



# Pulmonary Large Cell Neuroendocrine Carcinoma Associated With Lambert-Eaton Syndrome

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**ABSTRACT:** Lambert-Eaton syndrome is a rare paraneoplastic disorder of the neuromuscular junction, characterized by impaired release of acetylcholine, which causes proximal muscle weakness, depressed tendon reflexes, and autonomic changes. Most cases of Lambert-Eaton syndrome present in small-cell lung carcinoma, and only a few cases have been reported in other lung subtypes. Herein, we report a case of 69 years old male patient with Lambert-Eaton syndrome as a rare association with a pulmonary large-cell neuroendocrine carcinoma, which presented 5 months before neoplasm diagnosis. A lobectomy was auspiciously performed. A review of the literature is also presented.

**KEYWORDS:** Lambert-Eaton, myasthenic syndrome, large cell neuroendocrine carcinoma, lung cancer, paraneoplastic syndrome

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## Introduction

Lambert-Eaton syndrome (LES) is a rare paraneoplastic disorder of the neuromuscular junction, characterized by impaired release of acetylcholine due to autoantibodies to the voltage-gated calcium channels (VGCCs), which causes proximal muscle weakness, depressed tendon reflexes, and autonomic changes.<sup>1,2</sup> Most cases of LES present in small-cell lung carcinoma (SCLC) and only a few cases have been reported in other lung subtypes. In this article, we report an unusual case of pulmonary large-cell neuroendocrine carcinoma (LCNEC) diagnosed 5 months after the onset of LES. A literature search discovered only 3 similar cases published.<sup>3-5</sup>

## Case Report

A 69-year-old man with a past medical history of chronic obstructive pulmonary disease (COPD) due to smoking (55 pack/year) complained of right ocular pain, palpebral edema, and bilateral ptosis, 5 months prior to his admission. He then experienced progressive bilateral lower limb weakness. His neurological examination showed bilateral ptosis, asymmetric muscle weakness that was dominant in the proximal muscles of the upper and lower limbs, and diminished deep tendon reflexes +/+ + + +. Repetitive nerve stimulation (RNS) test showed a low compound muscle action potential amplitude at rest, significant decremental response at low frequency stimulation, and incremental response after high-frequency stimulation, making a diagnosis of LES. Antibodies were not made in this case.

A chest X-Ray showed a pulmonary nodule in the right lower lobe that measured 29 × 21 mm (Figure 1). Subsequent computed tomography (CT) scan of the chest confirmed the

pulmonary nodule (25.5 × 20.4 mm) located in the superior segment of the right inferior lobe (Figure 2). A [<sup>18</sup>F]-fluorodeoxyglucose positron emission tomography-CT showed an abnormal increased uptake of fluorodeoxyglucose in the mass previously described, without evidence for metastasis.

The patient underwent a percutaneous CT-guided needle biopsy that diagnosed a poorly differentiated non-small cell lung carcinoma. The patient was cleared for surgery and a right lower lobectomy via thoracotomy was performed (Figure 3). Surgery went well without complications and the patient was discharged home on POD 7. Final histopathology diagnosis showed a poorly differentiated large-cell neuroendocrine carcinoma of the lung (pT1bN0M0).

Histologically, the tumor showed nests and sheets of monomorphic neoplastic cells, arranged in trabecular and organoid pattern in some fields (Figure 4A) with geographic necrosis and scant well-formed rosettes (Figure 4B and C). At high magnification, these large tumor cells showed pleomorphism, an abundant eosinophilic cytoplasm with round nuclei and granular chromatin, so called salt and pepper pattern. High mitotic index ratio was also observed with 36 mitoses per 10 high power field (2 mm<sup>2</sup>) (Figure 4D).

These morphological features are suggestive of a LCNEC. Furthermore, immunohistochemistry was also performed, synaptophysin and CK7 were strongly positive. Tumoral cells showed weak and diffuse chromogranin positivity and high level Ki67 staining (70%) (Figure 4E–G). Napsin A, TTF1, CK5/6, p40, p63, and CD56 were negative. These immunohistochemistry results confirm neuroendocrine origin.

