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CASE REPORT | STOMACH

Isolated Gastritis Secondary to Immune Checkpoint Inhibitors Complicated by Superimposed Cytomegalovirus Infection

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ABSTRACT

Immune checkpoint inhibitors such as nivolumab increase the T-cell destruction of malignancies but can also trigger a broad variety of immune-related adverse events (irAEs). Colitis as an irAE is well-documented, but upper gastrointestinal tract involvement is primarily unrecognized. We present a patient who developed gastritis as an irAE after multiple cycles of nivolumab and initially responded well to steroid therapy but then developed superimposed cytomegalovirus infection. The similarity between both presentations highlights the importance of having a broad differential diagnosis in patients with gastrointestinal complaints treated with immune checkpoint inhibitors and the need for further studies to better characterize gastritis as an irAE.

INTRODUCTION

Programmed cell death protein 1, its ligand, and cytotoxic T-lymphocyte-associated antigen-4 are immune checkpoints that negatively regulate T-cell function. Immune checkpoint inhibitors (ICI) allow unregulated T-cell destruction of malignant cells and are used in a large number of cancers, such as melanoma, non-small cell lung cancer, and renal cell carcinoma, as well as gastric, colorectal, and hepatocellular carcinomas.[1,2] However, immune-related adverse events (irAEs) have been reported in association with ICI.[1,3] The most frequently affected organ systems are dermatologic, gastrointestinal (GI), hepatic, and endocrine, but all other systems have been involved.[1] Lower GI involvement is common but the upper GI system is typically spared; esophagitis or gastritis without colitis is rarer still, and few cases from nivolumab specifically have been reported.[4–10] Diagnosis can be challenging because irAEs can arise months after the initiation of therapy or even after cessation, but irAEs frequently improve with ICI discontinuation and corticosteroid administration.[1,3,4]

CASE REPORT

A 55-year-old man with a history of metastatic clear cell renal carcinoma developed progressive abdominal pain, nausea, and vomiting 7 months after starting nivolumab. Computed tomography at a local emergency department showed diffuse gastric inflammation. Subsequent esophagogastroduodenoscopy (EGD) showed severe mucosal erythema throughout the stomach. Biopsies from the body and antrum showed active chronic gastritis with erosions and were negative for metaplasia, dysplasia, malignancy, fungal elements, or *Helicobacter pylori* infection. He was given fluids and discharged on pantoprazole, famotidine, and sucralfate, but his symptoms progressed.

Three weeks later, the patient presented to our center with epigastric pain, nausea, hematemesis, melena, weight loss, and food intolerance. He denied diarrhea or hematochezia. He was hemodynamically stable but appeared ill, had epigastric tenderness, and

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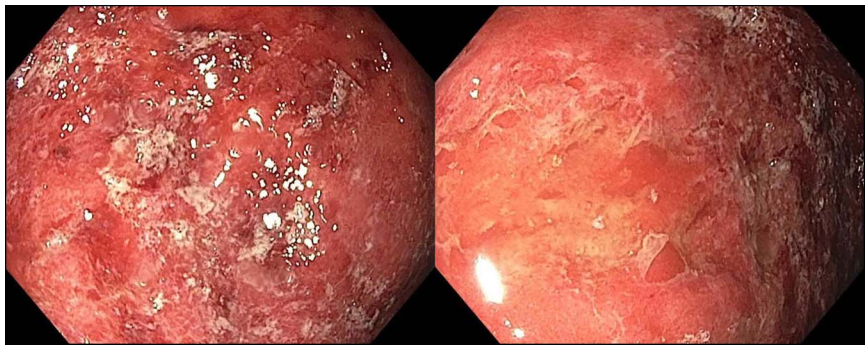

Figure 1. Second endoscopic evaluation showing immune checkpoint inhibitor gastritis. Fundus (left) and gastric body (right) demonstrating diffuse severely erythematous and friable mucosa, with mucosal sloughing found throughout the entire stomach.

was mildly anemic. Computed tomography showed diffuse gastric wall thickening. EGD revealed a diffuse severely erythematous and friable mucosa with mucosal sloughing in the entire examined stomach (Figure 1). The esophagus and duodenum were normal. Gastric biopsy showed infiltration of the lamina propria with inflammatory cells and erosive mucosa, suggestive of ICI-related gastritis (Figure 2). *Helicobacter pylori* and cytomegalovirus (CMV) immunostains were negative. Nivolumab was discontinued, and he was started on 2 mg/kg of methylprednisolone with rapid symptomatic improvement. He was discharged on the equivalent prednisone dose with plans for a slow taper but returned 2 weeks later with symptom recurrence.

