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Pembrolizumab-induced encephalitis in a patient with renal cell carcinoma post nephrectomy: A case report

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Abstract

A new category of immune-related adverse effects has been identified due to increasing use of immune checkpoint inhibitor therapy to treat solid organ cancers. Pembrolizumab approved for renal cell carcinoma also has neurological immune-related adverse effects causing long-term morbidity. We here present a case of renal cell carcinoma post nephrectomy with suspected pembrolizumab (anti-PD-1)-induced encephalitis presenting as light headedness and dizziness treated with high dose of corticosteroid and intravenous immunoglobulin. Lumbar puncture was performed which showed elevated protein, nucleated cells with lymphocyte predominant, suggestive of chemical meningitis. Scans were found to be normal while electroencephalogram showed diffuse cerebral dysfunction indicating encephalopathy. The patient was under pembrolizumab treatment so encephalitis was suspected. Clinical attention is necessary when patients receiving immune checkpoint inhibitors appear with new neurological symptoms to prevent long-term morbidity or even possible mortality.

Keywords

Pembrolizumab, renal cell carcinoma, meningitis, corticosteroid

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Introduction

Immune checkpoint inhibitor (ICI) therapy is increasingly used to treat solid organ cancers. As a result, a new category of immune-related adverse effects (irAEs) has been identified that is brought on by an increase in T-cell activity that results in autoimmunity. The uncommon ICI consequence known as neurological irAEs can cause long-term morbidity.[1] The US Food & Drug Administration recently approved pembrolizumab for the adjuvant treatment of renal cell carcinoma (RCC) patients at intermediate-high or high risk of recurrence following nephrectomy, or after nephrectomy and resection of metastatic lesions. Until disease recurrence, unacceptable toxicity, or up to 12 months, the patient had maintained disease-free survival (DFS) effect.[2]

We here present a case of RCC post nephrectomy with suspected pembrolizumab (anti-PD-1)-induced encephalitis presenting as lightheadedness and dizziness treated with high dose of corticosteroid and intravenous immunoglobulin (IVIG).

Case presentation

A 71-year-old male smoker patient presented to our hospital (Memorial Hospital Belleville, Belleville, IL, USA) from the emergency department on 1 August 2022 with a chief complaint of dizziness and lightheadedness after a recent fall at home with the loss of consciousness. He was recently discharged from Aderson Hospital with congestive heart failure and had hypotension during the presentation. He was advised to have Entresto and Lisinopril there. He was diagnosed with RCC in 2019 by retroperitoneoscopic

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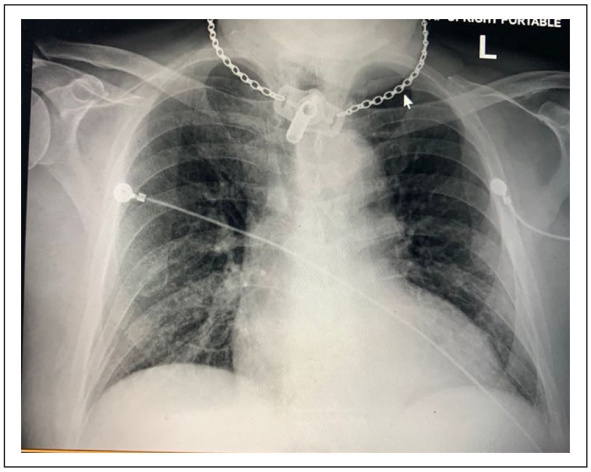

Figure 1. Chest X-ray AP view showing bibasilar opacities likely atelectasis and less likely developing pneumonia.

partial nephrectomy revealing pT1b, World Health Organization grade 2 with focal grade 4, clear cell RCC for which radical nephrectomy was performed, and was under pembrolizumab. The patient was on adjuvant pembrolizumab (at a dose of 200 mg) intravenously once every 3 weeks for up to 17 cycles. There was no prior medical history of fever, vomiting, difficulty swallowing, weakness, or balance, speech, or visual issues. The patient denied any changes in bowel or bladder habits, autonomic dysfunction, or loss of sensation. Past medical history included RCC, coronary artery disease, chronic kidney disease, colon polyps, hypercholesterolemia, hypertension, and pulmonary thrombo-embolism while past surgical history included appendectomy, colonoscopy, laparoscopic partial nephrectomy, renal cryoablation, and tracheostomy.

The patient smokes and drinks occasionally and has smoked for 40-pack years. There is no known neurological disease or a history of problems similar to these in the family. Under review of symptoms, there was shortness of breath and weakness.