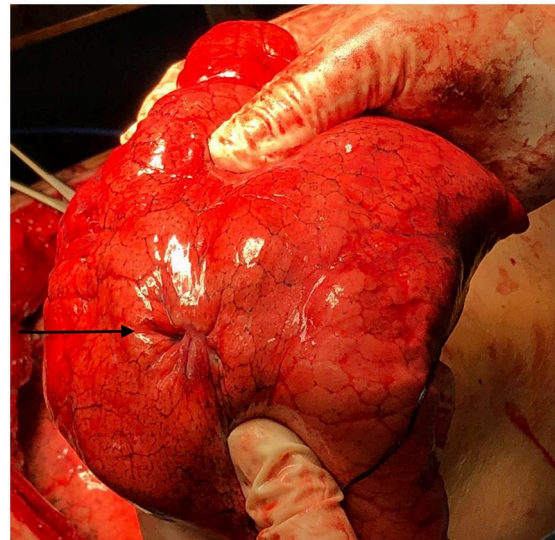


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**Figure 1.** Chest X-Ray showed a pulmonary nodule (arrow) in the right lower lobe that measured  $29 \times 21$  mm without any other lesions.



**Figure 3.** Lower right lobe of the lung. Black arrow showing the tumor.



**Figure 2.** Computed tomography (CT) scan of the chest with a pulmonary nodule ( $25.53 \times 20.44$  mm) located in the superior segment of the right inferior lobe adjacent to the pleura.

## Discussion

Lung cancer is the leading cause of death by cancer and the second cause of cancer worldwide, representing 28% of all cancer deaths. Its overall survival rate is only 16% in 5 years. Overall, lung cancer types can be divided into small cell lung carcinoma, non-small cell lung carcinoma, which can be sub-categorized into adenocarcinoma, squamous cell carcinoma and LCNEC, which was the diagnosis in our case, and others. Risk factors for lung cancer include smoking and pre-existing lung disease.<sup>6</sup> Our patient had both risk factors with a tobacco index of 55 pack/year and diagnosis of COPD.

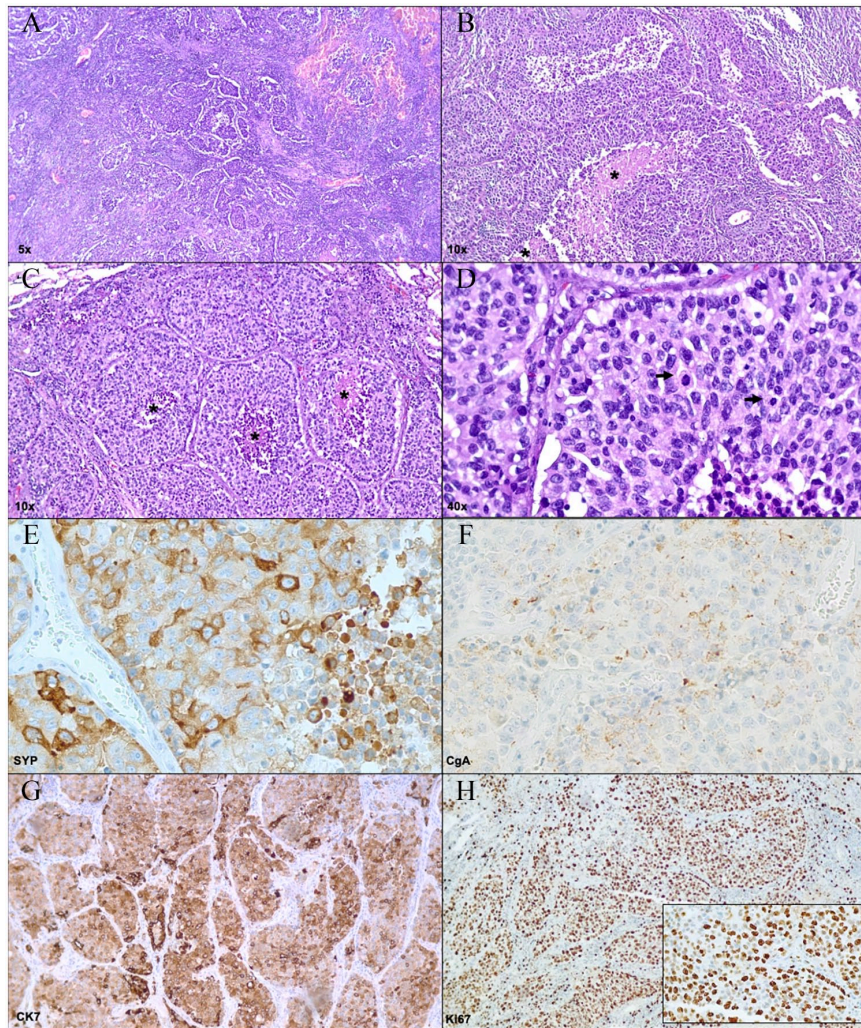
Lung cancer has one of the most diverse patterns of presentation of all neoplastic diseases.<sup>6</sup> Paraneoplastic syndromes are signs and symptoms that occur as a result of organ or tissue damage at locations that are remote from the site of primary

tumor.<sup>7</sup> Symptoms often precede the diagnosis of the associated lung cancer, generally by 6 months to 2 years.<sup>8</sup> In our patient, neoplasm diagnosis was made 5 months after presentation of LES symptoms.

