Case Report

PD-1-induced encephalopathy: a report of 2 cases on neurological toxicities with immune checkpoint inhibitors

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Background: Immune-related adverse effects (irAEs) often occur during immune checkpoint inhibitor (ICI) therapy. In the nervous system, the incidence of irAEs ranges from 0.1–12%, with 80% occurring within the first 4 months of ICI application. For complications of the nervous system, adequate diagnosis is made by signs, symptoms, imaging and cerebrospinal fluid. If severe irAEs occur, ICIs should be discontinued and patients should be treated with high-dose glucocorticoids, immunoglobulins, or immunosorbent therapy with systemic support. Patients who develop severe neurologic irAEs have a poorer prognosis.

Case Description: In this article, we report 2 cases of encephalopathy induced by anti-programmed cell death protein 1 (PD-1) monoclonal antibodies at the initial diagnoses. Our findings may help clinicians to differentiate between encephalopathy caused by immunotherapy and other neurological disorders. Case 1 was a 24-year-old male patient who had undergone PD-1 immunotherapy to treat olfactory neuroblastoma. After the 6th course of therapy, he began to develop persistent epilepsy, which decreased significantly after high doses of glucocorticoid and immunosorbent therapy were administered. Based on his medical history and laboratory examination results, PD-1-induced encephalopathy was the most likely diagnosis. Case 2 was a 67-year-old female patient who had been treated with PD-1/programmed death ligand-1 therapy for lung adenocarcinoma. She began to have headaches after 1 cycle of treatment, and her cognitive function gradually decreased with the continuation of immunotherapy.

Conclusions: These case reports show the difficulty in distinguishing PD-1-induced encephalopathy from other neurological disorders, especially paraneoplastic neurological syndromes. If not treated properly, patients' lives may be endangered. Thus, early identification and early treatment are very important.

Keywords: Immune checkpoint inhibitor (ICI); immune-related adverse effects (irAEs); anti-programmed cell death protein 1 monoclonal antibody (anti-PD-1 monoclonal antibody); encephalopathy; case report

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Introduction

Antigens from cancer cells are readily recognized by the immune system. However, a variety of mechanisms exist that allow these cells to evade detection by the immune system, including the expression of inhibitory ligands for lymphocyte immune checkpoint molecules (1). Under normal physiological conditions, immune checkpoints prevent autoimmunity by maintaining immunologic homeostasis (2). Immune checkpoint inhibitor (ICI) therapies, such as programmed cell death protein 1 (PD-1) blockade therapy and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) blockade therapy, have shown promising anti-tumor effects (3). In recent times, there has been the development of antagonistic antibodies targeting CTLA-4 (e.g., ipilimumab) and PD-1 (e.g., pembrolizumab and nivolumab). These antibodies have undergone testing for their effectiveness in prospective clinical trials involving various types of malignancies, including renal-cell carcinoma (4), non-small cell lung cancer (5-7), and metastatic melanoma (8,9). Although ICIs enhance anti-tumor immune reactivity resulting in tumor regression, they also reduce immune tolerance towards self-antigen and predispose to the development of autoimmunity. The side effects caused by ICIs are called immune-related adverse effects (irAEs) (10). Immunotherapy commonly affects the digestive, hepatic, dermatologic, endocrine, and pulmonary systems (11). irAEs may be pronounced and contribute to drug discontinuation, morbidity and mortality (12,13). Contrary to this, Hara and colleagues have reported that patients with upper gastrointestinal cancer who were treated with nivolumab had a better prognosis if they developed irAEs compared to those who did not. It is crucial to continue nivolumab in the long-term by detecting irAEs early and responding to them appropriately (14). In addition, there was also evidence from another study that malignancies with sarcopenia at the time of immunotherapy did not increase the risk of irAEs, and sarcopenia was not associated with irAEs (15).

In the last few years, clinical trials revealed that drugs targeting PD-1/programmed cell death ligand 1 (PD-L1) are superior in efficacy and tolerability to chemotherapy, enhancing disease control, overall survival, and quality of life in both first- and second-line settings (16-19). The anti-PD-1 monoclonal antibody is a humanized immunoglobulin G4 (IgG4) anti-PD-1 antibody that blocks the PD-1/PD-L1 pathway, and enhances the anti-tumor capacities of the host T cells (20,21). However, the initial clinical trials supporting the use of PD-(L)1 inhibitors may have underreported irAEs (22), possibly due to their delayed onset. There is limited information on the occurrence of neurological adverse reactions to ICIs. In prospective trials evaluating anti-CTLA-4 and/or anti-PD-1 antibodies, the incidence of any grade neurological irAE was 3.8% for anti-CTLA-4 antibodies, 6.1% for anti-PD-1 antibodies, and 12.0% for a combination of both. The occurrence of high-grade (i.e., grade 3–4) neurological irAEs appears to be higher in patients treated with anti-CTLA-4 therapy (0.7%) than in those treated with anti-PD-1 therapy (0.4%). Furthermore, trials assessing the combination of both antibodies found a similar incidence of high-grade neurological irAEs as with anti-CTLA-4 therapy alone (0.7%). The most prevalent symptom reported by patients was constitutional fatigue. Fatigue was observed in approximately 20–25% of patients, with grade 3 fatigue reported in 1.1–2.2% of cases. Other symptoms included asthenia (1.7–4.5% of patients) and decreased appetite (8.5–9.8% of patients), both of which were observed in varying grades (11).

