Difficult Differential Diagnosis of Paraneoplastic Neuromuscular Diseases Associated with Small Cell lung Cancer: A Report of Two Cases

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Lambert-Eaton myasthenic syndrome (LEMS) is a paraneoplastic neurological syndrome complication of small cell lung cancer (SCLC). The clinical symptoms of LEMS overlap with those of myasthenia gravis (MG), leading to misdiagnosis. Herein, we report two cases of SCLC with LEMS-like disease that were difficult to distinguish from MG because of atypical electromyographic findings without waxing patterns on high-frequency stimulation. Both patients responded poorly to oral pyridostigmine and intravenous immunoglobulin, and were reported to be positive for the anti-P/Q-type voltage-gated calcium channel antibody characteristic of LEMS. Differentiating between LEMS and MG based on clinical symptoms and EMG findings can be difficult.

Key words: Small cell lung cancer, Lambert-Eaton myasthenic syndrome, myasthenia gravis, anti-P/Q-type VGCC antibody

INTRODUCTION

Paraneoplastic neurological syndrome (PNS) is a neurological disorder caused by immune-mediated mechanisms associated with neoplasia. Small-cell lung cancer (SCLC) is associated with a high rate of PNS (9%) [1], the diagnosis and treatment of which are important for cancer management. Lambert-Eaton myasthenic syndrome (LEMS), in which neuromuscular dysfunction is triggered by anti-P/Q-type voltage-gated calcium-channel (VGCC) antibodies, has been reported to be a relatively common PNS in patients with SCLC [2]; however, myasthenia gravis (MG) may also develop in these patients [3, 4].

The diagnosis of LEMS is based on clinical symptoms, electrophysiological findings, and autoantibodies, differentiating it from other related diseases, such as MG and amyotrophic lateral sclerosis (ALS) [5]. The neuromuscular symptoms characteristic of LEMS include proximal muscle weakness, autonomic features, and areflexia; however, these symptoms are not specific to LEMS. In some cases, it can be difficult to distinguish between LEMS and MG [6]. For example, in one study investigating Dutch and British cohorts, 58% of patients were initially misdiagnosed, many with MG [7]. Therefore, electrophysiological findings are considered the most important factors for the diagnosis of LEMS [5]. Herein, we report two cases of PNS associated with SCLC in which LEMS was difficult to differentiate from MG because of atypical electromyographic findings.

CASE PRESENTATIONS

Case #1

A 53-year-old man was referred to our hospital because of walking disturbances due to lower-extremity muscle weakness and general malaise lasting 3 months. He presented with a diurnal variation in muscle weakness, which worsened in the evening. He had lost 7 kg of body weight in the last four months. He also reported dry mouth as signs of autonomic dysfunction.

A neurological examination revealed no ptosis or ophthalmoplegia. However, his Achilles tendon reflexes had decreased. A slight weakness of the bilateral iliopsoas and quadriceps muscles was also observed. The sensory nervous system and its coordinates remained intact. Laboratory tests revealed elevated serum levels of neuron-specific enolase (99.0 ng/mL) and pro-gastrin-releasing peptide (3910 pg/mL); however, creatine kinase levels showed no increase. Chest computed tomography (CT) revealed a tumor in the right pulmonary hilar region (Fig. 1A), but no abnormalities in the thymus. Pathological examination of the sample obtained via transbronchial biopsy revealed small-cell lung cancer. Metastatic lesions were observed in the mediastinal lymph nodes and bone (cT4N3M1c).

Electromyography (EMG) revealed a waning pattern with low-frequency stimulation (Fig. 2A), but no

