

CASE REPORT

Successful treatment of advanced lung adenocarcinoma complicated with Lambert-Eaton myasthenic syndrome: A case report and literature review

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Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune neuromuscular junction disorder. Antibodies against presynaptic voltage-gated calcium channels are produced in patients with LEMS, decreasing the calcium that can enter the nerve ending, hence the neuromuscular junction releases less acetylcholine.¹ Around 50% to 60% of patients with LEMS have an underlying malignancy, regarded as a special type of paraneoplastic syndrome, known as tumor associated LEMS (T-LEMS). Small-cell lung cancer (SCLC) is the most common in T-LEMS. Patients without cancer after a lengthy period are regarded as nontumor-related LEMS (NT-LEMS). The mechanism which causes the cancers and lack of cancers is not clear.² Few cases of lung adenocarcinoma complicated with LEMS

Abstract

Lambert-Eaton myasthenic syndrome (LEMS) is a rare disease characterized by involvement of the neuromuscular junction. Most cases have an underlying malignancy, especially small-cell lung cancer (SCLC), while adenocarcinoma is less common. Here, we report a rare case of metastatic lung adenocarcinoma complicated with LEMS. In this case, L858R mutation was detected in the 21st exon of the *EGFR* gene. First-line treatment with gefitinib was given, and the patient has survived for more than six years. Early diagnosis of LEMS and timely and effective treatment can result in a good prognosis. We also searched for “lung cancer”, or “carcinoma of lung”, or “adenocarcinoma of lung”, or “Lambert-Eaton myasthenic syndrome” in PubMed until 1 December 2019. Seven cases of lung adenocarcinoma complicated with LEMS were found, most of which had a poor prognosis.

Key points: This article reports a rare case of metastatic lung adenocarcinoma with *EGFR* mutation, complicated with LEMS. Gefitinib was given as first-line treatment, and resulted in a good prognosis.

have been reported. This article describes such a case who has remained in a stable condition and survived for more than six years.

Case report

A 63-year-old smoking male was admitted to Beijing Chao-Yang Hospital, Capital Medical University, on 12 November 2013 with a history of his left eyelid drooping without obvious cause for 10 days (Fig 1). The symptoms were more serious in the evening than morning, and complicated by blurred vision and diplopia. Past medical history included hypertension, diabetes mellitus, left facial neuritis, and pacemaker implantation.

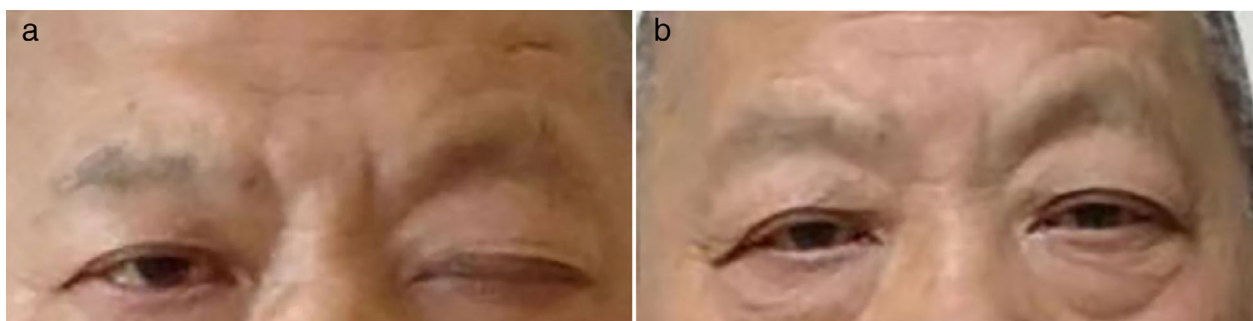


Figure 1 (a) Drooping of the left upper eyelid (December 2013). (b) The left upper eyelid was back to normal (6 January 2014).

Physical examination showed a symmetrical frontal stripe, he was unable to frown and his left eyelid drooped. Blood test results showed normal erythrocyte sedimentation rate, tuberculin test, C reactive protein, anti-dsDNA antibody, anti-guaninine peptide antibody, and antineutrophil cytoplasmic antibodies. Tuberculosis IgG/IgM antibody detected by colloidal gold method was positive, and antinuclear antibodies revealed S1:100. A chest CT scan was subsequently performed which revealed a left lower lobe nodule with non-uniform density and pleural retraction (Fig 2). A needle biopsy verified that it was adenocarcinoma. Gene detection of *EGFR* showed L858R mutation. Bone scan revealed multiple bone involvements.

