

CASE REPORT

Posterior reversible encephalopathy syndrome induced by nivolumab immunotherapy for non–small-cell lung cancer

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Key Clinical Message

Posterior reversible encephalopathy syndrome (PRES) is a neurological syndrome characterized by vasogenic cerebral edema with predominantly posterior involvement. Uncontrolled severe hypertension and endothelial dysfunction have been implicated as two main mechanisms. Clinicians should notice the development of PRES in hypertensive patients accompanying neurological changes, such as impaired vision and consciousness.

KEYWORDS

encephalopathy, hypertension, immune checkpoint inhibitor, nivolumab, vasogenic edema

1 | INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder characterized by various neurological symptoms such as headache, impaired vision or visual field deficits, consciousness, confusion, seizures, and focal neurological deficits.¹ In computed tomography (CT) and magnetic resonance imaging (MRI), PRES typically shows focal or confluent vasogenic cerebral edema with predominantly posterior involvement.² Although the exact mechanism of PRES remains unclear, arterial hypertension leading to cerebral hyperperfusion and endothelial dysfunction caused by circulating endogenous and exogenous toxins have been implicated as two main theories explaining the pathophysiology of PRES.¹

Immunotherapy using checkpoint inhibitors has been increasingly applied as novel treatment for various cancer types. Two antiprogrammed cell death protein (PD)-1 antibodies (Ab), pembrolizumab and nivolumab, and one antiprogrammed cell death ligand 1 antibody, atezolizumab, are currently approved to treat patients with advanced non–small-cell lung cancer (NSCLC). Due to their nature of enhancing the immune system, immune-related adverse events (irAEs) have also been increasingly observed in patients receiving these agents.^{3,4}

Recently, several cases of immunotherapy-related PRES have been reported as a rare cause of PRES in patients receiving ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4),⁵ both ipilimumab and nivolumab,⁶ nivolumab alone,⁷ or pembrolizumab.⁸ Here, we present a case of PRES occurring in a male patient receiving nivolumab for treating non–small-cell lung cancer.

2 | CASE REPORT

A 68-year-old man who had received four doses of immunotherapy with nivolumab (3 mg/kg intravenously every 2 weeks) for advanced NSCLC, squamous cell carcinoma, with single bone metastasis was admitted to our hospital because of sudden loss of vision, headache, nausea with vomiting, and weakness of both lower extremities. On physical examination after admission, the following results were obtained: blood pressure, 212/108 mm Hg; heart rate, 100/min; respiration rate, 22/min; and temperature, 36.8°C. Ophthalmologic evaluation was performed for his impaired vision, and hypertensive retinopathy and macular degeneration were diagnosed for both eyes. Because he was getting

confused, brain MRI with contrast enhancement was immediately performed to define acute intracranial abnormalities and overt brain metastasis. Results showed vasogenic edema consistent with PRES without intracranial hemorrhage (Figure 1A).

Before immunotherapy was initiated, the patient had received five cycles of platinum-based chemotherapy with gemcitabine (1000 mg/m²) and carboplatin (5 AUC). During the first-line cytotoxic chemotherapy, he had never experienced any neurological adverse event (AE). Although he had chronic renal failure and hypertension, they were well controlled by taking telmisartan 40 mg every day. His blood pressure very rarely exceeded 150/90 mm Hg when it was checked on each visit and at admissions before and after receiving cytotoxic chemotherapy. He had never discontinued taking antihypertensive medicine and continuously received hemodialysis for chronic renal failure three times a week. Because his lung cancer was defined to progress based on computed tomography taken 3 months after the completion of the first-line chemotherapy, immunotherapy with nivolumab was initiated after confirming more than 15% PD-L1 expression on tumor cells by PD-L1 VENTENA (SP263) assay. The last dose of nivolumab was given 16 days before the onset of PRES. After nivolumab immunotherapy was initiated, his blood pressure was increased stepwise. Although his blood pressures checked before the first and the second dose of nivolumab were given were less than 140/90 mm Hg for each, the blood pressure checked before discharge from

the hospital was increased to 156/78 mm Hg after the first dose and 151/76 mm Hg after the second dose. The dose of antihypertensive medicine was increased to telmisartan 80 mg a day after the second dose, his blood pressures checked before and after the third and the fourth doses were continuously increased to 158/90 and 176/84 mm Hg after the third dose, and 164/92 and 183/81 mm Hg after the fourth dose. Because, PRES is often associated with autoimmune diseases which are also presented as irAEs induced by immunotherapy, antinuclear antibody (ANA), anticytoplasmic antibody (ANCA), anti-Jo 1 antibody, aldolase, and thyroid function tests including triiodothyronine (T3), free thyroxine (T4), and thyroid-stimulating hormone (TSH) were checked, but all results were normal.