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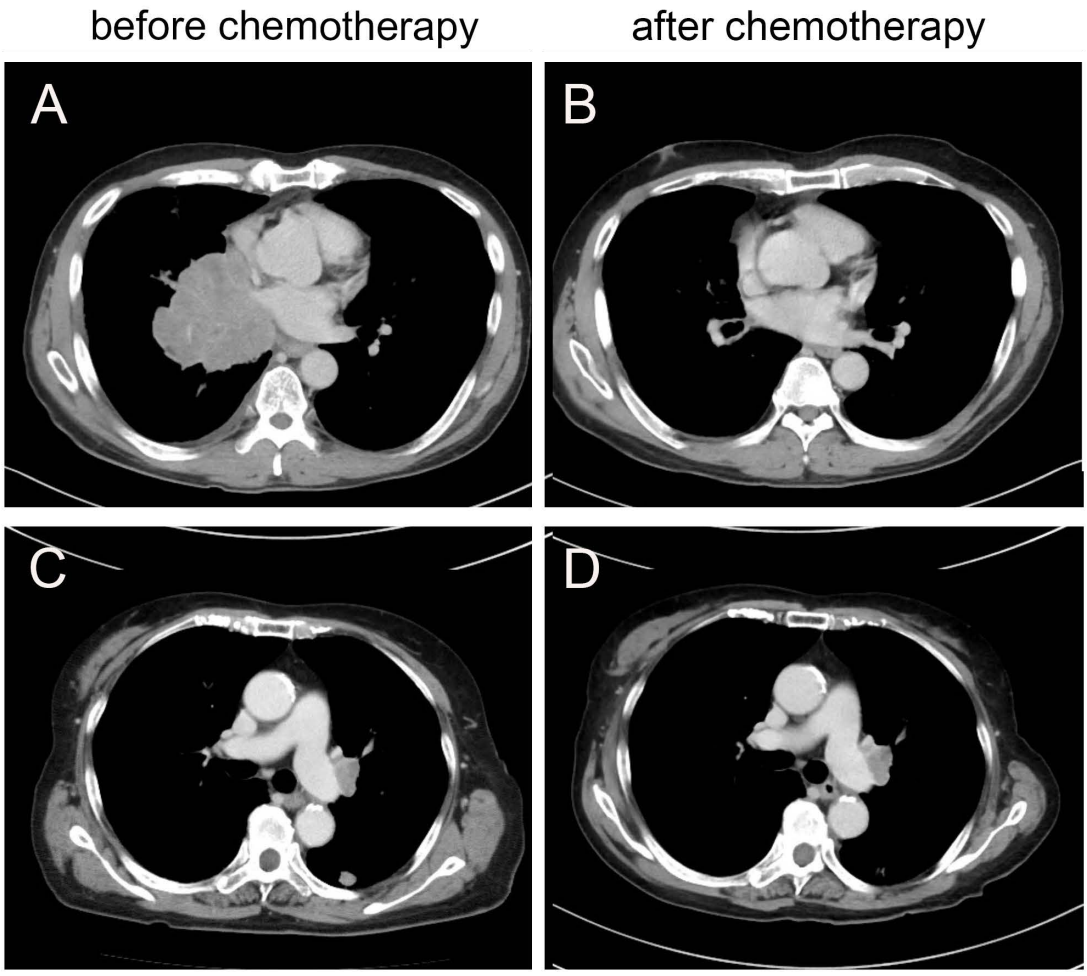

Fig. 1 Chest computed tomography (CT) findings
Chest computed tomography (CT) scan before and after chemotherapy. (A, B) Chest CT scan of a 53-year-old man (case #1) before (A) and 4 months after chemotherapy (B). (C–D) Chest CT scans of an 80-year-old woman (case #2) before (C) and 1 month after chemotherapy (D).

waxing pattern with high-frequency stimulation up to 20 Hz (not recorded). The amplitude of the initial compound muscle action potentials (CMAP) showed no decrease. Anti-acetylcholine receptor (AchR) antibody and anti-muscle-specific tyrosine kinase (MuSK) antibodies tested negative. The tensilon test was not performed because of difficulty in evaluation due to fluctuating myasthenic symptoms.

Based on these findings, seronegative MG was diagnosed, and the patient was treated with oral pyridostigmine and intravenous immunoglobulin (IVIG). Cisplatin plus etoposide was administered as chemotherapy for SCLC, achieving a marked reduction in tumor size. Despite these treatments, there was no improvement in neuromuscular symptoms (Fig. 1B). Later, a positive result for an anti-P/Q-type VGCC antibody was reported. However, the patient did not fully meet the diagnostic criteria for LEMS, and was therefore ultimately considered to have LEMS-like disease.

Case #2

An 80-year-old woman was referred to our hospital because of progressive walking disturbances over the six prior weeks. A neurological examination revealed ptosis and diplopia. She had no symptoms of autonomic dysfunction. The bilateral patellar and Achilles tendon reflexes were absent. Weakness was observed in the right iliopsoas muscle; however, the sensory nervous system and its coordinates remained intact. Laboratory tests revealed elevated levels of pro-GRP (147 pg/mL) in the serum; however, creatine kinase levels were normal. Chest computed tomography (CT) revealed a tumor in the left lower lobe (Fig. 1C), whereas no abnormalities were found in the thymus. A CT-guided biopsy was performed, and a diagnosis of SCLC with metastasis to the supraclavicular fossa lymph nodes (cT1N3M0) was made.

