



An autopsy case of autoimmune meningoencephalitis caused by pembrolizumab

Yuhi Hiraoka^{*}, Takaharu Ichikawa, Norihiro Kusumi, Azusa Matsumi, Takahumi Sakuma, Tomoyasu Tsushima

Department of Urology, National Hospital Organization Okayama Medical Center, 1711-1 Tamasu, Kita-ku, Okayama, 701-1192, Japan

ABSTRACT

A 91-year-old man was on his seventh course of pembrolizumab for recurrence of right renal pelvic cancer. On the 8th day of treatment, he was admitted to the hospital with idiopathic fever and malaise. On the 12th day, the patient experienced tonic convulsions and exhibited an impaired consciousness. Based on cerebrospinal fluid examination and the course of the disease, we diagnosed him with autoimmune meningoencephalitis as an immune-related adverse event triggered by pembrolizumab. We administered steroids, which restored the patient's consciousness. When he died of debility two months later, a pathological specimen was obtained, confirming the diagnosis of autoimmune meningoencephalitis.

1. Introduction

Pembrolizumab is an immune checkpoint inhibitor (ICI); ICIs are associated with autoimmune complications, called immune-related adverse events (irAEs), in various organs.¹ Here, we report a case of autoimmune meningoencephalitis as an irAE after treatment with pembrolizumab for renal pelvic cancer to raise awareness among urologists, as, to the best of our knowledge, there are no other reports on this condition.

2. Case presentation

A 91-year-old man, in good health and with no specific medical history, was diagnosed with right renal pelvic cancer, cT1N0M0, at 88 years of age. He opted to undergo surgery (right nephroureterectomy) and was diagnosed with pT3N2, cM0, pStage IV cancer. Because the evidence on the use of adjuvant chemotherapy was not clear at the time, and owing to his advanced age, the patient did not wish to undergo chemotherapy unless there was an apparent recurrence. Eight months after the surgery, multiple lymphadenopathy was observed. Therefore, after 6 months of gemcitabine cisplatin therapy, pembrolizumab was administered. No adverse events of note were observed during treatment, and the patient was in complete remission after six courses of pembrolizumab; therefore, treatment was terminated.

However, one year later, the patient had lymph node metastases, and

the seventh course of pembrolizumab was administered 14 months after the sixth. On the eighth day of treatment (the first day of illness), he presented with fever and malaise and was admitted to the hospital. At admission, he was clearly conscious, with a body temperature of 36.8 °C.

The clinical course is shown in Fig. 1. On the fourth day of illness, the patient's level of consciousness decreased to a Glasgow Coma Scale (GCS) score of E2V5M6, although we could not determine the cause upon imaging studies (Fig. 2). On the fifth day of illness, the patient was admitted to the intensive care unit because of the occurrence of tonic-clonic convulsions and a decreased level of consciousness (GCS score: E1V1M1). Cerebrospinal fluid examination (initial pressure, 14.5 mmH2O; protein levels, 470 mg/dL; sugar, 67 mg/dL; cell count, 28/μL; mononuclear cell percentage, 84.3%; adenosine deaminase, 14.8 U/L; and herpes simplex virus viral load, 1 × 10² copies/mL) suggested aseptic meningitis.

We considered the possibility of autoimmune meningitis, as there was no prior infection and the onset of the disease was several days after ICI administration, and, we started administering the antimicrobial (piperacillin/tazobactam) and antiviral (acyclovir) agents. On the sixth day of the patient's illness, an electroencephalogram revealed no evidence of epileptic seizures; hence, we diagnosed him with autoimmune meningoencephalitis and administered the first course of methylprednisolone (mPSL) pulse (1000 mg/day for 3 days). His GCS score improved to E4V5M4 by the 11th day. The second course of mPSL pulse was administered from days 13–16 of the patient's illness, and he was

^{*} Corresponding author.

E-mail addresses: p9sh0k9q@s.okayama-u.ac.jp (Y. Hiraoka), ichikawa.takaharu.eh@mail.hosp.go.jp (T. Ichikawa), kusumi.norihiro.uv@mail.hosp.go.jp (N. Kusumi), hayashi.azusa.zc@mail.hosp.go.jp (A. Matsumi), sakuma.takafumi.tk@mail.hosp.go.jp (T. Sakuma), yokotomo102@gmail.com (T. Tsushima).

