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【 CASE REPORT 】

Patient with Atezolizumab-induced Encephalitis in Hepatocellular Carcinoma

Kakeru Otomo, Masashi Fujita, Ryoji Sekine, Hidenori Sato, Naoto Abe, Tatsuro Sugaya, Chiharu Watanabe, Yosuke Takahata, Manabu Hayashi, Kazumichi Abe, Atsushi Takahashi and Hiromasa Ohira

Abstract:
A 65-year-old man treated with atezolizumab plus bevacizumab for hepatocellular carcinoma was admitted to our hospital with a fever, difficulty in moving, and aphasia. The patient became comatose immediately after admission. Imaging and cerebral fluid tests revealed no evidence of malignancy or infection. A diagnosis of atezolizumab-induced encephalitis was made, and steroid pulse therapy was initiated on admission, immediately after which the patient regained consciousness and was able to talk and walk. He was discharged with slight paralysis of his legs and was able to resume chemotherapy. An early diagnosis and treatment are required to improve the prognosis of encephalitis.

Key words: encephalitis, atezolizumab, immune checkpoint inhibitors, immune-related adverse events, hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most-common malignant tumor worldwide (1). In Barcelona Clinic Liver Cancer prognosis and treatment strategy, systemic therapy is recommended for patients at advanced or intermediate stages who are unsuitable for transarterial chemoembolization (TACE) (2). In 2019, treatment with molecular-targeting agents, including sorafenib (3), regorafenib (4), lenvatinib (5), and ramucirumab (6), was the standard treatment for patients with unresectable HCC, vascular invasion, or extrahepatic metastasis in Japan. In 2020, combination therapy with immune checkpoint inhibitors (ICIs), atezolizumab (ATZ), and bevacizumab (BEV) was approved as first-line therapy in Japan (7).

ICIs have dramatically advanced the treatment of various cancers, including HCC. ICIs, including anti-programmed cell death protein (PD)-1, anti-PD-ligand 1, and anti-cytotoxic T lymphocyte antigen-4, can induce tumor cell death by activating cytotoxic T cell responses and inhibiting tumor-induced immunosuppression (8). In contrast, T cell activation may induce immune-related adverse events (irAEs) primarily affecting the gastrointestinal tract, liver, and endocrine system, occurring in up to 65% of patients treated with ICIs (9). Notably, neurological irAEs (NirAEs) occur in an estimated 1-6% of ICI-treated patients, with possible sequelae that affect the quality of life or even fatal outcomes (8).

We herein report a case of ATZ-induced encephalitis in a patient with HCC.

Case Report

In February 2021, a 65-year-old man was admitted to our hospital with a 25-mm tumor in segment 4 of the liver. He had been undergoing treatment for hypertension and dyslipidemia for 30 years and had been receiving treatment for diabetes for 5 years. He consumed 90 g of alcohol daily. He was diagnosed with HCC and successfully treated with TACE. However, the HCC soon recurred, and TACE was performed again in June 2021. Lung metastases were de-

Department of Gastroenterology, Fukushima Medical University School of Medicine, Japan
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Correspondence to Dr. Masashi Fujita, mfujita@fmu.ac.jp

Table 1. Laboratory Findings on Admission.

Hematologic test		**Chemistry**			
White blood cell	4,700 /μL	Total protein	5.8 g/dL	TSH	0.47 μIU/mL
Neutrophil	84 %	Albumin	3.0 g/dL	Free T3	2.18 pg/mL
Lymphocyte	7 %	Total bilirubin	0.9 mg/dL	Free T4	1.08 ng/dL
Monocyte	9 %	AST	116 U/L	ACTH	80.9 pg/mL
Eosinophil	0 %	ALT	65 U/L	Cortisol	39.3 μg/dL
Basophil	0 %	LD	355 U/L		
Red blood cell	400×10^4 /μL	ALP	58 U/L	Anti-nuclear antibody	<80 negative
Hemoglobin	12.1 g/dL	γ-GTP	75 U/L	IgG	868 mg/dL
Platelet	10.8×10^4 /μL	Ammonia	28 μg/dL	IgA	304 mg/dL
				IgM	26 mg/dL
Coagulation		BUN	25 mg/dL		
PT	116.9 %	Creatinine	1.3 mg/dL	Alpha fetoprotein	376 ng/mL
APTT	27.5 s	Sodium	139 mmol/L	PIVKA-II	6,589 mAU/mL
FDP	6.4 μg/mL	Potassium	4.4 mmol/L		
D-dimer	3.5 μg/mL	Chloride	106 mmol/L	HBs-antigen	Negative
		Calcium	7.9 mg/dL	HBs-antibody	Negative
				HBc-antibody	Negative
		CRP	10.0 mg/dL	HCV-antibody	Negative
		Procalcitonin	0.34 ng/mL		
		β-D glucan	<6.0 pg/mL		

