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【 CASE REPORT 】

Atezolizumab-induced Encephalitis in a Patient with Hepatocellular Carcinoma: A Case Report and Literature Review

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Abstract:

We herein report a case of encephalitis in a 42-year-old woman with hepatocellular carcinoma following atezolizumab plus bevacizumab therapy. After two weeks of treatment, she was admitted for a high fever, impaired consciousness, and convulsive seizure refractory to diazepam. Magnetic resonance imaging revealed a hyperintense splenial lesion. A cerebrospinal fluid test excluded malignancy and infection. These findings were highly suggestive of a diagnosis of encephalitis due to atezolizumab, an immune-related adverse event. Steroid pulse therapy improved the fever and seizure. However, her incomplete right-sided paralysis and aphasia persisted. This is the first case report of encephalitis caused by atezolizumab plus bevacizumab therapy for hepatocellular carcinoma.

Key words: hepatocellular carcinoma, immune-related adverse events, encephalitis, atezolizumab plus bevacizumab, mild encephalitis/encephalopathy with a reversible splenial lesion

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Introduction

Over the last decade, immune checkpoint inhibitors (ICIs) have become novel immunotherapeutic agents for the treatment of various cancers. ICIs [e.g. anti-programmed death-1 (PD1), anti-programmed death ligand-1 (PD-L1), and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4)] can induce tumor cell death by activating T cells and inhibiting tumor-induced immunosuppression. However, immune-related adverse events (irAEs) related to ICIs have been reported.

Although irAEs may involve any organ, the skin, colon, endocrine organs, liver, and lungs are most commonly affected. Neurologic irAEs have been reported in 4.2% of patients, manifesting with a wide variety of clinical presentations (1). Neurologic irAEs can be classified as peripheral (e.g., Guillain-Barre syndrome, myasthenia gravis) or central (e.g., encephalitis, aseptic meningitis, and myelitis). Among central irAEs, encephalitis is considered a rare and sometimes insidious but potentially fatal adverse effect (2, 3).

Atezolizumab is a PD-L1 inhibitor approved for the treatment of non-small-cell lung cancer (NSCLC) (4, 5), small-cell lung cancer, advanced triple-negative breast cancer, and advanced hepatocellular carcinoma (HCC). Although the incidence of irAEs caused by atezolizumab is lower than that of other ICIs (6), several serious cases of encephalitis have been reported following atezolizumab therapy (2, 3, 7, 8).

We herein report a case of encephalitis in a patient with HCC following treatment with atezolizumab plus bevacizumab.

