

Subacute CNS Demyelination after Treatment with Nivolumab for Melanoma

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Abstract

Immunotherapy with monoclonal antibodies targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) or programmed cell death 1 (PD-1) has improved the survival of patients with metastatic melanoma. These agents carry a certain risk of adverse immune-related events. We present a patient with widely metastatic melanoma who was initially treated with ipilimumab and subsequently with nivolumab. After four infusions of nivolumab, he developed subacute multifocal central nervous system (CNS) demyelination. Nivolumab was discontinued and, despite immunosuppressive therapy, the largest lesion progressed significantly, whereas another lesion showed radiographic improvement. After further progression, the

patient succumbed to his CNS lesions 4 months later. Autopsy revealed extensive demyelination, a mild multifocal T-cell-rich perivascular lymphoid infiltrate, abundant macrophages, and necrosis. There was no metastatic melanoma in the brain. CNS demyelination has not been described in association with nivolumab. We hypothesize that the combination therapy of ipilimumab and subsequent nivolumab accounted for the severity of the demyelinating process in this patient. This case, with comprehensive clinical, molecular, and neuropathologic characterization, illustrates the need for awareness of these potential CNS complications with the use of multiple checkpoint inhibitors. *Cancer Immunol Res*; 3(12): 1299–302. ©2015 AACR.

Introduction

Immunotherapy with monoclonal antibodies, such as ipilimumab (which targets CTLA-4), or pembrolizumab and nivolumab (which target PD-1), has revolutionized the management of melanoma. Data accumulating from clinical trials suggest the efficacy of these so-called "checkpoint inhibitors" in treating metastatic melanoma, but less is known about the risk of immune-related adverse events (irAE). As some of the more common irAEs, these agents may cause skin rash or colitis, while hypophysitis, hepatitis, nephritis, and neuropathy are less common. Very little is known about central nervous system (CNS)-related irAEs. A recent double-blind phase III trial comparing combined nivolumab and ipilimumab versus monotherapy in untreated melanoma showed that immunologic grade 3 or 4 adverse events are more frequent in the combined group (nivolumab + ipilimumab: 55.0%; nivolumab: 16.3%; ipilimumab: 27.3%; ref. 1). We report the case of a 60-year-old man who

succumbed to progressive and subacute CNS demyelination that developed while he was receiving nivolumab following ipilimumab for metastatic melanoma. CNS demyelination has never been reported as a side effect of anti-PD-1 therapy, although a case of encephalopathy with a reversible splenic lesion was described in association with ipilimumab treatment (2). As the use of these agents increases, it is important to be aware of this rare but severe potential complication.

Case Presentation

A 60-year-old white man was diagnosed with a low-risk *in situ* cutaneous melanoma in 2002 that was managed by complete excision alone. The patient had no family history of melanoma or any other malignancy; his paternal grandfather had died from multiple sclerosis.

In October 2012, he developed abdominal pain and weight loss, and a CT scan revealed hepatic lesions. Biopsy showed a pigmented tumor composed of cells that stained positive for S-100, Melan-A, HMB-45, and vimentin, suggestive of melanoma. Genotyping of BRAF, NRAS, GNAQ, and GNA11 showed wild-type sequences.

No other primary lesion was identified. After two cycles of carboplatin/paclitaxel chemotherapy, we decided to discontinue chemotherapy and begin ipilimumab due to myelosuppression. After four infusions of ipilimumab, a CT scan of the abdomen and pelvis showed progression of the liver metastasis. The patient was enrolled in a trial of nivolumab (CHECKMATE BMS-037) approximately 2 months after the last dose of ipilimumab.

Two days after the fourth cycle of nivolumab (3 mg/kg every 2 weeks), the patient presented with subacute confusion, nausea, and vomiting. Clinical examination revealed apathy, fixed gaze, and marked psychomotor slowing. Brain MRI revealed the presence of white matter lesions in the right frontal and left

