Clinical Case Report

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Ophthalmoplegia associated with lung adenocarcinoma in a patient with the Lambert–Eaton myasthenic syndrome

A case report

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Abstract

Rationale: The Lambert–Eaton myasthenic syndrome (LEMS) is a neuromuscular disease; its unique symptoms of LEMS include dry mouth with a metallic taste, constipation, and erectile dysfunction. As it is quite rare, isolated ocular muscle impairment associated with LEMS east to ignore.

Patient concerns: A 65-year-old man presented with alternating ptosis and diplopia. Isolated ocular muscle impairment had lasted for 6 years, and the patient was initially diagnosed with ocular myasthenia gravis (MG). Treatment with azathioprine only slightly improved symptoms over the first 2 months; long-term treatment was not effective.

Diagnoses: Dynamic observation of chest computed tomography images revealed a slowly progressing nodule in the lower lobe of the left lung. The subsequent pathologic examination following mass resection confirmed a diagnosis of lung adenocarcinoma.

Interventions: The patient was ultimately diagnosed with the Lambert–Eaton myasthenic syndrome associated with pulmonary adenocarcinoma.

Outcomes: Resection of the lung tumor relieved all symptoms.

Lessons: Other causes of ocular MG symptoms should be considered when standard MG therapy is ineffective, especially the Lambert–Eaton myasthenic syndrome.

Abbreviations: AChR = acetylcholine receptor, CMAP = compound muscle action potential, CT = computed tomography, LEMS = Lambert–Eaton myasthenic syndrome, MCC = Merkel cell carcinoma, MG = myasthenia gravis, RNS = repetitive nerve stimulation, SCLC = small cell lung cancer, VGCC = voltage-gated calcium channels.

Keywords: diplopia, Lambert–Eaton myasthenic syndrome, lung adenocarcinoma, ptosis

1. Introduction

The Lambert–Eaton myasthenic syndrome (LEMS) is a neuromuscular disease caused by pathogenic autoantibodies directed against voltage-gated calcium channels (VGCCs) in presynaptic nerve terminals. Unique symptoms of LEMS include dry mouth with a metallic taste, constipation, and erectile dysfunction. Isolated ocular muscle impairment associated with LEMS is quite rare but has been reported.[1,2] Neuroendocrine tumors including small cell lung cancer (SCLC) and Merkel cell carcinoma (MCC) are the most common solid tumors associated with LEMS; however, lung adenocarcinomas are rarely seen with the condition.

Here, we describe a patient initially diagnosed with ocular myasthenia gravis (MG) living with this condition for several years. Following the failure of azathioprine and other standard therapies, a regular chest computed tomography (CT) scan was performed, which revealed a slowly progressing pulmonary nodule. Our findings may thus help consider other conditions that mimic ocular MG.

2. Case report

Reporting of this case was approved by local ethics review committees at Mianyang Central Hospital, and the patient provided written informed consent to have his case published.

2.1. Patient presentation

A 65-year-old male engineer presented at our outpatient clinic in October 2007 with a chief complaint of diplopia and ptosis in his left eye that had lasted for 1 week. The patient described a subacute onset and symptoms that did not affect his activities of daily living. The patient also had isolated postprandial hyperglycemia; however, he was not taking hypoglycemic agents. The patient denied experiencing limb weakness, limb fatigue, and weight loss; had never smoked; and rarely drank alcohol. He also

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denied any family history of neurologic disease, ocular disease, or other significant medical illnesses.

2.2. Clinical examinations and findings

Neurological examination revealed ptosis in the left eye and moderate ophthalmoparesis in both eyes. Strength was normal in all extremities; however, tendon reflexes were absent in the lower limbs. Sensation and autonomic function were both normal. The patient described his diplopia and ptosis as mild and volatile, respectively, and there were no notable increases after physical activity. Prostigmin testing results varied over time and were slightly positive or suspicious. Creatine kinase and thyroid function tests were within normal limits. Venereal disease research laboratory-rapid plasma reagin and treponema pallidum hemagglutination tests were negative. Serum testing for human immunodeficiency virus; hepatitis viruses; and antinuclear, acetylcholine receptor (AChR), and antineutrophil cytoplasmic antibodies was negative. Lumbar puncture did not reveal albuminocytologic dissociation.