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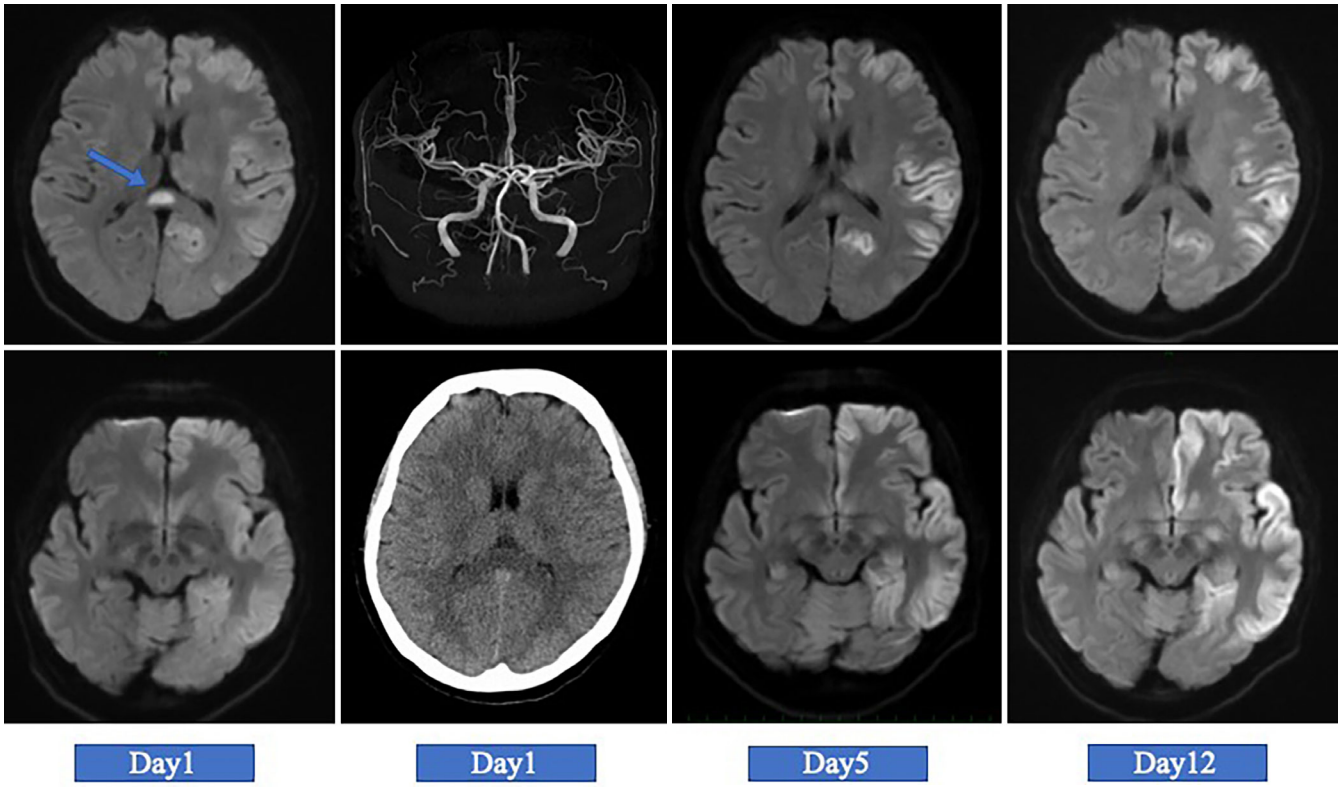

Figure. **(A) Initial brain magnetic resonance imaging (MRI) findings on the first day of intensive care admission. Initial diffusion-weighted MRI revealed a hyperintense signal (blue arrow) in the splenium of the corpus callosum, considered to be consistent with a diagnosis of mild encephalitis/encephalopathy with a reversible splenial lesion. Magnetic resonance angiography showed no abnormal findings or vascular occlusion, and head computed tomography (CT) showed no signs of bleeding. (B) Follow-up diffusion-weighted MRI showed the resolution of the hyperintense signal in the splenium of the corpus callosum. However, a hyperintense signal along the left cerebral cortex remained.**

Case Report

A 42-year-old woman with chronic hepatitis B caused by mother-to-child transmission was diagnosed in May 2020 with unresectable HCC. Computed tomography (CT) at the diagnosis showed multiple hepatic tumors with portal vein obstruction. Tumor marker tests revealed elevated levels of α-fetoprotein (AFP) (276,700 ng/mL) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) (16,124 mAU/mL). Combination therapy with oral lenvatinib (12 mg/body) and hepatic arterial infusion of cisplatin was initiated. However, after six months, hepatic tumors showed progressive disease. As such, atezolizumab and bevacizumab were given as second-line therapy. Blood tests revealed well-compensated liver disease (Child-Pugh class A) with an albumin-bilirubin grade of 2A in the absence of any history of hepatic encephalopathy.

However, after 12 days of atezolizumab plus bevacizumab therapy, the patient presented with a high fever without any signs of bacterial infection. Antipyretic therapy failed to improve her fever, which persisted for four days with signs of very mild peripheral sensory neuropathy. Rapid influenza diagnostic tests and reverse transcription-polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 were negative. On the 17th day of ICI therapy, she presented to the emergency room for acute-onset impaired consciousness (Glasgow Coma Scale E4V3M5) and a high fever (up to 40°C). A neurologic examination revealed no signs of nuchal rigidity. She then presented with convulsive seizures refractory to diazepam, which prompted admission to the intensive-care unit for airway protection via intubation. Treatment with propofol improved her status epilepticus.

