

Nivolumab-Induced Concomitant Severe Upper and Lower Gastrointestinal Immune-Related Adverse Effects

Albert Alhatem, MD^{1,2}, Krishan Patel, BA², Brenda Eriksen, MD³, Sarosh Bukhari, DO⁴, and Chen Liu, MD, PhD^{1,2,5}

¹Department of Pathology and Laboratory Medicine, Rutgers New Jersey Medical School, Newark, NJ

²Rutgers New Jersey Medical School, Newark, NJ

³Department of Pathology and Laboratory Medicine, Community Healthcare System, Munster, IN

⁴Division of Gastroenterology and Hepatology, Department of Medicine, Community Healthcare System, Munster, IN

⁵Robert Wood Johnson Medical School, New Brunswick, NJ

ABSTRACT

Immunotherapy agents such as cytotoxic T-lymphocyte antigen-4 and programmed cell death protein-1 inhibitors show efficacy in cancer therapy but are associated with immune-related adverse events. It commonly presents as diarrhea but can cause colitis, mimicking inflammatory bowel disease. Our patient is a 78-year-old man on nivolumab therapy for metastatic lung cancer who developed new onset nausea and diarrhea. Endoscopy revealed inflammation of the upper and lower gastrointestinal tract, and histology revealed transmural colon and gastric inflammation. We present a fascinating case of severe concomitant aphthous ulcers, esophagitis, gastritis, and enterocolitis.

INTRODUCTION

Immunotherapy has revolutionized therapy for metastatic cancer. Immune checkpoint inhibitors (ICIs) such as programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors are the most commonly used treatments. T cells have a PD-1 and checkpoint protein, which function as an “on-off switch” by binding PD-1 to prevent them from attacking the body’s own cells; CTLA-4 functions similarly in regulating the T cell function. Certain tumor cells, however, upregulate PD-1, thereby allowing them to evade immune targeting and proliferate freely.

Increased use of ICIs has also increased the incidence of immune-related adverse events (IRAEs). These manifest variably as organ dysfunction of the skin, gastrointestinal (GI) tract, lungs, liver, or endocrine organs.¹ Enterocolitis is common and manifests as abdominal pain, nausea, and diarrhea. In certain cases, it may mimic inflammatory bowel disease (IBD). Symptoms can be mild or can cause significant morbidity and mortality in patients with perforation or sepsis.² We discuss a rare case of an IRAE simultaneously involving the upper and lower GI tract during therapy with the PD-1 inhibitor nivolumab for metastatic lung adenocarcinoma.

CASE REPORT

A 78-year-old man diagnosed with metastatic adenocarcinoma of the lung in 2015 was treated with nivolumab immunotherapy and hemicolectomy. In 2016, he developed increased bloating, diarrhea, and loss of appetite. An initial workup was negative for infectious etiology, and abdominal x-ray did not demonstrate obstruction. Esophagogastroduodenoscopy revealed low-grade distal esophagitis resembling Barrett’s esophagus and antral gastritis (Figure 1). Biopsy of the esophagus revealed microabscess formation, intestinal metaplasia, and keratin pearl formation, whereas gastric lesions showed marked transmural inflammation, cryptitis, and dysplasia (Figure 2). Colonoscopy revealed ulcers of the terminal ileum and hemorrhage with biopsy revealing transmural acute and chronic

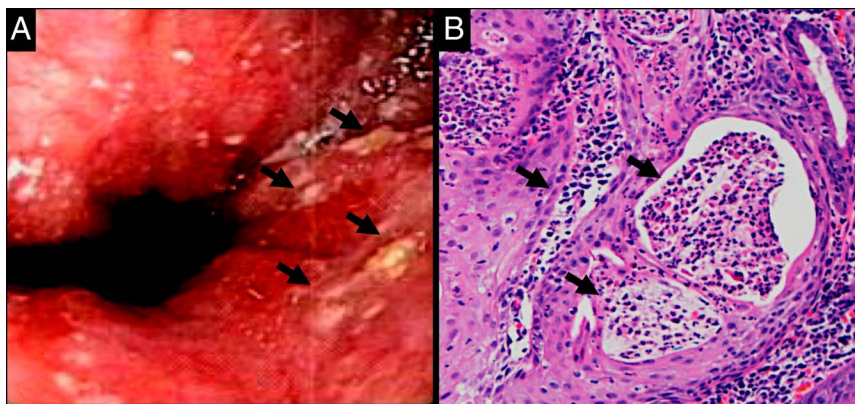


Figure 1. Esophagus after 1 year of nivolumab: (A) endoscopic image showing Barrett's esophagus (arrows) and (B) biopsy with hematoxylin and eosin staining showing microabscess formation (arrows).

