Ipilimumab-Induced Encephalopathy with a Reversible Splenial Lesion

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Abstract

Ipilimumab, an anti-cytotoxic T-lymphocyte antigen (CTLA)-4 monoclonal antibody, is a first-line therapy for stage IV melanoma. Although high-grade immune-related adverse events occur in 25% of patients receiving ipilimumab, serious neurologic toxicity primarily consisting of transient sensory and motor neuropathies affect less than one percent of patients. We present a case report of a melanoma patient who received high-dose ipilimumab at 10 mg/kg as first-line therapy for metastatic disease. After the third dose, the patient developed “mild” encephalopathy with a reversible splenial lesion (MERS) of the corpus callosum by MRI and neurogenic bladder, two novel immune-related adverse events during checkpoint inhibition. In addition to headache, delirium and altered consciousness commonly seen with MERS, the patient also developed tremor, gait instability, paresthesias and neurogenic bladder. The latter two were thought to represent sensory and autonomic neuropathies, respectively. The syndrome gradually resolved following intravenous methylprednisolone at 2mg/kg divided twice daily for 5 days and a slow taper of oral prednisone over 8 weeks.
Introduction

Ipilimumab, an anti-cytotoxic T-lymphocyte antigen (CTLA)-4 monoclonal antibody, improved overall survival compared to chemotherapy for advanced melanoma with 22% of treated patients alive at 3-year follow up (1, 2). Additional immune checkpoint inhibitors, pembrolizumab and nivolumab, targeting programmed cell death-1 (PD-1) were approved in 2014 and these inhibitors also unleashed the suppressed antitumor immune responses (3, 4). There has been only a single report of encephalopathy associated with ipilimumab therapy, and to our knowledge no report of neurogenic bladder (5). We present a case report of a melanoma patient who received high-dose ipilimumab as initial therapy for metastatic disease and developed novel immune-related adverse events consisting of encephalopathy with a reversible splenial lesion of the corpus callosum and neurogenic bladder.

