

Case Series

Severe Diarrhea in the Setting of Immune Checkpoint Inhibitors

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Abstract

Immune checkpoint inhibitors (ICPIs) are novel therapeutic agents targeting a variety of cancers by enhanced T cell activation. Immune-related adverse events (irAEs) commonly occur with ICPI use and can affect multiple organ systems including the gastrointestinal tract. Due to irAEs, the use of ICPIs is limited in autoimmune diseases. We present a case of microscopic colitis diagnosed after the initiation of nivolumab and a case of ipilimumab colitis and *Clostridium difficile* in the setting of Crohn's colitis.

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Introduction

Immune checkpoint inhibitors (ICPIs) are novel immunotherapy agents that are used to treat an increasingly wider array of cancers. ICPIs were initially used in metastatic melanoma and are now used in multiple malignancies [1, 2]. There are two categories of ICPIs that are currently used in clinical practice: anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) antibodies and anti-programmed cell death-protein 1 (anti-PD-1) antibodies. Anti-CTLA-4

antibodies include ipilimumab (Yervoy). Anti-PD-1 antibodies include nivolumab (Opdivo) and pembrolizumab (Keytruda). ICPIs increase T cell activation which can then lead to immune related adverse events, including those of the gastrointestinal tract [2]. We present 2 cases of severe diarrhea in the setting of ICPIs and autoimmune disease.

Case Reports

Case 1

A 74-year-old male with a history of metastatic pulmonary squamous cell carcinoma was admitted with 2 weeks of severe diarrhea. He had been started on second-line nivolumab 9 months prior to admission. He was only able to complete 10 cycles as he developed diarrhea that initially responded to steroids. On admission, he reported 10–15 episodes of large-volume watery stools per day without mucus, blood or significant abdominal pain. Stool studies for bacteria, viruses, and parasites were negative, and a fecal lactoferrin was positive. Computed tomography (CT) of the abdomen/pelvis with contrast showed mild mural thickening of the inferior cecum and terminal ileum. A colonoscopy was notable for a few 3- to 5-mm ulcerations scattered through entire colon and a 5-mm flat polypoid lesion in the transverse colon. Random biopsies including those of the polyp and ulcers were obtained. Pathology demonstrated preserved crypt architecture, marked propria lymphoplasmacytic inflammation, diffuse intraepithelial lymphocytosis, and marked increase in subepithelial collagen deposition (Fig. 1a). These features were consistent with collagenous colitis. The patient required two budesonide tapers starting at 9 mg daily for his diarrhea, and nivolumab was not restarted. Although the patient was started on docetaxel, he unfortunately had progression of his disease and ultimately died in hospice.

Case 2

A 68-year-old female with a history of stage III melanoma presented to her oncologist with diarrhea of 1 month's duration. An abdomen/pelvis CT revealed mucosal thickening of the terminal ileum. A colonoscopy noted mild inflammation from the transverse colon to cecum, sigmoid colon to descending colon, and moderate inflammation in the rectum. Biopsies of her terminal ileum and colon were consistent with Crohn's disease. She was referred to Gastroenterology and was started on mesalamine 2.4 g twice daily. She was then initiated on first-line pembrolizumab. A month after starting pembrolizumab, the patient was hospitalized for acute on chronic diarrhea. Her CT abdomen/pelvis and flexible sigmoidoscopy demonstrated nonspecific active chronic colitis. She improved with intravenous methylprednisolone 20 mg three times daily, transitioned to prednisone 40 mg daily, and eventually to a budesonide taper. Six months later, the patient was started on ipilimumab and nivolumab due to progression of her melanoma. The patient developed bloody diarrhea 3 days after initiating the new combination therapy. Repeat flexible sigmoidoscopy demonstrated severe inflammation from the rectum to the splenic flexure concerning for worsened colitis. Her pathology was notable for marked inflammation, cryptitis, and crypt cell apoptosis which was consistent with ipilimumab colitis (Fig. 1b). Her diarrhea improved with two doses of infliximab 200 mg and intravenous methylprednisolone 20 mg three times daily transitioned to a prednisone taper. One month later, she received another dose of the combination immunotherapy and experienced similar symptoms of diarrhea the following day. She also tested positive for *Clostridium difficile*. She was treated with oral vancomycin 250 mg every 6 h, intravenous

hydrocortisone 20 mg three times daily, and another slow prednisone taper. Unfortunately, she continued to decline and ultimately died in hospice.

