【 CASE REPORT 】

# Relapsed Myasthenia Gravis after Nivolumab Treatment

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**Abstract:**

Nivolumab is a newly introduced promising therapy for treating lung cancer that restores the anti-tumor immunity by disrupting programmed cell death-1-mediated immuno-suppressive signaling. Although "new-onset" autoimmune diseases are well-known immune-related adverse events, whether or not nivolumab exacerbates "pre-existing" autoimmune disease remains unclear. We herein report a patient with "pre-existing" myasthenia gravis in whom nivolumab was administered that flared up after the treatment with nivolumab. Regardless of the disease stability, nivolumab has the potential to exacerbate an autoimmune disease, and we must pay close attention to each patient's medical history before administering this agent.

**Key words:** non-small cell lung cancer, anti-programmed cell death (PD)-1 monoclonal antibody, nivolumab, immune-related adverse events (irAEs), myasthenia gravis (MG), autoimmune disease

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## Introduction

Nivolumab is a newly introduced, promising therapeutic choice for patients with lung cancer (1, 2). As an immune checkpoint inhibitor, nivolumab disrupts programmed cell death (PD)-1-mediated immunosuppressive signalling, which subsequently restores the anti-tumor immunity (3). Although its adverse effects are relatively mild, immune-related adverse events (irAEs) are infrequent but sometimes life-threatening complications (4). For this reason, physicians hesitate to prescribe treatment with nivolumab in patients with autoimmune disease, as this drug may aggravate their existing autoimmune disease.

However, such concerns are mainly based on the extrapolation of data from animal models or reports of new-onset fulminant autoimmune disease. Historically, subjects with autoimmune disease have been excluded from clinical trials; therefore, the definite effects of nivolumab on existing autoimmune disease are still unclear.

We herein report the case of a patient with pre-existing myasthenia gravis (MG) in whom nivolumab was administered and clearly demonstrate the effects of nivolumab on the autoimmune disease.

## Case Report

A 62-year-old Japanese woman with no smoking history experienced difficulty breathing, and she was diagnosed with primary neuroendocrine carcinoma of the trachea in December 2014 (Fig. 1A-E, arrow head). Since January 2015, she had received cytotoxic chemotherapies with carboplatin (day 1, AUC 6) plus weekly paclitaxel (day1/day8/Day15, 70 mg/m$^2$) every 3-4 weeks for four rounds; then with irinotecan (day1/day8/day15, 100 mg/m$^2$) for 1 round on August 2015. However, she developed severe diarrhea and paralytic ileus, so we abandoned further irinotecan treatment.

With the shrinkage of the tracheal mass, her dyspnea sensation improved, and she showed a good performance status (0-1) without any muscle weakness or arthralgia; however her disease progressed gradually, as suggested by the metastatic lymph node enlargement (Fig. 1D-H, arrowhead).