irAEs of the central nervous system are often of a high grade. Neurological adverse events resulting from ICIs are rare, especially encephalopathies; however, their recognition is important due to their potential severity (23,24). Notably, it is difficult to differentiate and diagnose encephalopathy caused by immunotherapy and autoimmune encephalitis caused by paraneoplastic syndromes (PNSs), a group of diseases related to malignant tumors. The pathogenesis of PNSs is mediated by immunity. Primary systemic tumors express proteins that are normally expressed only in neurons, and the body's immune response produces

Highlight box

Key findings

- Immune checkpoint inhibitors (ICIs) may induce encephalitis.

What is known and what is new?

- ICIs have been applied to an increasing number of cancers but can cause adverse reactions.
- To diagnose programmed cell death protein 1-induced encephalopathy needs to exclude paraneoplastic neurological syndromes.

What is the implication, and what should change now?

- For complications of the nervous system, a diagnosis might be made based on the sufficient collection of disease manifestations combined with imaging and cerebrospinal fluid examinations, especially the detection of paraneoplastic antibodies before treatment.

anti-neuronal antibodies, resulting in clinical symptoms. Serum and cerebrospinal fluid (CSF) can both detect these antibodies. These antibodies can be used as biomarkers to identify primary tumors, which is helpful in diagnosing specific types of tumors (25). Cancer patients treated with ICIs, especially those with small cell lung cancer (SCLC), are at risk of immune-mediated PNSs (e.g., melanoma and renal-cell carcinoma). Similarly, anti-CTLA-4 antibody treatment in mice resulted in paraneoplastic cerebellar degeneration on the following day (26). Thus, a PNS could be caused by the treatment itself in the case of SCLC patients undergoing an ICI.

In the near future, ICIs will be used by a progressively greater number of patients due to their undisputed clinical efficacy. However, currently, there is limited information available on the incidence, characteristics, and outcomes of neurologic irAEs associated with ICI treatment. Most of this information has been obtained from isolated case reports or basic safety reports conducted during clinical trials. Consequently, there is significant variation in the available information regarding the diagnosis and treatment approaches. Moreover, it is important to consider the impact of case selection and reporting bias. In this article, we report 2 cases of patients with PD-1-induced encephalopathy to extend understandings of the nature, timing, and management of the complication. We present this article in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2043/rc).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. The 2 cases reported in this article provided by Guangdong Sanjiu Brain Hospital from 2019–2020.

Case 1

In March 2020, an olfactory neuroblastoma in a 24-year-old man was diagnosed by pathology. His initial complaints were nasal obstruction and a loss of smell in January 2020. Epstein-Barr virus (EBV)-encoded small RNAs (EBERs) was negative, and the stage was C (*Figure 1*). Magnetic resonance imaging (MRI) on February 26, 2020, showed a bilateral nasal space-occupying lesion of approximately 7.8 cm × 5.8 cm × 7.7 cm, involving the surrounding tissue (*Figure 2A*).

On March 9, 2020, the patient was treated with etoposide (100 mg/m^2, d1–3) and cisplatin (25 mg/m^2, d1–3; Q21d) and then received the anti-PD-1 monoclonal antibody tislelizumab (200 mg) every 3 weeks. After 4 cycles of treatment, he developed hand-and-foot paralysis that improved through symptomatic treatment (details unknown).

On June 24, 2020, grand mal epilepsy occurred during the 6th course of application of tislelizumab and the treatment was terminated. The epilepsy was controlled with oxcarbazepine (0.3 g, bid) and sodium valproate (500 mg, bid). An MRI re-examination on July 2, 2020 showed that the primary tumor had shrunk (*Figure 2B*) and multiple abnormal signals in the right parietal sulcus and the left frontal lobe (*Figure 2C*). Linear enhancement of spinal cord membranes observed on T1-enhanced, fat-suppressed MRI imaging (*Figure 2D*).

The patient received local radiotherapy on July 30, 2020. The prescription doses were gross tumor volume (GTV; 68.10 Gy/30 f), clinical target volume (CTV1: 60 Gy/30 f, and CTV2: 54 Gy/30 f). After 6 rounds of radiotherapy, grand mal epilepsy, which lasted for 1 min, occurred again.

The patient was diagnosed with anti-PD-1 monoclonal antibody-induced autoimmune encephalopathy. His symptoms were alleviated by high doses of glucocorticoid and immunosorbent therapy on August 18 and August 20, 2020.

MRI review showed that the intracranial and spinal enhancement lesions had largely disappeared in axial T2 FLAIR images (*Figure 2E*) and sagittal T1 enhancement images (*Figure 2F*). Serum paraneoplastic antibody anti-Hu (*Table 1*: from Guangzhou Goldfield Diagnostic Laboratory) was mildly positive. The CSF was strongly positive for neuronal antibodies, which were considered to be anti-Hu. Radiotherapy was continued without further seizures. The patient's diagnosis and treatment schedule are shown in *Figure 3*.