<https://doi.org/10.1016/j.eucr.2022.102226>

Received 1 May 2022; Received in revised form 16 June 2022; Accepted 11 September 2022

Available online 12 September 2022

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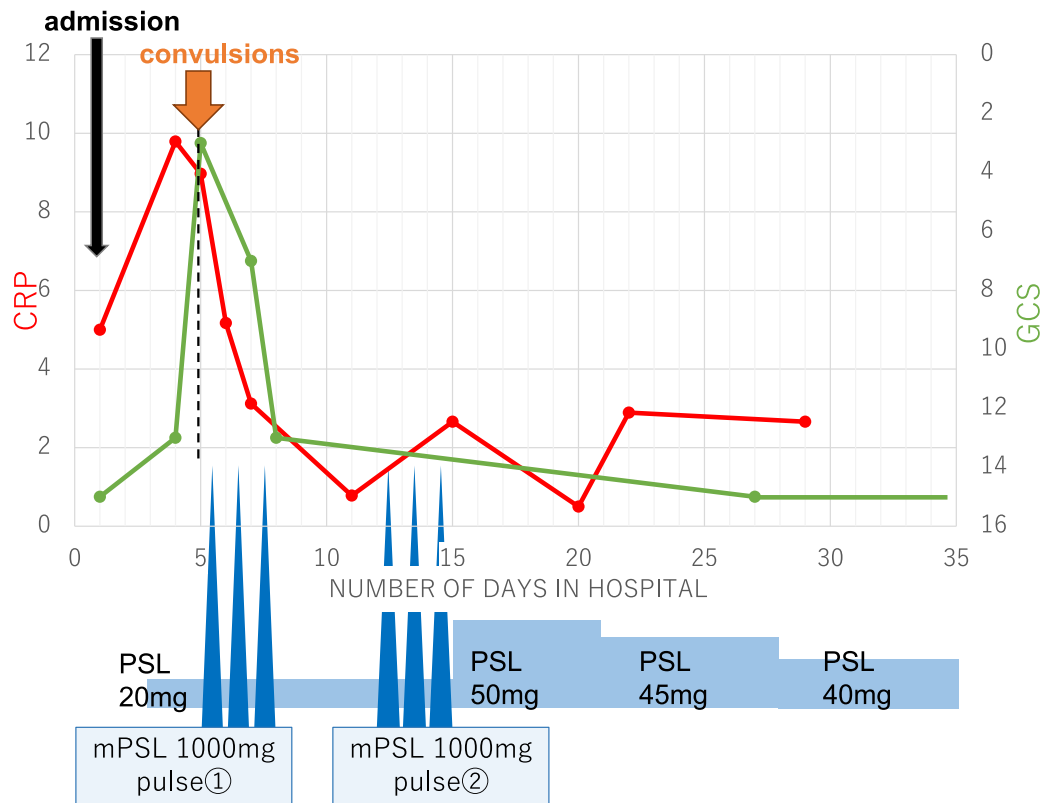


Fig. 1. Timeline of adverse events triggered by the seventh course of pembrolizumab for lymph node metastases in a 91-year-old patient

Day 5: Tonic-clonic convulsions appeared and disturbance of consciousness was observed. Day 6: We administered the first of two courses of mPSL pulse therapy (1000 mg/day for 3 days) while continuing antimicrobial and antiviral therapy. Day 11: Patient's GCS score improved to E4V5M4. Day 13: The second course of mPSL pulse was started. Day 15: mPSL pulse was terminated, and 50 mg of PSL was started, to be tapered one week at a time. Day 47: The dose of PSL was reduced to 30 mg, and the symptoms did not flare up. The patient was transferred to another hospital for rehabilitation. CRP: C-reactive protein, GCS: Glasgow Coma Scale, mPSL: methylprednisolone, PSL: prednisolone.

switched to oral prednisolone on the 16th day. The patient was discharged from the hospital on the 47th day of his illness without worsening even after weekly tapering of the prednisolone.

He died of debility owing to tumor exacerbation and bronchopneumonia approximately 2 months later. A postmortem pathological specimen was obtained (Fig. 3). Although the tissues were obtained two months after the symptoms of meningoencephalitis had resolved, the pathohistological results were consistent with that of autoimmune meningoencephalitis.

3. Discussion

ICIs are known to cause autoimmune disorders, called irAEs, in various organs.¹ The incidence of neurological irAEs of any grade caused by pembrolizumab is 6.3%. Most events are mild and present with non-specific symptoms, and irAEs grade 3–4, such as aseptic meningitis, occur in 0.2% of patients.² However, to our knowledge, no cases of meningoencephalitis have been reported in patients with urothelial carcinoma treated with anti-programmed cell death-1 (PD-1) inhibitors.

The clinical manifestations of autoimmune meningoencephalitis are non-specific and include headache, photophobia, rigidity, nausea, and vomiting. Only 73% of patients exhibit typical characteristics of meningoencephalitis on magnetic resonance images. Regarding laboratory results, cerebrospinal fluid reveals lymphocytic inflammation in 56% of patients with encephalitis. The differential diagnoses include infection, neoplastic lesions, and tumor-associated syndromes.³

The median time from ICI administration to the onset of encephalitis and meningitis is 8 weeks and 68 days, respectively, although the time to

onset ranges from a week to more than a year.⁴ Symptoms often progress over a period of days to a few weeks.

