CASE REPORT

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Nivolumab for the treatment of malignant melanoma in a patient with pre-existing myasthenia gravis

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ABSTRACT

A 79-year-old man with lymph node recurrence of malignant melanoma received nivolumab, an anti-programmed death 1 (PD-1) monoclonal antibody. He had pre-existing ocular myasthenia gravis (MG) and a continued small amount of corticosteroid. Grade 3 creatine phosphokinase elevation appeared after two doses of nivolumab, and the treatment was postponed until it improved to grade 1. After three doses of nivolumab, he experienced diplopia and facial muscle weakness which were consistent with an acute exacerbation of MG, and the symptoms relieved without additional treatment for MG. He achieved shrinkage of metastasis after ten doses of nivolumab. Although a case who died due to MG after administration of nivolumab was reported recently, pre-existing MG is considered not to be always a contraindication of nivolumab.

Key Words: malignant melanoma, nivolumab, anti-programmed death 1 (PD-1) monoclonal antibody, myasthenia gravis, creatine phosphokinase

INTRODUCTION

Nivolumab is an anti-programmed death 1 (PD-1) monoclonal antibody and has been reported to be useful for treatment of cancers including malignant melanoma. A recent case report documenting fatal nivolumab-related myasthenia gravis (MG)[1)] has caused concern about the risk of increased toxicity in patients with pre-existing MG who receive nivolumab for the management of metastatic melanoma. It is unclear what will occur if a patient with pre-existing MG receives nivolumab.

CASE REPORT

A 79-year-old man began to receive immune checkpoint therapy with nivolumab at a dose of 2 mg/kg every 3 weeks for the management of submandibular lymph node metastasis from malignant melanoma, which arose in his forehead 3 years ago and was previously treated with cytotoxic chemotherapy. The patient had a >20-year history of ocular MG according to Osser-

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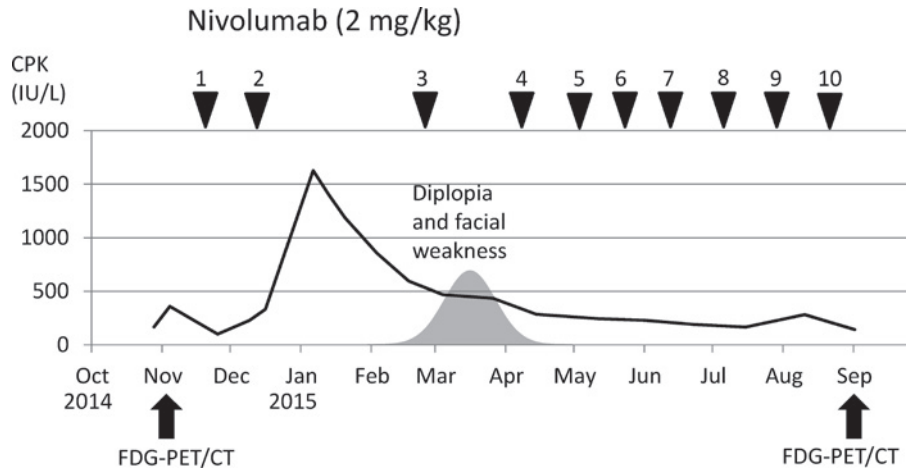

Fig. 1 Clinical course

man's classification. Durable remission was maintained by treatment with oral corticosteroids (3 mg every other day). A routine serum chemical test on day 43, after the patient had received 2 doses of nivolumab, revealed a grade 3 elevation of the creatine phosphokinase (CPK) level to 1,627 IU/L (institutional normal range, 62 to 287 IU/L) (Fig. 1). The patient did not experience muscle pain, muscle weakness, or any other symptoms. The results of thyroid function tests were normal. The CPK level decreased to 469 IU/L on day 100 and was at worst grade 1 subsequently. However, after the third dose of nivolumab, the patient had diplopia, facial muscle weakness, and difficulty in drinking water on day 106. These signs and symptoms were consistent with an acute exacerbation of MG. Positive results of an acetylcholine receptor antibody test (20.0 nmol/L, normal range, ≤0.2 nmol/L) supported the diagnosis. The symptoms resolved rapidly without "rescue" therapy with pyridostigmine or increased doses of corticosteroids. Apparent shrinkage of the metastatic lymph nodes was observed on computed tomographic imaging after the patient had received 10 doses of nivolumab (Fig. 2).

