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Case report

A case of severe encephalitis while on PD-1 immunotherapy for recurrent clear cell ovarian cancer

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ABSTRACT

Recurrent clear cell ovarian carcinoma is a difficult to treat condition and early trial data has suggested a possible role for immune checkpoint inhibitors. Nivolumab is an anti-PD-1 immunotherapy that has been used in this setting. While immune related toxicity of these agents has been well described, the occurrence of immune specific neurotoxicity is thought to be rare. We present a case of severe encephalitis while on PD-1 immunotherapy for a recurrent ovarian clear cell cancer and we believe this to be the first such reported case associated with the use of PD-1 inhibitor monotherapy. In this case, a 64-year-old woman with persistent clear cell ovarian cancer on Nivolumab presented with a severe fever of unknown origin and delirium; initial imaging and diagnostic work-up suggested a neurological etiology, but with no clear source. We concluded that this was a severe case of immune related encephalitis, thought to be brought about by the anti-PD-1 immunotherapy which responded well to systemic corticosteroids and plasmapheresis and the patient able to make a full recovery. We present a summary of the case and its management as well as a review of the literature on the previously reported neurotoxicity's of PD-1 inhibitors.

1. Introduction

Ovarian cancer is frequently diagnosed in advanced stages and typically exhibits a recurrent disease course requiring multiple lines of chemotherapy (Hamanishi et al., 2015). Clear cell ovarian cancer is thought to be particularly insensitive to chemotherapy and when diagnosed at advanced stages is often refractory to current cytotoxic chemotherapy (Hamanishi et al., 2015).

Immunotherapy has recently been demonstrated to have an important role in the management of a number of recurrent malignancies (Hamanishi et al., 2015). Programmed cell death-1 (PD-1) inhibitors have been among the most prominent and clinically active agents in this class (Kazandjian et al., 2016). Nivolumab is PD1 inhibitor that is currently FDA approved for Lung cancer and Melanoma (Raedler, 2015). Nivolumab has been studied in platinum resistant ovarian cancer and found to have modest activity in this setting. Of the 15% of responders, there were two patients with a durable complete response, one of whom had a clear cell histology (Brahmer et al., 2012). For this reason, we treated a patient with recurrent clear cell ovarian cancer with Nivolumab; and we now report on a severe neurologic toxicity that was observed and we believe was related to her immunotherapy (Williams et al., 2016).

Toxicity of PD-1 inhibitors has been observed to be related to immune system activation. The most commonly observed toxicities are those related to thyroid function, colitis, diarrhea, endocrinopathy, hepatitis, pruritus, pneumonitis, and various rashes (Linardou and Gogas, 2016; Friedman et al., 2016). Neurologically toxic side effects of immune checkpoint inhibition are rare occurring in less than 5% of patients (Weber et al., 2012; Linardou and Gogas, 2016; Friedman et al., 2016). These effects often vary in severity from mild transient peripheral neuropathies that resolve spontaneously, to persistent conditions that require prolonged steroid treatment (Weber et al., 2012, 2016; Linardou and Gogas, 2016; Friedman et al., 2016). Neurologically related effects documented thus far include paresthesia, dysesthesia, aseptic meningitis, temporal arteritis, Guillain-Barre-like syndrome, myasthenia gravis-like syndrome as well as sensory and motor neuropathy (Friedman et al., 2016; Andrews and Holden, 2012; Wilgenhof and Neyns, 2011). Death has been reported in one patient whom presented a Guillain-Barre-like syndrome (Friedman et al., 2016; Wilgenhof and Neyns, 2011); while several cases of myasthenia gravis-like syndrome, which resulted ascending motor paralysis, were able to make a full recovery within four-to-six weeks of onset (Weber et al.,

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2012; Liao et al., 2014).

The presentation of immune checkpoint inhibitor neurotoxicity generally occurs within the first six weeks of treatment initiation (Liao et al., 2014). A useful indicator of an immune related etiology is a high white blood cell count during a lumbar puncture (Friedman et al., 2016; Liao et al., 2014). When concerns of sensory or motor neuropathy arise, further examination techniques such as electromyograms as well as nerve conduction studies should be performed to facilitate in the characterization of the specific pathology (Linardou and Gogas, 2016). The course of treatment recommended by the Food and Drug Administration includes the cessation of anti-PD-1 medication administration and the initiation of a high dose corticosteroids such as methylprednisolone, prednisone or dexamethasone (Weber et al., 2012; Friedman et al., 2016; Kazandjian et al., 2016). While this line of treatment has been shown effective in a majority of cases, some patients may require additional treatment such as intravenous immunoglobulins and or plasmapheresis (Linardou and Gogas, 2016; Friedman et al., 2016; Andrews and Holden, 2012).

2. Case report

Written consent was obtained by this patient for the write up and publication of this case. A 64-year-old woman with recurrent progressive clear cell ovarian cancer was brought to an outside emergency room with a fever of unknown origin and delirium. Ten days earlier, the patient had been complaining of upper respiratory infection and sinus symptoms and was treated with Augmentin. The patient was seen by her gynecologic oncologist six days later with no complaints and was given her eight dose of Nivolumab. She had had no signs of toxicity from Nivolumab prior to this presentation.