Test for paraneoplastic syndrome antibodies of anti-Hu, anti-Ri, anti-Yo were negative. Neostigmine test, anti-acetylcholinesterase antibody, and muscle-specific tyrosine

kinase antibody were also negative. Electromyography examination was not conducted because of the patient's pacemaker.

The final diagnosis concluded that the patient had stage IV (T4, N3, M1b) left lower lobe lung adenocarcinoma, with left hilar lymph node, right mediastinal lymph node, right lung and multiple bone metastasis. The left eyelid drooping was an indication of LEMS as a result of adenocarcinoma.

The patient was subsequently treated with gefitinib which commenced on 7 December 2013. One month following his treatment, his left eyelid drooping symptom began to resolve (Fig 1). Chest scan on 6 January 2014 displayed a reduction in size of the left lung nodules (Fig 3). Follow-up CT examination was conducted every two to three months. Bone scan, abdominal ultrasound, and head

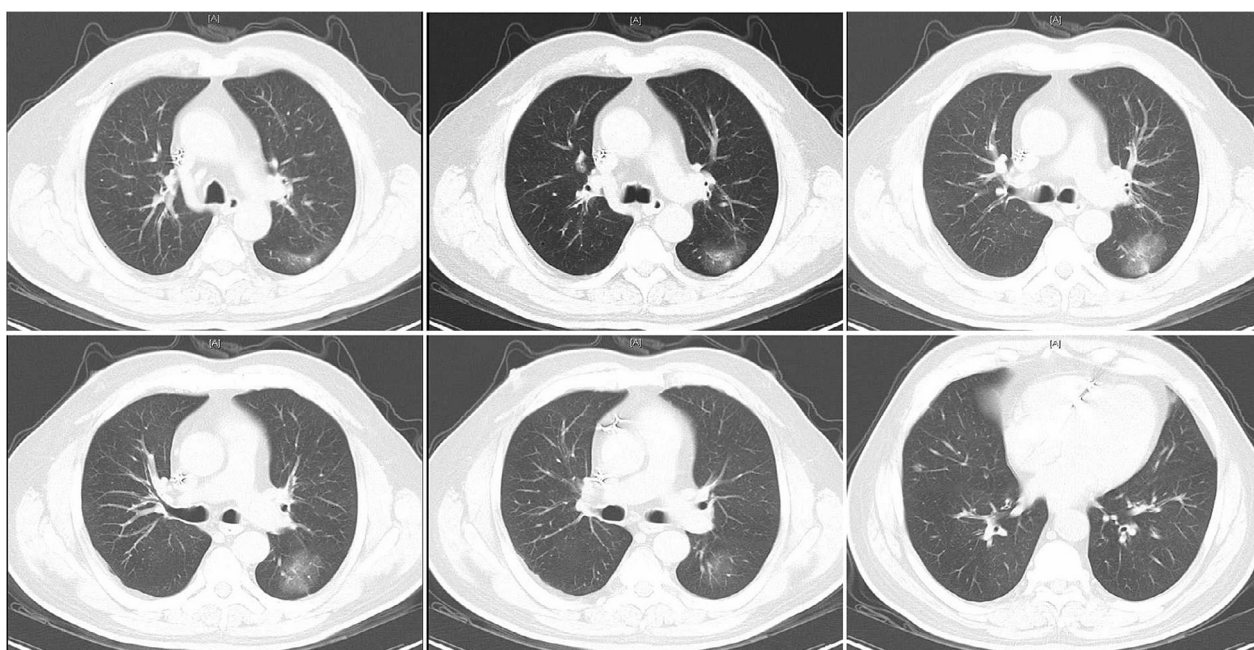


Figure 2 Blur nodules in the dorsal segment of the lower lobe of the left lung (19 Nov 2013).

