Journal of Cancer Research and Clinical Oncology (2024) 150:397
https://doi.org/10.1007/s00432-024-05918-9

CASE REPORT

Atezolizumab- and bevacizumab -induced encephalitis in a patient with advanced hepatocellular carcinoma: a case report and literature review

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Received: 26 June 2024 / Accepted: 10 August 2024 / Published online: 24 August 2024

Abstract

Treatment with atezolizumab and bevacizumab is the first-line therapy for unresectable hepatocellular carcinoma. Although immune checkpoint inhibitors are novel and effective treatments, they can induce immune-related adverse events. However, neurological immune-related adverse events have rarely been reported. We report the case of a man in his 40s with hepatocellular carcinoma who developed life-threatening encephalitis after atezolizumab plus bevacizumab was administered. The patient presented with fever, headache, altered mentality, and general epileptic seizures, ten days after administration. Cerebrospinal fluid analysis showed elevated white blood cells and elevated protein levels, but revealed no infection or malignancy. Brain magnetic resonance imaging showed diffuse leptomeningeal enhancement in both the cerebrum and cerebellum. As immune checkpoint inhibitor-induced encephalitis was strongly suspected, steroid pulse therapy was initiated and neurological symptoms quickly improved. The patient was discharged after 66 days of hospitalization, and administration of sorafenib and radiotherapy was started for the hepatocellular carcinoma on an outpatient basis. This case demonstrates the importance of recognizing neurological immune-related adverse events following atezolizumab and bevacizumab treatment for early intervention. We discuss this case in comparison to available literature and previous two cases of Atezolizumab- and bevacizumab- induced encephalitis in hepatocellular carcinoma.

Keywords Hepatocellular carcinoma · Atezolizumab · Bevacizumab · Immune-related adverse events · Encephalitis

Abbreviations

CSF	Cerebrospinal fluid
HCC	Hepatocellular carcinoma
ICI	Immune checkpoint inhibitor
irAEs	Immune-related adverse events
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1

Introduction

Immune checkpoint inhibitors (ICIs) have played a key role in cancer treatment strategies in recent years. Immune checkpoints, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 are expressed on cytotoxic T cells and mediate immunosuppression (Topalian et al. 2012). ICIs block immune checkpoints and activate cytotoxic T cells, subsequently enhancing antitumor activity to eliminate tumor cells (Topalian et al. 2012).

In the IMbrave150 study, the combination therapy with the ICIs, atezolizumab plus bevacizumab, showed superior results compared to those of sorafenib, the preexisting standard therapy, and the combination therapy is now currently accepted as the first-line treatment for unresectable hepatocellular carcinoma (HCC) (Finn et al. 2020). Although ICIs are novel and effective treatments, they can induce global T cell responses, which may lead to immune-related adverse

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events (irAEs). Adverse events commonly associated with ICIs have been reported to affect the skin, guts, lungs, liver and endocrine organs (thyroid and adrenal glands) (Baxi et al. 2018).

The incidence of neurological irAEs has been reported to be 2–7% (Dalakas 2018; Touat et al. 2017). The incidence of serious neurological irAEs, such as encephalitis, myelitis, Guillain-Barré syndrome, and myasthenia gravis, was reported to be below 1%, although these irAEs can be fatal (Cuzzubbo et al. 2017; Velasco et al. 2021; Satake et al. 2022; Özdirik et al. 2021; Kim et al. 2019). Here, we report the case of a patient with HCC who developed life-threatening encephalitis after treatment with atezolizumab plus bevacizumab.

Case description

A 45-year-old man who had chronic hepatitis B was diagnosed with HCC. Liver magnetic resonance imaging (MRI) and abdominal computed tomography revealed an 11 cm-sized HCC in segments 5 and 6. Positron emission tomography/computed tomography revealed tumor thrombosis in the right hepatic vein without extrahepatic metastasis. The alpha-fetoprotein level was 84.8 ng/mL, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) was 29051.6 mAU/mL. The Barcelona Clinic Liver Cancer stage was C while the liver function was preserved and no history of hepatic encephalopathy was noted (Child-Pugh class A).

