An Autopsy Case Involving a 12-year History of Amyotrophic Lateral Sclerosis with CIDP-like Polyneuropathy

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Abstract

Demyelinating polyneuropathy associated with amyotrophic lateral sclerosis (ALS) is quite rare. We herein present the case of a woman patient with a 12-year history of chronic inflammatory demyelinating polyneuropathy (CIDP)-like polyneuropathy who later developed bulbar palsy and respiratory failure. The autopsy findings revealed neuronal loss in the anterior horn and primary motor cortex with degeneration of the corticospinal tracts. Diffuse phosphorylated TAR DNA-binding protein of 43 kDa inclusions were observed in the anterior horn and cerebral cortices, including the temporal lobe. The final diagnosis was ALS with CIDP-like polyneuropathy. Compared with other reports of ALS with CIDP-like polyneuropathy, the present patient was younger and followed a relatively long clinical course, with no upper motor neuron signs.

Key words: amyotrophic lateral sclerosis, chronic inflammatory demyelinating polyneuropathy, autopsy, onion bulb formation, TAR DNA-binding protein of 43 kDa


Introduction

Amyotrophic lateral sclerosis (ALS) is a slowly progressive neurodegenerative disorder impairing both upper and lower motor neurons in the central nervous system, leading to death from respiratory failure, usually within three to five years of symptom onset (1). On the other hand, chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated demyelinating polyneuropathy that impairs the peripheral nervous system and shows various distributional patterns (2). Recently, some reports of ALS accompanied by CIDP-like polyneuropathy have been published (3-7). Although the pathological characteristics and treatment responses varied among the reported cases, the findings could represent a possible novel phenotype of motor neuron disease.

In this report, we present the case of a Japanese woman with autopsy-proven ALS associated with CIDP-like polyneuropathy whose disease onset was relatively young and disease progression was relatively slow compared to that observed in previously reported patients. This is an important case for understanding the range of the disease spectrum of this rare condition.

Case Report

The patient had no remarkable family or past medical history except for iron-deficiency anemia. At 37 years of age, she noticed a tendency to stumble due to slight weakness in the feet and cramps in the calves. At 39 years of age, she developed difficulty in performing dorsiflexion of the left

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foot with hypoesthesia and a tingling sensation in the bilateral hands. The muscle weakness in her legs gradually worsened, and she was referred to our hospital at 42 years of age. A neurological examination revealed distal dominant muscle weakness in the bilateral legs with slight atrophy, particularly in the left leg. Hyperalgesia with a multifocal distribution was found in the bilateral fingertips and areas innervated by peroneal nerves, sural nerves and the right plantar nerve. The left Achilles tendon reflex was absent. A nerve conduction study (NCS) performed at 43 years of age revealed loss of the F-wave in the left median, tibial and peroneal nerves. In addition, temporal dispersion was found in the bilateral fingertips and areas particularly in the left leg. Hyperalgesia with a multifocal distribution was found in the bilateral legs and areas innervated by peroneal nerves, sural nerves and the right plantar nerve. The left Achilles tendon reflex was absent. A blood test showed slight elevation of creatine kinase (258 IU/L). The cerebrospinal fluid was normal, with a normal protein level of 0.25 g/L. Anti-ganglioside antibodies, including anti-GM1 antibodies were negative. Brain MRI and spine MRI with gadolinium enhancement were normal, with no swelling or T2-hyperintense foci in the nerve roots. A nerve conduction study (NCS) performed at 43 years of age revealed loss of the F-wave in the left median, tibial and peroneal nerves. In addition, temporal dispersion was found in the left tibial nerve (Fig. 1). An epon-embodied specimen of the left sural nerve (Fig. 2a) revealed normal-density myelinated fibers (7,210/mm²) with scattered thinly myelinated fibers and a small number of areas of onion bulb formation (Fig. 2b). The unmyelinated fibers were mostly spared, without apparent axonal degeneration (Fig. 2c). The teased-fiber method revealed approximately 10% segmental demyelination and remyelination. Neither duplication nor deletion in the peripheral myelin protein-22 (PMP22) gene were found on a fluorescence in situ hybridization (FISH) analysis.

