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Case Report

Immune-related Neuromuscular Junction Disorder after Immune Checkpoint Inhibitor Treatment

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Abstract

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment and prolonged the survival of patients with various malignancies. Nevertheless, the expanded usage of ICIs is associated with increased reports of immune-related adverse events (irAEs), some of which can impair functional outcomes and worsen the prognosis. We present a fatal case of a patient presenting with progressive generalized weakness diagnosed with immune-related neuromuscular junction (NMJ) disorder after nivolumab treatment. By describing this case, we hope to raise awareness of rare irAEs such as immune-related NMJ disorder because prompt intervention is essential to minimize long-term sequelae and improve outcomes.

Keywords: Immune-related adverse event, myasthenia gravis, neuromuscular junction disorder

Introduction

Advances in immunotherapy, especially immune checkpoint inhibitors (ICIs), have changed the treatment landscape of various malignancies. Despite its efficacy, immunotherapy may cause immune-related adverse events (irAEs).[1] The manifestations of irAEs are unique and can involve any organ system, and although some irAEs are rare, they can be life-threatening.[2] Early recognition and appropriate management of these events are crucial. Here, we present a devastating complication of a neurologic irAE, neuromuscular junction (NMJ) disorder, in a patient with metastatic gastric cancer.

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Case Report

A 78-year-old woman with type 2 diabetes mellitus (DM) and dyslipidemia initially presented with weight loss and postprandial vomiting. She had received an endoscopic biopsy diagnosis of gastric adenocarcinoma of the cardia in mid-2019. The stage was classified as cT4aN3M1 according to the eighth edition of the American Joint Committee on Cancer, and the metastatic sites were para-aortic lymphadenopathies. HER2 immunohistochemical staining was classified as 3+.

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She received cisplatin and fluorouracil as the first-line treatment for 3 months. Because the disease progressed under this treatment, paclitaxel was administered as salvage therapy; however, new metastases developed in the liver and lungs 3 months following the start of paclitaxel. She applied for nivolumab, an anti-programmed cell death protein-1 (anti-PD-1) antibody, through the National Health Insurance (NHI) program of Taiwan, and agreed to undergo trastuzumab treatment while awaiting the results of her application. Two months after the addition of trastuzumab, the tumors decreased in size. At this time, the NHI program approved the nivolumab application, which was then added to her trastuzumab and paclitaxel treatment.

However, 1 month after initiating the triplet combination, we noted elevated transaminase levels (an aspartate aminotransferase level of 142 U/L and an alanine aminotransferase level of 137 U/L), which suggested the presence of immune-related hepatitis. Moreover, she reported progressive limb weakness accompanied by blurred vision, hoarseness, and frequent choking. A physical examination revealed that her Eastern Cooperative Oncology Group performance status had worsened from 1 to 3 and that the muscle power of the proximal limbs was relatively weak without asymmetry [Figure 1]. We also observed conjugate gaze palsy, ptosis, facial diplegia, flaccid dysarthria, neck weakness, and reduced vital capacity (800 mL). Chest radiograph demonstrated remarkable cardiomegaly and elevated right hemidiaphragm, both of which existed before the administration of nivolumab [Figure 2]. Neuromuscular junction (NMJ) disorder was highly suspected, although the patient's anti-acetylcholine receptor (AChR) antibody level was normal. A nerve conduction velocity test revealed sensorimotor polyneuropathy with axonal degeneration. These changes were probably due to chemotherapy-induced neurotoxicity and DM. Electromyography revealed mixed neurogenic and myopathic changes, and a repetitive nerve stimulation test (RNST) did not indicate a decremental response.

The patient also complained of chest tightness, and creatine kinase (CK) (288 U/L), creatine kinase-myocardial band (CK-MB) (148 U/L), and troponin T (TnT) (>10,000 ng/L) levels were elevated. An electrocardiogram [Figure 3] showed a QS pattern at the inferior and precordial leads, with poor R-wave progression and T-wave inversion at leads III and V1–2. In addition, echocardiography demonstrated a regional wall motion abnormality in the left anterior descending artery territory without reduced left ventricle ejection fraction or other structural abnormalities. No dynamic changes in serial CK or CK-MB levels [Figure 4] were noted, and the level of TnT was only marginally abnormal. The overall probability of myocarditis was low, and the electrocardiogram and echocardiography findings strongly suggested remote myocardial infarction. We concluded that the extremely high TnT level and mildly elevated CK level were attributable to myopathy and not suggestive of myositis.

