J Korean Med Sci 2004; 19: 753-5
ISSN 1011-8934

A Case of Lambert-Eaton Myasthenic Syndrome Associated with Atypical Bronchopulmonary Carcinoid Tumor

The Lambert-Eaton myasthenic syndrome (LEMS) is typically recognized as a paraneoplastic syndrome associated with a small cell lung carcinoma (SCLC), whereas LEMS with other neuroendocrine lung tumors, including carcinoids or large cell lung carcinoma, are highly unusual. Here, we report a rare case of LEMS with atypical bronchopulmonary carcinoid tumor: A 65-yr-old man presented with progressive leg weakness and a diagnosis of LEMS was made by serial repetitive nerve stimulation test. Chest CT revealed a lung nodule with enlargement of paratracheal lymph nodes, and surgically resected lesion showed pathological features of atypical carcinoid tumor. We concluded that LEMS could be associated with rare pulmonary neuroendocrine tumor other than SCLC, which necessitates pathologic confirmation followed by aggressive treatment for optimal management in these rare cases.

Key Words : *Lambert-Eaton Myasthenic Syndrome; Carcinoid Tumor; Electrodiagnosis*

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Received : 3 July 2003
Accepted : 6 October 2003

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INTRODUCTION

The Lambert-Eaton myasthenic syndrome (LEMS) is an uncommon presynaptic neuromuscular junction disorder. It is associated with cancer in 50% to 60% of cases, of which the overwhelming majority are small cell lung carcinomas (SCLC). LEMS associated with atypical pulmonary carcinoid tumor is extremely rare (1-3). Recently, Burns et al. reported two cases of LEMS with atypical pulmonary carcinoids which remitted after treatment (1). Atypical carcinoid tumors make up about 11% of bronchopulmonary carcinoids which represent 1 to 5% of all lung tumors (6). The 5-yr survival rate is about 60%, which is intermediate between that of typical carcinoids (95%) and small cell carcinomas (2%) (6). We describe here a rare case of LEMS with atypical pulmonary carcinoid tumor, which have shown transient clinical and electrophysiological remission after surgical resection and chemotherapy.

CASE REPORT

A 65-yr-old man presented with progressive weakness of legs in February 2001. He has noticed worsening difficulty in climbing stairs before five months, which seemed to be worse in the early mornings and then improved later in the daytime. He has been smoking two packs of cigarettes a day for 40 yr. The family history was unremarkable. Neurological examination showed mild proximal arm and leg weakness (MRC grade 4+) and hypoactive tendon reflexes. Cranial nerve and sensory examinations were normal. Nerve conduction study revealed low amplitude compound muscle action potentials (CMAPs) in peroneal and posterior tibial nerves with normal conduction velocities. In suspicion of LEMS, repetitive nerve stimulation test (RNST) was performed on abductor digiti minimi (ADM) and tibialis anterior (TA) muscles using Oh's methods (4). Despite some potentiation of CMAP after 30 sec of maximum voluntary contraction and incremental response at high rate (50 Hz) of stimulation (HRS) for 1 sec in both muscles, the results did not fully satisfied commonly used diagnostic criteria for LEMS (Table 1). On axonally stimulated single fiber electromyography (S-SFEMG), the jitter on the extensor digitorum communis muscle (EDC) was markedly increased (mean of mean consecutive difference: 158 μsec, upper normal limit; 25 μsec) with frequent impulse blockings (67%). Tensilon (Edrophonium) test and anti-acetylcholine receptor antibody assay were negative. The amount of salivary secretion measured by chewing gauze for 5 min was within normal limit (7.88 mg for 5 min, low normal limit; 7.5 mg for 5 min)(4). The second RNST 3 weeks later showed classical LEMS pattern; 133% increment in CMAP after short exercise, and 109% of incremental response at 50 Hz stimulation for 2 sec in ADM (Fig. 1). Chest radiography on admission revealed a nodule in right upper lung and chest

Table 1. Serial data of repetitive nerve stimulation test and stimulated single fiber electromyography

Date	CMAP			LRS (%)			HRS (%)		S-SFEMG*	
	Muscle	Rest (mV)	PEF (%)	2 Hz	3 Hz	5 Hz	1 sec	2 sec	Jitter	% blocking
2001. 2. 23	ADM	8.2	+70	-21	-22	-17	+30		158†	67
	EDB	1.6	+88	-33	-33	-25	+74			
3.16	ADM	5.8	+133	-31	-34	-31	+78	+109	144†	100
7.20	ADM	10.3	+23	-2	-6	-4	+10		33†	0
2002. 5.18	ADM	10.3	+54	-25	-31	-26	+22	+43		
8.29	ADM	6.7	+75	-31	-35	-33	+145			

CMAP, compound muscle action potential; LRS, low rate of stimulation; HRS, high rate stimulation; S-SFEMG, stimulated single fiber EMG; PEF, postexercise fascilitation; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; +, incremental response; -, decremental response.
*S-SFEMG was performed on the extensor digitorum communis muscle (EDC) at stimulation rate of 10 Hz. †Increased mean of mean consecutive difference (upper normal limits; 25 μsec).

