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【 CASE REPORT 】

Acute Cerebellar Ataxia Induced by Nivolumab

Reina Kawamura[1], Eiichiro Nagata[1], Masako Mukai[1], Yoichi Ohnuki[1], Tomohiko Matsuzaki[2], Kana Ohiwa[2], Tomoki Nakagawa[2], Mitsutomo Kohno[2], Ryota Masuda[2], Masayuki Iwazaki[2] and Shunya Takizawa[1]

Abstract:
A 54-year-old woman with adenocarcinoma of the lung and lymph node metastasis experienced nystagmus and cerebellar ataxia 2 weeks after initiating nivolumab therapy. An evaluation for several autoimmune-related antibodies and paraneoplastic syndrome yielded negative results. We eventually diagnosed the patient with nivolumab-induced acute cerebellar ataxia, after excluding other potential conditions. Her ataxic gait and nystagmus resolved shortly after intravenous steroid pulse therapy followed by the administration of decreasing doses of oral steroids. Nivolumab, an immune checkpoint inhibitor, is known to induce various neurological adverse events. However, this is the first report of acute cerebellar ataxia associated with nivolumab treatment.

Key words: acute cerebellar ataxia, nivolumab, immune checkpoint inhibitors, steroid pulse therapy

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Introduction

Immune checkpoint inhibitors (ICIs) have recently been shown to be very effective for the treatment of lung cancer, melanoma, and renal cell carcinoma. However, ICIs are associated with a relatively high incidence of severe and sometimes life-threatening immune system-related adverse events. ICIs can potentially induce immune-related adverse events in any organ (1).

Nivolumab is an ICI that targets programmed cell death-1 protein and IgG4 antibody and is approved for the treatment of squamous non-small-cell lung cancer in patients who have previously received chemotherapy. It can also trigger various immune-related adverse events in the central and peripheral nervous systems (2). Severe adverse events are typically observed in 5-10% of patients treated with nivolumab. The most frequently observed adverse events are autoimmune neurological disorders, such as myasthenia gravis, polymyositis, Guillain-Barré syndrome, and encephalitis (3, 4).

Although nivolumab is known to induce various neurological complications, the present study is the first report of nivolumab-induced acute cerebellar ataxia.

Case Report

A routine chest X-ray revealed an abnormal shadow in the right lung of a 54-year-old woman. She underwent bronchoscopy and was diagnosed with lung adenocarcinoma at our hospital. Nedaplatin and vinorelbine chemotherapy was initiated in February (Year 0) at our department of thoracic surgery after thoracoscopic partial resection of the lung. Metastasis positive for a genetic mutation of epidermal growth factor receptor was found in the right lower lung. Consequently, gefitinib therapy was initiated in October (Year 2). In March (Year 3), magnetic resonance imaging (MRI) revealed brain metastasis. Therefore, erlotinib therapy was initiated, and the metastasis disappeared by September (Year 3). In July (Year 4), the lung adenocarcinoma was found to have increased in size, and nivolumab therapy (intravenous 3 mg/kg) was initiated in August (Year 4). In September (Year 4), after completing two nivolumab cycles, the patient began to experience dizziness and nausea while walking. The

[1]Department of Neurology, Tokai University School of Medicine, Japan and [2]Department of Thoracic Surgery, Tokai University School of Medicine, Japan
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Correspondence to Dr. Eiichiro Nagata, enagata@is.icc.u-tokai.ac.jp

Table. Laboratory Findings.

