Clinical Case Report

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Coexistence of myasthenia gravis and Lambert–Eaton myasthenic syndrome in a small cell lung cancer patient

A case report

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Abstract

Rationale: Myasthenia gravis (MG) and Lambert–Eaton myasthenic syndrome (LEMS) are both neuromuscular junction diseases, and some controversy exists whether the 2 diseases occur at the same time.

Patient concerns: We report a case that a patient with presentation of acetylcholine receptor (AChR) antibody positive MG and LEMS associated with small cell lung cancer (SCLC).

Diagnoses: The patient firstly suffered from fluctuant symptoms, including slurred speech, double eyelid ptosis, and weakness of limbs. His clinical characteristics were consistent with the diagnosis of MG and were effective with the treatment of pyridostigmine bromide and corticosteroids. After 8 months, the performance of repeated electrical stimulation suggested presynaptic lesion, which supported the patient with LEMS. After further examination, malignant tumors were found in the liver and right lung, and the pathology proved small cell carcinoma.

Interventions: His clinical characteristics were effective with the treatment of pyridostigmine bromide and corticosteroids. Right hilar lesion and multiple metastatic tumors in liver shrunk after chemotherapy.

Outcomes: The patient's condition improved gradually. He was followed up for 17months without tumor progression.

Lessons: The case report illustrates that MG and LEMS may be coexisted in the same patient. In MG and LEMS, clinicians should consider the possibility of malignant tumors as early detection and treatment may significantly improve the patient's prognosis.

Abbreviations: AChRs = acetylcholine receptors, CAMP = compound muscle action potential, EMG = electromyography, LEMS = Lambert–Eaton myasthenic syndrome, MG = myasthenia gravis, MLOS = myasthenia gravis Lambert–Eaton overlap syndrome, MUSK = muscle specific tyrosine kinase, SCLC = small cell lung cancer, VGCC = voltage-gated calcium channel.

Keywords: Lambert–Eaton myasthenic syndrome, myasthenia gravis, myasthenia gravis Lambert–Eaton overlap syndrome, small cell lung cancer

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease that the neuromuscular transmission is disrupted as a result of an attack on postsynaptic antigenic targets, producing weakness of skeletal muscles which the most common ocular external muscle involvement. Lambert–Eaton myasthenic syndrome (LEMS) is also an autoimmune disorder of the neuromuscular junction, but differently from MG, the defect of transmission is presynaptic type. LEMS patients tend to have proximal leg weakness, and pure ocular symptoms are rare. There are also different in autoantibodies between MG and LEMS. Most commonly, MG is a T-cell-dependent disease with antibodies directed against postsynaptic acetylcholine receptors (AChRs). However, P/Q-type voltage-gated calcium channel (VGCC) antibodies are elevated in most patients with LEMS.

Although there has been controversial about the coexistence of MG and LEMS in the same patient, several case reports in the past years described the rare association of LEMS and MG.[1–3] Oh[4]reviewed 55 possible cases of the myasthenia gravis Lambert–Eaton overlap syndrome (MLOS) and discussed the various issues related to MLOS, finally thought that MLOS does exist.

Here, we describe a patient with presentation of AChR antibody positive MG and LEMS associated with small cell lung cancer (SCLC).

2. Case report

A patient, 60-year-old man, was admitted to our hospital because of poor speech, ptosis, and weakness of limbs over 20-days period. The patient had slurred speech, double eyelid ptosis, and

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weakness of limbs with difficulties in walking, holding, and staying balance. His symptoms fluctuated like that in the morning symptoms were mild, while symptoms were severe in the afternoon. He did not have any symptoms of autonomic dysfunction. The patient had a long history of smoking for 40 years and 60 cigarettes a day. His mother died of breast cancer and one of his sisters died of pancreatic cancer.

Neurological examination revealed mild bilateral ptosis without diplopia, mild limbs muscles weakness, paresis of the soft palate with dysphonia, especially with prolonged speech. Tendon reflexes were normal on the upper limbs and symmetrically diminished absent on the lower extremities. The pathologic reflex has not drawn out. There was no obvious abnormality in sensory examination. The rest of his neurological examination was normal.

Prostigmine test was positive. AChR antibody (AChR-Ab) is positive by enzyme linked immunosorbent assay assay, the optical density (OD) value of 1.133 (normal OD <0.566), but antibodies against the muscle specific tyrosine kinase (MUSK) is negative. Electromyography (EMG) showed that bilateral peroneal nerve, tibial nerve, median and ulnar nerve compound muscle action potential (CAMP) decreased, and sensory nerve conduction was not significantly abnormal. Repeated electrical stimulation (RNS) showed CMAP in abductor muscle of left hand decreased by 52.5% on low-frequency (3 Hz) stimulation and by 53.1% on 5 Hz stimulation. CMAP of left trapezius muscle decreased by 40.5% on 3 Hz stimulation, by 42.4% on 5 Hz stimulation. However, CMAP was not increased on high-frequency stimulation (30 Hz).