As soon as the patient was diagnosed with having PRES, he was treated with intravenous antihypertensive agent (nicardipine 5 mg/h continuously and labetalol 10 mg repeatedly) to control his blood pressure. After his blood pressure was strictly controlled not to exceed 140/90 mm Hg for several days after hospitalization, his consciousness and vision were spontaneously improved without using immunosuppressive agents such as corticosteroid. PRES lesion was resolved on the MRI taken after 2 weeks of supportive care with antihypertensive medicines (Figure 1B), and hypertensive retinopathy and macular degeneration were also improved. After 4 weeks of admission for PRES, although his previous neurological deficits were improved, he refused to treat his cancer with both immune checkpoint inhibitors

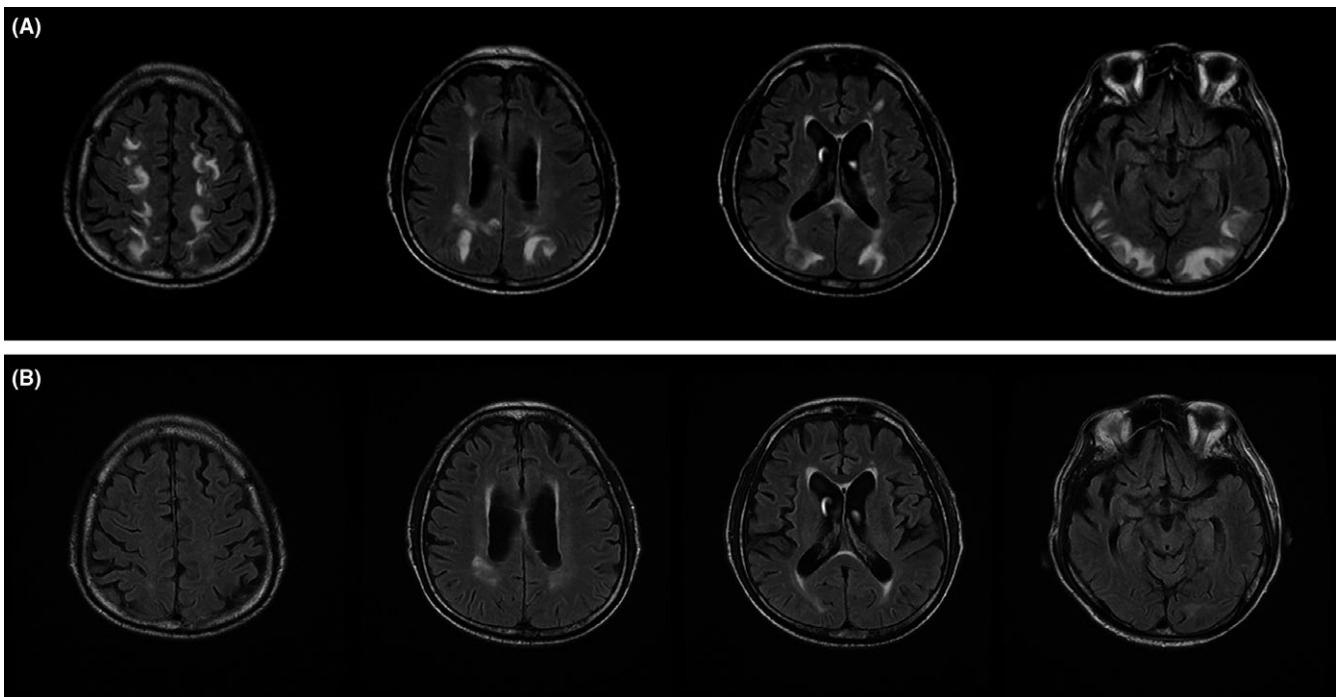


FIGURE 1 A, T2 FLAIR (fluid-attenuated inversion recovery)-weighted magnetic resonance imaging showing subcortical and deep white matter high signal intensity involving both cerebral hemispheres, especially temporooccipital and high frontoparietal areas. B, Two-week follow-up study showing decreased extent of high signal intensity lesions in subcortical and deep white matter of both cerebral hemispheres

and other conventional chemotherapeutic agents. He was transferred to another hospice hospital for symptomatic management and died from pneumonia at that hospital 2 months later.

