Lambert-Eaton Myasthenic Syndrome Associated with Synchronous Double Cancer: A Combination of Small Cell Carcinoma of the Cervix and Breast Carcinoma

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Abstract:
Lambert-Eaton myasthenic syndrome (LEMS) is most commonly associated with small cell lung carcinoma, while it is rarely associated with gynecological and breast carcinoma. We herein report a case of LEMS associated with synchronous double cancer, which was a combination of small cell carcinoma of the cervix and breast carcinoma. The early diagnosis and treatment of LEMS are important for achieving a good outcome. The possibility of accompanying paraneoplastic neurological syndrome must be sufficiently considered in gynecology and breast cancer patients. To our knowledge, this is the first report of LEMS associated with synchronous double cancer.

Key words: Lambert-Eaton myasthenic syndrome, double cancer, small cell carcinoma of the cervix, breast carcinoma

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Introduction
Lambert-Eaton myasthenic syndrome (LEMS) is a paraneoplastic myasthenic syndrome characterized by circulating antibodies against presynaptic P/Q-type voltage-gated calcium channels (VGCC); these antibodies inhibit neuromuscular transmission. This syndrome is most frequently associated with small cell carcinoma of the lung, although some cases with other lung and non-lung carcinoma have been reported (1). We herein report a case of LEMS associated with double cancer: namely, small cell carcinoma of the cervix and breast carcinoma.

Case Report
A 64-year-old Japanese woman underwent right mastectomy for breast carcinoma. The pathological examination showed invasive lobular carcinoma (Fig. 1). She had noticed general fatigue, leg weakness and a weight loss of 10 kg two months after mastectomy. In addition, she developed easy fatigability of the arms and dry mouth a few more weeks thereafter. Computed tomography to identify the source of these symptoms revealed an abnormal mass in the pelvis with multiple lymph node metastases. A gynecological examination with cervical pathology diagnosed her to have small cell carcinoma of the cervix, based on positive findings for chromogranin A and synaptophysin and a negative finding for cytokeratin 7 (Fig. 1). Total-body positron emission tomography (PET) showed no abnormal uptake outside of the pelvis, thus ruling out metastasis of lung carcinoma or a recurrence of breast carcinoma (Fig. 2). The advanced state (Stage 3b) of the cervical carcinoma was thought to be the cause of her serious condition, as small cell carcinoma of the cervix frequently shows an aggressive progression. After receiving combined treatment with local radiotherapy and chemotherapy for a month, her unsteady gait slightly improved, but the leg weakness and easy fatigability persisted, with the severity of the symptoms varying from day to day. She was referred to a neurologist to try
and identify any additional causes for her leg weakness, which had already persisted for five months.

On a neurological examination, ptosis was not seen, and the other cranial nerves were normal, including extraocular movement. Normal strength of the arms, marked weakness of hip flexion and mild weakness of knee extension were seen. The deep tendon reflexes were all depressed without post-exercise facilitation. The sensation and cerebellar function were intact. Except for dry mouth, no autonomic dysfunction was revealed. Urinary incontinence due to bladder invasion of a tumor was seen. Laboratory data showed a low creatine phosphate kinase level (CPK, 17 IU/L), which indicated a low possibility of myopathy. Hypokalemia (K, 2.9 mEq) was also seen, but periodic paralysis due to hyperthyroidism and primary aldosteronism were ruled out (FT3, 3.04 pg/mL; FT4, 1.47 ng/dL; thyroid stimulating hormone (TSH), 1.920 μIU/mL; plasma renin activity, 0.8 ng/mL/h; plasma aldosterone concentration, 56.0 pg/mL). Magnetic resonance imaging did not show any abnormalities in the brain or spinal cord. A nerve conduction study revealed low-amplitude compound muscle action potentials of 0.5 mV in the right abductor digiti minimi. Repetitive nerve stimulation testing (3 Hz) revealed 9.6% waning, and 386% facilitation was seen after isometric exercise for 10 seconds. An anti-P/Q-type VGCC antibody assay revealed a titer of 97.3 pmol/L (cut-off point <20.0 pmol/L), confirming the presence of LEMS. Although the administration of intravenous gammaglobulin (400 mg/kg × 5 days) resulted in no obvious improvement, the subsequent administration of pyridostigmine enabled her to climb the stairs without assistance, thus allowing her to maintain her quality of life for five months. Despite the continuation of chemotherapy, bone and liver metastases developed afterwards. She ultimately died approximately one year after the first symptoms of LEMS.

**Figure 1.** A histological examination of right mastectomy (a) and a biopsy from the cervix (b-d). a: Invasive lobular carcinoma on Hematoxylin and Eosin (H&E) staining. The tumor cells showed Her2: 1+, ER+:<90%, PgR+: 20%. b: Small round cells of the cervix on H&E staining. c, d: Positive staining for chromogranin A and synaptophysin.

**Figure 2.** Total-body positron emission tomography showed an abnormal mass and lymph nodes in the pelvis with left hydronephrosis and hydroureter. However, no abnormal uptake was observed outside of the pelvis.
Discussion

We reviewed the reported cases of paraneoplastic neuromuscular syndrome associated with gynecological or breast carcinoma, but such cases of LEMS with these carcinomas were rare (1-3). Indeed, only one case of recurrent paratracheal and hilar lymphadenopathy for LEMS associated with small cell carcinoma in the uterus was reported (4). Other gynecological or breast tumors with LEMS were uterine leiomyosarcoma (5), intravascular uterine leiomyoma (6) and breast carcinoma (7). The pathological diagnosis of breast carcinoma in this case was invasive lobular carcinoma (namely, adenocarcinoma), which is quite different from small cell carcinoma. Metastasis from breast carcinoma to the cervix uteri is extremely rare, with an estimated incidence of 0.8-1.7% (8). The results of PET in this case supported the notion that the pelvic tumor was not a recurrence of breast carcinoma. However, small cell carcinoma of the female genital tract is reported to be rare, constituting less than 2% of all gynecologic malignancies (9). Although small cell carcinoma of the cervix may often be misdiagnosed as squamous cell carcinoma, the diagnosis in this case was confirmed by an immunopathological study, showing this tumor to be derived from a neuroendocrine tumor. Given these findings, we concluded that LEMS existed simultaneously with breast and small cell carcinoma of the cervix in this patient, although we speculated that the tumor showing VGCC antigen was most likely small cell carcinoma of the cervix, not breast carcinoma. To our knowledge, no other reports have described a case of LEMS associated with synchronous double cancer.

The majority of patients with small cell carcinoma of the cervix present with an advanced disease stage, have lymph node metastasis, and are at a high risk for recurrence and disease progression (10). Urgent therapy is necessary to slow the progression of this disease. Because we prioritized treatment of the uterine cancer with an aggressive progression, we lost a great deal of time that could have been used to identify the cause of the leg weakness.

In conclusion, (i) neuromuscular diseases may be complicated with a malignant tumor; (ii) when leg weakness is seen, we should consider LEMS in the differential diagnosis; (iii) a systemic survey of malignant tumors, including gynecological carcinoma as well as lung small cell carcinoma, should be performed for LEMS patients; and (iv) the accurate diagnosis and urgent treatment such carcinomas are important.

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

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