Case 2

A 67-year-old female was diagnosed with NSCLC and multiple bone metastases on July 29th, 2019. The clinical stage of her tumor was IVB. Large cell adenocarcinoma was confirmed by pathologic examination. Tissue PCR

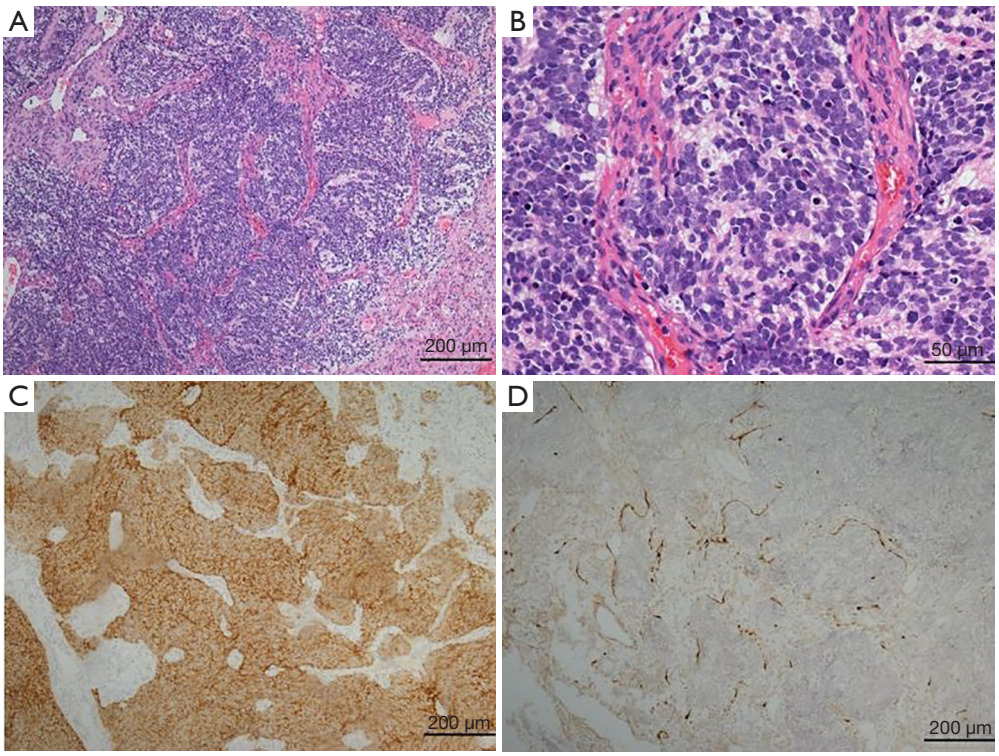

Figure 1 Pathological features of olfactory neuroblastoma. (A) The tumor cells were arranged in a lobulated or mass nest shape, surrounded by proliferative vascular fibrous stroma (hematoxylin and eosin, ×100); (B) the tumor cells were small, round, or short spindle shaped, with a deeply stained nucleus, a large nucleocytoplasmic ratio, obvious atypia, easy nuclear division, and a rich neurofibrillary tumor stroma (hematoxylin and eosin, ×400); (C) synaptophysin was diffusely positive in tumor cells (immunohistochemistry, ×200); (D) S100 was positive in Sertoli cells around the tumor cell nest (immunohistochemistry, ×200).

was positive for the L858R mutation in exon 21 of the epidermal growth factor receptor (EGFR) (*Figure 4*). Brain MRI showed negative imaging findings on T1-weighted, gadolinium-enhanced sequences (*Figure 5A*).

Once diagnosed with EGFR exon21 L858R mutation, the patient received afatinib (40 mg, qd) for 12 months. In August 2020, she developed symptoms of headache and double vision. Chest computed tomography (CT) showed that the lung lesions were larger than before, brain MRI showed multiple intracranial lesions (*Figure 5B*,*5C*), and her CSF cytologic examination results were positive. She was diagnosed with meningeal metastasis of lung adenocarcinoma.

The blood genetic tests did not suggest driver gene mutations. Her therapy was changed to pemetrexed (500 mg/m^2, d1), bevacizumab (7.5 mg/kg, d1), and carilizumab (200 mg, d1; Q21d). These treatments were recommended by the guidelines for NSCLC. However, her symptoms did not improve significantly. So these treatments had not continued. She received whole brain radiotherapy (WBRT) with a dose of 40 Gy/20 f plus temozolomide (75 mg/m^2) on September 17, 2020. After 10 rounds of radiotherapy, her symptoms of headache and double vision were alleviated. However, her cognitive function gradually decreased after WBRT.