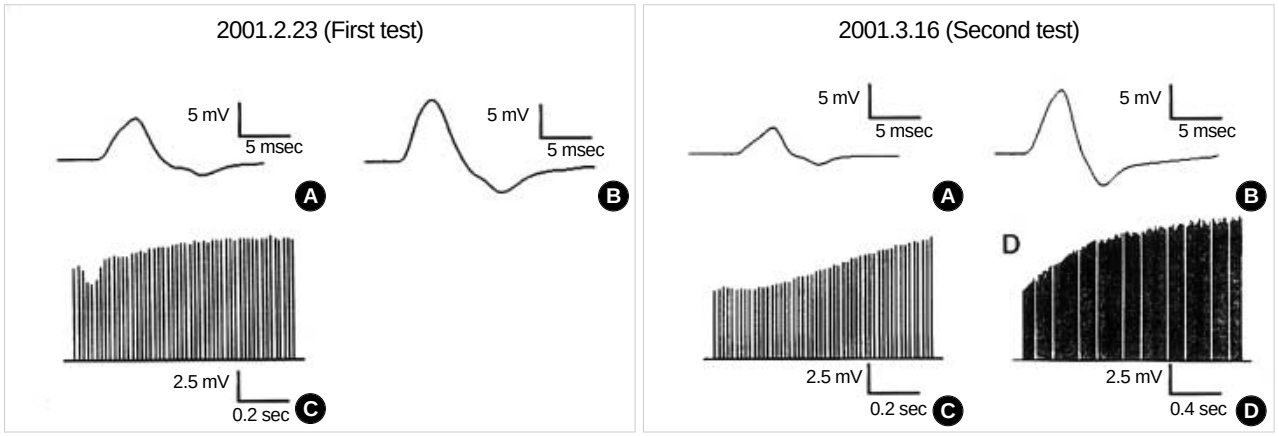

Fig. 1. Postexercise fascilitation and incremental response at high rate of stimuration in the abductor digiti minimi muscle. Note definite facilitation at high rate of stimulation is achieved by prolonged stimulation for 2 sec in second test. (A) Compound muscle action potential (CMAP) before exercise. (B) CMAP after 30 sec of exercise. (C) Response at 50/sec stimulation for 1 sec. (D) Response at 50/sec stimulation for 2 sec.

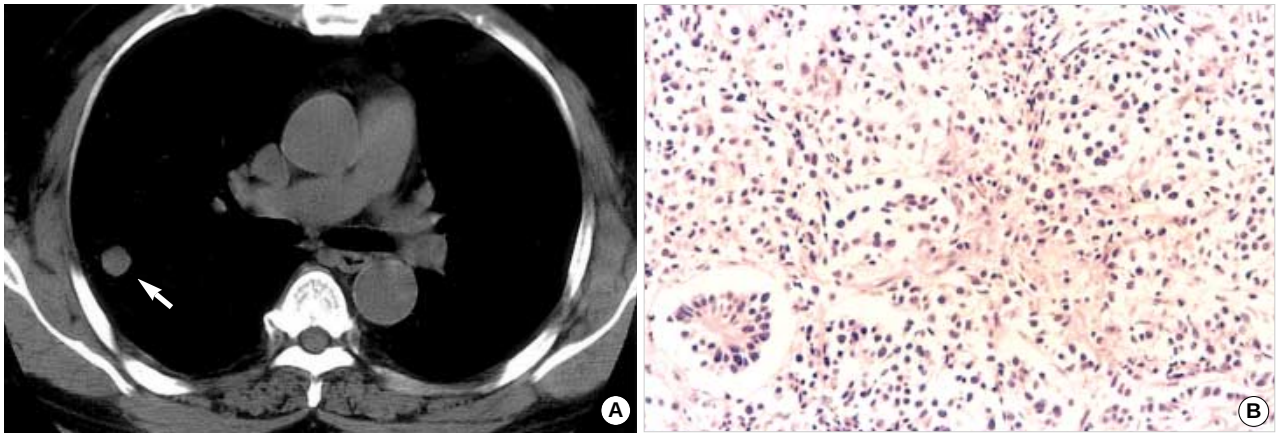

Fig. 2. (A) CT scan of the chest shows a 1.4 cm nodule (arrow) in the posterior segment of right upper lobe. (B) Atypical carcinoid tumor with mosaic patterns separated by thin fibrovascular stroma. The tumor cells have central round nuclei with abundant cytoplasm (H&E ×100).