Repetitive nerve stimulation (RNS) of facial nerves revealed a 50.2% decrement of the muscle electrical response (compound muscle action potential [CMAP]) to a 3-Hz stimulation. RNS testing was not performed beyond 10 Hz because it caused the patient extreme discomfort. A chest CT scan showed pulmonary nodules located in the lower lobe of the left lung; however, the patient refused to undergo a biopsy. Brain magnetic resonance imaging was normal.

Three different neurology departments at separate hospitals (Mianyang Central Hospital, West China Hospital, and Huashan Hospital) made an initial diagnosis of MG; however, a negative result for the AChR antibody casted doubt on this diagnosis. Nevertheless, the patient underwent pyridostigmine bromide therapy (180 mg/d) combined with prednisone (60 mg/d) for 1 month. Unfortunately, this MG treatment did not have a significant effect on the patient's symptoms. Since the steroid aggravated the patient's hyperglycemia, prednisone was discontinued and replaced with azathioprine, which led to an improvement in symptoms for 2 months. During this time, diplopia only minimally influenced the patient's daily activities, and the left eye ptosis had markedly improved.

The patient returned to our clinic in February 2008. His diplopia had again worsened, ptosis now affected both eyes, and extraocular muscle symptoms were more serious. Varying degrees of horizontal and vertical gaze paralysis had presented almost simultaneously, and the patient complained of continually alternating between aggravated diplopia volatility and blepharoptosis.

Over the next 2 years, the patient discontinued azathioprine because of continuous leukopenia and prednisone because of the negative impact on his diabetes. Subsequent treatment only involved mecobalamine (1.5 mg/d) and strict dietary blood sugar control. Unfortunately, ocular symptoms persisted, including alternating upper eyelid droop and continuous diplopia. All symptoms presented with dramatic variation and lacked the typical MG diurnal rhythms. The patient was unable to go outside independently when symptoms were most severe. Interestingly, ptosis slightly and transiently improved when the patient sustained an upward gaze.

Annual prostigmin testing was negative between 2008 and 2013. Repeat RNS of facial nerves revealed decrements within the range of 30.6% to 47.1% between 2008 and 2010. From 2007 to 2012, regular chest x-ray and CT scans were used to track a slowly progressing pulmonary nodule located in the lower lobe of the left lung. Despite the presence of an enlarging mass, the patient refused to undergo a lung biopsy. In November 2013, additional symptoms including fatigue and abnormal weight loss began to emerge. A chest CT scan showed a soft tissue mass in the lower left lung. RNS of the right ulnar nerves revealed a 109% increase in CMAP in response to a 20-Hz stimulus (Fig. 1). The patient agreed to undergo pulmonary tumor resection in January 2014, and pathological testing confirmed a moderately differentiated adenocarcinoma (Fig. 2). Molecular pathological testing showed that the patient had the wild-type epidermal growth factor receptor, was negative for anaplastic lymphoma kinase with the echinoderm microtubule-associated protein-like 4 expression, and had a serum neuron-specific enolase level of 10.2 ng/mL. Three days after tumor resection, all ophthalmic symptoms had resolved, including ptosis and moderate diplopia. All medications were discontinued following surgery. The patient was closely monitored over the next 23 months, but his symptoms did not recur (Fig. 3). Periodic CT scans have remained negative to date (Fig. 4).

3. Discussion

Moderate diplopia, ptosis, and, eventually, fatigue are characteristic symptoms of LEMS. We initially diagnosed the patient with ocular MG because of paresis of the nonproximal

