Substantial Improvement in a Nerve Conduction Study of Lymphoma-associated Demyelinating Neuropathy Treated by Intravenous Immunoglobulin and Chemotherapy

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Abstract:
A 64-year-old woman with lymphoma-associated demyelinating neuropathy was treated by 6 cycles of R-CHOP with intravenous immunoglobulin in the first 2 cycles. We noted substantial improvement in the findings of a nerve conduction study (NCS) after the first cycle, followed by more protracted improvement during the second to sixth cycles. The improvement of the neurological symptoms paralleled the findings of the NCS. Our case provides important information for understanding the etiology and optimization of treatments for lymphoma-associated demyelinating neuropathy.

Key words: lymphoma-associated demyelinating neuropathy, B-cell lymphoma, nerve conduction study

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Introduction

Lymphoma-associated demyelinating neuropathy is uncommon, and the pathogenesis and treatment remain to be established. In a review of immune-mediated neuropathies in patients with lymphoma, various types of neuropathy can occur, predominantly sensory polyneuropathy and sensorimotor polyneuropathy and less commonly multifocal motor neuropathy, among others (1). Demyelinating polyneuropathies are often reported based on electrophysiological findings. The treatment of lymphoma-associated demyelinating neuropathy includes cytotoxic chemotherapy and/or immunomodulatory therapy, such as intravenous immunoglobulin (IVIG), steroid, azathioprine, and plasmapheresis.

We herein report a patient with lymphoma-associated demyelinating neuropathy who presented with substantial improvement in a nerve conduction study (NCS) on treatment with IVIG and R-CHOP.

Case Report

A 64-year-old woman noticed weakness of the lower extremities and difficulty walking from the beginning of March 20XX and visited the previous hospital at the beginning of April the same year. She was suspected of suffering from Guillain-Barré syndrome based on albuminocytologic dissociation on a cerebrospinal fluid examination, and she was followed up carefully. However, her weakness worsened. Computed tomography (CT) showed a mass in the pelvis. She was therefore referred to our hospital for a further examination and treatment in the middle of May.

She had a history of hyperthyroidism and depression, and she was taking thiamazole. Superficial lymphadenopathy was not observed. She had no body weight loss, fever, or night sweats. Her consciousness was alert. The visual field was intact. The position and motility of the eyeballs were within normal limits. No abnormality of the superficial sensation of the face was noted. The uvula hung in the midline during articulation, but the movements of the soft palate appeared reduced. Swallowing was normal. The muscle tone of the whole body was slightly decreased. The muscles were not spastic or rigid. Manual muscle testing (MMT; right/left) revealed sternocleidomastoid 5/5, deltoid 5/5, biceps brachii 4/4, triceps brachii 3-/3-, wrist extensors 3/3, wrist flexors, 4/4, iliopsoas 2/2, quadriceps femoris 4/4, knee flexors 3/3,
ankle dorsiflexors 5/5, and ankle plantar flexors 5/5. The reflexes of jaw jerk, biceps, triceps, patellar, and Achilles tendon were absent. There were no Babinski or Chaddock signs. The senses of touch, pain, and temperature were normal. The deep sensation of the extremities was diminished bilaterally and was worse at the left upper extremity than at the right upper extremity. Ataxia was noted on finger-to-nose testing. A heel-to-knee test could not be performed because she could not move her legs sufficiently. She was bedridden and was unable to turn over by herself. She had strong pain in all of her extremities (7-10 out of 10 on a numeric rating scale).

