

Case Report

Overlapping of paraneoplastic limbic encephalitis and Lambert-Eaton myasthenic syndrome in a patient with small cell lung cancer: a rare case report

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Abstract: Paraneoplastic neurologic syndrome (PNS) is a rare group of disorders caused by nervous system damages in the setting of cancer unrelated to the tumor sites. It may affect one or more regions of the nervous system and occurred in less than 1 per 10,000 patients diagnosed with a malignancy. Patients with PNS may present symptoms or damages in the central and peripheral nervous system, the neuromuscular junction and muscle, which usually results in severely disabling. Nowadays, paraneoplastic limbic encephalitis (PLE) and Lambert-Eaton myasthenic syndrome (LEMS) are the most commonly reported types of PNS compared with the others. PLE is a rare disorder featured by personality change, seizure, irritability, and depression due to involvement of the limbic system secondary to an autoimmune response to neurons of the brain provoked by the antibodies. LEMS is well known as a classical paraneoplastic syndrome when the neuromuscular junction is affected. In this case, we report a case of paraneoplastic limbic encephalitis (PLE) and Lambert-Eaton myasthenic syndrome (LES) in an elderly Asian male with small cell lung cancer (SCLC).

Keywords: Paraneoplastic limbic encephalitis, Lambert-Eaton myasthenic syndrome, small-cell lung cancer, paraneoplastic neurologic syndrome

Introduction

Paraneoplastic neurologic syndrome (PNS) is a rare group of disorders caused by nervous system damages in the setting of cancer unrelated to the tumor sites. Patients with PNS may present symptoms or damages in the central and peripheral nervous system, the neuromuscular junction and muscle, which usually results in severely disabling. Nowadays, paraneoplastic limbic encephalitis (PLE) and Lambert-Eaton myasthenic syndrome (LEMS) are the most commonly reported types of PNS compared with the others. PLE is a rare disorder featured by personality change, seizure, irritability, and depression due to involvement of the limbic system secondary to an autoimmune response to neurons of the brain provoked by the antibodies [1-3]. LEMS is well known as a classical paraneoplastic syndrome when the neuromuscular junction is affected [4-6]. In this case, we

reported an overlap of PLE and LEMS secondary to small cell lung cancer (SCLC).

Case presentation

A 65-year-old male patient presented to the Emergency Department of our hospital in March 2014 with suspected seizure. His family members reported the patient showed intermittent episodes of anxiety, confusion and memory loss, as well as personality change and irritability within 3 weeks before admission. No focal or global neurologic deficits like numbness, weakness or cranial nerve abnormalities were identified. Computed tomography (CT) on brain revealed no abnormalities. Brain MRI demonstrated aberrant signals in the left basal ganglia, based on which chronic lacunar infarction was considered. Twenty-four hour electroencephalogram indicated multiple, irregular sharp-slow waves and sharp waves in the middle line of forehead, especially the right side.

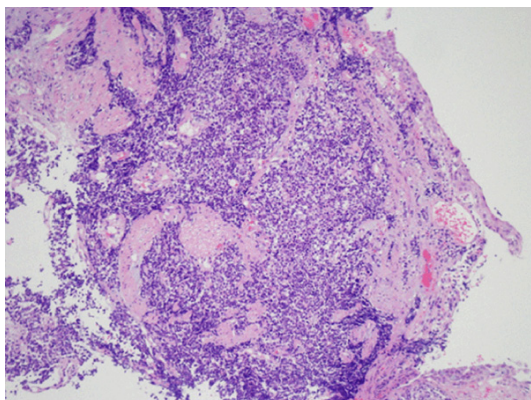


Figure 1. CT images of mediastina (A) and the lung (B). High density shadows were observed at the inferior lobe of right lung in proximity to the pulmonary hilum. The margins were clear and the lobes were distinguished. Soft tissue density was observed in the mediastina. Besides, high density shadows in strip-like and nodular patterns were noticed in the inferior lobe of right lung. Further, multiple swollen lymph nodes were identified in the mediastina.