Electromyography (EMG) revealed a decreased amplitude of the initial CMAP, and a waning pattern with low-frequency stimulation (Fig. 2B), but no waxing pattern with high-frequency stimulation up to 30 Hz (Fig. 2C). She tested negative for both anti-AChR and anti-MuSK antibodies. Tensilon test results were also negative. Based on a diagnosis of seronegative MG, the patient was treated with oral pyridostigmine and IVIG therapy. Chemotherapy with carboplatin and etoposide resulted in little radiological improvement (Fig. 1D). There was no improvement in neurological symptoms during the course of treatment. A positive test for anti-VGCC antibody was reported, and the patient was eventually considered to have LEMS-like disease.

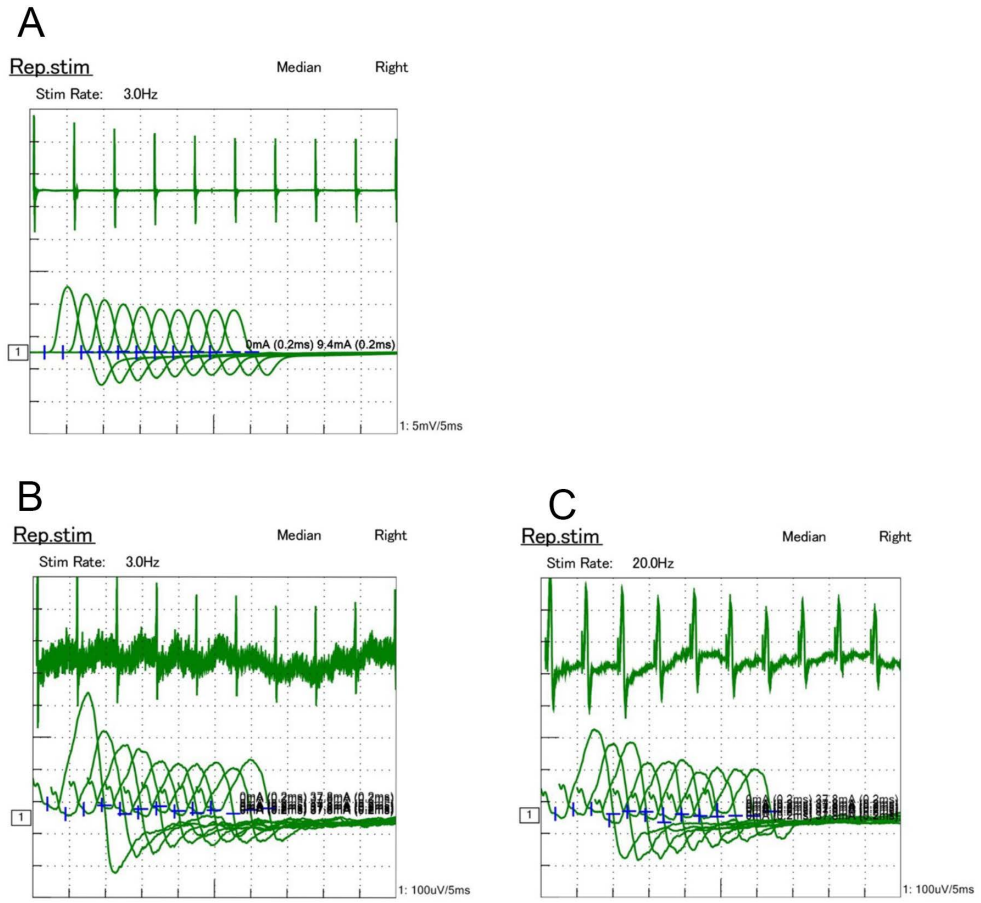

Fig. 2 Electromyogram findings
Repetitive nerve stimulation tests for cases #1 (A) and #2 (B) showing a waning pattern with low-frequency stimulation. No waxing pattern with high-frequency stimulation up to 20–30 Hz was present in either cases #1 (not recorded) or #2 (C).