Since the patient was suspected to have demyelinating polyneuropathy, intravenous immunoglobulin (IVIG) therapy (0.4 g/kg daily for five days) was administered, which achieved a partial effect on the left foot drop. The muscle strength of the left tibialis anterior increased from 2 to 3 according to a manual muscle test (MMT), and the patient’s gait improved. She also reported alleviation of the sensory disturbance in both hands. At that time, the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria for CIDP were met based on one electrodiagnostic criterion with two supportive criteria (8). She was discharged from the hospital on prednisolone therapy (20 mg orally per day).

Over the ensuing 12 months, the patient’s muscle strength gradually deteriorated. The bilateral patellar tendon reflexes were temporarily increased; however, no pathological reflexes were observed. A second cycle of IVIG therapy was administered at 43 years of age, which was again partially effective and improved the left leg strength from 2 to 3 on MMT, with the improvement lasting for the next several months. At 44 years of age, left arm weakness appeared, followed by right arm weakness. A neurological examination revealed muscle weakness in all four limbs with glove-and-stocking type hypesthesia. The IVIG therapy partially improved the muscle strength of the upper limbs, and the sensory disturbance was also slightly ameliorated, IVIG therapies was subsequently consecutively administered two to three times a year; however the efficacy gradually diminished. We were unable to confirm an objective neurological improvement after 45 years of age. Methylprednisolone pulse therapy and cyclosporin-A were also administered, although neither were effective. By 45 years of age, the weakness and muscle atrophy in all extremities had further progressed in association with the absence of deep tendon reflexes, and the patient was no longer able to stand. At 46 years of age, tongue atrophy with fasciculation, dysarthria and dysphagia emerged. The bulbar symptoms further worsened, and percutaneous endoscopic gastrostomy was performed. At 47 years of age, the muscle strength in all extremities was 1-2 on MMT, and the respiratory disturbance gradually progressed. The patient refused treatment with a ventilator and died of respiratory failure at 48 years of age, nearly 12 years after the onset. No cognitive deficits were noted throughout the patient’s clinical course, and no difficulties in executive decision making were observed.

**Autopsy findings**

The brain was of normal weight (1,220 g) with no marked atrophy or deformities. The structures of the cerebellum and brain stem also appeared to be within the normal limits. Routine Hematoxylin and Eosin (H&E) staining and Kluver-Barrera staining revealed preserved neurons in the hippocampus and cerebral cortices. On immunostaining, cytoplasmic inclusions of phosphorylated TAR DNA-binding protein of 43 kDa (TDP-43) were observed in the right frontal lobe cortex, right subiculum, granule cells of the hippocampus and adjacent temporal lobe cortex (Fig. 3a). In the motor cortices, loss of Betz cells and gliosis were observed on H&E staining. In the brain stem, partial loss and atrophy of motor neurons in the hypoglossal nuclei were found. The remaining neurons were negative for phosphorylated TDP-43.

The spinal cord was almost normally shaped, with no apparent systematic atrophy (Fig. 3b); however, staiinability was mildly reduced in the lateral funiculi. The spinal ventral
Figure 2. Pathological findings in peripheral nervous system. (a) Left sural nerve biopsy. There were scattered thinly myelinated fibers. Toluidine blue staining. (b) Electron micrography of onion bulb formation showed four to five concentric layers of Schwann cell processes. A few onion bulb formations, like this one, were observed in each nerve fascicle. (c) Electron micrography of unmyelinated fibers. Fibers were spared without axonal degeneration. (d) Spinal ventral roots. Large myelinated fibers were markedly reduced in number. Some remaining large fibers were thinly myelinated. Toluidine blue staining. (e) Spinal dorsal roots. Fibers were mostly spared compared to the ventral roots. (f) Lumbar plexus. Focal axonal loss, probably reflecting degeneration of motor neurons, was found. Elastica-Masson staining.