A nerve conduction study (NCS) showed a decreased amplitude and extended duration, especially with proximal stimulation, in the median, ulnar, and tibial nerves and decreased nerve conduction velocity in the median nerve, although the results of the tests at the previous hospital had been almost within normal limits except for a decreased nerve conduction velocity (Table 1). We speculated she had segmental demyelination of the motor neurons. Sensory nerve action potentials were not elicited on the NCS. We did not conduct a somatosensory evoked potential test. Laboratory findings showed soluble interleukin-2 receptor (sIL-2R) of 1,590 U/mL and immunoglobulin M (IgM) of 584 mg/dL. Serum immunofixation electrophoresis showed monoclonal IgM-κ. Serum immunosorbent assay (ELISA) showed that serum IgG and immunoglobulin A (IgA) did not react with GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, Gal-C, GalNAc-GD1a, GD1a/GD1b (Department of Neurology, Kindai University School of Medicine, Osaka, Japan), myelin-associated glycoprotein (MG), or sulfoglucuronyl paragloboside (SGPG; Athena Diagnostics, Marlborough, USA). We did not perform a sural nerve biopsy. Positron emission tomography (PET)/CT and magnetic resonance imaging (MRI) of pelvis showed a mass behind the rectum of 10 cm in the major axis. There were no other lesions detected on PET-CT or brain MRI. There was no spinal invasion. A bone marrow biopsy from the posterior iliac crest showed no infiltration of malignant cells. We therefore conducted a CT-guided needle biopsy. The malignant cells were small or medium in size, positive for CD20, CD5, bcl-2, bcl-6, and IgM-κ, and negative for CD10, CD11c, and CD23. We suspected mantle cell lymphoma, but the malignant cells were negative for cyclin D1 and SOX11. The Ki-67 index was about 10%. We were unable to perform a chromosome analysis because the specimens obtained by a needle biopsy were insufficient. We ultimately delivered a diagnosis of indolent B-cell lymphoma.

The neurological symptoms continued to worsen. At the

### Table 1. Nerve Conduction Study on Admission.

|                          | Latency (ms) | Duration (ms) | Amplitude (mV) |
|--------------------------|--------------|---------------|----------------|
| **Median Nerve**         |              |               |                |
| Palm                     | 2.5 [1.86±0.28, ULN 2.4] | 5.8          | 5.0 [6.9±3.2, LLN 3.5] |
| Wrist                    | 4.5 [4.2] [3.49±0.34, ULN 4.2] | 6.2 (5.1)   | 4.3 (9.3) [7.0±3.0, LLN 3.5] |
| Elbow                    | 9.7 (8.0) [7.39±0.69, ULN 8.8] | 8.9 (5.4)   | 2.3 (6.3) [7.0±2.7, LLN 3.5] |
| **Ulnar Nerve**          |              |               |                |
| Wrist                    | 3.1 (3.1) [2.59±0.39, ULN 3.4] | 7.4 (5.9)   | 2.3 (13.0) [5.7±2.0, LLN 2.8] |
| Bel Elb                  | 5.8 (8.1) [6.10±0.69, ULN 7.5] | 10.1 (6.2)  | 1.5 (8.7) [5.5±2.0, LLN 2.7] |
| Abo Elb                  | 9.1 (11.5) [8.04±0.76, ULN 9.6] | 11.0 (5.9)  | 0.62 (5.2) [5.5±1.9, LLN 2.7] |
| **Tibial Nerve**         |              |               |                |
| Ankle                    | 3.9 (3.0) [3.96±1.00, ULN 6.0] | 6.5 (5.1)   | 4.0 (22.2) [5.8±1.9, LLN 2.9] |
| Poplitéal                | 11.4 (10.4) [12.05±1.53, ULN 15.1] | 9.2 (5.7)   | 1.9 (15.2) [5.1±2.2, LLN 2.5] |