Combination therapy with atezolizumab (fixed dose, 1200 mg) and bevacizumab (15 mg/kg) was initiated. No side effects were observed immediately after administration; however, 10 days later, the patient developed fever and headache, resulting in hospitalization for further examination and treatment. On the 13th day, the patient presented with confusion and general epileptic seizures. He was subsequently admitted to the intensive care unit and required mechanical ventilation.

The results of the blood tests were as follows: white blood cells, 2430 cells/μL (81% neutrophils); C-reactive protein, 6.0 mg/dL; alanine transaminase, 87 U/L; aspartate transaminase, 199 U/L; total bilirubin, 0.74 mg/dL; potassium, 5.1 mmol/L; sodium, 135 mmol/L; glucose, 106 mg/dL; thyroid-stimulating hormone, 4.3 μIU/mL, free thyroxine, 0.75 ng/dL; and ammonia, 0.798 μg/mL. The antinuclear antibody test result was negative and the results of the rapid adrenocorticotropic hormone stimulation test were normal.

Cerebrospinal fluid (CSF) analysis showed 52 cells/μL of white blood cells (90% neutrophils), 72 cells/μL of red blood cells, > 600 mg/dL total protein, and 115 mg/dL glucose, and cytology tests were negative for malignant cells. Before the culture test results were available, intravenous vancomycin, ampicillin, cefepime, and acyclovir were administered.

Brain MRI revealed diffuse leptomeningeal enhancement in both cerebral cortical sulci and cerebellar folia (Fig. 1). No significant steno-occlusive lesions or other vascular abnormalities in the intracranial vessels, bleeding, or metastases were observed. The majority of the electroencephalogram was obscured by artifacts; however, no ictal or interictal epileptiform discharge could be seen on the recognizable parts.

Bacterial and fungal cultures of the CSF were eventually found to be negative, as was a polymerase chain reaction (PCR) test for viruses, and thus, as there was no evidence of infection, the antibiotics and acyclovir were discontinued. Steroid pulse therapy (methylprednisolone at 1 g daily for 5 days) was administered for the treatment of ICI-induced encephalitis on the 18th day.

One day after steroid administration, the patient's level of consciousness rapidly improved to the point where he obeyed a simple command and seizures ceased. The patient's respiration stabilized, leading to discontinuation of mechanical ventilation. However, on the 27th day, the patient experienced another general epileptic seizure. A 24-hour electroencephalogram and brain MRI revealed no abnormalities and after administration of antiepileptic drugs, gradual improvement in consciousness was observed again without any further treatment.

The patient exhibited motor weakness in both legs. Spine MRI showed no significant abnormalities; however, electromyography revealed findings suggestive of sensorimotor polyneuropathy. The patient had no history of diabetes and had not previously presented with symptoms related to polyneuropathy. Therefore, it was considered an immune-related polyneuropathy.

After 66 days of hospitalization, the patient's condition improved, and he was discharged. Paraparesis gradually improved, and during the most recent outpatient visit, the patient was able to walk almost three steps. Currently, the patient is undergoing sorafenib treatment and radiotherapy for HCC and is being followed-up on an outpatient basis (Fig. 2).

Discussion

ICIs have emerged as key agents in the treatment of cancers and have improved survival rates (Hodi et al. 2010). PD-1 and its ligand are checkpoints that act as negative regulators of T cells, inhibiting T cell activation and, consequently, preventing immune reactions. ICIs block the interaction between PD-1 and its ligand thus activating T cell responses to tumor cells (Topalian et al. 2012). However,

