Acetylcholine receptor antibody-positive myasthenia gravis associated with small-cell lung cancer
A case report

Masahiro Yamasaki, MD, PhD\textsuperscript{a,∗}, Kunihiko Funashi, MD\textsuperscript{a}, Naomi Saito, MD\textsuperscript{b}, Tomomi Yonekawa, MD, PhD\textsuperscript{c}, Takemori Yamawaki, MD, PhD\textsuperscript{d}, Daisuke Ihara, MD, PhD\textsuperscript{e}, Wakako Daido, MD\textsuperscript{a}, Sayaka Ishiyama, MD\textsuperscript{a}, Naoko Deguchi, MD\textsuperscript{a}, Masaya Taniwaki, MD, PhD\textsuperscript{a}, Noboru Hattori, MD, PhD\textsuperscript{f}

Abstract

Rationale: Only few cases of myasthenia gravis (MG) associated with small-cell lung cancer (SCLC) have been reported, and cases positive for acetylcholine receptor antibody (AChR-ab) are even rarer. The efficacy of standard MG treatment, such as cholinesterase inhibitor therapy, immunosuppressive therapy using steroids and immunosuppressive drugs, plasma exchange, and intravenous immune globulin (IVIg), for these cases is unclear.

Patient concerns and diagnoses: A 71-year-old man complained of bilateral eyelid ptosis. He also presented with dysphagia and masticatory muscle fatigue after chewing. The edrophonium test was positive, and the serum AChR-ab level was increased; therefore, the patient was diagnosed with MG. Computed tomography scan showed a nodule on the left upper lobe of the lung and mediastinal lymphadenopathy. Further examination revealed the lesion as SCLC. Finally, he was diagnosed with AChR-ab-positive MG associated with SCLC.

Interventions and outcomes: Oral pyridostigmine and tacrolimus were administered to treat MG; however, his symptoms worsened. Therefore, methylprednisolone and IVIg were administrated, which temporarily improved his symptoms. However, they remained uncontrolled. Meanwhile, chemotherapy with carboplatin and etoposide was administered to treat his SCLC. The lesions shrunk, and the MG symptoms and serum AChR-ab level also improved.

Lessons: AChR-ab-positive MG may develop as a comorbidity of SCLC. In such cases, management might require treatment for SCLC in addition to the standard MG treatment to stabilize the MG symptoms.

Abbreviations: AChR-ab = acetylcholine receptor antibody, CT = computed tomography, IVIg = intravenous immune globulin, LEMS = Lambert–Eaton myasthenic syndrome, MG = myasthenia gravis, ProGRP = pro-gastrin-releasing peptide, SCLC = small-cell lung cancer.

Keywords: acetylcholine receptor antibody, myasthenia gravis, small-cell lung cancer

1. Introduction

Small-cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer diagnoses\textsuperscript{1} and is often accompanied by paraneoplastic neurological syndrome, such as Lambert–Eaton myasthenic syndrome (LEMS).\textsuperscript{2,3}

LEMS is a rare autoimmune neuromuscular junction disorder. Symptoms include progressive weakness of extremities, cranial muscles, and bulbar muscles like myasthenia gravis (MG).\textsuperscript{1,3} LEMS is distinguished from MG by a characteristic electrophysiological picture and associated autoantibody—LEMS is associated with presynaptic P/Q-type voltage-gated calcium channels antibody, whereas MG is associated with acetylcholine receptor antibody (AChR-ab).\textsuperscript{3,4} A total of 47% to 62% of LEMS were associated with cancers, with SCLC being the most common.\textsuperscript{3} In addition, in a prospective study, LEMS occurred in 3% of SCLC patients.\textsuperscript{5} On the other hand, case reports of MG associated with SCLC are limited,\textsuperscript{6–9} and cases positive for AChR-ab are even rarer.\textsuperscript{6} Moreover, the efficacy of standard MG treatment, such as cholinesterase inhibitor therapy, immunosuppressive
therapy using steroids and immunosuppressive drugs, plasma exchange, and intravenous immune globulin (IVIg), for these cases is unclear.

Herein, we report a case of AChR-ab-positive MG associated with SCLC. Although the patient responded to standard MG treatment, the symptoms remained uncontrolled and only stabilized after chemotherapy for SCLC.

2. Case presentation

A 71-year-old man with a 41-pack-year smoking history presented to our hospital with a chief complaint of bilateral eyelid ptosis. No particular personal and family medical history was reported. Bilateral eyelid ptosis, dysphagia, and masticatory muscle fatigue after chewing were noted on physical examination. The edrophonium test was positive, and the serum AChR-ab level was increased (75 nmol/L; normal 0.2 nmol/L), which was strongly indicative of MG. Therefore, the patient was diagnosed with MG.

