Management of Crohn's Disease and Ulcerative Colitis Flare, Possibly Induced by Nivolumab Therapy: Two Cases and Review of The Literature

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Abstract

Malignancies can occur during the follow-up of patients with inflammatory bowel disease (IBD). Immune checkpoint inhibitors are increasingly used in the treatment of these malignancies due to their prolonged survival effects. Nivolumab, an immune checkpoint inhibitor, is used in cancer treatment. It works by blocking the PD-1 (programmed death) receptor on T cells, thereby enhancing the immune system's ability to fight cancer cells. However, this enhanced immune response can also lead to immune-related adverse events, including gastrointestinal complications. Herein, we present two patients diagnosed with inflammatory bowel disease flare on nivolumab therapy and review the literature.
Keywords: Anti PD-1, Crohn's disease, ulcerative colitis

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, relapsing, and remitting immune-mediated diseases affecting the intestines. CD can impact almost any part of the gastrointestinal system, resulting in a wide range of symptoms, most notably abdominal pain and diarrhea. UC affects the colon, with patients presenting with bloody diarrhea and urgency. The prevalence of these diseases is increasing worldwide. As a result, more patients with these conditions are being diagnosed with cancer.[1] This is especially significant with the introduction of immune checkpoint inhibitors in cancer treatment. Immune checkpoint inhibitors are designed to enhance the immune system's capacity to kill malignant cells and have been extensively studied in many types of cancer.[2] Nivolumab is one of the immune checkpoint inhibitors increasingly used in the treatment of various cancers. It increases the antitumor activity of T cells by inhibiting the PD-1 (programmed death) receptor on CD8+ T cells.[3] This process, which boosts the immune system's response to tumors, may lead to other immune-related side effects that can also affect the gastrointestinal tract.[3,4] We describe two patients who experienced a flare-up of inflammatory bowel disease with nivolumab treatment and present a brief review of the literature.

CASE 1

A 70-year-old male patient was admitted to our clinic with mucous, non-bloody diarrhea 10-15 times a day and tenesmus for one month. He reported a weight loss of 7 kg over the same period.

His vital signs were as follows: temperature 38.5 °C, heart rate 120 beats per minute, respiratory rate 14 per minute, and blood pressure 130/80 mmHg. Physical examination revealed minor tenderness in the right lower quadrant with hyperactive bowel sounds. No organomegaly or rebound tenderness was present.

Nine years ago, he was diagnosed with left-sided ulcerative colitis and subsequently received treatment consisting of mesalamine and azathioprine. Until 2021, he continued taking mesalamine 4 g/day and azathioprine. Azathioprine was discontinued in 2021 due to a diagnosis of small cell lung carcinoma, and since then, he has been receiving only mesalamine 4 g/day.

In March 2021, he underwent a left lung upper lobe lobectomy for small cell lung cancer. He received adjuvant chemotherapy consisting of four cycles of cisplatin and gemcitabine, as well as radiotherapy. He has been receiving nivolumab for 18 months due to non-response to previous treatments.

Stool examination showed no parasites. Stool amoeba and giardia antigen tests were negative. The fecal calprotectin level was 1122 µg/g.

Colonoscopy revealed that the mucosa was granular and vascular structures were erased in all segments of the colon. In the sigmoid colon, there were superficial ulcerations affecting 80-85% of the lumen. The rectal mucosa had a granular appearance, indicating Mayo 3 pancolitis (Figure 1). Endoscopic biopsy revealed active chronic colitis with ulceration, crypt distortion, and basal lymphoplasmacytosis.

Upon admission, the patient was started on mesalamine 800 mg three times a day, mesalamine enema once a day, methylprednisolone 20 mg twice a day intravenously, and metronidazole. After one week, prednisolone was switched to oral form at 32 mg/day with a tapering plan, decreasing by 4 mg every 4 days.

