■ Case vignette

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Epileptic Disorders

Recurrent autoimmune encephalitis related to immune checkpoint inhibitors

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Neurological immune-related adverse effects (nIRAEs) of immune checkpoint inhibitors (ICIs) have been increasingly reported. The continuation of these drugs following an ICI-induced encephalitis episode is controversial and usually results in immediate discontinuation of the treatment according to previous reports [1, 2]. The neurology community should be familiar with the side effects of ICIs, and decisions to maintain ICIs necessitate multidisciplinary approaches. Here, we report a patient with autoimmune encephalitis (AIE) related to nivolumab and pembrolizumab treatment, who continued nivolumab for two more years, during which she had a recurrent episode of encephalopathy.

A 57-year-old woman with Stage 4 lung adenocarcinoma and multiple cranial metastases underwent left-sided occipital metastasectomy and cranial radiation therapy. This was followed with pembrolizumab and nivolumab combination therapy at two months post-radiation. Ten days after the immunotherapy, she presented with fever and encephalopathy. The EEG revealed epileptiform discharges as spike and wave at the left temporooccipital area with a frequency of one cycle per second. Both EEG and clinical status of the patient improved with intravenous diazepam, suggestive of NCSE. Levetiracetam (LEV) was administered and lacosamide (LCM) added afterwards. Her MRI was normal other than the postsurgical scar. Cerebrospinal fluid analysis revealed 50 lymphocytes/mm^3, 55 mg/dL of protein and 67 mg/dL of glucose, whereas cultures and neuronal-specific antibodies were negative.

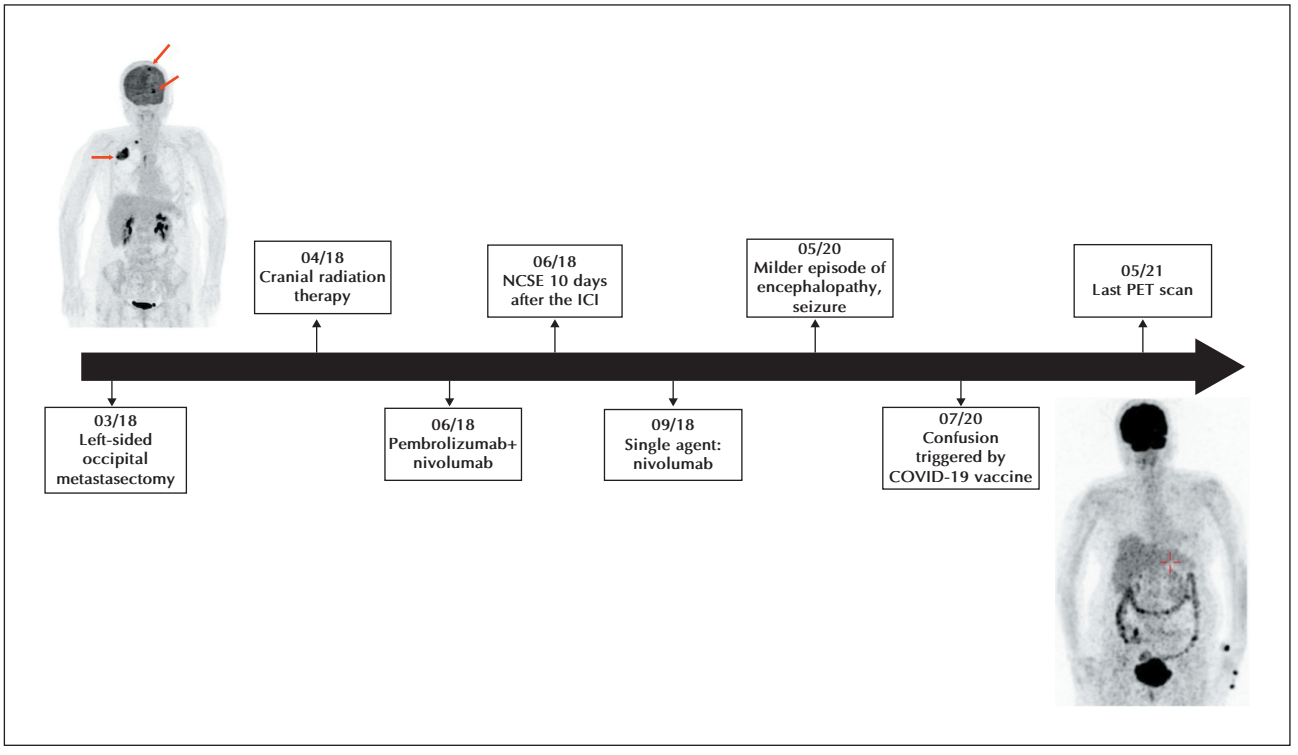
NCSE due to AIE was suspected. Complete recovery was achieved after administration of 1,000 mg methylprednisolone (five days) and IVIg (five days). After the resolution of NCSE, occasional left temporooccipital sharp waves continued. Oral methylprednisolone, LEV, and LCM were prescribed at discharge. The patient insisted on the continuation of the treatment; the oncologist decided to withdraw pembrolizumab and continue with lower doses of nivolumab infusions. As she had only rare focal aware sensorial seizures with elementary visual symptoms, LEV was gradually discontinued, while LCM and methylprednisolone were left unchanged. Three months after the initiation of nivolumab, her PET-CT and lung MRI demonstrated that all malignant lesions had dramatically disappeared; thus, the treatment lasted for two years. Just before her last dose, she had similar symptoms, including confusion, agitation, and unresponsiveness. As this occurred at the beginning of the COVID-19 pandemic, EEG and other diagnostic tests could not be performed. However, another episode of AIE was suspected, and she was empirically treated according to the NCSE protocol, continuing with IVIg for five days. Eventually, the patient fully recovered, and the most recent oncological work-up still showed no sign of cancer. However, her focal aware sensorial seizures increased in frequency and she complained of mild confusion after the inactivated SARS-CoV-2 vaccination, which was given