Because he had been on steroids for 3 weeks, a dose of infliximab 5 mg/kg was administered for suspected steroid-refractory irAE. Repeat EGD showed diffuse severe inflammation characterized by adherent blood, erosions, erythema, friability, granularity, and confluent ulcerations in the entire stomach (Figure 3). Biopsies were notable for severe ulceration and granulation with CMV cytopathic changes, suggestive of superimposed CMV gastritis (Figure 4). Serum CMV polymerase chain reaction was positive at 3,457 IU/mL. Steroids were tapered over an additional week, whereas ganciclovir was initiated, resulting in progressive symptom improvement. The patient self-discontinued ganciclovir after 5 weeks when the planned EGD to confirm clearance was delayed. Three months after CMV diagnosis, EGD showed a diffuse moderately erythematous, granular, and friable mucosa with nodularity and contact oozing in the entire stomach. Biopsies showed an ulcerative gastric mucosa with dense organized granulation tissue and reactive changes, negative for CMV. Serum CMV polymerase chain reaction was also negative. At the 2-month follow-up, he reported near resolution of symptoms.

DISCUSSION

This case highlights the clinical manifestations and management of a patient with gastritis that occurred after nivolumab and was complicated by superimposed CMV infection. IrAEs can be challenging to recognize. "Classic" chemotherapies have well-characterized toxicities, widely known outside of oncology. By contrast, understanding the variety of organ systems affected and variable presentation of irAEs can be difficult. The variable delay between therapy initiation and symptom onset further complicates diagnosis.[4] That our patient tolerated nivolumab treatment for more than 6 months before symptom onset is not unusual.[4]

Our patient presented with gastritis, which was unexpected. Lower GI tract involvement is common in checkpoint blockade but upper tract, especially in isolation, seems to be exceedingly rare. Gonzalez et al described a case series including 37 cases of colitis with only 1 case of upper GI involvement in which the entire GI tract was affected.[5] Only within the past few years have a handful of nivolumab-related gastritis cases been published. Kobayashi et al reported a case of gastritis

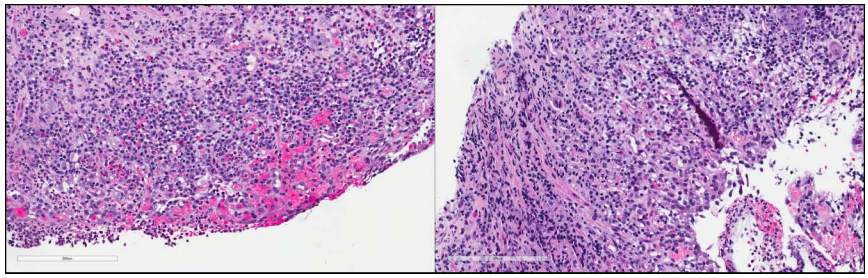

Figure 2. Gastric mucosa biopsies from second endoscopic evaluation. Severe active gastritis with erosion of body (left) and antrum (right) (hematoxylin and eosin stain, medium magnification).

