

Posterior reversible encephalopathy syndrome during enfortumab vedotin therapy: a case report

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Case Report

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Abstract

Background

Antibody–drug conjugates (ADCs) are widely used to treat solid malignancies. Enfortumab vedotin (EV) is an effective therapeutic option for advanced urothelial carcinoma. Although EV-associated neurotoxicity is most commonly reported as peripheral neuropathy, central nervous system complications, particularly posterior reversible encephalopathy syndrome (PRES), are rare. We report a case of PRES associated with EV therapy.

Case presentation:

A man in his 50s underwent right nephroureterectomy for urothelial carcinoma, followed by adjuvant nivolumab therapy. Subsequently, multiple liver metastases developed, and treatment with EV was initiated. One day after EV administration during the second cycle, the patient developed acute visual impairment and altered consciousness. Brain magnetic resonance imaging (MRI) with fluid-attenuated inversion recovery sequences revealed hyperintense lesions in the subcortical white matter, predominantly involving both occipital lobes, consistent with PRES. EV was discontinued, and conservative management was initiated. The patient's neurological symptoms improved rapidly, and follow-up MRI demonstrated complete radiological resolution of the lesions.

Conclusions

In patients who develop visual disturbances, altered mental status, or other central neurological symptoms after treatment with EV, PRES should be considered in the differential diagnosis in addition to brain metastases. Early diagnosis of PRES during EV therapy may prevent irreversible neurological sequelae. Prompt neuroimaging evaluation and appropriate management are essential to achieve favorable outcomes.

Background

Antibody–drug conjugates (ADCs) have rapidly expanded the therapeutic landscape for solid tumors by combining target specificity with potent cytotoxic effects. Enfortumab vedotin (EV), an ADC targeting nectin-4 conjugated with monomethyl auristatin E (MMAE), has demonstrated significant clinical benefits in advanced urothelial carcinoma.¹

Adverse neurological events associated with ADCs have primarily been reported as peripheral neuropathy related to microtubule inhibition by the cytotoxic payload.² Although central nervous system toxicity of EV has been suggested, relevant clinical evidence remains limited.³

Posterior reversible encephalopathy syndrome (PRES) is characterized by acute neurological symptoms, such as visual disturbances, altered consciousness, and seizures, accompanied by reversible vasogenic edema on neuroimaging.^{4,5} Early recognition is crucial because delayed diagnosis may result in irreversible neurological damage.⁶ To the best of our knowledge, PRES occurring during EV therapy has never been reported.

Reports of PRES occurring during treatment with ADCs are extremely limited, and clinical data regarding cases associated with EV are particularly scarce. In this report, we present a case of PRES that developed during EV therapy. The patient developed visual impairment and altered consciousness, with imaging findings suggestive of PRES.

Case presentation

The patient was a male in his 50s. His height was 169.1 cm, body weight 64.5 kg, and body mass index 22.6 kg/m². His general condition was good, and his performance status was 0. His medical history included appendicitis 41 years ago and hypertension diagnosed 3 years prior to presentation. The patient had no history of drug-related adverse events. He smoked 5–6 cigarettes per day from the age of 16 to 28 years, after which he quit smoking. He occasionally consumed alcohol.

He was diagnosed with right-sided urothelial carcinoma (cT3N0M0, Stage III) and underwent right nephroureterectomy in June of year X (Y – 6 months). The resected specimen revealed a tumor measuring 20×18 mm originating at the ureteropelvic junction. Histologically, the tumor was a high-grade invasive urothelial carcinoma that extended beyond the muscularis propria. Slight invasion into the periureteral adipose tissue was observed, and the pathological stage was determined to be pT3. In addition, marked lymphovascular invasion was noted predominantly in deeper invasive areas, with both lymphatic and venous invasion being positive.

Adjuvant therapy with nivolumab was initiated, starting at a dose of 480 mg/body in May of year X (Y – 5 months) and administered every 4 weeks for a total of four cycles. However, in January of year X (Y – 1 month), multiple liver metastases were detected. Simultaneously, the liver enzyme levels increased, with aspartate aminotransferase and alanine aminotransferase levels rising to 72 U/L and 86 U/L, respectively (baseline values: 19 U/L and 16 U/L). Given the insufficient therapeutic response, the treatment was switched to EV, which was initiated at 1.25 mg/kg (70 mg/body) and administered on days 1, 8, and 15 of a 28-day cycle for the first cycle. The concomitant medications included 5 mg lemborexant once daily, 60 mg fexofenadine hydrochloride twice daily, and 5 mg olanzapine (orally disintegrating tablets) once daily.