Figure 3. Pathological findings in central nervous system. (a) Dentate gyrus of the hippocampus. Phosphorylated TDP-43-positive inclusions were observed in the cytoplasm of granule cells. (b) Cervical cord at C6 level. Myelinated fiber of the lateral corticospinal tracts was observed by Klüver-Barrera staining. (c) Anterior horn of the lumbar cord. Severe neuronal loss was observed. Hematoxylin and Eosin (H&E) staining. (d) Anterior horn of the lumbar cord. A Bunina body was observed in the cytoplasm (arrow). H&E staining. (e) Anterior horn of the lumbar cord. Granular phosphorylated TDP-43 immunoreactivities were diffusely observed in the cytoplasm of the remaining lower motor neurons.
roots were somewhat atrophic compared to the dorsal roots. Although the anterior horn was not atrophied at any level of the spine, anterior horn cells were diffusely degenerated and reduced in number at the cervical (C6), thoracic (T4) and lumbar (L3) levels of the cord (Fig. 3c). A Bunina body was detected in a remaining motor neuron at the L3 level (Fig. 3d). Phosphorylated TDP-43-positive cytoplasmic inclusions were found in the anterior horn (Fig. 3e) on immunohistochemical staining. Although the volume of the lateral corticospinal tract was mostly preserved, myelin pallor was observed on Kluver-Barrera staining.

Peripheral nerves were sampled from the lumbar ventral and dorsal roots, lumbar plexus and proximal sciatic nerves. In the ventral roots, large myelinated fibers were reduced in number, and many small myelinated fibers were found (Fig. 2d). In the dorsal roots, the nerve fibers were mostly spared, showing a small number of thinly myelinated fibers (Fig. 2e). In the lumbar plexus, focal axonal loss was observed in some fascicles (Fig. 2f). There were some thinly myelinated fibers in the proximal sciatic nerves. No apparent infiltration of inflammatory cells was noted in the examined peripheral nerves. Muscles were sampled from the tongue, diaphragm and iliopsoas, all of which demonstrated neurogenic atrophy with fat infiltration.

Discussion

Because the patient was diagnosed with CIDP based on the nerve biopsy and NCS findings, the advent of bulbar palsy and respiratory failure, which are rare manifestations of CIDP (9), in the last two years was unexpected.

To our knowledge, the coexistence of ALS and demyelinating polyneuropathy resembling CIDP has been reported in 13 patients (3-7). Their clinical and pathological findings are summarized with those of the present patient in Table. The median age of onset was 64 years (range: 37-70 years old), and the median duration of disease (onset to respiratory failure) was 44 months (range: 11-142 months). ALS was diagnosed in all cases according to the El Escorial criteria (10) and/or autopsy findings (four cases). On the other hand, CIDP-like polyneuropathy was diagnosed on the initial admission using established diagnostic criteria (8, 11) based on NCS findings in most cases. Sural nerve pathology was described in eight cases, and demyelination was confirmed in all cases. Mononuclear cell infiltration in the peripheral nerves was observed in two cases, one at autopsy (5) and the other on a biopsy and at autopsy; the latter case involved Charcot-Marie-Tooth disease (6). All 14 patients received IVIG therapy, and some neurological improvements were reported in six cases. The effects of treatment lasted from a few weeks to several months, and addi-

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**Table. Clinical Characteristics, Pathological Findings, and Effectiveness of IVIG Therapy in 13 Previously Reported Cases of ALS with CIDP-like Polyneuropathy and the Present Case**

