〈Letter to the Editor〉

Successful reinstitution of nivolumab in combination with corticosteroids for metastatic malignant melanoma with myasthenia gravis as an immune-related adverse event

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Nivolumab is an immune checkpoint inhibitor directly targeting a negative immunoregulatory molecule of T cells, programmed cell death protein 1 (PD-1), with anti-tumor immune activity.The clinical benefits from anti-PD-1 antibodies against melanoma is quite remarkable. However, various immune-related adverse events (irAEs), such as interstitial pneumonia, have been reported[1)]. Grade3-4 irAEs were observed in 11.7%[1)], and 9.9%[2)] of nivolumab-treated melanoma patients[1)]. Myasthenia gravis (MG) is an autoimmune disease mediated by B-cells, which affects neuromuscular junctions. Anti-acetylcholine receptor antibodies (AChR-Ab) are highly specific for diagnosis[3)]. Several cases of the onset of MG by anti PD-1 antibody have been reported[4－8)]. Here, we report a case that a patient with melanoma developed MG after the second administration of nivolumab. The metastatic melanoma was successfully controlled by reinstituting nivolumab in combination with a low dose of corticosteroids.

A woman in her 70s presented with malignant melanoma in the middle of the lumbar region. Primary resection and sentinel lymph node (SLN) biopsy were performed. Pathologically, right inguinal SLN metastasis was positive. Then, right inguinal lymph node dissection (LND) was performed. Postoperatively, interferon beta treatment was initiated as an adjuvant therapy. Approximately 5 months after surgery, several subcutaneous, in-transit and lymph node metastasis were observed. After possible resection of these metastatic lesions, nivolumab therapy was started with a dose of 2 mg/kg every 3 weeks. Focal adjustment disorder appeared around 10 days after the second administration, then ptosis (Fig. 1) and muscle weakness were observed. AChR-Ab was elevated to 4.0 nmol/L (normal range ≤0.2 nmol/L). In addition, single fiber electromyography study was positive because of increased jitter in the frontalis muscle. MG was diagnosed. Nivolumab administration was discontinued and daily oral administration of 10 mg of prednisolone (PSL) and anticholinesterase drug was started, followed by

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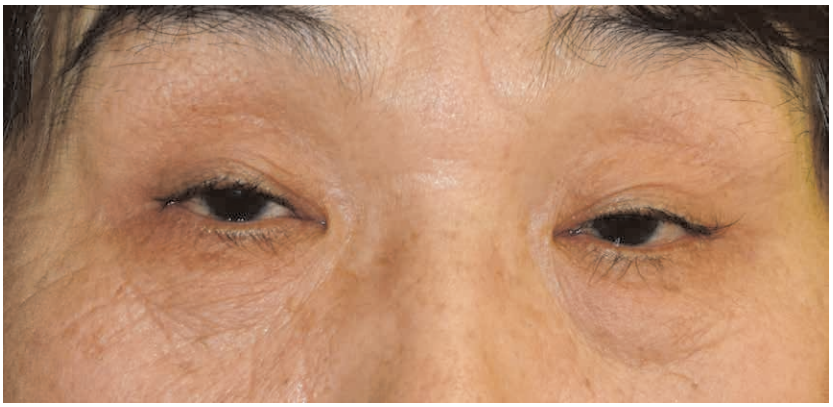

Fig. 1 Bilateral ptosis 24 days after the second treatment of nivolumab

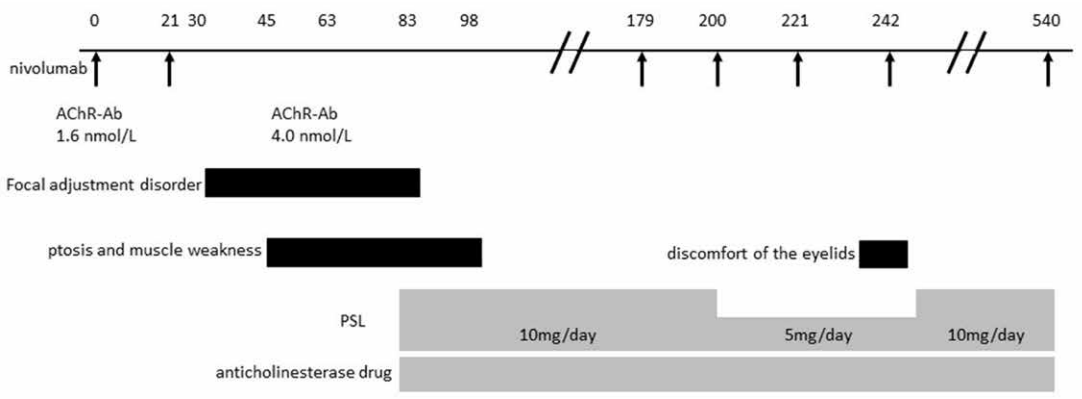

Fig. 2 The summary of the clinical course

improvement of the symptoms. Because lymph node metastasis gradually worsened, administration of 2 mg/kg of nivolumab every 3 weeks was reinstituted on the 158th day from the second administration in combination with PSL 10 mg daily. Since recurrence of MG was not observed, PSL was reduced to 5mg after the second restart. Due to that the patient complained discomfort of the eyelids after several weeks, the dose of PSL was increased again to 10 mg. After that, nivolumab treatment was able to be continued every 3 weeks. Lymph node enlargement was controlled, and the patient had a stable disease state for about 18 months. Fig. 2 summarizes the clinical course.

In this case, AChR-Ab was slightly elevated to 1.6 nmol/L using her serum before nivolumab administration in the retrospective examination. Similar cases of MG with AChR-Ab subclinically before nivolumab therapy had been reported[7,8]. Sakthivel P *et al*. showed that an expression of PD-1 on T cells and its ligand PD-L1 on monocytes was elevated in MG patients and suggested that PD-1 and PD-L1 might have a regulatory role behind autoimmune human MG[9]. By disrupting interaction between PD-1 and its ligands, it is assumed that nivolumab induced T-cell activation, resulting in elevation of AChR-Ab and consequently induced MG. There is no specific and general method to solve a dilemma related to reinstitution of nivolumab in serious irAE cases. The method

employed should be determined according to severity of MG in each case, because different clinically severe, prolonged, and even fatal case has been reported[7]. We demonstrated a method which was able to resume nivolumab without regression of MG in combination with PSL 10 mg daily. Although attenuation of the effect of nivolumab by corticosteroids is possible, the development of tumor was suppressed and the effect of nivolumab has been preserved in this case. Even if nivolumab therapy is forced to be discontinued in irAE cases, it is worth considering reinstitution of it with prednisolone in combination.

CONFLICT OF INTEREST

None

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