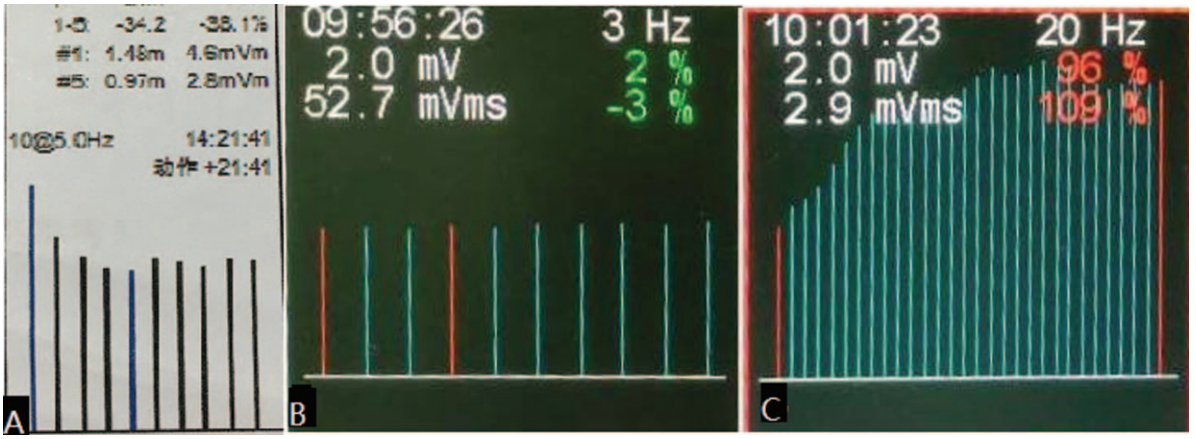

Figure 1. Histopathology of the left lung pathologically verified the diagnosis of adenocarcinoma. (A) × 200. (B) × 400.

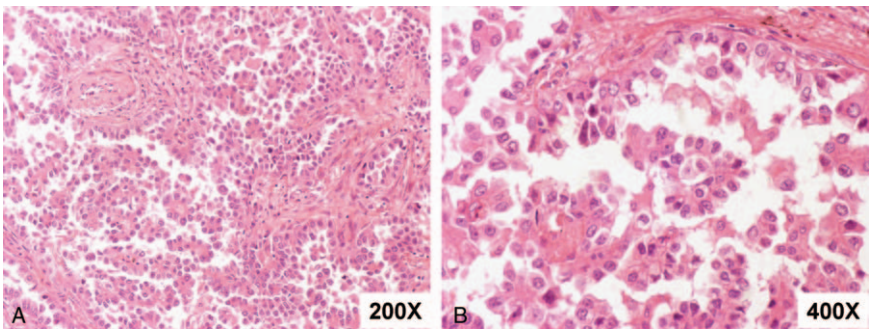

Figure 2. (A) In 2010, repeated nerve stimulation (RNS) of the left facial nerves showed a 38.1% compound muscle action potential (CMAP) decrease in response to a 5-Hz stimulation. (B) In 2013, RNS of the right ulnar nerves revealed no decrease in response to 3-Hz stimulation. (C) In 2013, a 109% increase in CMAP in response to 20-Hz stimulation. CMAP = compound muscle action potential, RNS = repeated nerve stimulation.

musculature (except for ocular muscle impairment) during the first 6 years of treatment. Furthermore, an MG diagnosis was made on the basis of a partial response to cholinesterase inhibitors/azathioprine combination therapy and a facial nerve CMAP deficit to lower frequency RNS stimuli. Additionally, the absence of incremental response at higher frequency RNS and VGCC antibody testing results delayed the LEMS diagnosis. Lung cancer was suspected because of the slow-growing pulmonary nodule; however, the patient refused to undergo a biopsy. Increment RNS testing up to 20 Hz in the ulnar nerves revealed a CMAP indicative of LEMS. Remarkably, lung tumor resection led to resolution of all nervous system symptoms, further confirming that LEMS associated with lung cancer was the correct diagnosis. The patient was monitored for 23 months following tumor resection, but neither the tumor nor nervous system symptoms recurred (Table 1).

Clinical recognition and early diagnosis of LEMS are important because of its close association with underlying malignant tumors. This condition may be detected in its very early stages because of a unique combination of symptoms, which includes dry mouth with a metallic taste, constipation, and erectile dysfunction.[1–3] Our case was unusual because LEMS is rarely associated with focal ocular muscle symptoms[3,4]; however, bilateral ophthalmoparesis and alternate blepharoptosis are common features of MG. In addition, AChR antibodies are most commonly associated with MG and are occasionally found in low amounts in patients with LEMS. In this case, testing results did not support an MG diagnosis.

Neuroendocrine tumors, including SCLC and MCC, are the most common solid tumors associated with paraneoplastic neuropathies. However, LEMS rarely occurs with non-SCLC. Our patient with non-SCLC differed from previously reported cases[5] because this patient experienced isolated ocular muscle impairment over a 6-year period, not knowing that this symptom was accompanied by a progressive lung adenocarcinoma. Perhaps because the lung tumor progressed quite slowly over the 6 years, MG symptoms were isolated to the ocular muscles.

