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CASE REPORT | INFLAMMATORY BOWEL DISEASE

De Novo Crohn's Disease 3 Years Following Immune Checkpoint Inhibitor Therapy

Matthew G. Bell, MD[1], Manuel Bonfim Braga Neto, MD, PhD[2], and Sunanda V. Kane, MD[3]

[1]*Department of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, AZ*
[2]*Department of Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, Cleveland, OH*
[3]*Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN*

ABSTRACT

Presented is a 76-year-old man with metastatic melanoma that was successfully treated with pembrolizumab, an immune checkpoint inhibitor (ICI). He underwent 20 months of ICI treatment without dose limiting side effects. Nearly 18 months after ICI discontinuation, the patient developed intermittent epigastric pain and diarrhea. Owing to mild symptoms, he was not immediately evaluated. Three years after ICI cessation, he was diagnosed with stricturing, jejunal Crohn's disease. He was treated with vedolizumab and displayed clinical and radiographic response to treatment. This case serves as an example of potential gastrointestinal-related, long-term autoimmune implications of ICI therapy, even in patients without acute side effects.

KEYWORDS: immune checkpoint inhibitor; pembrolizumab; Crohn's disease

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have become a mainstay in the treatment of multiple malignancies. Gastrointestinal side effects have been well described including an inflammatory bowel disease (IBD)-like enteritis/colitis that requires steroid or biologic-based treatment. However, most of these described side effects occur during or soon after the discontinuation of treatment. This report describes a case of Crohn's disease (CD) arising 3 years after the completion of pembrolizumab therapy.

CASE REPORT

The patient is a 76-year-old White man with medical history of hypertension and melanoma. He was a nonsmoker, without personal or family history of autoimmune disease. At the age of 71 years, the patient developed melanoma on the left chest with metastases to the axilla and was treated with surgical resection. At index resection, he was found to have stage IIIC disease and was subsequently treated with adjuvant radiation without systemic therapy. Less than 1 year after surgical resection and radiation, he developed recurrent disease. The decision was made to pursue systemic therapy; pembrolizumab was initiated. After 20 months of treatment, positron emission tomography scan displayed complete response and pembrolizumab was discontinued. During his course of ICI treatment, he never experienced dose-limiting adverse effects.

Eighteen months after completing pembrolizumab, he developed intermittent epigastric pain associated with mild diarrhea. A computed tomography scan with IV contrast displayed no intra-abdominal abnormalities. After a year of intermittent symptoms, upper endoscopy demonstrated diffuse erythema of the stomach without ulceration and cobblestone throughout the duodenum. Biopsies demonstrated superficial gastritis, no evidence of *H. Pylori*, and chronic duodenitis with normal villous architecture. A colonoscopy without terminal ileum examination was unremarkable. The patient's gastritis and duodenitis were attributed to nonsteroidal anti-inflammatory drug (NSAID) use, and he subsequently discontinued use. Despite NSAID discontinuation, he continued to have abdominal pain, diarrhea, and fifteen-pound weight loss. Nearly 3 years after pembrolizumab discontinuation, he underwent computed tomography enterography that demonstrated multiple, small bowel strictures with associated mucosal hyperenhancement concerning for CD or NSAID enteropathy (Figure 3). Laboratory assessment relieved C-reactive protein of 34.2,

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Correspondence: Matthew G. Bell, MD (bell.matthew@mayo.edu).

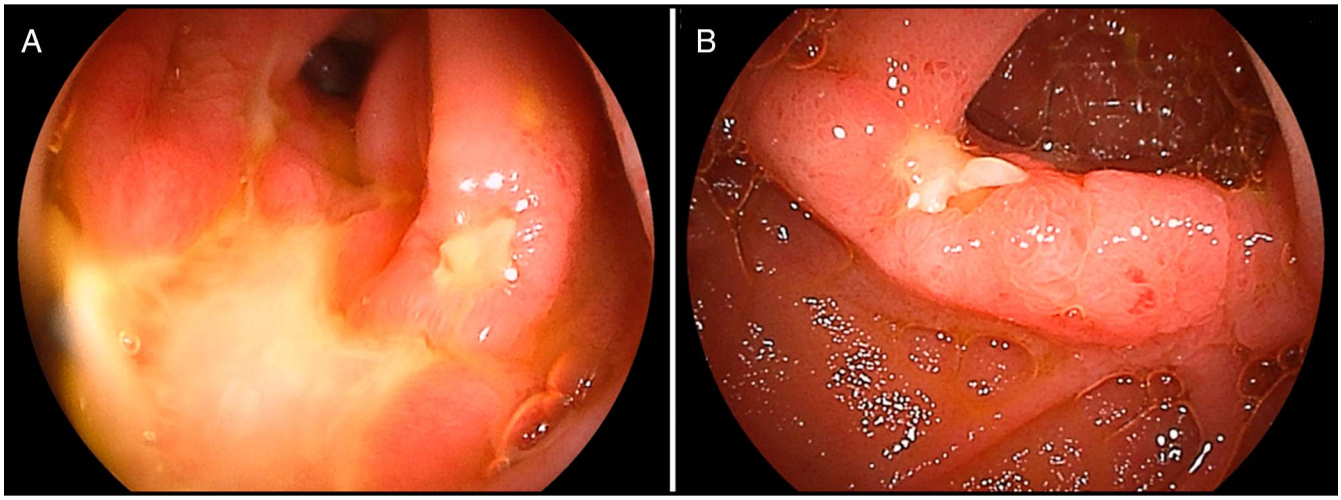

Figure 1. Images from double-balloon-assisted upper endoscopy displaying both stricturing (Panel A) and multiple ulcerations (Panel A and B) of the jejunum.