seven months after the termination of ICIs, however, the frequency of seizures returned back to baseline without any further treatment (*figure 1*).

In previously reported similar cases, the treatment was immediately discontinued, which is why the present case represents valuable evidence for the continuation of ICIs for selected patients with nIRAEs [1, 2]. The timing of the symptoms and recovery after immunotherapy suggest an immune-mediated event since the patient fulfils the criteria for "probable autoimmune encephalitis" [3]. As the neuronal-specific antibodies were negative, seronegative autoimmune encephalitis was diagnosed with an Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score of 8 and Response to Immunotherapy in Epilepsy and Encephalopathy (RITE2) score of 10 *(table 1A, B)*. APE2 is the updated version of the original APE; a predictive model aimed at aiding diagnosis and early treatment for autoimmune epilepsy, with 98% sensitivity and 84% specificity for a score of ≥4, reaching 100% sensitivity for a score of ≥7. RITE2 is the modified version of the original RITE; a predictive model aimed at supporting prognosis of autoimmune epilepsy, with 88% sensitivity and 84% specificity and favourable seizure outcome corresponding to a score of ≥7 [4, 5].

Although it may seem confusing whether the NCSE was caused by the previous occipital surgery or nIRAE, first there was neither residue nor recurrence of metastasis on MRI at the time of AIE, and second, according to the hypothesis put forward, the brain area that was previously damaged by both the traumatic effect of the surgery and radiation would have caused increased susceptibility to inflammatory reactions. The pro-inflammatory microenvironment created by this damage leads to aggregation of lymphocytes activated by ICI, which results in nIRAE [6-8]. This patient was considered to have Grade 3 encephalitis according to the Common Terminology Criteria for Adverse Events, and discontinuation of ICI is strongly advised by the American Society of Clinical Oncology Clinical Practice guideline in such cases [9]. Several reports have positively correlated the frequency of IRAE with anti-tumour efficacy, which may explain the favourable response in the present case [10]. Moreover, the milder severity of the recurrent episode could be attributed to continuation with a single and lower dose of ICI.

In conclusion, this case provides valuable information on the possibility of continuing ICI treatment in patients with nIRAEs by carefully judging the chance of tumour freedom versus adverse events on an individual patient basis. ■



■ **Figure 1.** Timeline showing the disease course of the patient.

▼ **Table 1.** Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score and Response to Immunotherapy in Epilepsy and Encephalopathy (RITE2) score of the patient, suggestive of seronegative autoimmune encephalitis.