inflammation, skip lesions, and acute cryptitis (Figure 3). Although these findings mimic IBD, this patient had no evidence of bowel inflammation on colonoscopy in 2014 and no known history of IBD, gastroesophageal reflux disease, or gastritis. A presumptive diagnosis of IRAE secondary to nivolumab was made, and symptoms resolved with the withdrawal of nivolumab for 6 weeks and prednisone therapy. Nivolumab therapy was subsequently restarted without any recurrence of IRAE, and repeat colonoscopy did not reveal any abnormalities.

DISCUSSION

IRAEs occur with ICI treatment because of systemic activation of the immune system and resulting organ damage. They represent an important class of adverse events with cancer therapy which are associated with poorer overall survival.^{1,2} The most common presentations of PD-1 inhibitors include rash, diarrhea, hypothyroidism, and pneumonitis, and these occur more often and severely with higher doses and combination anti-PD-1/CTLA-4 therapy.³ Enterocolitis ranges in severity from simple diarrhea to bowel necrosis and perforation.^{3,4} IRAEs of the upper GI tract similarly range in severity from nausea and vomiting to

esophagitis, gastritis, and oral mucositis.^{3,5,6} Although less common, the upper GI involvement may be more specific to PD-1 inhibitors.⁸⁻¹⁰

PD-1 inhibitors tend to have a lower frequency of overall and GI IRAEs than CTLA-4 inhibitors.^{2-4,7} It is hypothesized that CTLA-4 inhibitors upregulate early CD4+ T-cell activation in the lymph nodes, causing generalized immune activation. On the other hand, PLD-1 inhibitors target late T-cell proliferation and thus are able to generate a more localized immune response in the tumor microenvironment.⁸

Nivolumab-associated colitis (NAC) displays histologic and endoscopic features of ulcerative colitis, including contiguous inflammation, ulceration, and cryptitis with crypt abscesses.^{9,10} This case displayed mixed features of both Crohn disease (terminal ileum ulcers, transmural inflammation, and "skip lesions") and UC (cryptitis and crypt abscess). Previous case reports of IR-gastritis reported ulceration and hemorrhage.^{4,7,11} Histologically, both IBD and NAC exhibit neutrophilic and lymphocytic infiltration of the lamina propria, mucosal erosion, dysplasia, and apoptosis.^{4,10-12} Of note, 2 patients with UC in remission and NAC, histologic examination of the colon showed a pattern of

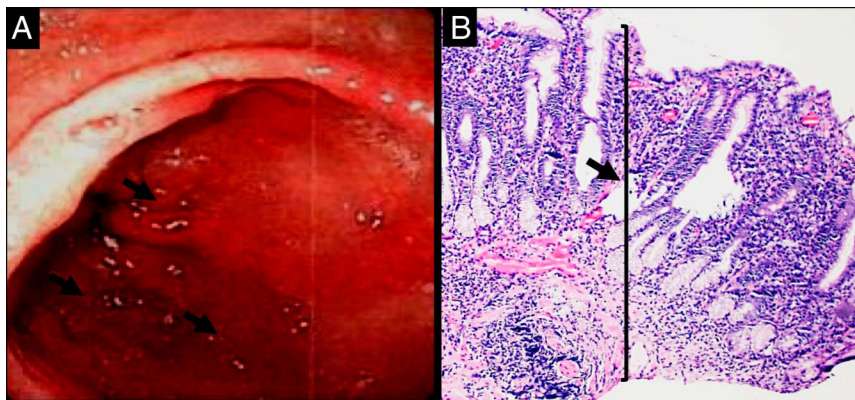


Figure 2. Abdomen after 1 year of nivolumab: (A) endoscopic image showing antral gastritis (arrow) and (B) biopsy with hematoxylin and eosin staining showing transmural acute and chronic inflammation (arrow).