PT: prothrombin time activity, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation product, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LD: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, CRP: C-reactive protein, TSH: thyroid stimulating hormone, ACTH: adrenocorticotropic hormone, Ig: immunoglobulin, PIVKA-II: protein induced by vitamin K absence or antagonists-II, HBs: hepatitis B surface, HBc: hepatitis B core, HCV: hepatitis C virus

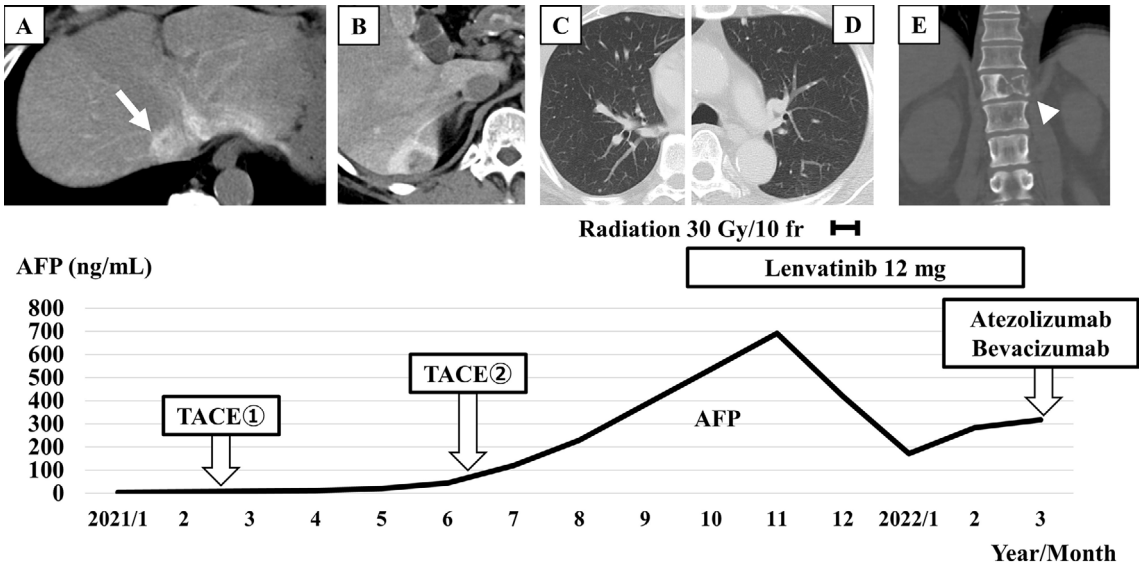

Figure 1. Clinical course of treatment before administration of atezolizumab and bevacizumab. A: Enhanced computed tomography (CT) during the first transarterial chemoembolization (TACE) session showing a hypovascular tumor in segment 8 of the liver (arrow). B: Enhanced CT after the second TACE session showing a new hypovascular tumor in segment 6 of the liver. C, D: Chest CT after the second TACE session showing multiple lung metastatic nodules. E: Abdominal CT showing bone metastasis at the 12th thoracic vertebra (arrowhead).

tected in September 2021; thus, oral administration of lenvatinib 12 mg per day was initiated. In December 2021, the patient underwent radiation therapy for a metastatic bone tumor in the 12th thoracic vertebra. In March 2022, ATZ/BEV therapy was initiated due to the progression of lung metastases (day 1) (Fig. 1). He was discharged from our hospital on