A brain MRI re-examination showed that the lesions had shrunk (*Figure 5D*,*5E*). Her lumbar puncture results indicated normal opening pressures (130 mmH_2O), which did not support the progression of meningeal metastases. On October 15, 2020, she started to use bevacizumab (5 mg/kg d1; Q21d), and her cognitive function improved. On October 20, 2020, she received pemetrexed (500 mg/m^2) after folic acid pre-treatment. The process was smooth. On October 22, 2020, she was treated with 500 mg of durvalumab. Durvalumab was approved by FDA for maintenance treatment of NSCLC. But on October 23, 2020, her headache and cognitive function were worse than before. The treatment had not continued.

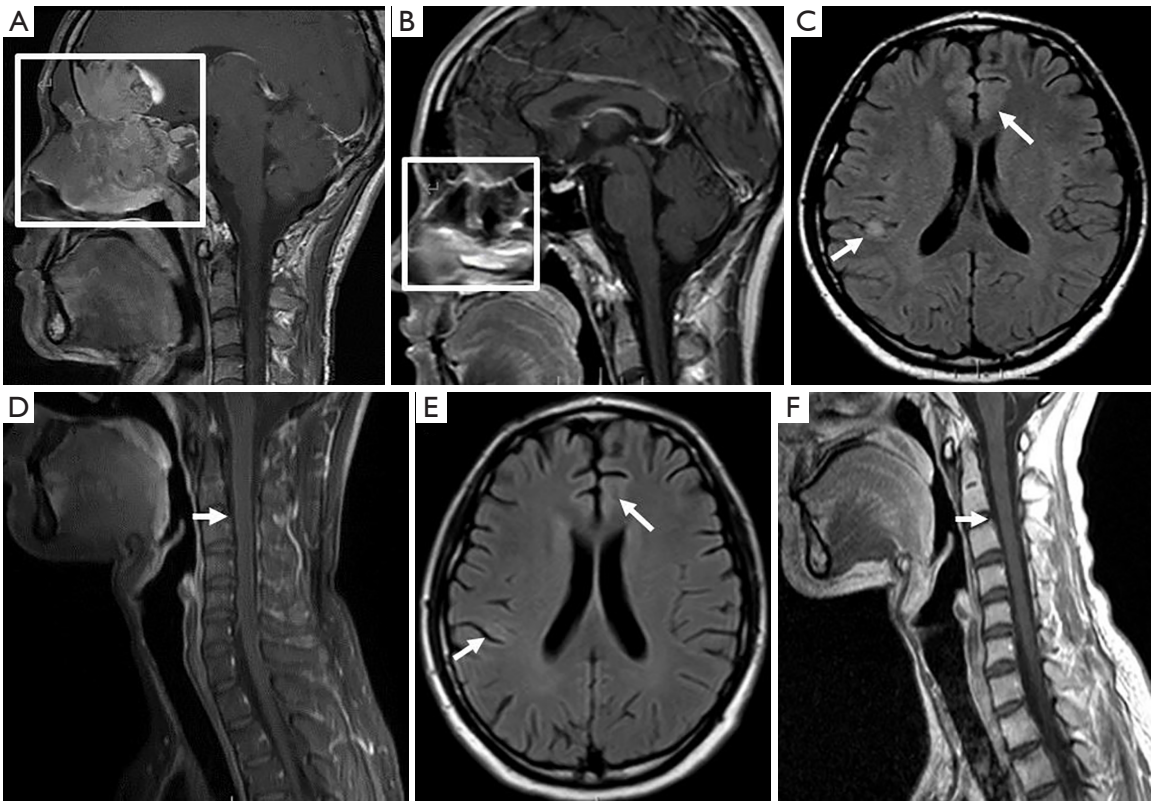

Figure 2 Changes in magnetic resonance imaging findings of olfactory neuroblastoma. A contrast-enhanced sagittal magnetic resonance T1-weighted sequence of the brain (A) showing an expansile lesion involving the ethmoid sinus, sphenoid sinus, nasal cavity, and frontal lobe with bone destruction. After 6 courses of chemotherapy and immunotherapy, a contrast-enhanced sagittal T1-weighted sequence (B) indicated that the above lesion had obviously diminished. At the same examination, an axial T2-weighted FLAIR sequence (C) revealed some new expansile lesions presenting as a hyperintensity nodule in the right parietal sulcus and a patch in the left frontal lobe. Linear, meningeal-enhanced thickening was observed on T1-weighted, fat-suppression, gadolinium-enhanced spinal magnetic resonance imaging representing leptomeningeal disease (D). The lesion was suspected to be immune encephalitis. After adsorption treatment, the new lesions had almost disappeared in the follow-up axial T2-weighted FLAIR (E) and sagittal T1-weighted contrast-enhanced images (F). Boxes show tumor location, and arrows show intracranial and spinal cord lesions. FLAIR, fluid attenuated inversion recovery.