Regarding the renal function, the baseline serum creatinine level was mildly elevated (1.9 mg/dL). From January of year X (Y – 1 month), it gradually increased, exceeding 4.0 mg/dL by the time of the second cycle of EV in year X (Y month). Furthermore, blood pressure, which was 118/72 mmHg at baseline, increased to 158/95 mmHg by year X (month Y).

Next day after the administration of the second cycle of EV, the patient became disoriented and experienced a reduction in visual acuity. Visual impairment was bilateral; however, the exact time of onset was unclear because of concomitant altered consciousness. Upon admission, the patient's level of consciousness according to Glasgow Coma Scale was E4V4M6. No headache or seizures were observed. Neurological examination revealed impaired visual acuity and disorientation; but focal neurological deficits, such as anisocoria, conjugate eye deviation, apparent paralysis, or aphasia, were absent. The patient's clinical course is shown in Fig. 1.

During the first cycle of EV, all three scheduled administrations were completed; however, the patient required hospitalization because of poor oral intake caused by nausea and vomiting. Subsequently, the second cycle was initiated. On day 2 of the second cycle, the patient developed acute visual impairment and altered consciousness. This event was classified as a grade 3 adverse event consistent with PRES according to the Common Terminology Criteria for Adverse Events version 5.0.

At the time of symptom onset, neurological examination revealed bilateral visual disturbances accompanied by disorientation, but no focal neurological deficits, such as hemiparesis, were observed. Ophthalmological evaluation revealed no remarkable abnormalities, suggesting a central nervous system etiology. Brain magnetic resonance imaging (MRI) using fluid-attenuated inversion recovery sequences demonstrated asymmetric hyperintense lesions predominantly in the subcortical white matter of both occipital lobes, partially extending into the parietal lobes. These findings were consistent with vasogenic edema and suggestive of PRES (Fig. 2). Brain metastases were considered unlikely. In collaboration with the neurology team, EV was discontinued, and the patient was managed conservatively under close neurological monitoring.

Thereafter, the patient's symptoms rapidly improved, and both visual impairment and altered consciousness resolved. Follow-up MRI confirmed improvement of the lesions, indicating a reversible clinical course consistent with that of PRES.

Discussion and Conclusions

The present report describes the development of PRES during the treatment of urothelial carcinoma with EV. Neurological toxicity associated with EV is primarily recognized as peripheral neuropathy,¹ and reports of central nervous system complications, particularly PRES, are extremely limited. This case is clinically significant, as it suggests that PRES should be considered in the differential diagnosis when acute visual disturbances and altered consciousness occur during EV therapy.

Sharing the clinical course, imaging findings, and management strategies of PRES occurring during EV treatment, as in the present case, is important to improve the diagnostic accuracy of the emerging central nervous system symptoms and ensure safe administration of anticancer drugs. Known risk factors for PRES include hypertension, rapid elevation of blood pressure, preeclampsia, renal diseases, such as nephrotic syndrome, renal dysfunction, liver disease, and exposure to chemotherapeutic

agents.⁶ In this case, in addition to established risk factors such as impaired renal function owing to the loss of one kidney and hypertension, a drug-related factor, namely EV administration, was also present.

EV is an ADC targeting nectin-4, with MMAE as its cytotoxic payload. Vascular endothelial injury caused by microtubule inhibition⁷ may have contributed to the development of vasogenic edema in the central nervous system.^{8,9,10} Furthermore, MMAE is a cytotoxic agent primarily metabolized in the liver, and in this case, hepatic dysfunction associated with liver metastases may have delayed its metabolism and excretion, leading to elevated blood concentrations. Consequently, MMAE-induced renal cellular injury may have worsened renal dysfunction, which was further exacerbated by continued EV administration, resulting in hypertension. The interplay between renal impairment and hypertension may have contributed to the development of PRES in our patient.

Although a direct causal relationship between EV administration and PRES could not be definitively established in this case, it is plausible that the syndrome developed because of multiple overlapping risk factors. Currently, PRES is not listed in the package insert or risk management plan for EV. Reports of PRES following EV administration are also extremely limited in the Pharmaceuticals and Medical Devices Agency database, with only one reported case for which detailed clinical information is lacking. Although PRES often follows a reversible course with early diagnosis and appropriate management, a delayed diagnosis may result in irreversible neurological deficits.⁶ However, PRES symptoms are nonspecific, and in this case, differentiation from more common conditions in patients with cancer, such as brain metastases or general clinical deterioration, was challenging.⁶ Therefore, when central neurological symptoms develop during EV treatment, it is crucial to consider drug-induced adverse events and promptly perform appropriate diagnostic evaluations, including early imaging studies.