A thorough medical history-taking confirmed that she had no history of autoimmune disease or any at present, including MG. Therefore, she started biweekly nivolumab treatment (3 mg/kg, 172 mg/kg) in September 2016, resulting in a decrease in the size of her lymph nodes after two rounds of treatment. Subsequently, she noticed general fatigue and
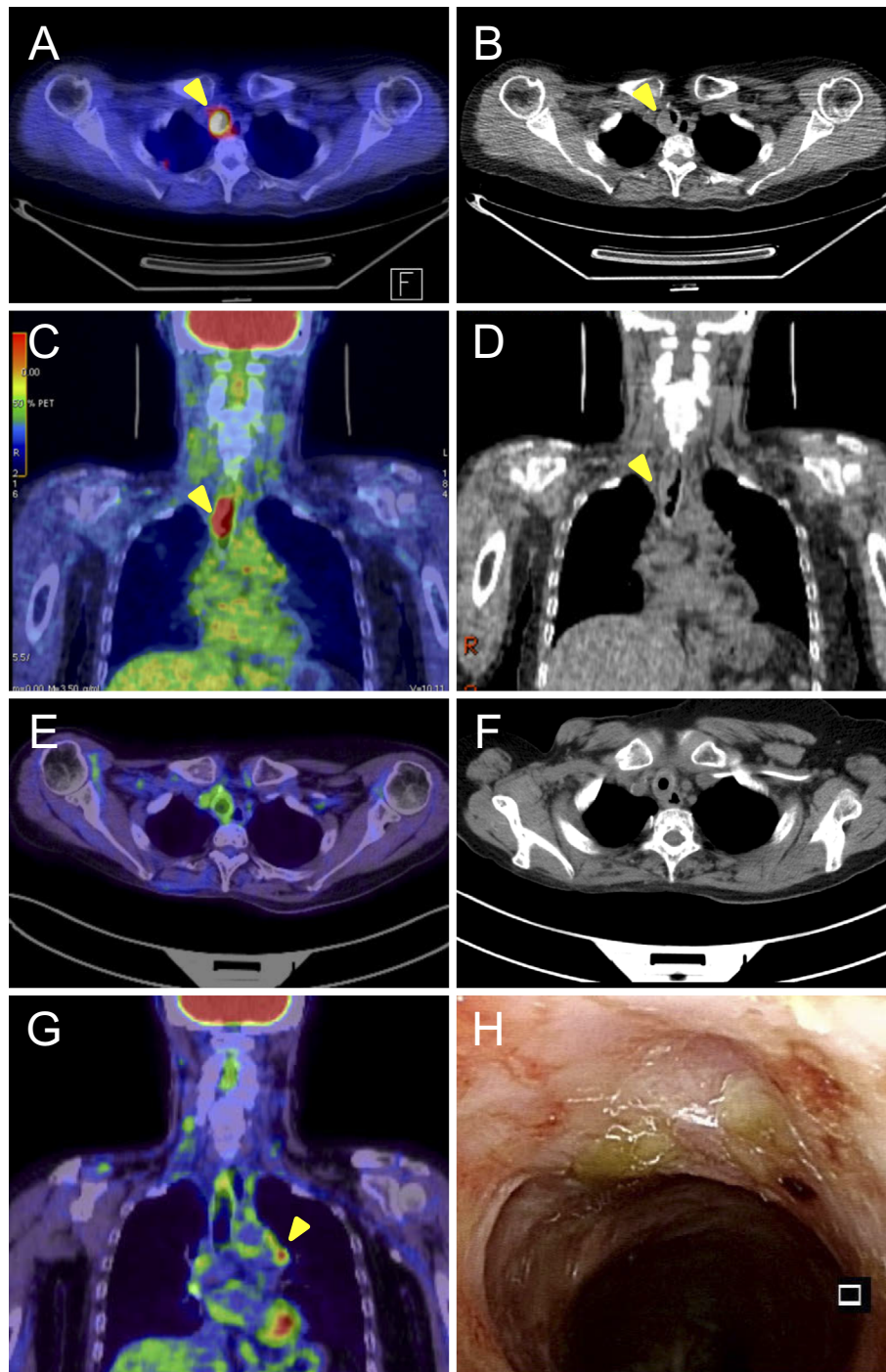
**Figure 1.** The positron emission tomography (PET) and chest computed tomography (CT) findings of the patients with tracheal neuroendocrine carcinoma. At the first admission, PET (A, C) and CT (B, D) showed a mass in the right side of the trachea. In September 2016, PET (E) and CT (F) showed a well-controlled tracheal mass, which was also confirmed by laryngoscope (H); however, PET showed fluoro-deoxyglucose (FDG)-avid striatum lymph node swelling (G).

