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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Checkpoint Inhibitor–Induced Colitis: A New Type of Inflammatory Bowel Disease?

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ABSTRACT

Checkpoint inhibitors are immune-stimulatory antibodies that have transformed the management and prognosis of individuals with metastatic melanoma and other cancers. Checkpoint inhibitor–induced colitis is an increasingly recognized immune-related adverse event that shares many of the same phenotypical, serological, and histological characteristics of both Crohn's disease and ulcerative colitis, suggesting that checkpoint inhibitor–induced colitis may represent a new inflammatory bowel disease phenotype. We report a 73-year-old man with metastatic melanoma who developed ipilimumab-induced colitis with subsequent transformation to Crohn's colitis-like phenotype after the addition of pembrolizumab.

INTRODUCTION

Checkpoint inhibitors are immune-stimulatory antibodies that function by blocking inhibitory signals to cytotoxic T-lymphocytes to enhance immune function. They have transformed the management and prognosis of individuals with advanced melanoma and other cancers.[1-3] The primary targets for checkpoint inhibitors include the cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4; e.g., ipilimumab) and the programmed cell death-1 receptor or its ligand (e.g., pembrolizumab and atezolizumab).[4] Despite their significant benefits, checkpoint inhibitors have been associated with a wide range of immune-related adverse events (irAEs).[5]

CASE REPORT

A 73-year-old white man with a past medical history of hypertension, aortic aneurysm, atrial fibrillation, coronary artery disease, Gleason 3-4 prostate cancer status post radical prostatectomy, and stage IIc metastatic melanoma presented to an outside hospital with abdominal pain and bloody diarrhea. He had recently started ipilimumab for high-risk metastatic melanoma as part of a clinical trial, but he had only completed 2 sessions prior to presentation. Initial work-up included stool cultures, cytomegalovirus (CMV) immunoperoxidase stains, and *Clostridium difficile* toxin, all of which were negative. A colonoscopy revealed marked diffuse, continuous, superficial inflammation of the colon, consistent with ipilumimab-induced colitis. Pathology was not available. Ipilumimab treatment was discontinued, and the patient was started on 70 mg prednisone daily. His colitis persisted despite steroids, and he required 3 hospital admissions for grade 3–4 colitis. Less than 1 month after he discontinued ipilimumab, he was started on infliximab. During his second dose of infliximab, he developed a severe, blistering rash concerning for Stevens-Johnson syndrome. Infliximab was immediately discontinued.

Over the next 2 years, the patient was treated with multiple steroid tapers but was never able to be weaned below 2 mg prednisone daily. His clinical course was complicated by septic shock secondary to *Escherichia coli* bacteremia, acute renal failure, and hemorrhagic stroke secondary to new brain metastases. As a result of neurologic

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metastases, the patient was started on pembrolizumab. After his fourth dose of pembrolizumab, he developed acute hepatitis with an aspartate aminotransferase peak of 1,533 U/L, an alanine aminotransferase peak of 1,721 U/L, and an alkaline phosphatase of 1,415 U/L. The pembrolizumab was discontinued. A liver biopsy revealed lymphocytic portal inflammation and scattered granulomas consistent with pembrolizumab-induced hepatitis, which responded well to treatment with 40 mg methylprednisolone twice daily. He was transitioned back to oral prednisone but developed fever, diarrhea, abdominal pain, and rectal bleeding, which led to hospitalization after tapering to 20 mg daily.

A colonoscopy revealed severe, deep, and punched out linear ulcers in the distal half of the rectum, as well as moderate erythema and superficial ulcerations with a granular appearance in the proximal rectum and distal sigmoid colon; skip lesions were also present. Pathology was notable for a normal terminal ileum, quiescent chronic colitis of the transverse colon, mildly active chronic colitis in the descending colon, and moderate to severe active chronic colitis in the rectosigmoid colon associated with a peri-rectal abscess. Stool cultures, CMV stains, and *C. difficile* toxin were negative. Based on the phenotypic presentation consistent with a Crohn's colitis-like phenotype, the patient was started on adalimumab and methotrexate with improvement in his symptoms. He was then able to completely taper off steroids with continued combination therapy. During this time, his melanoma went into remission, and he remains in remission 28 months after the discontinuation of pembrolizumab.