The patient received steroid treatment for a total of 17 days during his hospitalization, resulting in a decrease in stool frequency to 6-7 times per day. Vedolizumab 300 mg induction and maintenance therapy was started after complete clinical remission could not be achieved with steroid treatment. The patient was evaluated as having a nivolumab-associated ulcerative colitis flare, and nivolumab treatment was temporarily discontinued. Remission was achieved after vedolizumab treatment, and nivolumab treatment was restarted during oncologic follow-up.

CASE 2

A 46-year-old male patient with a prior diagnosis of Crohn's disease was hospitalized due to a 1.5-month history of abdominal pain, watery, bloodless diarrhea occurring 5-6 times daily, and a weight loss of 5 kg during the same period.

Physical examination findings indicated moderate pain in the right lower quadrant, with normal bowel sounds.

Three years ago, he was diagnosed with ileal Crohn's disease and was treated with 4 g of mesalamine and 75 mg of azathioprine daily. One year after the Crohn's disease diagnosis, azathioprine was discontinued due to lung adenocarcinoma, and he has been in clinical remission on mesalamine alone.

His medical history also includes ileocecal resection due to intussusception and right upper lobe wedge resection for lung adenocarcinoma. He had been receiving nivolumab therapy once every two weeks for 20 months due to disease progression after conventional adjuvant chemotherapy.

Stool examination showed no parasites, and stool amoeba and giardia antigen tests were negative. The fecal calprotectin level was 208 µg/g.

Colonoscopy revealed aphthous ulcers in the mucosa of the neoterminal ileum and remnant colon, indicating endoscopically active disease (Figure 2). Biopsy samples from the terminal ileum showed ulceration, crypt distortion, edematous, active chronic inflammatory mucosa rich in eosinophils. Colonic biopsies showed ulceration, cryptitis, crypt distortion, and lymphoid hyperplasia, suggesting active ileocolonic Crohn's disease.

The administration of induction doses of ustekinumab resulted in a decrease in the Crohn's Disease Activity Index (CDAI) score from 252 to 84.
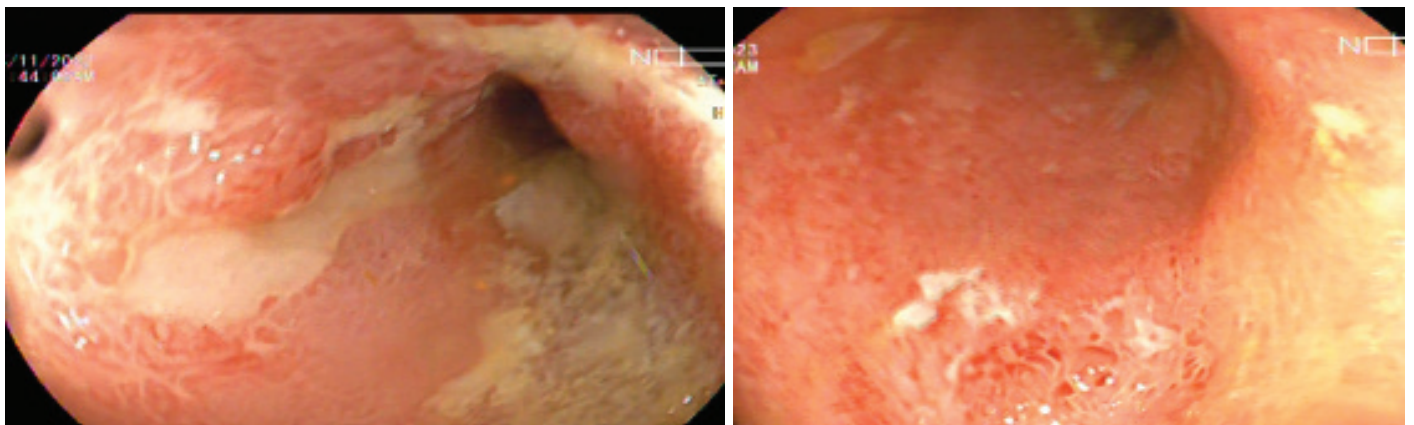

