A Case of Paraneoplastic Cerebellar Degeneration and Lambert-Eaton Myasthenic Syndrome Associated with Neuroendocrine Carcinoma of the Oropharynx

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Abstract:
Paraneoplastic cerebellar degeneration and Lambert-Eaton myasthenic syndrome (PCD-LEMS) are usually associated with small-cell lung carcinoma (SCLC). PCD-LEMS with extrapulmonary non-SCLC tumors; however, has not been previously reported. A 78-year-old man presented with dysarthria, dysphagia, staggering gait, and lower extremity muscle fatigue. He was diagnosed with PCD-LEMS associated with neuroendocrine carcinoma of the oropharynx, based on the histological findings of the biopsy, the existence of antibodies against P/Q-type voltage-gated calcium channels, and an incremental response of the compound muscle action potentials during repetitive nerve stimulation tests. Thus, PCD-LEMS should be included in the differential diagnosis of neurological dysfunction, even in extrapulmonary non-SCLC patients.

Key words: Lambert-Eaton myasthenic syndrome (LEMS), Paraneoplastic cerebellar degeneration (PCD), antibodies against P/Q-type voltage-gated calcium channels (VGCC), neuroendocrine carcinoma, oropharyngeal cancer

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Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder of neuromuscular junction transmission, which often presents with clinical features of proximal muscle weakness, diminished deep tendon reflexes, and autonomic dysfunction. Since more than half of patients have them, LEMS is often associated with tumors (1, 2), especially small-cell lung carcinoma (SCLC). Antibodies to P/Q-type voltage-gated calcium channels (VGCC), which have been detected in 85-95% of patients with LEMS, play a significant role in its pathogenesis (3-5). The antibodies inhibit the release of acetylcholine at the neuromuscular junction, which results in muscle weakness.

These antibodies are also associated with paraneoplastic cerebellar degeneration (PCD), regardless of whether PCD-related autoantibodies, such as anti-Yo, Hu, or Ri antibodies, are present in the serum (6). Although the precise mechanism by which PCD is caused in LEMS remains controversial, Fukuda et al. (6) reported that antibodies directed against P/Q-type VGCCs reduced the number of these channels in the molecular layer of the cerebellum. Importantly, a cohort of Japanese patients with PCD and LEMS (PCD-LEMS) reportedly had SCLC and high titers of P/Q-type VGCC antibodies (4). However, PCD-LEMS has not been reported in patients with extrapulmonary non-SCLC tumors.

We herein report a unique case of PCD-LEMS associated with a neuroendocrine carcinoma (NEC) of the oropharynx, in a patient who showed no recurrence of NEC in 16
Case Report

The patient was a 78-year-old man with a 60-pack-per-year smoking history and no history of alcohol consumption, whose gait gradually became unsteady. In the following months, he also suffered from dysarthria, dysphagia, and lower extremity muscle fatigue during walking. At five months after the onset of symptoms, he consulted an otolaryngologist for a tumor on the left side of the base of tongue and swelling of the cervical lymph nodes. Magnetic resonance T2-weighted “iterative decomposition of water and fat with echo asymmetry and least squares estimation” (IDEAL) water imaging revealed a 3.8×1.8 cm tumor on the left side of the base of the tongue (arrow).

We herein describe a case of PCD-LEMS associated with small-cell NEC of the oropharynx. Since NECs usually arise from lungs and gastrointestinal tract, NEC originating in the oropharynx, such as in the present case, is uncommon (8). Histologically, NECs can be mainly classified into small cell, large cell type, and mixed type (9). Among these various subtypes, small-cell NECs have been reported to have the potential to cause LEMS, because of their morphological and immunohistochemical similarity with SCLC (9). This hypothesis is supported by a few reports on LEMS with ex-
trapulmonary small-cell NECs of the seminal vesicles (10) or mediastinum (11). No cases of PCD-LEMS with small-cell NECs have previously been reported.

In the treatment of LEMS associated with cancer, anti-tumor therapy plays a significant role in achieving remission from LEMS symptoms, such as muscle weakness (12). On the other hand, the responsiveness of PCD to anti-tumor and immunosuppressive therapy is controversial. For example, a previous report described two patients with PCD-LEMS who responded to anti-tumor therapy and plasma exchange (13), but another study revealed that three patients with PCD-LEMS who received immunotherapy showed no apparent improvement of their cerebellar symptoms (14). In the present case, chemoradiotherapy and pyridostigmine improved the patient’s cerebellar ataxia, as well as his proximal muscle weakness, which is in line with the former report. One possibility is that the improvement of the patient’s cerebellar symptoms might have been dependent on the degree of downregulation of the P/Q-type VGCCs in the cerebellar molecular layer. If anti-tumor therapy is administered early, the degree of downregulation might not be as severe and might recover.

Extrapulmonary NECs are known to have a poor prognosis, despite combination therapy. The median survival ranges from 4-16 months (9). In particular, small-cell NECs of the head and neck are highly aggressive and tend to develop early regional or distant metastasis (8). Interestingly, our patient with oropharynx NEC was alive with no sign of recurrence after 16 months of follow-up. This long survival without a recurrence of NEC is similar to that described in a previous study on SCLC-LEMS, which was associated with anti-P/Q-type VGCC antibodies (15). The authors suggested that the autoimmune response with anti-P/Q-type VGCC antibodies might play a role in retarding tumor growth (15). Thus, the present case highlighted that the diagnosis of LEMS would be helpful for predicting the prognosis of patients with small-cell NEC, as well as those with SCLC.

In conclusion, PCD-LEMS could be associated with extrapulmonary small-cell NECs; and cerebellar ataxia in this condition might respond to anti-tumor therapy. PCD-LEMS should be considered, even in cases with extrapulmonary small-cell NECs, in the differential diagnosis of muscular weakness and cerebellar ataxia.

The authors state that they have no Conflict of Interest (COI).

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