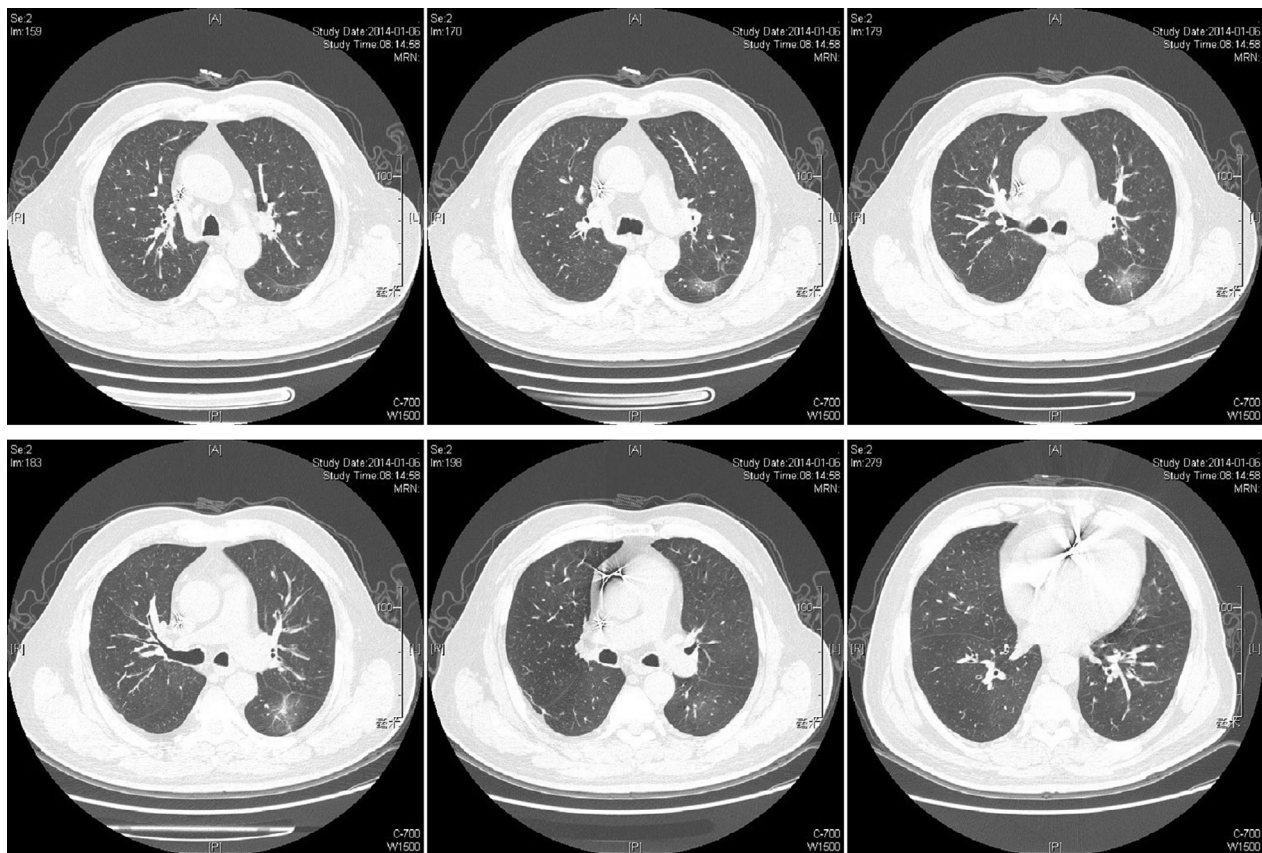


Figure 3 A chest scan was taken one month after gefitinib treatment, which indicated a reduction in size of the blur nodules.

MRI were examined every six months. The patient has remained in a stable condition with neither recurrence of metastasis nor left eyelid droop for more than six years.

We found seven similar cases of lung adenocarcinoma with LEMS (Table 1)³⁻⁹. All cases were diagnosed at an advanced stage, and only two of them were alive at the time of publication of the articles.

Discussion

The main clinical manifestations of LEMS are symmetrical limb proximal muscle weakness, decreased or absent tendon reflex, and autonomic nervous dysfunctions. Muscle weakness often starts in the lower limbs, with more serious symptoms in the morning than the evening. Activities have been reported to reduce the symptoms.

