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Nivolumab Toxicity Meets Leptomeningeal Carcinomatosis: A Case Report

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Abstract

Nivolumab (Opdivo) is an immune checkpoint inhibitor used in the treatment of multiple cancers including gastric adenocarcinoma. The diagnosis of antineoplastic therapy toxicity, such as nivolumab toxicity, occurs commonly in those receiving treatment with symptoms ranging from a rash to potentially death, which is an uncommon side effect. Patients who have cancer can develop the diagnosis of leptomeningeal carcinomatosis (LMC), which is considered rare, occurring in 2-4% of all cancers. The initial presentation with primarily neurological symptoms can occur in both diseases, however the prognosis and treatment varies greatly. In this case report, we discuss a patient with metastatic gastric adenocarcinoma reportedly in remission, who was initially being treated as having nivolumab toxicity, however 72 hours later he was found to have leptomeningeal carcinomatosis.

Keywords: leptomeningeal carcinomatosis, nivolumab, case report

Introduction

Nivolumab toxicity commonly presents with gastrointestinal manifestations such as colitis, pancreatitis and/or endocrinopathies including hyper/hypothyroidism and adrenal insufficiencies. Less likely are symptoms of encephalitis including headaches, confusion, isolated neurologic deficits, and imbalance [1]. These immunotherapy agents can affect multiple organs in the body and the presence of mild adverse events related to their use does not usually result in termination of these medications. However, there should be prompt evaluation given the risk of substantial mortality. The symptoms of nivolumab toxicity which can be subtle or atypical can mimic those of other neuro-inflammatory conditions, including leptomeningeal carcinomatosis [1,2].

Leptomeningeal carcinomatosis is a condition caused by malignant cells infiltrating the meninges commonly occurring with disease spread from another primary tumor. This disease continues to be underdiagnosed despite increasing advances in diagnostic imaging likely due to low index of suspicion. The development of this condition from gastric cancer is reported to be roughly 0.16% and it is accompanied with a poor prognosis. One study showed that the use of gadolinium enhanced MRI to assess for leptomeningeal carcinomatosis resulted in 82% positive results. However, the attainment of a lumbar puncture and CSF analysis is crucial for confirming the diagnosis [3].

This case discusses a patient with remission of gastric adenocarcinoma presenting acutely with altered mentation who was initially treated as a presumed nivolumab toxicity when he initially demonstrated complete response to steroid treatment. On arrival, all imaging and infectious workup was unremarkable. Although the steroids initially seemed to address his agitation and confusion, 72 hours after admission he returned to the original presentation of encephalitis on arrival. Upon further investigation, cells suspicious for malignancy were found in his lumbar puncture, ultimately leading to a rapid deterioration in our patient.

Case Description

Patient Information and Presenting Symptoms: Our patient is a 71-year-old male with a past medical history of well controlled diabetes, hypertension, and stage 4 metastatic gastric cardia adenocarcinoma that was first found in August of 2022. He had undergone gastrectomy, FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel) for 6 cycles, FOLFORI (fluorouracil, leucovorin, and irinotecan), and was receiving maintenance nivolumab. Our patient reports a recent PET scan six weeks prior showing complete remission of disease. He was scheduled for a follow up PET scan at an outpatient center, however when he arrived at the center with altered mental status, he was instead rerouted to the emergency department (ED) by his oncologist and that was where he was first seen by our team.

Once seen at bedside, he had difficulty raising his arms, wobbly gait, slurred speech, and new onset dementia. In addition to that, he had been involved in two car accidents within the past two

weeks secondary to falling asleep while driving. He was also experiencing daily persistent headaches which was uncommon for him. Wife, at bedside with patient, notes that he has had trouble falling asleep, falls, decreased appetite, and myalgias for the past 3 weeks as well. She mentioned that he would try to speak, but words would not come out properly, or at all. Of note, he recently visited his oncologist and was diagnosed with immunotherapy (nivolumab) toxicity secondary to a similar presentation of altered mentation one week prior. At that hospitalization, he received 4 doses methylprednisolone 40 mg IV and had near complete resolution of his symptoms and was subsequently discharged without medications.

Diagnostic Assessment: On arrival, a CT brain, MRI brain, EEG, and all other infectious workup was unremarkable. The laboratory findings included: white blood cell count 6.76x109/L, platelets 121x109/L, Na 135 mmol/L, K 3.4 mmol/L, and ammonia 21µmol/L. At that time, we began the patient on methylprednisolone 40 mg BID with near complete resolution of symptoms within 24 hours.

However, three days after admission his altered mentation resurfaced with new onset agitation, despite continued steroid use. Laboratory values at the time were unremarkable: white blood cell count 6.96x109/L, platelets 138x109/L, Na 136 mmol/L, K 3.9 mmol/L. A repeat CT brain was unremarkable, so we decided to proceed with a lumbar puncture. Lumbar puncture showed elevated protein, low glucose, and abnormal cells suspicious for malignancy.

