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Single Case

A Case of Immune-Related Aseptic Meningitis during Atezolizumab plus Bevacizumab for Hepatocellular Carcinoma

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Keywords
Atezolizumab · Bevacizumab · Immure-related adverse event · Aseptic meningitis

Abstract
Introduction: Immune checkpoint inhibitors are sometimes associated with immune-related adverse events during or after treatment. Among these, aseptic meningitis is a rare and serious complication. We report the first case of atezolizumab-induced aseptic meningitis, which occurred during treatment for advanced hepatocellular carcinoma (HCC). ***Case Presentation:*** A 74-year-old woman diagnosed with advanced HCC and treated with first-line atezolizumab plus bevacizumab developed anorexia, fatigue, and fever, after three treatment cycles. Cerebrospinal fluid examination showed slightly increased cell count and protein level but no infection or malignancy. Contrast enhancement along the cerebral sulcus was evident in contrast-enhanced magnetic resonance imaging, and the patient was diagnosed with aseptic meningitis associated with atezolizumab. Steroid therapy soon improved her clinical symptoms, and the contrast enhancement along the cerebral sulcus disappeared. ***Conclusion:*** Clinicians should monitor to avoid serious immune-related adverse events, such as aseptic meningitis, in patients during treatment of HCC with immune checkpoint inhibitors and make the diagnosis as soon as possible.

Introduction

Immune checkpoint inhibitors (ICIs) are systemic treatments for various cancers including hepatocellular carcinoma (HCC). Japan clinical guidelines and Barcelona Clinic Liver Cancer Group recommend atezolizumab plus bevacizumab (Atez+Bev) as first-line systemic

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treatment for unresectable HCC and advanced and intermediate stages [1, 2]. ICIs are known to cause diverse immune-related adverse events (irAEs) that are sometimes life threatening. Aseptic meningitis is a rare irAE that responds well to steroids if treated early [3]. Atezolizumab-induced immune-related aseptic meningitis has previously been reported in patients with lung cancer [4, 5] but not in patients with HCC.

Here, we report the first case of aseptic meningitis caused by Atez+Bev for advanced HCC. We emphasize to make an early diagnosis based on physical findings, laboratory data, and imaging and provide prompt effective treatment during ICIs-based therapy.

Case Report

A 74-year-old woman presented to our hospital complaining of right upper abdominal pain. Although she had a history of hypertension and hyperlipidemia, they were well controlled with medications. Enhanced computed tomography revealed multiple nodules with contrast enhancement in both lobes of her liver, including a nodule up to 10 cm in the right lobe (shown in Fig. 1a, b). Hepatitis viral tests including hepatitis B virus antigen and hepatitis C antibody showed negative, and the patient had no history of alcohol consumption. Her liver reserve function was preserved as Child-Pugh score 5, grade A, and her serum alpha-fetoprotein and des-gamma-carboxy prothrombin levels were elevated to 12,200 ng/mL and 9,463 AU/L, respectively. We diagnosed unresectable HCC and administered Atez+Bev as an outpatient.

Five days after 3 courses of Atez+Bev treatment, she showed anorexia and general fatigue. She was admitted to our hospital because her symptoms continued. She presented with fever and dysarthria, a body temperature of 38.1°C, disturbed consciousness Glasgow Coma Scale 14 (GCS, E4V4M6) but no neck stiffness. Her blood pressure elevated slightly to 154/112 mm Hg. Blood examinations were unremarkable, including blood count, electrolytes, ammonium level, and organ function, except for slight inflammatory change (C-reactive protein, 0.89 mg/dL). A urine test showed no sign of urinary tract infection. A computed tomography scan revealed the HCC had shrunk to 9 cm, but the reason for fever was not evident, excluding pneumonitis, cholangitis, and enterocolitis (shown in Fig. 2a, b). A cerebrospinal fluid (CSF) examination performed to evaluate disturbance of consciousness the day after admission showed slightly increased cell count (6/mm^3) and protein level (49 mg/dL) and normal glucose level (72 mg/dL). CSF cytology was negative for malignancy. Contrast-enhanced fluid-attenuated inversion recovery magnetic resonance imaging revealed contrast enhancement along the cerebral sulcus (shown in Fig. 3a). Based on her clinical presentation, CSF data, and MRI findings, she was diagnosed with aseptic meningitis probably caused by atezolizumab.