The patient's first symptom was ophthalmoplegia, which is rare in LEMS, and no electromyogram was performed due to the patient having a pacemaker. It is hard to identify with myasthenia gravis. As a result, this case was discussed by specialists in multiple disciplines, including neurology, electromyography, oncology, respiratory and cardiology. It was agreed that myasthenia gravis is a

recurrent and progressively worsening disease, but after antitumor treatment, the patient has no recurrent ophthalmoplegia for more than six years, so a diagnosis of T-LEMS was considered. Only 5% of patients with LEMS are diagnosed with cancer, and about 86% of the patients have LEMS symptoms before their tumor appears,¹⁰ thus a diagnosis of NT-LEMS should not be made easily, even if no tumor was found.

Few cases of lung adenocarcinoma complicated with LEMS have been previously reported. A PubMed literature search revealed seven published cases (Table 1), which were diagnosed at an advanced stage, with a poor prognosis. The patients ranged from 56–78 years of age (mean age, 68.3 ± 7.0 years). Six patients with adenocarcinoma diagnosed by biopsy, and one patient reported by Ramos-Yeo and Reyes⁸ were diagnosed by autopsy seven years after they had been diagnosed with LEMS. A lung resection was performed in three out of seven cases, of which two died of postoperative complications. Only two patients were still alive when the articles were published.

Effective antitumor therapy is crucial for T-LEMS. The *EGFR* gene mutation rates are 40% to 50% in Asian and Chinese patients with lung adenocarcinoma.^{11,12} Multiple

Table 1 Cases with lung adenocarcinoma complicated with LEMS in 1987–2019

References	Year	Cases	Gender	Age	Clinical manifestations	Imaging manifestations	Biopsy	Treatment	Outcome
Bukhari et al. ¹	2017	1	Female	78	Leg weakness	Mass in right upper lung	Percutaneous biopsy	Palliative radiation therapy	Death
Arai et al. ⁴	2012	1	Male	75	Leg weakness	Mass in right lower lung	Right lower lobectomy	Operation and palliative care	Unknown
Milanez et al. ⁵	2008	1	Male	66	Dysphagia and extensor weakness	Shadow of the apex nodules of the right lung	Right upper lobectomy	Operation and palliative care	Death
Chang et al. ⁶	2013	1	Male	73	Prosis, dysphagia and extensor weakness	Pretracheal regional lymph node enlargement	Thoracoscope	Unknown	Unknown
Tang et al. ⁷	2017	1	Male	65	Prosis and diplopia	Mass in left lower lung	Left lower lobectomy	Pyridostigmine bromide, steroid and operation	Alive
Ramos-Yeo et al. ⁸	1987	1	Male	56	Extensor weakness	Consolidation of the lower right lung	Autopsy	Palliative care	Death
Cai G et al. ⁹	2019	1	Female	65	Dysarthria, ataxia and autonomic dysfunction	Bilateral pneumonic tumors	Bronchoscope-guided biopsy	Chemotherapy and intravenous immunoglobulin	Alive

randomized stage III clinical studies^{13–20} have revealed that treatment with EGFR-TKIs (gefitinib, erlotinib, ectinib, afatinib, etc) improves progression-free survival. In this case with a sensitive *EGFR* mutation, gefitinib was given as first-line treatment, and the patient has survived for more than six years. Early diagnosis of LEMS and timely and effective treatment can bring a good prognosis.

LEMS is a rare disease, most diagnoses are associated with cancer, but it is extremely rare in lung adenocarcinoma. Relevant examinations are necessary for tumor screening in suspected LEMS patients. For T-LEMS, treatment should be given to improve the prognosis, while for NT-LEMS, a long period of follow-up should be done to avoid occult malignancy.

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Disclosure

No authors report any conflict of interest.