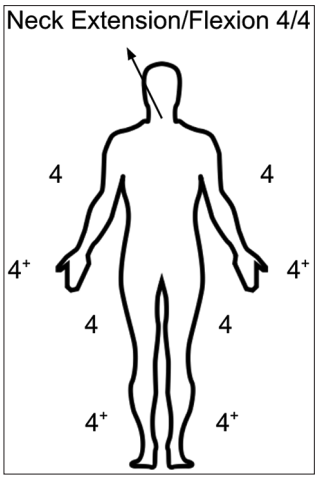

Figure 1: An illustration demonstrating relatively weak muscle strength of the proximal limbs on a scale from 0 to 5 (0 indicating no muscle contraction and 5 meaning normal)

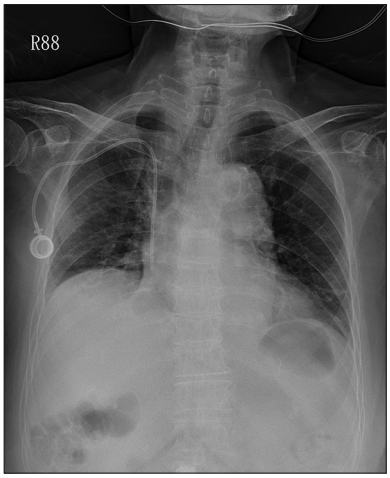

Figure 2: A chest radiograph revealing cardiomegaly and elevated right hemidiaphragm

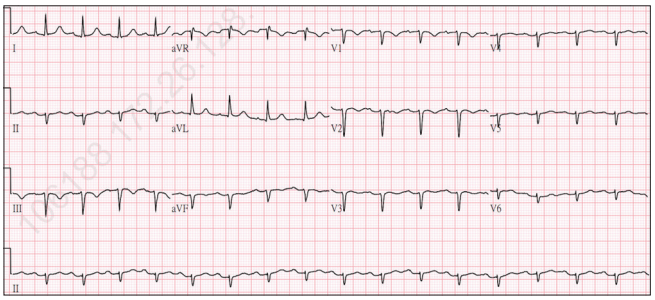

Figure 3: An electrocardiogram demonstrating a QS pattern at the inferior and precordial leads, with poor R-wave progression and T-wave inversion at leads III and V1–2

The absence of evolving ascending weakness and sensory abnormalities, except for existing chemotherapy-induced peripheral neuropathy, may not be suggestive of Guillain-Barré syndrome. Because of her advanced age, her family refused a lumbar puncture to obtain cerebrospinal fluid. Central nervous system imaging studies were not conducted given

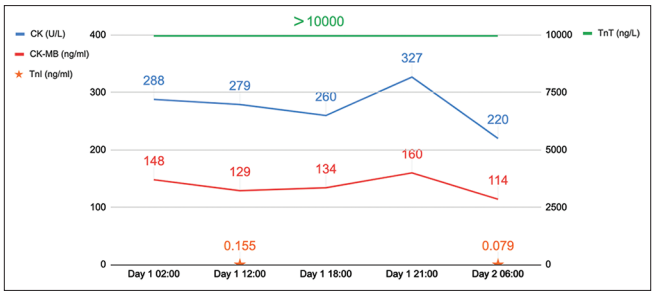

Figure 4: Serial examination results of creatine kinase (CK), creatine kinase-myocardial band (CK-MB), troponin I (TnI), and troponin T (TnT)

the absence of neurologic asymmetry and deteriorating bulbar symptoms.

Consequently, the patient was tentatively diagnosed with immune-related NMJ disorder with myopathy. In addition to pyridostigmine, methylprednisolone pulse therapy was administered; however, proximal weakness and reduced vital capacity remained 1 week later. She then received three sessions of double-filtration plasmapheresis (DFPP), which was discontinued on her request because she opted instead to receive conservative treatment. Mixed respiratory failure occurred 1 week after the initiation of DFPP, and she died 24 h after developing respiratory failure.

Discussion

This case report describes a patient who experienced a neurologic irAE after the administration of an anti-PD-1 antibody. The disease course was rapid and eventually fatal. In addition to the immune-related NMJ disorder presented here, neurologic irAEs include encephalitis, meningitis, myelitis, meningoradiculitis, Guillain-Barré-like syndrome, and peripheral neuropathy.[3] The incidence of all grades of neurologic irAEs has been reported to range from 3.8% to 6.1% with single-agent ICI treatment and 12.0% with a combination of PD-1 blockade and an anti-cytotoxic T-lymphocyte-associated protein-4 antibody.[3] High-grade neurologic irAEs are rare, with an incidence of <1%;[3] however, the mortality rate of these events can range from 12% to 17%.[2]

Immune-related NMJ disorders are rare. A study that reviewed postmarketing surveys of nivolumab in Japan reported NMJ disorders in 12 patients (0.12%) among 9869 individuals treated with nivolumab.[4] The disease progressed rapidly (2–7 days) in these patients, 2 of whom died.[4] Another review of 47 cases of immune-related NMJ disorders reported a mean onset time of approximately 1 month and an overall mortality rate of 44.7%,[5] markedly higher than that of classical myasthenia gravis (MG).[6] Most of the cases used monotherapy of PD-1 blockade (89.4%),[5] probably due to the broad indications of anti-PD-1 antibodies. Among the 47 patients, 19.1% had a history of MG.[5] Thus, screening for a history of MG and other neurologic disorders is necessary before administering ICIs. Early identification and expedited intervention are essential to prevent functional decline and improve survival.