A: Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score	Score
New-onset, rapidly progressive mental status changes that develop over 1–6 weeks or new-onset seizure activity (within one year of evaluation)	**1**
Neuropsychiatric changes; agitation, aggressiveness, emotional lability	**1**
Autonomic dysfunction (sustained atrial tachycardia or bradycardia, orthostatic hypotension ≥20 mmHg fall in systolic pressure or ≥ 10 mmHg fall in diastolic pressure within three minutes of standing calmly), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility	1
Viral prodrome (rhinorrhea, sore throat, low-grade fever) to be scored in the absence of underlying systemic malignancy within 5 years of neurological symptom onset	**2**
Faciobrachial dystonic seizures	3
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	2
Seizure refractory to at least two anti-seizure medications	2
CSF findings consistent with inflammation (elevated CSF protein >50 mg/dL and/or lymphocytic pleocytosis >5 cells/mcL, if the total number of CSF RBC is <1000 cells/mcL)	**2**
Brain MRI suggesting encephalitis (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter, or both compatible with demyelination or inflammation)	2
Systemic cancer diagnosed within 5 years of neurological symptom onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	**2**
Total score of the patient	**8**
B: Response to Immunotherapy in Epilepsy and Encephalopathy (RITE2) score	**Score**
New-onset, rapidly progressive mental status changes that develop over 1–6 weeks or new-onset seizure activity (within one year of evaluation)	**1**
Neuropsychiatric changes; agitation, aggressiveness, emotional lability	**1**
Autonomic dysfunction (sustained atrial tachycardia or bradycardia, orthostatic hypotension ≥20 mmHg fall in systolic pressure or ≥ 10 mmHg fall in diastolic pressure within three minutes of standing calmly), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility]	1
Viral prodrome (rhinorrhea, sore throat, low grade fever) to be scored in the absence of underlying systemic malignancy within 5 years of neurological symptom onset	**2**
Faciobrachial dystonic seizures	3
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	2
Seizure refractory to at least two anti-seizure medications	2
CSF findings consistent with inflammation (elevated CSF protein >50 mg/dL and/or lymphocytic pleocytosis >5 cells/mcL, if the total number of CSF RBC is <1000 cells/mcL)	**2**
Brain MRI suggesting encephalitis (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter, or both compatible with demyelination or inflammation)	2
Systemic cancer diagnosed within 5 years of neurological symptom onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	**2**
Immunotherapy initiated within 6 months of symptom onset	**2**
Neural plasma membrane autoantibody detected (NMDAR, GABAAR, GABABR, AMPAR, DPPX, mGluR1, mGluR2, mGluR5, LGI1, IgLON5, CASPR2 or MOG)	2
Total score of the patient	**10**

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

Disclosures.
The authors declare that they have not any personal or financial interest.

References

1. Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, *et al*. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. *Lung Cancer* 2018; 115: 71-4.

2. Özdirik B, Jost-Brinkmann F, Savic LJ, Mohr R, Tacke F, Ploner CJ, *et al*. Atezolizumab and bevacizumab-induced encephalitis in advanced hepatocellular carcinoma: case report and literature review. *Medicine (Baltimore)* 2021; 100 (24): e26377.

3. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, *et al*. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; 15(4): 391-404.

4. Dubey D, Kothapalli N, McKeon A, Flanagan EP, Lennon VA, Klein CJ, *et al*. Predictors of neural-specific autoantibodies and immunotherapy response in patients with cognitive dysfunction. *J Neuroimmunol* 2018; 323: 62-72.

5. Dubey D, Singh J, Britton JW, Pittock SJ, Flanagan EP, Lennon VA, *et al*. Predictive models in the diagnosis and treatment of autoimmune epilepsy. *Epilepsia* 2017; 58: 1181-9.

6. Du Four S, Hong A, Chan M, Charakidis M, Duerinck J, Wilgenhof S, *et al*. Symptomatic histologically proven necrosis of brain following stereotactic radiation and ipilimumab in six lesions in four melanoma patients. *Case Rep Oncol Med* 2014;417913.

7. Williams TJ, Benavides DR, Patrice KA, Dalmau JO, de Ávila AL, Le DT, *et al*. Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. *JAMA Neurol* 2016; 73: 928-33.

8. Bross SP, Mongelluzzo GJ, Conger AR, Patel MA, Vadakara J, Grant M, *et al*. Case report of immuno-oncotherapy (IO) provoked encephalitis mimicking brain metastasis in a patient with history of traumatic brain injury. *World Neurosurg* 2020; 139: 483-7.

9. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, *et al*. 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* 2018; 36(17): 1714-68.

10. Stuby J, Herren T, Schwegler Naumburger G, Papet C, Rudiger A. Immune checkpoint inhibitor therapy-associated encephalitis: a case series and review of the literature. *Swiss Med Wkly* 2020; 150: w20377.

TEST YOURSELF

(1) Which one of the following is not considered a potential risk factor for the development of autoimmune encephalitis in a cancer patient under ICI treatment?

A. Prior radiation therapy
B. Prior cranial surgery
C. Prior chemotherapy

(2) Which one of the following is a treatment recommendation for Grade 3-4 encephalopathy?

A. High-dose methylprednisolone
B. Suspension of ICI
C. Escalation to IVIG, rituximab, or plasmapheresis
D. All of the above

(3) Which one of the following statements is false according to the case presented here?

A. Neurological immune-related adverse events should be considered in the differential diagnosis of any patient with new-onset neurological findings and a history of ICI treatment.
B. CSF findings of such a patient can be limited to mild protein elevation and pleocytosis.
C. Antibody negativity excludes the diagnosis of autoimmune encephalitis.
D. Continuation of ICIs may still be possible by carefully judging pros and cons on an individual patient basis.

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