NCV: nerve conduction velocity. Bel Elb: below elbow, Abo Elb: above elbow

The numbers inside the round brackets show the values at the previous hospital. The numbers inside the square brackets show the mean±standard deviation, and the upper limit of normal (ULN) or lower limit of normal (LLN) of latency, amplitude and nerve conduction velocity.
end of May, she was able to lift her upper and lower extremities but could not keep them raised. She needed full physical assistance to roll her body over. Her cough reflex was diminished. She developed severe aspiration pneumonia due to impaired swallowing and was intubated, subsequently undergoing tracheotomy. At the beginning of June, she was able to draw her knees up but could not lift her lower extremities, nor could she lift her arms straight. She was able to flex and extend the ankles. She had no problems moving her neck or face, such as with nodding or moving her mouth. Her superficial sensation became worse than when she had first presented at our hospital. The sense of vibration and position also worsened further. By the middle of June, the superficial sensation was markedly decreased in the upper and lower extremities. She could no longer draw her knees up. MMT showed deltoid 2/2, biceps brachii 3/3-2, quadriceps femoris 1/1, ankle dorsiflexors 2/1.

Treatment for the neuropathy was needed urgently. We performed IVIG and cytotoxic chemotherapy (R-CHOP without vincristine, given every three weeks for six cycles). The first two cycles of the chemotherapy were performed with IVIG, and the other four cycles were performed alone. We started the first cycle of chemotherapy and IVIG in the middle of June.

After the first cycle of IVIG, the movement of her extremities, especially the upper extremities, improved. MMT showed deltoid 2/2, biceps brachii 3/3, wrist flexors 3/3, quadriceps femoris 2/2, ankle dorsiflexors 3/3, and ankle plantarflexors 2-/2-. The grip strength markedly improved, and the movement of the lower extremities slightly improved. She became able to draw her knees up again. The reflexes of the biceps and patellar tendon were absent. The superficial sensation was slightly improved, but the impaired deep sensation was not changed.

After the second cycle of IVIG, she was able to lift her legs again. The coordination of the movements of the arms improved. She was able to lift her upper extremities in their full range. She could point her fingers at a communication board more smoothly than before. She could push a nurse call button as well as the buttons on a DVD player. MMT showed deltoid 3/3, biceps brachii 3/3, wrist flexors 3/3, quadriceps femoris 2/2, ankle dorsiflexors 3/3, and ankle plantarflexors 2-/2-. The superficial sensation was mildly improved. She had hoarseness with a speech cannula. Jelly was aspirated above the cuff of the tracheostomy tube during swallowing training.

We conducted the third cycle in the beginning of August. The movement and sensation of the extremities were almost unchanged. After the fourth, fifth, and sixth cycles, the movement gradually improved. After she had completed six cycles, in the middle of October, she was able to take earphones on and off, remove a DVD from a DVD case, and change the discs in a player. She could lift her legs straight up. The swallowing function was improved, and she had no aspiration on swallowing training. The superficial and deep

Table 2. The Laboratory Findings on Admission.

|          |              |
|----------|--------------|
| WBC      | 16.8×10^9 /L |
| Neutrophils | 79.0 %      |
| Lymphocytes | 11.0 %      |
| Monocytes | 8.0 %        |
| Eosinophils | 2.0 %       |
| Basophils | 0.0 %        |
| RBC      | 4.70×10^{12} /L |
| Hb       | 13.9 g/dL    |
| Ht       | 41.2 %       |
| MCV      | 87.7 fL      |
| Pt       | 23.9×10^{10} /L |
| HbA1c    | 5.4 %        |
| Glu      | 122 mg/dL    |
| TSH      | 0.230 μIU/mL (0.35 - 4.94) |
| fT4      | 1.07 ng/dL (0.7 - 1.48) |
| fT3      | 1.26 pg/mL (1.71 - 3.71) |
| ALT      | 13 U/L       |
| LDH      | 162 U/L      |
| CK       | 17 U/L       |
| TP       | 6.8 g/dL     |
| Alb      | 3.4 g/dL     |
| Na       | 141 mEq/L    |
| K        | 3.8 mEq/L    |
| Cl       | 101 mEq/L    |
| CRP      | 8.5 mg/dL    |
| sIL-2R   | 1,590 U/mL (124 - 466) |
| β2MG     | 1.8 mg/dL (1.1 - 2.5) |
| T 1g      | 2MG 1.8 mg/dL |
| TSH: thyroid stimulating hormone, fT4: free thyroxine 4, fT3: free thyroxine 3, sIL-2R: soluble interleukin-2 receptor, β2MG: beta-2 microglobulin, HIV: human immunodeficiency virus, HTLV-1: human T-cell leukemia virus type 1
| The numbers inside the brackets show the normal range.