The standard treatment is still undefined. Patients were often treated with high-dose intravenous steroids and tapering oral doses. It has been reported that after intravenous injection of mPSL 1000 mg/day or 0.5–2 mg/kg, PSL 0.5–1 mg/kg was orally tapered over 4–12 weeks.^{3,4} Herein, the onset of symptoms within a few days of ICI administration suggested the possibility of autoimmune meningoencephalitis. We diagnosed the patient with autoimmune meningoencephalitis as an irAE and continued steroid treatment. The patient's level of consciousness recovered remarkably soon after starting the steroid pulse therapy.

Clinicians should be aware of the possibility of autoimmune meningoencephalitis and recommend the following procedures when the mental status of a patient on ICI changes. First, suspect an adverse effect of irAE as the cause of the change in mental status. Second, perform a CSF examination; procurement of results of viral PCR and culture tests is time-consuming. Hence, when autoimmune meningoencephalitis is suspected, steroid therapy should be started while concurrently treating the patient for infectious meningoencephalitis.

This case is also valuable because we could perform a pathological autopsy. To the best of our knowledge, there have been only four prior reports of autopsies of autoimmune meningoencephalitis cases.⁵ Typical pathological findings include perivascular or diffuse CD8-positive T-cells, CD3-positive T-cells, and macrophage infiltration. Herein, we observed shedding of the meningeal sheath and T-cell-dominant lymphocytic infiltration around the blood vessels, consistent with autoimmune meningoencephalitis as an irAE.

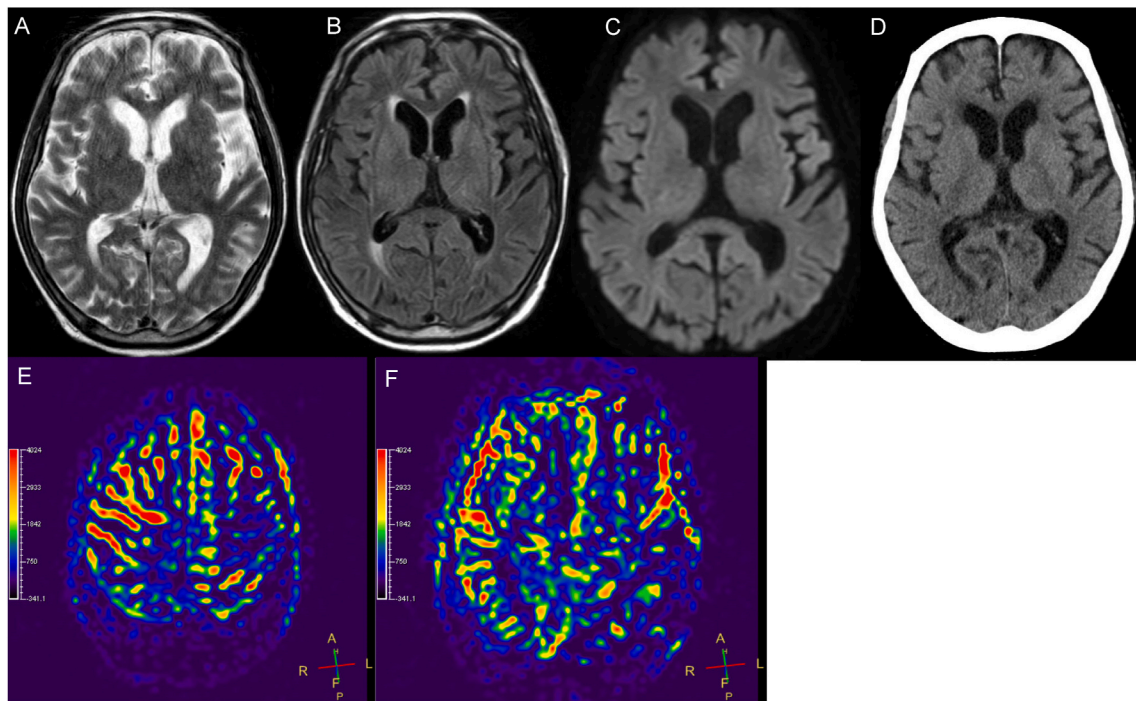


Fig. 2. Imaging studies on day 4 of the patient's illness

A: T2-weighted image, B: FLAIR, C: Diffusion-weighted image, D: CT

E, F: Cerebral blood flow SPECT

A, B, C: There were no high-signal areas on any of these images suggestive of encephalitis or meningitis. D: No hemorrhage or other causes of the disturbance of consciousness were observed. E, F: There was a decreased blood flow in the left parietal lobe. FLAIR: fluid-attenuated inversion recovery, CT: computed tomography, SPECT: single-photon emission computed tomography.