DISCUSSION

MG and LEMS are both autoimmune diseases of the neuromuscular junction which present with similar neuromuscular symptoms, including muscle weakness and electrophysiological abnormalities. The most important difference between the MG and LEMS is that repetitive muscle contractions cause a decrease in muscle strength in the MG, and an increase in muscle strength in the LEMS. The waxing pattern with high-frequency stimulation is a characteristic finding in 84–97% of LEMS cases, whereas it is rare in MG (0.7%) [8, 9]. Therefore, a significant increment with a marked increase in the CMAP amplitude during high-frequency (10 to 50 Hz) repetitive nerve stimulation tests (waxing pattern) is positioned as the most important component in the diagnostic criteria of LEMS in the 2022 guidelines [5]. However, atypical LEMS cases without a waxing pattern during high-frequency stimulation, such as the two cases presented in this report, are difficult to diagnose. Other electrophysiological findings in LEMS include a decrease in CMAP and a waning pattern at low stimulation rates. Waning patterns during low-frequency stimulation are observed in 81–94% of LEMS and 40–80% of MG cases, and are considered a common electrophysiological finding in both diseases [8, 10]. In the present two cases, a decrease in CMAP was observed in case 2 but not in case 1, whereas a waning pattern during low-frequency stimulation was observed in both cases. Additionally, progressive decrease was observed with low-frequency stimulation in both cases. Because a high-rate stimulation in the repetitive nerve stimulation test is associated with severe pain, post-exercise facilitation (PEF) is recommended as an alternative with high sensitivity and specificity (sensitivity 84–96%, specificity 100%) for the diagnosis of LEMS [11, 12]. However, we were unable to evaluate PEF in these cases because of the limited functionality of the EMG device used in our institute. Although neither patient met the proposed diagnostic criteria of LEMS due to the absence of increment after maximum voluntary contraction, a clinical diagnosis of LEMS-like disease was made based on the lack of clinical findings of ALS and the fact that other criteria, including the production of autoantibodies, were generally met.

The two cases in the present report were positive for the anti-VGCC antibody, which reduces acetylcholine release from presynaptic nerve terminals [13]. P/Q-type VGCCs account for more than 95 percent of the functional receptors at the neuromuscular junction, and are thought to be major immunological targets in LEMS [14, 15]. Anti-P/Q VGCC antibodies are positive in 91.7%–100% of patients with LEMS, but are rarely found in patients with MG or other related diseases [16, 17]. The anti-P/Q VGCC assay is now commercially

available, and is considered an important diagnostic criterion [5]. Patients with neuromuscular diseases accompanied by atypical electromyographic findings in the absence of anti-AChR/MuSK antibodies, as in the current cases and those in previous reports [3, 4, 18], should be examined for anti-VGCC antibodies.

Substantial differences exist between the treatment strategies for LEMS and MG. Early fast-acting treatment strategies comprising corticosteroids and calcineurin inhibitors are effective [19, 20] and are recommended for the treatment of MG [5]. However, the efficacy of anticancer therapies for cancer-associated MG, including SCLC, is limited [21]. In contrast, the neuromuscular symptoms of LEMS associated with SCLC improve with antitumor therapy [22]. If symptoms are not controlled by antitumor therapy, the 2022 Japanese clinical guidelines recommend administering immunotherapy, such as corticosteroids, immunoglobulin, or plasma exchange [5]. Physicians should also be cautious to apply immunosuppressive therapy in patients with neoplasm-related neuromuscular junction diseases as immunosuppression may pose a risk for cancer progression [23] and hamper the efficacy of immune checkpoint inhibitors. As such, it is important to differentiate between LEMS and MG to determine the initial therapy.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest.