There was no neoplasm on chest computed tomogaraphy (CT), and thymoma and thymic hyperplasia were also not found. Abdominal ultrasonography revealed a rough wall of the gallbladder. Cerebrospinal fluid examination showed no abnormalities. Routine hematological, chemical, and serological tests including immune markers and tumor markers revealed no abnormalities. The paraneoplastic syndrome index of Amphiphysin, CV2, PNMA2 (Ma2/Ta), Ri, Yo, Hu were negative. The indexes of autoimmune peripheral neuropathy including GM1, GM2, GM3, D1a, D1b, T1b, and Q1b were also negative. Cranial magnetic resonance imaging (MRI) showed multiple lacunar infarction in the right lateral ventricle, anterior horn, basal ganglia, and thalamus and it could not explain the symptoms and signs of the patients. The patient's condition was aggravated after admission, and the diagnosis of myasthenia gravis (MG) was considered after the completion of the examination. His symptoms gradually improved after treatment with pyridostigmine bromide (180 mg/d) and methylprednisolone (40 mg/d), but not completely cured. Then the patient returned home to continue his medication.

Eight months later, the patient discontinued the drugs and was hospitalized again due to exacerbations. His limb weakness aggravated without walking independently, accompanied by worse slurred speech, bilateral ptosis, dysphagia, and inability to cough. EMG examination again showed that the amplitude of CMAPs in bilateral median nerve, bilateral ulnar nerve, bilateral tibial nerve, and bilateral peroneal nerve decreased. RNS test showed CAMP obviously decreased in the right median nerve electrical stimulation (abductor pollicis brevis) and accessory nerve (posterior border of sternocleidomastoid midpoint), 3 Hz decreased by 38% and 40%, respectively, the 5 HZ decreased by 37% and 41%. CAMP of right median nerve and tibial nerve stimulation increased by 105% and 109% on high frequency stimulation (30 Hz). Again, the prostigmine test was positive and the patient was treated with neostigmine and methylprednisolone. Further examination revealed other conditions. Tumor markers increased significantly, including the determination of serum gastrin release peptide precursor (proGRP) (>5000.00 pg/mL), carcinoembryonic antigen (106.90 ng/mL), carbohydrate antigen CA125 (50.78 U/mL), and neuron specific enolase (141.50 ng/mL). The chest CT showed no obvious abnormalities. Abdominal CT scan and enhancement suggested multiple foci of abnormal liver enhancement (Fig. 1C), which was considered metastasis, and multiple enlarged lymph nodes in the retroperitoneum. Biopsy of the liver indicated small cell carcinoma in fibrous connective tissue. Immunohistochemistry showed that CK+, vimentin−, Syn+, CgA+, CD56+, TTF-1+, and proliferation index of Ki-67 was about 70% (Fig. 2F–H). The patient was given etoposide and cisplatin chemotherapy while continuing pyridostigmine bromide and prednisone. The chest CT was examined several times, and a mass was found in the right lung 3 months later (Fig. 1A). Bronchoscopy pathology showed SCLC (Fig. 2A, C–E), which was the same with liver biopsy. The patient was eventually diagnosed with multiple metastasis of SCLC, MG, and LEMS.

At present, the patient was followed up for 17months without tumor progression. Right hilar lesion and multiple metastatic tumors in liver shrunk after chemotherapy (Fig. 1B, D). His condition was stable, and limb weakness was markedly improved though drooping eyelids were still present. The patient continued to receive antineoplastic treatment without new metastasis.

3. Discussion

MG and LEMS are both neuromuscular junction disorders involving the postsynaptic membrane and presynaptic membrane, respectively. The clinical manifestations of the 2 diseases are similar and also have some differences, and there is some controversy about whether the 2 diseases exist at the same time. However, many cases have been reported to support the coexistence or overlap of the 2 diseases.[1–3] The incidence of the 2 diseases is not high. According to the report,[5] the incidence of MG ranges between 9 and 30 out of 1 million and the prevalence ranges from 100 to 140 out of 1 million. However, recent study has shown a prevalence of >200 in 1 million.[6] While LEMS is rare, with an estimated incidence of 0.5 out of 1 million and a prevalence of 2.3 out of 1 million.[5] The cases which coexist of the 2 diseases at the same time is rather rare, mostly in the form of case reports.[1–3,7] MG coexisting LEMS with SCLC is even rarer. Of the 55 MLOS patients Oh et al[4] reviewed, there were only 7 patients with SCLC.