Case Presentation

A 41-year-old Caucasian male underwent complete resection of stage IIIC BRAF V600E mutated melanoma from his back with an ulcerated primary and a single, involved macroscopic regional lymph node. Eighteen months later, PET CT scans revealed stage IV melanoma with hypermetabolic metastases involving the liver, bones and a subcarinal lymph node. Biopsy of the subcarinal node confirmed metastatic melanoma. After signed informed consent, the patient was enrolled in an Eastern Cooperative Oncology Group clinical trial in which he was randomly allocated to receive high-dose ipilimumab monotherapy at 10 mg/kg IV every 3 weeks. The patient tolerated the first two doses well with only grade 1 fatigue and grade 2 erythematous maculopapular rash that was treated with antihistamines and topical steroid cream.
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Ten days after the third dose of ipilimumab, he developed diffuse arthralgias, myalgias, chills, night sweats, mild headache and fevers up to 104° F. Blood cultures, urine culture, chest radiograph, influenza rapid antigen-detection assay, complete blood count and serum chemistries were unremarkable. After four days of continued symptoms, oral prednisone was initiated at 30 mg per day for a presumed immune-related adverse event (irAE) from ipilimumab of moderate severity, grade 2. Three days later, flu-like symptoms persisted, and he developed new onset expressive aphasia, decreased motor dexterity, gait ataxia, and self-awareness of discontinuous thought processes. He denied any focal neurologic symptoms including sensory loss, weakness, vision change or bulbar dysfunction. He was admitted to the medical oncology service where neurologic exam revealed slowness of thought, fluent speech with mild difficulty finding words, intention tremor with mild postural tremor of the left arm, dysmetria limited to lower extremities and broad-based gait with ataxia. Brain MRI with gadolinium compared to a normal MRI obtained one week prior to the first dose of ipilimumab revealed a new area of restricted diffusion in the posterior splenium of the corpus callosum with corresponding T2 hyperintensity on fluid attenuation inversion recovery (FLAIR) and no abnormal enhancement or evidence of melanoma metastasis (Figure 1). CT scans of the chest, abdomen and pelvis showed early evidence of minor melanoma response to ipilimumab with less than 20% shrinkage of pre-existing lesions and no new metastases. There was no evidence of infection or endocrinopathy and thyroid function studies and ammonia were normal. Prednisone was increased to 1 mg/kg (110 mg daily) divided twice daily and ipilimumab was permanently discontinued due to encephalopathy. After a three-day hospitalization, he was discharged and went home to continue the same prednisone dose with resolution of fever, chills, arthralgias, myalgias and headache. Cognition, speech and gait were slowly improving.
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Nine days later, he required readmission to the neurology service for lower extremity paresthesias and new onset of neurogenic bladder with post-void residual volume of 1800cc. He had no history of benign prostatic hypertrophy and did not improve with tamsulosin. MRI with gadolinium of the lumbosacral spine was normal and CT scans of the abdomen and pelvis obtained 10 days earlier were negative for anatomic abnormalities of the urinary tract. Serum creatinine remained normal. Neurologic exam revealed bilateral, high frequency tremor with intention affecting the upper extremities, impaired rapid alternating movements, difficulty with tandem gait and a positive Romberg sign. In addition, he had absent reflexes at the patellae and ankles with preserved deep tendon reflexes in the upper extremities associated with impaired lower extremity proprioception and vibration sensation. Repeat brain MRI with gadolinium compared to the exam 11 days earlier showed that T2 hyperintensity within the corpus callosum was reduced on FLAIR, remaining faintly hyperintense on T2-weighted images and diffusion-weighted (B1000) images with progressive normalization on Apparent Diffusion Coefficient (ADC) images (Figure 2). These findings were thought to reflect cell wall breakdown with release of intracellular fluid and resolving extracellular edema of the corpus callosum as a result of focal irreversible axonal damage. With Wallerian degeneration, there could be some progression of T2 hyperintensity over time. Cerebrospinal fluid studies were consistent with an aseptic inflammatory event with minimally elevated protein, pleocytosis of 128 white blood cells per cubic mm (normal ≤ 5) with lymphocytic predominance, absence of oligoclonal bands and normal IgG synthesis rate. Cytology was negative for melanoma cells. Serologic tests for connective tissue disorders including anti-DNA antibody, anti-nuclear antibody screen and rheumatoid factor were all negative. Urinalysis was normal. Urology consultation diagnosed neurogenic bladder which was managed by in and out catheterization. The attending neurologist
believed that the patient’s presentation was consistent with a nervous system inflammatory event initially primarily affecting the central nervous system, but also with peripheral components manifest by peripheral sensory neuropathy and neurogenic bladder. Due to the slow pace of improvement in cognition, speech and gait stability as well as progression of tremor, paresthesias and urinary retention after 12 days of oral prednisone at 1 mg/kg daily, his therapy was changed to intravenous methylprednisolone at 2 mg/kg divided twice daily for 5 days. Thereafter, all neurologic signs and symptoms were approximately 50% improved with the exception of neurogenic bladder which was stable. He was discharged home on prednisone 1 mg/kg divided twice daily to taper by 10 mg per day every 4 days and in and out bladder catheterization. Cognition and speech approached baseline within one week, and urinary retention resolved within two weeks. Following completion of an 8-week steroid taper, the patient had only a minimal high frequency tremor with intention and minimal paresthesias in the left foot that did not interfere with his activities of daily living or ability to work as a college professor. His gait was normal by exam, but required extra attention when descending stairs, and very subtle memory impairment persisted at the time of manuscript submission four months after the occurrence of this irAE.

**Discussion**

Serious neurologic toxicity affects fewer than 1% of patients receiving ipilimumab at 3 mg/kg (the FDA-approved dose) or 10 mg/kg, a dose widely used in ongoing clinical trials (1, 6). Transient peripheral neuropathies, both sensory and motor, are the most common neurologic toxicities associated with ipilimumab. Rare cases of Guillain-Barre´-type syndrome, myasthenia
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gravis-type syndrome, aseptic meningitis, transverse myelitis and enteric neuropathy with severe constipation have been reported (7, 8).