Figure 1. In sigmoid colon, superficial ulcerations surrounding 80-85% of the lumen,rectal mucosa was granular in appearance;indicated that mayo 3,pancolitis.
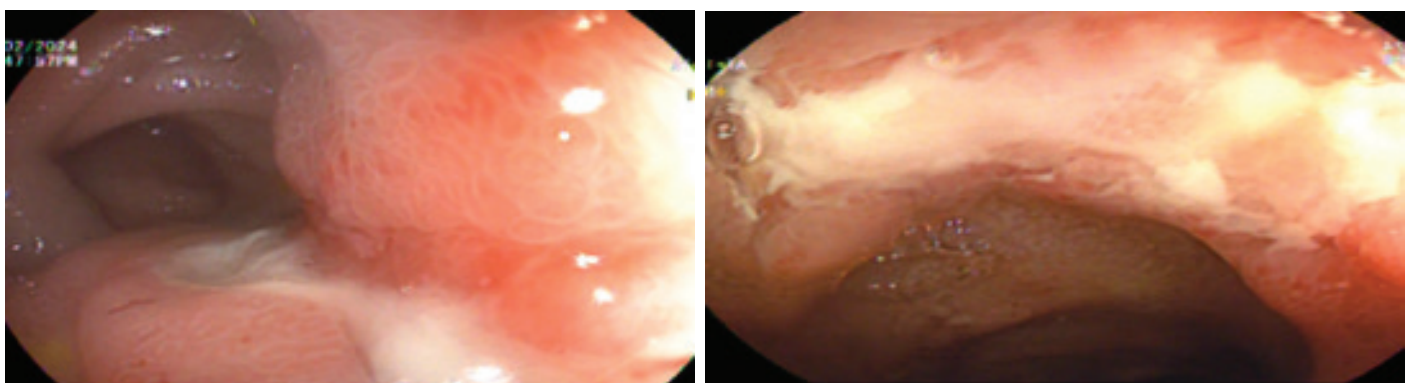

Figure 2. Aphthous ulcers in the mucosa of the neoterminal ileum and remnant colon.

Immune Checkpoint Inhibitor-Related Gastrointestinal Side Effects (irAEs) and Preexisting Inflammatory Bowel Disease

Immune checkpoint inhibitors (ICIs) can be classified as anti-PD-1 (programmed cell death protein) antibodies, anti-PD-L1 (programmed death ligand) antibodies, and anti-CTLA-4 antibodies. Nivolumab, a PD-1 inhibitor, is used to treat various cancers, such as non-small cell and small cell lung cancer, renal cell carcinoma, and head and neck cancer. In tumor tissue, PD-1 interacts with PD-L1/PD-L2 to significantly suppress immune function. PD-1/PD-L1 inhibitors bind to these targets, blocking the PD-1/PD-L1 signaling pathway and significantly enhancing T cell function and tumor immunity. However, immune checkpoint inhibitors can also induce autoimmune diseases.[5]

Colitis linked to immune-related adverse events exhibits similar endoscopic features and treatment responses to ulcerative colitis (UC).[6-8] In addition, many patients with prior inflammatory bowel disease and cancer require immune checkpoint inhibitors. Immune checkpoint inhibitor treatment studies often exclude patients with established autoimmune diseases, and evidence on the efficacy of PD-1 inhibitors on disease progression and the treatment of underlying inflammatory bowel disease activation under these treatments is limited.[9,10]

In a systematic review and meta-analysis carried out by Meserve et al., it was shown that 40% of patients (95% CI, 26%–55%) reported a recurrence of inflammatory bowel disease when using immune checkpoint inhibitors. In patients who experienced a recurrence, 76% needed corticosteroids, and 37% required biologic treatment. Overall, 35% of individuals diagnosed with inflammatory bowel disease ceased using immune checkpoint inhibitors.[11]

Herein, we present two cases of preexisting inflammatory bowel disease that were in long-term remission but developed flares under nivolumab treatment, requiring the use of biological agents for treatment.

