Clinical presentation and differential diagnosis of Lambert-Eaton myasthenic syndrome

Xiujuan Wu, MM, *Juan Wang,* MM, *Ye Liu,* MD, *Kangding Liu,* MD.

ABSTRACT

أن متلازمة لامبرت إيتون مصاحبة للوهن العضلي كثيراً ما يصاحبها أورام خبيثة خاصة سرطان الرئة ذو الخلايا الصغيرة. نستعرض في هذا التقرير حالة مريضة تعاني من اعتلال النخاع الرقبي منذ 5 أعوام، والتي جاءت تشكو من ضعف متكرر و متزايد في الأطراف. شخصت المريضة بمتلازمة لامبرت إيتون للوهن العضلي وسرطان الرئة ذو الخلايا الصغيرة بعد فحصها عن طريق تخطيط لكهربة العضل وتصوير مقطعي للصدر وإجراء منظار للقصبات الألياقية مع أخذ خزعة بالفرشاة. يسلط هذا التقرير الضوء على الحاجة المستمرة لأن يكون الطبيب متيقظاً في تشخيصه لحالات لامبرت إيتون للوهن العضلي وأن يأخذ بعين الإعتبارشكوى المريض ونتائج الفحص السريري، كما يتوصل بدقة إلى تشخيص تفريقي لحالة لامبرت إيتون للوهن العضلي و حالات الوهن الأخرى.

Lambert-Eaton myasthenic syndrome (LEMS) is frequently associated with malignancy, especially small cell lung cancer (SCLC). Here, we describe a patient with a 5-year history of cervical myelopathy who presented with recurrent limb weakness of her limbs and complained of recent progressive weakness. Following an examination that included electromyography, a chest CT scan, and a bronchofiberscopy examination with brushing biopsy, the patient was diagnosed with LEMS and SCLC. This case report highlights the ongoing need for clinicians to be observant for cases of LEMS, to consider both patient history and physical examination data, and to accurately obtain a differential diagnosis between LEMS and other diseases, which also cause weakness.

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From the Departments of Neurology (Wu, Wang, Liu K) and Pathology (Liu Y), The First Bethune Hospital of Jilin University, Changchun, Jilin Province, China.

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Address correspondence and reprint request to: Dr. Kangding Liu, Department of Neurology, The First Bethune Hospital of Jilin University, Changchun 130021, Jilin Province, China. Tel. +86 13596189310. Fax. +86 043188782378. E-mail: kangdingliu@163.com

Usually, paraneoplastic neurological syndrome is attributable to autoimmune processes directed against so-called onconeural antigens, that is, antigens common to cancerous cells and the nervous system. Lambert-Eaton myasthenic syndrome (LEMS), the most common manifestation of paraneoplastic neurological syndrome, is divided into 2 categories: with carcinoma and without carcinoma. Both categories of LEMS have an autoimmune basis. The most common type of carcinoma associated with LEMS is small cell lung cancer (SCLC). However, due to the absence of early clinical signs, SCLC is difficult to diagnose. Consequently, the high rate of missed and delayed diagnosis contributes to a poor prognosis of patients with SCLC.[1] However, in cases where patients have SCLC in combination with LEMS, a primary diagnosis of LEMS can lead to an opportunity to identify SCLC in its early stages, and thus ultimately lead to a better prognosis than that seen in patients with SCLC alone. However, there is not a specific clinical manifestation of LEMS, or a conclusive test for its diagnosis. The most commonly reported symptom by patients with LEMS is proximal muscle weakness, a non-specific symptom that is associated with many other diseases.[2] The present case report of a patient diagnosed with LEMS underscores the notion that clinicians must remain observant for cases of LEMS, particularly when the symptom of weakness is present. Although weakness is associated with other diseases, we demonstrate here how it can serve as a critical aspect for obtaining a differential diagnosis of LEMS.

Case Report. A 45-year-old Han woman with a 5-year history of cervical myelopathy presented with progressive weakness of her arms and legs in the preceding month and difficulty walking for the preceding 2 weeks. She also had a history of weakness and hypesthesia that had been treated successfully with cervical physical therapy and herbal medicines, which she could not identify by name. She had never been a smoker. During the most recent episode that brought her to our hospital, she was experiencing increasing weakness in both her

arms and her legs, and the weakness was not improving in response to the aforementioned treatments. Prior to surgery for the cervical myelopathy, she was diagnosed with hyponatremia and hypochloremia, which were treated with hypertonic saline (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., Shanghai, and Jilin Kelun Cornell Pharmaceutical Co., Ltd., Jilin, China). However, the fluid restriction did not improve and, as a result, she sought treatment at our hospital.

