-4-Ig). She developed progressive numbness and tingling sensations in the distal parts of all limbs at the age of 50 years, followed by weakness of both upper limbs 6 months later. Neurological examination revealed severe muscle weakness and atrophy of the right upper limb with proximal dominance, diffuse moderate weakness of the left upper limb, severe sensory impairment of all modalities of four limbs in glove and stocking distribution, wide-based gait with positive Romberg's sign, and absence of all tendon reflexes. She was diagnosed with NMOSD due to positive serum anti-AQP4 antibodies and a longitudinally extensive cervical spinal cord lesion on MR images. Intravenous methylprednisolone pulse therapy, plasma exchange and intravenous immunoglobulin administration were performed, which improved the spinal cord lesion on MRI, but did not ameliorate her symptoms. Notably, she also had axonal neuropathy characterized by asymmetrical, multifocal swelling of peripheral nerves by MR neurography. Histopathological examination of the biopsied sural nerve revealed axonal degeneration and endoneurial edema but no inflammatory cell infiltration. Although she was treated with intravenous methylprednisolone, intravenous immunoglobulin, oral prednisolone, tacrolimus and tocilizumab, her symptoms gradually progressed. Neurologists should be aware of co-existing intractable axonal neuropathy in NMOSD cases presenting as immunotherapy-resistant sensorimotor disturbances.

1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD) is an autoimmune disorder of the central nervous system (CNS) associated with anti-aquaporin 4 (AQP4) antibodies. Although combined central and peripheral demyelination (CCPD) is referred to as an overlapping condition of multiple sclerosis and chronic inflammatory demyelinating polyneuropathy (CIDP) (Ogata et al., 2016), little is known about the radiological and histopathological features of peripheral nervous system (PNS) involvement in patients with NMOSD. Involvement of the PNS in NMOSD, especially radiculopathy, was reported to have demyelinating features by nerve conduction study (NCS) and histopathology (Kim et al., 2017). We report a case of NMOSD in a patient who developed intractable axonal neuropathy with multifocal swelling of peripheral nerves on magnetic resonance (MR) neurography.

2. Case report

The patient was a 52-year-old female with autoimmune comorbidities of rheumatoid arthritis (RA) and polymyositis. At the age of 40 years, she developed bilateral proximal muscle weakness. She was diagnosed with polymyositis based on clinical symptoms of myopathy,

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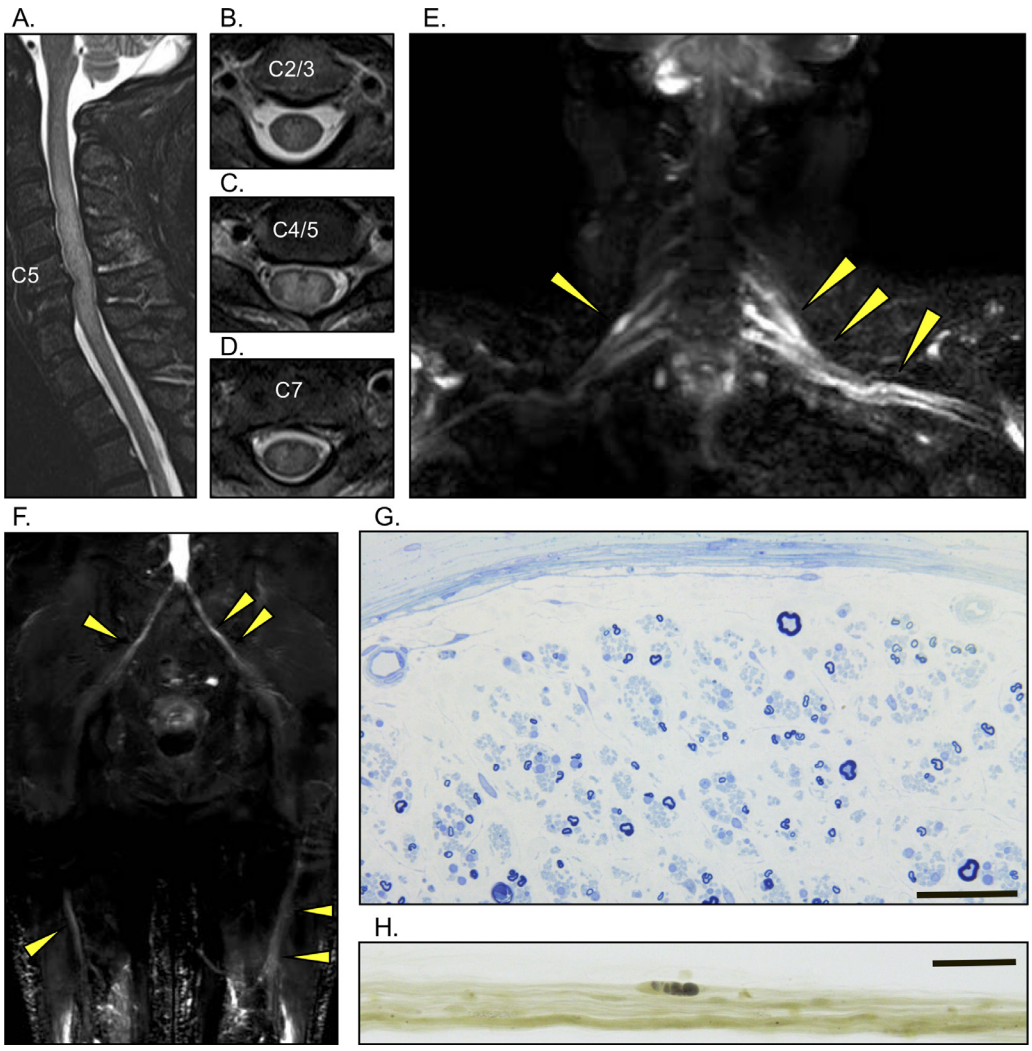