MG is often involved in skeletal muscle, and the extraocular muscles are the most vulnerable. About 50% to 60% of patients present initially with isolated ocular involvement, most of whom will generalize. 15% to 25% of patients have only ocular involvement throughout their course (called ocular MG).[5] The throat muscles, respiratory muscles, and limb muscles can be involved. The main symptoms are muscular pathological fatigue, symptom fluctuation, and the neostigmine test is positive. LEMS is characterized by fatigue and weakness in the limbs and trunk muscles while the cranial nerve is not susceptible to involvement. The proximal limb is heavier than the distal end, and the lower limb is more common. The muscle weakness in the quiescent state is improved by a few seconds of vigorous contraction. Physical examination revealed a decrease or disappearance of tendon reflex and LEMS is insensitive to neostigmine. In addition to

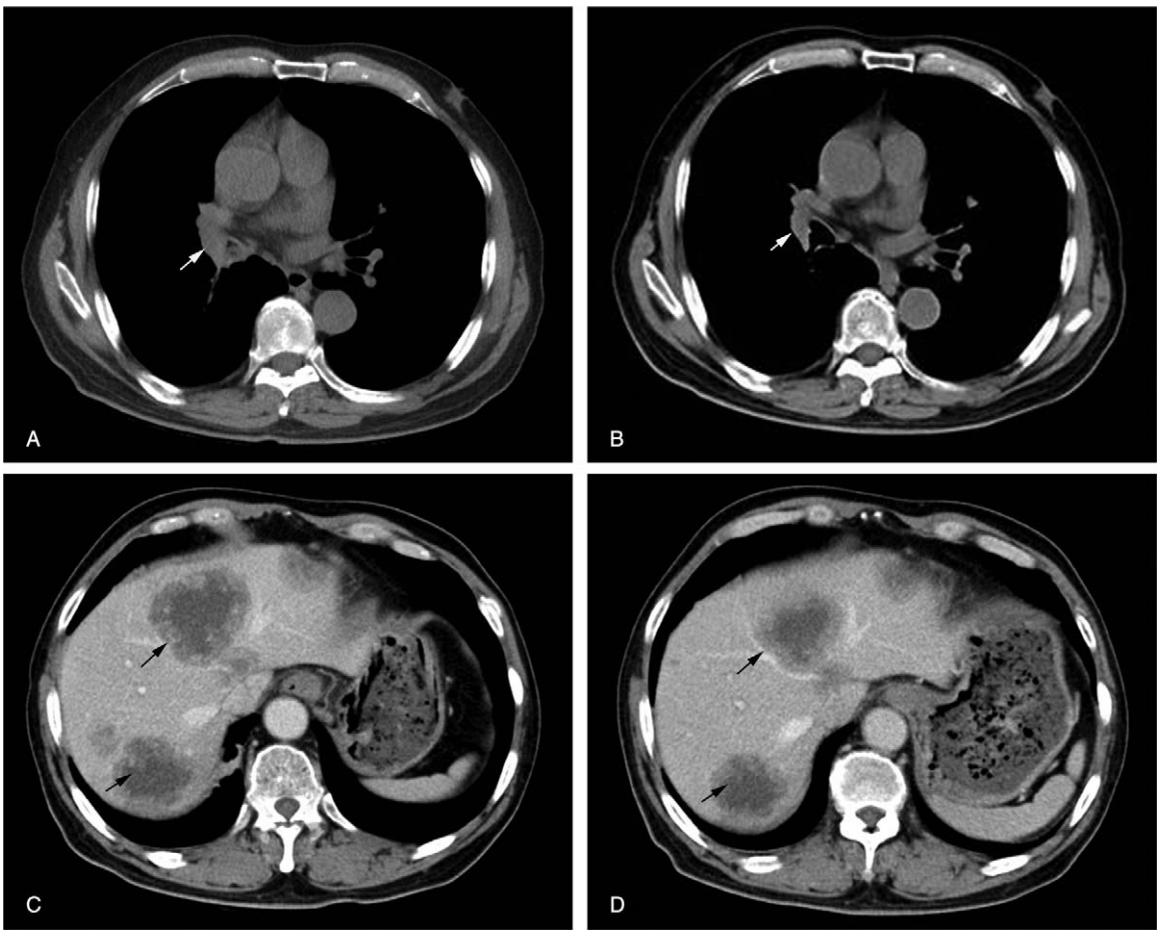

Figure 1. Primary lung lesions and liver metastases on CT scans. (A) Right hilar lesion before chemotherapy. (B) Right hilar lesion shrunk after chemotherapy. (C) Multiple metastatic tumors in liver. (D) Reduction of multiple liver lesions happened after chemotherapy. CT = computed tomography.

clinical manifestations, serological tests and electrophysiological examinations are needed to identify the 2 diseases.

