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Case Report

Gemcitabine/Cisplatin/Pembrolizumab-Induced Posterior Reversible Encephalopathy Syndrome

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a syndrome related to endothelial dysfunction and disorder in cerebral autoregulation. The clinical manifestations include seizures, headache, mental alteration, and visual disturbance. The causes of PRES are diverse and include renal failure, transfusion, transplantation, endocrine disorders, autoimmune diseases, and cytotoxic and immunosuppressive agents. Various anti-cancer drugs such as gemcitabine and platinum can also cause PRES, and a few case reports have discussed the effect of immunotherapy on PRES. In this article, we present a case who developed PRES after receiving gemcitabine, cisplatin, and pembrolizumab. We also review previous cases with gemcitabine/cisplatin- and immunotherapy-induced PRES. Most of these cases had a good clinical outcome, the resolution of neurologic signs varied from days to weeks.

Keywords: Gemcitabine, immunotherapy, posterior reversible encephalopathy syndrome, urothelial carcinoma

Introduction

Posterior reversible encephalopathy syndrome (PRES) was first introduced in 1996 as a syndrome related to disorders of cerebral autoregulation and endothelial damage. The pathophysiology involves the breakdown of the blood–brain barrier leading to interstitial extravasation of plasma and macromolecules.[1] Clinical manifestations include seizures, headache, mental alteration, and visual disturbance. The causes of PRES are very diverse and include renal failure, transfusion, transplantation, endocrine disorders, autoimmune diseases, and cytotoxic and immunosuppressive agents.[2] Various anticancer drugs including gemcitabine and platinum can also cause PRES; however, few case reports have discussed immunotherapy-related PRES. Herein, we present a case with gemcitabine/cisplatin/pembrolizumab-induced PRES and accomplish a review of the literature. Ethical approval for this study was obtained from our hospital, and we informed both the patient and the patient's family about this study and obtained written informed consent (T-KMUH-17043).

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Case Report

This 59-year-old female denied any previous systemic diseases and had an Eastern Cooperative Oncology Group performance status of 0–1. She had felt low back pain for 2 months (since February 2018). Urothelial carcinoma with multiple lung and bone metastases was diagnosed after a series of examinations. Spinal magnetic resonance imaging (MRI) disclosed multiple pathological fractures in bilateral hip bones, right acetabulum, and multiple vertebral bodies. She received image-guided radiotherapy to spinal metastatic lesions with a total dose of 3000 cGy/10fx from April 2018 to May 2018. Her low back pain worsened after spinal radiation, so she received laminectomy and tumor removal surgery. We started immunotherapy (pembrolizumab 100 mg on day 1) combined with gemcitabine and cisplatin (GC, gemcitabine 1000 mg/m^2 on days 1, 8, and 15, and cisplatin 60 mg/m^2 on day 1, for 3 weeks) at the end of May 2018. An interim bone scan showed a dramatic improvement. However, she had nausea, abdominal discomfort, severe headache with a hypertensive emergency, and visual disturbance during the fifth cycle of chemotherapy on September 21, 2018. An initial brain computed tomography showed no intracranial lesions and an ophthalmology examination was normal. She suffered a tonic-clonic seizure with a loss of consciousness for 2 min. Hours later, she became drowsy and lethargic. There were no abnormal findings in blood tests, and cortisol level, thyroid function, and ammonia level were within normal ranges. Brain MRI revealed abnormal cortical and subcortical lesions at bilateral parieto-occipital lobes, compatible with PRES [Figure 1]. She received an anti-convulsion agent (levetiracetam) and also had a nicardipine pump for the hypertensive emergency. Her blood pressure returned to normal range after 2 days, and nicardipine pump was gradually tapered and discontinued. One day later, her visual disturbance recovered completely and she had clear consciousness. No seizure episodes occurred afterward. After 1 week, she was discharged without neurologic sequela.