The LEMS diagnosis was ultimately based on characteristic clinical findings, electrophysiological studies, and antibody testing. The most important clinical feature of LEMS is a significant reduction in the CMAP amplitude of motor nerves[6,7] that is caused by the lack of ACh release at the nerve junction. The easiest and most reliable way to assess this transmission defect is to give a brief isometric voluntary muscle contraction and

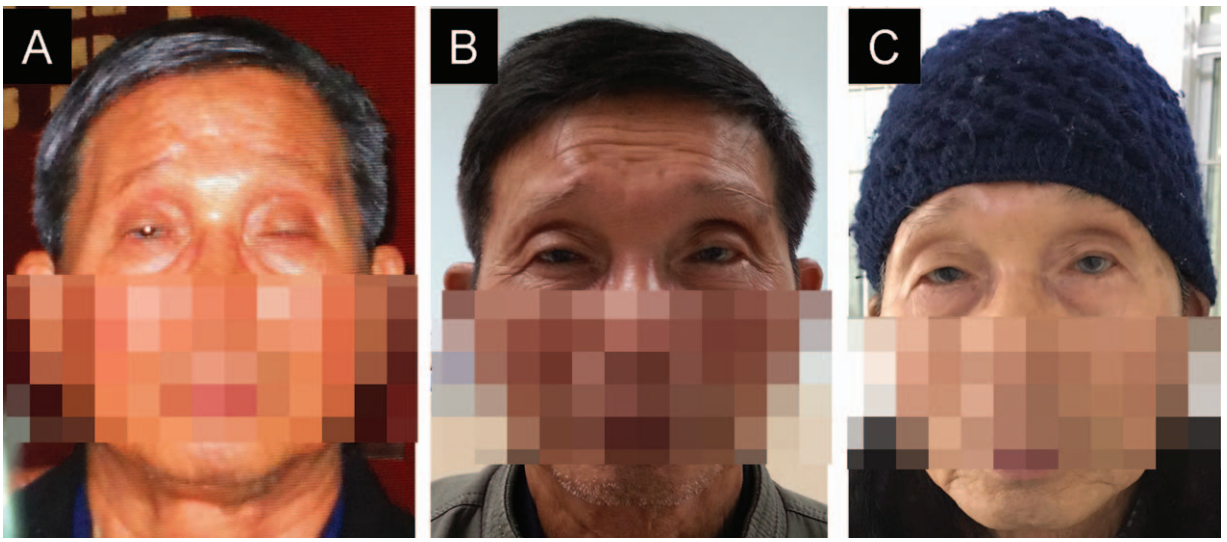

Figure 3. (A) Asymmetric bilateral ptosis was present before resection (October, 2012), (B) 1 month after lung adenocarcinoma resection (February 2014), and (C) 2 years after lung adenocarcinoma resection (January 2016).