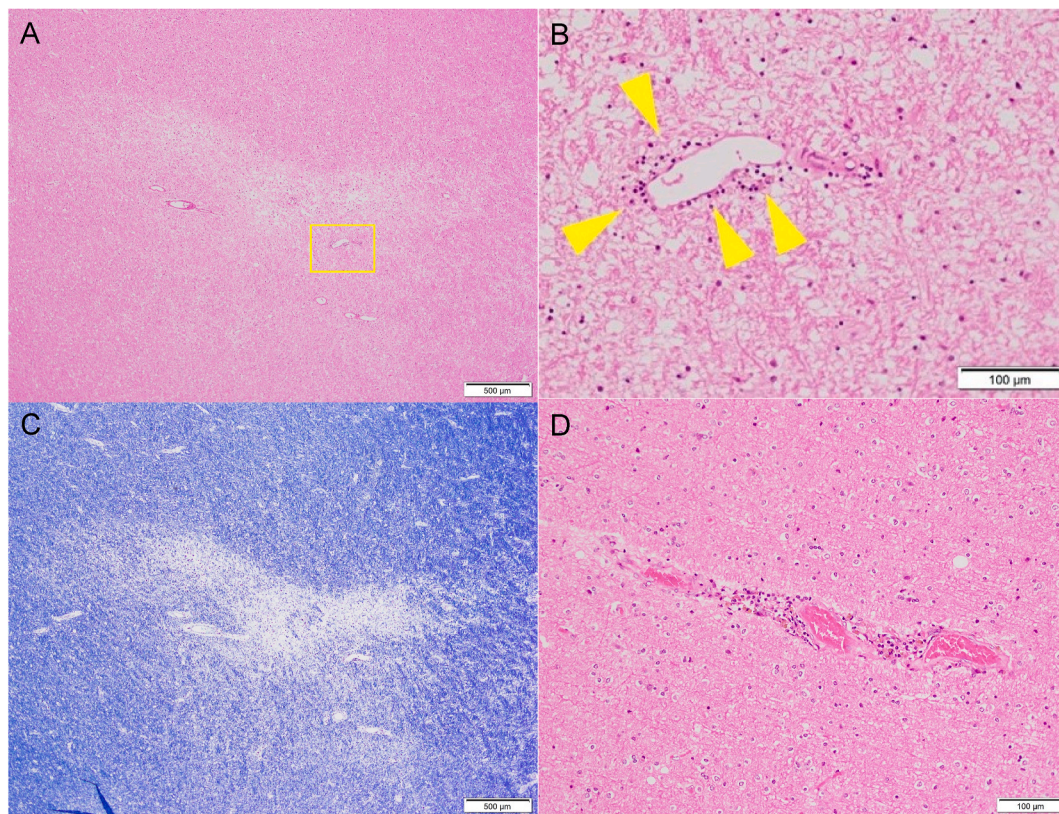


Fig. 3. Pathological findings of the postmortem specimen obtained 78 days after the patient became ill. A: HE-staining of the left parietal lobe. A decreased density of nerve fibers was observed, suggesting demyelination. B: Magnified image of a blood vessel in the specimen revealing lymphocytic infiltration in the surrounding area (arrowheads). The lymphocytes were CD3+/CD20-, and, therefore, identified as T-cells. C: KB-staining of the same section as in panel A. Demyelination was observed. D: Another vessel in the left parietal lobe revealing a higher degree of lymphocytic infiltration. Scattered demyelination was observed in the left frontal and parietal lobes, with lymphocytic infiltration around the vessels. HE: hematoxylin-eosin, CD: cluster of differentiation, KB: Kliver-Barrera.

4. Conclusion

To our knowledge, we report the first case of meningoencephalitis caused by administration of an anti-PD-1 inhibitor for urothelial carcinoma. ICIs are being increasingly used widely, and the number of cases of irAEs is expected to increase. As early intervention may lead to a better prognosis, it is important that urologists be aware of the possibility of meningoencephalitis caused by treatment with ICIs.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Funding

This manuscript did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Contributions

Yuhi Hiraoka: manuscript writing.
 Takaharu Ichikawa: manuscript editing.
 Norihiro Kusumi: manuscript editing.
 Azusa Matsumi: manuscript editing.
 Takahumi Sakuma: manuscript editing.
 Tomoyasu Tsushima: manuscript editing.

Declarations of competing interest

The authors declare no conflict of interest.

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Glossary

ICI: immune checkpoint inhibitor
irAE: immune-related adverse event
GCS: Glasgow coma scale
mPSL: methylprednisolone
PD-1: programmed cell death-1