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【 CASE REPORT 】

Steroid-responsive Nivolumab-induced Involuntary Movement with Anti-thyroid Antibodies

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Abstract:
We herein report a 68-year-old man with neurologic immune-related adverse events (irAEs) who exhibited nivolumab-induced steroid-responsive progressive ataxia, tremor, and anti-thyroid antibodies. His symptoms matched abnormalities on N-isopropyl-p-(123I)-iodoamphetamine single-photon emission computed tomography (SPECT) and dopamine transporter SPECT. Based on these clinical findings, we diagnosed the patient with a condition similar to the cerebellar type of Hashimoto's encephalopathy with nivolumab-induced anti-thyroid antibodies. Neurologic irAEs can be difficult to diagnose due to their varied clinical courses and lack of specific examinations. Therefore, a comprehensive approach, including assessments of autoantibodies and functional imaging, might be important for the diagnosis of neurologic irAEs.

Key words: nivolumab, immune related adverse event, DAT, SPECT, anti-thyroid antibody, Hashimoto's encephalopathy

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Introduction

Nivolumab is a representative monoclonal antibody against programmed cell death protein 1 (PD-1). Although immune-checkpoint inhibitors (ICIs) are widely used for anti-cancer therapy, they can cause immune-related adverse events (irAEs). Representative irAEs are dermatosis and digestive symptoms, but neurological irAEs, such as myasthenia gravis (MG) and Guillain-Barré syndrome, have also been reported (1).

We herein report a patient with subacute progressive ataxia without parkinsonism except for tremor, combined with intractable nausea and dizziness; the patient was euthyroid and had anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies. Paraneoplastic neurological antibodies and evidence of brain metastasis were absent. I-2 β-carbomethoxy-3 β- (4-iodophenyl) -N- (3-fluoropropyl) nortropane (I-FP-CIT) dopamine transporter single-photon emission computed tomography (DAT-SPECT) and N-isopropyl-p-(123I)-iodoamphetamine SPECT (IMP-SPECT) revealed abnormal findings, which were consistent with the patient's symptoms. Steroid treatment markedly improved the neurological symptoms. Given this clinical course, we speculated that the patient had a neurological irAE, similar to Hashimoto's encephalopathy, induced by nivolumab.

Case Report

A 68-year-old man with gastric cancer and multiple hepatic metastases began nivolumab treatment (3 mg/kg biweekly) because standard chemotherapy had been ineffective. After starting nivolumab, the tumor size decreased along with tumor marker levels. However, the patient experienced dizziness on movement and nausea after the sixth nivolumab injection. Nivolumab treatment was continued because of its cancer suppression efficacy. The patient's walking difficulty persisted, and involuntary tremor-like movement of both hands appeared, which gradually worsened. A neurologist was consulted, and two months after the initial neurological symptoms appeared, a neurologic examination identified irregular left-dominant involuntary movement of

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Table. Laboratory Findings.

folic acid	6.4 ng/mL	Anti-Amphiphysin antibody	negative	[Cerebrospinal fluid]	
Vitamin.B12	654 pg/mL	Anti-CV2 antibody	negative	Initial pressure	90 mmH_2O
Vitamin.E	1.78 mg/dL	Anti-Ma2/Ta antibody	negative	Protein	35 mg/dL
ACE	19.7 IU/L	Anti-Ri antibody	negative	Sugar	63 mg/dL
Fe	87 μg/dL	Anti-Yo antibody	negative	Cell count	4 /μL
Ferritin	24 ng/mL	Anti-Hu antibody	negative	Neutrophil	0 /μL
Cu	91 μg/dL	Anti-recoverin antibody	negative	Lymphocyte	4 /μL
Ceruloplasmin	19 mg/dL	Anti-SOX1 antibody	negative	IgG-index	0.47
ESR	7 mm/h	Anti-titin antibody	negative	OCBs	negative
Anti-nuclear antibody	negative	Anti-zic4 antibody	negative	MBP	<31.3 pg/mL
RF	8 U/L	Anti-GAD65 antibody	negative	CEA	<0.5 ng/mL
Anti-SS-A antibody	<1.0 U/L	Anti-Tr antibody	negative	Anti-GAD antibody	<0.5 ng/mL
Anti-SS-B antibody	<1.0 U/L	CEA	8.5 ng/mL	Anti-TPO antibody	<9 IU/mL
PR3-ANCA	<1.0 U/L	CA19-9	12 U/mL	Anti-Tg antibody	<10 IU/mL
MPO-ANCA	<1.0 U/L	sIL-2R	545 U/mL		
IgG	1,031 mg/dL	AFP	7 ng/mL	Cytology	negative
IgA	240 mg/dL	VZV-IgG EIA	6.7		
IgM	32 mg/dL	VZV-IgM EIA	0.31		
CH50	48.3 CH50/mL	HSV-IgG EIA	75.3		
Free T3	2.7 pg/mL	HSV-IgM EIA	0.39		
Free T4	0.9 ng/dL	EBV VCAI-IgG	320 times		
TSH	1.96 μIU/mL	EBV VCAI-IgM	<10 times		
Anti-TPO antibody	130 IU/mL	EBV EBNA-IgG	40 times		
Anti-Tg antibody	479 IU/mL	CMV-IgG	43 UA/mL		
Cortisol	58.7 μg/dL	CMV-IgM	negative I.D.		
ACTH	15.1 pg/mL	Anti-HBs antigen	negative		
Anti-GQ1b IgG antibody	negative	Anti-HCV antibody	negative		
Anti-GAD antibody	negative	RPR	negative		
Anti-AChR antibody	<0.3 nmol/L	TPHA	negative		