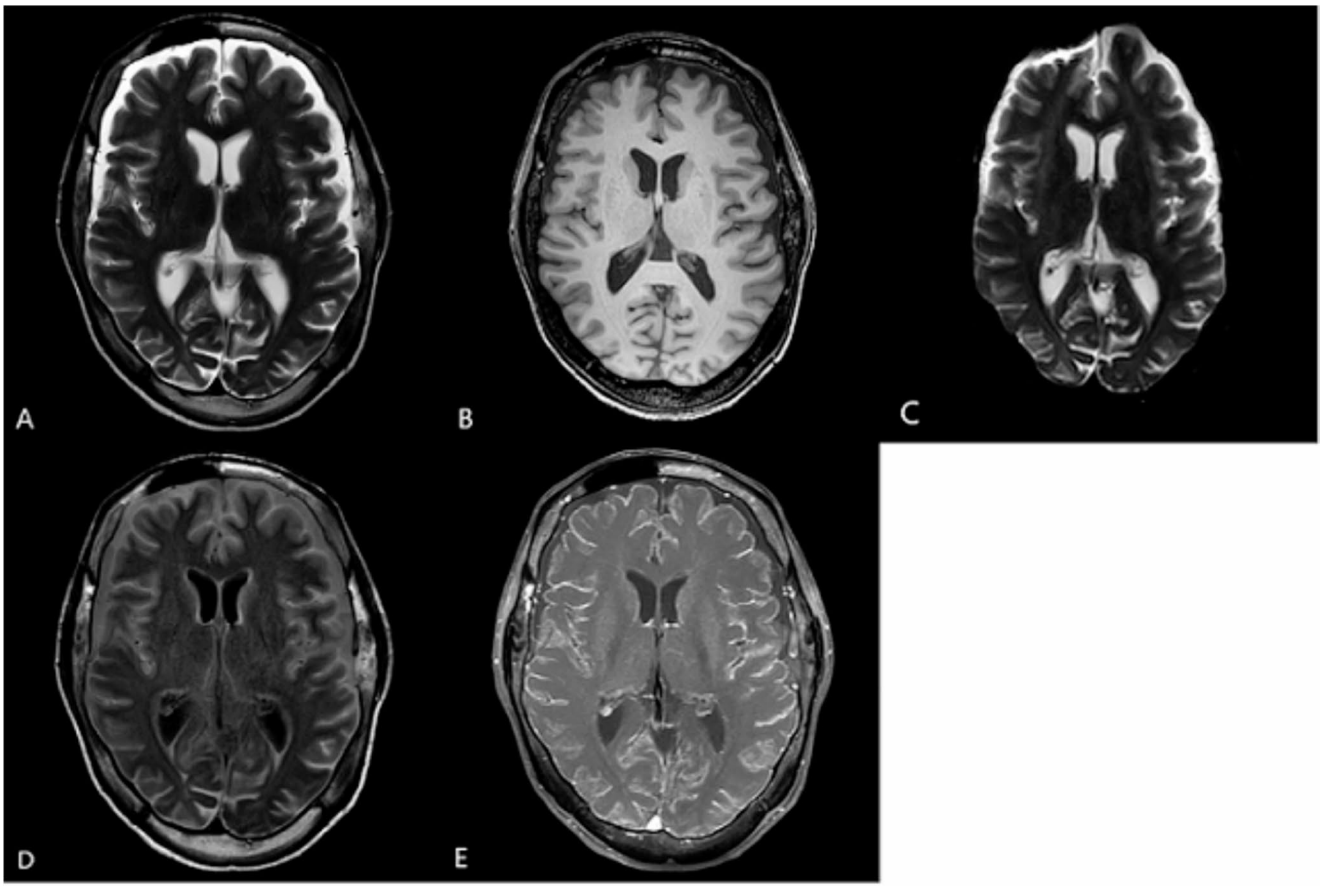

Fig. 1 Magnetic resonance imaging (MRI) of atezolizumab- and bevacizumab-induced encephalitis. Axial contrast-enhanced MRI T1 showed diffuse leptomeningeal enhancement in both cerebral cortical sulci and cerebellar folia. (**A**) Axial T2, (**B**) axial T1, (**C**) diffusion-weighted imaging, (**D**) T2 fluid-attenuated inversion recovery, and (**E**) T1 enhance