A brain MRI re-examination on October 26, 2020, revealed aggravation of cerebral oedema, and dehydration was ineffective (*Figure 5F*). The patient had a history of hypothyroidism and thyroxin replacement. During the PD-1 treatment, her thyroid function continued to decline, and her serum cortisol level gradually decreased. On October 30, 2020, cortisol at 23.5 μg/L was detected (*Table 2*). After prednisone (5 mg qd) was administered, the patient developed psycho-behavioral abnormalities, including suspicion and a delusion of being killed. Her cognitive function was tested by Montreal Cognitive Assessment (MoCA) (*Table 3*). She developed a fever on November 16, 2020, with a temperature of 38.5 ℃. Chest CT showed diffuse exudation in both lungs. Combined with her medical history, immune pneumonia was not ruled out. The patient was treated with methylprednisolone (40 mg), after which her temperature returned to normal, but her mental symptoms did not improve significantly. The patient's diagnosis and treatment timeline are illustrated in *Figure 6*.

Discussion

In the above 2 cases, epilepsy, cognitive decline, and mental behavioral abnormalities occurred during PD-1 immunotherapy. The symptoms of encephalitis caused by ICIs are diverse and atypical, making diagnosis challenging. Thus, we sought to examine the diagnosis and treatment approaches. PD-1-induced encephalopathy requires timely

Table 1 Paraneoplastic antibodies in the serum and cerebrospinal fluid of case 1

Antibody	Test method	Result	Reference interval
Anti-GAD65	BLOT	Negative (–)	Negative (–)
Anti-Zic4	BLOT	Negative (–)	Negative (–)
Anti-Tr (DNER)	BLOT	Negative (–)	Negative (–)
Anti-SOX1	BLOT	Negative (–)	Negative (–)
Anti-Ma2	BLOT	Negative (–)	Negative (–)
Anti-Ma1	BLOT	Negative (–)	Negative (–)
Anti-Amphiphysin	BLOT	Negative (–)	Negative (–)
Anti-CV2	BLOT	Negative (–)	Negative (–)
Anti-Ri	BLOT	Negative (–)	Negative (–)
Anti-Yo	BLOT	Negative (–)	Negative (–)
Anti-Hu	BLOT	Positive (+)	Negative (–)

BLOT, blotting method.

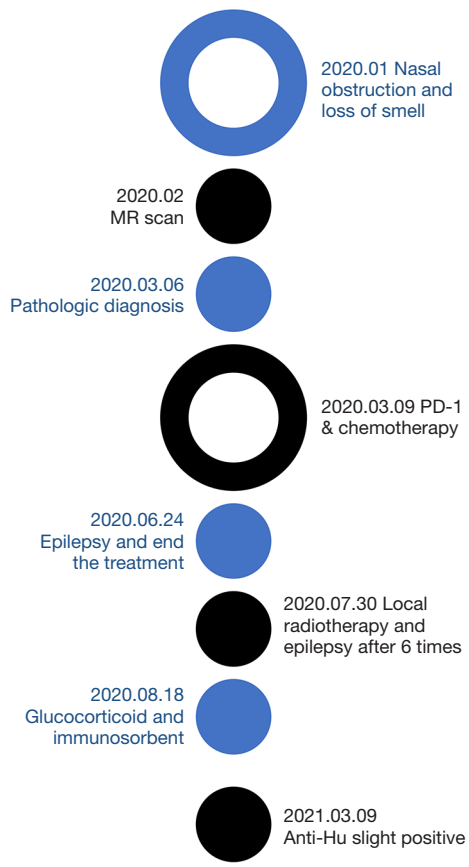

Figure 3 A timeline of the major diagnoses and treatments for case 1. MR, magnetic resonance; PD-1, programmed cell death protein-1.

differential diagnosis and treatment to effectively prevent tumor progression and prolong patient survival.

Immunotherapy showed good efficacy for solid tumors, and the commonly used efficacy predictors included PD-L1 and tumor mutation burden (TMB) (27). Patients with various cancers have greatly benefited from the use of ICIs, such as PD-1/PD-L1 inhibitors (28). The diagnostic assessment of response to immunotherapy was performed with response evaluation criteria in solid tumors (RECIST) 1.1 criteria (29). Based on a recent study conducted by Larkin *et al.*, it has been found that immune-mediated encephalitis typically manifests around 55 days (with a range of 18–297 days) after undergoing ICI treatment (13). The occurrence of immune-mediated encephalitis in patients treated with PD-1 is estimated to be approximately 0.2%, and it includes various forms such as limbic encephalitis (LE), brainstem encephalitis, and necrotizing encephalitis (30-32). The main symptoms of immune-mediated encephalitis are headache, fever, insanity, memory impairment, sleepiness, hallucinations, seizures, neck strength, decreased mental state, impaired attention, and disorientation (33,34). However, these symptoms lack specificity. Cases of encephalitis caused by PD-1 need to be distinguished from infectious diseases, metabolic diseases, brain metastases, cerebrovascular diseases and meningeal metastases, especially LE in PNSs. When relevant symptoms are present, brain MRI and CSF examinations are required (35). MRI can reveal the limited diffusion of the limbic system (32). Additionally, the T2 FLAIR sequence can show a symmetrical high signal in the

