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CASE REPORT | STOMACH

Isolated Immune Checkpoint Inhibitor-Induced Gastritis Leading to Gastrocolic Fistula Formation

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ABSTRACT

Immune checkpoint inhibitors (ICIs) are important immunotherapeutic tools with known potential for adverse events (immune-related adverse events [irAEs]) in the gastrointestinal system. Although ICI-induced colitis and diarrhea are well documented, irAEs localized to the stomach are less frequently described. The management of most irAEs is suspension of ICI therapy and immune suppression. In rare cases of ICI-induced gastritis, treatment strategies of immune suppression have been scarcely described. To our knowledge, there have been no reported cases of severe ICI-induced gastritis leading to fistula formation. This case report describes a patient with isolated ICI-induced gastritis leading to an ulcer with gastrocolic fistula and his treatment course.

KEYWORDS: gastritis; immune checkpoint inhibitors; immune-related adverse events; fistula

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are a class of immunomodulatory antibodies that enhance the body's ability to kill dysplastic cells, including anti-programmed cell death protein 1 (anti-PD-1) and anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) therapies. However, in doing so, ICIs induce overactivation of the immune system resulting in immune-related adverse events (irAEs), most commonly in the skin and gastrointestinal system. IrAEs affect many organ systems and are graded on a scale of 1 (asymptomatic or mildly symptomatic) to 4 (life-threatening).[1] ICI-induced colitis is well described in the literature, with an estimated incidence of up to 54%.[2] This is not the case with ICI-induced gastritis—a comparatively rare entity. One study estimated that 0.8% of patients on ICI therapy had biopsy-proven ICI-induced gastritis and only 0.2% had isolated ICI-induced gastritis.[3] The management of significant irAEs is withholding therapy and using corticosteroids or biologic agents depending on severity.[1] Given the rarity of isolated ICI-induced gastritis, such management has not been well documented. We present a patient with isolated ICI-induced gastritis with fistula formation and his response to different therapeutic modalities.

CASE REPORT

A 66-year-old man with the diagnosis of stage III melanoma began nivolumab (anti-PD-1, 480 mg every 4 weeks) therapy. He initially suffered mild nausea and epigastric discomfort, which reportedly did not require treatment. After 8 cycles of nivolumab over as many months, he had no remaining evidence of malignant disease and had achieved remission. However, 2 weeks after completion of therapy, he began to have worsening abdominal pain, watery diarrhea, and fecaloid vomiting.

Based on symptoms, he was diagnosed with grade 3 ICI-induced colitis and nivolumab was stopped. A contrasted computed tomography scan of the abdomen showed a new mass (6.8 × 4.2 × 5.5 cm) on the greater curvature of the gastric body with communication to the proximal transverse colon, not present on an abdominal computed tomography scan obtained 2 months ago. Subsequently, esophagogastroduodenoscopy (EGD) revealed intragastric feculent material and a large 4 cm cavitary, ulcerated lesion along the greater curvature of the stomach (Figure 1). Biopsies of the lesion showed chronic active gastritis without malignant findings. Owing to concerns for sampling error, the patient underwent repeat EGD and colonoscopy. The EGD was unchanged, and the colonoscopy confirmed the cavitary opening was part of a fistula to the proximal transverse colon; the remainder of the colonic

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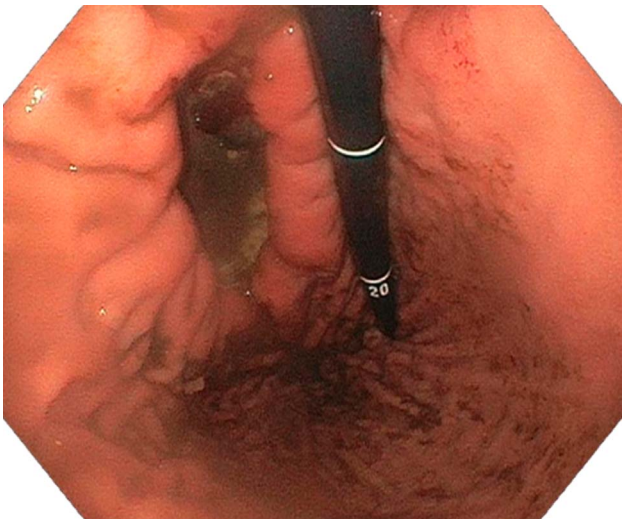