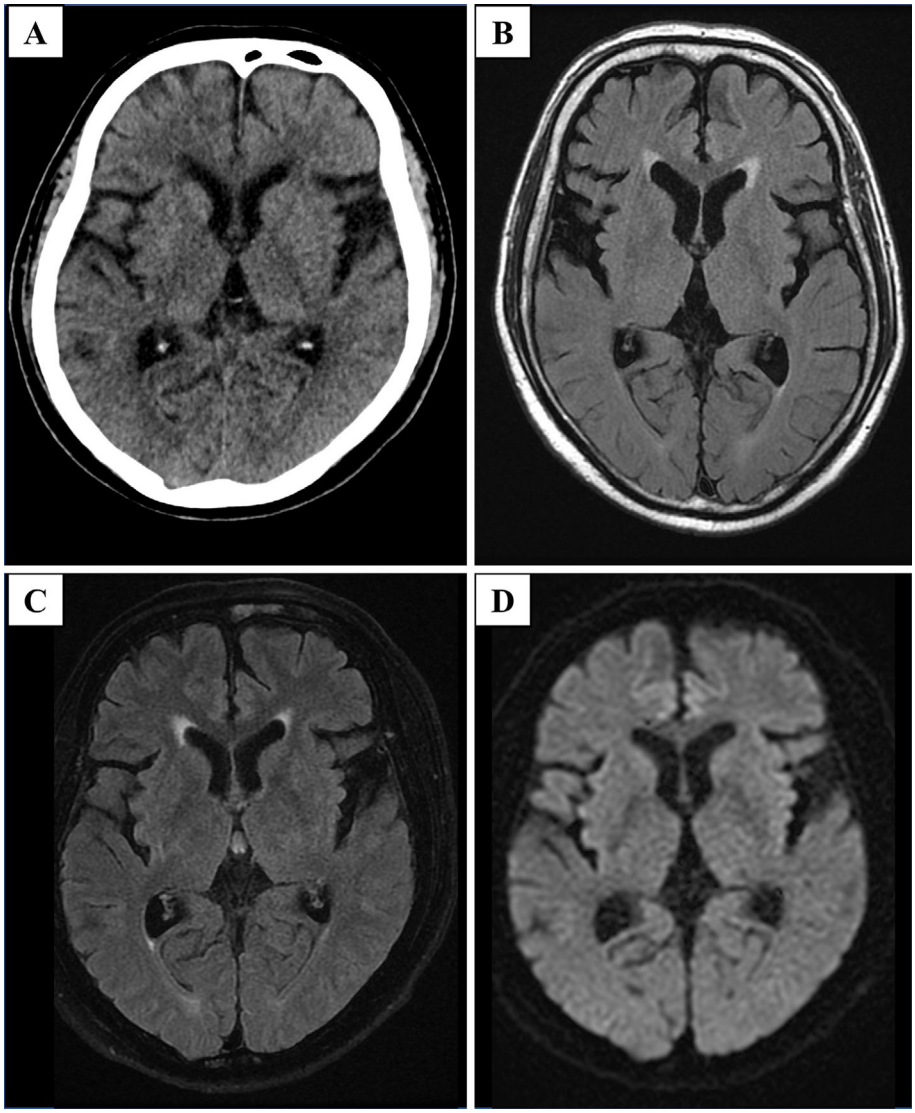

Figure 2. Image findings on admission. A: Head computed tomography (CT). B: T2-weighted magnetic resonance imaging (MRI). C: Fluid-attenuated inversion recovery MRI. D: Diffusion-weighted MRI. Neither head CT nor MRI showed obvious abnormalities.

day 4 without any adverse events. However, on day 16, he experienced general malaise, and on day 17, he developed a headache, fever, and aphasia, leading to admission to our hospital.

On admission, the patient presented with impaired consciousness, aphasia, difficulty moving (Glasgow Coma Scale E4V1M4), high fever (38.9°C), urinary incontinence, and drooling. His height was 163.1 cm, and his body weight was 71.4 kg. An examination of the head, neck, chest, abdomen, and limbs revealed no abnormalities. Although several neurological evaluations could not be performed owing to the lack of obedience, there were no obvious neurological abnormalities, such as meningeal irritation.

Laboratory findings showed elevated transaminase and γ-glutamyl transpeptidase levels and strong positivity for C-reactive protein (Table 1). Increases in adrenocorticotropic hormone and cortisol levels were also observed, but our endocrinologist determined that these elevations were physiological and had little relation to disturbance of consciousness. Neither head computed tomography nor magnetic resonance imaging (MRI) showed obvious abnormalities (Fig. 2). Furthermore, a cerebrospinal fluid (CSF) test revealed increased protein levels (Table 2).