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temporoparietal lobes (Fig. 1A–C), consistent with tumefactive demyelination. A lumbar puncture confirmed the presence of myelin-basic protein (11.0 $\mu\text{g/L}$; normal: 0.0–4.0 $\mu\text{g/L}$), oligoclonal bands, and proteinorachia (0.88 g/L). The other parameters were normal (white blood cells = 0, red blood cells = 0, glucose = 4.9, no malignant cells, and negative results for infectious organisms, including PCR for cytomegalovirus, varicella zoster virus, herpes simplex virus, JC virus, and BK virus, as well as tests for acid-fast bacilli, cryptococcal Ag, and fungus). A CT scan of his abdomen and pelvis showed enlargement of some lymph nodes and a splenic metastasis. He was treated for 5 days with high-dose methylprednisolone intravenously (1 g per day) followed by intravenous immune globulin (IVIG, 2 g/kg) over 5 days. After these treatments, apathy, eye contact, and communication improved, although the patient remained mildly disoriented. He was discharged in early November 2013 to palliative care. His family claimed he improved considerably over the following weeks with almost complete return to his cognitive and functional baseline.

In January 2014, the patient was readmitted with subacute left-sided weakness, and an MRI of his brain revealed progression of the right frontal lesion toward the precentral gyrus and splenium of the corpus callosum (Fig. 1D–F). In contrast, there was radiographic improvement of the left temporoparietal lesion, which had almost completely resolved. The MRI showed patchy diffusion and an enhancement pattern consistent with acute and active demyelination in the right frontal lobe. A second course of IVIG (2 g/kg over 5 days) was administered, but the patient had no improvement of his neurologic status and died in May 2014.

A CT scan 2 months prior to death had demonstrated disease progression in the liver. The patient was part of the rapid autopsy program. Autopsy confirmed the presence of metastatic melanoma, with extensive spread to liver, pancreas, spleen, stomach, and

heart. Interestingly, the brain did not show any metastatic lesions. The clinical pattern of spread and wild-type BRAF status suggested the possibility of uveal melanoma. However, no obvious lesions were found in the eyes. Examination of the brain confirmed the presence of widespread demyelination in the right frontal and left temporoparietal white matter with infiltration of macrophages containing myelin debris, reactive astrocytes, focal perivascular lymphoid inflammation, and areas of early cavitation (Fig. 2A–F). Moreover, sections through the cervical, thoracic, and lumbar cord showed pallor in the left-sided corticospinal tract. Immunohistochemistry showed the presence of both CD4⁺ (helper) and CD8⁺ (cytotoxic) T cells. Among these, CD4⁺ cells were somewhat smaller in number and were mostly confined to perivascular spaces, whereas CD8⁺ cells were seen perivascularly and at the edge of acutely demyelinating plaques.

Discussion

Although immunotherapy has revolutionized the treatment of cancers such as melanoma, it can also cause serious IrAEs. We present the case of a 60-year-old man with metastatic melanoma who, after 3 months of nivolumab therapy subsequent to treatment with ipilimumab, developed contrast-enhancing demyelination of the CNS. Clinical improvement followed treatment with IVIG and high-dose corticosteroids, but a relapse unresponsive to further immunosuppression was fatal.

Ipilimumab is a humanized IgG4 monoclonal antibody that targets CTLA-4, an inhibitory coreceptor on T cells that down-regulates immune responses (2, 3). Ipilimumab improves overall survival for patients with stage III and IV melanoma (4), compared with vaccine (5) or dacarbazine (6). Nivolumab is a humanized IgG4 monoclonal antibody that blocks ligand activation of the PD-1 receptor on activated T cells. Tumor-infiltrating