Figure 1. Esophagogastroduodenoscopy performed to visualize the mass seen on the greater curvature of the stomach by computed tomography revealed intragastric feculent material and a large 4 cm cavitary, ulcerated lesion.

mucosa appeared normal. The colonic biopsies were unremarkable; however, the gastric ulcer and fistula biopsies revealed acute inflammation, granulation tissue, and increased apoptosis consistent with ICI-induced gastritis, without melanoma cells identified in SOX10, S100, and Melan-A immunostains. Surgery was consulted, and patient underwent surgical repair of fistula consisting of resection of gastrocolic fistula with en bloc partial gastrectomy, small bowel resection, transverse colectomy, mobilization of the splenic flexure, handsewn end-to-side duodenojejunostomy, and stapled colocolostomy. Stool testing was negative, and there was no medical treatment for the fistula before surgery except loperamide as needed for symptomatic management of diarrhea. Ultimately, the patient had complete resolution of his presenting symptoms. On an 8-week follow-up of EGD and colonoscopy, only a 18 mm scar on the proximal greater curvature of the stomach from surgical resection of the mass remained along with a healing end-to-side colo-colonic anastomosis (Figure 2). The tissue appeared grossly healthy, and biopsies showed focal mucosal scar without gastritis or colitis. The patient's symptoms resolved, and his weight returned to baseline.

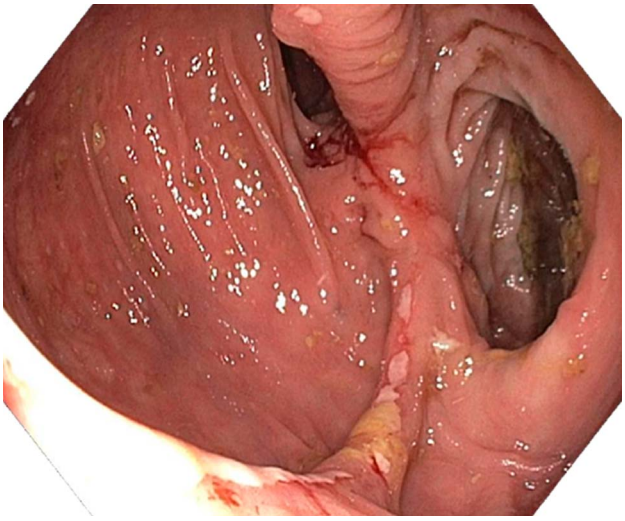

Figure 2. Eight weeks after surgical closure of the fistula, a follow-up colonoscopy showed a healing end-to-side colo-colonic anastomosis.

DISCUSSION

This case report describes a case of ICI-induced gastritis localized to the upper gastrointestinal tract and a unique phenotype necessitating surgical management.

At the outset, it is notable that anti-PD-1 therapy resulted in such severe gastritis. A 2018 systematic review and meta-analysis found that 70% of fatal irAEs with anti-TLA4 therapy were attributable to colitis vs 17% of fatal IrAEs with anti-PD-1 therapy.[4] Isolated gastritis numbers were expectedly low in that study, and it could be that anti-PD-1 therapy is more likely to cause gastritis.

Interestingly, ICI-induced gastrocolic fistulation has not previously been described. The mechanism of ICI-induced gastritis has been theorized to be similar to inflammatory bowel disease as patients with preexisting inflammatory bowel disease experience increased flares during ICI therapy. Transmural inflammation, a hallmark of Crohn's disease, is required for fistula formation, which supports a similar mechanism in ICI-induced gastritis.[5] This case is an exception to the general principle of irAE management: immunosuppression would not have been sufficient or helpful for our patient, who required direct intervention. Although there are endoscopic approaches to fistula management, this requires healthy tissue surrounding the fistula, which was not an option with the large, cratered ulceration in this case, and surgical intervention was necessary.[6] This case also illustrates that not all diarrhea in patients with ICI therapy is due to colitis. With negative biopsies for inflammation, the patient's diarrhea was due to a high-output gastrocolic fistula. Finally, the case highlights the elevated level of diagnostic suspicion that must be maintained in patients on ICI therapy who present with metastatic findings not typical of the underlying malignancy.

DISCLOSURES

Author contributions: S. Shrivastava and N. Patel both contributed to the conception, drafting, and editing of the submitted manuscript. Both authors reviewed and approved the final version of the manuscript. N. Patel is the article guarantor.

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