In a retrospective study by Raffels et al.[12] at a single reference center involving 13 patients previously diagnosed with inflammatory bowel disease, flares occurred in three patients with UC and one patient with CD during ICI therapy. The median time from the start of ICI therapy to the onset of flares was five months for both UC and CD patients. Only one patient who experienced a flare was on biologic therapy before starting ICI. Our two patients had been on nivolumab therapy for more than 15 months when their flares occurred.

Diagnosis and Treatment

Symptoms can include watery or bloody diarrhea, fever, anal pain, rectal bleeding, weight loss, and nausea/vomiting. It is important to rule out alternative causes, such as progressive disease or infections like Clostridium difficile or other bacterial/viral infections. Grade 1 diarrhea is defined as an increase in bowel movements with diarrhea occurring twice in one day. For treatment, oral rehydration therapy, electrolyte support, and antimotility agents are sufficient.[13]

For persistent grade 2 diarrhea, a colonoscopy with biopsies should be performed to confirm or rule out colitis.[14,15]

Grade 3 or 4 diarrhea is defined as seven or more diarrheal bowel movements in 24 hours. Patients with grade 3 or 4 diarrhea should discontinue ICI medication and be administered parenteral methylprednisolone 1-2 mg/kg, in addition to parenteral hydration and electrolyte support.

With this treatment, symptoms are generally expected to decrease within 1-2 weeks.[16]

After excluding perforation and sepsis, immunosuppressive treatment escalation should be performed in steroid-refractory cases. Case studies have demonstrated the efficacy of infliximab in treating steroid-resistant patients.[17,18] Additionally, mesalamine is useful in ICI-associated colitis due to its anti-inflammatory effects.[16,19]

DISCUSSION

Crohn's disease and ulcerative colitis are chronic diseases characterized by periods of relapse and remission. During follow-up, patients with these conditions may develop malignancies, leading to the increased use of immune checkpoint inhibitors, such as nivolumab, in oncologic treatments. These inhibitors are valued for their ability to prolong survival and even achieve curative effects in some malignancies. However, nivolumab has been shown to induce colitis that resembles inflammatory bowel disease, accompanied by immune-mediated gastrointestinal adverse effects. Additionally, it may worsen pre-existing inflammatory bowel disease. Flare-ups were observed in 37% of patients diagnosed with inflammatory bowel disease who were on immune checkpoint inhibitor therapy.[12]

Our two cases involved patients who were in endoscopic and clinical remission before starting nivolumab treatment and did not receive biological therapy initially. In cases where patients are steroid-refractory, the escalation of immunosuppressive therapy with biologic agents is recommended.

A study by Hong et al.[20] found no statistically significant difference in the number of new cancer cases between the group treated with vedolizumab or ustekinumab and the group that did not receive immunosuppressive treatment. In our cases, we preferred ustekinumab for remission induction in the patient with Crohn's disease and vedolizumab for the patient with ulcerative colitis.

Despite its common use, there is very little information on managing cancer patients with inflammatory bowel disease who are under ICI treatment, with most data restricted to case reports and case series.

Determining whether a patient with inflammatory bowel disease (IBD) under ICI treatment is experiencing a disease flare or has developed drug-related colitis can be challenging based solely on clinical data when they present with symptoms like diarrhea, abdominal pain, and fever. The timing of symptom onset relative to the start of ICI treatment can be informative, as most immune checkpoint inhibitor colitis-related symptoms typically appear within the first few weeks to months after initiating ICI therapy.[21] Pathology from endoscopic biopsies is also helpful. The predominant histopathological features of anti-CTLA-4 and anti-PD-1-induced colitis typically include lamina propria expansion due to a dense lymphoplasmacytic infiltrate, intraepithelial lymphocytosis, crypt apoptosis, neutrophilic cryptitis and crypt abscesses, along with the absence of granulomas.[22,23] Particularly, the presence of crypt apoptosis, which is atypical for inflammatory bowel disease, can be an indicator of ICI-induced colitis in this patient group.[24]

With the two cases we have presented, we highlight the need for prospective studies involving ICI-treated IBD patients. It is crucial to establish guidelines for the diagnosis, treatment, and short- and long-term management of IBD patients under immune checkpoint inhibitor treatment.

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