Table 3. Cerebrospinal Fluid Examination.

| Appearance | normal |
|------------|--------|
| Cytology   | negative |
| WBC        | 1 /μL (1 - 3) |
| Total protein | 492 mg/dL (10 - 40) |
| Albumin    | 3.265 μg/mL |
| IgG        | 56.9 mg/dL |
| Glucose    | 73 mg/dL (40 - 75) |
| Chloride   | 119 mEq/L (120 - 125) |
| sIL-2R     | 125 U/mL |
| Myelin basic protein | negative |
| Oligoclonal band | negative |
| The numbers inside the brackets show the normal range. |
Lymphoma-associated demyelinating neuropathy is very rare disease. A sural nerve biopsy is sometimes performed to rule out the infiltration of lymphoma cells. However, the utility of such a biopsy is limited for the diagnosis of neuropathy associated with lymphoma, as biopsies only assess a distal portion of the peripheral nervous system (2). In our patient, we were unable to rule out neurolymphomatosis completely. However, the neuropathy symptoms were involved in a wide portion of the body, despite the indolent nature of the lymphoma, and PET-CT, MRI, and CSF examinations revealed no evidence of neural invasion of the lymphoma cells. We therefore presumed that a paraneoplastic mechanism was involved in our patient.

Although autoantibodies directed against specific peripheral nerve antigens are sometimes involved in the cause of lymphoma-associated neuropathy, we detected no autoantibodies in our patient (1). The lymphoma cells expressed IgM-λ, and monoclonal IgM-λ was found in the serum. The lymphoma cells may have been secreting IgM-λ monoclonal protein, which may have been involved in the pathogenesis of the neuropathy. Koike et al. reported that the most frequent form of paraneoplastic neuropathy in patients with malignancy was sensory neuropathy, while sensorimotor neuropathy, such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, were less frequent forms (3). In cases of paraneoplastic polynuropathy in patients with lymphoma, sensorimotor neuropathy or demyelinating neuropathy is often observed (1). We speculate that the present patient had segmental demyelination of the motor neurons, based on the electrophysiological findings of

![Image](https://example.com/image.png)

**Figure 1.**  a: Amplitude.  b: Duration.  c: Nerve conduction velocity. An NCS was performed in the left arm and leg four times at our hospital: before we initiated the treatment, after the first cycle, after the second cycle, and after the sixth cycle of R-CHOP. An NCS before the treatment showed a decreased amplitude and extended duration with proximal stimulation (i.e. median nerve stimulated at the elbow and ulnar nerve stimulated above the elbow) and a decreased nerve conduction velocity in the median nerve (a: b: c). The decreased amplitude and extended duration showed considerable improvement after the first cycle of treatment, followed by more gradual improvement during the second to sixth cycles (a: b). The decreased nerve conduction velocity was partially improved after six cycles of treatment (Palm-Wrist in median nerve) (c).

sensations of the upper extremities were normal. However, the deep sensations showed a complete deficit in the lower extremities, and the superficial sensations showed a deficit in the feet. MMT revealed deltoid 3+/3+, biceps brachii 4/3+, triceps brachii 4/3+, iliopsoas 2/2, quadriceps femes 3/3, and ankle plantarflexors 2/2. The grip (right/left) was 8.3/7.9 kg. In the NCSs, we observed substantial improvement in the decreased amplitude and extended duration of the motor neurons with proximal stimulation (i.e. median nerve stimulated at the elbow and ulnar nerve stimulated above the elbow) after the first cycle, followed by more gradual improvement from the second to sixth cycles, and the decreased nerve conduction velocity of the median nerve also only partially improved (Palm - Wrist in median nerve) (Fig. 1, 2). The sensory nerve remained undetectable. When she completed the treatment, a laboratory examination showed sIL-2R of 818 U/mL and IgM of 175 mg/dL. The monoclonal IgM level was decreased but remained detectable.