anemia with a hemoglobin of 11.6 (mean corpuscular volume 88.2), and no evidence of vitamin D or B12 deficiencies indicative of malabsorption.

Traditional upper endoscopy could not reach the lesion of interest, and the necessity of tissue acquisition limited utilization of capsule endoscopy. Anterograde double-balloon enteroscopy was used and showed multiple ulcers in the jejunum with luminal strictures (Figure 1). Biopsies displayed active, chronic enteritis and ulceration without granulomas (Figure 2), no dysplasia, and cytomegalovirus immunostaining was negative. Tuberculosis was excluded with a negative QuantiFERON. He was diagnosed with stricturing, jejunal CD. Without severe symptoms, a steroid-sparing agent was preferred. Vedolizumab was initiated with radiographic (Figure 3) and clinical response at 3 and 6 months, respectively.

DISCUSSION

We describe a case of 76-year-old man who presented with pain and diarrhea and was found to have jejunal CD 3 years after the completion of pembrolizumab treatment. Our hypothesis is that exposure to ICIs may have triggered de novo IBD, although causality cannot be ascertained.

ICIs are becoming common treatment for a variety of neoplasms.[1] This class includes the inhibitors of CTLA-4, PD-1, and PD-L1. Each of these has the same basic mechanism of action: inhibition of proteins that block the activation of the immune system and promoting immune destruction of cancer.[2,3] However, this broad immune disinhibition comes with side effects related to induced autoimmunity. The common gastrointestinal (GI) side effects of anti-PD-1 treatment are diarrhea (17%), hepatitis (1%–6%), colitis (1.2%–2.8%), and much less commonly enteritis and gastritis.[4,5] The median onset of enterocolitis during anti-PD-1 monotherapy is roughly 6–18 weeks with pembrolizumab displaying a longer median time to symptom onset.[4] While most cases of ICI-related diarrhea/colitis present in the first months of treatment, instances of delayed symptom onset have been described; however, these cases still began with active ICI therapy.[6,7] Anti-PD-1 induced colitis is also associated with histologic evidence

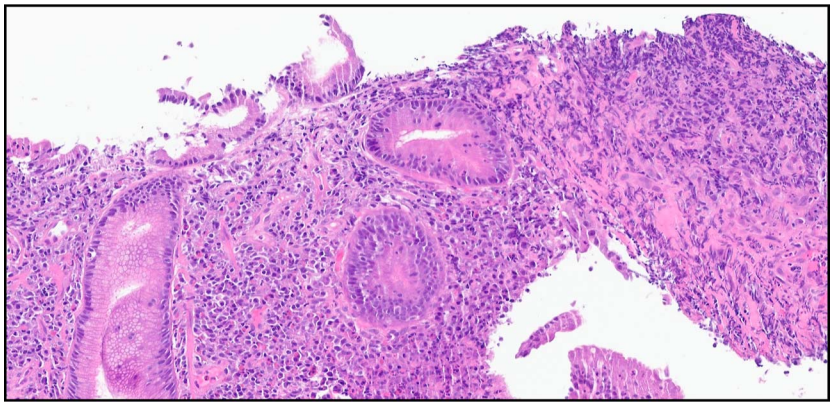

Figure 2. Biopsy of a proximal jejunal ulcer (conventional hematoxylin and eosin stain) displaying mild-to-moderate, active, chronic enteritis with ulceration consistent with inflammatory bowel disease.

