A 64-year-old man presented with diplopia, muscle weakness, a pulmonary nodule and mediastinal widening on a chest radiograph. He was diagnosed with clinical stage IIIA (T2aN2M0) lung cancer. His neurological symptoms worsened following the initiation of thoracic radiation therapy (60 Gy) and chemotherapy. A diagnosis of myasthenia gravis (MG) was confirmed with a repetitive nerve stimulation test that showed a waning pattern, and a positive edrophonium test, although neither anti-acetylcholine receptor antibodies nor anti-muscle-specific tyrosine kinase antibodies were detected. The ptosis and limb muscle weakness improved with prednisolone and acetylcholinesterase inhibitor treatment, and a partial response of the lung cancer to chemoradiotherapy was obtained. However, the ptosis and limb muscle weakness worsened again following a recurrence of the lung cancer. The herein described case, in which lung cancer and MG occurred and recurred simultaneously, suggests that MG can develop as a paraneoplastic syndrome of lung cancer.

Key words: lung cancer, seronegative myasthenia gravis, paraneoplastic syndrome

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Introduction

Lambert-Eaton myasthenic syndrome is well-known as a neuromuscular paraneoplastic syndrome of lung cancer, especially of small cell lung cancer (1). However, several cases of lung cancer complicated with myasthenia gravis (MG) have also been reported (2-12). MG is an autoimmune neuromuscular disease caused by autoantibodies against nicotinic acetylcholine receptors (nAChRs) in neuromuscular junctions. Clinically, the disease is characterized by such symptoms as muscle weakness and easy fatigability with diurnal variation, and is classified into general and ocular types. Dyspnea and dysphagia develop rapidly once myasthenic crisis (acute exacerbation) occurs.

In MG, 70-80% of cases are positive, and 20-30% cases are negative or seronegative, for serum anti-nAChR antibodies. Recently, antibodies against muscle-specific tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4) were found in the patients who were previously classified as “seronegative MG” (13-15).

We herein report a rare case of lung cancer complicated with seronegative MG.

Case Report

A 64-year-old man exhibited muscle weakness in his lower extremities and diplopia. A magnetic resonance image (MRI) of his head and spine, which had been performed at a local clinic, did not show any abnormality. One month later, he developed shortness of breath and his chest radiograph showed a nodule in the right upper lung field and mediastinal widening. He was referred to the Tokai University Hospital for the examination of the pulmonary nodule. He
had recently quit smoking after 55 years. A chest radiograph and computed tomography (CT) showed a 2 cm in diameter nodule in the upper lobe of the right lung and enlarged mediastinal lymph nodes (Fig. 1). There were no abnormalities found in the thymus. A transbronchial biopsy of the pulmonary nodule was performed, and the pathological examination revealed the proliferation of tumor cells displaying a small nested or tubular architecture. An immunohistochemical, examination determined that the tumor cells expressed the adenocarcinoma-related marker thyroid transcription factor (TTF)-1, squamous cell carcinoma-related markers CK5/6 and p40, as well as neuroendocrine markers (chromogranin A, synaptophysin, and CD56). Based on these data, a pathological diagnosis of poorly differentiated carcinoma that was complicated with seronegative MG was made. Further investigation using positron emission tomography-CT confirmed a diagnosis of lung cancer at the clinical stage of IIIA (T2aN2M0). Based on his neurological symptoms, his Eastern Cooperative Oncology Group performance status was a 2. He was admitted to the hospital for chemoradiotherapy.

At admission a neurological examination revealed bilateral ptosis without eye movement disturbance. His ophthalmological symptoms, such as diplopia and ptosis, exhibited diurnal variation, with worsening in the evening. Slight muscle weakness of his bilateral iliopsoas muscles was observed. His sensory nervous systems and coordination were intact. Thoracic radiation therapy (60 Gy) and chemotherapy with vinorelbine and cisplatin were initiated; however he became bed-bound due to progressive muscle weakness in the upper and lower limbs, and to severe fatigability. No abnormalities were observed on either the head and spinal MRI or the cerebrospinal fluid examination. The repetitive nerve stimulation test of the right median nerve with electromyography revealed a waning pattern, and the edrophonium test was positive (Fig. 2). These findings confirmed the diagnosis of MG. Neither an anti-nAchR nor an anti-MuSK antibody test was positive.

The antiemetic agents dexamethasone (4-8 mg/day, 4 days) followed by prednisolone (5 mg/day) were provided for the chemotherapy-related nausea. Once the diagnosis of MG was confirmed, the daily dose of prednisolone was increased to 10 mg/day and an acetylcholinesterase inhibitor was initiated, which improved the limb muscle weakness. Chemoradiotherapy was effective, and a partial response was obtained. His condition was stable for 4 months until recurrence of the lung cancer occurred. At this time his ptosis and muscle weakness worsened even after the dose of the oral corticosteroid and acetylcholinesterase inhibitor were increased. He received docetaxel and TS-1 treatment as the second- and third-line chemotherapy, respectively. However, neither chemotherapeutic agent was effective and his symptoms of MG did not improve. He died in the course of one year. No autopsy was performed.

**Discussion**

We herein presented a case of poorly differentiated lung carcinoma that was complicated with seronegative MG. A thymoma was absent, and the MG-associated neurological symptoms paralleled with the progression and regression of the lung cancer, thus suggesting that, in this case, the MG developed as a paraneoplastic syndrome of lung cancer.