After admission, as the patient rapidly became unconscious and comatose, steroid pulse therapy (methylprednisolone 1,000 mg for 3 days) was administered in combination with acyclovir (ACV) and piperacillin/tazobactam (PIPC/TAZ) (Fig. 3). On day 2 of hospitalization, he regained consciousness and was able to communicate verbally; on day 5, he was able to walk. A gadolinium-enhanced MRI of the head performed on day 6 did not show any abnormalities. Herpes simplex virus (HSV) polymerase chain reaction (PCR) in the CSF, 12 paraneoplastic neurological syndrome (PNS)-related antibodies, and culture tests (including blood, urine, and CSF) performed at the time of admission were all negative (Table 2); thus, administration of ACV and PIPC/TAZ was discontinued on day 6. The steroid dose was tapered, and the patient was discharged on day 31 with slight

Table 2. Laboratory Findings in Cerebrospinal Fluid, Serum Analysis and Culture Tests Results.

Infectious parameters		Paraneoplastic and autoimmune parameters		Cerebrospinal fluid	
CMV-IgG	Positive	Anti-amyphiphysin antibody	Negative	Cell count	7 /μL
CMV-IgM	Negative	Anti-CV2 antibody	Negative	Protein level	146 mg/dL
HSV-IgG	Positive	Anti-Ma2/Ta antibody	Negative	Glucose level	72 mg/dL
HSV-IgM	Negative	Anti-Ri antibody	Negative	HSV-PCR	Negative
VZV-IgG	Positive	Anti-Yo antibody	Negative	Cytology	No malignancy
VZV-IgM	Negative	Anti-Hu antibody	Negative		
Measles-IgG	Positive	Anti-recoverin antibody	Negative	**Culture tests**	
Measles-IgM	Negative	Anti-SOX1 antibody	Negative	Blood	Negative
Candida antigen	Negative	Anti-titin andibody	Negative	Urine	Negative
Aspergillosis antigen	Negative	Anti-GAD65 antibody	Negative	Cerebrospinal fluid	Negative
Cryptococcus antigen	Negative	Anti-DNER antibody	Negative		

PNS: paraneoplastic neurological syndrome, CMV: cytomegalovirus, HSV: herpes simplex virus, VZV: varicella zoster virus, Ig: immunoglobulin, PCR: polymerase chain reaction

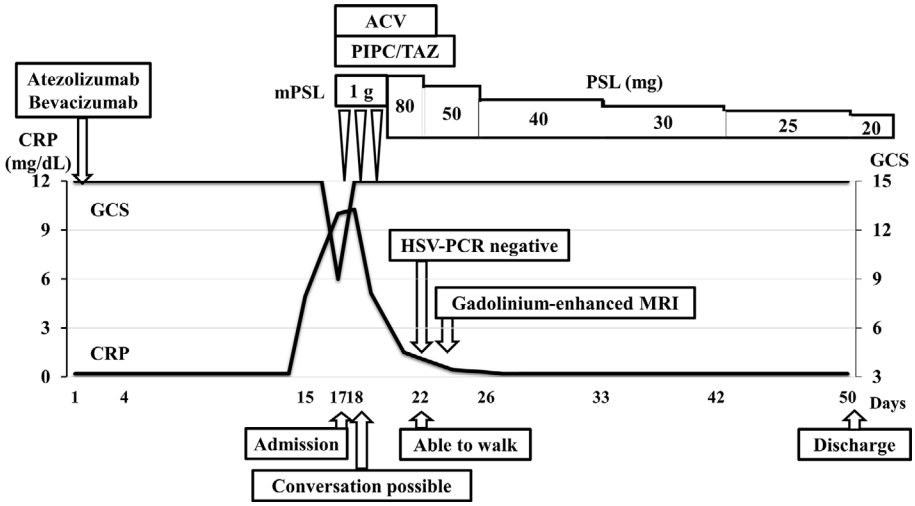

Figure 3. Clinical course of treatment after administration of atezolizumab and bevacizumab. ACV: acyclovir, PIPC/TAZ: piperacillin/tazobactam, mPSL: methylprednisolone, PSL: prednisolone, CRP: C-reactive protein, GCS: Glasgow Coma Scale, HSV: herpes simplex virus, PCR: polymerase chain reaction, MRI: magnetic resonance imaging

leg paralysis. During hospitalization, imaging findings showed no cancer progression, and no increase in tumor markers was observed. Two months after discharge, steroid therapy was discontinued, and chemotherapy with sorafenib was resumed; however, he died of progressive disease 10 months later.