LES is a rare paraneoplastic disorder of the neuromuscular junction, characterized by impaired release of acetylcholine, which causes proximal muscle weakness, depressed tendon reflexes, and autonomic changes. Muscle weakness is often relieved after repetitive use which helps differentiate the diagnosis with myasthenia gravis.<sup>2</sup> Diagnosis includes the presence of antibodies to presynaptic P/Q-type and N-type voltage gated calcium channel and an incremental pattern on electrodiagnostic studies.<sup>1,2</sup> In our case, diagnosis of LES was made with a repetitive nerve stimulation test. SCLC is almost always the type found associated with LES and it is rarely associated with other subtypes of lung cancer.<sup>2-5</sup> However, our patient had a final diagnosis LCNEC, which is an extremely rare association. Morphologic findings (monomorphic large cell population, neuroendocrine features, geographical necrosis, and high mitotic count  $>30$  mitoses/ $2\text{mm}^2$ ) in addition to, positive expression of a single neuroendocrine marker, even strong or weak staining, are essential criteria accepted to support LCNC diagnosis. We only found 2 similar cases published in the literature of LES associated with LCNEC (Table 1).<sup>3-5</sup> LES usually improves after successful cancer therapy and treatment should focus on the underlying cancer.<sup>2</sup>

In conclusion, LES can present months or years before the identification of a lung neoplasm and diagnosis of this rare paraneoplastic disorder should include the study of an underlying malignancy, small-cell lung carcinoma being the most common; nevertheless, this paraneoplastic syndrome can present with other types of lung cancer, as our case. Symptoms of LES usually improve after tumor resection and treatment should be focused to the primary tumor.





**Figure 4.** Histologic findings of lung tumor: (A) H&E stained sections at low power (5 $\times$ ) show organoid nests of large neoplastic cells, (B and C) geographic necrosis marked with an \* (10 $\times$ ), (D) at high power (40 $\times$ ) neoplastic cells contain abundant eosinophilic cytoplasm, granular or salt and pepper chromatin pattern with a mitotic account of 36 mitoses per 2mm<sup>2</sup> (arrows), and (E-H) immunohistochemistry (40 $\times$ ) shows positive cytoplasmic staining for synaptophysin and CK7, weak and diffuse chromogranin staining, and Ki67 was highly expressed (70%).

**Table 1.** Case reports of Lambert-Eaton myasthenic syndrome (LEMS) associated with large-cell lung carcinoma.

CASE NUMBER	REFERENCES	AGE/SEX	CLINICAL MANIFESTATIONS	TYPE OF CANCER	TREATMENT	LAST KNOWN OUTCOME
1	Demirer et al <sup>4</sup>	66/F	Proximal limb weakness, orthostatic hypotension, anhidrosis, hyporeflexia, weight loss	Large-cell neuroendocrine carcinoma of the lung	Mediastinoscopy and biopsy. Chemotherapy and radiotherapy.	Surviving at 17 months after therapy without neurologic deficit
2	Burns et al <sup>5</sup>	N/A	N/A	Atypical carcinoid vs large-cell neuroendocrine carcinoma	N/A	N/A
3	Grommes et al <sup>3</sup>	51/M	Non-localizing sensory disturbance and proximal lower limb weakness, hyporeflexia	Large-cell neuroendocrine carcinoma of the lung	Pyridostigmine and intravenous immunoglobulin. Right upper lobectomy with en bloc resection of the azygous vein and mediastinal lymph-node dissection	Surviving at 3 months after tumor resection with an improvement of symptoms

Abbreviation: N/A, not available.

### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. All procedures performed in studies involving human participants were in accordance with the ethical standards of Tecnológico de Monterrey ethics committee and institutional review board number 230 and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written consent is available for review by the Editor-in-Chief of this Journal on request.

### Author Contributions

PHA and MGU performed research database and wrote the first draft. AVV collected and analyzed the data on the methods and result section. DFLA wrote discussion section and edited the final version of the manuscript. SRP: designed the manuscript and performed research database. JEPS and RSM helped with the design of the figures and tables, as well as edited the final version of the manuscript. All authors contributed to the design and interpretation of the study and to further drafts. MGU is the guarantor.

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