AChR: acetylcholine receptor, ACTH: adrenocorticotropic hormone, AFP: α-fetoprotein, ANCA: antineutrophil cytoplasmic antibody, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, CMV: cytomegalovirus, EBV: Epstein-Barr virus, ESR: erythrocyte sedimentation rate, HBs: hepatitis B surface, HCV: hepatitis C virus, HSV: herpes simplex virus, GAD: glutamic acid decarboxylase, MBP: myelin basic protein, MPO: myeloperoxidase, OCBs: oligoclonal bands, PR3: proteinase3, RF: rheumatoid factor, RPR: rapid plasma reagin, sIL-2R: soluble interleukin-2 receptor, Tg: thyroglobulin, TPHA: treponema pallidum hemagglutination assay, TPO: thyroid peroxidase, VZV: varicella zoster virus

both hands, comprising ataxia, postural tremor (Supplementary material), truncal ataxia, and dizziness on movement. However, the patient did not experience unconsciousness, nystagmus, paralysis, rigidity, akinesis, or bathyhypesthesia.

The findings of laboratory examinations are shown in Table. The patient was euthyroid but had elevated anti-TPO (130 IU/mL) and anti-Tg (479 IU/mL) antibody levels. There were no antibodies suggestive of paraneoplastic neurological syndrome (PNS), nor were there collagen disease markers, anti-GQ1b-IgG antibodies, anti-glutamic acid decarboxylase (GAD) antibodies, or anti-acetylcholine receptor (AChR) antibodies. The tumor marker levels improved to almost normal.

There were no remarkable findings in the cerebrospinal fluid (CSF), nor on electroencephalography (EEG), nerve conduction studies, or somatosensory evoked potential examinations. Head gadolinium-enhanced magnetic resonance imaging did not show any remarkable abnormalities, including cerebellar atrophy, stroke, and metastasis (Figure A and B); in contrast, IMP-SPECT revealed a cerebral blood flow (CBF) reduction in both occipital lobes and the cerebellar vermis (Figure C). Truncal ataxia was consistent with abnormal findings in the cerebellar vermis. Although the left-dominant tremor-like involuntary movement was difficult to explain based on the IMP-SPECT findings, DAT-SPECT showed a decreased radiotracer uptake in the right basal ganglia, which matched the left-dominant tremor-like involuntary movement (Figure D). We speculated that the patient's symptoms represented irAEs induced by nivolumab.

He underwent steroid pulse therapy (1 g/day, 3 days) with oral steroid (prednisolone 40 mg/day). Dizziness, nausea, and truncal ataxia dramatically improved within a few days after steroid pulse therapy. The irregular involuntary movements of the hands also gradually improved (Supplementary material). The patient was discharged and demonstrated an ability to walk 10 days after steroid introduction; nivolumab and steroid therapy were continued. Anti-TPO and anti-Tg antibody levels normalized three months after steroid treatment. Steroid treatment was gradually tapered to prednisolone 10 mg/day at 4 months. Ataxia and dizziness showed sustained improvement at the six-month follow-up despite