Discussion

We herein report a case of ATZ-induced encephalitis in a patient with HCC. Although he fell into a coma immediately after admission, the coma and accompanying aphasia improved the day after the administration of steroid pulse therapy.

NirAEs include myasthenia gravis/myasthenic syndrome, aseptic meningitis, autoimmune encephalitis, sensory motor neuropathy, Guillain-Barré-like syndrome, painful sensory neuropathy, enteric neuropathy, transverse myelitis, and posterior reversible encephalopathy syndrome (10). NirAEs occur in 1-6% of patients treated with ICIs. Severe NirAEs grade ≥3 occurred in <1% of the patients. In particular, encephalitis is a rare event with an incidence of 0.1-0.2% (11). Encephalitis presents with a variety of clinical manifestations, including a headache, fever, impaired consciousness, ataxia, convulsions, and hallucinations (12). Approximately half of patients have abnormal findings on head MRI, mainly characterized by high signal intensity on T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR) (13). Velasco et al. reported that antineuronal autoantibody positivity and abnormal MRI findings were associated with poor outcomes, whereas a fever and more inflammatory changes in the CSF were associated with better outcomes (13).

For the diagnosis of NirAEs, it is important to rule out central nervous system progression of cancer, infection, and metabolic derangement, including hypophysitis, adrenal in-

Table 3. Case Reports of Encephalitis Due to Atezolizumab.

Reference	Disease	Age	Gender	Onset of symptoms	Symptoms	Cerebrospinal fluid	MRI findings	Treatment	Prognosis
14	HCC	68	Male	Day 13	Fever, difficulty moving	Not performed	Normal	mPSL 1 g for 3 days	Immediate improvement after steroid therapy Discharged on Day 54
15	HCC	42	Female	Day 13	Fever, impaired consciousness, convulsion	High cell count, elevated protein levels	Hyperintensity in the corpus callosum on T2 image, FLAIR image and DWI Hyperintensity in left cerebral cortex on DWI	mPSL 1 g for 3 days	Convulsion improved on Day 16, fever improved on Day 18 Aftereffects: right hemiparesis, right hemi-spatial neglect, aphasia Died on Day 110
16	HCC	70	Female	Day 11	Cognitive impairment, aphasia, impaired consciousness	High cell count, elevated protein levels	Normal	mPSL 100 mg on Day 13-15 mPSL 1 g on Day 21-24 Plasma exchange, tracheal intubation	Severe neurological aftereffects Died on Day 77
17	HCC	68	Male	Day 14	Fever, impaired consciousness	Elevated protein levels	Old cerebral infarction	mPSL 1 g on Day 16-18	Immediate improvement after steroid therapy Discharged on Day 38 Received lenvatinib therapy on Day 60
18	NSCLC	56	Male	Day 11	Fever, impaired consciousness, aphasia	High cell count, elevated protein levels	Normal	mPSL 1 g on Day 12-14	Discharged on Day 26 without aftereffects Commencement of docetaxil/ramucirumab combination therapy
19	NSCLC	78	Male	Day 14	Fever, impaired consciousness	High cell count, elevated protain levels	Normal	mPSL 1 g for 5 days	Improved
20	NSCLC	48	Male	Day 17	Fever, headache, impaired consciousness, convulsions	High cell count, elevated protein levels	Hyperintensity in bilateral temporal lobe on FLAIR image	mPSL 1 g on Day 20-22, immunoglobulin	Paresthesia of the limbs remained
21	NSCLC	72	Female	30 weeks	Gait disorder, impaired consciousness	Elevated IgG levels, oligoclonal band positive	Hyperintensity in bilateral thalamus	Steroid therapy, immunoglobulin 9 weeks after onset	Bedridden Died of aspiration pneumonia 7 months after onset of encephalitis
22	NSCLC	48	Female	Day 14	Fever, disorientation, memory impairment, aphasia	High cell count, elevated protein and glucose levels	Pachy- and leptomeningitis	mPSL 1 g for 3 days	Complete resolution 1 year after onset
23	SCLC	66	Male	2 months (after three courses)	Disorientation, dysphagia, gait disturbance	High protein levels	Hyperintensity in bilateral temporal lobes on FLAIR image	Steroid pulse therapy, immunoglobin	Dysphagia improved, but gait disturbance did not
24	Cervical	53	Female	Day 14	Impaired consciousness, headache, meningeal signs	High cell count	Diffuse leptomeningeal enhancement	High dose steroid	No aftereffects
25	Breast	38	Female	Day 11	Fever, impaired consciousness, convulsion	Inframmatory cells	Diffuse subtle hyperintensity in the sulci on T2 image	Dexamethasone 24 mg daily tracheal intubation	Discharged 2 weeks after admission with mild lower extremity weakness and numbness
26	Breast	65	Female	Day 53	Coma, respiratory failure	Not performed	Hyperintensity in cerebellar hemisphere, vermis of the cerebellum, bilateral frontal lobe, temporal lobe, parietal lobe and occipital cortex on T2 and DWI image	Steroid therapy	Dead
27	Bladder	59	Female	Day 13	Confusion, spastic tremors	Rare lymphocytes	A 1-cm metastasis in central nervous system	Steroids	Recovery with residual weakness Died of progressive disease
28	Bladder	49	Male	Day 14	Coma, convulsion	50 white blood cells	Diffuse leptomeningeal enhancement	Steroids, immunoglobin	Resolved Died of progressive disease
Our case	HCC	65	Male	Day 16	Fever, difficulty moving, coma, aphasia	High cell count, elevated protein levels	Normal	mPSL 1 g for 3 days	Immediate improvement after steroid therapy, discharged on Day 50 Died 12 months after onset of encephalitis