After she had completed six cycles of the chemotherapy, she moved to another hospital for rehabilitation. After changing hospitals, she experienced further improvement in her neurological symptoms, especially her upper body strength. She was able to move about in a wheelchair by herself at four months after the treatment was completed. The pain in the extremities almost completely disappeared. She was decannulated and thereafter was able to eat normal foods orally. The tumor had shrunk and maintained its size on repeated CT at four months after the treatment.

**Discussion**
Figure 2. Nerve conduction studies in the left median nerve. We performed NCS before the treatment (a), after the first cycle (b), after the second cycle (c), and after the treatment had finished (d).

a decreased amplitude and extended duration, especially with proximal stimulation, in the median, ulnar, and tibial nerves and a decreased nerve conduction velocity in the median nerve on an NCS.

The treatment of lymphoma-associated demyelinating neuropathy includes cytotoxic chemotherapy and/or immunomodulatory therapy, such as IVIG, steroid, azathioprine, and plasmapheresis. Lymphoma that is presumed to be indolent can be managed with a “watchful waiting” approach after immune therapy for the neuropathy (4). However, we conducted IVIG and R-CHOP in the hopes of obtaining a more reliable effect, as our patient had severe and progressive neuropathy. The neuropathy rapidly improved with the first cycle, showing more protracted improvement afterward. The improvement of the neurological symptoms was parallel to the findings of NCS. We were unable to determine whether IVIG or R-CHOP was more effective on the neuropathy because they were performed almost simultaneously.

A few articles have mentioned the biphasic recovery of neuropathy in cases other than lymphoma-associated neuropathy. Allen et al. performed an NCS in patients with diabetic neuropathy after simultaneous pancreas and kidney transplantation (5). The conduction velocity improved in a biphasic pattern, with a rapid initial recovery followed by subsequent stabilization. In contrast, the recovery of the nerve amplitude was monophasic and continued for up to eight years. They speculated that the early improvement in the conduction velocity might be due to the correction of uremia, and the gradual improvement of the nerve action potential amplitude indicated axonal regeneration. Nielsen studied the recovery of uremic neuropathy after renal transplantation (6). The conduction velocity, evoked muscle and nerve potential amplitudes, and vibratory perception thresholds showed a biphasic course with an early rapid improvement followed by a considerably more protracted restoration. Nielsen speculated that the early improvement might reflect a rapid improvement in the membrane function in nerve axons and muscle cells after the resolution of uremic intoxication, and the late and protracted improvement might reflect regenerative changes in the nerves and muscles. We found no articles describing the biphasic electrophysiological course in patients with neuropathy associated with lymphoma after chemotherapy and IVIG treatment. The biphasic improvement in our patient may indicate that the inflammation subsided in the acute phase, with subsequent recovery of the neurons, although further electrophysiological and histopathological studies are needed.
Conclusion

We encountered a case of lymphoma-associated demyelinating neuropathy that presented with severe neurological symptoms. IVIG and cytotoxic chemotherapy were effective for treating the neuropathy. We saw rapid improvement after the first cycle of chemotherapy and gradual improvement subsequently. The biphasic improvement of the neuropathy may indicate that the inflammation in the acute phase subsided, with subsequent recovery of the neurons. Physicians encountering patients with lymphoma-associated polyneuropathy that does not respond to the initial treatment may obtain improvement by continuing the treatment. The present case is very important and helpful for understanding the etiology and determining the optimum treatment of lymphoma-associated demyelinating neuropathy.

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

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