Alternative to steroid therapy for myasthenia gravis and myositis occurring as immune-related adverse events

1. Introduction

Immunotherapy with immune checkpoint inhibitors has dramatically changed the treatment landscape for patients with cancer. Nivolumab, one of the anti-programmed cell death-1 agents, is now the most widely used immune checkpoint inhibitor in the treatment of various advanced cancers. Programmed cell death-1 blockade leads to enhancement of the immunity against cancers in the tumor microenvironment; however, this shift in the balance of the immune system can also produce immune-related adverse events involving multiple organs. Myasthenia gravis (MG) is known to be a serious immune-related adverse event in neuromuscular disorders that is characterized by concomitance with myositis and/or myocarditis [1]. A neurologist in cooperation with an oncologist plays an important role in the safety management of cancer immunotherapy.

2. Case report

A 79-year-old Japanese woman who suffered from advanced-stage renal cell cancer with multiple lung metastases received six different regimens of cancer treatment, but their effects were insufficient. Although she took pravastatin, she had no history of autoimmune diseases or a smoking habit. She received two cycles of nivolumab monotherapy as the seventh regiment on day 1 and day 19. After she first noticed back pain and bilateral ptosis on day 24, she gradually developed difficulty in standing and walking until day 30. A neurological examination revealed bilateral ptosis and grade 4 trunk and limb weakness assessed using manual muscle strength (Medical Research Council scale grade). An administration of edrophonium resulted in improvement of the ptosis, but not of the neck and limb weakness. Her serum creatine kinase level was increased to 5,350 IU/L. Neither anti-acetylcholine receptor nor anti-muscle-specific kinase antibodies were detectable. There were also no autoantibodies against signal recognition particles, 3-hydroxy-3-methylglutary-coenzyme A reductase, or anti-aminoacyl-tRNA synthetase. However, anti-striational autoantibodies including both anti-titin and anti-Kv1.4 antibodies were detected using cytometric cell-based

assays. Muscle MRI demonstrated inflammatory changes of the proximal lower limb muscles and paraspinal muscles. With regard to electrophysiological evaluation, repetitive stimulation of the ulnar nerve demonstrated a 20% decrement of the compound motor action potential. There were no changes in the electrocardiogram and no reduction of the ejection fraction on the echocardiogram. Based on these findings, we diagnosed her as having nivolumab-associated MG (MG Foundation America class IIa with a quantitative MG score of 10) accompanied by myositis.

We hospitalized her in the neurological unit on day 33 and then closely monitored her clinical course. After admission, her symptoms gradually improved, and the ptosis and limb weakness disappeared on day 41 without corticosteroids. Her muscle pain also disappeared, and her serum creatine kinase level returned to normal range. The third cycle of nivolumab therapy was cancelled, and she went back home on day 45. Sorafenib was administered to her as the eighth regimen; however, it was also stopped due to proteinuria. Although she did not receive cancer treatment afterwards, her renal cell cancer remained stable for 22 months.

3. Discussion

Prompt diagnosis and initiation of steroids therapy are recommended for the treatment of neuromuscular immune-related adverse events in accordance to the guidelines of the American Society of Clinical Oncology and the European Society for Medical Oncology. Contrary to these recommendations, we did not select steroids therapy for MG and myositis based on our careful follow-up during the patient's hospitalization. Fortunately, her neuromuscular symptoms disappeared within 17 days. The clinical course of the present patient suggests that generalized MG and myositis occurring as immune-related adverse events could be curable only through the discontinuation of immune checkpoint inhibitors. It should be remembered that myocarditis should be fully excluded in the clinical setting because it is usually lethal.

The development of immune-related adverse events is associated with a survival benefit in patients with melanoma and non-small-cell lung cancer [2, 3]. In the same way, we consider

that only two cycles of nivolumab monotherapy may have been effective for treating our patient's renal cell cancer. The use of corticosteroids for the treatment of immune-mediated adverse events in cancer patients is not associated with decreased efficacy of immune checkpoint inhibitors [4]. In contrast, since corticosteroids have an immunosuppressive effect on T-cell function, it is notable that the use of these agents potentially decreases the efficacy of immune checkpoint inhibitors. In fact, Arbour et al. reported that the baseline corticosteroid use of over 10 mg of prednisone was associated with poorer outcomes in patients with non-small-cell lung cancer who were treated with programmed cell death-1 blockade [5].

We emphasize that not selecting steroids therapy for MG and myositis may enhance the effect of the cancer immunotherapy, resulted in her longer survival.

Conflicting interests

Authors declare no Conflict of Interests for this article.

Disclosure of ethical statement

All informed consent was obtained from the patient.

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