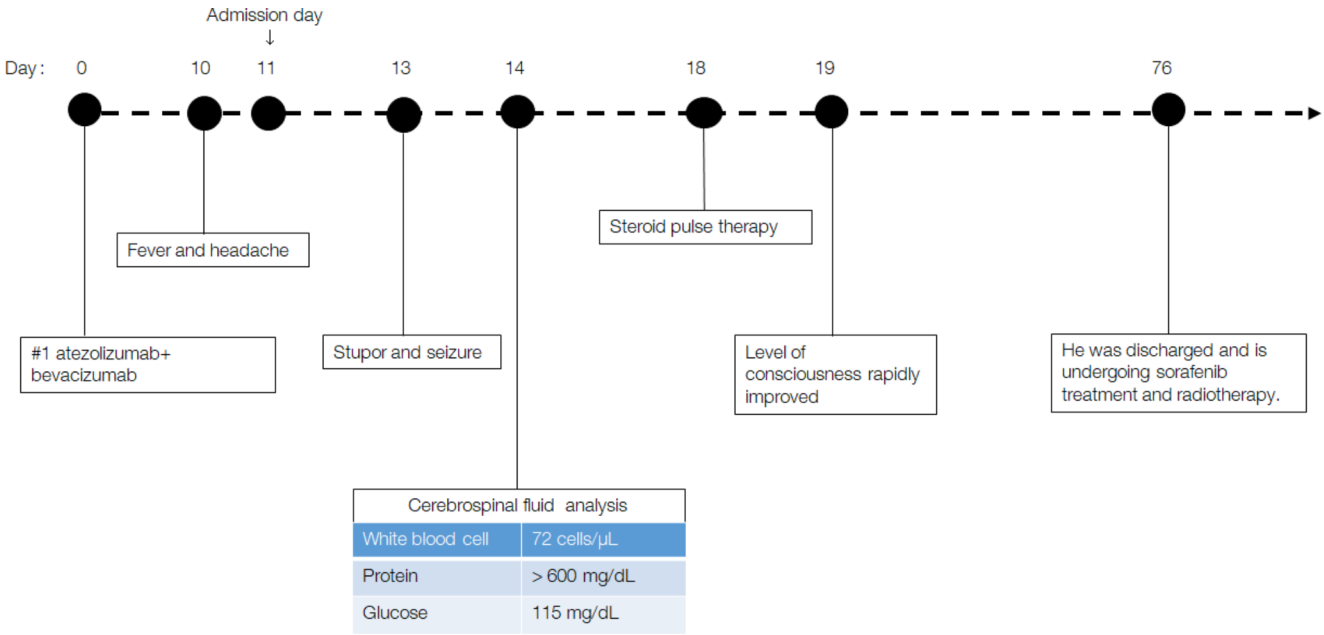

Fig. 2 Clinical course of the patient

Table 1 Characteristics of previously reported cases of atezolizumab-and bevacizumab-induced encephalitis in patients with hepatocellular carcinoma

	Satake T et al. 2022	Özdirik B et al. 2021	Our case
Sex	Female	Female	Male
Age, years	42	70	45
Onset of symptoms after atezolizumab/ bevacizumab treatment	12 days	10 days	10 days
Symptoms	Impaired cognition, fever, seizures	Impaired cognition and language, somnolence, emesis, dyspnea	Impaired cognition, fever, headache, seizures
Cerebrospinal fluid results	Increased cell count and protein levels	Increased cell count and protein levels	Increased cell count and protein levels
Magnetic resonance imaging findings	Mild encephalitis/encephalopathy with reversible splenial lesion	No abnormal findings	Diffuse leptomeningeal enhancement
Treatment	Steroid pulse therapy	Steroid pulse therapy and plasmapheresis	Steroid pulse therapy
Outcome	Paralysis and aphasia persisted. Death 1 month after discharge owing to cancer progression.	Patient was able to masticate and swallow, but active mobilization was still not possible. Death 66 days after initial treatment owing to multiorgan failure.	Patient showed alert mentality and obeyed a command. Patient was discharged and started on sorafenib and radiotherapy.