HCC: hepatocellular carcinoma, NSCLC: non-small-cell lung cancer, SCLC: small-cell lung cancer, Ig: immunoglobulin, MRI: magnetic resonance imaging, FLAIR: fluid-attenuated inversion recovery, DWI: diffusion-weighted imaging, mPSL: methylprednisolone

sufficiency, and hypothyroidism, as causes of neurological symptoms (10). In the present case, a metastatic brain tumor, bacterial meningitis, endocrine abnormalities, and hepatic encephalopathy were ruled out based on blood tests, MRI findings, and CSF tests at admission. Autoimmune encephalitis due to NirAEs was suspected based on the clinical course up to admission, but the possibility of encephalitis due to HSV, bacteria, or PNS could not be ruled out. However, the patient's consciousness worsened rapidly after admission, and sudden respiratory arrest and severe sequelae were possible. Therefore, we decided to start steroid pulse therapy on the day of admission while using both antibiotics and antiviral drugs, and as a result, the patient's neurological symptoms improved rapidly. HSV-PCR at the time of admission was later negative, and since the patient recovered with steroid pulse therapy, infectious encephalitis and PNS were ruled out, and ATZ-induced encephalitis was diagnosed.

Table 3 shows the clinical characteristics of patients with encephalitis due to ATZ reported previously (14-28). The most common symptom is impaired consciousness, including coma, followed by a fever; the present case had both symptoms. Touat et al. reported that encephalitis developed 4-28 weeks after ICIs administration (11). However, in most reported cases, including ours, severe neurological symptoms appeared approximately two weeks after the first administration of ATZ. In addition, T2-weighted imaging, FLAIR, and diffusion-weighted MRI showed high intensity in many cases, but in some cases, including the present case, no obvious abnormalities were observed. The CSF showed an increase in cell count and high protein levels in many cases, including our case. Patients who were treated with high-dose methylprednisolone from an early stage after the onset often experienced improvement in symptoms, but those who received a low dose of steroids or whose therapeutic intervention was delayed had aftereffects or died. Our patient was also treated with high-dose methylprednisolone immediately after admission, which improved the symptoms and allowed him to continue treatment for HCC. The Working Group of The Japanese Society of Pharmaceutical Oncology recommends steroid pulse therapy, intravenous immunoglobulin, and blood purification therapy if grade ≥3 encephalitis does not improve after administration of 1-2 mg/kg/day prednisolone (29). However, taking our results together with the results of previous reports, it may be necessary to consider starting aggressive treatment such as steroid pulse therapy as soon as possible. Indeed, our patient received steroid pulse therapy immediately after admission, resulting in discharge without major sequelae and allowing for the resumption of chemotherapy. Graus et al. proposed initiating early treatment even before antibody test results if the clinical course and laboratory findings suggested autoimmune encephalitis (30). If the patient responds well to steroid therapy, it is recommended that oral steroids be tapered over approximately four to six weeks (31). However, it has also been reported that a maintenance dose such as 5-10 mg/day may be required to prevent disease relapse (32).