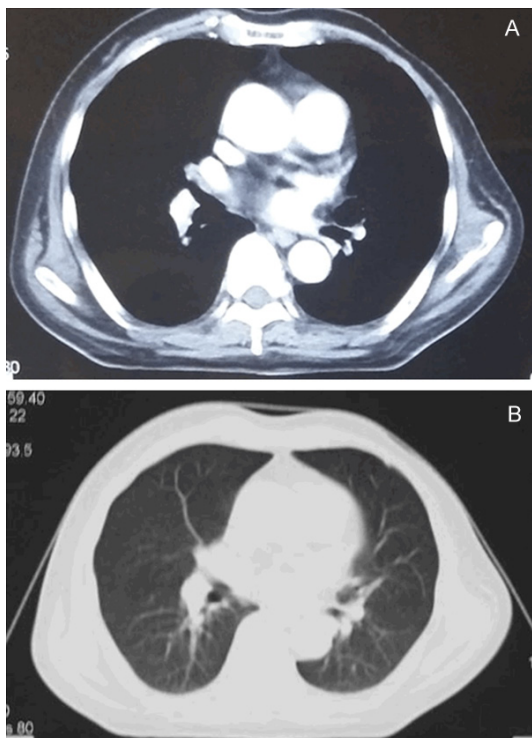


Figure 2. Histology from a lung biopsy showing infiltration of the right lobe with neoplastic cells, consistent with small cell lung cancer (H&E, 100×).

The cerebrospinal fluid (CSF) analysis results were as follows: protein, 0.38 g/L; glucose, 4.17 mmol/L; Cl, 130.5 mmol/L; white blood

cell count, $15 \times 10^6/L$; apocyte, 0.07; monocyte, 0.93. On this basis, the patient was diagnosed with limbic encephalitis, and he showed complete symptomatic relief after medication of antiepileptics. Two months later, the patient visited our hospital for the routine physical check. Chest computerized tomography (CT) confirmed a right hilar mass with extensive mediastinal involvement (**Figure 1**), but no distant metastases were identified. The patient was diagnosed with small cell lung cancer (SCLC) according to the transbronchial biopsy (**Figure 2**). Taken together, we confirmed that the patient suffered from PLE.

Subsequently, the patient received one cycle of chemotherapy (EP regimen). The second cycle of chemotherapy was performed 3 weeks (June 2015) later using topotecan. In July, the patient showed asthenia, systematic fatigue and disability. Physical examination at the time of admission revealed diminished ability and difficulty to sustain upward gaze for more than 30 seconds. It was difficult for the patient to sustain hold against gravity of the upper extremities. However, a transient recovery, such as standing up from the bed or seat, was noticed after moderate exercise. Electromyogram was performed, which revealed a decrease of compound muscle action potential (56%) upon the stimulation of right ulnar nerve under a frequency of 3 Hz. In addition, a 7.3-fold increase was observed in the compound muscle action potential upon the stimulation with a frequency of 20 Hz (**Table 1**). Taken together, the patient was diagnosed with LEMS.

As the diagnosis of SCLC was definite, sequential radiotherapy was performed subsequently with total doses of 5400cGy/27F in pGTVnd and 4860cGy/27F in PTV respectively. Subsequent CT scanning confirmed a positive response to treatment with an elimination of mediastinal metastasis. No ventilation dysfunction was found in lung base throughout the hospitalization fortunately. His cognition and confusion were markedly improved; the weakness of muscle was not progressed.