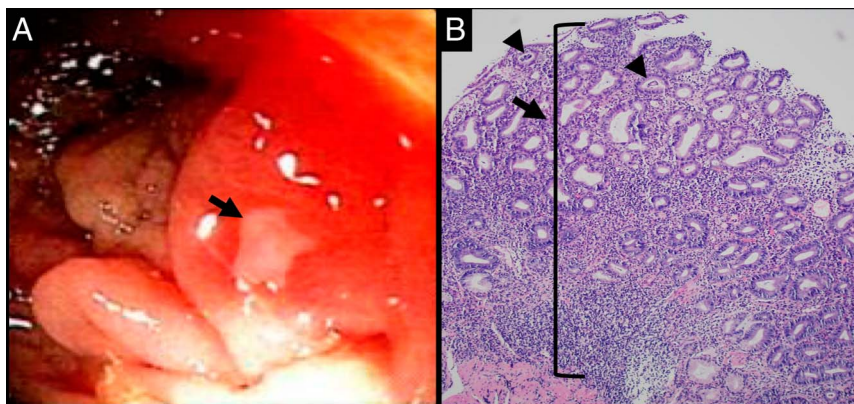


Figure 3. Colon after 1 year of nivolumab: (A) endoscopic image showing ulcers (arrow) and (B) biopsy with hematoxylin and eosin staining transmurals acute and chronic inflammation (arrow) with acute cryptitis (arrowheads).

acute colitis distinct from their previous IBD flare-ups, suggesting unique pathophysiology of NAC from IBD.

Current risk factors for NAC include cancer type (melanoma vs lung and renal cell carcinoma), increasing dose and combination ICI therapy, and baseline gut biome profiles.¹³ It appears that previous IBD increases the risk of colitis, but these data are scarce.^{3,9}

The relationship between immunotherapy and the gut microbiome is also being explored for treatment and susceptibility to IRAE. Impairment of baseline anergy to enteric flora (from PD-1/CTLA-4 blockade), inflammation, and eosinophilia is observed with ICI therapy.^{3,4,9} A study of ipilimumab therapy for melanoma demonstrated lower titers of classic IBD antibodies such as p-ANCA in patients with IRAE colitis.¹⁴ Fecal calprotectin and serum antimicrobial titers similarly were not elevated in a pattern consistent with classic IBD. Thus, although IBD and IRAE both involve dysbiosis, their mechanisms appear to be unique.

Collins et al studied 20 patients who were confirmed as GI IRAE related to anti-PD-1, which occurred 4.2 months after the initiation of anti-PD-1.¹⁵ Four patients had inflammation of the upper GI tract (nivolumab [n = 2] and pembrolizumab [n = 2]). Upper GI endoscopy showed necrotic gastritis with poor gastric distensibility in 2 of 4 patients, gastric erythema and normal endoscopy in 1 of 4 each. Colonoscopy was either normal (3/4) or showed patchy colonic erythema (1/4). Ileum was normal in all 4 patients. Gastric biopsies of the 2 patients with ulcerative and necrotic gastritis showed large necrosis of the epithelium and an inflammatory infiltrate with neutrophils and lymphocytes. Duodenal biopsies were taken in 3 of 4 patients with upper GI symptoms and showed partial villus blunting, intraepithelial lymphocytosis (>30/100 enterocytes; n = 2) and lymphocytic and plasma cell infiltration of the lamina propria (n = 2). The 3 patients with normal colonoscopies had normal colonic biopsies; the patient with colonic erythema had a lamina propria infiltration with lymphocytes and neutrophils.

In addition, the study mentioned that in patients with a predominating colonic inflammation, gastric and duodenal inflammation was identified, particularly intraepithelial CD8 lymphocytosis.¹⁵ Anti-PD1 seems to induce widespread GI inflammation, but the clinical presentation might differ between patients according to the organ predominantly affected, colon or upper GI tract. The clinical presentation of GI IRAE may result from the nature of the local antigen and its corresponding TCR because it has been described in a nivolumab-related myocarditis case.¹⁶

Our case showed a severe form of concomitant Barrett's esophagus, transmural gastritis, and transmural enterocolitis resolved by withholding nivolumab and infusing corticosteroid. Although a previous study described the possibility of having widespread GI inflammation with differences based on the predominantly involved organ, the presentation, in this case, is unique because of the severity and the concomitant Barrett's esophagitis, transmural gastritis, and transmural and skipped enterocolitis lesions. This side effect could be explained as a mimicker of Crohn-like features, but there are data, suggesting that the mechanism is unique to immunotherapy and further studies are required to characterize it.

