■ Clinical commentary

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Epileptic Disorders

A case of repetitive seizures following immune checkpoint inhibitor therapy as a feature of autoimmune encephalitis

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ABSTRACT

Pembrolizumab, an immune-checkpoint inhibitor (ICI), is a humanized monoclonal antibody that binds to programmed cell death-1 receptor (PD-1) and thereby inhibits binding to its ligand, which inhibits the suppression of activated T cells by cancer cells, resulting in enhancing antitumour immunity. Although several cases of encephalitis have been reported as immune-related adverse effects of ICIs, epilepsy has not been reported following ICI treatment. We describe the case of an elderly woman with bladder carcinoma who experienced two episodes of generalized seizures after treatment with pembrolizumab. The episodes were atypical of encephalitis, because the seizures were completely responsive to AEDs and the CSF parameters normalized completely without immunotherapy. Since interictal EEG revealed persistent epileptic discharges after the seizures, pembrolizumab was considered to have induced a chronic state of epileptogenicity as the possible pathology, with a clinical picture similar to that of autoimmune epilepsy. The possibility that ICIs may cause an immune-related adverse effect, such as a chronic epileptic condition, should be considered, since ICIs are used widely.

Key words: immune-checkpoint inhibitors, autoimmune epilepsy, temporal intermittent rhythmic delta activity, blood brain barrier, immune-related adverse effect

The administration of immune-checkpoint inhibitors (ICIs) is a recent addition to chemotherapy. ICIs are used as treatment for various types of tumours, resulting in a dramatic improvement in patients' clinical outcome [1]. ICIs are monoclonal antibodies which act by blocking intrinsic down-regulators of the immune system. The two most effective checkpoint targets are programmed cell death-1 receptor (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Inhibition of these physiological checkpoints activates the activity of cytotoxic T-cells, leading to tumour death [2, 3]. These ICIs have reportedly induced immune-related adverse effects (irAEs) including neurological deficits, such as acute encephalitis [4-6]. Herein, we report the case of an elderly woman with squamous cell carcinoma of the bladder, who experienced several attacks of generalized seizures following treatment with a PD-1 inhibitor. The clinical picture, which included seizures after treatment with a PD-1 inhibitor, might be autoimmune epilepsy [7, 8]. The association between