His general status was fair upon arrival, with a Glasgow coma score of 15/15.[3] There was no clubbing, cyanosis, lymphadenopathy, icterus, or pallor. Vitals signs showed blood pressure of 63/46 mm of mercury, pulse rate 59 beats/min, respirations of 24 breaths/min, saturation 97% on room air, and temperature 97.1°F. On pulmonary examination, rhonchi were present. On neurological testing, his cranial nerves, sensory, and coordination tests under his higher mental functions were all normal without any meningeal signs. His blood workup was unremarkable.

Chest X-ray showed bibasilar opacities, likely atelectasis, and less likely developing pneumonia (Figure 1). Computed tomography (CT) scan of the head showed no acute findings (Figure 2). Magnetic resonance imaging (MRI) T1-weighted fluid-attenuated inversion recovery (FLAIR) scans were normal (Figure 3).

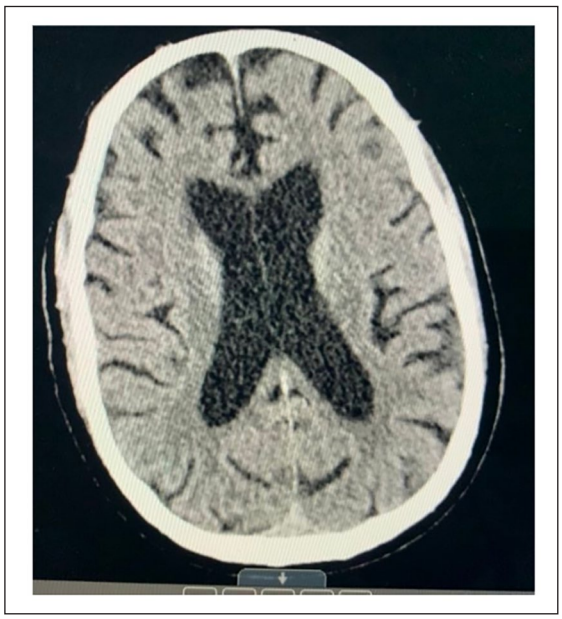

Figure 2. Non-contrast CT scan of the head (axial) showing normal findings.

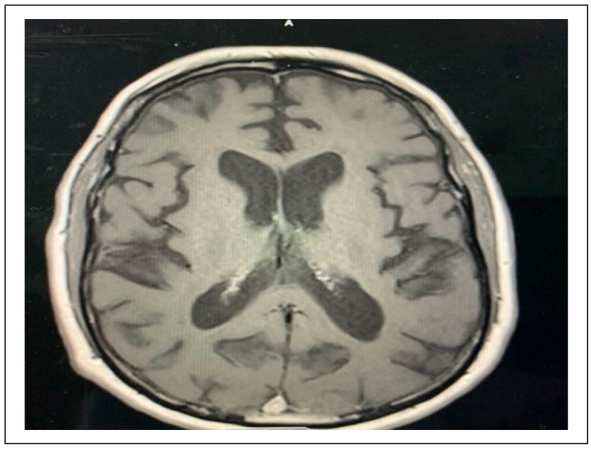

Figure 3. T1-weighted FLAIR MRI scan of the head (axial) showing normal findings.

The patient had a lumbar puncture which showed elevated protein (101 mg/dL), and nucleated cells (51 cells) with 91% lymphocyte suggestive of chemical meningitis. The cerebrospinal fluid (CSF) paraneoplastic panel was within normal limits. Electroencephalogram (EEG) showed diffuse cerebral dysfunction indicating encephalopathy.

The patient was under pembrolizumab treatment and encephalitis was suspected. Pembrolizumab was stopped, and the patient started on a high dose of corticosteroid and IVIG was started. The patient is improving and is on constant follow-up. He was discharged to home under a tapering dose of prednisolone starting from 40 mg for 3 days. On last visit, his health status (mainly dizziness and weakness) is improving. MRI was not performed at follow-up.

