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, while another lesion showed radiographic improvement. After further progression, the patient succumbed to his CNS lesions four 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 neuropathological characterization, illustrates the need for awareness of these potential CNS complications with the use of multiple checkpoint inhibitors.
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 suggests the efficacy of these so-called "checkpoint inhibitors" in treating metastatic melanoma but less is known about the risk of immune-related adverse events (IrAEs). 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 CNS-related IrAEs. A recent double-blind phase 3 trial comparing combined nivolumab and ipilimumab vs. 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%) (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 splenial lesion was described in association with ipilimumab (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 computed tomography (CT) scan revealed hepatic lesions. Biopsy demonstrated 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 demonstrated 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 demonstrated a 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 two weeks) the patient presented with subacute confusion, nausea, and vomiting. Clinical exam revealed apathy, fixed gaze, and marked psychomotor slowing. Brain magnetic resonance imaging (MRI) demonstrated the presence of white matter lesions in the right frontal and left temporo-parietal lobes (Fig. 1, A-C), consistent with tumefactive demyelination. A lumbar puncture confirmed the presence of myelin-basic protein (11.0 mcg/L; normal: 0.0-4.0 mcg/L), oligoclonal bands, and proteinorachia (0.88g/L). The other parameters were normal (WBC=0, RBC=0, glucose=4.9, no malignant cells, and negative results for infectious organisms, including polymerase chain reaction for cytomegalovirus, VZV, HSV, JCV, 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 with 5 days of high-dose methylprednisolone IV (1 g per day) followed by intravenous immune globulin (IVIG, 2g/kg) over 5 days. After these treatments, apathy, eye contact and communication improved, although he 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 MR scan of his brain demonstrated progression of the right frontal lesion towards the precentral gyrus and splenium of the corpus callosum (Fig. 1, D-F). In contrast, there was radiographic improvement of the left temporo-parietal lesion, which had almost completely resolved. The MRI scan demonstrated patchy diffusion and an enhancement pattern consistent with acute and active demyelination in the right frontal lobe. A second course of IVIG (2g/kg over 5 days) was administered but the patient had no improvement of his neurological 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 confirming 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 temporo-parietal white matter with infiltration of macrophages containing myelin debris, reactive astrocytes, focal perivascular lymphoid inflammation, and areas of early cavitation (Fig. 2, A-F). Moreover, sections through the cervical, thoracic and lumbar cord showed pallor in the left-sided corticospinal tract. Immunohistochemistry demonstrated the presence of both CD4+ (helper) and CD8+ (cytotoxic) T cells. Among these, CD4+ cells where somewhat smaller in number and were mostly confined to perivascular spaces while 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 three months of nivolumab therapy post-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 co-receptor on T cells that down-regulates immune responses (2-3). Ipilimumab improves overall survival for patients with stage III and IV melanoma (4), compared to 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 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 (MS). 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 MS, 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 MS; the diffusion restriction and enhancement patterns were consistent with subacute tumefactive demyelination.

Neurological 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 (CIDP) (19). In the case with nerve pathology available (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 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 when on immunosuppressive treatment, whereas the left temporo-parietal lesion improved radiologically. Histologically,
the right frontal lesion showed extensive necrosis and astrogliosis, whereas the left temporo-parietal lesion contained sheets of macrophages, an absence of necrosis, and no significant astrogliosis. These histological 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 know if 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 MS were contributing risk factors.

The published algorithms to manage autoimmune complications from ipilimumab and nivolumab, as well as guidelines to treat MS 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.
Authors’ contributions

Conception and design: W. P. Mason, D. Hogg

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Acquisition of data: C. Maurice, T.-R. Kiehl, P. Bavi, M.H.A. Roehrl

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P. Bavi, M.H.A. Roehrl, D. Hogg

Other (image acquisition and coordination of appropriate parameters and physics principles as they apply to this article with description of findings): C. Maurice, P. Bavi,
Figure Legend

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 temporo-parietal lesions. (B) T1 post-gadolinium 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 temporo-parietal lesion and progression and cavitation of the right frontal lesion. (E) T1 post-gadolinium 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.
Histopathological features (all images at 10x 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 (lower left), sheets of macrophages (lower right, arrowheads) and residual myelin (blue, upper left). (B) Immunohistochemistry for CD68, labeling macrophages (arrows). (C) CD45 stain revealing lymphocytes (arrow). (D) and (E) CD4 and CD8 stains, respectively demonstrating a mixture of T-helper and T-cytotoxic cells. (F) Luxol-H&E stain from left temporo-parietal lesion, showing sheets of macrophages in the lower left of the image, surrounded by residual myelin (blue) in white matter.
References

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