In serological tests, there are many differences between MG and LEMS. Although the sensitivity of antibody testing is low in some situations especially ocular MG, the specificity for the diagnosis of MG is very high (>99% for AChR antibodies).[8] AChR antibodies are present in 50% of patients with ocular MG and 85% of patients with generalized MG.[8] MuSK antibodies are found in approximately 40% (range of 0–70%) of the 15% AChR-negative generalized MG group but are rarely positive in patients with ocular MG.[5] More recently, LRP4 antibodies have been found in a small number of patients who are negative for AChR and MuSK.[9] Autoantibodies to agrin are thought another autoantigen in patients with MG and may be pathogenic through inhibition of agrin/LRP4/MuSK signaling at the neuromuscular junction.[10] However, as known, the antigenic target in LEMS is the P/Q type voltage-gated calcium channel (VGCC) on the presynaptic nerve terminal. Antibodies against P/Q type VGCCs inhibit acetylcholine release from the motor nerve terminals, resulting in skeletal muscle weakness.

In electrophysiologic testing, repetitive nerve stimulation (RNS) and single fiber EMG are important in dignosing MG. The repetitive low rate nerve stimulation (2–5 Hz) showed reduced compound muscle action potential amplitudes (CMAP) (always over 10%) in MG. But, the classical pattern of LEMS includes a low CMAP amplitude at rest, decremental response (10–15%) on low-frequency stimulation, and an incremental response (>100%) on high-frequency stimulation (10–30 Hz) or after brief intense exercise.[3] Single fiber EMG is of little significance in MG and LEMS in both of whom can be found abnormal.[5] According to the review of Oh et al,[4] all MLOS patients met the diagnostic criteria for LEMS in RNS test: a low CMAP amplitude, a decremental response in the low rate stimulation (LRS), an incremental response with brief exercise or at high rate stimulation (HRS) ranged from +85% to +3400%. In our patient, the performance of RNS after 8 months also met the diagnostic criteria for LEMS, which suggested presynaptic lesion.

According to associating with carcinoma, LEMS is divided into paraneoplastic (P-LEMS) and primary autoimmune groups (also called NP-LEMS). In paraneoplastic LEMS, an underlying SCLC is almost always present. However, pathologic thymic involvement, either thymic hyperplasia or a thymoma, is found in the majority of patients with AChR MG. A thymoma is found in 10% to 20% of patients with MG, while MG occurs in 30% to 50% of thymoma cases.[5] MG also is reported as a presenting feature in the patient with lung cancer, which means that MG can be a paraneoplastic syndrome, such as LEMS.[11]

Oh et al[4] gave the diagnostic criteria for MLOS which must required to meet both criteria of MG and LEMS. According to analysis of clinical features he showed that these patients have common MG and LEMS symptoms: oculobulbar paresis and good response to anti-cholinesterase for MG and limb weakness