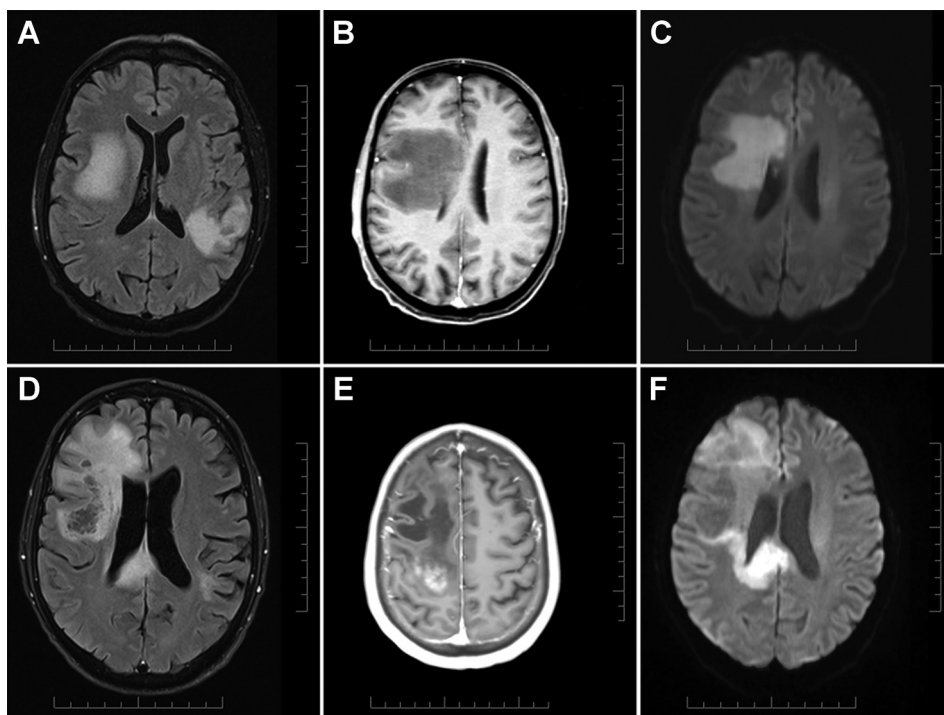


Figure 1.

Brain MRI at the time of first (A, B, and C) and second (D, E, and F) admission, showing acute tumefactive demyelinating lesions. A, T2/Flair Brain MRI: demyelinating right frontal and left temporoparietal lesions. B, T1 postgadolinium brain MRI: right frontal demyelinating lesion sparing the cortex with minimal enhancement. C, diffusion weighted imaging (DWI) sequence: diffusion restriction confirming the acute nature of the lesion. D, T2/Flair Brain MRI: improvement of the previous left temporoparietal lesion and progression and cavitation of the right frontal lesion. E, T1 postgadolinium brain MRI: progression of the enhancement in the right frontal lesion. F, DWI sequence: new areas of diffusion restriction compatible with the new demyelinating lesions.

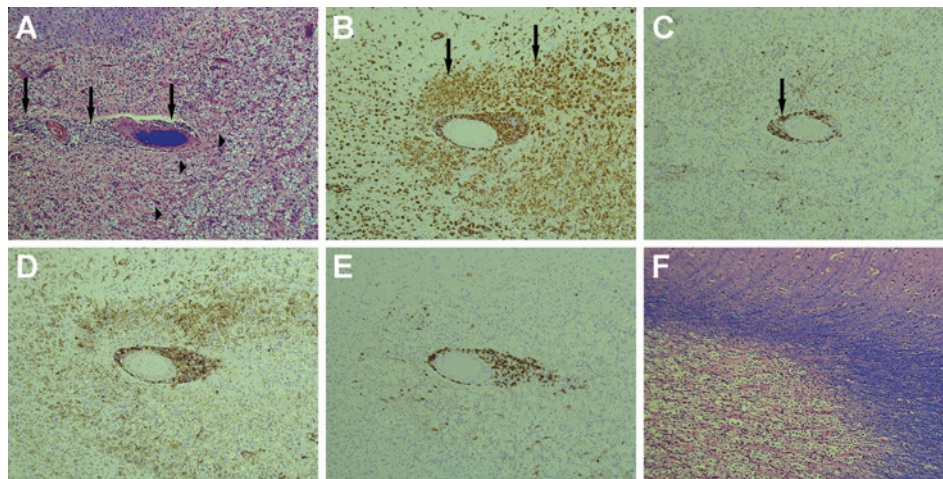


Figure 2.

Histopathologic features (all images at $\times 10$ magnification). A, luxol-hematoxylin and eosin (H&E) stain from right frontal lesion, showing a central blood vessel with mild lymphocytic cuffing (arrows), area of severe astrocytic gliosis (bottom left), sheets of macrophages (bottom right, arrowheads), and residual myelin (blue, top left). B, immunohistochemistry for CD68, labeling macrophages (arrows). C, CD45 stain revealing lymphocytes (arrow). D and E, CD4 and CD8 stains, respectively, showing a mixture of T-helper and T-cytotoxic cells. F, luxol-H&E stain from left temporoparietal lesion, showing sheets of macrophages in the bottom left of the image, surrounded by residual myelin (blue) in white matter.