Magnetic resonance imaging (MRI) showed a hyperintense lesion in the splenium of the corpus callosum on T2-weighted imaging (T2WI), fluid-attenuated inversion recovery (FLAIR) imaging, and diffusion-weighted imaging (DWI) (Figure A). These findings were considered to be consistent with the clinicoradiologic diagnosis of mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). In addition, DWI also revealed extensive hyperintense signals along the left cerebral cortex. These hyperintense signals were distributed along the left cerebral cortex regardless of vascular territory, and magnetic resonance angiography showed no abnormal findings and vascular occlu-

Table 1. Laboratory Data of the Patient on the First Day of Intensive Care Admission.

TP	5.7 (g/dL)	WBC	2100 (/μL)
ALB	2.6 (g/dL)	HGB	9.1 (g/dL)
GLU	151 (mg/dL)	PLT	7.1 (10^4/μL)
T-Bil	0.3 (mg/dL)		
GOT	116 (U/L)	PT-INR	1.07
GPT	35 (U/L)	APTT	28.9 (s)
LDH	385 (U/L)	D-dimer	3.8 (μg/mL)
ALP	50 (U/L)		
γ-GTP	54 (U/L)	β-D-glucan	<6.0 (pg/mL)
CK	2,627 (U/L)		
CRP	1.99 (mg/dL)	TSH	3.04 (μIU/mL)
BUN	22 (mg/dL)	FT4	1.13 (ng/dL)
CRE	0.86 (mg/dL)	FT3	2.16 (pg/mL)
Na	141 mmol/L	ACTH	9.3 (pg/mL)
K	3.6 mmol/L	Cortisol	37.86 (μg/dL)
Cl	109 mmol/L		
Ca	7.6 (mg/dL)		
Mg	2.3 (mg/dL)		

TP: total protein, ALB: albumin, GLU: glucose, T-Bil: total bilirubin, GOT: glutamic oxaloacetic transaminase, GPT: glutamic pyruvic transaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, CK: creatinine kinase, CRP: C-reactive protein, BUN: blood urea nitrogen, CRE: creatinine, WBC: white blood cell, HGB: hemoglobin, PLT: platelet, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, TSH: thyroid-stimulating hormone, FT4: free thyroxine, FT3: free triiodothyronine, ACTH: adrenocorticotropic hormone

sion. We excluded cerebral infarction and diagnosed these hyperintense signals along the left cerebral cortex as likely being due to encephalopathy following seizures. However, MRI showed no metastatic brain tumors, and head CT showed no signs of cerebral hemorrhaging.

We were unable to determine the cause of seizures from blood tests (Table 1). A cerebrospinal fluid (CSF) cell count demonstrated an elevated white blood cell count (514 cells/μL) with marked predominance of polymorphonuclear leukocytes. Furthermore, a CSF test revealed increased levels of protein (236 mg/dL) and glucose (82 mg/dL). CSF cultures were negative for bacterial and fungal growth. In addition, polymerase chain reaction for viruses (i.e. cytomegalovirus, human herpesvirus 6, human parechovirus, varicella zoster virus, enterovirus, herpes simplex virus 1, and herpes simplex virus 2) was negative. CSF cytology revealed no malignant cells. These findings excluded the possibility of metastatic brain tumor, bacterial meningitis, and herpes simplex encephalitis. Atezolizumab was thus deemed the likely etiology of the patient's encephalitis. However, an electroencephalogram and serum antibody tests (e.g., anti-Hu) for paraneoplastic neurologic syndromes (PNS) were not performed.

