

CASE REPORT

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Immunotherapy-mediated encephalitis in an oncological patient

Dinesh Keerty, Marlene Grenier, Edwin Peguero, Bjorn Holmstrom

ABSTRACT

Introduction: Autoimmune encephalitis causes subacute deficits of memory and cognition, often followed by suppressed level of consciousness or coma. Checkpoint inhibition is the mainstay of treatment in metastatic melanoma. More recently combination of cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed-death-1 (PD-1) blockade has resulted in improved response rates and overall survival in treatment naïve patients. Neurological toxicities are an emerging consequence of the use of checkpoint inhibitors. We are here to present a case of neurotoxicity from the use of immunotherapy.

Case Report: A 63-year-old female with metastatic melanoma to brain and breast presented to the emergency department with altered mental status. She was disoriented to time and place and unable to follow commands. She had received two doses of immunotherapy with ipilimumab and nivolumab. Her last dose was administered two weeks prior. She developed low grade fever and fatigue over the past week prompting evaluation by her local oncologist who prescribed her sulfamethoxazole-trimethoprim for possible urinary tract infection. She never picked up the prescription and two days later she went to an urgent care for worsening lethargy and fever. An infectious

workup was negative. She presented to our emergency department with incoherent speech and inability to comprehend. Infectious workup was again negative. Her labs were unremarkable except for hyponatremia with sodium of 123 mmol/L. A computed tomography (CT) scan of the head was negative. Magnetic resonance imaging (MRI) of the brain was done and the report did not show the previously noted brain lesions. Neurology was consulted and an electroencephalography (EEG) was done showing frequent temporal intermittent rhythmic activity (TIRDA) in the right hemisphere consistent with a tendency for seizures. There were no ictal discharges but EEG did show moderate diffuse nonspecific encephalopathy. Lumbar puncture was negative for any viral etiologies such as herpes simplex along with cell counts that were in normal range. She was started on levetiracetam and methylprednisolone 2 mg/kg daily. Within 24 hours of initiating steroids and prior to her sodium correcting, she became alert and oriented with improved ability to follow commands. After 48 hours of steroids and antiepileptic treatment, a repeat EEG was done which showed no abnormal activity. She was monitored for four more days in hospital with eventual return to her baseline. **Conclusion:** Counseling patients receiving immunotherapy to report any new symptoms promptly is imperative as early identification of immune-mediated adverse events leads to better outcomes. Providers should have a high index of suspicion for immune-mediated adverse events in all patients on immunotherapy presenting with new symptoms. Early identification of an immune-mediated adverse event is crucial for better patient outcomes.

Keywords: Adverse events, Encephalitis, Immunotherapy, Melanoma

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INTRODUCTION

Autoimmune encephalitis causes subacute deficits of memory and cognition, often followed by suppressed level of consciousness or coma. Checkpoint inhibition is the mainstay of treatment in metastatic melanoma. More recently combination of cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed-death-1 (PD-1) blockade has resulted in improved response rates and overall survival in treatment naïve patients [1]. Neurological toxicities are an emerging consequence of the use of checkpoint inhibitors. We are here to present a case of neurotoxicity from the use of immunotherapy.

CASE REPORT

A 63-year-old female with metastatic melanoma to brain and breast presented to the emergency department with altered mental status. She was disoriented to time and place and unable to follow commands. She had received two doses of immunotherapy with ipilimumab and nivolumab. Her last dose was administered two weeks prior. She developed low grade fever and fatigue over the past week prompting evaluation by her local oncologist who prescribed her sulfamethoxazole-trimethoprim for possible urinary tract infection. She never picked up the prescription and two days later she went to an urgent care for worsening lethargy and fever. An infectious workup was negative. She presented to our emergency department with incoherent speech and inability to comprehend. Infectious workup was again negative. Her labs were unremarkable except for hyponatremia with sodium of 123 mmol/L. A CT scan of the head was negative. Magnetic resonance imaging of the brain was done and the report did not show the previously noted brain lesions. Neurology was consulted and an EEG was done showing frequent TIRDA in the right hemisphere consistent with a tendency for seizures (Figure 1). There were no ictal discharges but EEG did show moderate diffuse nonspecific encephalopathy. Lumbar puncture was negative for any viral etiologies, such as herpes simplex along with cell counts that were in normal range. She was started on levetiracetam and methylprednisolone 2 mg/kg daily. Within 24 hours of initiating steroids and prior to her sodium correcting, she became alert and oriented with improved ability to follow commands. After 48 hours of steroids and antiepileptic treatment, a repeat EEG was done and showed no abnormal activity. She was monitored for four more days in hospital with eventual return to her baseline.