WBC	17,100 /μL	Anti-nuclear antibody	negative	[Cerebrospinal fluid]	
(Seg/Stab 88%, Lympho 6.5%)		MPO-ANCA	<1.0 U/mL	Initial pressure	5 cmH_2O
Hb	12.6 g/dL	PR3-ANCA	<1.0 U/mL	Protein	56 mg/dL
Plt	31.5×10^4 /μL	Anti-GM1 IgG antibody	negative	Sugar	71 mg/dL
INR	1.27	Anti-GQ1b IgG antibody	negative	Cell count	10 cells/mm^3
D-dimer	2.9 μg/mL	Anti-GAD antibody	negative	(Neutrophil 0/ Lymphocyte 10)	
Alb	3.0 g/dL	Anti-TPO antibody	25 IU/mL	IgG-index	0.55
AST	211 U/L	Anti-Tg antibody	22 IU/mL	MBP	<40 pg/mL
ALT	129 U/L	TSH	2.220 μIU/mL	OCB	negative
LDH	1,229 U/L	Free T4	1.01 ng/dL		
γ-GTP	50 U/L	Free T3	1.14 ng/dL	Cytology	Class II
BUN	11 mg/dL	HSV-IgG	negative		
Cr	0.64 mg/dL	HSV-IgM	negative		
Na	134 mEq/L	VZV-IgG	45.8		
K	3.9 mEq/L	VZV-IgM	negative		
CRP	11.29 mg/dL	EBV	negative		
HbA1c	5.9 %				
IgG	1,778 mg/dL				
IgA	306 mg/dL				
IgM	253 mg/dL				
IgE	178 IU/mL				
IgG-4	43.5 mg/dL				

The antibodies associated with paraneoplastic syndrome (La, Co, Tr, GAD65, Zic4, Titin, SOX1, Rec, Hu, Yo, Ri, Ma2/Ta, CV2, Amp) all negative.

MBP: myelin basic protein, OCB: oligoclonal IgG band, TPO: thyroid peroxidase, Tg: thyroglobulin, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3-anti-neutrophil cytoplasmic antibody

symptoms worsened daily, and she was hospitalized in September (Year 4). Physiological findings were mostly normal, but neurological findings revealed downbeat nystagmus, signs of cerebellar dysfunction on nose-to-finger test, wide-based gait, and truncal ataxia. Laboratory test results (Table) revealed no abnormal findings, including autoimmune antibodies associated with paraneoplastic syndrome (PNS). A cerebrospinal fluid (CSF) analysis showed a slight elevation of protein and cell counts. There were no abnormal findings of cytology in the CSF. We evaluated the patient for antiviral titers against herpes simplex, varicella zoster, and Epstein-Barr virus, as well as autoimmune antibodies such as GM1, GQ1b, and PNS-associated antibodies. No specific abnormalities were found. Lung X-ray and computed tomography (CT) revealed a large mass in the right lung. Brain MRI, MR angiography, and cerebral blood flow on single-photon emission CT showed no abnormalities. Finally, the patient was diagnosed with nivolumab-induced acute cerebellar ataxia after ruling out other possible differential diagnoses.

The patient's symptoms worsened following administration of 10 mg/day dexamethasone for 3 days, prompting a switch to 1,000 mg/day intravenous methylprednisolone (IVMP) for three days, followed by oral prednisolone (PSL) starting at 30 mg/day and gradually decreasing the dose. Cerebellar ataxia and nystagmus were almost completely resolved after IVMP administration, but while receiving 5 mg/day PSL, the patient developed pneumonia, which ultimately led to her death in October (Year 4) (Figure).

Discussion

Cerebellar ataxia is a neurological disorder wherein the coordination of motor activity is impaired. Possible causes include infection, neuroinflammatory disorders, stroke, and ingestion of toxic substances, among others. Acute cerebellar ataxia is often observed in children. Most cases are associated with viral infections or occur following the appearance of an infectious disease, although the most common etiologies are benign (5-7). In this case, the number of cells was very slightly elevated in the CSF of the patient. However, the patient had no fever or meningeal irritations, such as stiffness of the neck or Kernig's sign. Furthermore, her MRI findings appeared to be normal. Therefore, cerebellitis and meningitis could not be diagnosed.