The strength of this case lies in the clear temporal relationship between EV administration and the onset of neurological symptoms as well as in the elucidation of typical PRES findings and their reversibility through serial MRI evaluations. However, as this is a single-case report, there are inherent limitations in establishing causality. Nevertheless, this report highlights the importance of early imaging assessment when central nervous system symptoms arise during EV therapy. Our study may contribute to better understanding of rare but potentially serious central neurotoxicity associated with ADCs, particularly EV, and support the establishment of safer treatment strategies and early intervention systems for continued therapy.

In conclusion, we described a case of urothelial carcinoma in which PRES developed during treatment with EV. When central nervous system symptoms such as visual disturbance or altered consciousness occur during EV therapy, PRES should be considered in the differential diagnosis, in addition to brain metastasis, and prompt imaging evaluation and appropriate management are essential.

Abbreviations

ADC Antibody

Declarations

Ethics approval and consent to participate

This study was approved by the Clinical Research Review Committee of Kameda Medical Center, Tetsushokai Medical Corporation (Approval No. 25-037) and was conducted in accordance with the principles of the Declaration of Helsinki.

. The Clinical Research Review Committee waived the requirement for informed consent because obtaining such consent was deemed impracticable.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. Restrictions apply due to the protection of participant privacy.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MI collected the clinical data, performed the literature review, and drafted the manuscript. IH, KK, and RF supervised the preparation of the manuscript and critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

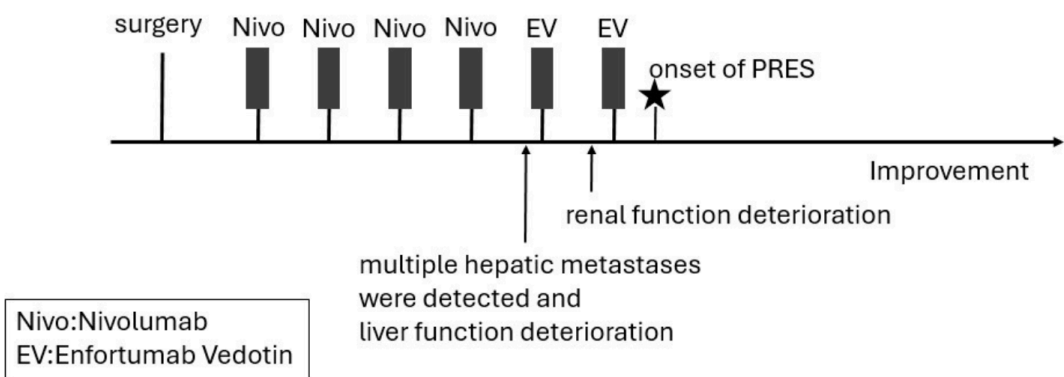


Figure 1

Clinical course

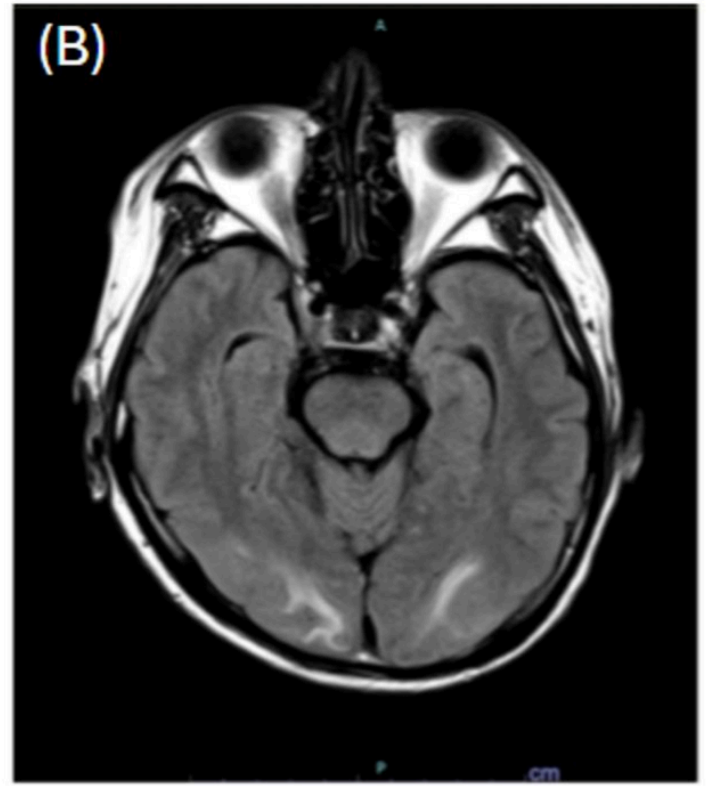


Figure 2

Brain MRI (fluid-attenuated inversion recovery) at symptom onset (A) and during follow-up (B).