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A Case Report of Steroid Responsive Nivolumab-Induced Encephalitis

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Abstract

Nivolumab (Opdivo) approval for the treatment of non-small cell lung cancer (NSCLC) prompts recognition of its future use in various cancers. Although rare, occurring in 1% to 3% of treated cases, nivolumab along with other immune checkpoint inhibitors are associated with immune-related encephalitis. With its prospective use, nivolumab-induced encephalitis illustrates the necessity of early recognition and successful management to decrease morbidity and mortality. We describe a treated case of nivolumab-induced encephalitis. A 74-year-old male with a history of stage 4 squamous NSCLC presenting with insidious altered mental status following his first dose of nivolumab. After an extensive workup that proved negative, the patient received intravenous steroids with gradual improvement of mental status. Patient subsequently returned to baseline and was discharged with oral steroid taper. Nivolumab-induced encephalitis is a diagnosis of exclusion with nonspecific signs and symptoms. Immediate recognition of patients prescribed nivolumab chemotherapy could potentially prevent fatal complications of neurotoxicity.

Keywords

nivolumab, encephalitis, non-small cell lung cancer, immune-related Adverse events, neurotoxicity

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Background

Nivolumab is a fully immunoglobulin G (IgG4) monoclonal antibody US Food and Drug Administration (FDA)-approved immune checkpoint inhibitors (ICPIs) therapy to treat advanced melanoma, squamous NSCLC, and renal cell carcinoma. With low immunogenic potential, high affinity and specificity for blocking the programmed cell death-1 (PD-1), nivolumab aids T cells to recognize and destroy tumor cells.[1-4] Nivolumab has replaced docetaxel in the treatment of advanced, squamous NSCLC during or after platinum chemotherapy as a second-line therapy due to decreased mortality, increased overall survival, and better tolerability.[1-5] Although rare, nivolumab can cause immune-related adverse events (irAE) that include but not limited to colitis, hepatitis, nephritis, pneumonitis, pancreatitis, renal dysfunction, hypothyroidism, and hyperthyroidism with the upregulation of T-cell activation. Immune checkpoint inhibitor-induced encephalitis occurs in 1% to 3% of treated cases and present with nonspecific signs of confusion, autonomic instability, waxing, and waning mental and a negative workup.[5] Nivolumab may likely be approved to treat other cancer entities, hence the importance of potential side effect recognition. With its prospective use, nivolumab-induced encephalitis illustrates the necessity of early recognition and successful management to decrease morbidity and mortality. This case describes a gradual response to steroidal therapy of a patient who developed nivolumab-induced encephalitis.

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Case Presentation

A 74-year-old male with a history of stage 4 squamous NSCLC with metastasis to the liver and brain after 4 cycles of paclitaxel and carboplatin (MYSTIC trial), stereotactic radiosurgery, and salvage nivolumab chemotherapy presented to an outside hospital (OSH) with progressive altered mental status. Within 1 week of nivolumab treatment, patient was reported to have gradual decrease in mental status. Prior to admission, the patient sustained a ground level fall 3 feet away from his bed in his bedroom. He was mumbling words, unable to follow commands, and inability to stand on his own intuition. Per witness, no seizure activity, loss of bowel or bladder control, or tongue biting was noted. Of note, patient had a fall 3 days prior to admission and sustained ecchymoses of left eye and left orbital floor fracture. On physical examination, patient was noted to have significant weakness of lower extremity. Patient was evaluated by otolaryngology to continue conservative management and followed by maxillofacial surgery. Although being admitted, patient was alert and oriented to person only. Notable cough with sputum production, urinary retention, and decreased proximal strength of lower extremities with a slow wide–based gait. Initial urine drug screen proved negative and head computed tomography scan showed no evidence of acute changes. Neurology was consulted at OSH. The patient was evaluated and prescribed IV decadron and haldol for agitation. Magnetic resonance imaging was not conducted, as patient was unable to lie still due to claustrophobia.

For further management, the patient was transferred to Moffitt Cancer Center. Per examination, the patient was noted to be alert and oriented to person, place, and time with clear and coherent speech. Upon arrival, the patient received thiamine and folate, along with nivolumab chemotherapy. With workup, the patient showed low normal T4 with normal thyroid stimulating hormone consistent with euthyroid sick syndrome. Infectious etiologies of Methicillin - resistant staph aureus and vancomycin-resistant enterococci polymerase chain reaction proved negative. Arterial blood gas proved within normal limits (WNLs). Positive but likely contaminated urine culture of *Staphylococcus* species, coagulase negative, was treated with trimethoprim-sulfamethoxazole. Chest X-ray demonstrated no acute changes. After consultation with physical and occupational therapist, inpatient rehabilitation was recommended. Radiation oncologist did not feel the altered mental status was related to the patient's brain metastases. Decadron was discontinued per recommendation of the radiation oncologist due to hallucinations and agitation. Neurology oncologist was consulted and recommended electroencephalogram (EEG) and lumbar puncture for inflammatory process (encephalitis secondary to nivolumab treatment), infectious, or leptominengeal disease. Neurologist was consulted for EEG to rule out nonconvulsive seizures. The EEG showed mild slowing and no evidence of seizure activity. Per neurologist, etiology was likely multifactorial, consisting of medication side effect, toxic/metabolic etiologies, and paraneoplastic compounded with sleep deprivation. The neurologist also recommended keeping day and night cycles intact for delirium precautions.