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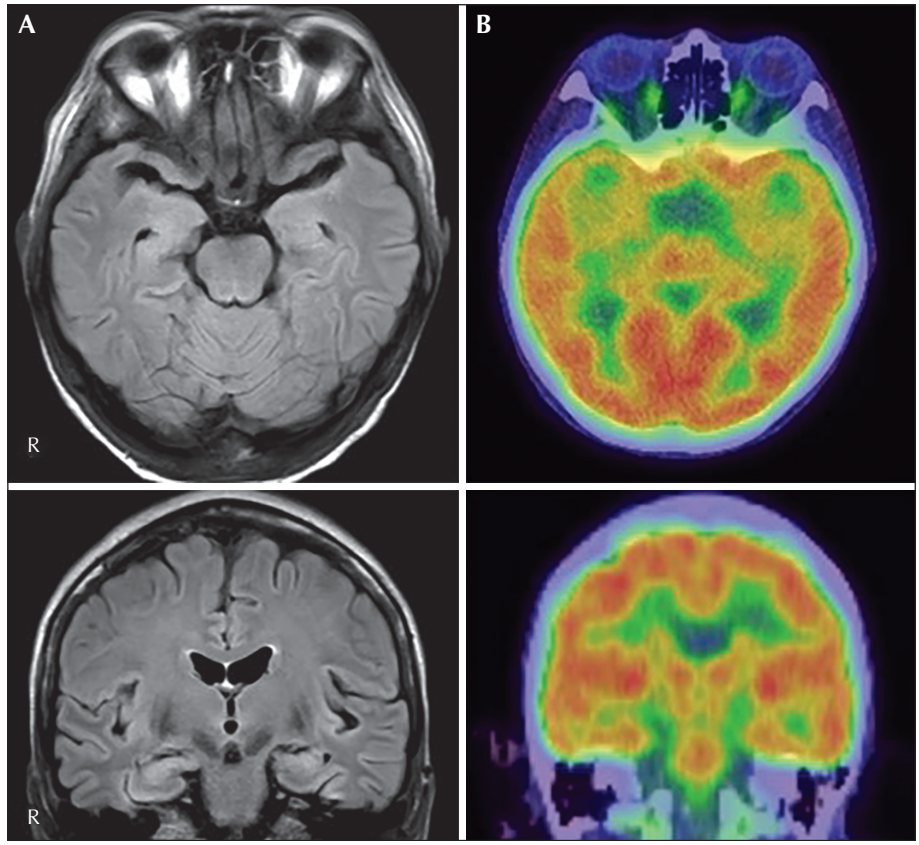
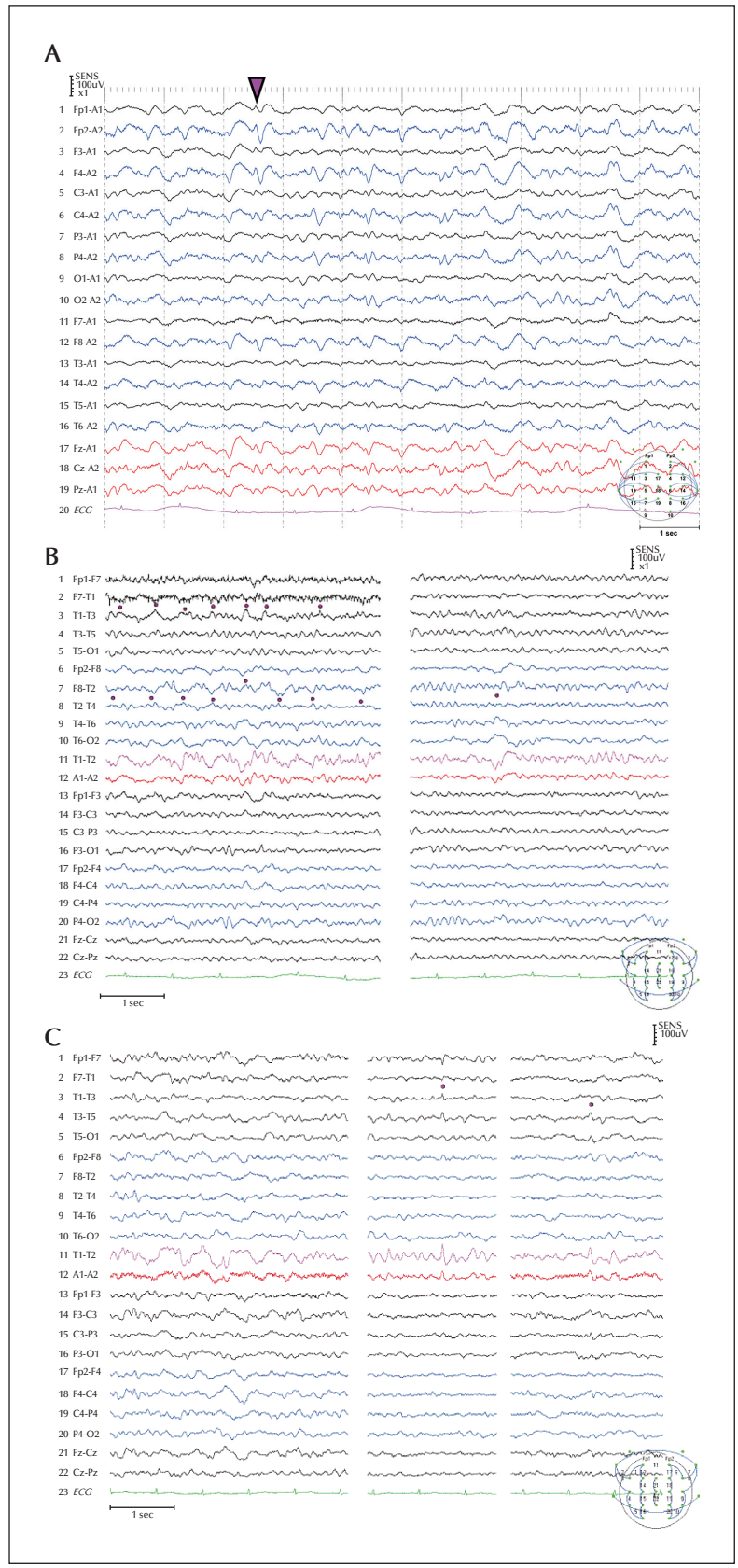
PD-1 inhibitors and autoimmune epilepsy as an irAE of ICIs has not been previously clarified.

