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【 CASE REPORT 】

Eribulin Mesylate-related Multifocal Demyelinating Neuropathy with Myokymia in a Breast Cancer Patient

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Abstract:
We herein report a 48-year-old woman receiving eribulin mesylate for breast cancer who presented with gait disorder, distal limb paresthesia, and weakness progressing monthly. A nerve conduction study indicated demyelination with multifocal conduction block. Considering the immune-mediated pathology of her condition, she was administered intravenous immunoglobulin. Her neurological symptoms improved promptly after intravenous immunoglobulin therapy and eribulin withdrawal. Furthermore, the limb myokymia seen at the time of admission disappeared. Her symptoms continued to improve without additional treatment. We conclude that eribulin was a rare cause of demyelinating neuropathy with multifocal conduction block derived from immune-mediated pathology.

Key words: eribulin mesylate, breast cancer, multifocal neuropathy, demyelination, myokymia

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Introduction

Eribulin mesylate is a microtubule inhibitor used to treat recurrent breast cancer and malignant soft tissue tumors. Neuropathy is reported to be a common side effect of eribulin (1, 2). Peripheral neuropathy secondary to microtubule inhibitors usually causes distal limb paresthesia with a characteristic "stocking-glove" distribution, suggesting length-dependent obstacles caused by the disruption of microtubule-dependent transport (3). The main mechanism underlying microtubule inhibitors-related neuropathy has been reported to be axonal injury, and there are no reports of the frequency of demyelination with conduction block (4).

We herein report a woman who experienced reversible demyelinating neuropathy with multifocal conduction block and myokymia that instantly improved on receiving intravenous immunoglobulin and the withdrawal of eribulin, suggesting an immunological mechanism underlying eribulin-related neuropathy.

Case Report

A 48-year-old woman with breast cancer was admitted to our department in May 2020 with a chief complaint of gait disorder. She had been treated with tamoxifen, trastuzumab, pertuzumab, and denosumab for cervical metastasis (C5-6) from May 2018 onwards. Tamoxifen was replaced with eribulin (2 mg per week, for 2 of every 3 weeks) in March 2019 due to the expansion of the primary lesion and increase in tumor markers. In July 2019, she experienced upper limb clumsiness and lower limb paresthesia; subsequently, she noticed gait unsteadiness in December 2019. Since the symptoms were initially thought to be due to compression of the cervical spinal cord, she underwent posterior cervical spinal fusion in January 2020; however, her symptoms worsened despite the surgery. Her gait disorder progressed weekly, and eventually she became unable to walk. She had no medical history other than breast cancer and a family history of neurological disorders.

An examination on admission revealed that the patient had asymmetric limb weakness, especially in the proximal

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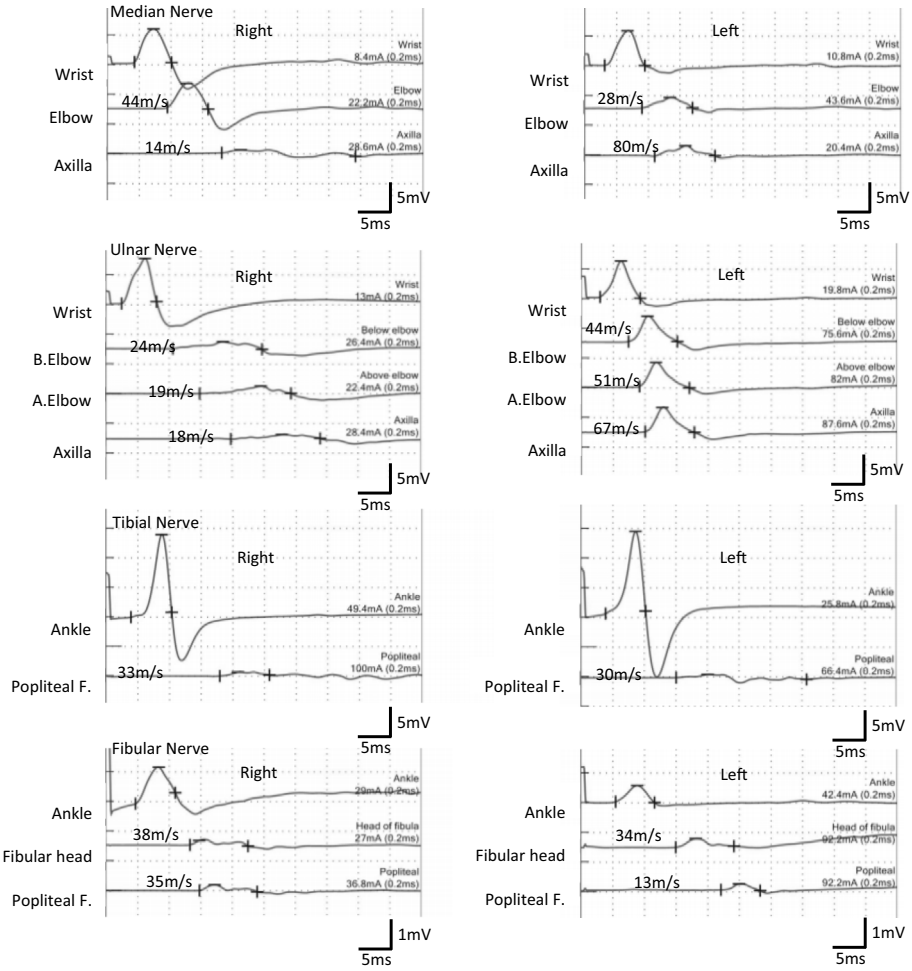