muscle weakness from mid-October 2016 (25 days after the first treatment with nivolumab), and her blood test results showed a significant increase in the creatine phosphokinase (CK) level (14,229 IU/L; normal range 50-200 IU/L) when she visited for the third treatment with nivolumab (day 34). Before the introduction of nivolumab, her CK level had been confirmed to be in the normal range (82 IU/L at day 1 before the nivolumab treatment), and she did not have any thyroid disease and was taking no medications known to be associated with muscle side effects. She was immediately admitted to her primary hospital with a diagnosis of polymyositis with rhabdomyolysis due to nivolumab, and treatment with methylprednisolone (2 mg/kg, 125 mg/body weight/day) was started. With the administration of a systemic corticosteroid, her symptoms improved gradually, and the CK level decreased favourably (Fig. 2). In November
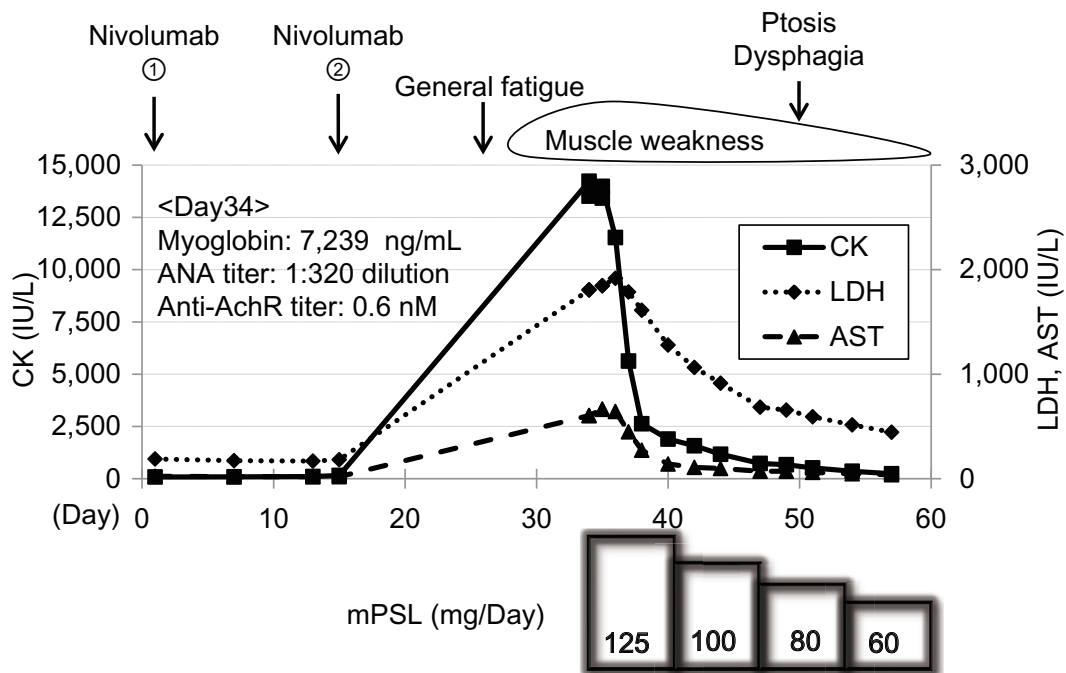
**Figure 2.** The clinical course of the patient after the induction of nivolumab treatment, including laboratory data, symptoms, and treatment. AchR: acethylcholine receptor, ANA: anti-nuclear antibody, CK: creatine phosphokinase, LDH: lactate dehydrogenase, AST: aspartate transaminase, mPSL: methylprednisolone

2016 (day 49), she was transferred to our hospital for the general management of irAEs.

At the time of admission, she had chief complaints of bilateral ptosis and diplopia, despite improvement in her general and proximal muscle strength. In addition, she had slurred speech, swallowing difficulty, and limited facial expression. Initially, she denied a history of autoimmune disease; however, it became apparent from her medical record that she had been treated for ocular type MG 15 years earlier at the neurological department; this diagnosis was supported by a positive edrophonium test result and increased titer of anti-acetylcholine receptor (AchR) antibody (5.8 nmol/L; normal range 0.0-0.3 nmol/L). At that time, she had stopped her regular visits, because her symptoms had gradually improved with the short-term administration of pyridostigmine. Therefore, we concluded that the treatment with nivolumab had induced polymyositis with rhabdomyolysis and the symptoms of pre-existing MG, which was further supported by an increase in the titers of both anti-AchR antibody (0.6 nmol/L) and anti-muscle specific kinase (MuSK) antibody (0.02 nmol/L; normal range 0.00-0.01 nmol/L).