She reported no family history of disease, and had experienced cervical myelopathy over the past 5 years. Her recent symptoms included blurred vision over several days (which improved without treatment), no loss of weight, dizziness associated with body posture, nausea, vomiting, and neck stiffness. She did not report dyspnea, a persistent cough, or hemoptysis. She also experienced normal urination and defecation, and did not maintain any unhealthy habits.

Physical examination and additional testing. A physical examination conducted to evaluate muscle bulk, strength, tone, coordination movement, and sensation was found to be normal, while hyporeflexia was observed in both knees. An auxiliary examination revealed normal levels of creatase, creatine kinase, adrenocorticotropic hormone, hypophyseal hormones including thyroid stimulating hormone, prolactin, growth hormone, menotropin, luteinizing hormone, and tumor markers including alpha-fetoprotein, carbohydrate antigen 19-9, neuron-specific enolase, carcinoembryonic antigen, carbohydrate antigen 242, carbohydrate antigen 125, prostate-specific antigen, chorionic gonadotrophin, and ferritin. Hydrocortisone levels detected in the blood (at 8 and 16 hours) and urine (at 24 hours) were also normal. Unfortunately, anti-Hu, anti-Yo, and anti-Ri antibody detection tests were not performed, nor the antibodies of voltage-gated calcium channels (VGCCs) were tested. A lumbar puncture was performed, and normal biochemistry, cytology, and immunoglobulin G levels were detected in the CSF. Ion levels in the blood were the only signs of the presence of hyponatremia and hypochloremia, with sodium levels fluctuating from 115-130 mmol, and chloride levels fluctuating from 83-95 mmol. Treatment with hypertonic saline and fluid restriction did not improve these conditions, and a poor response to neostigmine was also noted.

A 1.5-T MRI scan of the brain was normal, while a 3.0-T cervical MRI scan detected several issues (**Figure 1**). For example, C3-7 vertebral bone hyperplasia was detected, as well as disc degeneration at the C3-4 and C6-7 segments, with spinal canal stenosis detected at the corresponding levels. Cervical cord compression was also present at C4-5 and C5-6, with spinal canal stenosis detected at the corresponding levels. Electromyography of the right hand detected a reduced action potential amplitude after repetitive peripheral nerve stimulation at low frequency and increased amplitude at high frequency. These results suggested the presence of LEMS. A chest CT scan was subsequently performed (**Figure 2**), and peripheral lung space-occupying lesions were detected in the lower lobes, which extended to the mediastinum and the lymph node of the left lung. A bronchofiberscopy examination to collect brushing biopsies also revealed the presence of SCLC (**Figure 3**), consistent with the observations of hyponatremia and hypochloremia in the patient. Immunohistochemical examinations of biopsy specimens were needed to

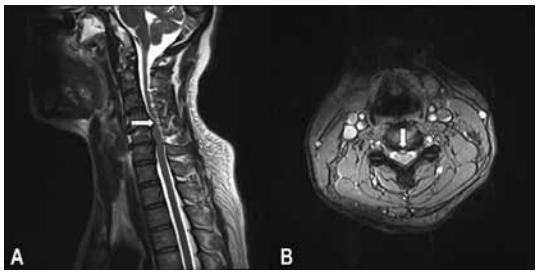

Figure 1 - A 3.0-T cervical MRI scan showed evidence of a C3-7 vertebral bone hyperplasia (arrows), as well as disc degeneration at the C3-4 and C6-7 segments. Cervical cord compression is also observed at C4-5 and C5-6, with spinal canal stenosis at the corresponding levels. **A)** The sagittal view on a T2-weighted image. **B)** The axial view on a T2-weighted image.

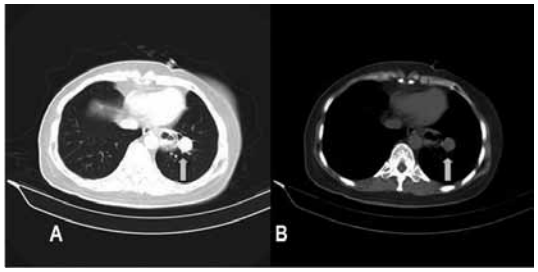

Figure 2 - A chest CT scan showing the presence of space-occupying lesions (arrows) in the lower lobes of the peripheral lung. Note that the lesions extended to the mediastinum and the lymph node of the left lung. **A)** The lung window. **B)** The mediastinal window.

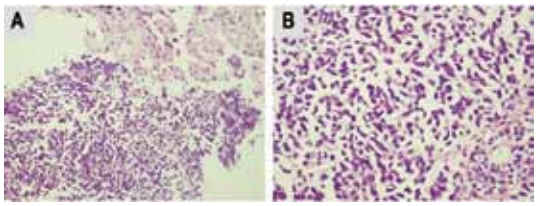

Figure 3 - Brushing biopsies collected during a bronchofiberscopy examination revealed small cell lung cancer. A wide-field (200×) magnification photomicrograph is shown in **A)** and a close-up (400×) photomicrograph of the same specimen is shown in **B)**.

confirm the presence of SCLC. However, the patient discharged herself before immunohistochemical examinations of biopsy specimens could be performed. In a follow-up by telephone one year later, it was confirmed that she was admitted at another hospital where she received chemotherapy and radiotherapy, and that her weakness subsequently was markedly improved.