MG is often associated with thymoma, although it may also accompany other malignant neoplasms. Papatestas et al. reported that, in 1,243 cases with MG, 94 cases (7.4 %) had extrathymic malignancies (16). Similarly, Levin et al. re-

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**Figure 1.** Chest imaging on admission. A chest X-radiograph (a) and computed tomography-scan (b) showed a nodule, 2cm in diameter, in the upper lobe of the right lung, and enlarged mediastinal lymph nodes.

**Figure 2.** Repetitive nerve stimulation test. Repetitive nerve stimulation of the right median nerve revealed a waning pattern.
Table. Reported Cases of Lung Cancer with Myasthenia Gravis.

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Histology of cancer</th>
<th>Stage of cancer</th>
<th>MG type</th>
<th>Anti-nAChR antibody</th>
<th>Meta or Synchronous</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>62 F</td>
<td>Ad</td>
<td>IA</td>
<td>Ocular</td>
<td>+</td>
<td>+</td>
<td>Synchronous: MG developed at the recurrence of lung cancer</td>
</tr>
<tr>
<td>69 F</td>
<td>Ad</td>
<td>NA</td>
<td>General</td>
<td>+</td>
<td>+</td>
<td>Synchronous</td>
</tr>
<tr>
<td>62 M</td>
<td>NSCLC</td>
<td>NA</td>
<td>General</td>
<td>+</td>
<td>+</td>
<td>Synchronous</td>
</tr>
<tr>
<td>46 M</td>
<td>La, Ad</td>
<td>NA</td>
<td>Ocular</td>
<td>+</td>
<td>+</td>
<td>Synchronous</td>
</tr>
<tr>
<td>77 M</td>
<td>Sq</td>
<td>IB</td>
<td>General</td>
<td>–</td>
<td>+</td>
<td>Metachronous: Lung cancer developed 6 years after MG</td>
</tr>
<tr>
<td>55 M</td>
<td>NSCLC</td>
<td>NA</td>
<td>General</td>
<td>–</td>
<td>+</td>
<td>Metachronous: MG developed 2 years after surgery of lung cancer</td>
</tr>
<tr>
<td>65 M</td>
<td>SCLC</td>
<td>NA</td>
<td>General</td>
<td>–</td>
<td>+</td>
<td>Synchronous</td>
</tr>
<tr>
<td>76 F</td>
<td>Ad</td>
<td>IA</td>
<td>General</td>
<td>–</td>
<td>–</td>
<td>Synchronous</td>
</tr>
<tr>
<td>55 M</td>
<td>SCLC</td>
<td>IIA</td>
<td>General</td>
<td>NA</td>
<td>–</td>
<td>Synchronous</td>
</tr>
<tr>
<td>49 M</td>
<td>SCLC</td>
<td>NA</td>
<td>General</td>
<td>NA</td>
<td>–</td>
<td>Synchronous</td>
</tr>
<tr>
<td>57 M</td>
<td>SCLC</td>
<td>IV</td>
<td>General</td>
<td>–</td>
<td>–</td>
<td>Metachronous: Lung cancer developed 18 months after MG</td>
</tr>
</tbody>
</table>


ported that of 188 MG patients examined, 29 (15.4%) presented with an extrathymic malignant tumor (17), and Monden et al. reported extrathymic malignancies in 5 out of 296 (1.7%) patients with MG (18). Leukemia, lymphoma, breast cancer, and colon cancer were the most common extrathymic malignant tumors found in these patients with MG (17, 18).

There are a limited number of lung cancer cases that also present with MG. Table shows the previously-reported cases of MG that were accompanied by lung cancer, of which 7/11 cases were also positive for anti-nAChR antibodies (2-12). In most cases (85%) anti-nAChR antibody-positive MG is accompanied by non-small cell lung cancer. In contrast, Lambert-Eaton myasthenic syndrome is almost exclusively found in patients with small cell lung cancer, but it is rare in cases with non-small cell lung cancer (1). On the other hand, three out of the four cases of seronegative MG (75%) were found in the patients with small cell lung cancer. Katoaka et al. reported a case with seronegative MG in which early-stage adenocarcinoma was also accidentally found, although the causality is unclear in this case (4).

Our case showed worsening of neuromuscular symptoms at the recurrence of the lung cancer, suggesting a causal relationship between seronegative MG and lung cancer. It has been demonstrated that peptides cross-reacting with nAChR are expressed on the thymic epithelium, and induce anti-nAChR antibody-producing lymphocytes in the germinal centers of thymoma (19, 20). Similarly, the nAChR is expressed on human small cell lung cancer cell lines, and bronchial and alveolar epithelial cells (21-23), thus a similar mechanism may account for the production of anti-nAChR antibody in the patients with lung cancer.

Anti-MuSK antibodies were detected in 24-70% of the cases with seronegative MG (13). Our case was negative for anti-MuSK antibodies, however, this result might be a false-negative since the serum sample examined was obtained after the initiation of chemoradiotherapy and corticosteroid treatment. It is also possible that there are other auto-antibodies present, such as anti-LRP4, that were not examined (14, 15).

The treatment of MG includes acetylcholinesterase inhibitors, corticosteroids and other immunosuppressants, high dose intravenous immunoglobulin therapy, plasma exchange or thymectomy. Initially, our case responded well to the combination of acetylcholinesterase inhibitors and corticosteroids, concurrent with chemoradiotherapy for the lung cancer. However, after the lung cancer recurred the neuromuscular symptoms worsened even during treatment with an acetylcholinesterase inhibitor and corticosteroids. This finding suggests that the timely and appropriate treatment of lung cancer is critical to also controlling the symptoms of MG.

In conclusion, we experienced a case of lung cancer that was complicated by seronegative MG. This case indicates that physicians should be aware of MG as a potential paraneoplastic syndrome that may be associated with lung cancer.

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

References
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