Discussion

PRES is a neurological disorder with a (sub) acute onset characterized by various neurological symptoms, which may include headache, impaired visual acuity or visual field deficits, disorders of consciousness, confusion, seizures, and focal neurological deficits.[3] In a majority of patients, the clinical presentation includes elevated arterial blood pressure and may involve a hypertensive emergency. For patients with malignancy, PRES is usually encountered after multi-drug chemotherapy, especially during combination high-dose chemotherapy. The reported drugs include cytarabine, cisplatin, gemcitabine, tiazofurine, bevacizumab (Avastin), and some kinase inhibitors.[4] Few case reports have mentioned the relationship between immunotherapy and PRES. Immune checkpoint inhibitors currently approved by the Food and Drug Administration include ipilimumab (an anti-CTLA-4 monoclonal antibody); pembrolizumab and nivolumab (programmed death-1 (PD-1) antibodies), and atezolizumab, durvalumab, and avelumab (programmed death ligand-1 (PD-L1) antibodies).[5] In one mini-review discussing immune checkpoint inhibitor-related central nervous system (CNS) toxicity, 15 cases developed encephalopathies (ipilimumab monotherapy [9 of 15 cases, 60%], simultaneous or sequential use of ipilimumab with an anti-PD-1 antibody [3 of 15 cases, 20%], and anti-PD-1 monotherapy [3 of 15 cases, 20%]).[6]

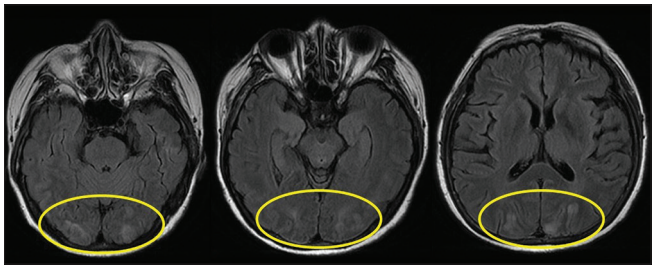

Figure 1: Diagnostic brain magnetic resonance imaging (axial fluid-attenuated inversion recovery weighted image): the area in the yellow circles showed abnormal cortical and subcortical lesions at the bilateral parieto-occipital lobes

The efficacy of pembrolizumab has been proven in melanoma, renal cell carcinoma, urothelial carcinoma, and non-small-cell lung cancer (NSCLC). The adverse events associated with pembrolizumab are related to an increase in immune response and include rash, pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hypothyroidism.[7] Immune-related adverse effects in neurological complications can involve both the CNS and peripheral nervous system, and the presentations range from nonspecific symptoms to clinical syndromes, including chronic inflammatory demyelinating polyneuropathy, transverse myelitis, meningitis, limbic encephalitis, and PRES.[8] The possible explanation for the association between PRES and immune checkpoint inhibitors may be the immune activation of damaged vascular endothelial cells caused by cytokine-mediated inflammatory responses.[9] Whether GC combined with pembrolizumab increases the risk of PRES is unclear.

We reviewed previous cases with gemcitabine, GC, and gemcitabine/immunotherapy-induced PRES [Table 1].[3,9-12] The initial presentations included headache, consciousness disturbance, and convulsions. Most of these cases had good clinical outcomes with full-recovery, and the resolution of neurologic signs occurred within weeks, which is consistent with previously documented cases of PRES. One 68-year-old man with advanced NSCLC with bone metastasis who received the GC regimen combined with nivolumab developed PRES after 16 days after the last dose of nivolumab, and he was successfully treated with supportive care and antihypertensive agents.[13] Another case report regarding monotherapy with pembrolizumab involved a 26-year-old woman with relapsed Hodgkin lymphoma after hematopoietic stem cell transplantation who developed PRES 10 days after her first dose of pembrolizumab.[9] Another interesting case report was a 64-year-old-woman who had advanced lung

Table 1: Cases with posterior reversible encephalopathy syndrome complication during the treatment with gemcitbine, gemcitabine/cisplatin, gemcitabine + pacilitaxel, gemcitabine/cisplatin + pembrolizumab, gemcitabine/cisplatin + nivolumab, ipilimumab + pembrolizumab, and durvalumab + ramucirumab regimens

