CASE REPORT

Acute Cerebellar Ataxia Induced by Nivolumab

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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
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. No specific 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.

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-

**Table. Laboratory Findings.**

| WBC (Seg/Stab 88%, Lympho 6.5%) | Anti-nuclear antibody | negative | [Cerebrospinal fluid] |
|--------------------------------|-----------------------|----------|----------------------|
| Hb 12.6 g/dL                  | MPO-ANCA <1.0 U/mL    |          | Initial pressure 5 cmH2O |
| Plt 3.5x10^4 /μL             | PR3-ANCA <1.0 U/mL   |          | Protein 56 mg/dL     |
| INR 1.27                     | Anti-GM1 IgG antibody | negative | Sugar 71 mg/dL       |
| D-dimer 2.9 µg/mL            | Anti-GQ1b IgG antibody| negative | Cell count 10 cells/mm³ |
| Alb 3.0 g/dL                 | Anti-TPO antibody     | 25 IU/mL | (Neutrophil 0/Lymphocyte 10) |
| 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 |                  |
| 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                |                       |          |                  |
| IgG4 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

**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.

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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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