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Case report

Acute cerebellar ataxia due to Epstein-Barr virus under administration of an immune checkpoint inhibitor

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SUMMARY

A 71-year-old male patient with adenocarcinoma of the lung and contralateral lung metastasis under administration of pembrolizumab had symptoms of cerebellar ataxia. We suspected that the symptoms were immune-related adverse events (irAE), but the patient was subsequently diagnosed as cerebellitis due to Epstein-Barr virus (EBV) infection. After steroid pulse therapy, the symptoms of cerebellar ataxia improved immediately. Immune checkpoint inhibitors (ICI) can induce neurological adverse events and cause acute cerebellar ataxia. Initially, irAEs were suspected in this case. His clinical data suggested that reactivation of the virus had occurred because the ICI affected his immune system. This is the first report of a case of acute cerebellar ataxia due to EBV under administration of an ICI.

BACKGROUND

The use of immune checkpoint inhibitors (ICI) in lung cancer treatment has become one of the standard treatments for advanced and metastatic lung cancer. Although ICI treatment is considered to have low incidence of total toxicity, various immune-related adverse events (irAEs) related to ICI treatment, which differ from those caused by chemotherapy, have been reported. ICIs are known to induce various neurological irAEs including cerebellar ataxia.[1] Consequently, when ataxia develops during ICI treatment, ICI-related irAEs should be highly suspected.

Acute cerebellar ataxia has various causes. Ataxias in adults are caused by acquired, non-genetic factors including stroke, infection, toxicity, immunity, paraneoplasia, vitamin deficiency and metabolic diseases.[2] Extensive laboratory examinations should be performed to achieve a correct diagnosis.

In the current case, further examinations showed that ataxia was caused by reactivation of Epstein-Barr virus (EBV) infection rather than irAEs related to ICI use. In this report, we present a case where the diagnosis of acute cerebellar ataxia related to either viral infection or ICI-related irAEs was difficult.

CASE PRESENTATION

In January, a male patient aged 71 years developed dyspnoea and visited a clinic. A chest X-ray showed consolidations of both lungs, and he was referred to our hospital to evaluate the possibility of lung cancer. A CT scan showed masses in both lungs. A tumour in the right lung was biopsied by bronchoscopy and adenocarcinoma was histologically detected. Epidermal growth factor receptor mutation and rearrangement of anaplastic lymphoma kinase were negative and the expression rate of programmed death - ligand 1 (PD-L1), a ligand for programmed cell death 1 (PD-1), was 2% as analysed by immunohistochemistry. Fluorodeoxyglucose-positron emission tomography (FDG-PET) and brain MRI revealed no lymph node metastasis and no distant metastasis except for pulmonary metastases. The patient was diagnosed with lung adenocarcinoma with contralateral lung metastasis and classified as clinical stage IVA.

He was administered chemotherapy with carboplatin, paclitaxel and bevacizumab. His tumours shrunk and it was considered a partial response. Two months after the initiation of treatment, tumours in both lungs had increased in size, and his disease state was evaluated as progression of disease. Pembrolizumab was started as a second-line treatment and administered every 3 weeks. After two cycles of the treatment, no adverse events were reported. When he visited our hospital to receive a third cycle, he complained of dizziness that had initiated several days before the visit. He had dysarthria and gait disorder. He could not walk without support. Neurological examination showed cerebellar ataxia. In particular, dysarthria, failure of tandem gait test, dysmetria and decomposition were observed. Although blood tests (table 1) and brain MRI found no significant abnormal findings, adverse events of pembrolizumab were suspected.

INVESTIGATIONS

He was hospitalised immediately. He was referred to neurologists who considered that the symptoms were irAEs derived from the ICI treatment. We decided to observe the patient without steroid treatment at first.

There was no improvement in his symptoms and a cerebrospinal fluid (CSF) examination was performed (table 2).