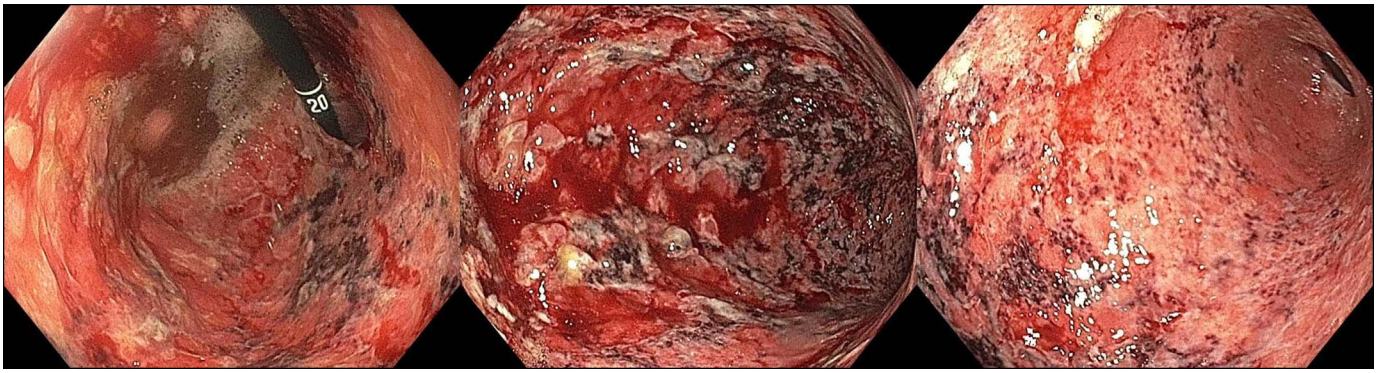

Figure 3. Third endoscopic evaluation showing ICI-related gastritis with superimposed CMV infection. Fundus (left); gastric body (middle); and antrum (right) demonstrating diffuse severe inflammation characterized by adherent blood, erosions, erythema, friability, granularity, and confluent ulcerations throughout the entire stomach. CMV, cytomegalovirus; ICI, immune checkpoint inhibitors.

after 4 months of nivolumab.[6] Boike et al described a case of esophagitis and gastritis after nivolumab in a woman with preexisting lymphocytic colitis.[7] Nishimura et al described a case of hemorrhagic gastritis related to nivolumab, ipilimumab, and infection with *Helicobacter pylori*.[8] For our patient's diagnosis, gross inflammation on endoscopy with marked inflammatory cell infiltration of the mucosa and glandular atrophy combined with the clinical history were crucial. Rapid symptom improvement with corticosteroids further supported irAE.

Development of superimposed CMV infection presented another diagnostic challenge because the patient experienced identical symptoms from a new, distinct etiology. Developing symptoms before tapering hinted at a different process because patients typically respond well to corticosteroids.[3,9,10] However, steroid-resistant irAE do occur, which is why infliximab was attempted while awaiting CMV confirmation.[11,12] The nivolumab drug label explicitly recommends considering CMV or other infectious etiologies in corticosteroid-refractory colitis.[2] The difference in histopathologic appearance between nivolumab-related and CMV gastritis was essential: marked infiltration of lymphocytes and neutrophils in the mucosa negative for all infectious stains vs viral inclusions and immunohistochemical stain showing nuclear reactivity (Figures 2 and 4). The disrupted mucosa from irAE combined with prolonged steroid therapy likely predisposed the patient to CMV infection/reactivation.

An array of side effects can occur from immune upregulation by checkpoint inhibitors, and the range of recognized effects continues to widen because the use of drug class increases. Further studies are needed to better characterize the incidence, natural history, and outcome of ICI-related gastritis and other rare irAEs. For almost any presentation in patients on ICIs, it is essential to maintain a broad differential that includes irAE, even if few cases have yet been documented. However, common etiologies, such as infection, in an immunocompromised patient should not be excluded, even if other etiologies had previously been identified.

DISCLOSURES

Author contributions: AH Nguyen and BT Sagvand wrote the article, revised the article for intellectual content, and approved the final article. T. Legesse provided the histology figures, revised the article for intellectual content, and approved the final article. DG Hwang revised the article for intellectual content and approved the final article. RK Cross revised the article for intellectual content, approved the final article, and is the article guarantor.

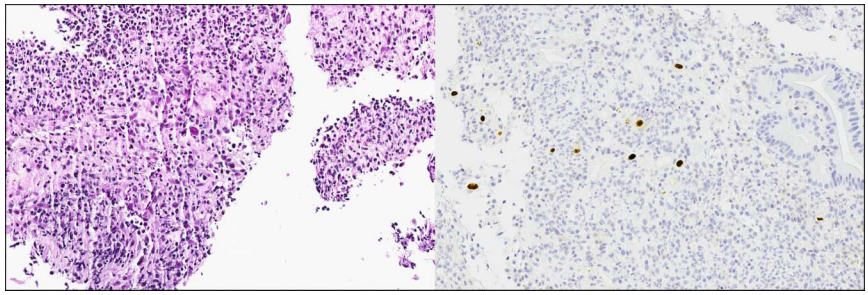

Figure 4. Gastric mucosal biopsies from third endoscopic evaluation. Completely ulcerated mucosa with the granulation tissue and scattered cells with CMV cytopathic changes (left, hematoxylin and eosin stain, medium magnification). Immunohistochemical stain for CMV showing nuclear reactivity in virus-infected cells (right). CMV, cytomegalovirus.

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Informed consent was obtained for this case report.

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