Treatment of IRAE should be started promptly after ruling out other diagnosis such as infection and performing endoscopy. Gastritis requires additional evaluation for *Helicobacter pylori* and high-dose proton pump inhibitor therapy. Initial therapy primarily consists of intravenous corticosteroids and hydration. More severe cases require immunosuppressive agents such as mesalamine or infliximab or cessation of immunotherapy.^{1-3,9,11} A high index of suspicion for IRAEs should be maintained in any patient who has received immunotherapy because of the delayed onset of IRAEs. This patient was successfully treated with temporary cessation of therapy and corticosteroids. In general, GI IRAEs are reversible and responsive to therapy.

Future research aims to further uncover the pathophysiology of potential biomarkers for IRAE which may be used to modify

treatment and develop personalized drug regimens. Better histologic characterization specific to IRAEs is warranted to improve diagnostic accuracy, especially for cases where the temporal relationship to cancer therapy is less apparent.

DISCLOSURES

Author contributions: A. Alhatem and K. Patel wrote the manuscript. A. Alhatem and B. Eriksen conceptualized the manuscript, B. Eriksen and C. Liu revised the manuscript, and S. Bukhari provided the resources. A. Alhatem is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received May 28, 2019; Accepted September 11, 2019

REFERENCES

1. Ksienski D, Wai ES, Croteau N, et al. Efficacy of nivolumab and pembrolizumab in patients with advanced non-small-cell lung cancer needing treatment interruption because of adverse events: A retrospective multicenter analysis. *Clin Lung Cancer*. 2019;20(1):e97–106.
2. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the society for immunotherapy of cancer (SITC) toxicity management working group. *J Immunother Cancer*. 2017;5(1):95.
3. Soularue E, Lepage P, Colombel JF, et al. Enterocolitis due to immune checkpoint inhibitors: A systematic review. *Gut*. 2018;67(11):2056–67.
4. Gonzalez RS, Salaria SN, Bohannon CD, Huber AR, Feely MM, Shi C. PD-1 inhibitor gastroenterocolitis: Case series and appraisal of “immunomodulatory gastroenterocolitis”. *Histopathology*. 2017;70(4):558–67.
5. Acero Brand FZ, Suter N, Adam JP, et al. Severe immune mucositis and esophagitis in metastatic squamous carcinoma of the larynx associated with pembrolizumab. *J Immunother Cancer*. 2018;6(1):22.
6. Horisberger A, La Rosa S, Zurcher JP, et al. A severe case of refractory esophageal stenosis induced by nivolumab and responding to tocilizumab therapy. *J Immunother Cancer*. 2018;6(1):156.
7. Iranzo I, Huguet JM, Suárez P, Ferrer-Barceló L, Iranzo V, Sempere J. Endoscopic evaluation of immunotherapy-induced gastrointestinal toxicity. *World J Gastrointest Endosc*. 2018;10(12):392–9.
8. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: A systematic review. *Ann Oncol*. 2017;28(10):2377–85.
9. Yamauchi R, Araki T, Mitsuyama K, et al. The characteristics of nivolumab-induced colitis: An evaluation of three cases and a literature review. *BMC Gastroenterol*. 2018;18(1):135.
10. Chen JH, Pezhouh MK, Lauwers GY, Masia R. Histopathologic features of colitis due to immunotherapy with anti-PD-1 antibodies. *Am J Surg Pathol*. 2017;41(5):643–54.
11. Kobayashi M, Yamaguchi O, Nagata K, Nonaka K, Ryoza S. Acute hemorrhagic gastritis after nivolumab treatment. *Gastrointest Endosc*. 2017;86(5):915–6.
12. Nishimura Y, Yasuda M, Ocho K, et al. Severe gastritis after administration of nivolumab and ipilimumab. *Case Rep Oncol*. 2018;11(2):549–56.
13. Chaput N, Lepage P, Coutzac C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol*. 2017;28(6):1368–79.
14. Berman D, Parker SM, Siegel J, et al. Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma. *Cancer Immun*. 2010;10:11.
15. Collins M, Michot JM, Danlos FX, et al. Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies. *Ann Oncol*. 2017;28(11):2860–5.
16. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375(18):1749–55.

Copyright: © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of The American College of Gastroenterology. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.