REFERENCES

1) Gozzard P, Woodhall M, Chapman C, Nibber A, Waters P, Vincent A, *et al*. Paraneoplastic neurologic disorders in small cell lung carcinoma: A prospective study. Neurology 2015; 85: 235–9.
2) Elrington GM, Murray NM, Spiro SG, Newsom-Davis J. Neurological paraneoplastic syndromes in patients with small cell lung cancer. A prospective survey of 150 patients. J Neurol Neurosurg Psychiatry 1991; 54: 764–7.
3) Fujita J, Yamadori I, Yamaji Y, Yamagishi Y, Takigawa K, Takahara J. Myasthenia gravis associated with small-cell carcinoma of the lung. Chest 1994; 105: 624–5.
4) Miyoshi R, Yamaji Y, Shima S, Fujita J, Okada H, Takahara J. A case of small cell lung cancer that developed during therapy for myasthenia gravis. Nihon Kyobu Shikkan Gakkai Zasshi 1995; 33: 456–62.
5) Murai H, Utsugisawa K, Motomura M, Imai T, Uzawa A, Suzuki S. The Japanese clinical guidelines 2022 for myasthenia gravis and Lambert-Eaton myasthenic syndrome. Clinical and Experimental Neuroimmunology 2023; 14: 19–27.
6) Wirtz PW, Sotodeh M, Nijnuis M, Van Doorn PA, Van Engelen BG, Hintzen RQ, *et al*. Difference in distribution of muscle weakness between myasthenia gravis and the Lambert-Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatry 2002; 73: 766–8.
7) Titulaer MJ, Lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol 2011; 10: 1098–107.
8) Oh SJ, Kurokawa K, Claussen GC, Ryan HF, Jr. Electrophysiological diagnostic criteria of Lambert-Eaton myasthenic syndrome. Muscle Nerve 2005; 32: 515–20.
9) Yoshikawa H, Adachi Y, Nakamura Y, Kuriyama N, Murai H, Nomura Y, *et al*. Nationwide survey of Lambert-Eaton myasthenic syndrome in Japan. BMJ Neurol Open 2022; 4: e000291.
10) Iwanami T, Sonoo M, Hatanaka Y, Hokkoku K, Oishi C, Shimizu T. Decremental responses to repetitive nerve stimulation (RNS) in motor neuron disease. Clin Neurophysiol 2011; 122: 2530–6.
11) Hatanaka Y, Oh SJ. Ten-second exercise is superior to 30-second exercise for post-exercise facilitation in diagnosing Lambert-Eaton myasthenic syndrome. Muscle Nerve 2008; 37: 572–5.
12) Chiou-Tan FY, Gilchrist JM. Repetitive nerve stimulation and single-fiber electromyography in the evaluation of patients with suspected myasthenia gravis or Lambert-Eaton myasthenic syndrome: Review of recent literature. Muscle Nerve 2015; 52: 455–62.
13) Bekircan-Kurt CE, Derle Ciftci E, Kurne AT, Anlar B. Voltage gated calcium channel antibody-related neurological diseases. World J Clin Cases 2015; 3: 293–300.
14) Lang B, Pinto A, Giovannini F, Newsom-Davis J, Vincent A. Pathogenic autoantibodies in the lambert-eaton myasthenic syndrome. Ann N Y Acad Sci 2003; 998: 187–95.
15) Pinto A, Gillard S, Moss F, Whyte K, Brust P, Williams M, *et al*. Human autoantibodies specific for the alpha1A calcium channel subunit reduce both P-type and Q-type calcium currents in cerebellar neurons. Proc Natl Acad Sci U S A 1998; 95: 8328–33.
16) Motomura M, Lang B, Johnston I, Palace J, Vincent A, Newsom-Davis J. Incidence of serum anti-P/O-type and anti-N-type calcium channel autoantibodies in the Lambert-Eaton myasthenic syndrome. J Neurol Sci 1997; 147: 35–42.
17) Lennon VA, Kryzer TJ, Griesmann GE, O'Suilleabhain PE, Windebank AJ, Woppmann A, *et al*. Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. N Engl J Med 1995; 332: 1467–74.
18) Chang A, Wang HC, Hsu WC. Lambert-Eaton myasthenic syndrome in mixed small cell carcinoma and adenocarcinoma of extrapulmonary origin. J Clin Neurosci 2013; 20: 604–6.
19) Utsugisawa K, Nagane Y, Akaishi T, Suzuki Y, Imai T, Tsuda E, *et al*. Early fast-acting treatment strategy against generalized myasthenia gravis. Muscle Nerve 2017; 55: 794–801.
20) Nagane Y, Suzuki S, Suzuki N, Utsugisawa K. Early aggressive treatment strategy against myasthenia gravis. Eur Neurol 2011; 65: 16–22.
21) Niimi K, Nagata E, Murata N, Sato M, Tanaka J, Horio Y, *et al*. Lung cancer associated with seronegative myasthenia gravis. Intern Med 2015; 54: 1381–4.
22) Chalk CH, Murray NM, Newsom-Davis J, O'Neill JH, Spiro SG. Response of the Lambert-Eaton myasthenic syndrome to treatment of associated small-cell lung carcinoma. Neurology 1990; 40: 1552–6.
23) Takahashi M, Horio Y, Takihara T, Enokida K, Miyaoka M, Hirabayashi K, *et al*. Regression of Lung Squamous Cell Carcinoma after the Withdrawal of Cyclosporin A Combined with Pirfenidone Treatment in a Patient with Idiopathic Pulmonary Fibrosis. Intern Med 2021; 60: 617–21.