Case Report of Delayed Encephalopathy From Pembrolizumab

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Introduction: Pembrolizumab is an immune checkpoint inhibitor (ICI) used to treat many types of advanced cancer. ICIs can cause encephalopathy, a severe immune-related adverse event, which is a diagnosis of exclusion. Pembrolizumab immune-related adverse events typically develop early (within a few months) in treatment; presentation after a year is extremely rare.

Case Presentation: A 70-year-old White female with metastatic endometrial cancer treated with pembrolizumab for 19 months presented with generalized weakness that rapidly progressed to confusion, delusions, and hallucinations.

Discussion: After ruling out other causes of encephalopathy via broad-based testing of blood and cerebrospinal fluid and imaging, her neurologic status improved after treatment with high-dose glucocorticoids and intravenous immunoglobulin.

Conclusions: Pembrolizumab is an ICI that can cause encephalopathy, which is challenging to diagnose. While immune-related adverse events typically emerge soon after starting treatment, pembrolizumab-induced encephalopathy can be delayed significantly.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have been used to treat advanced malignancies since 2011.[1] ICIs target cell-surface molecules that enable cancer cells to avoid immune cell-mediated destruction.[2] Pembrolizumab, an ICI that binds programmed cell death-1 (PD-1), improves survival of patients with metastatic endometrial cancer.[3] ICIs carry the risk of side effects known as immune-related adverse events (irAEs) that can affect essentially any organ.[4] Severe, grade 3 or 4, irAEs affect less than 1% of patients.[5] Neurological irAEs account for about 1% to 3% of all irAEs while being treated with ICI monotherapy.[5] Anti PD-1 therapies, specifically, have been implicated in severe neurotoxic irAEs, such as encephalitis, noninfective meningitis, peripheral neuropathy, myasthenia gravis, vague neurological weakness syndrome, and other types of neurologic deterioration.[6,7] Pembrolizumab-induced encephalopathy previously has been shown to occur weeks or months after treatment,[5,8-11] but cases of this severe irAE presenting after more than a year of treatment have not been reported previously.

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CASE PRESENTATION

A 70-year-old White female with stage IV endometrial cancer and a past medical history of hypertension, chronic kidney disease stage III, hypothyroidism, unprovoked deep venous thrombosis, and pulmonary embolism on chronic anticoagulation was brought to the emergency department (ED) by her husband for acute sharp pain in her right fifth toe and confusion. She also had had 2 weeks of worsening generalized weakness. Her metastatic disease was stable (ie, not progressive) since starting pembrolizumab and lenvatinib 17 months earlier; her last pembrolizumab monthly infusion was 2 weeks prior. At that oncology clinic visit, her lenvatinib was stopped due to concerns it was causing excessive uterine bleeding and worsening anemia; her hemoglobin had dropped from 10.2 to 7.7 g/dL over 2 weeks. Her ED evaluation revealed hemoglobin 7.4 g/dL, normal urinalysis, computed tomography (CT) abdomen/pelvis with intravenous (IV) contrast showing a stable uterine mass and widespread lymph node enlargement, a CT chest angiogram without pulmonary embolism, and strong pulses from her fourth and fifth right toes by doppler. Cultures from her portacath were obtained and she was transfused 1 unit of packed red blood cells (pRBCs), which significantly improved her weakness. She and her husband felt comfortable discharging home; however, she returned the following day after her portacath cultures returned positive for *Streptococcus salivarius* after 14 hours. Other than improved anemia (hemoglobin 9.3 g/dL), her testing

was unremarkable. She was admitted for IV antibiotics (ceftriaxone) for bacteremia and anemia.