Clinical manifestations of immune-related NMJ disorders are similar to those of classical MG but are characterized by more prominent involvement of the respiratory muscles, which can lead to life-threatening myasthenic crises.[5] Immune-related NMJ disorders often present alongside other irAEs (74.5%),[5] such as myositis (65.7%) and myocarditis (31.4%). A greater extent of vital organ involvement is associated with a worse prognosis.

Myositis with or without myonecrosis is often reflected by myalgia and marked CK elevation. A definite diagnosis of myositis should be determined through a muscle biopsy or magnetic resonance imaging. In our case, the absence of muscle pain, muscle tenderness, and rhabdomyolysis indicated a low probability of myositis or myonecrosis. Consequently, we suspect that the difference between the levels of TnT and CK was mainly due to myopathy,[7] because TnT can also be expressed in skeletal muscles.[7,8]

Traditional diagnostic methods for classical MG, such as the edrophonium test, ice-pack test, RNST, and single-fiber electromyography, may not be suitable for diagnosing immune-related NMJ disorders. The positive rate of RNST (47.8%) is lower for immune-related NMJ disorders[5] than for classical MG (75% of the generalized type).[6] In addition, common autoantibodies in classical MG, including anti-AChR and anti-muscle-specific kinase, are frequently negative in immune-related NMJ disorders (33.2% and 94.7%, respectively),[5] compared with classical MG (15% and 60%, respectively).[6] This explains the negative results of the RNST and anti-AChR antibody test in our patient.

The management of immune-related NMJ disorders must be individualized based on the clinical severity and extent of concomitant organ involvement. Along with the interruption or even permanent discontinuation of ICIs, treatment strategies may include acetylcholinesterase inhibitors, corticosteroids, intravenous immunoglobulins, and plasmapheresis.[6,9,10] Medications that potentially worsen myasthenia or induce myopathy should be avoided. Steroid-sparing immunosuppressants are typically not required and should only be considered in refractory cases.[10] Multidisciplinary consultation is also recommended. In our case, the patient's limited improvement demonstrated the poor treatment response of immune-related NMJ disorder compared with classical MG.

With the expanded indications of ICIs in various cancer types, it is vital to recognize and address irAEs. Despite the rarity of neurologic irAEs, their timely diagnosis and comprehensive evaluation are crucial given the rapid symptom progression and possibility of fatality associated with these events.

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Ethical approval

This study is approved by the IRB of National Taiwan University Hospital (IRB approval number: 202107039W). The patient consent was waived by the IRB.

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Conflicts of interest

There are no conflicts of interest.

References

1. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, *et al*. Adverse effects of immune-checkpoint inhibitors: Epidemiology, management and surveillance. Nat Rev Clin Oncol 2019;16:563-80.
2. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, *et al*. Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. JAMA Oncol 2018;4:1721-8.
3. Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, *et al*. Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature. Eur J Cancer 2017;73:1-8.
4. Suzuki S, Ishikawa N, Konoeda F, Seki N, Fukushima S, Takahashi K, *et al*. Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. Neurology 2017;89:1127-34.
5. Huang YT, Chen YP, Lin WC, Su WC, Sun YT. Immune checkpoint inhibitor-induced myasthenia gravis. Front Neurol 2020;11:634.
6. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: Emerging clinical and biological heterogeneity. Lancet Neurol 2009;8:475-90.
7. Schmid J, Liesinger L, Birner-Gruenberger R, Stojakovic T, Scharnagl H, Dieplinger B, *et al*. Elevated cardiac troponin T in patients with skeletal myopathies. J Am Coll Cardiol 2018;71:1540-9.
8. Bodor GS, Survant L, Voss EM, Smith S, Porterfield D, Apple FS. Cardiac troponin T composition in normal and regenerating human skeletal muscle. Clin Chem 1997;43:476-84.
9. Gilhus NE, Verschuuren JJ. Myasthenia gravis: Subgroup classification and therapeutic strategies. Lancet Neurol 2015;14:1023-36.
10. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, *et al*. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2018;36:1714-68.