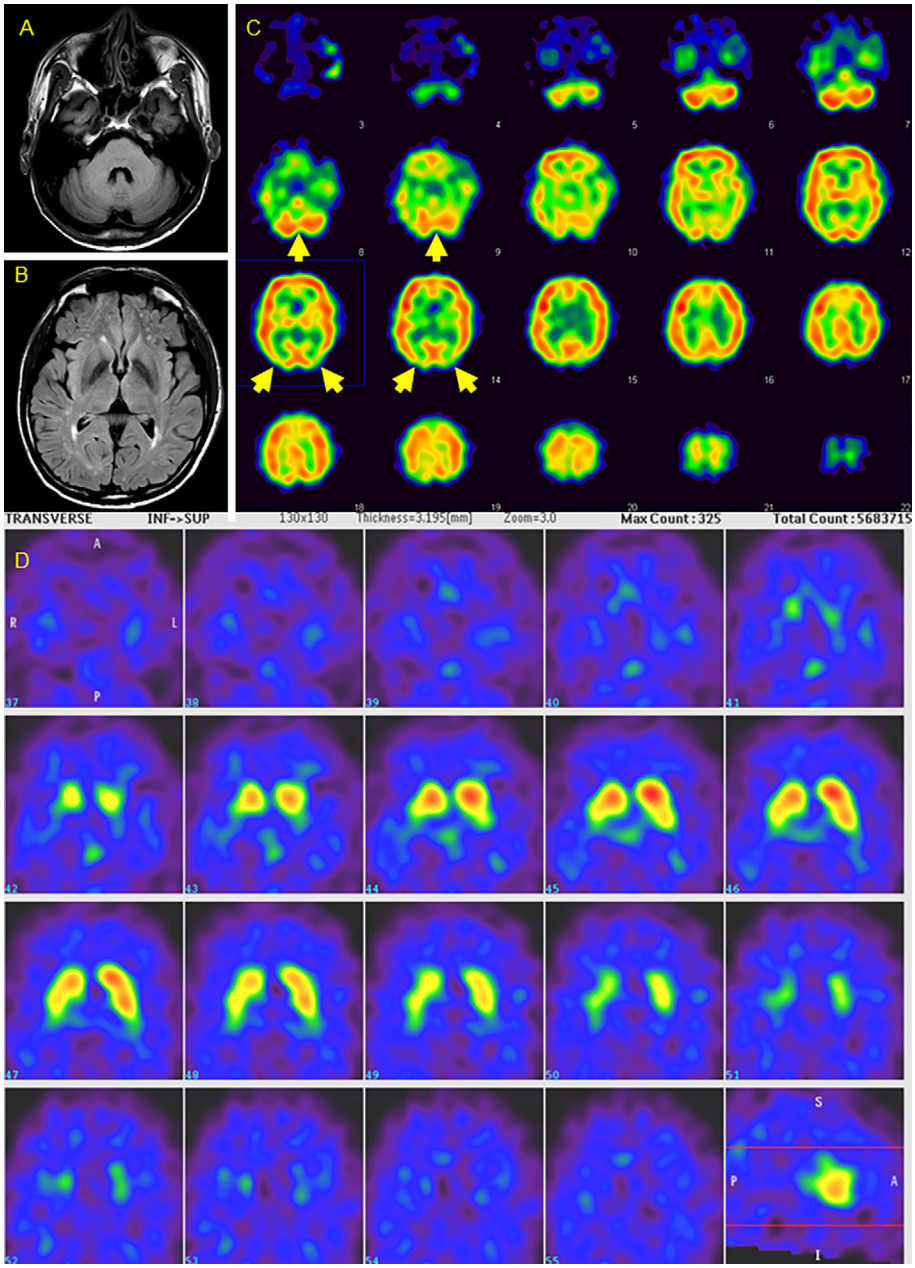

Figure. **Magnetic resonance imaging, IMP-SPECT, and DAT-SPECT findings. There were no abnormal findings on brain magnetic resonance imaging, such as cerebellar atrophy, stroke, or metastasis (A: T1-weighted image; B: fluid-attenuated inversion recovery). IMP-SPECT revealed cerebral blood flow reduction in both occipital lobes and the cerebellar vermis (arrow) (C). DAT-SPECT showed a decreased radiotracer uptake in the right basal ganglia (D). IMP-SPECT: N-isopropyl-p-(123I)-iodoamphetamine single-photon emission computed tomography, DAT-SPECT: I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (I-FP-CIT) dopamine transporter single-photon emission computed tomography**

continuous nivolumab therapy.

Discussion

Neurologic irAEs induced by ICIs are rare (1-3%), and reports of encephalitis are rarer still (1). Neurologic irAEs show features that differ from typical neurological diseases. Disease processes and clinical features vary, and there are few abnormalities in laboratory examinations and imaging studies; furthermore, immunotherapies are effective.