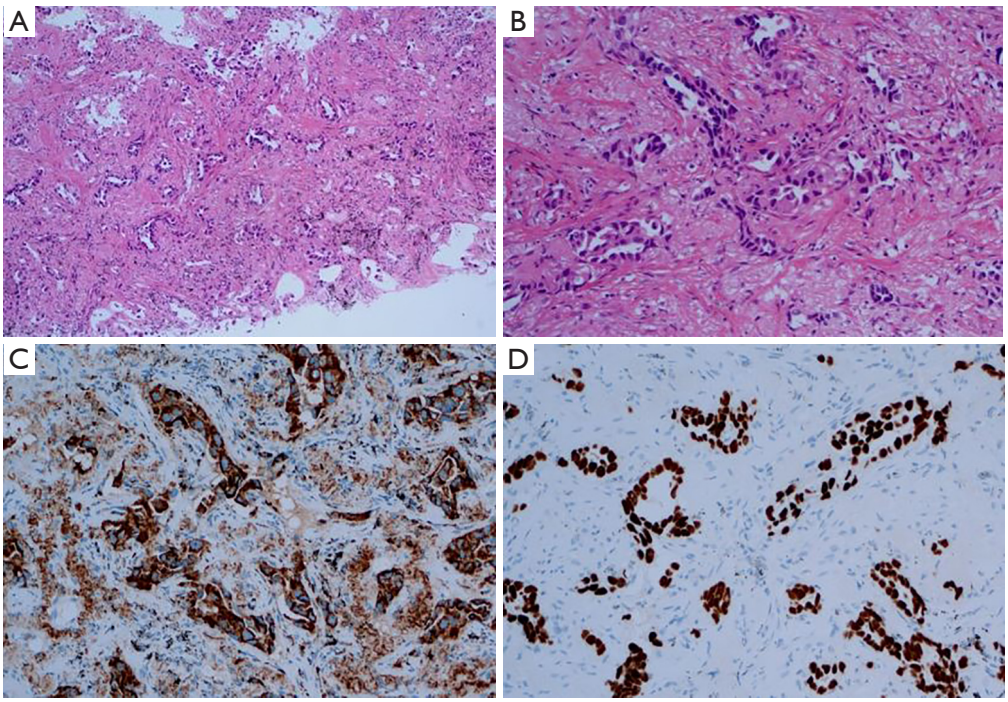

Figure 4 Pathological features of lung adenocarcinoma. (A) Irregular lumen and various glandular structures were found in fibrous stroma (hematoxylin and eosin, ×100); (B) heterotypic tumor cells were arranged into an irregular gland cavity or cord structure, and cell heterotopicity was obvious (hematoxylin and eosin, ×400); (C) the tumor cytoplasm was diffusely positive for Napsin-A (immunochemistry, ×200); (D) the tumor nucleus was diffusely positive for transcription termination factor 1 (immunohistochemistry, ×200).

bilateral thalamus in some cases (36). MRI T1-sequence enhancement scans showed linear enhancement of both dura and floppy meninges in PD-1-induced encephalopathy (32,37). The CSF analysis results were abnormal in both two reported cases. The routine examinations of CSF showed an increase in cells and protein abundance (38). An increase in cell number is mainly due to lymphocytosis but may also involve neutrophilia. The appearance of neutrophils often suggests a necrotic process in the lesion. In addition, the increase in CSF IgG suggests that ICIs have an effect on B cell function and differentiation (39). However, when an autoimmune neurologic condition is suspected, practice involves testing of both serum and CSF with autoantibody panels. Importantly, newly identified neural autoantibodies are not included on paraneoplastic panels, such as IgLON5, a neural cell adhesion molecule (40). Antibodies against N-methyl-D-aspartate receptors, which are associated with autoimmune encephalitis, should be tested (41).

Notably, pathological findings are lacking in most cases. Following the elimination of bacterial or viral infections, high-dose steroids need to be applied (35). In practice, treatment is carried out according to the severity of the disease. Classification and management of ICI related encephalitis were shown in *Table 4* (42). A number of paraneoplastic antibodies have been reported in cases of encephalitis, including antibodies to N-methyl-D-aspartate receptors and contactin-associated protein-like 2 or anti-Hu antibodies (34). These paraneoplastic-associated antibodies often cause LE. It has been shown that LE usually refers to a tumor anti-neuron antibody (such as anti-Hu) and cell surface antibody [alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic antibody (AMPAR)] (43). The clinical features of LE are short-term memory loss, seizures, irritability, depression, and cognitive decline in subacute onset. When anti-Hu is positive in SCLC patients, LE is rarely isolated and is usually complicated by diffuse and multifocal encephalomyelitis. Such encephalitis is mediated by cytotoxic T cells and thus has a poor response to treatment. Approximately 30% of LE cases positive for anti-Ma2 can be improved by tumor targeted therapy and immunotherapy (44). AMPAR-positive LE has obvious mental symptoms, of which 64% are related to paraneoplastic tumors (45). Anti-GABA-B-associated LE is usually accompanied by severe seizures in the early