Discussion. Typically, proximal leg muscle weakness is the first major symptom noted by patients with LEMS. Patients go on to develop difficulties with getting out of a chair, climbing stairs, and walking. Weakness then spreads from proximal to distal muscles, involving the feet and hands, and from caudal to cranial regions, eventually reaching the oculo-bulbar region. Interestingly, the speed of progression is much more pronounced in cases of SCLC-LEMS than cases of LEMS without carcinoma.[3] Patients may also complain of muscle aches, stiffness, numbness, and paresthesias of the distal limbs. However, these symptoms should not contribute to any sensory nerve action potential abnormalities revealed by electrical testing. Furthermore, the autonomic symptoms reported by patients with LEMS most commonly involve dry mouth, followed by dry eyes, constipation, urinary changes, and blurred vision.[1,3] All of the above syndrome features may be caused by antibodies against VGCCs, and the resultant production of VGCC antibodies reduces the amount of acetylcholine released in neuromuscular junctions.[1]

In the present case, the patient's chief complaint was progressive weakness of the limbs, especially the proximal muscles. There were no obvious aggravating factors associated with the onset of this weakness. However, the patient complained of dizziness associated with body posture, nausea, vomiting, and blurred vision, which might represent autonomic symptoms, or may be consistent with the hyponatremia and hypochloremia that had been detected in the patient. Because SCLC has also been shown to cause syndrome of inappropriate anti-diuretic hormone secretion (SIADH),[4-6] additional laboratory evidence was needed to determine whether this patients symptoms could be due to SIADH rather than LEMS.

A diagnosis of LEMS is based on clinical signs and symptoms, electrophysiological studies, and antibody testing. In particular, a combination of proximal muscle weakness, autonomic features, and areflexia are common. However, given that many other diseases present with muscle weakness, LEMS must be differentially diagnosed. Therefore, using the present case report, we demonstrate below how a differential diagnosis of LEMS can be made relative to several other diseases.

Cervical myelopathy. Cervical myelopathy is characterized by spinal cord compression due to physiologic narrowing of the sagittal diameter of the spinal canal, secondary to congenital and degenerative changes in the cervical spine. Cervical cord compressive myelopathy is the most common cause of spinal cord dysfunction in older individuals, especially those with a history of cervical myelopathy. In both cervical myelopathy and LEMS, limb weakness does not fluctuate, although there are additional symptoms associated with cervical myelopathy. These include neck stiffness, paraparesis and quadriparesis, urinary urgency, hesitation, and frequency but rarely incontinence. Patients also demonstrate spasticity with exaggerated reflexes observed below the level of cord compression (which differs from LEMS), motor weakness, sensory loss, and extensor plantar responses. Moreover, a specific symptom associated with cervical myelopathy is Hoffmann's sign. In the present case, the patient reported progressive weakness, which in combination with her past history of cervical myelopathy, suggested that surgical intervention was needed. However, the physical examination subsequently performed was not consistent with a diagnosis of cervical myelopathy. In addition, hyponatremia and hypochloremia exhibited by the patient could not be treated with hypertonic saline and fluid restriction. Therefore, the patient was proposed to have SIADH which is usually caused by a carcinoma, especially SCLC.[5] However, an electromyography examination further confirmed a diagnosis of LEMS, and ultimately a chest CT and bronchofiberscope examination with brushing biopsy revealed SCLC-LEMS. These results were also consistent with the hyponatremia and hypochloremia previously detected.

Myasthenia gravis. Myasthenia gravis (MG) is a relatively rare autoimmune disorder of the peripheral nerves where antibodies target acetylcholine (ACh) nicotinic postsynaptic receptors at myoneural junctions. A reduction in the number of ACh receptors results in a progressive reduction in muscle strength with repeated use of the muscle, while recovery of muscle strength is achieved following a period of rest. This fluctuation in muscle strength is in contrast with the progressive weakness associated with cases of LEMS. Moreover, the distribution of muscle weakness characteristic of MG follows a pattern. For example, initially 85% of patients have involvement of the eyelids and extraocular muscles, resulting in ptosis, or diplopia, or both.[7] Although diplopia and dysphagia are common in MG, they are rarely observed in LEMS.[8] In addition, tendon reflexes are normal in cases of MG, whereas tendon reflexes tend to be absent or reduced in cases of LEMS. A positive response to neostigmine is also helpful in establishing a

diagnosis. However, this symptom is not unique to MG, and patients with LEMS typically exhibit a relatively poor response to neostigmine. Electromyography with repetitive peripheral nerve stimulation (RNS) can be used to probe for LEMS-specific physiological signs; namely, a reduced action potential amplitude following low-frequency RNS and an increased action potential amplitude with high-frequency stimulation. Therefore, given that the patient of the present case report complained of progressive weakness that did not fluctuate, exhibited a poor response to neostigmine, and had an electromyography profile consistent with LEMS, a differential diagnosis of LEMS versus MG was obtained.