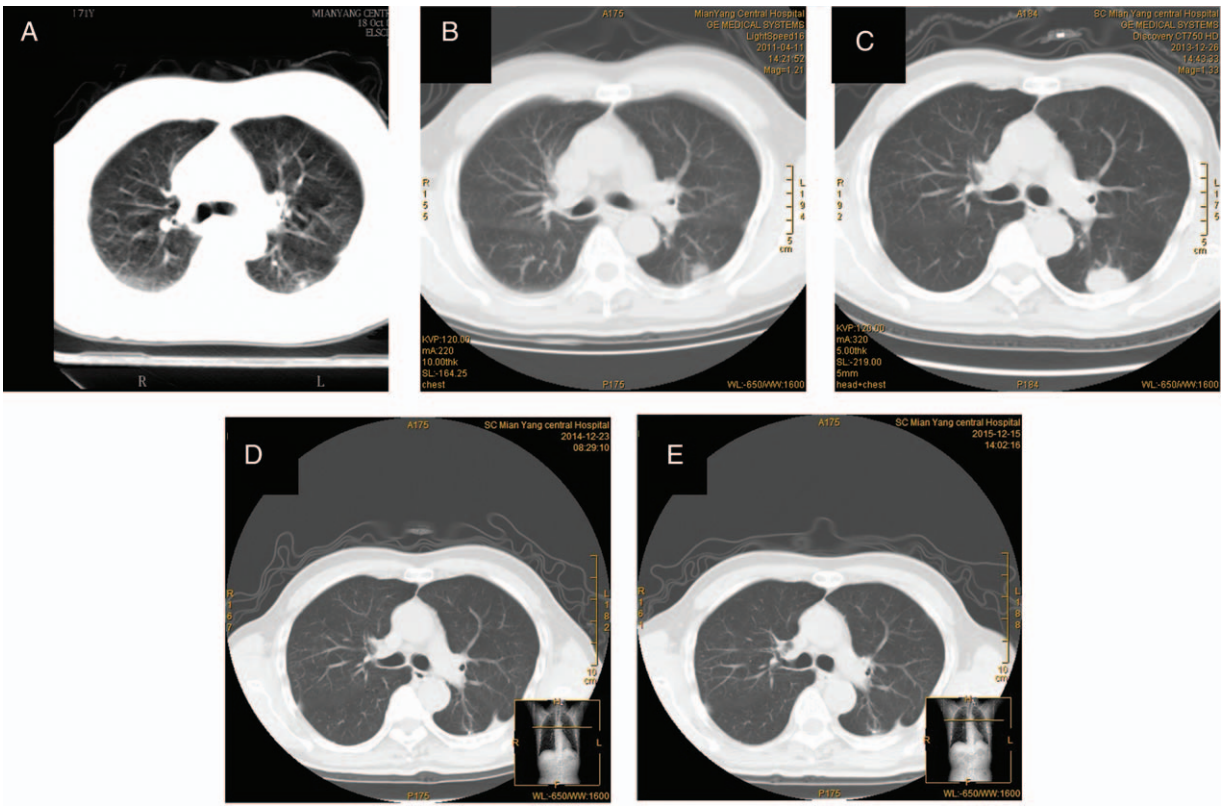

Figure 4. Chest computed tomography scan findings from (A) October 2007, (B) April 2011, (C) December 2013 (preoperative scan), (D) December 2014 (23 months after tumor resection), and (E) December 2015.

measure the CMAP amplitude before and after exercise. Amplitude increases greater than 60% in several muscles confirm the LEMS diagnosis. Some also consider an improvement in ptosis following a sustained upward gaze, as observed in the current case, to be indicative of LEMS.[8]

Unfortunately, exercise is difficult to perform and measure for most patients with LEMS. However, higher frequency RNS would show an incremental response, promoting presynaptic ACh release at the nerve junction.[3,4,7] In patients with LEMS, high frequency RNS increases the amplitude of successive CMAPs (post-activation facilitation) because of accumulated calcium in the nerve terminal, which enhances ACh release.[7] Elevated VGCC antibody levels are indicative of LEMS, particularly the paraneoplastic variant, in which almost all patients are antibody positive. More than 90% of all LEMS patients have antibodies directed against P/Q-type VGCCs.[9] However, in 15% of cases, including those associated with MCC (histologically and antigenically related to SCLC),[10] P/Q-type VGCC antibodies are not detectable.[3] Anti-Hu (antineuronal nuclear antibody, type 1) is a useful biomarker of neurological paraneoplastic syndrome (paraneoplastic neurological syndrome, PNS). This test has an especially high specificity and sensitivity for diagnosing SCLC with PNS.[11] Unfortunately, efficient laboratory testing for VGCC and Hu antibodies was not available in most Chinese medical institutions until 2 years ago. Therefore, preoperative antibody testing was not performed in this patient. However, 6 months after tumor resection, the anti-Hu antibody was not found in his serum or cerebrospinal fluid. Therefore, the LEMS diagnosis was made based on lung adenocarcinoma presentation and surgical findings. Subsequent patient follow-up (23 months) revealed that all symptoms had resolved and that the tumor did not recur, confirming our

Table 1

Test results and therapies before and after tumor dissection.

Year	Symptoms	CSF	RNS	Neostigmine test	AchR	Curation
October 2007–February 2008	Diplopia unilateral ptosis	Normal	–50.2% (3 Hz)	Suspicious	Negative	Pyridostigmine& Bromide/Azathioprine
February 2008–October 2013	Diplopia bilateral ptosis	Normal	–30.6–47.1% (3 Hz, 5 Hz, 7 Hz)	Negative	Negative	Azathioprine/Mecobalamine
November 2013–December 2013	Diplopia bilateral ptosis fatigue		+109% (20 Hz)	Negative	Negative	Mecobalamine
January 2014			Tumor dissection			
February 2014–December 2015	None	Normal	Normal (3 Hz, 20 Hz)	–	–	None

AChR = acetylcholine receptor, CSF = cerebrospinal fluid, RNS = repeated nerve stimulation.

diagnosis. We should therefore consider other conditions that mimic ocular MG such as LEMS when standard treatment is ineffective.

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