<table>
<thead>
<tr>
<th>Ref</th>
<th>Onset age, sex</th>
<th>Duration [months]</th>
<th>Fasc.</th>
<th>Sens. Dist.</th>
<th>Peripheral nerve pathology</th>
<th>CNS pathology</th>
<th>TDP-43 or Bunina body (C/S)</th>
<th>IVIG (E/I)</th>
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<tr>
<td>3</td>
<td>44, M (FALS)</td>
<td>20</td>
<td>+</td>
<td>-</td>
<td>MCI</td>
<td>U, L</td>
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<tr>
<td>3</td>
<td>63, M (FALS)</td>
<td>13</td>
<td>+</td>
<td>-</td>
<td>n.d.</td>
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<tr>
<td>3</td>
<td>52, M</td>
<td>38</td>
<td>+</td>
<td>-</td>
<td>n.d.</td>
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<tr>
<td>4</td>
<td>57, F</td>
<td>77</td>
<td>-</td>
<td>+</td>
<td>n.d.</td>
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<tr>
<td>4</td>
<td>68, F</td>
<td>38</td>
<td>+</td>
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<tr>
<td>5</td>
<td>66, M</td>
<td>59</td>
<td>-</td>
<td>+</td>
<td>OB, Dmy</td>
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<td>I</td>
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<tr>
<td>5</td>
<td>50, M</td>
<td>50</td>
<td>+</td>
<td>-</td>
<td>OB, Dmy</td>
<td>n.d.</td>
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<tr>
<td>6</td>
<td>70, M (CMT1A)</td>
<td>43</td>
<td>-</td>
<td>+</td>
<td>OB, Dmy,</td>
<td>U, L</td>
<td>S</td>
<td>E</td>
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<tr>
<td>7</td>
<td>45, M (CMT1A)</td>
<td>48</td>
<td>-</td>
<td>+</td>
<td>OB, Dmy</td>
<td>n.d.</td>
<td>n.d.</td>
<td>E</td>
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<tr>
<td>7</td>
<td>68, M (the present case)</td>
<td>11</td>
<td>+</td>
<td>-</td>
<td>Dmy</td>
<td>U, L</td>
<td>S</td>
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<tr>
<td>7</td>
<td>37, F</td>
<td>142</td>
<td>-</td>
<td>+</td>
<td>OB, Dmy</td>
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tional courses of IVIG therapy were ineffective, except in the present case. Some patients appeared to develop symptoms of ALS after the period of clinical manifestations of CIDP-like polyneuropathy, while others showed symptoms suggestive of ALS, such as upper motor neuron signs, on the initial presentation. Among the latter patients, the manifestations on the initial presentation were consistent with those of ALS, except for the NCS findings in some cases, including two patients with familial ALS (3). Whether CIDP-like polyneuropathy evolved as an epiphenomenon of ALS or existed as a comorbidity of ALS was unclear in most of the cases.

Compared with the 13 previously reported patients, our patient was younger at disease onset, and the duration of disease was especially long. The lack of upper motor neuron signs made the diagnosis more difficult. Although a small number of ALS patients are known to exhibit slow disease progression of up to 10 years or more (12-14) and present with only lower motor neuron signs clinically (14, 15), the neuropathy may have partially contributed to the present patient’s symptoms, which improved with IVIG therapy. After 45 years of age, when the IVIG therapy no longer achieved any objective improvements, the muscle weakness may have been attributable to ALS, because we did not find any typical CIDP lesions at autopsy, such as onion bulb formation or inflammatory infiltration, although we can not exclude the possibility that such lesions evolved in the peripheral nervous system at sites other than those we were able to examine.

Although it is difficult to infer a causal relationship between the CIDP-like polyneuropathy and ALS in the present patient, this and previously reported cases suggest that some patients with ALS exhibit forms of demyelinating polyneuropathy that fulfill the diagnostic criteria for CIDP at the initial presentation. Such types of neuropathy can be partially improved with IVIG therapy, although the final outcome depends on the progression of ALS. Diagnosing ALS clinically is especially difficult if the disease course is prolonged and upper motor neuron signs are absent, as observed in the present case.

The authors state that they have no Conflict of Interest (COI).

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