Discussion

The incidence of PNS is extremely lower with a rate of less than 1/10000 [1]. In the majority of these cases, several regions of the nervous system were affected including cerebrum,

Table 1. The result of neurophysiological tests with adequate repetitive stimulation: compound motor action potentials (CMAP) amplitude was up to a 56% decrement at low frequency repetitive stimulation (3 Hz supramaximal stimulation) and up to 729% increment at high frequency stimulation (20 Hz supramaximal stimulation)

Repetitive electrical stimulation	Event	Frequency	Time	Amplitude
Musculi abductor digiti quinti	1	10@2 Hz	14:05:24	-11.7
	2	10@2 Hz	14:05:34	-19.4
	3	10@3 Hz	14:05:42	-38.4
	4	10@3 Hz	14:05:49	-56.0
	5	10@5 Hz	14:05:58	-18.6
	6	10@5 Hz	14:06:06	-13.3
	7	30@20 Hz	14:06:15	729

spine, neuromuscular junction and muscle [7]. To date, PNS is considered as a disease not related to tumor, metastasis, or metabolites due to the presence of anti-neural antibody in these patients [2].

Nowadays, the final diagnosis of PNS is largely depend on the essential components, including clinical symptoms, cancer diagnosed within 4 years after the onset of neurologic symptoms, exclusion of other causes, as well as any of the followings: brain MRI showed a lesion in temporal lobe and/or brain stem, cerebrospinal fluid analysis indicating inflammation without positive cytology, and/or epileptic discharge in temporal lobes by ECG analysis [2]. In this case, the patient was finally confirmed with PLE and LEMS due to the presence of all standards above mentioned.

The most common types of neoplasms associated with PLE are SCLC, testicular tumor, thymoma, Hodgkin's lymphoma and breast cancer [3]. Limbic system consisted of hippocampus, amygdala, nucleus anterior thalamic and limbic cortex, is essential for the memory, learning, and higher emotion. Typically, PLE manifests with seizures and changes in memory, mood and personality. Brain MRI is the most sensitive radiological method for the diagnosis of PLE. Hyperintense lesions were observed in the medial temporal lobes and these are best visualized in T2 and axial FLAIR sequences without significant contrast enhancement [3].

As the patient showed mild elevation of protein or monocyte count, lumbar puncture was performed to exclude the leptomeningeal metastasis and to detect other inflammatory or immune-

mediated neurologic disorder. The orthodox autoimmune antibodies in CSF were tested, including anti-HU, anti-R1, and anti-YO. The anti-HU is commonly found in approximately 50% of the PLE cases. Meanwhile, anti-R1 antibodies are less commonly detected, but it supports the diagnoses of PLE most peculiarly [7, 8]. Electroencephalography can be a useful tool to support the diagnosis of PLE, as it demonstrate focal or generalized

slow and/or sharp wave predominantly in the temporal regions [8, 9]. In a previous study, Lawn et al summarized the clinical, MRI and electroencephalographic features of PLE (10), which were cognitive dysfunction (92%), seizures (58%) and psychiatric symptoms (50%). Serum paraneoplastic neuronal antibodies were identified in a majority (64%) of these patients. Abnormal CSF was found in 78% of these patients. In this case, the patient was diagnosed with SCLC, coupled with a distinctive history of altered personality, cognitive disorder and seizure activity that strongly suggested PLE. CSF sample was obtained, the results indicated negative results and no serum neuronal antibodies, and however, such facts could not exclude the PLE.

Lambert-Eaton myasthenic syndrome (LEMS) is a rare but well-known paraneoplastic disorder featured by fatigability and muscle weakness predominantly involving the proximal extremity. In addition, it has been acknowledged as an autoimmune disease that harasses the normally credible neurotransmission at the neuromuscular junction. Such disruption is thought to result from an auto antibody-mediated removal of a subset of the P/Q-type Ca^{2+} channels involved with neurotransmitter release [8]. Antibodies to voltage-gated calcium channels (VGCC) in motor and autonomic nerve terminals contributes to the disruption of calcium influx and reduction of acetylcholine release [11]. These antibodies are usually found in patient with Lambert-Eaton myasthenic syndrome [4]. In approximately 50% of the patients, LEMS is reflected by a paraneoplastic manifestation and most commonly associated with SCLC

expressing VGCCs in the plasma membrane [5]. The diagnosis of LEMS depends on a combination of physical examination and measurement of serum VGCC antibody [6]. Neurophysiological studies had some limitations since EMG studies without repetitive stimulation at appropriate frequencies may not be specific. In this case, the patient was confirmed with LEMS considering the transient recovery of muscle weakness in proximal extremity.

