Case Report

Identification and Management of Posterior Reversible Encephalopathy Syndrome in a Patient Enrolled in an Immunotherapy Combination Phase I Clinical Trial: A Case Study

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ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is a rare potential immune-related adverse event (irAE) of checkpoint inhibitors. PRES is a disorder that has a variety of clinical and radiological features, which makes it a challenge for advanced practice registered nurses to diagnose. IrAEs such as PRES require prompt recognition and intervention to optimize clinical outcomes.

Key words: Checkpoint inhibitors, Phase I clinical trial, posterior reversible encephalopathy syndrome

Introduction

Phase I clinical trials are conducted to explore safety, tolerability, adverse events (AEs), and the pharmacokinetics of novel drugs.[1] Recently, Phase I clinical trials have consisted of immune checkpoint inhibitors (ICIs) in combination with radiation, molecularly targeted therapies, or other immunotherapy agents.[2] These ICI combination trials have the potential for therapeutic synergy, however, often, the benefits of ICIs can be equipoised by rare immune-related AEs (irAEs) such as posterior reversible encephalopathy syndrome (PRES).[3,4]

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Case Report

A 50-year-old female with refractory high-grade neuroendocrine carcinoma of the retroperitoneum currently cycle 2, day 8 of an ICI combination Phase I clinical trial, presented to the emergency center through ground ambulance with new-onset grand mal seizure with generalized tonic-clonic activity, severe headache, nausea, and vomiting. Of note, the patient's family reported a

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2-week history of poor oral intake of food and water by the patient. The patient received Versed in route to the hospital. On arrival, the patient did not have any seizure activity and was arousable but confused. Physical examination in the emergency center revealed: heart rate of 139/min, blood pressure of 132/95 mmHg, respiration rate of 18/min, temperature of 36.7°C, and oxygen saturation of 100%. Blood work demonstrated glucose of 106, CO_2 of 21, chloride of 98, potassium of 3.6, sodium of 134, creatinine of 4.95, magnesium of 2.3, ammonia of 29, lactic acid of 0.6, antineutrophil antibody vasculitis panel negative, and ANA titer <1:40. Magnetic resonance imaging (MRI) of the brain without contrast showed scattered, symmetrical T2 fluid-attenuated inversion recovery hyperintensity within bilateral posterior cerebral hemispheres without associated infarct or hemorrhage. In the emergency center, the patient was treated with Ativan and Keppra intravenously (IV), a consult was placed for neurology. Subsequently, the patient was placed on Vimpat 100 mg twice/day orally. She did not have any additional seizure episodes and did not require any immunosuppressants. While hospitalized, the patient became hypertensive, with systolic blood pressures ranging between 140 and 170 mmHg. The patient was initially started on Hydralazine 50 mg three times a day and Labetalol 20 mg every 8 h as needed, which was later changed to Nifedipine 20 mg daily with adequate control of blood pressure. A nephrologist was consulted to manage the acute kidney injury (AKI). Renal ultrasound showed increased renal echotexture. Lactic acidosis, starvation ketosis, and infection were ruled out as a cause of the AKI. The patient was treated with gentle IV hydration. She made a full recovery and was discharged from the hospital. Subsequently, she was seen in the clinic with a follow-up MRI of the brain, which showed complete resolution of the T2 abnormality. Nonetheless, the patient was removed from the Phase I clinical trial secondary to PRES. Informed consent was obtained from the patient.

Discussion

The exact underlying pathophysiology of PRES is not well known, although it is believed to be secondary to rapidly developing hypertension that exceeds the upper limits of cerebral blood flow autoregulation that causes hyperperfusion, which leads to the dysfunction of the blood–brain barrier, thus allowing the interstitial extravasation of plasma and macromolecules.[5,6] PRES is often seen in young or middle-aged adults with an incidence rate that varies from 2% to 25%.[5] In addition, PRES has been associated with chronic and acute kidney disease, solid organ transplantation, and use of immunosuppressive drugs.[5,7]

PRES can be a challenge to diagnose because of the variety of neurological signs and symptoms, which can develop within hours or several days or weeks.[6] However, PRES should be considered in patients who present with seizures, altered consciousness, visual disturbance, or headache, particularly in the context of acute hypertension.[6] Although most patients are likely to present with hypertension, approximately 15% to 20% of patients may be normotensive or hypotensive during the initial evaluation.[4] Given that the signs and symptoms of PRES are nonspecific, advanced practice registered nurses (APRN) are challenged to distinguish PRES from other neurological diseases. The differential diagnosis of PRES might include reversible cerebral vasoconstriction syndrome, infectious encephalitis, malignant tumor, or other vasculitis process.[6] A trigger is usually identifiable, most commonly acute hypertension, but patients often have other comorbidities or medications that may predispose them to developing PRES.[6]

There are no laboratory findings specific to PRES. If an APRN suspects PRES, brain imaging is needed to exclude differential diagnoses.[6] In general, radiologic findings of PRES show regions of T2 signal abnormality on the MRI.[6] Other potential findings that are seen with the brain MRI include a dominant parieto-occipital pattern, holohemispheric watershed pattern, and superior frontal sulcus pattern.[6]

There is no specific treatment for PRES, however if recognized and treated promptly, the rapid onset of symptoms and radiologic features usually fully resolve within days to weeks.[6] Yet, >10%–44% of patients may experience persistent neurologic deficits if treatment is delayed.[8] In addition, PRES can reoccur with an overall mortality of 3%–6%.[6]

In general, the APRN will prescribe antiepileptic drugs for seizures as they would in any other neurological disorder, which can be tapered as soon as the patient is asymptomatic, and the imaging lesions have fully reversed.[6,9] Specific antihypertensive medications have not been fully evaluated in the treatment of hypertensive encephalopathy in PRES, therefore the selection of drugs is based on the APRN's preference and recommended treatment guidelines.[10] If the APRN suspects that PRES is caused by a specific medication, then the medication should be temporarily placed on hold or discontinued permanently.

Conclusions

IrAEs such as PRES require prompt recognition and intervention to optimize clinical outcomes. As ICI enters day-to-day clinical practice, it is crucial that multidisciplinary collaborations are established to improve the recognition and management of common or rare irAEs.

Thus, as part of the multidisciplinary team, APRNs should become familiar with irAEs to facilitate proper evaluation and referral to the correct specialist.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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