References

- Titulaer MJ, Lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: From clinical characteristics to therapeutic strategies. *Lancet Neurol* 2011; **10** (12): 1098–107. [https://doi.org/10.1016/s1474-4422\(11\)70245-9](https://doi.org/10.1016/s1474-4422(11)70245-9).
- Titulaer MJ, Maddison P, Sont JK et al. Clinical Dutch-English Lambert-Eaton myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. *J Clin Oncol* 2011; **29** (7): 902–8. <https://doi.org/10.1200/JCO.2010.32.0440>.
- Bukhari S, Soomro R, Fawwad S et al. Adenocarcinoma of lung presenting as Lambert-Eaton Myasthenic syndrome. *J Investig Med High Impact Case Rep* 2017; **5** (3): 1–4. <https://doi.org/10.1177/2324709617721251>.
- Arai H, Inui K, Hashimoto K et al. Lung adenocarcinoma with Lambert–Eaton myasthenic syndrome indicated by voltage-gated calcium channel: A case report. *J Med Case Reports* 2012; **6**: 281.1–5. <https://doi.org/10.1186/1752-1947-6-281>.
- Milanez FM, Pereira CA, Trindade PH et al. Lung adenocarcinoma, dermatomyositis, and Lambert-Eaton myasthenic syndrome: A rare combination. *J Bras Pneumol* 2008; **34** (5): 333–6.
- Chang A, Wang HC, Hsu WC et al. Lambert-Eaton myasthenic syndrome in mixed small cell carcinoma and adenocarcinoma of extrapulmonary origin. *J Clin Neurosci* 2013; **20** (4): 604–6. <https://doi.org/10.1016/j.jocn.2012.02.039>.

- 7 Tang Y, Wang K, Chen Z *et al.* Ophthalmoplegia associated with lung adenocarcinoma in a patient with the Lambert–Eaton myasthenic syndrome a case report. *Medicine* 2017; **96** (22): 1–5. <https://doi.org/10.1097/MD.0000000000006484>.
- 8 Ramos-Yeo YL, Reyes CV. Myasthenic syndrome (Eaton–Lambert syndrome) associated with pulmonary adenocarcinoma. *J Surg Oncol* 1987; **34** (4): 239–42.
- 9 Cai G, Sun X, Yu J, Meng X, Li J. Non-small cell lung cancer associated with late-onset Lambert–Eaton myasthenic syndrome and paraneoplastic cerebellar degeneration. *Neurol Sci* 2019. <https://doi.org/10.1007/s10072-019-04139-0>.
- 10 Wirtz PW, Smallegange TM, Wintzen AR. Differences in clinical features between the Lambert–Eaton myasthenic syndrome with and without cancer: An analysis of 227 published cases. *Clin Neurol Neurosurg* 2002; **104** (4): 359–63.
- 11 Shi Y, Au JS, Thongprasert SA *et al.* A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* 2014; **9** (2): 154–62. <https://doi.org/10.1097/JTO.0000000000000033>.
- 12 Gou LY, Wu YL. Prevalence of driver mutations in non-small-cell lung cancers in the People’s Republic of China. *Lung Cancer* 2014; **5**: 1–9. <https://doi.org/10.2147/LCCT.S40817>.
- 13 Mok TS, Wu YL, Thongprasert S *et al.* Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361** (10): 947–57. <https://doi.org/10.1056/NEJMoa0810699>.
- 14 Han JY, Park K, Kim SW *et al.* First-SIGNAL: First-line single-agent irressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol* 2012; **30** (10): 1122–8. <https://doi.org/10.1200/JCO.2011.36.8456>.
- 15 Mitsudomi T, Morita S, Yatabe Y *et al.* Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. *Lancet Oncol* 2010; **11** (2): 121–8. [https://doi.org/10.1016/S1470-2045\(09\)70364-X](https://doi.org/10.1016/S1470-2045(09)70364-X).
- 16 Rosell R, Carcereny E, Gervais R *et al.* Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; **13** (3): 239–46. [https://doi.org/10.1016/S1470-2045\(11\)70393-X](https://doi.org/10.1016/S1470-2045(11)70393-X).
- 17 Zhou C, Wu YL, Chen G *et al.* Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; **12** (8): 735–42. [https://doi.org/10.1016/S1470-2045\(11\)70184-X](https://doi.org/10.1016/S1470-2045(11)70184-X).
- 18 Wu YL, Zhou C, Liang CK *et al.* First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: Analyses from the phase III, randomized, open-label, ENSURE Study. *Ann Oncol* 2015; **26** (9): 1883–9. <https://doi.org/10.1093/annonc/mdv270>.
- 19 Sequist LV, Yang JCH, Yamamoto N *et al.* Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutation. *J Clin Oncol* 2013; **31** (27): 3327–34. <https://doi.org/10.1200/JCO.2012.44.2806>.
- 20 Wu YL, Zhou C, Hu CP *et al.* Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-lung 6): An open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15** (2): 213–22. [https://doi.org/10.1016/S1470-2045\(13\)70604-1](https://doi.org/10.1016/S1470-2045(13)70604-1).