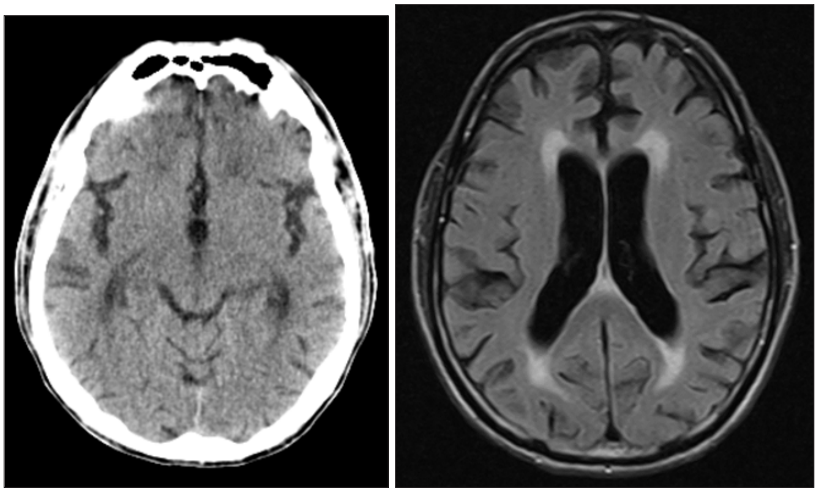

Figure 1: Computed tomography brain on arrival and magnetic resonance imaging brain with rebound altered mentation at 72 hours showing no acute process.

Therapeutic Intervention: Neurology was consulted and they diagnosed our patient with metabolic encephalopathy due to antineoplastic therapy. When they saw the patient, it was the first 24 hours after admission when he was back to his baseline and neurology signed off from the case. Hematology-Oncology was consulted and they recommended continuation of steroid treatment as he was showing marked improvement and he did not meet criteria for inpatient chemotherapy treatment. The treatment of leptomeningeal carcinomatosis usually consists of intrathecal injections of chemotherapy, methotrexate being the most used. This method of chemotherapy can directly target the CSF without crossing the blood-brain barrier. The years leading to his arrival in our ED, he had undergone gastrectomy and an extensive chemotherapy regimen. Since his clinical status deteriorated rapidly within days, his family ultimately decided to transition to comfort care only. Shortly after, he was sent home with hospice care and he passed away within one week. After the patient was discharged, we received the cytology from the CSF, results were positive for pancytokeratin, CK7, low molecular weight cytokeratin, and EMA; they were negative for CD163. These results are consistent with metastatic adenocarcinoma.

Discussion

In this paper, we describe our patient who was initially found to have gastric adenocarcinoma incidentally after a work related fall. Despite receiving chemotherapy with FLOT without resolution of symptoms, he underwent a gastrectomy and FOLFORI treatment with remission in metastatic gastric adenocarcinoma. When admitted to our hospital, he had discontinued nivolumab one week prior, which he was taking as maintenance treatment. Upon presentation, he was initially being managed as having a nivolumab toxicity.

Immune checkpoint inhibitors function by blocking pathways called checkpoints, thereby allowing the human immune system to control the immune response. The PD-1 receptor is expressed on the surface of the cytotoxic T cells that interact with their ligands; in the case of PD-1 it is the programmed death-ligand 1 (PD-L1). In cancer, these pathways are “hijacked” to allow evasion of cytotoxic T-cell mediated cell-death. Nivolumab works by preventing the receptor (PD-1) from binding to ligand (PD-L1), thus creating disrupted signaling and cell death. These agents can have many adverse effects and when considered moderate to severe they can lead to death. Hence, it is of utmost importance to detect serious adverse events and

terminate these agents. The toxicities are divided into four grades [1-4] and the general recommendations are irrespective of organ system. Grade 1 toxicities are mild, and the checkpoint inhibitors are usually continued. For grade 2 and grade 3 toxicities, it is recommended to hold the medication and begin corticosteroids 0.5 -1 mg/kg/d of prednisone or equivalent for 4 weeks, up to 6 weeks. Current recommendations state that grade 4 toxicities warrant permanent discontinuation of the medication [2].

Many novel therapies for treatment resistant cancer include monoclonal antibodies; however, since the diagnosis of serious and fatal toxicity is rare, the manifestations of toxicity are overlooked [4]. In recent studies, nivolumab toxicity has many adverse effects. Some of the most common ones have been the following: 25% of patients have experienced fatigue, 17% have experienced pruritus and 13% of patients have experienced diarrhea. Beyond that, less than 1% of patients have experienced neurologic symptoms such as headaches, encephalitis, and cranial nerve palsies [5]. The most important thing, however, is that most of the symptoms resolve upon stopping the medication and starting treatment with steroids, as our patient initially did.

It should be noted that this presentation may be similar to leptomeningeal carcinomatosis. The most common presenting symptoms for which are headache, neuropathy, numbness, tingling, and difficulty with coordination [6]. This was not suspected initially, seeing that only 5% of cancer patients end up developing leptomeningeal carcinomatosis and there are only 110,000 patients diagnosed in the U.S. annually [7]. About 20% of patients on nivolumab have toxicity symptoms [8]. Thus, as a result, initially the prognosis of our patient, who we diagnosed with mild to moderate immunotherapy toxicity, was generally favorable. The treatment for patients with LMC is usually palliative with either intrathecal chemotherapy, whole brain radiotherapy, or both [9]. However, the median survival of those diagnosed with gastric leptomeningeal carcinomatosis is two to four months with therapy and at most six weeks if left untreated [10]. Our patient passed away three weeks after first presenting neurological symptoms.

Conclusion

This case highlights the importance of careful triage and evaluation of new-onset neurological symptoms in a patient with a history of gastric adenocarcinoma reportedly in remission prior to arrival. The presentation of a patient with new-onset headaches, confusion, and gait disturbances can be a manifestation of a recurrence of cancer presenting as leptomeningeal carcinomatosis and/or nivolumab or other immunotherapy toxicity. Both diagnoses can present identically and a high index of clinical suspicion is required to promptly differentiate them as treatment and prognosis vary significantly.

Consent

The corresponding authors attest that the subject of this case report is deceased, and verbal consent was obtained at the time of his hospitalization.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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