ICIs can induce adverse events by activating a nonspecific T cell response that can affect any organ system, leading to autoimmune effects (Baxi et al. 2018).

To our knowledge, only two case reports of atezolizumab- and bevacizumab-induced encephalitis have been reported in patients with HCC; (Satake et al. 2022; Özdirik et al. 2021) the patient characteristics of which are summarized in Table 1. In accordance with these previous case reports, our case had a latent period of 10 days. However, a median time of 1.5 to 3 months between ICI administration and the appearance of neurological irAEs has been indicated in some reviews (Cuzzubbo et al. 2017; Velasco et al. 2021; Vogrig et al. 2020). Similar to other cases and literatures, our patient presented with fever, headache, seizures, and impaired cognition. CSF analysis revealed pleocytosis and elevated protein levels, consistent with the findings of similar cases (Table 1). However, while diffuse leptomeningeal enhancement was observed on MRI in our case, the brain MRI was normal in one of these cases and the other indicated mild encephalitis/encephalopathy with reversible splenial lesion.

No paraneoplastic antibody tests were performed in the present case. Paraneoplastic syndrome commonly occurs in gynecologic tumors, breast cancer, lung cancer, and hematologic malignancies, (Pelosof and Gerber 2010) and usually occurs before cancer is diagnosed (Honnorat and Antoine 2007; Darnell and Posner 2003). In our case, after only one cycle of atezolizumab plus bevacizumab treatment, neurological symptoms appeared and rapidly progressed, although cranial nerve examinations were normal. No distant metastasis was observed, CSF cytology revealed no tumor cells, and brain MRI showed diffuse leptomeningeal enhancement. Considering these factors, we excluded paraneoplastic syndrome.

Treatment for ICI-induced encephalitis includes the discontinuation of ICI in all grades of severity, and concurrent administration of intravenous acyclovir is recommended until PCR results are obtained. Methylprednisolone (1–2 mg/kg) should be initiated to suppress autoimmune T cell activity. If symptoms are severe and progressive, or oligoclonal bands are present, corticosteroid pulse therapy with methylprednisolone (1 g daily) delivered intravenously for 3–5 days plus intravenous immunoglobulin (2 g/kg) over 5 days may be offered. If symptoms do not improve, rituximab or plasmapheresis may be administered to help neutralize ICIs (Schneider et al. 2021). As ICI-induced encephalitis was strongly suspected in the present case, steroid pulse therapy alone was initiated owing to insurance coverage issues. The neurological symptoms quickly improved after administration, supporting the ICI-induced encephalitis diagnosis.

The paraparesis gradually improved in the patient of the present case. Chemotherapy-induced peripheral neuropathy is a delayed effect of a chemotherapy agent, leading a chronic pain syndrome and persistent paraparesis (Staff et al. 2017).

It is crucial for healthcare providers to have a thorough understanding of the irAEs associated with ICIs and implement appropriate management strategies. Despite the low incidence, awareness of the neurological irAEs associated with ICIs, in particular, is paramount, as timely diagnosis and treatment can improve patient outcomes.

Acknowledgements At the time of this case, Byoung Kuk Jang was affiliated with the Department of Internal Medicine, Keimyung University School of Medicine in Daegu, Korea.

Author contributions Conceptualization: Min Sagong, Byoung Kuk Jang. Data curation: Min Sagong. Investigation: Min Sagong, Keun Tae Kim. Visualization: Min Sagong, Keun Tae Kim. Writing - original draft: Min Sagong, Keun Tae Kim. Writing - review & editing: Byoung Kuk Jang.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflicts of interest The authors have no potential conflicts of interest to disclose.

Patient consent Informed consent was obtained from the patient for the purpose of publication.

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