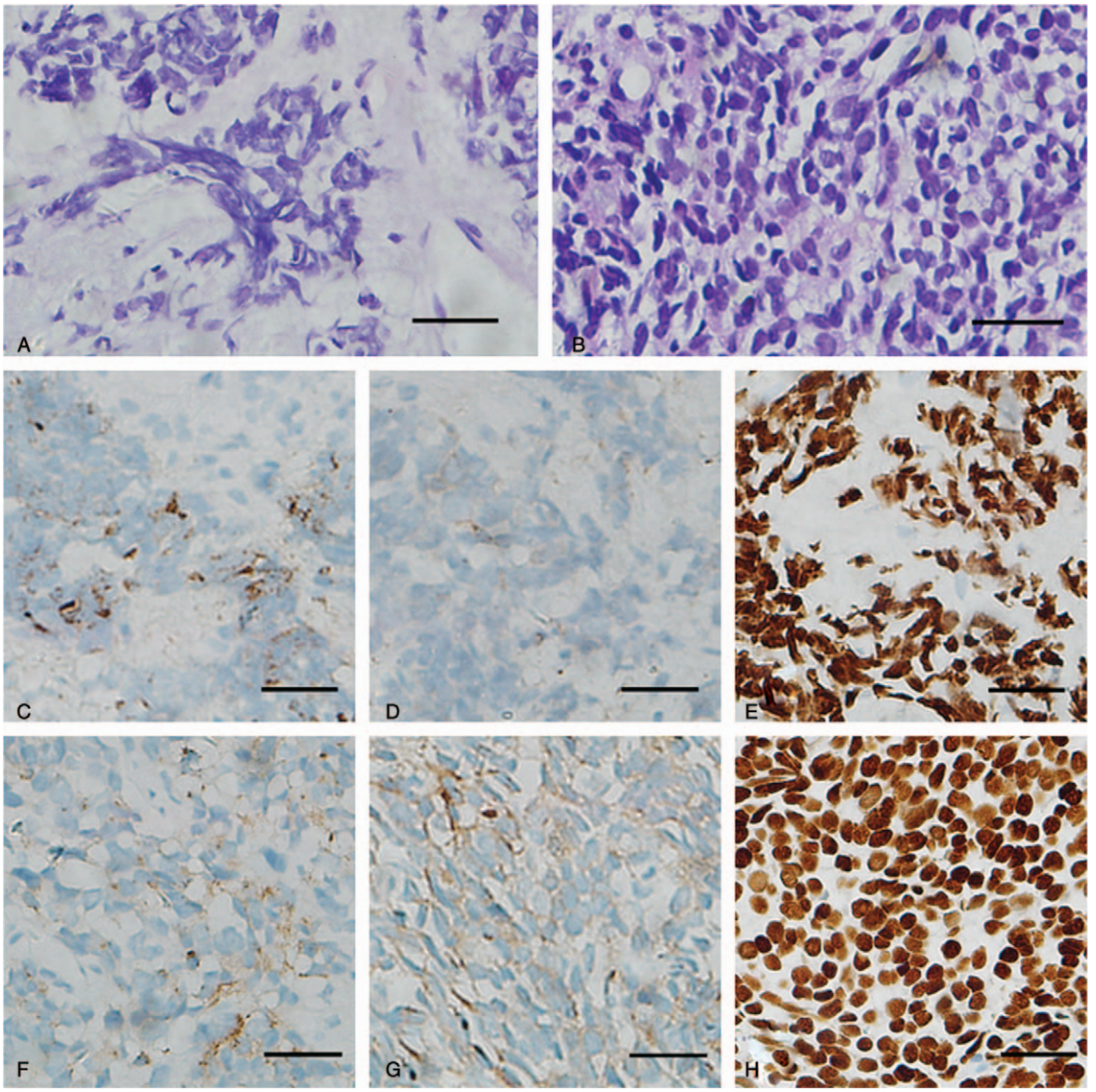

Figure 2. Fiberoptic bronchoscopy biopsy (A, C, D, E) and needle biopsy of liver (B, F, G, H) findings. Immunohistochemistry showed that CgA+ (C, F), Syn+ (D, G), TTF-1+ (E, H). Bars = 100 μm for (A–H).

and decreased or absent reflexes for LEMS with the classical LEMS pattern in the RNS test. In this patient, MG and LEMS coexist simultaneously. Obviously, our patient is in line with the report and also meets the MOLS dignostic criteria.

The exact mechanism underlying the coexistence of MG and LEMS remains unclear. However, since both MG and LEMS are autoimmune diseases, many autoimmune diseases can occur simultaneously due to the imbalance and complexity of the immune network. Domínguez Molinero et al[12] found that epithelial cells in 0.48% of vesical tumors can express neuroendocrine immunohistochemical markers. These tumors may be associated to paraneoplastic syndromes of the endocrine and neurological types, usually the tumor and LEMS more closely, but sometimes occasions to MG. Different studies had found that the tumor cells can express AchR, which induce antibodies against the neuromotor plaque, resulting in MG. Other study[4] thought that it is possible that molecular mimicry between a single viral or bacterial epitope and a small sequence region in AChRs and VGCCs may act as anti-coantigens of AChRs and VGCCs, triggering 2 different autoimmune responses, each at the postsynaptic and presynaptic neuromuscular junction, producing MG and LEMS in the same patient. The coexistence mechanism of the 2 diseases needs further study.

In conclusion, LEMS is generally considered to be a paraneoplastic syndrome type, while MG and MG coexisting LEMS can also may be a paraneoplastic syndrome. Therefore, when found emergence of MG, LEMS, or the 2 diseases coexisting, clinicians should consider the possibility of malignant tumor. Early detection and treatment of malignant tumor through diagnosing a paraneoplastic syndrome may significantly improve patient prognosis.

Author contributions

Methodology: Zhonghua Zhao, Rui Jia, Jinbo Chen, Qi Zheng.

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