

Complete response to pembrolizumab in a patient with metastatic colon cancer with microsatellite instability and a history of Guillain-Barre syndrome

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Abstract: Currently, clinical trials with programmed death-1 (PD-1) inhibitors exclude patients with preexisting autoimmune disorders such as Guillain-Barre syndrome (GBS). Therefore, the scientific literature has limited information about the efficacy and safety of PD-1 inhibitors in cancer patients with autoimmune disorders. Immune checkpoint inhibitors can exacerbate preexisting autoimmune disorders and can induce severe immune-related adverse events. Here, we report the case of a 73-year-old female patient with history of GBS and mismatch repair deficient metastatic colorectal cancer who achieved a durable complete response to pembrolizumab. The patient was maintained on intravenous immunoglobulin (IVIG) during her treatment without any neurological exacerbations. This case highlights the feasibility of PD-1 inhibitors in select patients with neurological autoimmune disorders and calls for more systematic evaluation of checkpoint inhibitors in patients with cancer and GBS, especially with the known link between this disorder and malignancy.

Keywords: Pembrolizumab; Guillain-Barre syndrome (GBS); microsatellite instability-high (MSI-H)

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Introduction

Programmed death-1/programmed death-ligand 1 (PD-1/ PD-L1) blockade have demonstrated substantial anti-tumor activity across multiple cancer types, and are approved by Food and Drug Administration (FDA) for the treatment of melanoma (1,2), lung cancer (3-5), renal cancer (6), Hodgkin's lymphoma (7), and microsatellite instabilityhigh (MSI-H) metastatic colorectal cancer (8,9), among others. A pivotal study of pembrolizumab demonstrated a 53% objective response in cancers with microsatellite instability (MSI) across 12 different tumor types (10). This, among other supporting studies, lead to the approval of pembrolizumab by the FDA for the treatment of solid tumors with MSI, including colorectal cancer (8,10). However, post-approval use of pembrolizumab in MSI-H patients and history of immune disorders has been limited, and no experience has been reported in patients with Guillain-Barre syndrome (GBS).

GBS typically occurs after immune response to a preceding infection that cross-reacts with peripheral nerve components because of molecular mimicry, resulting in demyelinating polyradiculoneuropathy (11,12). In addition, GBS can be the result of a paraneoplastic syndrome, particularly in the setting of non-small cell lung cancer (13,14). In addition, GBS has been recently reported in the setting of immunotherapy in patients with cancer. Ipilimumab, a CTLA-4 checkpoint inhibitor, was associated with GBS in melanoma patients; these were managed with high-dose corticosteroid therapy and ipilimumab discontinuation (15-19). Therefore, considerable concern exists regarding the use of immunotherapy in patients with pre-existing GBS. This concern is heightened by reports of excessive exacerbations of autoimmune disorders with immunotherapy, with both PD-1 and CTL-A4 inhibitors. Ipilimumab monotherapy was associated with exacerbation of autoimmune disorder in 27% of melanoma patients with pre-existing auto-immune disorders, most of which were manageable with corticosteroid (20). Likewise, 38% of melanoma patients experienced flare of preexisting autoimmune disorders with PD-1 inhibitors, most of which were mild and manageable with corticosteroid (21). These reports suggested that checkpoint blockade can be given to cancer patients with autoimmune disorders despite greater toxicity.

Here we report the case of a 73-year-old female patient, with metastatic colon cancer and a history of GBS. The patient was treated with pembrolizumab and achieved a complete response. Furthermore, the patient is in clinical remission for more than 18 months with no notable toxicities except for fatigue and myalgias. Her GBS was managed by maintenance with intravenous immunoglobulin (IVIG), before, during, and after pembrolizumab and without any acute neurological exacerbations.

Case presentation

A 73-year-old Caucasian female patient was referred to our clinic in March, 2016 for metastatic colon cancer. Her past medical history was significant for history of DCIS treated surgically and in remission since 2011, a diagnosis of pulmonary embolism on maintenance rivaroxaban, and a diagnosis of GBS since 2014. Her GBS occurred after an influenza-like illness and was initially associated with significant neurological deficits which reversed with IVIG treatment. She has been under the care of Neurology service and had been maintained since her GBS diagnosis on IVIG every 4 weeks. Her colorectal cancer history is significant for a right hemicolectomy in February 2015 with a pathological stage T3N2aM0 adenocarcinoma and with a poor differentiation. She received 6 months of adjuvant capecitabine given her limited performance status, neurological history, and easy fatigability. Three months after completion of adjuvant therapy, a wholebody PET/CT scan revealed multiple FDG-avid enlarged retroperitoneal lymph nodes and a 4.7 cm right anterior pelvic mass with a (standardized uptake value) SUV of 24.5. A biopsy of the pelvic mass confirmed metastatic colorectal cancer.