In this case, the patient suffered from PLE and PNS presenting as LEMS. To our knowledge, this is the first case after literature research using the key words of “Lambert-Eaton Myasthenic Syndrome” and “Paraneoplastic limbic encephalitis” in the PubMed and Medline. Previously, Kaira et al [12] reported a case of small-cell lung cancer with voltage-gated calcium channel antibody-positive paraneoplastic limbic encephalitis. In that case, the patient did not presented as LES despite the positive VGCC antibody. On this basis, we speculate that there might be crosstalk between the pathogenesis of LEMS and PLE.

Conclusion

In this case, we report an overlap of paraneoplastic limbic encephalitis (PLE) and Lambert-Eaton myasthenic syndrome (LES) in an elderly Asian male with small cell lung cancer (SCLC). For the patients with personality change or seizure, a possibility of malignant cancer may be raised and early screening is needed. The treatment of PNS should be focused on the cancer treatment, and the symptoms may be alleviated after tumor control. There may be a direct correlation between the LEMS and PLE, and further studies are needed to confirm this.

Disclosure of conflict of interest

None.

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References

[1] Honnorat J and Antoine JC. Paraneoplastic neurological syndromes. *Orphanet J Rare Dis* 2007; 2: 22.

[2] Said S, Cooper CJ, Reyna E, Alkhateeb H, Diaz J and Nahleh Z. Paraneoplastic limbic encephalitis, an uncommon presentation of a common cancer: Case report and discussion. *Am J Case Rep* 2013; 14: 391.

[3] Fahim A, Butt M and McGivern DV. A case of limbic encephalitis presenting as a paraneoplastic manifestation of limited stage small cell lung cancer: a case report. *J Med Case Rep* 2010; 4: 408.

[4] Payne M, Bradbury P, Lang B, Vincent A, Han C, Newsom-Davis J, Talbot D. Prospective study into the incidence of Lambert Eaton myasthenic syndrome in small cell lung cancer. *J Thorac Oncol* 2010; 5: 34-8.

[5] Hülsbrink R and Hashemolhosseini S. Lambert-Eaton myasthenic syndrome-Diagnosis, pathogenesis and therapy. *Clin Neurophysiol* 2014; 125: 2328-36.

[6] Katada E, Nakamura T, Watanabe H, Matsukawa N, Ojika K and Sobue G. [Lambert-Eaton myasthenic syndrome associated with pulmonary squamous cell carcinoma and circulating anti-P/Q-type voltage-gated calcium channel antibody]. *Rinsho Shinkeigaku* 2010; 50: 17-9.

[7] Lalani N and Haq R. Prognostic effect of early treatment of paraneoplastic limbic encephalitis in a patient with small-cell lung cancer. *Current Oncology* 2012; 19: e353.

[8] White D and Beringer T. Paraneoplastic limbic encephalitis in an elderly patient with small cell lung carcinoma. *Ulster Med J* 2010; 79: 22.

[9] Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB and Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain* 2000; 123: 1481-94.

[10] Lawn ND, Westmoreland BF, Kiely MJ, Lennon VA and Vernino S. Clinical, magnetic resonance imaging, and electroencephalographic findings in paraneoplastic limbic encephalitis. *Mayo Clin Proc* 2003; 78: 1363-8.

[11] Dai Y, Li P, Yan S, Xia X, Li Z and Xia M. Lung squamous carcinoma with two paraneoplastic syndromes: dermatomyositis and Lambert-Eaton myasthenic syndrome. *Clin Respir J* 2014; [Epub ahead of print].

[12] Kaira K, Okamura T, Takahashi H, Horiguchi N, Sunaga N, Hisada T, Yamada M. Small-cell lung cancer with voltage-gated calcium channel antibody-positive paraneoplastic limbic encephalitis: a case report. *J Med Case Rep* 2014; 8: 119.