Case study

The patient was a 64-year-old, right-handed Japanese woman with squamous cell carcinoma of the bladder (T3N0M0 Stage III). She had a medical history of Hashimoto's disease, and medically well-controlled hypertension and asthma during the last 10 years. She had no history of febrile convulsion or epilepsy. She underwent total hysterectomy and radiotherapy for uterine body and cervix adenocarcinoma at the age of 50 years. She underwent cutaneous ureterostomy for urinary diversion and subsequent chemotherapy (two cycles with cisplatin and gemcitabine, followed by three cycles with gemcitabine, docetaxel and carboplatin) following the diagnosis of bladder cancer, because she refused to undergo radical cystectomy, given her history of radiotherapy to the pelvis. However, her tumour progressed to T4N0M0 Stage IV. Thus, nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) were administered at a private clinic over a period of about five months, followed by cross-over to pembrolizumab (PD-1 inhibitor, 200 mg every three weeks). She underwent transverse colostomy due to bladder tumour invasion into the colon after 16 cycles of pembrolizumab for 12 months. Although she completely recovered from the general anaesthesia, she experienced recurrent vomiting several hours after surgery and gradually lost consciousness (Japan Coma Scale I-3 to II-20), and finally exhibited a sudden generalized tonic-clonic seizure (GTCS). Laboratory data, including biochemistry profile, thyroid function and C-reactive protein, were within normal limits or corresponded to baseline status. She tested positive for thyroglobulin antibody and thyroid peroxidase antibody. Lumbar puncture revealed normal opening pressure (11 cm H_2O). CSF examination revealed



■ **Figure 1.** MRI and FDG-PET. (A) On the day of the first seizure, brain MRI (axial and coronal FLAIR images) did not show any hyperintensity or atrophy in the brain including the bilateral limbic system. (B) On the 45th day after the first seizure, FDG-PET showed no change in the metabolism of the brain including the bilateral limbic system.


A
SENS 100uV x1
1 Fp1-A1
2 Fp2-A2
3 F3-A1
4 F4-A2
5 C3-A1
6 C4-A2
7 P3-A1
8 P4-A2
9 O1-A1
10 O2-A2
11 F7-A1
12 F8-A2
13 T3-A1
14 T4-A2
15 T5-A1
16 T6-A2
17 Fz-A1
18 Cz-A2
19 Pz-A1
20 ECG
1 sec
B
SENS 100uV x1
1 Fp1-F7
2 F7-T1
3 T1-T3
4 T3-T5
5 T5-O1
6 Fp2-F8
7 F8-T2
8 T2-T4
9 T4-T6
10 T6-O2
11 T1-T2
12 A1-A2
13 Fp1-F3
14 F3-C3
15 C3-P3
16 P3-O1
17 Fp2-F4
18 F4-C4
19 C4-P4
20 P4-O2
21 Fz-Cz
22 Cz-Pz
23 ECG
1 sec
C
SENS 100uV
1 Fp1-F7
2 F7-T1
3 T1-T3
4 T3-T5
5 T5-O1
6 Fp2-F8
7 F8-T2
8 T2-T4
9 T4-T6
10 T6-O2
11 T1-T2
12 A1-A2
13 Fp1-F3
14 F3-C3
15 C3-P3
16 P3-O1
17 Fp2-F4
18 F4-C4
19 C4-P4
20 P4-O2
21 Fz-Cz
22 Cz-Pz
23 ECG
1 sec