Shortly into her hospital stay, she became more confused and agitated with clear signs of pain and discomfort, which were treated with oxycodone and acetaminophen; her husband was activated as her designated power of attorney. Her portacath was removed to control the source of the infection; however, antibiotics were stopped on day 5 because none of her blood cultures ever showed bacterial growth. A head CT and brain magnetic resonance imaging (MRI) found no cause for her encephalopathy. An electroencephalogram (EEG) revealed a nonspecific, moderate global disturbance in cerebral function. Her neurologic condition continued to decline while waiting 3 days after stopping her anticoagulation—apixaban—to perform a lumbar puncture. Her cerebrospinal fluid (CSF) showed 9 total nucleated cells per microliter (reference range: 0-5 cells/microliter), 13% neutrophils (reference range: 2% +/- 4%), 73% lymphocytes (reference range: 60% +/- 20%), and 14% monocytes (reference range: 30% +/- 15%). Protein in the lumbar puncture was elevated at 114 mg/dL (reference range: 15-45mg/dL). CSF gram and fungal stains were negative. CSF glucose was 48 mg/dL compared to serum glucose of 87 mg/dL.

While waiting for additional CSF studies to return (eg, a wide range of autoantibodies, herpes simplex virus polymerase chain reaction [PCR], varicella zoster virus PCR, bacterial and fungal cultures, Lyme PCR), the patient was maintained on empiric acyclovir and started on methylprednisolone 1 g IV daily for 5 days due to concern for autoimmune encephalopathy secondary to pembrolizumab treatment. On the second day of methylprednisolone treatment, her mentation improved, though not completely. Acyclovir was stopped after herpes simplex virus and varicella-zoster virus studies returned negative.

Unfortunately, 2 days after completing the 5-day methylprednisolone regimen, the patient's mentation declined again; this time, she began to experience delusions and hallucinations. A repeat brain MRI at this point was nonrevelatory. She was initiated on nightly olanzapine and a prednisone taper starting at 60 mg per day, but this was not effective. She was then restarted on IV methylprednisolone 125 mg daily, which helped minimally, so the dose was increased to 1 g daily and 1 g/kg/day intravenous immunoglobulin (IVIG) was added to her immunosuppressive regimen. She experienced brief periods of lucidity with the high-dose methylprednisolone and IVIG but mostly remained significantly encephalopathic. Eventually, she was transitioned back to IV methylprednisolone 125 mg daily and concomitantly began a regimen that involved weekly IVIG 0.5 g/kg alternating with weekly IV methylprednisolone 1000 mg. After about 2 weeks of this regimen, she became significantly more mentally alert and had more linear thoughts without significant hallucinations or delusions.

The patient's hospitalization was further complicated by acute on chronic blood loss anemia requiring transfusion of a total of 11 units of pRBCs (administered 1-2 units at a time), right fifth toe and foot pain requiring opioid analgesics, and a nosocomial, Enterobacter cloacae complex urinary tract infection treated with cefepime. CT angiography of the abdomen and pelvis showed no bleeding source; furthermore, upper and lower endoscopy found no gastrointestinal source of bleeding. Her persistently worsening anemia eventually was determined to be of uterine origin due to her known malignancy. She received palliative external beam radiation therapy in an attempt to stymy the bleeding, which was not successful. Radiologic imaging of her right foot and rheumatological workup were unremarkable. An ankle-brachial index (ABI) prompted CT angiography of the patient's lower extremities that revealed multiple tandem stenoses of the right femoral artery greater than 70%. She was subsequently started on a high-intensity heparin drip, and a repeat ABI of her right and left legs were 0.54 and 1.05, respectively. Ultrasound showed occlusion of the right proximal superficial femoral artery. She underwent a right superficial femoral artery thrombectomy and stent placement for treatment of blue toe syndrome, which significantly improved her pain. For this active issue, rivaroxaban and clopidogrel were recommended but held due to her anemia requiring many transfusions.

Ultimately, after treating her blue toe syndrome, urinary tract infection, and encephalopathy with high-dose methylprednisolone and IVIG, the patient's neurologic function improved significantly; however, her mental status never fully recovered and would fluctuate significantly throughout the day. She and her husband eventually chose to transition to comfort care. She returned home with hospice support and passed peacefully.