At our hospital, we were unable to detect any elevation in myositis-associated auto-antibodies such as anti-Jo-1 antibody or anti-aminoacyl-tRNA synthetase (ARS) antibody. Interestingly, her cardiac muscle enzymes, such as CK-MB (162 IU/L; normal range 0-12 IU/L) and Troponin-T (0.921 ng/mL; normal range 0.00-0.10), were also elevated, although the findings on both electrocardiogram and cardiac ultrasonography were normal. Diagnostic chest radiograph and computed tomography only revealed lymphadenopathy

due to neuroendocrine carcinoma without any anterior mediastinal mass, such as thymoma. The results of a blood gas analysis showed normal oxygen levels without hypercapnia, and her ocular symptoms and dysphagia resolved rapidly without the use of pyridostigmine. Systemic corticosteroids were tapered slowly, and she returned to her primary hospital.

She is now being followed closely without any treatment, but both the tracheal mass and the metastatic lymph nodes have remained the same size.

## Discussion

Nivolumab is a humanized IgG4 subclass monoclonal antibody against PD-1, which normally functions as a negative regulator of immune cells, such as T lymphocytes (5). The effect of nivolumab on non-squamous non-small-cell lung carcinoma was clearly shown in the clinical trial "CheckMate 057" (1), and its effect on other histological types was recently reported. In 2016, the "CheckMate 032" trial showed the effectiveness of nivolumab plus ipilimumab for treating recurrent small-cell lung cancer (6). In addition, Daido et al. suggested for the first time in 2017 the effectiveness of nivolumab for treating large cell neuroendocrine carcinoma (LCNEC) (7). Although LCNEC is a relatively rare (3%) and aggressive lung cancer (8, 9), no definite evidence-based treatment has yet been shown (9, 10). Our findings are compatible with those in these previous reports suggesting that nivolumab might be a useful choice for the treatment of LCNEC. Further studies to confirm the effects

of nivolumab on various histological types might be necessary.

Although treatment with nivolumab enhances the immune response against tumor cells, it has also been suggested to activate anti-self-immunological reactions, as double-bladed immune modulation seems to invalidate immunological tolerance and then induce new-onset autoimmune diseases (4), such as MG (11, 12). However, whether or not nivolumab really exacerbates existing or remitted autoimmune disease remains unclear (13). Some retrospective analyses have suggested that the toxicity profiles of immune checkpoint inhibitors seemed to be similar between subjects with a history of autoimmune diseases and those without such a history (14, 15), and most of these cases seemed to be mild and therefore manageable with the continuation of treatment. Of note, the incidence of flare might differ based on the autoimmune disease. For example, disease exacerbation seemed to be relatively uncommon for rheumatologic disorders (rheumatoid arthritis, lupus, and psoriasis) and rare with gastrointestinal or neurological disease (16); the presence of an underlying autoimmune disease might therefore not be an absolute contraindication for treatment with immune checkpoint inhibitors.

In our case, nivolumab was administered to a patient with pre-existing MG because she initially did not declare a history of autoimmune disease. With nivolumab treatment, she developed polymyositis with rhabdomyolysis following the relapse of MG symptoms. Therefore, our case is a rare but definite report showing the strict association of nivolumab with new-onset and pre-existing autoimmune disease. In clinical practice, it is sometimes difficult to obtain a thorough medical history, especially when the events occurred so long ago that even the patients have forgotten them. Interestingly, in the present case, nivolumab seemed to induce a relapse of the autoimmune disease despite a long period of remission. This suggests that the indication of nivolumab treatment should not be determined solely based on the present condition (stable or unstable) of the autoimmune disease. In addition, the patient may not have considered MG to be an autoimmunity-associated disease; if so, we healthcare professionals must confirm the medical history from the perspective of its connection with autoimmune diseases. Taking a thorough medical history (not limited to autoimmune diseases) from both the patients and their relatives is undoubtedly necessary; however, social support via medical record sharing through an electronic network would also be help.