Figure 1. The motor nerve conduction study on admission. Temporal dispersion and decreased conduction velocities indicating demyelination were observed. Multifocal asymmetrical conduction block was seen on the forearm and lower leg. B.Elbow: below elbow, A.Elbow: above elbow, Popliteal F.: popliteal fossa

right upper limb and both distal lower limbs, diminished deep tendon reflexes, and paresthesia of the right palm, left first-third fingers, and lower legs. Her vibration sensation of the lower limbs was severely impaired, and she was unable to walk due to ataxia. We also found intermittent myokymic movements on her forearms and lower legs.

Her nerve conduction studies (NCSs) showed decreased conduction velocities and temporal dispersion in all of the motor nerves that were analyzed (Fig. 1). The NCS findings were also characterized by asymmetrical and multifocal conduction block, with most distal amplitudes being normal. An electrodiagnostic inching study on the left median nerve showed conduction block on the proximal forearm (elbow-9 cm). In the F-wave test, A waves were observed on the median, ulnar, and tibial nerves (Fig. 2). The sensory nerve action potential of the median and ulnar nerves also showed temporal dispersion at the same segment as the motor nerves involved (Fig. 3).

The blood tests did not detect monoclonal immunoglobulin, anti-ganglioside antibodies (IgG and IgM for GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, Gal-C and GalNAc-GD1a, IgG for GD1a/GD1b), anti-neurofascin 155 antibody, or anti-contactin-1 antibody. Carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) levels were within the normal range (<4.9 ng/mL, <26.9 U/mL). The cerebrospinal fluid test showed no increase in protein levels (22 mg/dL) or cell counts (0/μL).

Furthermore, cervical magnetic resonance imaging (MRI) did not suggest progression of the spinal cord compression, and lumber MRI showed no enlargement or contrast enhancement of the lumbar plexus. Needle electromyography showed fasciculation potentials, myokymic discharges, and large polyphasic motor unit potentials on her right abductor pollicis brevis, left quadriceps, and left peroneus longus; however, there were no fibrillation potentials or positive sharp waves at rest. A neuromuscular echogram revealed frequent fasciculation and myokymia on limb muscles, but there was no change in nerve diameter in the area where the conduction block was observed.

We considered multifocal acquired demyelinating sensory and motor (MADSAM)-type chronic inflammatory demyelinating polyneuropathy (CIDP), eribulin-related chemotherapy-induced neuropathy, and paraneoplastic neuropathy as the differential diagnoses.