DISCUSSION

Anti-PD-1 antibodies enhance immune response to tumor cells and to normal host tissues as well, and cause adverse effects related to the autoimmune diseases.[2] Other immune checkpoint inhibitors, anti-programmed death-ligand 1 (PD-L1) antibodies and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibodies, also have been reported to cause immune-related diseases, such as myositis and myasthenia gravis.[3-5]

The present case with pre-existing MG showed CPK elevation, and symptoms suggesting deterioration of MG such as diplopia and facial muscle weakness after nivolumab administration. After suspending nivolumab, CPK decreased and symptoms improved, and nivolumab was able to be administered safely. Since CPK elevation is not usually observed in MG patients, we could not exclude the possibility the symptoms were caused by myositis but not by MG. Although it is not easy to distinguish symptoms of MG from those of myositis, the difference in the time of onset of CPK elevation and that of symptom exacerbation tends to indicate that the symptoms derived from MG rather than myositis.

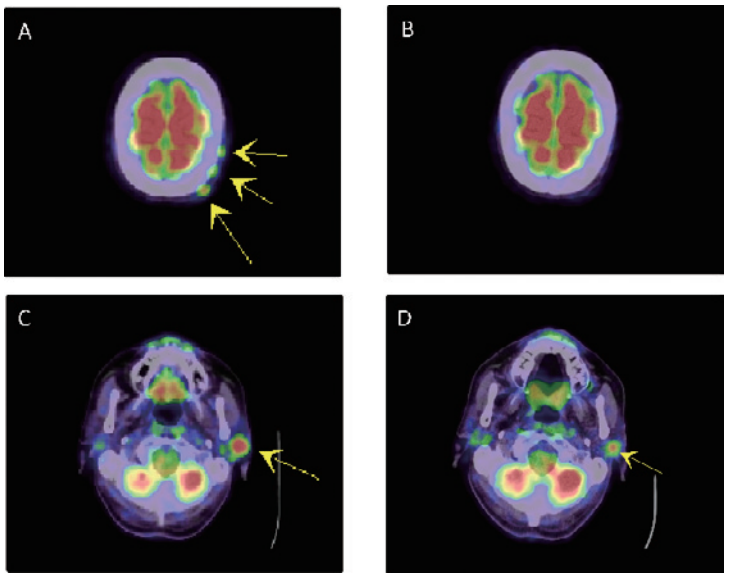

Fig. 2 FDG-PET/CT before and after administration of nivolumab
Uptake of lymph node metastases decreased after ten doses of nivolumab.
A and C: before treatment. B and D: after treatment.
A and B: head. C and D: neck.

In a case previously reported[1], an acetylcholine receptor antibody test was low-titer positive (2.9 nmol/L) before the onset of MG induced by nivolumab. As for the present case, the antibody was 15.2 nmol/L one year and seven months prior to the beginning of nivolumab treatment, and it increased to 20 nmol/L when MG was exacerbated. The antibody titer is considered to be useful to predict the onset of MG and to observe MG symptoms.

There are no clear criteria to decide whether nivolumab is allowed to be restarted after discontinuation of the administration due to adverse events such as CPK elevation or MG exacerbation. We consider that the restart with careful observation might be allowed when the adverse events improved to mild symptoms, for instance, NCI-CTCAE Grade 1.

Despite the transient exacerbation of MG-associated symptoms, this patient-tolerated nivolumab therapy went well and provided substantial benefit, suggesting that the drug is not necessarily contraindicated in patients with preexisting MG. Nivolumab-related MG might have a distinct etiological background from that of primary MG.

CONFLICTS OF INTEREST

Yuichi Ando received honoraria from Ono Pharmaceutical Co., Ltd., and has held a consultant/advisory role with Ono Pharmaceutical Co., Ltd..

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