Intriguingly, the development of irAEs might be positively associated with a survival outcome, even after nivolumab interruption or treatment with systemic corticosteroids (17). This was suggested in patients with pre-existing autoimmune diseases who were treated with ipilimumab, another immune checkpoint inhibitor (16), and was also true in our case wherein nivolumab had a long-lasting effect on the control of LCNEC. However, while autoimmune diseases might not pose an absolute contraindication to treatment with immune

checkpoint inhibitors (18), we must carefully consider the presence of an underlying autoimmune disease and monitor the treatment course closely.

Our patient had an increased CK level and proximal limb muscle weakness, neither of which are typical findings of MG. We suspect that polymyositis with rhabdomyolysis affected the course of MG. This is supported by the following findings: 1) the titers of anti-AchR and anti-MuSK antibodies were increased, 2) the relatively characteristic localization of muscles (i.e., periorbital region) was not observed, and 3) MG symptoms were present even after the remission of rhabdomyolysis. Such a disease course was also reported in previous reports which described that the appearance of MG might be slightly different from those of typical MG in the subjects treated by immune checkpoint inhibitors (19, 20). In addition, our patient's original MG was "ocular-type" MG, which might also explain the atypical presentation of her neuromuscular symptoms. Therefore, the symptoms of MG may have been another event associated with nivolumab treatment. Although the new-onset or relapse of neurological irAEs seems to be very rare (14, 15), physicians should be sure to monitor patients with pre-existing MG closely.

Why PD-1 blockade by nivolumab induced MG or myositis remains unclear. Recent studies have revealed a link between the PD-1/L1 pathway and humoral immunity. For example, Khan et al. suggested the importance of PD-L1-positive regulatory B cells, which supressed follicular helper T cells ($T_{FH}$ cells) with resultant inactivation of the memory B cells and plasma cells (21). Therefore, humoral immunity against muscle components seems necessary in the pathogenesis of nivolumab-induced MG. In contrast, myositis seems to be cause by the infiltration of CD8+ lymphocytes. Suzuki et al. found that around 0.8% of MG patients were complicated by myositis or myocarditis through such a cytotoxic mechanism (22). Furthermore, in cases of nivolumab-induced MG with myositis, the infiltration of clonally expanded T cells (especially CD8+ T cells) was reported around the muscles (19); therefore, a cytotoxic mechanism also contributes to the pathogenesis of MG-induced myositis. These previous findings suggest that nivolumab might induce both humoral and cytotoxic mechanisms with the resultant clinical presentations of MG and myositis, respectively.

Given that nivolumab is an IgG4 subtype monoclonal antibody, the circulating nivolumab dynamics might be assessed by measuring the serum IgG4 titer. In the present case, the IgG4 titer (normal range: 4.0-108.0 mg/dL) decreased gradually from 112 mg/dL (day 36) to 83 mg/dL (day 49) as the systemic steroid exerted its effect. Of course, the effect of nivolumab might not necessarily correspond to the serum antibody level, but the IgG4 titer would show how much nivolumab was still left in the body; therefore, the serum IgG4 evaluation might be a useful index for monitoring drug-associated side effects.

In conclusion, this was a rare case in which nivolumab

treatment was strongly associated with the exaggeration of a "pre-existing" autoimmune disease (in our case, MG). Underlying autoimmune disorders require close monitoring, but they might not be an absolute contraindication to nivolumab treatment in the era of personalized medicine.

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

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