3 | DISCUSSION

Posterior reversible encephalopathy syndrome is a syndrome demonstrating neurological symptoms and signs including headache, visual disturbance, and focal neurological deficits, and typical imaging alterations consistent with cerebral edema predominantly distributed in the posterior parietal and occipital lobe on MRI or CT.^{2,9} Even if the underlying pathophysiology developing PRES remains poorly understood, cerebral hyperperfusion causing vascular leakage and vasogenic edema in patients with severe uncontrolled arterial hypertension, such as hypertensive crisis or emergency, and endothelial dysfunction by circulating endogenous or exogenous toxins in patients receiving chemotherapy and cytotoxic agents or in patients with preeclampsia, sepsis, and autoimmune disease have been implicated as two main mechanisms.¹ In addition, PRES can be manifested in patients without hypertension while endothelial dysfunction, hypoperfusion, and vasoconstriction may lead to altered integrity of the blood-brain barrier.¹⁰ Because a high percentage of PRES patients have underlying autoimmune diseases, the possibility of developing PRES in patients receiving immunotherapy can be suspected, considering the nature of immunotherapy in enhancing systemic immunity.

Recently, several cases of PRES developed in female patients receiving immune checkpoint inhibitors have been reported.⁵⁻⁸ Among these, two case reports described high blood pressure at the diagnosis of PRES: 170/90 mm Hg in a patient receiving ipilimumab for melanoma treatment⁵ and 148/95 mm Hg in a patient receiving nivolumab for lung cancer.⁷ In the current case, as soon as we defined PRES, we reviewed his previous blood pressure levels from his medical records. Interestingly, we found serial increment of his blood pressure after repeated use of nivolumab. His blood pressure checked after nivolumab use was serially increased from 151/76 to 183/81 mm Hg despite the increment of the dose of antihypertensive medicine. Because he received hemodialysis at other dialysis clinic during the course of immunotherapy, whether his blood pressure was well controlled or not between each immunotherapy was unknown. However, when he received hemodialysis at our hospital during the first-line cytotoxic chemotherapy, his blood pressure was maintained stable, presenting less than 150/90 mm Hg for every visit. Hypertension is one of occasional side effects (>1%) after nivolumab treatment,¹¹ and thus, making hypertension controlled to uncontrolled

by nivolumab might be an important contributor to the development of PRES.

Enhanced systemic immune system after nivolumab treatment may be another contributor to the development of PRES. There have been increasing number of reports describing irAEs, such as myasthenia gravis,¹² polymyositis,¹³ anti-N-methyl-D-aspartate receptor antibody encephalitis,¹⁴ chronic inflammatory demyelination polyradiculopathy,¹⁵ and progressive encephalomyelitis with rigidity and myoclonus¹⁶ in patients who received nivolumab, and showed positive response to high dose steroids and plasma exchange. However, considering that the current patient was spontaneously improved just by strictly controlling hypertension without steroid use, it seems that uncontrolled hypertension was more important contributor to PRES development.

Even if the safety and efficacy of nivolumab compared to cytotoxic chemotherapeutic agent, docetaxel, have been proven by two large phase III trials: CheckMate 057 and CheckMate 017, demonstrating higher median survival (9.2-12.2 months vs 6.0-9.4 months) and lower serious adverse events (7%-10% vs 54%-55%),^{17,18} the relative safety of nivolumab does not mean its complete safety, and the possibility of developing various AEs still remains concerned in the medical field. Therefore, special attention is needed to detect potentially life-threatening AEs earlier when these unfamiliar treatments were tried.

4 | CONCLUSION

Posterior reversible encephalopathy syndrome can be developed as a rare AE in patients receiving immune checkpoint inhibitors for cancer treatment. Although the mechanism is uncertain, sudden transition from controlled to uncontrolled hypertension might be an important cause of the disease. Thus, clinicians should pay special attention to the development of newly diagnosed or uncontrolled hypertension during immunotherapy for early detection or prevention of this serious AE.

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None.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

DK: managed the patient and prepared the manuscript.

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