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Considering the right sidedness location of primary tumor and co-existing neuropathy, she was offered firstline treatment with folinic acid, 5-fluorouracil, irinotecan (FOLFIRI) and bevacizumab. Unfortunately, the patient developed severe fatigue and lower extremity cellulitis after 2 cycles of systemic chemotherapy, despite considerable dose reductions. In the interim, next generation sequencing (NGS) of her tumor by FoundationOne® (Foundation Medicine, Inc., Cambridge, MA, USA) revealed the presence of a BRAF V600E mutation, MSI, and a high tumor mutation burden (73/MB). Given her intolerance to chemotherapy, we discussed the possibility of treatment with PD-1 inhibitors with maintenance IVIG and counseled her about the possibility of an autoimmune disease flare. The patient consented to treatment and received pembrolizumab intravenously at 200 mg every 3 weeks. From May 13, 2016, to July 06, 2017, she received 20 cycles of pembrolizumab without toxicities except for mild worsening of existing fatigue and increased myalgias. Her GBS continued to be managed by maintenance IVIG every 4 weeks without flares. Surveillance CT scan showed significant and persistent reduction in tumor burden throughout therapy, with complete remission being attained in January 2017 (Figure 1). Pembrolizumab was discontinued in July 2017 following 6 months of complete remission. She continues to be monitored by CT scans and CEA every 3 months and is in full remission as of her last CEA and imaging studies from May of 2018.

Discussion

PD-1/PD-L1 blockades have been approved for the treatment of metastatic colorectal cancers with MSI-H, however, its safety and efficacy in patients with autoimmune disorders, particularly GBS, is largely unknown. Here, we presented a case of complete response to pembrolizumab in a 73-year-old woman with metastatic colon cancer, MSI-H tumor, and a history of GBS.

The PD-1/PD-L pathway plays a critical role in maintaining both peripheral and central T-cell mediated immune tolerance. Disruption of PD-1 signaling results in the development of multiorgan autoimmunity such as lupus and type I diabetes (22,23). In addition, accelerated graft rejection in patients with organ transplantation has been attributed to PD-1/PD-L1 blockade (24). As a result, it is widely acknowledged that immune checkpoint inhibitors enhance the activation of autoreactive T cells, leading to exacerbation of autoimmune disorders and causing a variety

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Figure 1 CT image of a complete response in an MSI-H recurrent colon adenocarcinoma arising in the right rectus muscle in the pelvic area and retroperitoneal lymph node metastasis: (A) baseline right abdominal wall metastasis; (B) complete response of abdominal wall metastasis to pembrolizumab; (C) baseline retroperitoneal lymph node metastasis; and (D) complete response of retroperitoneal lymph node metastasis to pembrolizumab.

of immune-related adverse events (irAEs) (25). Therefore, patients with preexisting autoimmune disorders are excluded from PD-1 inhibitors in clinical trials (9).

A recent retrospective study focused on the toxicities of anti-PD-1 in melanoma patients with preexisting autoimmune disorders found that 38% of patients with autoimmune disorders (n=52) had a flare of pre-existing autoimmune disease after the first dose of anti-PD-1 treatment, and no patients with neurological (N=5, GBS =2) disorders experienced exacerbations of their disease with therapy (21). Patients who experienced flares were managed with oral immune suppressants, and only 2 (10%) patients discontinued anti-PD-1 treatment permanently. One possible explanation for this discordance is the heterogeneity of the pathogenesis of autoimmune disease, of which many autoimmune disorders do not rely on PD-1/PD-L1 pathway primarily. GBS is thought to be an antibody mediated autoimmune disease generated by B cells, while autoimmune disorders like psoriasis and rheumatoid arthritis are characterized by T cell mediated immune response primarily (26-28). Interestingly, the antitumor activity response rate in melanoma patients with preexisting autoimmune disorders was 33%, which is comparable to response rates with PD-1 inhibitors in first-line clinical trials (21,29). Taken together, these data suggest that patients with prior autoimmune disorder are at increased risk of PD-1 inhibitor related toxicities, but such toxicities can be manageable with many of these patients achieving clinical benefits.

In one case of metastatic melanoma with history of GBS and psoriasis, treatment with sequential ipilimumab, pembrolizumab, and nivolumab showed clinical activity without significant immune-related toxicities. Unfortunately, this patient passed away due to disease progression within 12 months after initiation of checkpoint inhibitors (30). Our patient was found to have an MSI-H, *BRAF* V600E mutated metastatic colorectal cancer and was intolerant to systemic chemotherapy. She had a complete response to pembrolizumab, and her GBS was managed without any flare by IVIG every 4 weeks. To our knowledge, this is the first case describing the long-term feasibility of pembrolizumab in a patient with GBS. The

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long-term follow-up on this case should provide some reassurance in the management of patients with history of controlled GBS with PD-1 inhibitors. Additional studies should be done to investigate the tolerance of various check-point inhibitors in patients with history of autoimmune disorders. As important, these studies should investigate the impact of checkpoint inhibitors vis-à-vis the autoimmune pathophysiology. GBS may be a unique autoimmune disorder that is not subject to an auto-immune flare with PD-1 inhibitors. Additional investigation in this area is warranted.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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