Prednisolone (80 mg, 1.2 mg/kg) was started and on the following day her consciousness level and fever improved (GCS E4V5M6). Prednisolone dose was tapered from 80 to 40 mg by 20 mg reductions interspaced by 5 days. The contrast effect along the cerebral sulcus had disappeared from fluid-attenuated inversion recovery magnetic resonance imaging by 8 days after commencing prednisolone treatment (shown in Fig. 3b). The patient was discharged on day 14 of hospitalization, and steroid dose was tapered weekly. Although the tumor seemed to respond to Atez+Bev treatment, treatment was discontinued due to the adverse event. When the prednisolone dose was less than 10 mg, the patient was treated with lenvatinib plus transcatheter arterial chemoembolization. The steroid was tapered off by 13 weeks. She has been then treated with molecular targeted agents sequentially more than 15 months as an outpatient. Recurrence of neurological involvement and neurological symptoms was not observed 12 months after completing steroid treatment.

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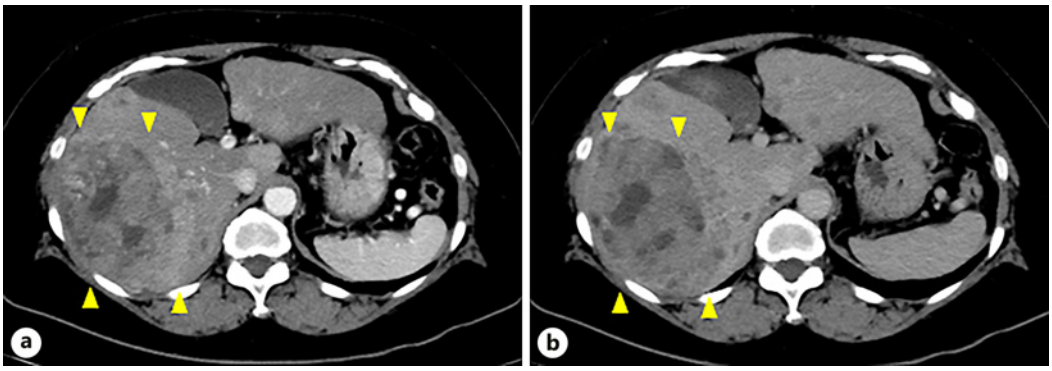

Fig. 1. CT scan before treatment for hepatocellular carcinoma. **a** Early phase. **b** Late phase. Multiple nodules in the liver, including a nodule up to 10 cm in the right lobe (yellow arrowheads).

Discussion

Although ICIs are known to cause various autoimmune-related side effects, aseptic meningitis is rare among them. The OAK study, the first randomized phase-III trial that reported the results of anti-programmed death-ligand 1 (PD-L1) monoclonal antibody for non-small-cell lung carcinoma (NSCLC), showed the frequency of meningitis and encephalitis by atezolizumab was 0.7% [6]. The IMbrave 150 trial, which was a phase-III randomized trial to determine the safety and efficacy of Atez+Bev for unresectable HCC, reported no patients developed meningitis [7]. On the other hand, there have been limited cases with encephalitis induced by Atez+Bev treatment for HCC [8]. The irAE encephalitis developed between 2 weeks after treatment initiation similar to reported cases with meningitis. However, in present case, the symptoms developed after 3 courses of Atez+Bev treatment that was later than previous reports.

