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CASE REPORT

A Rare Case of Pembrolizumab Associated Encephalopathy

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Abstract

We present a unique case of a 55-year-old man with confusion thought to be due to pembrolizumab which he was receiving for renal cell carcinoma. His workup for other possible etiologies for encephalopathy was negative. He was treated with high dose intravenous methylprednisolone followed by prednisone taper and intravenous immunoglobulin with gradual improvement in his mentation.

Keywords: Pembrolizumab, Encephalopathy, Immune checkpoint inhibitors, Immune-related adverse events

1. Introduction

Immune checkpoint inhibitors (ICIs), including pembrolizumab, have been shown to improve survival and are becoming the mainstay of treatment for patients with various malignancies including renal cell carcinoma.[1–3] Despite their benefits, they have been frequently associated with immune-related adverse events (irAEs) which mostly include gastrointestinal, skin, and endocrine adverse events.[1] Neurological irAEs have been reported in less than 3% of cases[1,4] and are mostly seen with combination ICIs.[4] We present an unusual case of encephalopathy in a patient on pembrolizumab for metastatic renal cell carcinoma that improved with steroid and immunoglobulin use.

2. Case description

Our patient is a 55-year-old man who presented to the emergency department with orthostatic dizziness leading to a fall. The patient was not eating or drinking adequately for the past 3 days. He also had chronic diarrhea which was attributed to chemotherapy. The patient stated that his last drink was several weeks ago. His past medical history was significant for renal cell carcinoma with pulmonary metastases, hypertension, asthma, chronic kidney disease stage 3, and alcohol use. He was on pembrolizumab 200 mg every 3 weeks for 9 months with the last dose 2 weeks before presentation. His home medications included albuterol inhaler, amlodipine, apixaban, bisoprolol, diphenoxylate-atropine, fenofibrate, lisinopril, montelukast, ondansetron, pantoprazole, prochlorperazine, and budesonide/formoterol. His temperature was 36.3 °C, his heart rate was 113 beats per minute, his blood pressure was 111/62 mmHg while lying, and he was maintaining saturation on room air. The examination was otherwise unremarkable. Patient presented with a creatinine of 4.64 mg/dL (reference range: 0.60–1.30 mg/dL) and his baseline creatinine around 1.3 mg/dL. His creatinine on subsequent days with hydration was 2.47 mg/dL and 1.71 mg/dL. His serum calcium was 12.4 mg/dL (reference range: 8.6–10.3 mg/dL) on admission, which resolved with intravenous (IV) fluid resuscitation. Computed tomography (CT) head/C-spine without contrast negative for any acute abnormalities. CT chest/abdomen/pelvis without contrast was negative for any acute abnormalities. A

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urine drug screen was negative. Blood cultures were negative for growth.

The next day, the patient was noted to be lethargic. His rectal temperature was 102.4 °F. Given his history of alcohol withdrawal complicated by delirium tremens, and withdrawal seizures, he was placed on a Clinical Institute Withdrawal Assessment for Alcohol (CIWA) protocol to receive lorazepam. He was transferred to the intensive care unit for tremulousness, worsening oxygenation, increased oral secretions, failure to protect his airway, and septic shock. He was thought to be in delirium tremens, and septic shock made worse with his immunocompromised status. The patient was intubated for airway support. He was placed on a lorazepam drip, norepinephrine drip, and placed on empiric intravenous (IV) vancomycin and piperacillin-tazobactam. A repeat chest x-ray showed developing small bilateral pleural effusions and lower lobe alveolar opacities which may reflect aspiration pneumonia and small parapneumonic effusions. His sputum culture was growing methicillin-sensitive *Staphylococcus aureus* (MSSA). He was placed on IV piperacillin-tazobactam to complete a 7-day course. A CT head was again negative for any acute abnormalities. He was off vasopressors and was successfully extubated 10 days later. He remained confused.