There was an increase in the numbers of lymphocytes and protein levels, with no decrease in sugar levels or abnormalities of the IgG index in the CSF. MBP was measured to exclude degenerative diseases such as multiple sclerosis and interleukin

Table 1 Laboratory findings on admission

WBC	8430	/μL	Ca	9.4	mg/dL	SLX	110	U/mL
Neutophils	77.2	%	UN	16.6	mg/dL	CEA	2.0	ng/mL
Lymphocytes	15.3	%	Cre	0.88	mg/dL	Anti-GAD antibody	<5.0	U/mL
Monocytes	4.9	%	AST	25	U/L	PR3-ANCA	<1.0	EU
Eosinophils	0.7	%	ALT	29	U/L	MPO-ANCA	<1.0	EU
Haemoglobin	15.8	g/dL	LDH	184	U/L	IgG-4	61.4	mg/dL
D-D	2.7	μg/mL	γGT	66	U/L	Anti-Tg antibody	10.4	IU/mL
TP	6.8	g/dL	ALP	232	U/L	Anti-TPO antibody	5.5	
Albumin	3.5	g/dL	T-Bil	0.8	mg/dL	FT4	1.71	ng/dL
Na	141	mmol/L	CRP	0.61	mg/dL	FT3	2.89	pg/mL
K	3.8	mmol/L	CYFRA	4.6	ng/mL	Anti-ACTH antibody	<0.2	nmol/L
Cl	107	mmol/L						

ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoembryonic antigen; Cre, Creatinine; CRP, C reactive protein; CYFRA, cytokeratin 19 fragment; D-D, D-dimer; FT3, free triiodothyonine; FT4, free thyroxine; GAD, glutamic acid decarboxylase; γ-GT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; PR3-ANCA, proteinase-3-anti-neutrophil cytoplasmic antibody; SLX, sialyl Lewis-x antigen; T-bil, total bilirubin; Tg, thyroglobulin; TP, total protein; TPO, thyroid peroxidase; UN, urea nitrogen.

6 (IL-6) was evaluated to exclude meningitis related to collagen disease. Both myelin basic protein (MBP) and IL-6 in CSF were negative. Based on this result, aseptic meningitis or cerebellitis was assumed as a diagnosis. The CSF and blood were immediately sent to a commercial laboratory for the analyses of related viruses. The next day after the Central nervous system (CNS) test, we initiated steroid pulse therapy with methyl-prednisolone 500 mg/day for 3 days. The results of virus-related tests revealed EBV reactivation. The data in table 3 show that EBV-DNA was detected in the blood and CSF; IgG against EBV-viral capsid antigen (VCA) was elevated compared with IgM antibody against EBV VCA and IgG against EBV-early antigen and antibody against EBV-nuclear were weakly positive. Based on these results, we diagnosed the patient as cerebellitis caused by EBV reactivation.

DIFFERENTIAL DIAGNOSIS

At this point, we had considered this event as an irAE that frequently occurred during or after immune checkpoint treatment. Since neurologists in our hospital routinely have checked

Table 2 Findings of cerebrospinal fluid before the treatment

Initial pressure	150	mmH_2O
Cell count	8	/μL
Lymphocyte	8	/μL
Neutrophil	<1	/μL
Atypical cells	(–)	
Protein	114	mg/dL
Sugar	53	mg/dL
IL-6	4.5	pg/mL
MBP	126	pg/mL
IgG-Index	0.51	

IL-6, interleukin 6; MBP, myelin basic protein.

Table 3 Laboratory findings after the treatment

Blood	
EBV-DNA	6.4×10^1 copies/10^6 cells
HSV-DNA	$<2.0\times10^1$ copies/10^6 cells
VZV-DNA	$<2.0\times10^1$ copies/10^6 cells
CMV-DNA	$<2.0\times10^1$ copies/10^6 cells
HHV-6-DNA	$<2.0\times10^1$ copies/10^6 cells
EBV-VCA-IgG	Positive
EBV-VCA-IgM	Positive
EBV-EA-IgG	Negative
EBNA	Positive
CSF	
EBV-DNA	2.0×10^2 copies/10^6 cells
HSV-DNA	$<1.0\times10^2$ copies/10^6 cells
VZV-DNA	$<1.0\times10^2$ copies/10^6 cells
CMV-DNA	$<1.0\times10^2$ copies/10^6 cells
HHV-6-DNA	$<1.0\times10^2$ copies/10^6 cells

CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBNA, antibody against EBV-nuclear; EBV, Epstein-Barr virus; EBV-EA-IgG, IgG against EBV-early antigen; EBV-VCA-IgG, IgG against EBV-viral capsid antigen; HHV, human herpes virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

virus infections in the case of encephalitis or meningitis, We could reach the exact diagnosis.