The mechanism of immune-related meningitis remains unclear. A case report revealed activated memory CD4+ T cells were highly enriched in an inflamed region, and cytotoxic CD4+ and CD8+ T cells infiltrated into the central nervous system of patients with checkpoint inhibitor-associated immune encephalitis [9]. In CSF examination of the present case, the cell count was slightly high, and the protein and glucose levels were slightly high and normal, respectively. CSF cytologic examination lacked malignant findings and bacterial infectious meningitis and carcinomatous meningitis were ruled out. National Comprehensive Cancer Network (NCCN) recommends ruling out herpes simplex viral infection by polymerase chain reaction (PCR) [10]. In our case, a PCR test for herpes simplex virus could not be performed due to insufficient CSF sample. However, the small increase in cell count suggested ruling out viral meningitis, and all other findings were compatible with the diagnosis of aseptic meningitis. In aseptic meningitis, drug-induced aseptic meningitis (DIAM) is known among which nonsteroidal anti-inflammatory drugs, antibiotics, immunoglobulins, and monoclonal antibodies such as anti-tumor necrosis factor alpha or cetuximab have been reported as causative agents [11, 12]. Bevacizumab has not been previously reported as a cause of DIAM. The clinical course of DIAM due to anti-tumor necrosis factor alpha or cetuximab has rapid onset (within hours after start of treatment) and severe pleocytosis in CSF [11, 12], which differ markedly from the present case. However, bevacizumab-related aseptic meningitis is no less likely, so immune-related aseptic meningitis was suspected in the present case.

MRI showed a contrast effect on the cerebral sulcus before treatment, and the finding supported the diagnosis. MRI taken after steroid treatment initiation showed the contrast effect had disappeared. Although CSF examination has been used to evaluate treatment efficacy elsewhere [4], MRI was a valuable examination tool in the present case. MRI may be useful to reveal

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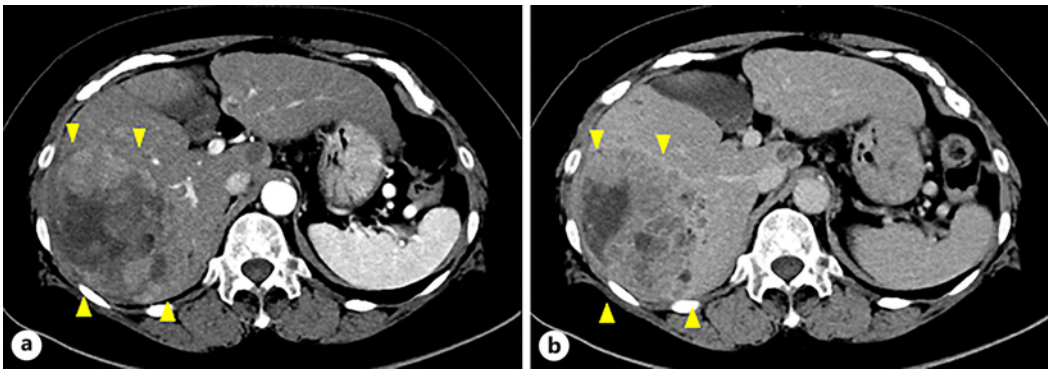

Fig. 2. CT scan performed at symptom onset. **a** Early phase. **b** Late phase. No findings of fever but hepatocellular carcinoma shrank to 9 cm (yellow arrowheads).

