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IMAGE | STOMACH

Combination Checkpoint Inhibitor-Induced Hemorrhagic Gastritis

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CASE REPORT

A 37-year-old woman with Stage IV metastatic melanoma to the lung, liver, bone, and brain previously on chemotherapy, followed by single-agent nivolumab (programmed cell death protein 1 inhibitor) with disease progression, followed by combination ipilimumab (cytotoxic T-lymphocyte-associated protein 4 inhibitor) and nivolumab presented to the clinic with nausea, vomiting, and inability to tolerate oral intake. She had received a total of 4 doses of nivolumab monotherapy (along with systemic chemotherapy) every 4 weeks. She was then switched to combination therapy of nivolumab and ipilimumab every 4 weeks and received a total of 2 doses of combination therapy before symptom onset (approximately 8 weeks after initiating combination therapy). She endorsed mild epigastric discomfort; however, she denied dysphagia, odynophagia, reflux disease, or hematochezia. Trials of ondasetron, lorazepam, and prochlorperazine produced mild improvement in symptoms. She was not on a proton pump inhibitor and had never previously had an upper endoscopy or colonoscopy. Family history was unremarkable for gastrointestinal (GI) malignancy. Vital signs and physical examination were within normal limits. Laboratory testing was within normal limits without evidence of anemia or leukocytosis. Abdominal and pelvic computed tomography revealed no inflammatory process or obstructive bowel pattern to explain her symptoms. Upper endoscopy revealed a normal-appearing esophagus, patchy hemorrhagic and inflamed mucosa with exudate in the gastric antrum and prepyloric region, and normal-appearing duodenum (Figure 1). A pathologic review of the gastric biopsies demonstrated gastric mucosa with severe chronic active gastritis with increased intraepithelial lymphocytosis with evidence of increased apoptotic activity consistent with checkpoint inhibitor-induced gastritis (Figure 2). *Helicobacter pylori* and viral immunostaining were negative. She was initiated on prednisone

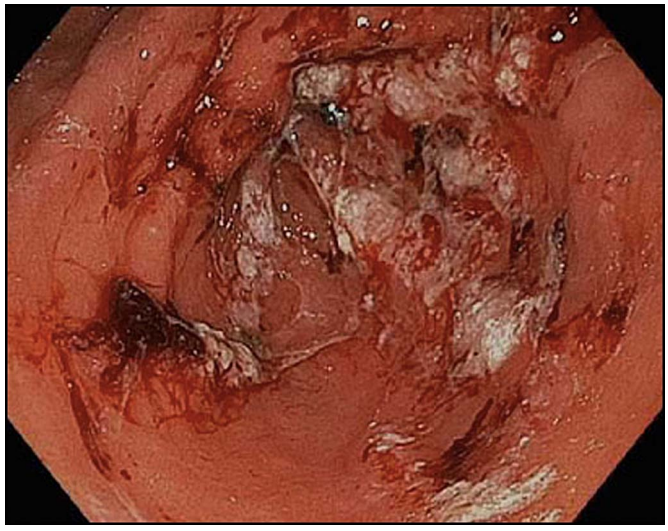

Figure 1. Patchy hemorrhagic and inflamed mucosa with exudate and extravasation of blood in the gastric antrum and prepyloric region encountered during upper endoscopy.

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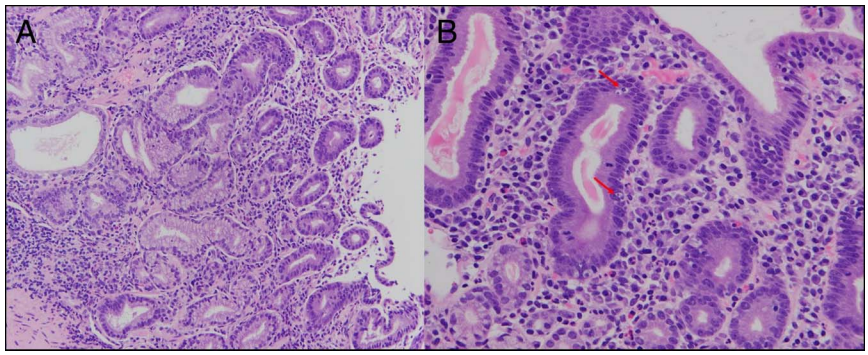

Figure 2. Gastric biopsy showing (A) severe chronic active gastritis and the presence of increased intraepithelial lymphocytes (200× magnification) and (B) chronic active gastritis with increased apoptotic activity (red arrows) (400× magnification).

1 mg/kg with resolution of symptoms at the follow-up. She remains on prednisone taper. Repeat upper endoscopy 66 weeks later revealed marked improvement with resolution of antral and prepyloric inflammation (Figure 3).

Immune checkpoint inhibitors (programmed cell death protein 1 inhibitors and cytotoxic T-lymphocyte-associated protein 4 inhibitors) are associated with adverse events (AEs) in 15%–90% of cases, with GI symptoms being the second most common AE encountered.[1] Severe AEs have been reported in more than 60% of patients receiving combination therapy, such as nivolumab and ipilimumab.[2] Common GI symptoms of checkpoint inhibitors include diarrhea, urgency, abdominal pain, and nausea. Gastric involvement is rare, with the colon being the most commonly affected GI location with combined immune checkpoint blockade therapy.[3] Diagnosis usually entails cross-sectional imaging to evaluate for inflammation and endoscopy with biopsies. The mainstay of treatment is immunosuppression with the use of corticosteroids or immunomodulatory agents such as infliximab in refractory cases.[3] Several reports have recognized pembrolizumab as a cause of hemorrhagic gastritis with fewer data available on hemorrhagic gastritis from a combination checkpoint inhibitor.[4,5] This case highlights the importance of recognizing hemorrhagic gastritis as a cause of abdominal pain and nausea and as an adverse reaction of nivolumab and ipilimumab combination therapy.

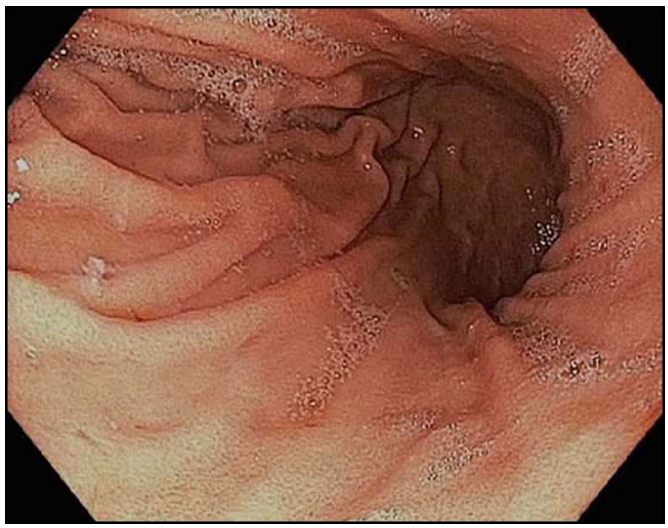

Figure 3. Normal-appearing gastric mucosa at the follow-up endoscopy 6 weeks after treatment with prednisone.

DISCLOSURES

Author contributions: AN Bazarbashi and R. Dolan reviewed the literature, wrote, and revised the manuscript for intellectual content. J. Yang provided the pathology images. M. Perencevich edited the manuscript, revised the manuscript for intellectual content, and approved the final manuscript. AN Bazarbashi is the article guarantor.

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