Patients with pre-existing neurological autoimmune diseases were likely to be in the high-risk group. Eight patients with a history of multiple sclerosis experienced rapid progression of neurological symptoms after treatment with pembrolizumab and nivolumab (33). Paraneoplastic antibodies are associated with various neurological diseases, and their presence may increase the risk of encephalitis (34, 35). However, in the present case, all 12 types of antibodies were negative, and a previous review reported that 48% of patients with ICI-associated encephalitis were negative for paraneoplastic antibodies (36). Individual risk factors for irAEs have been studied, and a previous report suggested that the gastrointestinal flora was associated with altering the efficacy and toxicity of immunotherapy (37). However, the relationship between acquired factors, including lifestyle habits such as smoking and drinking, and irAEs has not been clarified.

There is no preventive measure for NirAEs, especially in patients who are not predisposed to autoimmune diseases. Furthermore, it is often difficult to perform adequate examinations during a severe course. In the present case, with the cooperation of a neurologist, we were able to promptly diagnose and treat the patient based on the MRI and CSF results. In cases where neurological symptoms develop during ICI treatment, prompt and appropriate treatment should be provided in cooperation with a neurologist.

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

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin **68**: 394-424, 2018.
2. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol **76**: 681-693, 2022.
3. Llovet JM, Ricci S, Mazzaferro V, et al.; the SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med **359**: 378-390, 2008.
4. Bruix J, Qin S, Merle P, et al.; the RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet **389**: 56-66, 2017.
5. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet **391**: 1163-1173, 2018.
6. Zhu AX, Kang YK, Yen CJ, et al.; the REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol **20**: 282-296, 2019.
7. Finn RS, Qin S, Ikeda M, et al.; the IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med **382**: 1894-1905, 2020.
8. Albarrán V, Chamorro J, Rosero DI, et al. Neurologic toxicity of immune checkpoint inhibitors: a review of literature. Front Phar-