Subsequently, on the same day as the patient’s consultation, a computed tomography (CT) scan was conducted to confirm the existence of thymic neoplasm. The CT scan showed a nodule in the left upper lobe of the lung as well as mediastinal lymphadenopathy (Fig. 1A and B), but no thymic lesion was observed. The levels of the serum tumor markers carcinoembryonic antigen, cytokeratin-19 fragment, and pro-gastrin-releasing peptide (ProGRP) were all within the normal range.

On the day of consultation, the patient’s MG was treated with oral pyridostigmine, a cholinesterase inhibitor, and tacrolimus, an immunosuppressive agent, administered daily at 120 and 2 mg, respectively in ambulatory care, and the symptoms of MG were relieved. While the nodule was detected via CT earlier, biopsy could not be performed immediately owing to several already pending cases of other patients who had presented to our hospital for endobronchial examination. This resulted in the patient being placed on the waiting list. However, subsequent disease progression was observed. After fifty-two days from the initiation of MG treatment, the patient was re-admitted to our hospital with developed dyspnea, weakness of the extremities, and worsened ptosis. He was then administered intravenous methylprednisolone (500 mg daily for 3 days) and IVIg (25 g daily for 5 days), and the tacrolimus dosage was increased to 3 mg daily. Pyridostigmine was stopped because the patient reported diarrhea as an adverse effect. A temporarily improvement of the MG symptoms was noted.

Seventy-two days from the date of first consultation, the patient underwent an endobronchial ultrasonography-guided transbronchial needle aspiration, and the tumor was diagnosed as SCLC via histopathological examination of the biopsy specimen (Fig. 1C). Immunohistochemical staining of the specimen showed synaptophysin positivity of the tumor cells (Fig. 1D). In particular, he was diagnosed with SCLC, cT1aN3M1b (M1b: left cervical lymph node metastasis), stage IVB after further examination.

After the lung cancer diagnosis, MG symptoms of dysphagia and diplopia were worsened. Although IVIg was re-initiated, the patient’s condition did not improve. To treat his SCLC, an intravenous cisplatin 80 mg/m² and etoposide 80 mg/m² were administered on day 1 and 1–3, respectively, every 4 weeks, and concurrent radiation therapy (total 45 Gy) was added on days 1–21 of the first cycle. Administration of tacrolimus 3 mg

![Figure 1](image_url). (A) Computed tomography (CT) scan showed a nodule in the lobe of the left upper lung (arrow). (B) CT scan also showed mediastinal lymphadenopathy. (C) Histopathological findings of a biopsy specimen indicated small-cell carcinoma (hematoxylin and eosin stain, magnification ×400). (D) Immunohistochemical staining of the specimen showed synaptophysin positivity of the tumor cells (magnification ×400). CT = computed tomography.
daily was also continued. After 2 cycles of the chemotherapy, a contrast-enhanced CT revealed improvement of the lung cancer lesions (Fig. 2A and B). The MG symptoms were also improved (Fig. 3). The chemotherapy was continued for a further 4 cycles, following which, chest x-rays and serum ProGRP—a biomarker of SCLC—were monitored via monthly follow-up examinations. A CT scan was conducted every 3 months, and the lung cancer lesions were confirmed as being stable. Serum AChR-ab level was decreased to 8.0 nmol/L (Fig. 3) 6 months after initiation of the chemotherapy. To date, the patient is alive with no complaints and no disease progression of MG, and his serum AChR-ab level remain stable and he continues to take tacrolimus 3 mg daily. However, ProGRP increased to 148.8 and 237.9 pg/mL after 9 and 10 months, respectively, from the start of the first-line chemotherapy without tumor progression on CT and brain magnetic resonance imaging. As SCLC progression was noted, second-line chemotherapy of amrubicin hydrochloride mono-therapy was initiated.

Informed consent was obtained from the patient for publication of the findings of this case report.

3. Discussion

The present case shows two important clinical observations. First, of which is that AChR-ab-positive MG may develop in an SCLC patient. To the best of our knowledge, only four cases of MG associated with SCLC have been reported. Moreover, of these, only one case was AChR-ab positive, making our patient...
the second case of AChR-ab-positive MG associated with SCLC to be reported. While the present case initially presented with bilateral eyelid ptosis and edrophonium test positivity, the most typical initial symptom of MG is ocular weakness with asymmetric ptosis and binocular diplopia.\cite{Herbst2008}

On the other hand, the most typical initial symptom of LEMS is proximal weakness in the legs.\cite{Raspotnig2013}

In addition to AChR-ab positivity, positive edrophonium test supports the MG diagnosis.\cite{Herbst2008}

Therefore, although a previous study showed that 13% of LEMS was AChR-ab positive\cite{Fujita2017} and he was not examined via electrophysiology, the case was diagnosed as MG.