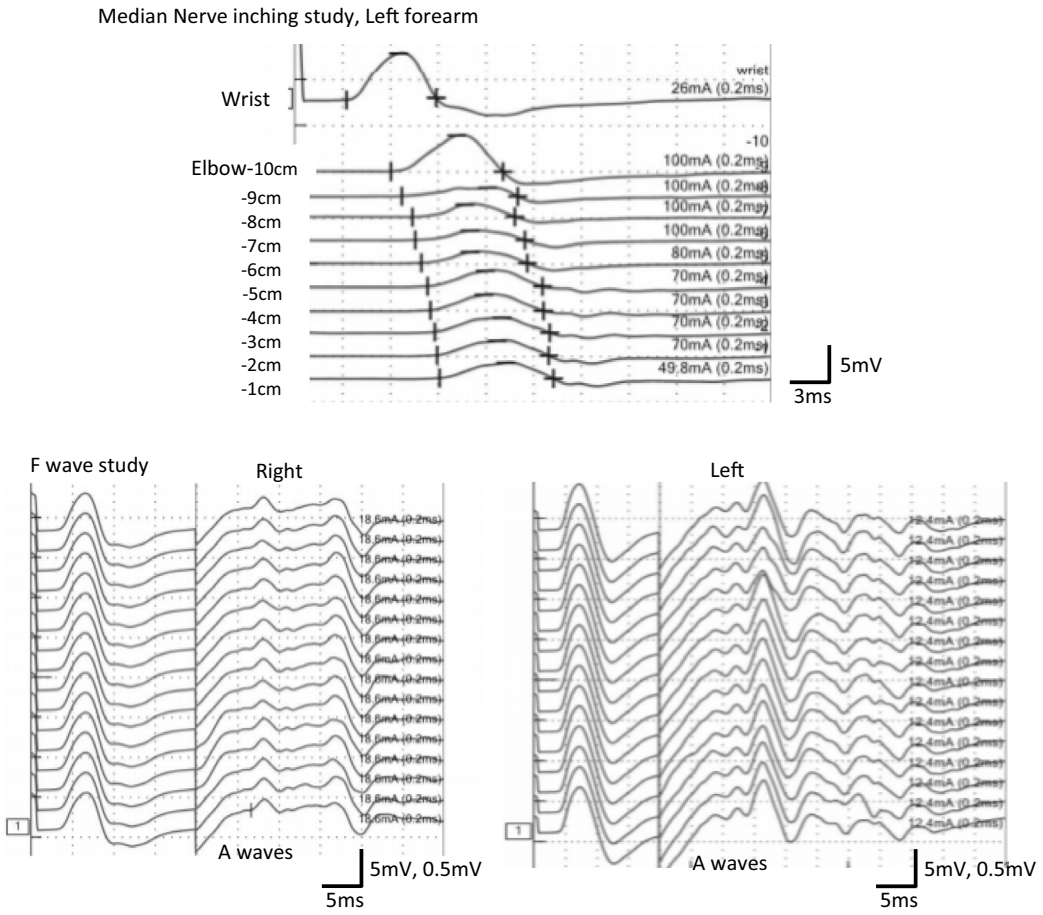

Figure 2. **Left median nerve inching test and F wave test. Conduction block was found 9 cm distal to the left elbow. A wave was observed on both the median nerves.**

We started intravenous immunoglobulin (IVIG) 400 mg/kg for 5 days, assuming the immune-mediated pathology of her condition. Within two weeks, the ataxia and muscle strength of the distal lower limbs improved, accompanying a decrease in the frequency of myokymia, and the patient started walking more stably. Eribulin was discontinued because of suspicion of association with neuropathy. She was discharged on the 23rd day of admission. During outpatient follow-up, we noted that her gait improved monthly without the need for additional treatments. NCSs performed two months later showed no significant improvement, but neuromuscular echography showed that the limb myokymia had almost disappeared.

Discussion

Eribulin mesylate, an inhibitor of microtubule dynamics, was synthesized with reference to a natural substance called halichondrin B1 extracted from the marine organism halichondria (1). A previous study reported that the incidence of peripheral neuropathy with eribulin treatment was 35%, which was the most common adverse event leading to the discontinuation of eribulin (1). Other microtubule inhibitors, such as vincristine and paclitaxel, also cause neuropathy, the main mechanism of which is axonopathy (5). However, the present case of eribulin-related neuropathy was characterized by 1) multifocal demyelinating neuropathy with conduction block, 2) myokymia, and 3) responsiveness to immunotherapy. To our knowledge, there has only been one other case report on demyelinating neuropathy after the administration of eribulin, wherein the patient presented with multifocal conduction block and myokymia, similar to our case (6). However, that case involved no immunotherapy intervention, or apparent improvement in the symptoms, and the patient ultimately passed away from breast cancer progression within half a year.