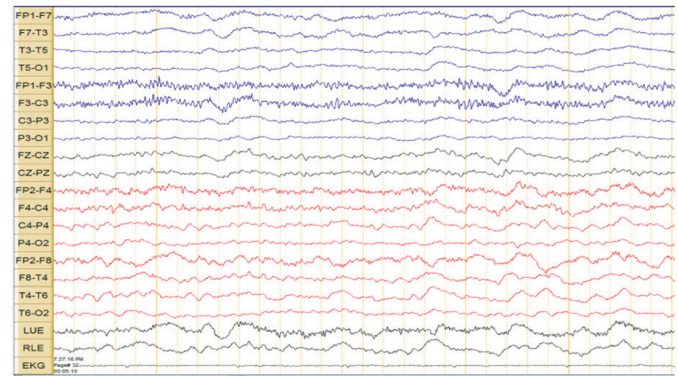


Figure 1: Patient electroencephalography depicting TIRDA. The above EEG depicts frequent temporal intermittent rhythmic delta activity (TIRDA) on the right hemisphere. It also shows bi-hemispheric slowing with higher voltage delta and less beta activity in the right hemisphere. The study is consistent for tendency for seizures with a possible localization in the right hemisphere. It is also consistent with moderate diffuse nonspecific encephalopathy.

DISCUSSION

Immunotherapy has emerged as a main treatment modality for metastatic melanoma. The combination of ipilimumab and nivolumab has shown increased efficacy and increased progression free survival. Nivolumab is an anti-PD-1 drug that promotes the tumor killing effects of T-cells, and ipilimumab, an anti CTLA-4 drug, promotes the growth of T-cells [2]. Stimulation of the immune system response can induce symptoms resembling autoimmune disorders [3]. Immune-related adverse events including encephalitis are on the rise with the increasing use of these checkpoint inhibitors to treat melanoma as well as various other cancers. Some authors have surmised that immune-mediated encephalitis induced by checkpoint inhibitors has typically occurred at the beginning of therapy rather than after multiple dose treatments [4, 5]. The treatment algorithm, as approved by the National Comprehensive Cancer Network, recommends immediate neurology consultation and an MRI of the brain with and without contrast. An EEG and lumbar puncture with cerebrospinal fluid studies should be performed prior to the initiation of systemic steroids. If there is no response to systemic steroids within 24 hours of initiation, intravenous immunoglobulin (IVIG) has been recommended [6]. The exact cause of encephalitis is unknown but many have surmised that it may be due to *N*-methyl-D-aspartate (NMDA) receptors. *N*-methyl-D-aspartate receptors are present on the surface of melanocytes, highly mutated in patients with melanoma [7]. Antibodies against abnormal NMDA receptors in melanoma have been hypothesized to induce encephalitis, as these cross-react with NMDA receptors in the brain [5]. Cerebrospinal fluid examination for paraneoplastic antibodies such as anti-NMDA receptor is recommended to distinguish the etiology [3].

CONCLUSION

Counseling patients receiving immunotherapy to report any new symptoms promptly is imperative as early identification of immune-mediated adverse events leads to better outcomes. Providers should have a high index of suspicion for immune-mediated adverse events in all patients on immunotherapy presenting with new symptoms. Early identification of an immune-mediated adverse event is crucial for better patient outcomes.

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Author Contributions

Dinesh Keerty – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Marlene Grenier – Design of the work, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Edwin Peguero – Design of the work, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Bjorn Holmstrom – Design of the work, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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