In contrast to acute cerebellar ataxia, adult cerebellar ataxia can have various causes, such as toxicity, metabolism disorders, autoimmune disorders, and PNS. Regarding cerebellar ataxia associated with autoimmune antibodies, such as anti-GAD or anti-gluten antibodies, and hypothyroidism (Hashimoto's thyroiditis) (8), illness generally presents with a subacute onset and is accompanied by consciousness disturbance and other neurological symptoms, such as seizure, aphasia, and hemiplegia. Furthermore, most cases of tumor-induced PNS are subacute and progressive, and their appearance commonly precedes the detection of a tumor by several months to several years. However, estimating the contribution of ICIs to the development of neurological immune-

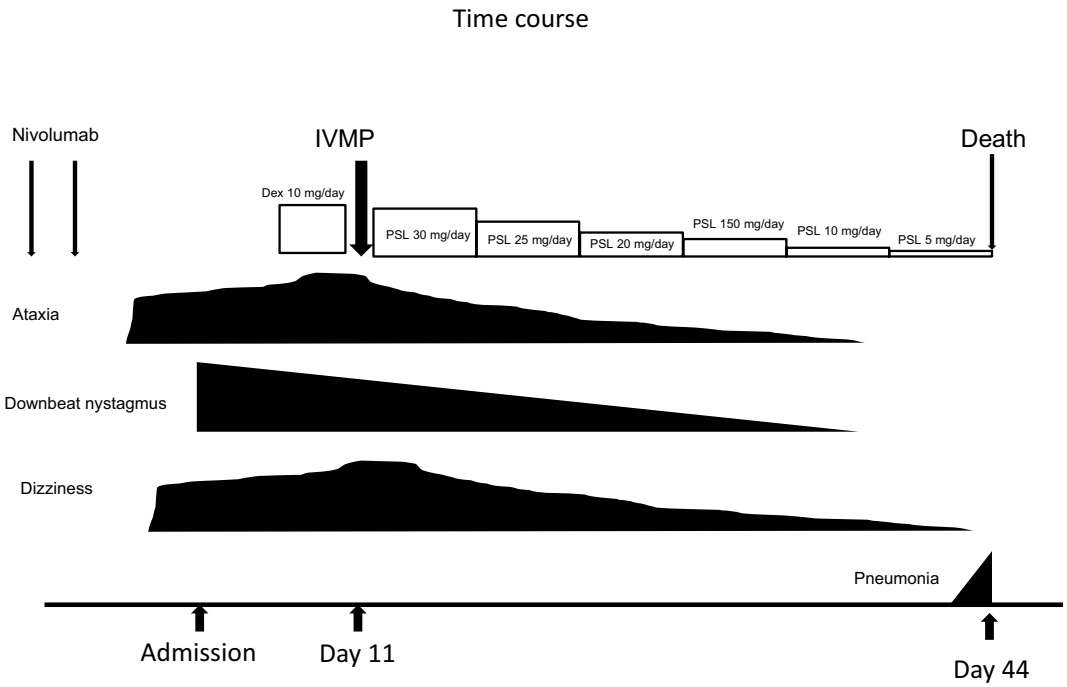

Figure. Clinical time course. After the second round of nivolumab therapy, the patient began to experience dizziness and nausea while walking. The symptoms worsened daily, and she was hospitalized. We administered intravenous methylprednisolone (IVMP) for 3 days followed by oral prednisolone (PSL) at an initial dose of 30 mg/day, which was gradually decreased. The symptoms improved following IVMP therapy. However, the patient developed pneumonia, which ultimately led to her death on Day 44.

related adverse events following immune checkpoint inhibition is difficult. Although the manner in which ICIs alter the immune circumstance in the body remains unclear, ICIs may facilitate T- and B-cell interactions with neuronal epitopes. This hypothesis will require further investigation. We had not previously encountered acute cerebellar ataxia as a result of nivolumab therapy. Steroids were the first-choice treatment for this patient, but 10 mg/day dexamethazone for 3 days was not effective. High-dose IVMP was effective in quickly attenuating the adverse events of nivolumab (9).

As ICIs are used with increasing frequency in patients with malignant tumors, healthcare professionals should consider treatment-related neurological adverse events among the possible diagnoses of acute-onset neurological syndromes with unclear etiologies. The early recognition and management of neurological immune-related adverse events are essential for ensuring clinical recovery and minimizing the effects of drug-related toxicity.

The authors state that they have no Conflict of Interest (COI).

Reina Kawamura and Eiichiro Nagata contributed equally to this work.

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