On the first day of intensive care admission, steroid pulse therapy (methylprednisolone 1,000 mg for 3 days) was initiated for the treatment of encephalitis. Levetiracetam (1,000 mg/day) was also given as anticonvulsant therapy. Fortunately, her seizure and fever disappeared on the third and fifth day of intensive care admission, respectively. A follow-up CSF test performed on the fifth day demonstrated a decrease in the white blood cell count to 43 cells/μL. Due to these improvements, the patient was extubated.

At that time, a neurologic examination showed right-sided paralysis, right hemispatial neglect, and aphasia. On the 12th day of intensive care admission, MRI demonstrated the disappearance of the hyperintense signal in the splenium of the corpus callosum on T2WI, FLAIR, and DWI (Figure B). However, the extensive hyperintense signal along the left cerebral cortex persisted (Figure B). Furthermore, although her hemispatial neglect had improved, her incomplete right-sided paralysis and aphasia persisted despite continued rehabilitation. On the 45th day of hospitalization, the patient was discharged with remaining paralysis and aphasia.

One month after discharge, the patient was readmitted. Blood tests and CT demonstrated elevated liver enzymes, generalized edema, and ascites caused by tumor progression. Unfortunately, the patient died 109 days after the initiation of atezolizumab plus bevacizumab therapy.

Discussion

We have described a case of encephalitis following atezolizumab plus bevacizumab therapy in a patient with HCC. To our knowledge, this is the first case report of encephalitis caused by atezolizumab plus bevacizumab therapy for HCC, although it is a known adverse event listed on the package insert. In our case, high-dose steroid therapy with tapering (i.e. 1,000 mg methylprednisolone for 3 days) was an effective treatment for encephalitis. However, the patient's paralysis and aphasia persisted.

Neurologic irAEs are rare complications of ICI therapy, with an overall incidence ranging from 2% to 4%. Among these cases, grade 3-4 toxicities are uncommon (<1%) (9). A literature review of 59 clinical trials involving 9,208 cancer patients showed the following incidence of neurologic irAEs based on ICI therapy: anti-CTLA4 (3.8%), anti-PD1 (6.1%), and combined anti-PD1 and anti-CTLA4 (12%) (10). Furthermore, although neurologic irAEs may present at any time, the median time to the onset was six weeks after the initiation of ICIs (10).

To our knowledge, only four cases of encephalitis following atezolizumab therapy have been reported (7, 8, 11, 12). Table 2 shows the characteristics and differences among these cases, including our case. In Phases I and II of the POPLAR trial, encephalitis was not reported among NSCLC patients treated with atezolizumab. In contrast, the OAK phase III randomized controlled trial reported that 5 of the 609 (0.8%) patients with NSCLC developed encephalitis following atezolizumab therapy (4). In addition, the IMpower 150 trial, a randomized phase III study, reported one case of posterior reversible encephalopathy syndrome in a patient who received atezolizumab (5). These patients presented with a fever and impaired consciousness about two weeks

Table 2. Characteristics of Previously Reported Cases of Encephalitis Following Atezolizumab Therapy.

	(11)	(12)	(8)	(7)	Our case
Sex	Man	Man	Woman	Woman	Woman
Age (years)	78	56	53	59	42
Disease	Metastatic lung adenocarcinoma	Metastatic lung adenocarcinoma	Metastatic cervical squamous cell carcinoma	Metastatic bladder cancer	Hepatocellular carcinoma
ICI treatment	Atezolizumab	Atezolizumab with carboplatin plus nab-paclitaxel	Atezolizumab plus bevacizumab	Atezolizumab	Atezolizumab plus bevacizumab
Onset of symptoms	NA	Day17	Day13	Day21	Day12
Symptoms	Disturbance of consciousness, pyrexia	Disturbance of consciousness, pyrexia	Headache, meningeal signs	Disturbance of consciousness, pyrexia	Disturbance of consciousness, pyrexia, convulsion
Cerebrospinal fluid	High cell count	Elevated protein levels and IL-6	High cell count elevated protein levels	Normal	High cell count elevated protein levels
MRI findings	Normal	Normal	Diffuse leptomeningeal enhancement	Normal	MERS
Treatment	Steroid pulse	Steroid pulse	High-dose steroids	High-dose steroids	Steroid pulse with ventilator
Outcome	Recovery	Recovery	Recovery	Recovery	Recovery with after effect