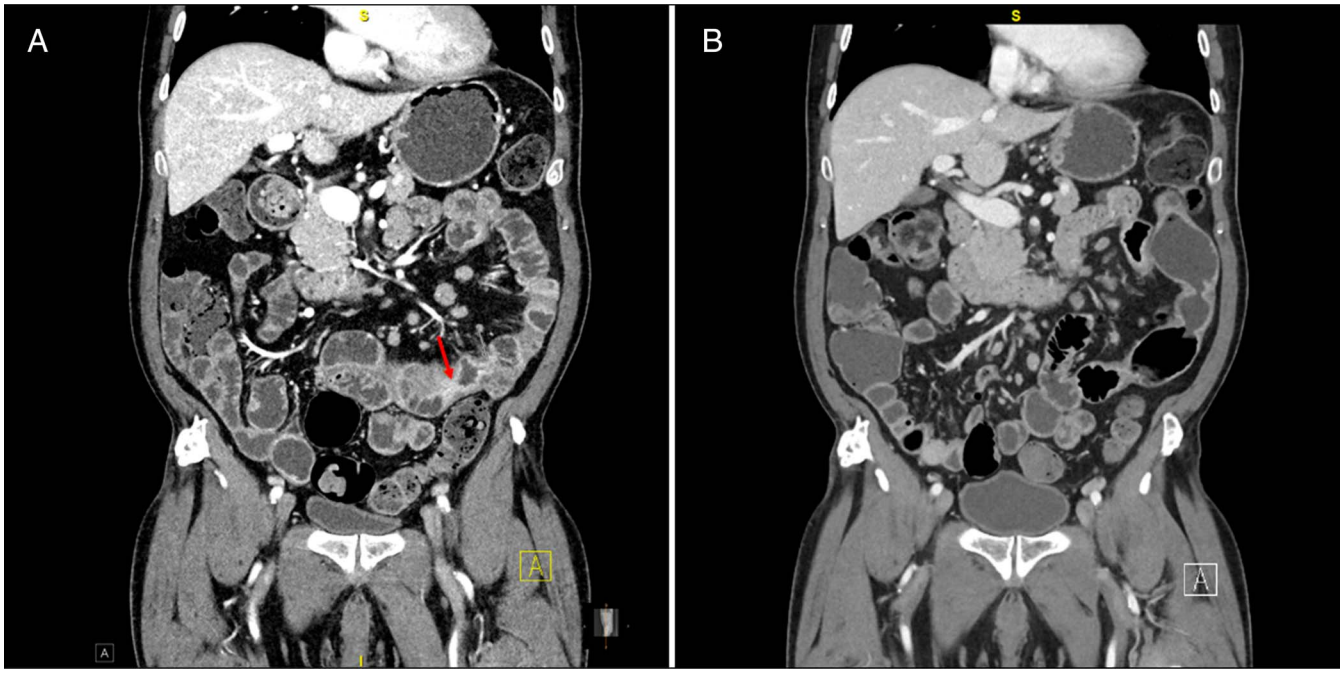

Figure 3. Panel (A): CT enterography, performed before treatment initiation, displaying evidence of jejunal stricture (red arrow) with associated wall thickening, mucosal hyperenhancement, and fat stranding consistent with inflammation. Panel (B): Abdominal CT with IV contrast performed 3 months after the initiation of vedolizumab displaying overall improvement of the areas of jejunal wall thickening and mucosal hyperenhancement with persistent luminal strictures consistent with recent IBD diagnosis and treatment. CT, computed tomography.

of acute inflammation with chronic characteristics only arising with recurrent episodes.[7] Our patient developed symptoms over a year after pembrolizumab discontinuation, and initial biopsies displayed chronic inflammation making typical ICI enteritis extremely unlikely.

Cases of de novo IBD following ICI therapy have been reported and are believed to arise due the uncoupling of the immune checkpoints as well as distortion of the gut microbiome.[8] To our knowledge, there are only 2 other reports of similar, delayed, ICI-induced IBD.[9,10] However, it is important to note that both reported cases also experienced acute colitis/enteritis that required ICI termination. Akel et al reported a 71-year-old man who underwent ipilimumab treatment of melanoma. Ipilimumab treatment was halted after the development of colitis that abated with steroid treatment, but 3 years later, the patient developed IBD-like chronic colitis.[9] The second case is that of 73-year-old man with melanoma who experienced treatment-limiting colitis during ipilimumab and pembrolizumab treatments. This patient also developed histologic evidence of IBD-like chronic colitis 2 years after ICI discontinuation.[10] Thus, ours is the first reported case of ICI-induced IBD occurring outside the framework of an acute treatment-induced colitis/enteritis.

In terms of our case, both endoscopic and histologic evaluations supported the diagnosis of CD. Histologically, the finding of chronic small bowel inflammation is consistent with other reports of ICI-induced IBD-like enteritis and the delayed-onset cases.[9–11] We considered the possibility that this could represent smoldering ICI enteritis. However, this would be unlikely to arise years after ICI discontinuation. ICI enteritis typically arises soon after introduction of the immunotherapy (median 18 weeks), and our patient was asymptomatic during his 20 month course.[4,12]

This case does not represent a classic presentation for IBD of the elderly. The patient did not have any common risk factors of CD including personal/family history of autoimmunity, tobacco use, or GI comorbidities.[13] In addition, our patient was older than the expected age for IBD onset, as less than 15% of IBD cases are diagnosed after the age of 60 years and even a smaller portion after the age of 70 years.[14,15] This case serves as an example of long-term autoimmune implications of ICI therapy, even in patients who do not develop acute side effects. Those who prescribe or monitor ICI treatment should have a lower threshold for GI evaluation in patients with unexplained or smoldering symptoms.

DISCLOSURES

Author contributions: All authors shared in interpretation, drafting, revision, and approval. S. Kane is the article guarantor.

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Informed consent was obtained for this case report.

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