Age	Gender	Diagnosis	C/T	Cycle	Total G dose (mg)	Onset (Days)	Presentation	Prognosis
55	Female	Pancreas cancer	G	2nd	5000	8	C/C, V/D, S/Z, epigastric pain	FR
59	Female	Breast cancer	G	X	2260	5	Severe abdominal pain, N/V, anorexia	FR
41	Female	Leiomyosarcoma	G	4th	12,000	13	Lethargy, H/A, V/D	FR
74	Female	Pancreatic cancer	G	3rd	9000	1	H/A, S/Z, V/D	FR
50	Male	Urothelial carcinoma	GC	2nd	6000	35	C/C	PR
58	Female	Gallbladder cancer	GC	3rd	7200	14	H/A, dizziness, S/Z	FR
40	Female	Gallbladder cancer	GC	4th	14,400	10	C/C, S/Z	PR
58	Female	Cholangiocarcinoma	GC	6th	20,400	1	Agitated, C/C	FR
63	Female	Ovarian carcinoma	GC + PTX	5th	10,000	5	C/C, S/Z	X
59*	Female	Urothelial carcinoma	GC + Pem	5th	16,000	7	H/A, V/D, S/Z, epigastric pain	FR
68	Male	NSCLC	GC + Niv	5th	5000	16	H/A, V/D, N/V	PR
47	Female	NSCLC	GC then Niv	2nd dose Niv	--	24	S/Z, V/D	PR
26	Female	Hodgkin lymphoma	Ipil then Pem	1st dose Pem	--	10	S/Z	FR
64	Female	NSCLC	Durv+Ram	--	--	--	H/A, V/D, S/Z	FR

*Our case. C/T: Chemotherapy, NSCLC: Non-small-cell lung cancer, G: Gemcitabine, C: Cisplatin, GC: Gemcitabine/cisplatin, PTX: Paclitaxel, Pem: Pembrolizumab, Niv: Nivolumab, Ipil: Ipilimumab, Durv: Durvalumab, Ram: Ramucirumab, FR: Full recovery, PR: Partial recovery, C/C: Consciousness change, H/A: Headache, N/V: Nausea/vomiting, V/D: Visual disturbance, S/Z: Seizure/convulsion

adenocarcinoma and was treated with an anti-programmed cell death-1 ligand 1 antibody (durvalumab) and vascular endothelial growth factor 2 antibody (ramucirumab) after receiving first-line cisplatin–pemetrexed and subsequently developed PRES.[11] The complexity of diseases themselves and immune reaction effects on the brain–blood barrier could be possible explanations for PRES. In summary, to recognize PRES properly, identifying the causative agent and removing offending factors is important. Robust data regarding the relationship between PRES and immunotherapy are lacking in the literature. Further investigations are needed to provide more information about immunotherapy and its association with PRES.

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Conflicts of interest

There are no conflicts of interest.

References

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, *et al*. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494-500.
2. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: Clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol 2015;14:914-25.
3. Kabre RS, Kamble KM. Gemcitabine and Cisplatin induced posterior reversible encephalopathy syndrome: A case report with review of literature. J Res Pharm Pract 2016;5:297-300.
4. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: Fundamental imaging and clinical features. AJNR Am J Neuroradiol 2008;29:1036-42.
5. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med 2018;378:158-68.
6. Blackmon JT, Viator TM, Conry RM. Central nervous system toxicities of anti-cancer immune checkpoint blockade. J Neurol Neuromed 2016;1:39-45.
7. Wang M, Ma X, Guo L, Xia F. Safety and efficacy profile of pembrolizumab in solid cancer: Pooled reanalysis based on randomized controlled trials. Drug Des Devel Ther 2017;11:2851-60.
8. Feng S, Coward J, McCaffrey E, Coucher J, Kalokerinos P, O'Byrne K. Pembrolizumab-Induced Encephalopathy: A Review of Neurological Toxicities with Immune Checkpoint Inhibitors. J Thorac Oncol 2017;12:1626-35.
9. LaPorte J, Solh M, Ouanounou S. Posterior reversible encephalopathy syndrome following pembrolizumab therapy for relapsed Hodgkin's lymphoma. J Oncol Pharm Pract 2017;23:71-4.
10. Ishihara M, Matsutani N, Ota S, Seki N. A Case of Posterior Reversible Encephalopathy Syndrome Induced by Cisplatin/Pemetrexed Chemotherapy for Lung Cancer. Case Rep Oncol 2017;10:235-8.
11. Perez JR, Hernández R, Lage Y, Rupérez AB, Ruiz E, Hernández T. Posterior reversible encephalopathy syndrome (PRES) in a patient treated with a novel combination treatment with anti-PDL1 antibody (Durvalumab) and VEGFR2 antibody (Ramucirumab). Arch Clin Med Case Rep 2020;4:008-14.
12. Hussein HM, Dornfeld B, Schneider DJ. Nivolumab-induced posterior reversible encephalopathy syndrome. Neurol Clin Pract 2017;7:455-6.
13. Kim D. Posterior reversible encephalopathy syndrome induced by nivolumab immunotherapy for non-small-cell lung cancer. Clin Case Rep 2019;7:935-8.