Following steroid discontinuation, patient was noted to be alert and oriented to person only, agitated, confused, experienced visual hallucinations but cooperative at times of inappropriate mood. Psychiatrist was consulted and recommended risperdal for his agitation and combativeness along with seroquel for insomnia as needed. Initial results of cerebrospinal fluid (CSF) culture with gram stain proved negative of white blood count, acid-fast bacilli, and bacterial or fungal elements with normal glucose range. For the next 4 days pending CSF encephalitis panel results, the patient's mental status waxed and waned. With a negative workup of infectious causes, electrolyte imbalances, and hepatic/kidney injury, patient was prescribed IV Solu-Medrol on day 5 of hospital stay. Cerebrospinal fluid polymerase chain reaction of cytomegalovirus and herpes simplex virus proved negative. Paraneoplastic etiologies of adrenocorticotropic hormone (positive cortisol stimulation test with cosyntropin) and hypercalcemia (Ca was WNL) proved negative. Patient became alert and oriented to person and place but not time. By day 3 of steroidal treatment, the patient was at his baseline. Patient was discharged on 6-week steroid taper and insulin for steroid hyperglycemia was continued. Nivolumab therapy was discontinued.

Discussion

The goal of checkpoint or inhibitory receptor blockade is to restore immune effector cells to recognize and eliminate evasive cancer cells.[6] Unlike treatment modalities that target the cancer cells, immunotherapy targets the molecules involved in regulation of T cells.[7] Cytotoxic T lymphocyte-associated antigen-4[8] and PD-1 are inhibitory receptors that inactivate T cells. These inhibitory receptors aid in cancer's ability to evade immune response.[6] Many cancer cells produce the ligand PD-L1. Upon binding to the PD-1 receptor, PD-L1 reduce T-cell proliferation, cytokine production, and cytotoxic activity.[6] By blocking the inhibitor, T cells are continually activated and clear the cancer, thus blocking a negative regulator of T-cell activation. By immune modulation, nivolumab reinvigorates antitumor response and harnesses the immune system to achieve tumor control, stabilization, and potential eradication of disease.[8] This is consistent with nivolumab's ability to occupy PD-1 receptors for up to 3 months after treatment which enhances T-cell responses and cytokine production.[5] This enhanced T-cell response could prove detrimental in certain patients, thereby causing irAE.

The underlying pathophysiology of irAE is an imbalance in immunologic tolerance, uncontrolled immune response leading to T-cell inflammatory infiltration of solid organs, and increased serum inflammatory cytokines affecting normal cells.[5,8,9] There are reported cases of immune-mediated neurotoxicity in the literature, such as mild encephalopathy with reversible splenial lesion,[4] encephalitis,[10] posterior reversible encephalopathy syndrome,[11] extensive subacute meningo-radiculo-nevritis.[12] Per their package insert, immune-mediated encephalitis occurred in 0.2% (3/1994) patients receiving

nivolumab/opdivo.[12] Patients may present with nonspecific signs and symptoms characterized by headache, fever, confusion, memory problems, sleepiness, hallucinations, seizures, stiff neck, decreased mental status, impaired attention, and disorientation.[5,10,13] Our patient presented with repeated falls secondary to muscle weakness, confusion, memory problems, hallucinations, autonomic instability, waxing and waning mental status, and a negative workup. With most symptoms of nivolumab-induced encephalitis being nonspecific, a notable risk factor is the short interval between symptom onset and administration of ICPI therapy. Nivolumab-induced encephalitis is a diagnosis of exclusion. In patients with new-onset moderate to severe neurologic signs or symptoms, other causes such as metastases,[9] infections, paraneoplastic conditions,[14] and toxic/metabolite must be ruled out.

Management guidelines of nivolumab-induced encephalitis are based on symptom severity.[13] The symptom severity of immune-mediated neurological adverse reactions ranges from grades 1 to 4. Grade 1 (asymptomatic or mild symptoms), grade 2 (new-onset moderate or severe neurologic signs or symptoms), and grades 3 to 4 (immune-mediated encephalitis with confusion and personality changes). For grade 1, continue treatment but if symptoms worsen treat as grades 2 to 4. For grade 2, withhold dose, consider consulting neurologist. If improved to baseline, resume treatment. If symptoms worsen or no improvement, treat as grades 3 to 4. For grades 3 to 4, permanently discontinue nivolumab. Consult neurologist and administer 1 mg to 2mg/kg/d of prednisone equivalents followed by corticosteroid taper. If improved, taper steroids. If worsened or atypical presentation, consider alternative immunosuppressive therapies.[13] If there is disease progression or the steroids are insufficient, intravenous immunoglobulins or plasmapheresis could be considered. To prevent further progression, mycophenolate mofetil or infliximab may be considered as immune-suppressive agents[5] or steroid-sparing agents. If irAE is suspected, rapid delivery of high-dose glucocorticoid steroids may halt or reverse neurologic complications. Per the drug manufacturer, our patient had grades 3 to 4: new-onset severe symptoms, limiting self-care ADL, and life threatening per Common Terminology Criteria for Adverse Events.[15] Our patient received Solu-Medrol with gradual improvement and an oral steroid taper of 6 weeks. This provided gradual reversal of the ICPI encephalitis. Due to the long half-life of nivolumab, steroids must be tapered slowly over a period of at least 1 month.[5] Although rare, there is 1 reported case of fatal limbic encephalitis after 7.2 months of exposure despite discontinuation of nivolumab and administration of corticosteroids.[13] Hence, the importance of immediate recognition of patients prescribed nivolumab chemotherapy could potentially prevent fatal complications of neurotoxicity.

Authors' Note

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