The patient was brought to the emergency room after being found alone, staring at the wall, not responding to commands, having a temperature of 104–105 °F and having soiled the bed. The patient was not experiencing any hallucinations. Emergency medical services started the patient on vancomycin, rocephin and decadron before arriving in the emergency room. In the ED she had a normal heart rate, responsive eye movement and reactive pupils, temperature ranging from 104 to 105 °F, stiff arms and legs, occasional spasms but otherwise obtunded consistent with hyperthermia. She was empirically given acyclovir, meropenem, and vacomycin in addition to standard cooling measures.

Magnetic resonance imaging of the brain, with and without contrast, did not reveal any obvious encephalitis or metastasis. A contrast chest CT scan did find atelectasis and small bilateral effusions, but with no clear source of infection. She did not have an EEG. The patient's white blood cell count, comprehensive metabolic panel, urine analysis and cerebral spinal fluid culture results were all within normal limits other than severe hypocalcemia. Home medications included 30 mg of paroxetine daily, a dose that would unlikely cause serotonin syndrome, and atorvastatin.

In the first 12 h after presentation she seemed to improve, with some recovery in her mental status, this quickly declined again, and recurrent refractory high fevers resumed. She was immediately transferred to a tertiary care hospital with a concern for immune mediated encephalitis related to PD-1 immunotherapy. Upon transfer she was treated with a high dose of steroids (3 g of methylprednisolone four times daily) and plasmapheresis as well as empiric meropenem and acyclovir.

Two days after admission, her neurological symptoms were markedly improved compared to admission. Antibiotics were stopped when all cultures were negative. She was noted to exhibit neurologic improvement after each session of plasmapheresis. Plasmapheresis was done to clear any possible residual drug, which is a IgG4 anti-PD1 monoclonal antibody, in the system. Given the severity of her presentation the most aggressive measures were initiated empirically. She was treated with a total of 10 sessions of plasmapheresis, daily × 3 days then every other day until she had completed 10. Over the next few weeks she had ongoing improvement and she was eventually discharged to a rehab facility. It took her several months of intensive rehab to return to baseline neurologic functioning.

Laboratory testing for autoimmune encephalopathy on the patient's serum alone identified one antibody, Glutamic Acid Decarboxylase 65 (GAD65), consistent with thyrogastric disorders including thyroiditis, pernicious anemia, and type one diabetes, but which has a low specificity for autoimmune encephalopathy. The GAD65 antibody level was 0.06 nm/l, while figures which hold predictive value for neurological autoimmunity are 20.0 nm/l or higher. No cerebrospinal fluid sent for autoimmune encephalopathy testing, but cultures were all negative for infectious etiologies. HSV PCR on the spinal fluid was also negative. She did not have a full panel for paraneoplastic syndrome.

3. Discussion

The neurotoxicity of Nivolumab and other PD-1 inhibitors is rare and is largely defined by isolated case reports. It has so far been observed that less than 5% of patients taking immune checkpoint inhibitors experience a neurologically toxic side effect of varying severity (Friedman et al., 2016). Some of the more common neurologically toxic effects include paresthesia, aseptic meningitis, temporal meningitis, a myasthenia gravis-like syndrome, and a Guillian-Barre syndrome (Friedman et al., 2016). These more typical neurological side effects are diagnosed using a high white blood cell count from a lumbar puncture (Friedman et al., 2016). There are two recently reported cases in the literature of suspected autoimmune encephalitis, however both of these patients had preceding brain metastasis and were treated with dual agent immune checkpoint inhibitors (Nivolumab and Ipilimumab) (Williams et al., 2016). Additionally, both of these cases occurred shortly after the first dose of therapy (Williams et al., 2016).

What makes this case different, is a low white blood cell count in the cerebral spinal fluid, a cerebral spinal fluid protein count of 50, lack of any detectable brain metastasis, and number of doses of Nivolumab received before any symptoms arose. Additionally, previous cases of autoimmune encephalitis have not shown any fever associated with the illness (Williams et al., 2016). While there have been previous reports of patients developing mild encephalopathy from an PD-1 inhibitor, our findings lead us to believe this to be the first case of severe autoimmune encephalitis related to PD1 inhibitor monotherapy (Weber et al., 2016). The diagnosis of encephalitis was made due to the behavioral and personality changes accompanied with the altered state of consciousness and general stiffness (Armangue et al., 2014). This patient is not believed to have had limbic encephalitis, the more common autoimmune encephalitis, due to the MRI of the brain not showing any abnormalities such as uni- or bilateral increase in T2/FLAIR signals in the medial temporal lobe (Armangue et al., 2014).

As the use of novel immunotherapy for the management of ovarian and other cancers increases, it is critical for providers to be aware of the unique toxicities associated with these agents. The prompt recognition and appropriate treatment of these toxicities is essential to minimizing long term side effects.

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