■ **Figure 2.** Interictal EEGs. The EEGs are presented with a time constant of 0.3 seconds, and a high frequency filter of 60 Hz. (A) Post-ictal EEG showing generalized slow activities and triphasic waves (pink arrowhead), suggestive of metabolic encephalopathy on the day of the first seizure. (B) On the 45th day after the second seizure, the interictal EEG shows bilateral and right-dominant intermittent semi-rhythmic (but occasionally rhythmic) delta activities, and bitemporal intermittent delta waves. These focal slow waves appeared in the right and left temporal regions independently at irregular intervals. Pink dots indicate a region with a negative phase reverse. (C) On the 85th day after the second seizure, interictal EEG still shows irregular and intermittent slow waves in the temporal regions. Sharp transient waves, which are frequent in the left temporal region, are also visible. Pink dots indicate a region with a negative phase reverse.

normal glucose concentration, elevated protein (112 mg/dL), and mild lymphocytic pleocytosis (9/mm^3, 86% mononuclear cells), without any growth on culture. The polymerase chain reaction assay for herpes simplex virus and CSF cytology were negative. Anti-neuronal antibodies (against amphiphysin, CV2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, Tr, Caspr2, and LGI1) were also absent. No new lesions such as cerebral metastases were visible on brain MRI. The amygdala and hippocampus appeared normal in intensity and size on FLAIR (*figure 1A*). The seizure was clearly responsive to intravenous diazepam (10 mg) administration. EEG, which was performed immediately after GTCS resolution, revealed rhythmic delta activity and triphasic waves (*figure 2A*). Given the possibility of an irAE, pembrolizumab was withdrawn, and levetiracetam was started to prevent seizures. The patient's consciousness improved completely within a day without any residual neurological deficit. She was discharged a few days after the seizure. Interictal fluorodeoxyglucose positron emission tomography of the brain showed normal uptake within the bilateral limbic system (*figure 1B*).

Seven weeks after the initial seizure, she was readmitted due to urinary tract infection and treated with cefmetazole. One day after the antibiotic therapy, she exhibited another GTCS. CSF showed polymorphonuclear pleocytosis (318/mm^3, 96% polynucleate cells) and markedly high protein levels (250 mg/dL). Increased myelin basic protein (MBP) was also observed (868 pg/mL). The differential diagnosis included neurological emergencies. However, blood and CSF cultures were both negative, and this seizure was also completely responsive to diazepam. As her consciousness improved within a day, without residual neurological impairment, she was discharged. Follow-up CSF examination including MBP was completely normal. Interictal EEG (performed six weeks after the second seizure) showed bilateral and independent repetitive runs of irregular, but occasionally rhythmic, delta activities, which were more pronounced on the right side (*figure 2B*). Focal sharp transient waves (in left temporal regions) were still visible on interictal EEG (three months after the second seizure) (*figure 2C*). Although no further seizure occurred after changing the AED from levetiracetam to valproic acid, she died six months after the initial seizure due to several further instances of urinary tract infection and haemorrhage caused by the bladder tumour.