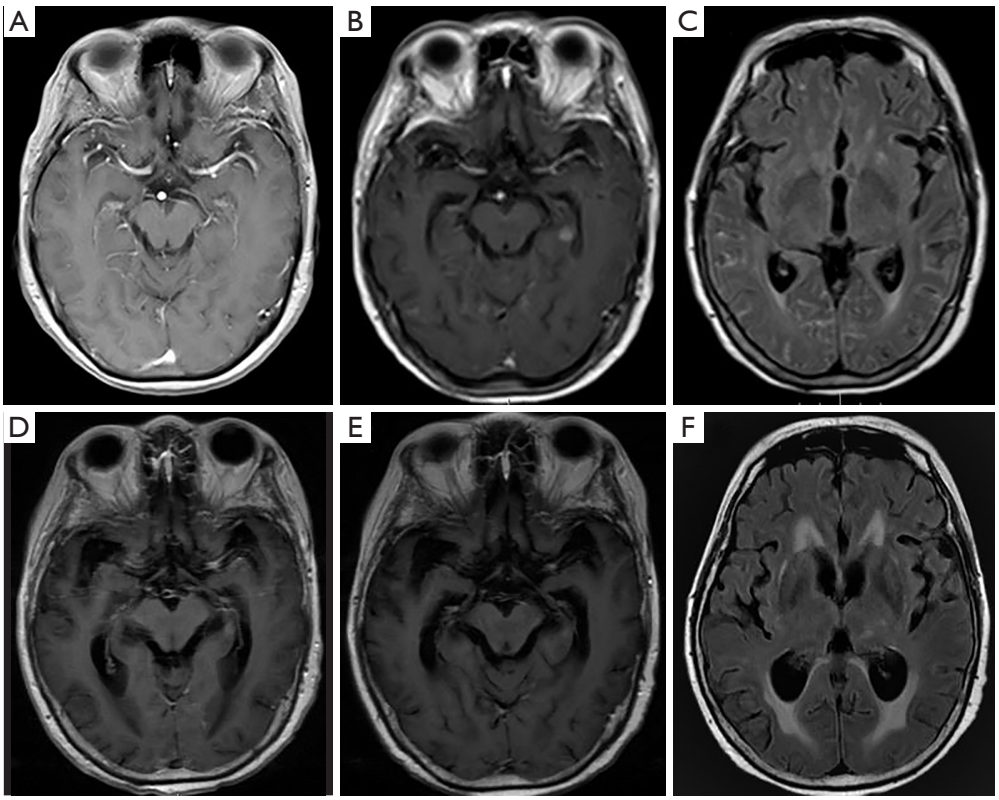

Figure 5 Positive magnetic resonance imaging findings of meningeal metastasis of lung adenocarcinoma. A 67-year-old female was diagnosed with lung adenocarcinoma. At first, she had a negative imaging finding on a T1-weighted, gadolinium-enhanced sequence (A). After 3 months, contrast-enhanced T1-weighted magnetic resonance imaging showed abnormal meningeal enhancement and nodular enhancement in the left hippocampus (B). More meningeal lesions were found in axial T2-weighted FLAIR (fluid-attenuated inversion recovery), and the gadolinium-enhanced sequence presented multiple linear hyperintensities (C). After radiotherapy, the T1-weighted, gadolinium-enhanced sequence showed that the above meningeal lesions had gradually disappeared (D,E). Conversely, based on the axial T2-weighted FLAIR sequence, hydrocephalus was worse than before (F). FLAIR, fluid attenuated inversion recovery.

Table 2 Endocrine examination for case 2

Test	Ref.	Sep 11, 2020	Oct 15, 2020	Oct 30, 2020	Nov 05, 2020
FT4, pmol/L	12–22	14.1	14.1	10.1	12
ACTH, ng/L	7.2–63.3	8.2	2.9	1.8	2.1
Cortisol, μg/L	62–194	63.4	13.6	23.5	10.7
Total thyroxine, nmol/L	66–181	88.3	78.2	58.1	53.2
FT3, pmol/L	3.1–6.8	2.17	1.52	1.43	1.32
TSH, mIU/L	0.27–4.2	5.26	0.57	0.72	0.3

FT4, free thyroxine; ACTH, adrenocorticotropic hormone; FT3, free triiodothyronine; TSH, thyroid stimulating hormone.

stage, approximately half of which are associated with paraneoplastic tumors (46).

In case 1, while epilepsy occurred after PD-1 treatment and was consistent with the time point of immunotherapy-mediated encephalitis. So, this case diagnosed PD-1-induced encephalitis. In some cases, PNSs may be associated with the

initiation of the ICIs. It was reported that ICIs could induce both humoral and cell-mediated paraneoplastic neurologic syndromes (47). According to Müller-Jensen *et al.*, there is an association between neuronal autoantibody profiles in 73 cancer patients, both with and without ICI-induced neurological immune adverse events. In their study, they found that ICI treatment could induce brain-reactive autoantibodies; however, these autoantibodies weren't necessarily associated with neurological symptoms. In conclusion, patients with and without neurologically irAEs are both likely to develop brain-reactive autoantibodies after receiving ICIs (48). Therefore, despite the patient in case 1 subsequently showing a positive result for anti-Hu, an antibody associated with PNS, we established a conclusive diagnosis of encephalitis induced by PD-1. The limitation of the diagnostic and therapeutic process in Case 1 was that paraneoplastic-associated antibodies were not detected prior to immunotherapy, and IgG in the CSF was not further evaluated. Case 2 involved a patient diagnosed with NSCLC and meningeal metastasis. After PD-1 treatment, the patient presented with obvious mental symptoms and cognitive impairment. Yshii and the colleagues have shown that patients with lung cancer treated with ICIs are at higher risk for PNSs (26). Evidence has additionally demonstrated that endocrine irAEs are a prevailing complication of ICI treatment. It is imperative

Table 3 The cognitive function of case 2 worsened

Item	Score of Sep 16, 2020	Score of Nov 05, 2020
MoCA	18	4
Immediate memory	4	1
Delayed memory	3	2
Language fluency	24	2
Digital conversion	30	0

MoCA, Montreal Cognitive Assessment.