Mild encephalopathy with a reversible splenial lesion (MERS) is characterized by an isolated lesion with transiently reduced diffusion in the splenium of the corpus callosum on brain MRI which typically resolves within 1-4 weeks (9, 10). Fever precedes the onset of neurologic symptoms, which typically include headache, delirium and disturbed consciousness. In a series of fifteen patients with MERS, ataxia and tremor were observed in one patient each, and paresthesias were not reported (10). MERS is associated with a variety of medical conditions involving immune activation including viral or less often bacterial infections, autoimmune disorders and malignancy (11). Pathogenesis is thought to relate to elevated levels of serum proinflammatory cytokines including IL1, IL6 and tumor necrosis factor (TNF) which have been associated with immune checkpoint inhibition (12) as well as activation of the neuroendocrine-immune axis that modifies afferent neural pathways leading to central nervous system inflammation (13). Increased T2 and FLAIR signal intensity on MRI are thought to represent axonal edema and/or inflammatory cell infiltrates (14). Our patient experienced an unusually severe variant of MERS during ipilimumab therapy with typical radiographic features, headache, delirium and impaired consciousness, but additionally tremor, gait instability, paresthesias and neurogenic bladder. Most of these symptoms could result from injury to the corpus callosum, a tightly packed bundle of approximately 200 million axons facilitating communication between the cerebral hemispheres as well as between visual, auditory, language and motor centers. Neurogenic bladder and paresthesias not reported with MERS likely represented autonomic and sensory neuropathies, respectively.
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This is the first reported case of MERS associated with ipilimumab and our patient lacked other risk factors such as viral or bacterial infection. He did present with a prodrome of fever, but blood and urine cultures, chest radiograph and influenza antigen-detection assay were negative. Fever has been reported in 14% of melanoma patients receiving 10 mg/kg of ipilimumab (15). Thus, MERS in our patient convincingly represented an irAE from ipilimumab. Even if an unidentified viral infection contributed, our patient’s case was significantly more severe and required greater therapeutic intervention than the vast majority of MERS, likely due to hyperimmune activation from ipilimumab.

The only previous report of encephalopathy associated with ipilimumab was a case of posterior reversible encephalopathy syndrome (PRES) occurring ten days after the first dose of ipilimumab, an uncommon time course for a serious irAE, and in the setting of hypertension and acute renal failure, two other common causes of PRES (5). PRES is closely related to MERS with similar transient diffusion restriction on brain MRI preferentially affecting the parietal and occipital lobes thought secondary to decreased sympathetic innervation of the posterior circulation (16). Although the pathogenesis of these syndromes overlap, PRES is predominantly a vasogenic process with hypertension as the most common cause, and MERS is predominantly related to immune activation (9, 10, 16).

Our patient also is the first reported case of neurogenic bladder associated with ipilimumab. This arose in a previously healthy 41-year-old male while fully ambulatory at home on no medications associated with urinary retention. This was thought to represent an autonomic neuropathy distinct from the constellation of symptoms resulting from the splenial lesion. There has been only one previous report of autonomic neuropathy associated with ipilimumab in a melanoma patient developing inflammatory enteric neuropathy with severe constipation (7).
immune checkpoint inhibitors become more widely used to treat melanoma and other malignancies, investigators and clinicians must be attuned to the potential for uncommon neurologic toxicities.

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References


Figure 1. Brain MRI images at baseline one week before the first dose of ipilimumab (top row) and at the onset of clinical encephalopathy (bottom row) including from left to right diffusion-weighted B1000 images, fluid-attenuation inversion recovery (FLAIR) and T2 turbo spin-echo (TSE) images. Hyper-intensity in the splenium was not visible at baseline and was clearly evident at the onset of clinical encephalopathy with correlating decreased apparent diffusion coefficient (ADC.)

Figure 2. Brain MRI images after 11 days of high-dose prednisone; from left to right DWI B1000, FLAIR and T2 TSE images. There was correlating early normalization of the ADC, and the respective hyper-intensity in the splenium had substantially decreased.
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