macol **13**: 774170, 2022.
9. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol **13**: 473-486, 2016.
10. Brahmer JR, Lacchetti C, Schneider BJ, et al.; the National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol **36**: 1714-1768, 2018.
11. Touat M, Talmasov D, Ricard D, Psimaras D. Neurological toxicities associated with immune-checkpoint inhibitors. Curr Opin Neurol **30**: 659-668, 2017.
12. Johnson DB, McDonnell WJ, Gonzaalez-Ericsson PI, et al. A case report of clonal EBV-like memory $CD4^+$ T cell activation in fatal checkpoint inhibitor-induced encephalitis. Nat Med **25**: 1243-1250, 2019.
13. Velasco R, Villagran M, Jove M, et al. Encephalitis induced by immune checkpoint inhibitors: a systematic review. JAMA Neurol **78**: 864-873, 2021.
14. Hirata T, Sugimoto K, Kakegawa T, et al. A case of suspected autoimmune encephalitis after the introduction of atezolizumab + bevacizumab therapy for hepatocellular carcinoma. Kanzo (J Jpn Soc Hepatol) **62**: 590-592, 2021 (in Japanese).
15. Satake T, Maruki Y, Kudo Y, et al. Atezolizumab-induced encephalitis in a patient with hepatocellular carcinoma: a case report and literature review. Intern Med **61**: 2619-2623, 2022.
16. Özdirik B, Jost-Brinkmann F, Savic Lj, et al. Atezolizumab and bevacizumab-induced encephalitis in advanced hepatocellular carcinoma: case report and literature review. Medicine (Baltimore) **100**: e26377, 2021.
17. Osuga T, Miyanishi K, Ito R, et al. Occurrence of autoimmune encephalitis in a patient with hepatocellular carcinoma after atezolizumab and bevacizumab combination therapy: a case study. Kanzo (J Jpn Soc Hepatol) **64**: 559-556, 2023 (in Japanese).
18. Yamaguchi Y, Nagasawa H, Katagiri Y, Wada M. Atezolizumab-associated encephalitis in metastatic lung adenocarcinoma: a case report. J Med Case Rep **14**: 88, 2020.
19. Arakawa M, Yamazaki M, Toda Y, et al. Atezolizumab-induced encephalitis in metastatic lung cancer: a case report and literacture review. eNeurologicalSci **14**: 49-50, 2018.
20. Watanabe S, Yoshizumi K, Moriguchi S, et al. Nivolumab treatment followed by atezolizumab induced encephalitis and neuropathy with antiganglioside antibodies. eNeurologicalSci **25**: 100386, 2021.
21. Nishijima H, Kon T, Seino Y, et al. Bilateral thalamic lesions associated with atezolizumab-Induced encephalitis: a follow-up report with autopsy findings. Neurology **98**: 204-205, 2022.
22. Robert L, Langner-Lemercier S, Angibaud A, et al. Immune-related encephalitis in two patients treated with immune checkpoint inhibitor. Clin Lung Cancer **21**: 474-447, 2020.
23. Nakashima K, Demura Y, Kurokawa K, et al. Immune checkpoint inhibitor-induced limbic encephalitis during treatment with atezolizumab in a patient with small-cell lung cancer: a case report and review of the literature. Case Reports Immunol **2022**: 9290922, 2022.
24. Laserna A, Tummala S, Patel N, EI Hamouda DEM, Gutiérrez C. Atezolizumab-related encephalitis in the intensive care unit: case report and review of the literature. SAGE Open Med Case Rep **6**: 2050313X18792422, 2018.
25. Nader R, Tannoury E, Rizk T, Ghanem H. Atezolizumab-induced encephalitis in a patient with metastatic breast cancer: a case report and review of neurological adverse events associated with checkpoint inhibitors. Autops Case Rep **11**: e2021261, 2021.
26. Chen G, Zhang C, Lan J, Low Z, Zhang H, Zhao Y. Atezolizumab-associated encephalitis in metastatic breast cancer: a case report. Oncol Lett **24**: 324, 2022.
27. Levine JJ, Somer RA, Hosoya H, Squillante C. Atezolizumab-induced encephalitis in metastatic bladder cancer: a case report and review of the literature. Clin Genitourin Cancer **15**: e847-e849, 2017.
28. Kim A, Keam B, Cheun H, Lee ST, Gook HS, Han MK. Immune-checkpoint-inhibitor-induced severe autoimmune encephalitis treated by steroid and intravenous immunoglobulin. J Clin Neurol **15**: 259-261, 2019.
29. Japanese Society of Pharmaceutical Oncology. Cancer Immunotherapy Guidelines. 3rd ed. Kanehara Shuppan, Tokyo, 2023: 68-74.
30. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol **15**: 391-404, 2016.
31. Dubey D, David WS, Reynolds KL, et al. Severe neurological toxicity of immune checkpoint inhibitors: growing spectrum. Ann Neurol **87**: 659-669, 2020.
32. Seki M, Kitano S, Suzuki S. Neurological disorders associated with immune checkpoint inhibitors: an association with autoantibodies. Cancer Immunol Immunother **71**: 769-775, 2022.
33. Garcia CR, Jayswal R, Adams V, Anthony LB, Villano JL. Multiple sclerosis outcomes after cancer immunotherapy. Clin Transl Oncol **21**: 1336-1342, 2019.
34. Gozzard P, Maddison P. Which antibody and which cancer in which paraneoplastic syndromes? Pract Neurol **10**: 260-270, 2010.
35. Gill A, Perez MA, Perrone CM, Bae CJ, Pruitt AA, Lancaster E. A case series of PD-1 inhibitor-associated paraneoplastic neurologic syndromes. J Neuroimmunol **334**: 576980, 2019.
36. Stuby J, Herren T, Naumburger GS, Paget C, Rudiger A. Immune checkpoint inhibitor therapy-associated encephalitis: a case series and review of the literature. Swiss Med Wkly **150**: w20377, 2020.
37. Inamura K. Roles of microbiota in response to cancer immunotherapy. Semin Cancer Biol **65**: 164-175, 2020.