Fig. 1. MR images and histopathology of the biopsied sural nerve. (A–D) Cervical spinal cord MR images 6 months after disease onset. (A) Sagittal and (B–D) axial T2-weighted MR images of the cervical spinal cord 6 months after disease onset. A longitudinally extensive spinal cord lesion is visible between the C2/3 and C7 spine levels. (E) MR neurography of the cervical roots and brachial plexuses 11 months after disease onset. Arrowheads indicate the asymmetrical, multifocal swelling of peripheral nerves. (F) MR neurography of the lumbosacral roots and plexuses 11 months after disease onset. Arrowheads indicate the swelling of proximal and distal segments of the sciatic nerves. (G) Epon-embedded toluidine-blue staining of the biopsied sural nerve. Significant loss of myelinated fibers and endoneurial edema are shown. Scale bar = 50 μm. (H) Teased fiber preparation of the sural nerve. Axonal degeneration is apparent but no evidence of demyelination was observed. Scale bar = 50 μm.

increased serum creatine kinase, positive anti-Jo-1 antibody and compatible histopathological features, and treated with oral prednisolone. At 41, she developed hand/finger stiffness and pain and was diagnosed with RA.

At the age of 50 years, while taking 10 mg of oral prednisolone, 2 mg of oral tacrolimus and 500 mg of monthly intravenous abatacept (cytotoxic T-lymphocyte-associated protein 4-Ig), she developed dysesthesia in the distal part of all extremities. Six months later, she noticed a subacute progressing weakness of both upper limbs and was admitted to a hospital where she was diagnosed with NMOSD due to positive serum anti-AQP4 antibodies by enzyme linked immunosorbent assay and a longitudinally extensive spinal cord lesion at C2–C6 levels by MR imaging (Fig. 1(A–D)). Two courses of intravenous methylprednisolone pulse therapy (1000 mg daily for 3 consecutive days) and plasma exchange were performed in a previous hospital, but her symptoms did not improve and she was transferred to our hospital.

On admission, general physical examination revealed hand and finger deformities and a moderate limitation in neck movement. Neurological examination revealed severe muscle weakness and atrophy of the right upper extremity with proximal dominance, diffuse moderate weakness of the left upper extremity, symmetrical mild proximal-dominant weakness of both lower extremities, severe sensory impairment of all modalities of four limbs in glove and stocking distribution, wide-based gait with positive Romberg's sign, and absence of all tendon reflexes. Blood tests showed normal levels of serum creatine kinase, positive anti-aminoacyl-tRNA synthetase antibodies, and positive anti-AQP4 antibodies by cell-based assay, whereas other autoantibodies including IgM anti-GM1 ganglioside, anti-neurofascin 155, anti-neurofascin 186 and anti-contactin 1 antibodies were negative. Her cerebrospinal fluid was acellular with normal total protein levels, normal myelin basic protein levels and no oligoclonal IgG bands. NCS revealed a marked decrease in compound muscle action potentials (right median, 1.82 mV; left median, 3.51 mV; right ulnar 1.31 mV; left ulnar 1.63 mV), but normal distal latencies, normal nerve conduction velocities and no conduction block in the median and ulnar nerves. F wave-evoked frequencies were decreased in the bilateral median (right, 25%; left, 63%) and right ulnar nerves (right, 6%; left, 81%), whereas F wave minimum latencies were normal. Sensory nerve action potentials were markedly decreased or absent in the median, ulnar and sural nerves. MR images showed that the swollen T2 hyperintense lesion in the cervical spinal cord was diminished with no gadolinium enhancement. Notably, MR neurography disclosed asymmetrical multifocal swollen hyperintense lesions in the bilateral cervical nerve roots and plexuses (Fig. 1(E)) and bilateral proximal and distal sciatic nerves (Fig. 1(F)).