A representative neurologic irAE of nivolumab is MG. Nivolumab-induced MG (nivoMG) reportedly differs from conventional non-drug-induced MG (2): the clinical course of nivoMG is more acute, progressive, and severe, and affected patients exhibit markedly elevated creatine kinase levels. However, nivoMG is also steroid-responsive and shows a high positive ratio to anti-AChR antibody, as with conventional MG. The specific pathogenesis of nivoMG is un-

known; however, nivolumab can block programmed cell death-1 signaling, which results in the activation of autoreactive T cells and the production of pathogenic autoantibodies (3, 4).

In the present case, we speculated that the patient had a neurological irAE, similar to Hashimoto's encephalopathy. However, nivolumab-induced Hashimoto's encephalopathy might differ from conventional Hashimoto's encephalopathy, similar to how nivoMG and conventional MG differ. Conventional Hashimoto's encephalopathy is associated with the presence of autoantibodies, such as anti-thyroid antibodies and anti-amino [NH(2)]-terminal of alpha-enolase (NAE) antibody (5). In the present case, the presence of anti-NAE antibody could not be evaluated, and anti-thyroid antibodies were not examined before nivolumab introduction. Therefore, whether or not the production of pathogenic antibodies induced by nivolumab resulted in the involuntary movement is unclear. To our knowledge, there have been no reports of nivolumab-induced Hashimoto's encephalopathy. Kawamura et al. described a patient who had nivolumab-induced acute cerebellar ataxia with slight elevation of anti-TPO antibody level (25 U/mL), but they also did not examine the anti-NAE antibody level (6). Further reports are needed in order to clarify the associations between pathogenic autoantibodies and irAEs, especially those associated with involuntary movement.

Although the specific mechanism underlying our patient's symptoms is unclear, we speculate that nivolumab-induced involuntary movement was caused by an etiology similar to cerebellar-type Hashimoto's encephalopathy. Most patients with Hashimoto's encephalopathy have elevated levels of anti-TPO and anti-Tg antibodies. Hashimoto's encephalopathy may present with elevated protein levels in the CSF and slow waves on EEG; however, cerebellar-type is unlikely to show such abnormalities (7). Hashimoto's encephalopathy is the most prevalent cause of autoimmune ataxia without tumors (51%) and is unlikely to include nystagmus, as observed in anti-GAD antibody-positive cerebellar ataxia or gluten ataxia (8). Cerebellar syndrome is a major type of PNS, but our patient had no antibodies for PNS; furthermore, ataxia caused by PNS does not typically disappear with the use of steroids alone. The symptoms in this case are therefore similar to those of Hashimoto's encephalopathy.

In the present case, IMP-SPECT and DAT-SPECT showed abnormal findings. In patients with Hashimoto's encephalopathy, CBF reduction on SPECT is a common diagnostic finding. Although the reduction area is non-specific and varies among patients, regional CBF is significantly decreased in the bilateral anterior cingulate areas and left prefrontal cortex among patients with Hashimoto's encephalopathy who have neuropsychiatric symptoms (9). Notably, the reduction area might lead to specific symptoms. In our patient, however, CBF reduction in the occipital area was not accompanied by visual field defects. In contrast, CBF reduction in the cerebellar vermis corresponded to truncal ataxia without nystagmus.

DAT-SPECT revealed a decreased radiotracer uptake in the right basal ganglia in our patient, which might correspond to his symptoms of left-dominant involuntary movement. Floyd et al. reported that DAT-SPECT showed normal dopamine transporter uptake in a patient with ICI-induced parkinsonism (10). Although drug-induced parkinsonism generally causes no abnormalities that are visible on DAT-SPECT, whether or not parkinsonism in patients with irAEs results in similar DAT-SPECT findings is unclear. The involuntary movements in our patient were dramatically improved by steroid treatment without dopamine replacement. Therefore, we speculated that these symptoms were not induced by an extrapyramidal system deficit but by an immune-related etiology. Functional imaging, such as IMP-SPECT and DAT-SPECT, might improve our understanding of the etiology of involuntary movement induced by ICIs.

Conclusion

We encountered a patient who exhibited involuntary movement with anti-thyroid antibodies, due to nivolumab treatment. These symptoms were consistent with several abnormalities on brain functional imaging, and the patient's good response to steroid treatment suggested that the symptoms were neurologic irAEs, similar to the etiology of Hashimoto's encephalopathy. Because ICIs have been widely and rapidly adapted as anti-cancer therapies, a comprehensive approach, involving detailed imaging studies and close cooperation between oncologists and neurologists, is essential for the diagnosis and management of neurologic irAEs.

Written informed consent was obtained from the patient for the publication of this case report.

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

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