DISCUSSION

Pembrolizumab-induced encephalopathy usually develops early in treatment but can have a delayed onset. Accurate and timely diagnosis is difficult because it is a diagnosis of exclusion; patients with severe sepsis, bacterial meningitis, aseptic meningitis, viral encephalitis, autoimmunity, and thrombotic thrombocytopenic purpura can present similarly.[5] Our patient's persistent anemia, intense pain from blue toe syndrome, and urinary tract infection complicated her clinical picture since all can contribute to delirium; however, even after addressing these conditions, her neurologic function remained significantly impaired.

There are similarities and important differences among our case and others reported in the literature. Most reported cases of pembrolizumab-induced encephalitis have been associated with leptomeningeal enhancements or hyperintensities of periventricular white matter; however, these were absent in our case.[5,10,12] In a case presented by Basnet et al, a 55-year-old-man on 9 months of pembrolizumab treatment for metastatic renal cell carcinoma became encephalopathic and also was found to have a CT and MRI of the brain that did not show any acute abnormalities, negative CSF meningitis/encephalitis and autoantibody panel

results, and EEG monitoring with no evidence of seizure.[8] Usually, immune-mediated encephalitis is associated with a pleocytosis and an elevated protein level in the CSF,[5,8,11] as was found in our case.

The pathophysiology behind irAEs is considered to be primarily due to T-cell and IgG-dependent mediated hypersensitivity reactions from cross-reactivity between tumor cell and non-tumor cell antigens.[8,9,13] Another proposed mechanism is that ICIs bind to non-tumor cell antigens and give rise to an antibody or complement-mediated response.[8,9] By definition, irAEs are caused by off-target immunologic activity and treatment is centered on immunosuppression via glucocorticoids and IVIG, although no standard has been established at this time.[14] It is also essential to discontinue the offending ICI.

Neurological irAEs are categorized into 4 levels of severity, with grades 3 and 4 best describing our patient: a limited ability to care for self and progressively worsening.[14] The 2021 American Society of Clinical Oncology guideline suggests starting patients on empiric IV acyclovir until CSF PCR results are available and starting methylprednisolone 1 g IV daily for 3 to 5 days plus IVIG 0.4 g/kg/day over 5 days or plasmapheresis followed by a steroid taper.[14] A case reported by Gao et al describes a 55-year-old man with metastatic small cell carcinoma treated with 4 rounds of pembrolizumab over 4 months and developing a GAD65-antibody-associated autoimmune encephalitis.[15] He received IVIG at 0.4 g/kg/day for 5 days but without glucocorticoids due to concern that this would contribute to tumor recurrence;[15] nevertheless, his neurologic function recovered.[15] Another case of pembrolizumab-induced encephalopathy was treated successfully with IVIG 10 g/100 mL infusion 36 g daily for 4 days with 40 mg IV methylprednisolone every 8 hours for 1 day, which was then increased to 250 mg every 6 hours the following day for 5 subsequent days, then followed by 40 mg every 8 hours again for 4 days.[10] Another case reported effective treatment with 1 g IV methylprednisolone for 3 days.[9]

CONCLUSIONS

This case is unique due to the delayed neurological irAE, which developed after our patient had been treated with pembrolizumab for 19 months. This should prompt hospitalists and oncologists to consider this diagnosis of exclusion outside of its typical pattern of emerging early in ICI treatment. This case also highlights the challenges and importance of identifying and treating other potential causes of encephalopathy and delirium in patients receiving ICI therapy.

The optimal choice and dosing of immunosuppressive medications for treatment of pembrolizumab-induced encephalopathy remains unclear since they carry a risk of worsening tumor recurrence and progression. In the case of a severe neurological irAE, as we saw, the benefits of immunosuppression far outweigh the risks. Given the inherently poor prognosis of advanced malignancy, it is especially important to regularly reassess these patients' neurologic function, capacity, and goals of care throughout their hospital stay. We hope that this case study will help future patients and their care teams obtain an accurate diagnosis and initiate treatment as early as possible.

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