It was unclear why the patient was still encephalopathic. He looked ill and appeared toxic. The patient again decompensated and had to be intubated and was placed back on norepinephrine. A diagnostic bronchoscopy was performed, and the patient was noted to have right lower lobe pneumonia with tan-colored secretions which were suctioned. The patient remained persistently febrile with a maximum temperature of 103.5 °F requiring a cooling blanket. The patient was put on empiric antibiotics (ampicillin, vancomycin, cefepime, and acyclovir) for meningitis which were later discontinued. A lumbar puncture was performed. The opening pressure was 17 mm Hg. 12 mL of spinal fluid was collected. Lumbar tap was clear, and CSF showed 22 cmm WBCs (reference range: 0–5 cmm) with 83% lymphocytes (reference range: 0–50%), 90 mg/dL protein (reference range: 15–45 mg/dL), and glucose 40 mg/dL (reference range: 40–70 mg/dL). Cerebrospinal fluid (CSF) cultures showed no growth and gram stain did not show any organisms. His Gram stain was negative. Meningitis/encephalitis panel (PCR testing for *Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis* (encapsulated), *Streptococcus agalactiae, Streptococcus pneumoniae*, *Cytomegalovirus*, *Enterovirus*, Herpes Simplex virus 1 and 2, Human Herpesvirus 6, Human Parecho virus, Varicella zoster virus, *Cryptococcus neoformans/gattii*) was negative. CSF paraneoplastic antibody panels (Amphiphysin Antibody, AGNA-1, ANNA-1, ANNA-2, ANNA-3, CRMP-5 Antibody IgG, PCA-Tr, PCA-1, and PCA-2) were also negative. CSF cytology showed rare, atypical cellular clusters which may reflect reactive inflammatory cells or reactive ependymal elements. Magnetic resonance imaging (MRI) of the brain was negative for any acute intracranial abnormalities. Electroencephalography (EEG) monitoring showed severe generalized slowing, but no epileptiform abnormalities or seizures were ident ified. With the possibility of pembrolizumab-induced encephalopathy, he was placed on a trial of immune globulin (human) (GAMUNEX-C) 10 g/100 mL (10%) infusion 36 g daily for 4 days and was started on IV methylprednisolone 40 mg every 8 h which was increased to 250 mg Q6H the next day for 5 days and was tapered to 40 mg every 8 h for 4 days. The patient was noted to have a gradual improvement in his mental status. He was able to open his eyes to stimulation and when his name was called before initiation of steroids. After 3–4 days of initiation, he was awake and alert and followed simple commands. He was alert and oriented to person, place, and time (year only) but had word-finding difficulty and a delayed response to questioning after a week. He was switched to prednisone 60 mg daily after 10 days of IV methylprednisolone with plans to taper by 10 mg every week. Wernicke encephalopathy and delirium tremens were initially considered given the patient's history of alcohol use. However, the patient did not have oculomotor dysfunction or gait ataxia. His MRI did not show diencephalic or periventricular lesions, hemorrhages, or mamillary body atrophy. He did not improve with thiamine. Delirium tremens was also considered as the patient was agitated and had a history of alcohol use. However, he did not improve even after 2 weeks' stay in the hospital. He improved only after he was started on high-dose steroids and immunoglobulin.

3. Discussion

irAEs are thought to be Type II (T-cell dependent) and type II (IgG-dependent) hypersensitivity reactions.[1] Cross-reactivity between the tumor cell and normal tissue antigens is the most likely mechanism for the development of irAEs with ICIs.[1,5] This contrasts with chemotherapy which affects systems with rapidly dividing cells.[6] ICIs may directly attach to normal tissue antigens and induce antibody or complement-mediated reaction.[1] Neurological irAEs most commonly affect the peripheral nervous system (peripheral neuropathy, myopathy, and myasthenia gravis) (Psimaras) and

less likely the central nervous system (CNS) (aseptic meningitis, encephalopathy/encephalitis, Guillain-Barre like syndrome, multiple sclerosis exacerbation, seizures, neurosarcoidosis, posterior reversible encephalopathy syndrome, cerebellar syndrome with ataxia, headache, transverse myelitis, leptomeningeal disease, and meningoradiculitis).[4,6] A thorough workup to rule out other potential infectious, metabolic abnormalities, progression of malignancies, paraneoplastic syndrome, etc. should be done before establishing a diagnosis of irAEs. Workup should include an MRI brain/spine with/without contrast and lumbar puncture with infectious, serologic, and paraneoplastic workup.[4]

Treatment should be started early if suspected cases.[2] High-dose steroids with oral prednisolone (1 mg/kg) or intravenous (IV) methylprednisolone (1–2 mg/kg) and discontinuation of ICIs are the mainstay of treatment for irAEs.[1,2,4] Higher doses of IV methylprednisolone are required for it to reach a therapeutic concentration inside the CNS.[5] If the patient is worsening, IV methylprednisolone 1 g daily for 3–5 days along with intravenous immunoglobulin 2 g/kg for 5 days may be tried.[4] Plasmapheresis and rituximab have been used in patients that do not improve with steroids.[1,2,7] The optimal treatment for immune-mediated neurological reactions has yet to be determined.[7] Reynolds et al. reported using high-dose steroids for 2 weeks with a gradual taper over 4 weeks.[4] Rechallenge may be considered in patients with mild irAEs.[1] Most patients (73%) show partial to complete recovery on discontinuation of ICIs[6] with a median time to the improvement of 4 weeks.[4]

4. Conclusion

Neurologic irAEs will become more common with the widespread use of ICIs[4] for different solid and hematologic malignancies.[8] Most of the irAEs are usually reversible with discontinuation of ICIs and institution of treatment.[2] Clinicians should be aware of the potential neurologic complications of pembrolizumab and other ICIs for early diagnosis and institution of immunosuppressive therapy.

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Conflict of Interest

None.

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