Case Report

A Case of Nivolumab-Induced Severe Mononeuropathy Multiplex and Rhabdomyolysis

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1.Introduction

Nivolumab, one of the immune checkpoint inhibitors, is a human IgG4 monoclonal antibody to human programmed cell death-1 (PD-1). The drug has significant clinical benefits in the treatment of metastatic melanoma, non–small cell lung cancer, and renal cell carcinoma [1–4]. However, it may cause immune-related adverse events (irAEs) in various organs. Although neurological disturbances due to irAEs are rare [5], our patient suffered from concurrent severe mononeuropathy multiplex and rhabdomyolysis.

2. Case Presentation

An 81-year-old Japanese man with no history of autoimmune disorders and no other significant past medical history underwent tumorectomy for primary anterior mediastinal malignant melanoma, and 4 years later, he was administered nivolumab (3 mg/kg) for multiple liver metastases. On the 8th day after nivolumab administration, he developed symmetric weakness and sensory disturbance after nivolumab monotherapy. He was diagnosed with nivolumab-induced mononeuropathy multiplex and rhabdomyolysis based on serologic examination, muscle biopsy, magnetic resonance imaging of the limbs, and a nerve conduction study. A course of intravenous methylprednisolone (mPSL) was initiated at 1 g/day for 3 days. After that, oral prednisolone (PSL) was started at 1 mg/kg/day and gradually tapered. Limb muscle strength improved, but when PSL was reduced to 0.3 mg/kg/day, the weakness recurred, and a nerve conduction study showed exacerbation of mononeuropathy multiplex. The patient was again administered intravenous mPSL (0.5 g/day for 3 days) followed by oral PSL at 0.5 mg/kg/day and his neurological symptoms improved. Nivolumab, an immune checkpoint inhibitor, is used for the treatment of advanced melanoma and other cancers and causes various immune-related adverse events (irAEs). However, neurological irAEs related to nivolumab are rare. Furthermore, there are no reports of simultaneous nerve and muscle impairment. Unexpected irAEs affecting various organs should be recognized and treated appropriately.
Autoantibodies to the following were all negative: acetylcholine receptor, signal recognition particle, gangliosides (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, and Gal-C), nuclear antigens, neutrophil cytoplasmic antigens, Jo-1, thyroglobulin, and thyroid peroxidase. Cerebrospinal fluid was negative for malignant cells and showed normal levels of protein (27 mg/dL) and glucose (85 mg/dL). The number of cells was not increased (1/μL). A nerve conduction study showed mononeuropathy multiplex (Table 1); on the 10th day after nivolumab administration, the left ulnar nerve was severely impaired, but the other three nerves of upper limbs were relatively spared. In addition, repetitive stimulation tests (3 and 5 Hz) of the bilateral trapezius muscles showed no abnormalities. T2-weighted magnetic resonance imaging scans with and without fat suppression demonstrated diffuse high signal intensity in the muscles of the lower limbs and partially edematous changes in the subcutaneous tissues (Figure 1). Skin biopsy of the left lower leg with livedo

| Nerve (right side) | Day of examination | Wristankle latency, ms (amplitude) | Elbowkneel latency, ms (amplitude) | Velocity (m/s) |
|--------------------|--------------------|-----------------------------------|-----------------------------------|---------------|
| Median             |                    |                                   |                                   |               |
| Right Motor        | 10                 | 3.30 (16.7 mV)                    | 6.93 (16.4 mV)                    | 57.9          |
|                    | 38                 | 3.39 (11.6 mV)                    | 8.16 (2.7 mV)                     | 45.0          |
| Sensory            | 10                 | 2.64 (2.3 μV)                     | —                                 | 51.1          |
|                    | 38                 | 2.98 (3.7 μV)                     | —                                 | 50.3          |
| Left Motor         | 10                 | 3.51 (3.9 mV)                     | 7.32 (3.5 mV)                     | 52.5          |
| Sensory            | 10                 | 2.46 (4.3 μV)                     | —                                 | 64.2          |
| Right Motor        | 10                 | 2.67 (7.7 mV)                     | 7.32 (4.0 mV)                     | 44.1          |
|                    | 38                 | 2.76 (11.2 mV)                    | 7.32 (10.9 mV)                    | 54.2          |
| Sensory            | 10                 | 2.30 (2.3 μV)                     | —                                 | 60.9          |
|                    | 38                 | 2.42 (2.1 μV)                     | —                                 | 53.7          |
| Ulnar              |                    |                                   |                                   |               |
| Right Motor        | 10                 | 2.88 (0.10 mV)                    | 8.07 (0.05 mV)                    | 33.7          |
| Sensory            | 10                 | n.e.                              | n.e.                              | —             |
| Left Motor         | 10                 | 4.30 (0.07 mV)                    | n.e.                              | —             |
| Sensory            | 10                 | n.e.                              | n.e.                              | —             |

Day of examination, number of days since nivolumab administration; n.e., not evoked. Abnormal data are italicized.

Figure 1: MRI of the lower limbs ((a)–(c) thighs; (d)–(f) legs). T2-weighted ((a) and (d)) and short T1 inversion recovery images (fat suppression method; (b), (c), (e), and (f)). The level of cross-section images ((c) and (f)) is indicated by red dashed lines in the coronal images ((b) and (e)).
Nivolumab, an anti–PD-1-specific monoclonal antibody, has significant therapeutic effects in the treatment of various cancers, such as metastatic melanoma, non–small cell lung cancer, and renal cell carcinoma [1–4]. However, it is also associated with immune-related adverse events (irAEs) which are attributed to excessive T-cell activation. In our case, nivolumab administration initially resulted in bilaterally symmetric weakness of the proximal muscles accompanied by a prominent elevation of myogenic enzyme levels due to rhabdomyolysis, followed a few days later by muscular irAEs. Corticosteroids were somewhat effective, dose reduction resulted in recurrence and worsening of the neurological impairment. Despite the fact that autoantibody tests were negative, the underlying mechanism in this case was considered to be an immune response caused by nivolumab. Steroids may need to be decreased very carefully in such patients.

Nivolumab has remarkable clinical benefits for patients with various cancers and will be used more and more widely in the future. We should recognize the presence of irAEs in various organs when using immune checkpoint inhibitors such as nivolumab.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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3. Discussion

Nivolumab treatment has been effective for neurological or muscular irAEs [12]. In our case, the patient responded to treatment with corticosteroids, but dose reduction resulted in recurrence and worsening of the neurological impairment. Despite the fact that autoantibody tests were negative, the underlying mechanism in this case was considered to be an immune response caused by nivolumab. Steroids may need to be decreased very carefully in such patients.

Although corticosteroids are often used to treat irAEs, no standard treatments have been established for rare irAEs such as those affecting muscles and nerves [11]. There are also cases in which plasmapheresis or intravenous immunoglobulin has been effective for neurological or muscular irAEs [12]. In our case, the patient responded to treatment with corticosteroids, but dose reduction resulted in recurrence and worsening of the neurological impairment. Despite the fact that autoantibody tests were negative, the underlying mechanism in this case was considered to be an immune response caused by nivolumab. Steroids may need to be decreased very carefully in such patients.

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