CT disclosed a speculated, 1.4 cm-sized enhancing nodule and enlarged right upper paratracheal lymph node (Fig. 2A). The material from CT-guided needle biopsy showed malignant tumor cells, which was initially read out as adenocarcinoma. After two serial courses of chemotherapy with paclitaxol and carboplatin, the nodule in right upper lobe and mediastinal lymph node were resected in May 2001. Detailed microscopic examination showed mosaic pattern with cellu-

lar pleomorphism and increased mitotic activity, which is considered intermediate between that of typical carcinoid and small cell carcinoma. Immunohistochemical stains for neuroendocrine markers, such as chromogranin A, synaptophysin, and neuron-specific enolase were all positive and was finally interpreted as atypical carcinoid (Fig. 2B). The antibody titer against the P/Q type voltage-gated calcium channel, sent after surgical resection was negative (less than 1.0 pmol/L; upper limit of normal; 20 pmol/L). After surgery, his strength has improved to almost premorbid level. The typical RNS features of LEMS normalized 2 months later (Table 1) and S-SFEMG findings also improved. However, his improvement was shortlived. In May 2002, he was reevaluated due to clinical worsening, showing a waddling of gait and fatigable weakness of proximal muscles in all limbs. Tumor recurrence was detected on chest CT. RNST abnormalities recurred as the same patterns as the initial test; normal CMAP, decremental response at LRS, and mild incremental response at HRS. It was 3 months after tumor recurrence that 145% of incremental response at HRS was achieved (Table 1). Despite several additional cycles of chemotherapy, he remained mildly disabled.

DISCUSSION

We describe a rare case of LEMS associated with atypical bronchopulmonary carcinoid tumor. No more than 5 cases could be found in English literatures (1-3), all of which, however, lacked description of detailed clinical features and electrophysiological patterns.

LEMS results from an autoimmune attack directed against the voltage-gated calcium channels (VGCCs) on the presynaptic motor nerve terminal. It was first described as a paraneoplastic syndrome in patients with lung cancer but we now know about half of the patients with LEMS do not have cancer. When tumor occurs in LEMS, it is usually SCLC (5, 9). Recently, Burns et al. (1) reported LEMS associated with other pulmonary neuroendocrine carcinomas with prolonged remission; two patients with atypical carcinoids and one patient with large cell neuroendocine carcinoma. In the spectrum of neuroendocrine tumors of the lung, which can be divided into the typical carcinoid, atypical carcinoid, SCLC and large cell neuroendocrine carcinoma, atypical carcinoids occupy the middle ground in terms of pathological features as well as natural history and prognosis (6). LEMS in the setting of underlying atypical carcinoid lung tumor, unlike those associated with SCLC, may be better responsive to treatment with variable long-term remission (1). In our case, clinical and electrophysiological remission was achieved by surgical resection and chemotherapy, but failed to remain in prolonged remission after tumor recurrence.

It is noteworthy that our case initially did not satisfy the electrophysiological criteria of LEMS, and the follow-up study 3 weeks later revealed marked facilitation of CMAP compatible with LEMS. It is known that electrophysiologic findings of LEMS may occasionally overlap with those seen in myasthenia gravis; a decremental response at low stimulations rate, normal CMAP amplitudes and absent facilitation at high stimulation rate. Furthermore, facilitation up to 50% can also be seen in myasthenia gravis (7), complicating electrophysiologic diagnosis not to be straightforward between the two myasthenic syndromes. Otherwise, it is believed that these patterns represent a mild form of LEMS, based on the observation that many LEMS patients show these patterns as they improve with treatment (8). Our case demonstrates how repeated serial RNST can help diagnosis when initial findings are equivocal. In addition, prolonged stimulation up to 2 sec or more may be needed for full extent of facilitation (8).

We concluded that LEMS could be associated with pulmonary neuroendocrine tumor other than SCLC, which necessitates pathologic confirmation followed by aggressive treatment for optimal management in these rare cases.

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