Sural nerve biopsy was performed 14 months after the onset to evaluate the pathogenesis of neuropathy. Hematoxylin-eosin staining showed no inflammatory cell infiltration or extracellular deposits. Epon-embedded toluidine blue staining demonstrated endoneurial edema, severe loss of large diameter myelinated fibers, moderate loss of small-diameter fibers with no evidence of thinning of the myelin sheath, and onion-bulb formation (Fig. 1(G)). Axonal degeneration was observed, but segmental demyelination and remyelination were absent in the teased fibers (Fig. 1(H)). We administered intravenous

immunoglobulin (0.4 g/kg daily for 5 consecutive days) and two courses of intravenous methylprednisolone pulse therapy (1000 mg daily for 3 consecutive days), and initiated tocilizumab (anti-IL-6 receptor monoclonal antibody) instead of abatacept with the expectation of affecting both NMOSD and RA; however upper limb weakness and sensory disturbance progressed gradually, and findings suggestive of axonal sensorimotor neuropathy were not improved by NCS.

3. Discussion

We report a case of NMOSD in a patient who developed immune therapy-resistant axonal neuropathy in addition to acute transverse myelitis. Although the exact onset of neuropathy was not determined, we speculate that axonal neuropathy coincided with transverse myelitis in the present case given the preceding distal dysesthesia and consistent absence of all tendon reflexes. We initially considered CCPD, an autoimmune demyelinating disorder affecting both the CNS and PNS, as a differential diagnosis. However, no findings suggestive of demyelination were obtained by NCS throughout the disease course in addition to histopathological analysis of the biopsied sural nerve. Furthermore, all autoantibodies examined were negative including anti-nodal/paranodal antibodies. Therefore, the present case does not seem to belong to the disease spectrum of CCPD or CIDP.

The involvement of the PNS was reported to occur in a small proportion of NMOSD patients and to be mainly demyelinating radiculopathy, presumably caused by the disruption of AQP4 in the transitional zone of the CNS-PNS boundary (Kim et al., 2017). Only one report has described a case of NMOSD without anti-AQP4 antibodies who developed axonal sensorimotor neuropathy confirmed by NCS, which favorably responded to immunotherapy of methylprednisolone, plasma exchange and rituximab (Feyissa et al., 2015). A similar clinical presentation was also reported in a case series of Sjögren syndrome including a case of concomitant transverse myelitis and motor-dominant axonal sensorimotor neuropathy and another case of sensorimotor axonal neuropathy with sural nerve pathology of moderate loss of large and small diameter myelinated fibers and no inflammatory cell infiltration (Mochizuki et al., 2002). Intriguingly, the present case demonstrated multifocal swelling of the peripheral nerves on MR neurography. Localized swelling of the peripheral nerves was observed in various diseases afflicting the PNS including CIDP (Duggins et al., 1999). Although the appearance of multifocal swelling in the present case is reminiscent of multifocal motor neuropathy or multifocal acquired demyelinating sensory and motor neuropathy, findings suggestive of demyelination were consistently absent. RA occasionally causes vasculitic neuropathy; however, swelling of peripheral nerves has not been reported in RA-related vasculitic neuropathy. Although inflammatory cell infiltration was not observed, endoneurial edema seen in the present patient may suggest disruption of the blood nerve barrier by preceding inflammation (Uceyler et al., 2016), which may contribute to the localized swelling and signal abnormalities of the peripheral nerves seen by MR neurography. In addition, it is also possible that Wallerian degeneration following the extensive spinal anterior horn damage could cause the axonal neuropathy at least in motor nerve axons, and the extension of severe inflammation to the dorsal roots induced sensory nerve degeneration. However, it should be noted that the sural nerve biopsy was performed long after the initiation of immunotherapy, which might have masked neural inflammation. Therefore, we speculate that unknown autoimmune mechanisms underlie the severe intractable axonal neuropathy coincident with the occurrence of NMOSD. Neurologists should be aware of the potential for axonal neuropathy in NMOSD cases presenting as areflexia with other signs of PNS involvement. In such cases, MR neurography might be useful to visualize potential PNS involvement.

Conflict of interest

None declared.

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