Discussion

A severe immunological-related side effect of ICIs therapy is encephalitis. The ICI-induced encephalitis (ICI-iE) spectrum includes both totally cured and deadly forms of the disease. ICIs may cause an undetected preexisting paraneoplastic encephalitic condition.[4] It is generally known that these adverse outcomes are a result of increased T-cell activity and can result in a wide range of autoimmune sequelae that can cause clinical syndromes such as colitis, pneumonitis, and hepatitis. The differentials are myasthenia gravis, Guillain–Barre syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), transverse myelitis, meningitis, limbic encephalitis, and posterior reversible encephalopathy syndrome (PRES).[1]

The wide variety of signs and symptoms associated with neurological irAEs makes diagnosis challenging. Atypical characteristics frequently appear in clinical presentations. Despite a possible autoimmune mechanism, no reliable indicators or autoantibodies have been found.[5] ICI-induced toxicity must be taken into account in the differential diagnosis of a patient who has a history of malignancy, is receiving ICI treatment now or in the past, and shows symptoms of encephalitis or neurotoxicity as well as changed mental status.[6]

It is not well understood how often neurotoxicity is in patients receiving ICI therapy. According to a review of the literature, the incidence of neurotoxicity for ICIs like pembrolizumab is 6.1%. Patients may exhibit signs of both the upper and lower motor neurons or a combination of neurological symptoms that do not fit any one diagnosis.[6] In phase III clinical studies, the prevalence of neurological irAEs is frequently underreported and poorly defined. It is challenging to foresee which patients would be at higher risk of developing neurological irAEs.[1] PD-1 inhibitors may cause greater risk over time because of their prolonged duration of use. Immune checkpoint drugs pose a risk of neurological adverse events at any point in the course of therapy; however, in a cohort study, presentations within the first 4 months predominated.[7] Thus, in our patient also encephalitis was diagnosed late because of the above reasons.

There are many different diagnostic tools utilized for diagnosis. To track the development of the illness and how well it responds to treatment, a comprehensive neurologic examination is necessary. To aid in a quick diagnosis, if available, diagnostic modalities such as brain MRI, lumbar puncture, nerve conduction testing, and EEG should be swiftly ordered. CSF leukocytosis or proteinemia with oligoclonal bands are two symptoms that can indicate inflammatory or demyelinating diseases.[8,9]

Only ample literature was published on pembrolizumab-induced encephalitis in different cancer cases. Using lumbar puncture (CSF analysis), encephalitis was identified in a 55-year-old male alcoholic patient with metastatic renal cell cancer who was receiving pembrolizumab treatment. Imaging results were non-diagnostic. He was treated with IVIG and steroids for 5 days until a gradual return to normal mental status and remained on a steroid taper when the pembrolizumab was abruptly stopped.[6] A case report of pembrolizumab-induced encephalitis in papillary carcinoma of the thyroid with a symptom of episodic aphasia was also published. The patient received high-dose steroids with minimal response. The clinical improvement with reduced episode frequency was noted after IVIG induction and rituximab maintenance therapy.[10]

Two case reports on small lung cell cancer treated with pembrolizumab had autoimmune encephalitis with symptoms like generalized weakness, disorientation, myoclonic jerks, altered level of consciousness, and ataxia gait. In the former case report, corticosteroids were continued and the patient reacted well while pembrolizumab was continued, while in the latter the patient received IVIG therapy for autoimmune encephalitis with continuous pembrolizumab therapy without suspension of tumor treatment.[11–13]

The ideal corticosteroid dosage is a topic of discussion. Prednisone or methylprednisolone at a dose of either 2 mg/kg/day or 1 mg/kg/day should be used to treat irAEs when taking high-dose steroids, according to the general advice. However, it has been observed that higher doses of methylprednisolone taken intravenously (500–1000 mg/d) are required to treat central nervous system irAEs due to a lower peak concentration in the CSF than in plasma.[14]

On literature review, we found out that our case is the second such reported case of pembrolizumab-induced encephalitis in patient RCC post nephrectomy. In our case report, pembrolizumab was held and a high dose of corticosteroid and IVIG was started. CSF analysis was diagnostic in our case as in the previous case report.

ICI-induced encephalitis has a low mortality rate and a generally favorable prognosis. The therapeutic approach and prognosis counseling will be guided by the clinical presentation and the systematic measurement of autoantibodies.[4]

Conclusion

The increased use of ICI therapy will lead to an increase in neurological irAEs. Clinical attention is necessary when patients receiving ICIs appear with new neurological symptoms. To further understand the causes, management, and prevention of neurological irAEs, more study is needed. It is crucial to recognize, diagnose, and treat these patients with corticosteroids as soon as possible in order to prevent long-term morbidity or even possible mortality.

Author contributions

All authors contributed to the conduct of this research and read and approved the final version of the manuscript.

Data availability

The data supporting the findings of the case are available upon request to the corresponding author.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for anonymized patient information to be published in this article.

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