Discussion

Our patient, an elderly woman with bladder tumour (without brain metastatic lesions), had a first ever seizure episode and a subsequent seizure (loss of consciousness followed by GTCS) after treatment with pembrolizumab. Both seizures might have been induced by the trauma of surgery and/or urinary tract infection, similar to episodes of acute symptomatic seizures. However, the clinical features, CSF data (pleocytosis and elevated proteins), and EEG findings during these episodes suggest that acute encephalitis was the major underlying pathology. Thus, encephalitis as an irAE of pembrolizumab administration should be considered as the pathology [9-12] because these seizures occurred only after pembrolizumab administration. Furthermore, given the history of Hashimoto's disease and high levels of thyroglobulin and thyroid peroxidase antibody, ICIs may have induced Hashimoto's encephalitis as a form of autoimmune encephalitis [4], of which the major clinical manifestation was GTCS.

ICIs cause upregulation of cytotoxic T-cell activity, leading to tumour death by inhibiting the physiological checkpoints. This action occasionally disrupts immune tolerance and subsequently causes autoimmune syndromes such as irAE [13]. The possible irAEs include acute encephalitis [4-6]. Several cases of irAE encephalitis caused by pembrolizumab, which is a humanized monoclonal IgG4-κ isotype antibody designed to block the negative immune regulatory signalling of PD-1 receptor expressed by T-cells [14], have also been reported. All these cases of encephalitis were ameliorated after discontinuation of pembrolizumab and administration of high-dose corticosteroids [9-12]. In contrast, symptoms of the

present case improved immediately after the administration of AEDs without the use of immunotherapy. The normalization of CSF data (pleocytosis and elevated protein) at the second seizure was also of note. Furthermore, it is noteworthy that epileptic EEG findings were observed not only in the acute phase (peri-ictal period), but also in the chronic phase even after the withdrawal of pembrolizumab. Focal slowing similar to that of temporal intermittent rhythmic delta activity, which is a specific finding suggestive of epileptic activity [15], the so called "aborted spike", was observed persistently. These lines of EEG evidence suggest that epileptogenicity was persistently present during the acute to chronic period from the initial seizure, which probably occurred after pembrolizumab administration. As the laterality of epileptic findings changed during the period, an inflammatory condition may have been present as a background to epileptogenicity in our case. Thus, it is conceivable that the clinical picture of the present case might be that of autoimmune epilepsy, which is a phenotype of autoimmune encephalitis manifesting mainly with epilepsy in association with antineuronal antibodies. The sub-acute course of epilepsy, history of malignancy and autoimmune disease (Hashimoto's disease), and temporal variation in the epileptic EEG findings were the potential factors associated with autoimmune epilepsy [7, 8]. This patient's findings can be interpreted as positive for autoimmune epilepsy according to recent diagnostic scales [16].

Immune responses of autoimmune epilepsy are initiated by proteins expressed in the plasma membrane or cytoplasm [17]. During these processes, antineuronal antibodies against these proteins cross the blood-brain barrier (BBB) and cause neuronal destruction. Thus, we speculate that the ICI might have caused a condition that was akin to autoimmune epilepsy by disrupting the BBB. The theory of transient collapse of the BBB was partly supported by the dramatic transient increase and subsequent recovery of MBP levels in the present case.

Although corticosteroids are recommended for patients with irAEs, especially for those with encephalitis [18], in the present case, the clinical presentation noticeably improved before the use of corticosteroids. Thus, we acknowledge that the possible impact of corticosteroids on preventing seizures is unclear. As a different type of ICI, besides pembrolizumab, was used in the present case at a private clinic (the dose of these drugs was unknown), the difference in the effect of these drugs on the seizures is unclear. Furthermore, although the patient tested negative for antineuronal antibodies, paraneoplastic neurological syndrome was one of the differential diagnoses. Although these limitations should be investigated in the future, the occurrence of seizures after the administration of ICIs in our patient suggests that the chronic epileptic condition observed was an irAE, with a pathology similar to that of autoimmune epilepsy. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors have no conflicts of interest directly relevant to the content of this article.

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TEST YOURSELF

(1) What is the treatment for encephalitis as a neurological irAE?

(2) What are the clinical factors related to autoimmune epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.