Our second observation was that SCLC treatment in addition to the standard MG treatment may be necessary to stabilize the MG symptoms in these cases. The recommended treatment for elderly-onset MG is a combination of low-dose corticosteroids and immunosuppressive agents. Thymectomy is also a treatment option.\cite{Payne2008}

However, in cases of MG associated with thymoma or thymic cancer, the primary diseases should be managed using anticancer treatment such as surgical resection, radiotherapy, and/or chemotherapy.\cite{Hazard2013}

In the present case, the standard MG treatment failed to stabilize the MG symptoms; thus, anticancer therapy was administered, which controlled the MG symptoms. Among three previous case reports of synchronous SCLC and MG,\cite{Herbst2008}-\cite{Raspotnig2013} the efficacy of SCLC treatment for controlling MG was described in only one report.\cite{Fujita2017}

This report also described that combination therapy of standard MG treatment and anticancer treatment stabilized the MG symptoms. This indicates that simultaneous treatment of both the SCLC and MG, that is, standard MG treatment and anticancer therapy, might be necessary to stabilize the MG symptoms.

However, whether immunosuppressive drugs should be continued after the MG symptoms stabilize remains unclear. In general, immunosuppressive drugs are continued as maintenance therapy after the MG symptoms are controlled. Also, in the present case, tacrolimus was continued after stabilization of MG symptoms. The MG symptoms and the serum level of AChR-ab also stabilized. However, clinicians should consider that some immunosuppressive agents have a risk of carcinogenesis. Patients who underwent liver transplant have been reported to have a higher risk of carcinogenesis than those who did not, and tacrolimus-based immunosuppression was a significant risk factor for the increased risk.\cite{Nakamura2010}

Thus, tapering the dose or stopping the use of immunosuppressive agents carefully after the MG symptoms stabilize is reasonable.

In conclusion, we report a case of AChR-ab-positive MG associated with SCLC. AChR-ab-positive MG may develop in an SCLC patient, and management of the MG symptoms might require simultaneous treatment of the SCLC and MG in these cases.

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Author contributions

Data curation: Kunihiko Funaishi, Naomi Saito, Tomomi Yonekawa, Takemori Yamawaki, Daisuke Ihara, Wakako Daido, Sayaka Ishiyama, Naoko Deguchi, Masaya Taniwaki.

Writing – original draft: Masahiro Yamasaki.

Writing – review & editing: Takemori Yamawaki, Noboru Hattori.

References

[1] Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med 2008;359:1367–80.
[2] Raspotnig M, Vedeler C, Storstein A. Paraneoplastic neurological syndromes in lung cancer patients with or without onconeural antibodies. J Neurol Sci 2015;348:41–5.
[3] Schoser B, Eymard B, Datt J, et al. Lambert-Eaton myasthenic syndrome (LEMS): a rare autoimmune presynaptic disorder often associated with cancer. J Neurol 2017;264:1854–63.
[4] Juel VC, Massey JM. Myasthenia gravis. Orphanet J Rare Dis 2007;2:44.
[5] Payne M, Bradbury P, Lang B, et al. Prospective study into the incidence of Lambert Eaton myasthenic syndrome in small cell lung cancer. J Thorac Oncol 2010;5:34–8.
[6] Ohura M, Jjong D, Oh SJ. Seropositive myasthenia gravis associated with small-cell lung carcinoma. J Clin Neuro 2011;7:43–6.
[7] Hazard PB, Bertorini TE, Griffin JP. Myasthenia gravis associated with small cell carcinoma of the lung. J Tenn Med Assoc 1986;79:273–6.
[8] Fujita J, Yamadori I, Yamaji Y, et al. Myasthenia gravis associated with small-cell carcinoma of the lung. Chest 1994;105:624–5.
[9] Miyoshi R, Yamaji Y, Shima S, et al. A case of small cell lung cancer that developed during therapy for myasthenia gravis (Japanese). Nihon Kyobu Shikkan Gakkai Zasshi 1995;33:456–62.
[10] Lennon VA. Serologic profile of myasthenia gravis and distinction from the Lambert-Eaton myasthenic syndrome. Neurology 1997;48(suppl 5):S23–7.
[11] Matsumoto H, Ugawa Y. Myasthenia gravis: a review. J Gen Fam Med 2016;17:211–7.
[12] Wimmer CD, Angele MK, Schwarz B, et al. Impact of cyclosporine versus tacrolimus on the incidence of de novo malignancy following liver transplantation: a single center experience with 609 patients. Transpl Int 2013;26:999–1006.