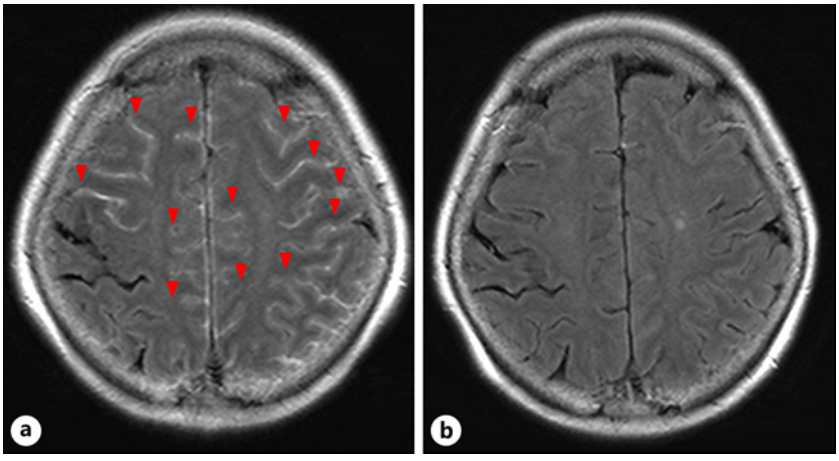

Fig. 3. Contrast-enhanced FLAIR MRI of the brain. **a** Imaging before steroid treatment revealing contrast enhancement along the cerebral sulcus (red arrowheads). **b** Image taken 8 days after commencing steroid treatment indicating the contrast effect along the cerebral sulcus disappeared.

meningitis findings since it is less invasive than CSF examination. However, in a review of the literature, no remarkable signs were revealed in 56.4% of patients with irAE meningitis examined by MRI [13], so it is important to evaluate such patients using a combination of CSF and MRI.

NCCN recommends a therapeutical approach based on adverse event severity according to Common Terminology Criteria for Adverse Events (CTCAE) [10]. It endorses management of inpatient care for grade 3 and 4 patients. High-dose corticosteroid is the first-line recommended treatment [10]. Toyozawa et al. [5] used steroid pulse (1,000 mg for 3 days) as first-line treatment for atezolizumab-induced meningitis with NSCLC. Ogawa et al. [4] started with methyl-prednisolone 1,000 mg for 3 days for atezolizumab-related meningitis with NSCLC, then switched to prednisolone at a dose of 1 mg/kg to taper off. In both cases, the disease improved quickly with initial therapy. Steroid therapy is generally effective, but some patients with poor response to steroids may need IVIg or plasmapheresis [14].

The decision to reintroduce ICIs after improvement of irAEs is a contentious issue. The learned bodies NCCN recommends reintroducing ICIs in cases that experienced grade 1 or 2 adverse events [11], whereas Simonnagio et al. [15] reported that 59% of patients who had experienced grade 3 or 4 irAEs suffered recurrence when ICIs were reintroduced. They mentioned the necessity to consider the potential severity of irAE recurrence with

re-administered ICIs but did not recommend re-challenge for cardiac or neurologic irAEs. In the present case, the patient showed adverse event severity grade 3 according to CTCAE; we therefore discontinued Atez+Bev therapy and did not reintroduce it.

This may be the first case of meningitis caused by atezolizumab for HCC and the first report to describe detailed information about atezolizumab-induced aseptic meningitis with HCC. In Japan, atezolizumab was approved for NSCLC in January 2018 and HCC in September 2020. The short period since approval may be the reason for no previous report of atezolizumab-induced meningitis with HCC. We anticipate that bevacizumab might be associated with development or pathogenesis of aseptic meningitis in a small cohort of HCC cases in the future because Atez+Bev therapy is mainstream treatment for unresectable HCC. Accumulation of cases that develop aseptic meningitis during Atez+Bez treatment for HCC, and investigation to tease out any mitigating features in these patients that may render them susceptible to irAEs is recommended. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535476).

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval was not required in accordance with local or national guidelines.

Conflict of Interest Statement

All authors declare that they have no conflict of interest.

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Author Contributions

Hiroki Kawanaka and Kazuto Tajiri wrote this manuscript. Nozomu Muraishi, Aiko Murayama, and Ichiro Yasuda edited this manuscript. Takamasa Nukui collected the data of cerebral spinal fluid of the patient. All authors approved the final version of the manuscript.

Data Availability Statement

All data from this case are presented in the article. Further inquiries can be directed to the corresponding author.

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