ICI: immune checkpoint inhibitor, NA: not available, IL-6: inerleukin-6, MRI: magnetic resonance imaging, MERS: mild encephalitis/encephalopathy with a reversible splenial lesion

after treatment with atezolizumab, suggesting that these might be initial clues for ICI-induced encephalitis. Interestingly, four out of the five encephalitis cases in the OAK trial occurred in Japanese patients. Based on the post-marketing investigations published by pharmaceutical companies in Japan, the frequency of grade >3 encephalitis caused by atezolizumab-based treatment (including both monotherapy and combination therapy) was reported to be 0% in advanced triple-negative breast cancer patients, 0.47% in NSCLC patients, and 0.10% in HCC patients, including our case. The difference in frequencies among individuals and races may be ascribed to a particular immunogenetic background. According to a Korean report, HLA-B*27:05 might be related to encephalitis induced by atezolizumab (13).

Although MRI may be performed for the diagnosis of ICI-induced encephalitis, no specific findings have been established. In our case, MRI showed a hyperintense signal in the splenium of the corpus callosum on T2WI, FLAIR, and DWI, which was thus considered to be consistent with the images of MERS. MERS is a clinicoradiologic syndrome characterized by transient splenial lesions with hyperintense signals on T2WI, FLAIR, and DWI (14). In general, MERS patients present with neurologic symptoms (e.g., impaired consciousness or seizures). However, most patients recover within a month, irrespective of treatment. Although the exact pathogenesis of MERS is still not fully understood, viral infections, epilepsy, autoimmune disorders, and malignancy are implicated.

To our knowledge, ipilimumab-induced encephalitis in a patient with melanoma was the only reported case of ICI-related MERS (15). Our patient is the first case of MERS caused by atezolizumab. In both cases, steroid therapy improved the patient's neurologic symptoms with some remnant subtle complications. These case reports suggest that ICI-induced MERS might be difficult to manage completely.

Several limitations associated with the diagnosis in the present study warrant mention. Since the patient was intubated and a prompt diagnosis was essential, an electroencephalogram and paraneoplastic antibody tests could not be performed. Both of these examinations are recommended to differentiate ICI-induced encephalitis from PNS. However, the relationship between ICI-induced encephalitis and PNS remains unclear. CSF paraneoplastic and auto-immune antibody panels are often positive in patients with suspected ICI-induced encephalitis. According to a case series and literature search, ≥1 antibodies could be detected in 13 of 25 (52%) patients with ICI-associated encephalitis (16). The presence of paraneoplastic antibodies may increase the risk of developing ICI-associated encephalitis (17). Regarding MRI, typical imaging findings of paraneoplastic limbic encephalitis include T2 hyperintensity and swelling of the mesial temporal lobes (18). In our case, MRI showed findings of MERS, making it difficult to differentiate between ICI-associated encephalitis and PNS. No MRI images characteristic of PNS have yet been reported. However, HCC is rarely involved with PNS (19, 20). In addition, although classical PNSs are known to usually precede a cancer diagnosis, ICI-induced encephalitis or neurotoxicity develops when the cancer has already been diagnosed, generally shortly after the initiation of ICI treatment, demonstrating a timely association with the agent (21). Encephalitis due to ICI was therefore strongly suspected in the present case.

As ICIs become more widely used for the treatment of various cancers, it is important to consider the possibility of encephalitis among patients treated with ICIs. Further investigations are necessary to develop effective diagnostic methods and therapies for the timely diagnosis and management of ICI-related encephalitis.

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

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