Motor neuron disease. It is critical that neurologists make a differential diagnosis of LEMS versus motor neuron disease (MND), a conglomerate of progressive neurological disorders that destroy the cells that control essential muscles. The MND disorders are characterized by progressive weakness, muscle atrophy and fasciculation, spasticity, dysarthria, and respiratory compromise without any sensation deficits. The symptoms may originate in one region, and typically spread to involve other areas. Over the span of several years, most patients come to require help with activities of daily living. Symptoms usually emerge between 50-70 years of age. Patients with emergent LEMS may complain of progressive weakness, muscle loss, and spasticity, or stiffness of the limbs. Neurologic examination reveals specific signs of upper and lower motor neuron degeneration, including Hoffmann's sign in the fingers, the Babinski sign, overactive tendon reflexes, weakness, and fasciculation. These signs can occur in any muscle group, including the arms, legs, torso, and bulbar region.

Chronic inflammatory demyelinating polyradiculoneuropathy and acute inflammatory demyelinating polyradiculoneuropathy. Patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or acute inflammatory demyelinating polyradiculoneuropathy (AIDP) can also present with weakness similar to that observed in patients with LEMS. However, cases of CIDP have been shown to involve a chronically progressive, or relapsing, symmetric sensorimotor disorder with cytoalbuminologic dissociation and interstitial, and perivascular, endoneurial infiltration by lymphocytes and macrophages. In contrast, cases of LEMS usually involve weakness without hypesthesia. The CIDP also frequently starts insidiously and evolves slowly, either in a slowly progressive or relapsing manner, with partial or complete recovery experienced between recurrences. In the present case, while a relapsing course was observed, an examination of CSF did not support a diagnosis of CIDP. On the other hand, AIDP is an autoimmune process that is characterized by progressive weakness and areflexia, relative symmetry, mild sensory involvement, cranial nerve involvement, autonomic dysfunction involvement, and an absence of fever. The AIDP is also believed to be caused by immunologic attacks that are directed against myelin components, with the damage to the myelin sheath leading to segmental demyelination and decreased nerve conduction velocity. Protein and albuminocytologic dissociation in the CSF also strongly supports a diagnosis of AIDP. However, although the patient presented with progressive weakness and hyporeflexia, the normal CSF detected excluded a possible diagnosis of AIDP.

In conclusion, since clinical symptoms of LEMS are usually present before a carcinoma is detected, a diagnosis of LEMS may lead to early detection of SCLC. With SCLC being sensitive to chemotherapy and radiation, patient survival for cases of LEMS-SCLC could thereby be improved. Therefore, the present case report highlights the need to pay particular attention to weakness of limbs as a symptom in combination with a detailed patient history and a physical examination in order to accurately diagnose LEMS, and potentially SCLC as well.

References

1. Simon JI, Herbison GJ, Levy G. Case report: a case review of Lambert-Eaton myasthenic syndrome and low back pain. ***Curr Rev Musculoskelet Med*** 2011; 4: 1-5.
2. Vincent A, Clover L, Buckley C, Grimley Evans J, Rothwell PM; UK Myasthenia Gravis Survey. Evidence of underdiagnosis of myasthenia gravis in older people. ***J Neurol Neurosurg Psychiatry*** 2003; 74: 1105-1108.
3. Titulaer MJ, Lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. ***Lancet Neurol*** 2011; 10: 1098-1107.
4. Sher T, Dy GK, Adjei AA. Small Cell Lung Cancer. ***Mayo Clin Proc*** 2008; 83: 355-367.
5. Kobayashi T, Watanabe T, Ashinuma H, Amano H, Kuroda F, Tada Y, et al. [A case of small-cell lung carcinoma accompanied by the syndrome of inappropriate secretion of antidiuretic hormone and Lambert-Eaton myasthenic syndrome]. ***Nihon Kokyuki Gakkai Zasshi*** 2011; 49: 197-202. Japanese
6. Fernandez-Torron R, Arcocha J, López-Picazo JM, Pardo J, Tamura MA, Carretero C, et al. Isolated dysphagia due to paraneoplastic myasthenic syndrome with anti-P/Q-type voltage-gated calcium-channel and anti-acetylcholine receptor antibodies. ***Neuromuscul Disord*** 2011; 21: 126-128.
7. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. ***Muscle Nerve*** 2008: 37: 141-149.
8. 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: 766-768.