Other kinds of infections including tuberculosis, cryptococcus, herpes and cytomegalovirus should be considered as differential diagnoses.

In addition, We frequently experience brain metastasis and meningitis cartinomatosa in patients with lung cancer.

TREATMENT

After the diagnosis of EBV cerebellitis, second steroid pulse therapy was administered according to the standard treatment for moderate-to-severe acute cerebellar ataxia due to EBV. Steroid therapy was discontinued and a second CSF examination was performed after completion of the pulse therapy. CSF examination showed that protein levels in the CSF had decreased and that EBV-DNA was not detected.

OUTCOME AND FOLLOW-UP

The symptoms of cerebellar ataxia improved completely and he was discharged from the hospital 35 days after admission.

The patient is asymptomatic at the time of this report. He has been treated for lung cancer.

DISCUSSION

Acute cerebellar ataxia has various causes including infection, stroke and degenerative disease. Acute cerebellar ataxia caused by EBV is often diagnosed in children but has also been reported in young people and adults.[3] This neurological disease can develop because of acute or chronic viral infection, and reactivation. At first, we considered his symptoms as irAE related to ICI based on his treatment history. As a result of further examinations, cerebellitis due to the reactivation of EBV was diagnosed. However, acute cerebellar ataxia due to irAE was not fully excluded because ICI caused various adverse events. Except disorders of the nervous system, various irAE have been reported: endocrine diseases including thyroid disease, type 1 diabetes and adrenal insufficiency, interstitial pneumonia, skin disorders, renal dysfunction. It was previously reported that

neurological irAEs was observed in 11.5% of all-grade cases receiving ICI.[4]

We suspected that reactivation of the virus by ICI had occurred in this case. Recently, a study from the USA reported that approximately 7% of malignant melanoma patients who received ICI developed a serious infection.[5] In addition, a Japanese study reported that tuberculosis developed in patients receiving nivolumab treatment.[6]

Reports of the reactivation of latently infected viruses such as EBV were not found when performing a literature search. Although limitation in the current case is lack of data of EBV infection before the event, we assume that the case was previously infected with EBV by EBV seroanalysis. Since EBV reactivation might have occurred by chance or by ICI treatment, we suggest that it should be further examined in the future. We continue to accumulate cases and examine whether reactivation of viruses occurs by examining patients with neurological disorders and latently infected viruses during and post-ICI administration.

In summary, we believe that this case of acute cerebellar ataxia was caused by the reactivation of EBV by ICI. However, the mechanism involved is unclear. Therefore, we will continue to collect similar cases for analysis.

Patient's perspective

I felt strong dizziness and a swaying sensation when I was given two cycles of pembrolizumab treatment. I was a little better at the time of admission but still had the symptoms. Thanks to the hospitalisation, the cause was found and I received appropriate treatment, after which the symptoms disappeared.

Learning points

- When neurological disorders during immune checkpoint inhibitors (ICI) treatment are encountered, the role of immune-related adverse events should be determined.
- We should pay attention to various infections and virus reactivation during ICI treatment.
- We should investigate the mechanism and prevalence of virus reactivation induced by ICI treatment.

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REFERENCES

1 Kawamura R, Nagata E, Mukai M, *et al*. Acute cerebellar ataxia induced by nivolumab. *Intern Med* 2017;56:3357–9.
2 Javalkar V, Kelley RE, Gonzalez-Toledo E, *et al*. Acute ataxias: differential diagnosis and treatment approach. *Neurol Clin* 2014;32:881–91.
3 ClaireLM, McColganP. Peter Martinet : Acute cerebellar ataxia due to Epstein-Barr virus. *Practical Neurology* 2012;12:238–40.
4 Zimmer L, Goldinger SM, Hofmann L, *et al*. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016;60:210–25.
5 Del Castillo M, Romero FA, Argüello E, *et al*. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. *Clin Infect Dis* 2016;63:1490–3.
6 Fujita K, Terashima T, Mio T, *et al*. Anti-Pd1 antibody treatment and the development of acute pulmonary tuberculosis. *J Thorac Oncol* 2016;11:2238–40.