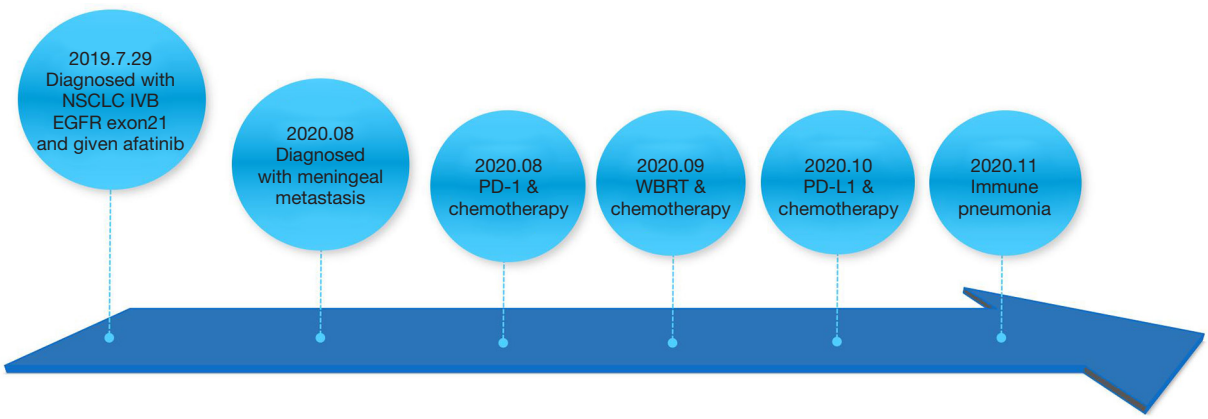

Figure 6 A timeline of the major diagnoses and treatments for case 2. NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; PD-1, anti-programmed cell death protein 1; WBRT, whole brain radiotherapy; PD-L1, programmed cell death ligand 1.

Table 4 Classification and management of ICI related encephalitis

Severity	Representation	Management
G1	Mild symptoms not limiting daily life	ICI treatment be maintained and the diagnostic process started. If there is no improvement or symptom deterioration, ICIs should be stopped permanently
G2	New moderate or severe neurological signs or symptoms	ICI treatment can be maintained temporarily, but symptoms and signs should be closely monitored. Antiviral drugs or antibiotics may empirically use as prevention
G3–G4	Severe limitations in daily life activities or life threatening or encephalitis with psycho-behavioral abnormalities	ICIs should be permanently stopped, and high-dose glucocorticoids (0.5–1 mg/kg/d) should be given if there is no infection

ICI, immune checkpoint inhibitor.

to attentively monitor endocrine function alongside ICI administration to promptly identify and manage such adverse events. Nonetheless, the exact mechanisms responsible for endocrine irAEs remain ambiguous and presumably entail a multifaceted interaction between T-cell activation and the regeneration of glands, which might be associated with inherent organ-specific autoimmunity (49). The limitation of Case 2 was that paraneoplasm-associated antibodies were not tested before or after immunotherapy, nor was IgG in the CSF tested. Immunotherapy for lung cancer often leads to abnormal thyroid function (50). In this case, thyroid function and cortisol decreased continuously, which can also lead to a decline in mental symptoms and cognitive function. High-dose hormone, gamma globulin and immunosorbent therapy were not used. However, there were also irregularities in the patient's treatment. Thus, PD-1-induced encephalopathy could not be clearly diagnosed. Furthermore, if the above treatments did not improve, encephalopathic manifestations due to tumor progression should be considered rather than PD-1 encephalopathy.

Timely diagnosis and treatment are crucial, as PD-1-induced encephalopathy can lead to serious sequelae or death. However, stopping ICI treatment may reduce the therapeutic efficiency of drugs. Severe encephalopathy caused by PD-1 may also shorten the survival time of patients. Thus, a multidisciplinary team should participate in the management decisions for patients treated with PD-1 immunotherapy.

Conclusions

While ICIs have been increasingly used in cancer treatment, they can also lead to irAEs. This paragraph discusses two cases that provide detailed information about the clinical manifestations, differential diagnosis, treatment process of PD-1-induced encephalopathy. To diagnose PD-1-induced encephalopathy, it is important to rule out PNSs. However, it is worth noting that PNSs often occur during immunotherapy. Therefore, it is necessary to promptly test for PNS antibodies in both serum fluid and CSF.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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