Our case of eribulin-related neuropathy showed prominent multifocal demyelination, with NCS findings consistent with MADSAM-type CIDP. MADSAM is characterized by multifocal conduction block in the intermediate nerve trunk, the mechanism of which is speculated to be cell-mediated immunity (7), along with a poorer responsiveness to immunoglobulin and plasmapheresis than typical CIDP (8). Our case was distinguished from MADSAM in that the patient was clearly responsive to immunotherapy and kept improving without additional treatment. Although we did not perform a nerve biopsy, resulting in an insufficient pathological evaluation, the prompt response to IVIG in our case suggested that eribulin administration caused secondary immune-mediated neuropathy involving a mechanism different from

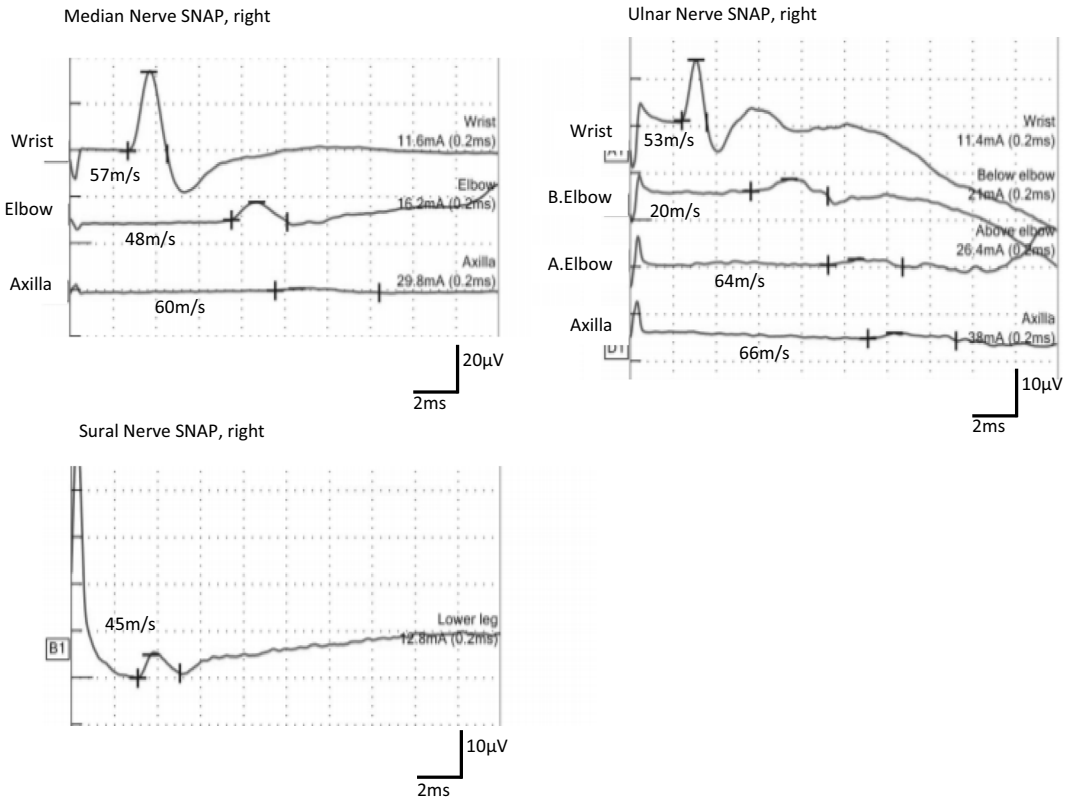

Figure 3. **The sensory nerve conduction study on admission. Right median and ulnar nerves showed temporal dispersion at the same segment of the motor nerves involved. B.Elbow: below elbow, A.Elbow: above elbow, SNAP: sensory nerve action potential**

MADSAM.

The disappearance of myokymia in the lower extremities after the administration of immunotherapy was another characteristic feature of our case. Limb myokymia has been reported in other demyelinating peripheral nerve disorders, such as Guillain-Barre syndrome (9, 10) and CIDP (11, 12). MMN also presents fasciculation and myokymia (13) but differs from our case in that it does not show sensory nerve damage. Gerard and Michel reported that conduction blocks lasting more than three months show fasciculation potentials and sometimes even myokymic discharges (14). A few earlier studies mentioned the relationship between axonal hyperpolarization distal to the site of the conduction block and myokymia (15, 16). Myokymia disappeared in our patient along with the improvement in other clinical symptoms after the initiation of immunotherapy. Although eribulin-related demyelinating neuropathy is rarely reported, and the detailed mechanism is unclear, the fact that myokymia was a characteristic finding in both the previously reported case (6) and our own suggests that demyelination involving conduction block secondary to eribulin administration may present with unknown pathophysiological conditions related to myokymia.

In conclusion, it can be inferred from the present case that eribulin can cause demyelinating neuropathy and requires differentiation from other acquired demyelinating neuropathies. If the neuropathy is severe, not only the discontinuation of eribulin but also intervention with immunotherapy may be effective. Further research concerning the detailed mechanism underlying eribulin-induced neuropathy is warranted.

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

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