Discussion

ICPIs work primarily by inhibiting T-cell inhibitory signals and lead to increased T cell activation which then leads to increased anti-tumor T-cell response [2]. Due to increased T cell activation, autoimmune-like adverse events can occur. These autoimmune-like adverse events have been labelled immune-related adverse events (irAEs) [2]. irAEs most commonly affect the skin and gastrointestinal organ systems. Gastrointestinal irAEs include diarrhea, colitis, hepatotoxicity, pancreatitis, esophagitis, and inflammatory enteric neuropathy with constipation [3, 4]. Life-threatening consequences such as perforation have also been described [2].

Gastroenterologists are typically consulted when patients develop significant diarrhea. CT abdomen/pelvis can demonstrate evidence of colitis with bowel wall thickening and mesenteric engorgement [2]. After ruling out infectious etiologies of diarrhea such as *C. difficile*, colonoscopy is typically pursued. On colonoscopy, the findings are nonspecific and can range from normal mucosa to ulceration of the colon and ileum [5, 6]. Typically, lesions are predominantly in the descending colon [2, 3]. On biopsy, neutrophilic and lymphocytic infiltrates as well as cryptitis and crypt abscesses have been described [5, 7–9].

After diagnosing immune-related enterocolitis, patients should be started on high-dose steroid therapy. If the patient remains refractory to high-dose steroids, infliximab can be considered. If the patient continues to have significant diarrhea refractory to steroids and infliximab, tacrolimus or mycophenolate mofetil are also utilized. In severe cases, colectomy may be required [2].

Due to the autoimmune-like process of ICPIs, aggravation of known inflammatory conditions or discovery of occult inflammatory conditions has also been described. There have been 2 case reports of microscopic colitis diagnosed after the initiation of pembrolizumab and ipilimumab [10, 11]. In addition, there have been 3 case reports of ICPI use in Crohn's disease. In one patient, there was a possible flare of Crohn's disease after a patient was started on pembrolizumab for metastatic colon cancer [12]. In another patient, ipilimumab-induced colitis was diagnosed in a patient with Crohn's disease on ipilimumab for metastatic melanoma [13]. Finally, in a separate patient, an intra-abdominal abscess concerning for Crohn's disease flare was diagnosed in a patient with Crohn's disease on pembrolizumab [14].

We describe the first case of microscopic colitis after the initiation of nivolumab. In addition, we describe a case of ipilimumab colitis and *C. difficile* in the setting of Crohn's disease. Our cases highlight the importance of investigating a broad differential when managing patients with diarrhea on ICPIs.

Statement of Ethics

Both patients described were deceased by the time of abstract submission. Consent was obtained from the first patient's wife. The emergency contact for the second patient was unable to be reached.

Disclosure Statement

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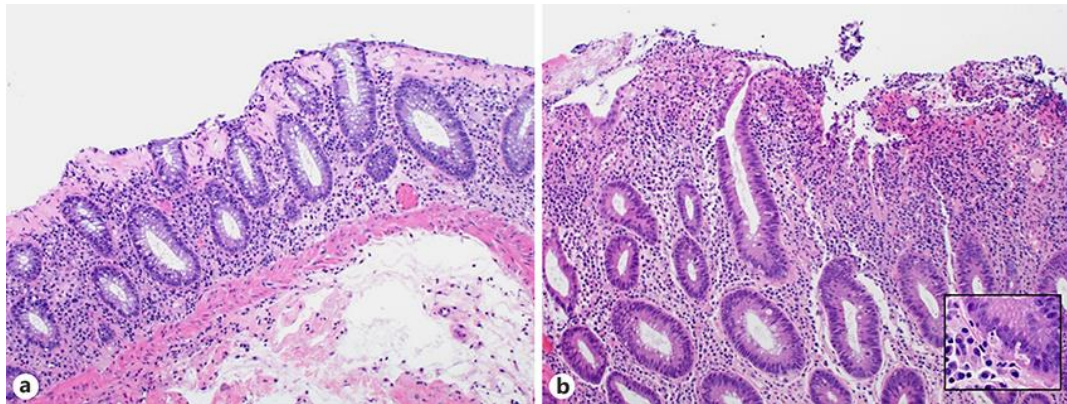


Fig. 1. **a** Colonic biopsy demonstrating marked thickening of subepithelial collagen layer, consistent with collagenous colitis. **b** Colonic biopsy demonstrating marked inflammation, cryptitis, and crypt cell apoptosis. **Inset** demonstrates increase in crypt cell apoptosis. Hematoxylin and eosin-stained biopsy specimens at $\times 100$ magnification, **inset** at $\times 400$ magnification.