T cells often express high amounts of PD-1, suggesting that PD-1 blockade may reverse cancer-associated T-cell exhaustion (7). Simultaneous blockade of several nonredundant negative regulatory pathways may enhance T-cell functions for enhanced antitumor immunity (8). In a phase I study with 86 patients, a substantial proportion of patients with stage III and IV melanoma experienced tumor regression after treatment with the both nivolumab and ipilimumab, albeit at the cost of a high number of IrAEs (9).

The CNS is under continual immune surveillance to detect and eliminate potential mediators of infection and damage (10). PD-1 and PD-L1 have been studied extensively in animal models of autoimmunity and in multiple sclerosis. In experimental autoimmune encephalomyelitis (EAE), the interaction between PD-1 and PD-L1 influences disease severity. In particular, PD-1 blockade results in a more severe form of EAE (11). On the other hand, high PD-L1 expression prompts a primary tolerogenic program in EAE (12). In multiple sclerosis, increased expression of PD-1 and PD-L1 results in decreased T-cell proliferation and increased apoptosis of MBP-specific cells, which is associated with disease remission (13). *In vitro* experiments showed that blocking PD-L1 on human endothelial cells results in increased transmigration of activated T cells (14, 15). In our case, the radiographic appearance of the demyelinating lesions did not have the typical characteristics of multiple sclerosis; the diffusion restriction and enhancement patterns were consistent with subacute tumefactive demyelination.

Neurologic complications of checkpoint inhibitors are rare and have mostly been reported to involve the peripheral nervous system. For example, IrAEs for ipilimumab include Guillain-Barré syndrome (16–18), multifocal radiculoneuropathy, and chronic inflammatory demyelinating polyneuropathy (19). In a case report for a patient with nerve pathology (17), the biopsy showed inflammation around endoneurial microvessels and subperineurial edema and inflammation. A patient on ipilimumab developed mild encephalopathy with a lesion in the splenium of the corpus

callosum (2) that resolved after treatment with methylprednisolone. What sets our case apart from these reported cases is the progressive nature of the patient's left frontal lesion that showed resistance to immunosuppressive therapy and ultimately led to the fatal outcome. Whether this is an effect of nivolumab alone or also the result of the preceding ipilimumab remains unclear. The interval between the two drugs was short (2 months); therefore, residual ipilimumab effects cannot be excluded. The patient's large right frontal lesion continued to progress during immunosuppressive treatment, whereas the left temporoparietal lesion improved radiologically. Histologically, the right frontal lesion showed extensive necrosis and astrogliosis, whereas the left temporoparietal lesion contained sheets of macrophages, an absence of necrosis, and no significant astrogliosis. These histologic differences may explain the imaging differences.

Only safety data from larger studies and potentially postmarketing experience will define the exact risk of nivolumab-related immunopathologies. Nevertheless, our case provides plausible evidence for aberrant immune system activation and CNS demyelination after treatment with this antibody to PD-1. We suggest that pretreatment with ipilimumab may have also played a role in the development of demyelination. The novelty of these treatment combinations requires further study to discern whether the sequence of ipilimumab followed by nivolumab versus nivolumab followed by ipilimumab is associated with more severe side effects. We do not know whether our patient's ethnic background and positive family history of multiple sclerosis were contributing risk factors.

The published algorithms to manage autoimmune complications of ipilimumab and nivolumab, as well as guidelines to treat multiple sclerosis, were used to plan therapy for our patient. High-dose steroids and IVIG may have transiently improved the clinical situation in our patient but did not prevent his death. Additional medications, such as cyclophosphamide, mycophenolate mofetil, and tacrolimus, might find use as part of a regimen to control T-cell proliferation, although experience with these

drugs for this indication is currently limited. After consultation with the patient's family, we agreed to discontinue treatment after the second attempt with IVIG, but the role of plasmapheresis and other immunotherapies needs to be evaluated in similar cases. With additional cases of demyelination anticipated as the use of these agents increases, an effective treatment algorithm will likely evolve.

Disclosure of Potential Conflicts of Interest

D. Hogg is a consultant/advisory board member for Bristol-Myers Squibb, GlaxoSmithKline, Novartis, and Roche. No potential conflicts of interest were disclosed by the other authors.

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Writing, review, and/or revision of the manuscript: C. Maurice, R. Schneider, T.-R. Kiehl, M.H.A. Roehrl, W.P. Mason, D. Hogg

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