DISCUSSION

Checkpoint inhibitors have dramatically changed the management of metastatic melanoma, and they offer promising new treatment strategies for many other malignancies. Anti-CTLA-4 and anti–programmed cell death-1 (anti-PD1) blocking antibodies represent the 2 major targets for checkpoint inhibitors. These immunomodulatory antibodies work synergistically, though through separate pathways, to strengthen the effector T cell response while simultaneously diminishing the stores of regulatory T cells, thus resulting in the robust immune-inflammatory response required for tumor destruction.[6-7]

Polymorphisms of PD-1 and CTLA-4 are associated with many autoimmune disorders.[8] Not surprisingly, the use of PD-1 and CTLA-4 antibodies have resulted in the appearance of a number of irAEs, namely endocrinopathies, pneumonitis, hepatitis, and colitis, which present similarly, if not identically, to their autoimmune counterparts. These irAEs occur in as many as 70% of patients treated with anti-PD1 anitbodies and in as many as 90% of patients treated with anti-CTLA-4 antibodies.[8] The typical time course for iRAEs occurs within 3–6 months of initiation of treatment; however, delayed adverse events can occur up to 1 year after drug initiation.[8] Additionally, the risk of irAEs caused by anti-CTLA-4 appears to be dose-dependent, while cumulative toxicities were not reported in patients taking anti-PD1.[8]

Checkpoint inhibitor–induced colitis (CIC) is an increasingly recognized irAE that ranges from mild diarrhea and abdominal pain (grade 1–2) to severe colitis (grade 3), intestinal perforation (grade 4), and even death (grade 5).[1,9,10] Diarrhea occurs in approximately 31–36% and 13–20% of patients receiving ipilimumab and pembrolizumab, respectively. Among such patients, only 5% of those taking ipilimumab and less than 2% of those taking pembrolizumab experience grade 3–4 colitis, which is characterized by abdominal pain, mucus or blood in the stool, fever, and, in severe cases, emergent surgery or death. While PD1 inhibitor–induced colitis is poorly described in the literature, anti-CTLA-4 colitis typically presents with extensive colitis and superficial ulcerations, mimicking an ulcerative colitis (UC) phenotype.[11] Rarely it can be complicated by anal fissures, intra-abdominal abscesses, or anal fistulas with abscesses, similar to the pattern of complications among patients with Crohn's disease (CD).[11] Furthermore, anti-CTLA-4 colitis has been shown to induce antibodies to both pANCA and anti-OmpC, serologies that are rarely elevated simultaneously and are typically specific to UC and CD, respectively.[11,12] It is becoming apparent that CIC shares many of the same phenotypical, serological, and histological characteristics of both CD and UC; however, patients tend to present with a more severe and accelerated phenotype, and distinction can usually be made via endoscopic biopsy, which often shows acute rather than chronic inflammation.[13] Additionally, in the vast majority of patients, symptoms resolve with the discontinuation of the checkpoint inhibitor and the temporary introduction of steroids or biologic agents.

Our case was unique in that the patient was started on combination therapy with adalimumab and methotrexate. Our patient had an allergic reaction that prohibited the use of infliximab, but the severity of his symptoms were such that, in concordance with American Gastroenterology Association clinical guidelines for inflammatory bowel disease, he warranted combination therapy with a different anti-tumor necrosis factor (anti-TNF) agent as well as an immunomodulator.[14] Taken together, this suggests that CIC may represent a new inflammatory bowel disease phenotype.[12,15]

Our case documents the progression of anti-CTLA-4 colitis to a Crohn's colitis-like phenotype after sequential checkpoint inhibitor therapy. Our patient had a potentially severe allergic reaction to infliximab that prohibited its continued

use, and he remained poorly controlled on chronic steroids for more than 3 years. After additional metastases were identified, he was treated with pembrolizumab and subsequently developed a peri-rectal abscess with skip lesions and endoscopic evidence of both acute and chronic colitis, consistent with a Crohn's colitis-like phenotype. This suggests that CIC may eventually differentiate into either CD or UC. Further studies are needed to better describe this entity and to determine whether CIC should be treated as a distinct phenotype within the inflammatory bowel disease family, as well as to identify biomarkers predictive of the disease and its course, and potentially, to help clarify which patients may benefit from treatment with anti-TNF or other biologics.[16] Additionally, given the increased risk of melanoma and non-melanoma skin cancer associated with anti-TNF agents, further studies are needed to evaluate the risk of melanoma recurrence in patients treated with anti-TNF agents or other biologics for irAE compared to those treated with steroids alone.[17]

DISCLOSURES

Author Contributions: M. Bertha wrote and edited the manuscript. E. Bellaguara, T. Kuzel, and S. Hanauer edited the manuscript. S. Hanauer is the article guarantor.

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