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CASE REPORT | COLON

The Perfect Storm: An Unusual Cause of Intestinal Perforation in a Solid Organ Transplant Patient

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ABSTRACT

Immunosuppressants are used to prevent rejection in transplant patients. Many of these medications commonly cause gastrointestinal (GI) symptoms. We present a 38-year-old kidney and pancreas transplant recipient who had severe ulceration throughout his GI tract leading to perforations of his stomach and cecum, despite early discontinuation of mycophenolate mofetil—the most likely culprit medication. The ongoing injury observed despite holding mycophenolate suggests a possible compounding effect of tacrolimus and everolimus. Both these agents are underrepresented causes of GI injury. This perfect storm of agents may have accounted for the severity and extensive presentation observed in our patient.

KEYWORDS: drug-induced colitis; transplant; perforation

INTRODUCTION

Gastrointestinal (GI) injury is common among solid organ transplant recipients. While many etiologies of GI injury are similar between transplant and nontransplant patients, there are some major differences that must be considered. Most notably, there is a higher incidence of opportunistic pathogens (eg, Cryptosporidium or cytomegalovirus), drug-induced injury, and the development of graft-versus-host disease. For transplant recipients, it is important to diagnose the specific cause of GI symptoms and to provide appropriate therapy to prevent complications. We report an unusual case of GI injury resulting in severe GI bleeding followed by both a gastric and colonic perforation in a solid organ transplant recipient.

CASE REPORT

A 38-year-old man with a history of end-stage renal disease secondary to type 1 diabetes mellitus leading to sequential kidney and pancreas transplant in 2019 on tacrolimus, mycophenolate, and low-dose prednisone presented to our hospital with acute-onset bloody diarrhea for 24 hours and a 20–30 lb weight loss (Figure 1). His hemoglobin on admission was 7.1 g/dL (10.5 g/dL the previous week). Initial esophagogastroduodenoscopy showed 1 linear esophageal ulcer and severely ulcerated mucosa in the stomach (Figure 2). The lesion was >30 mm and covered ~75% of the gastric antrum. Colonoscopy showed a severely ulcerated mucosa in the cecum and ileocecal valve (Figure 2). Biopsies obtained from the center of the ulcer, the ulcer edge, and surrounding tissue were negative for cytomegalovirus and herpes simplex virus. Corresponding serum and stool tests were negative for infection as well. At this time, mycophenolate was held. The patient's rectal bleeding resolved, and the patient was discharged with plans to repeat outpatient endoscopy to assess for healing.

Unfortunately, the patient was readmitted a month later with ongoing bloody diarrhea. At this time, mycophenolate was still being held and everolimus had been initiated. Despite this, the patient developed melena. Esophagogastroduodenoscopy showed a stable partially obstructing cratered gastric antrum ulcer, now with a pulsating bleeding vessel. Two clips were placed with complete hemostasis (Figure 2). Colonoscopy showed a continuous area of the nonbleeding ulcerated mucosa with a large overlying blood clot in the cecum. The cecum biopsy showed deep ulceration, and random pan-colonic biopsies showed frequent crypt apoptosis, injury, and loss, suggestive of drug-induced injury (Figure 2). Given this concern, everolimus was held; however, tacrolimus and prednisone

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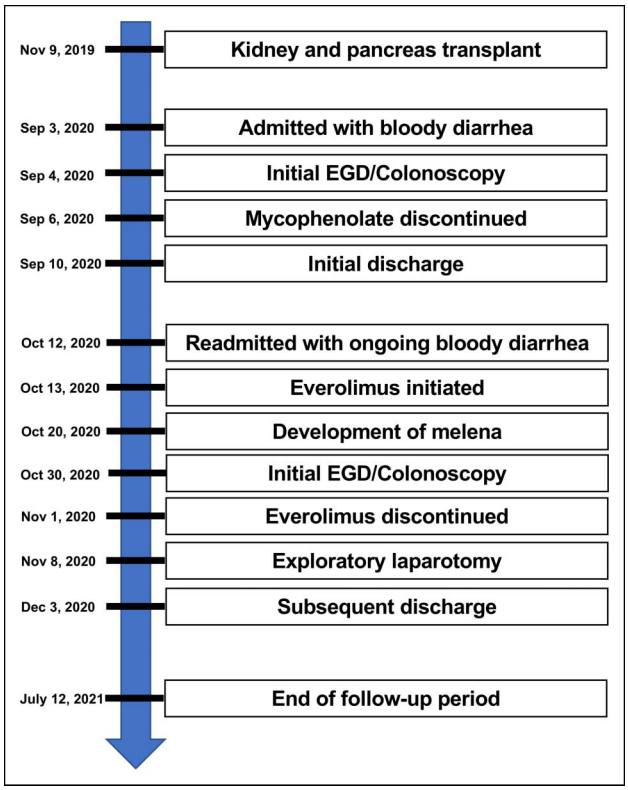

Figure 1. The patient's clinical time line. EGD, esophagogastroduo denoscopy.

were continued. Approximately 1 week after endoscopy, the patient was found to have peritonitis on examination with abdominal x-ray demonstrating free air. The patient was emergently taken to the operating room for an exploratory laparotomy. Perforations were noted in the stomach and cecum, and the patient underwent a Graham patch repair and ileocecectomy. After the procedure, the patient remained stable and was discharged on tacrolimus and prednisone. Mycophenolate and everolimus were permanently discontinued. No reoccurrence of symptoms or complications was reported within 8 months of charted follow-up.

DISCUSSION

Drug-induced GI injury is common among solid organ transplant recipients, with immunosuppressive medications being the most well-established.[1] When a diagnosis of drug-induced GI injury is suspected, it is important to exclude alternative causes (ie, infection) and subsequently discontinue the offending agent while monitoring for improvement.[2] In our case, a diagnosis of drug-induced GI injury was suspected after excluding infectious etiologies and inflammatory bowel disease and was supported by classic features of drug-induced GI injury on histology (Figure 2).

Our case was unique for several reasons. First, the patient's GI injury continued to worsen despite holding mycophenolate. The ongoing injury observed despite holding mycophenolate suggests a possible compounding effect of other immunosuppressant medications in addition to mycophenolate, which was likely still in the patient's system at the time of his perforation. Second, the GI injury was extensive, involving the esophagus, stomach, small intestine, and colon. Third, the patient's GI injury represented a very severe presentation, causing a full-thickness injury resulting in a perforation to both the upper and lower GI tracts.

Oddly, this patient's clinical course continued to worsen despite holding the most common culprit medication, mycophenolate. Mycophenolate has been reported to cause GI symptoms in 45% of patients, with enteritis/colitis being present in 2%–9% of cases.[3] Mycophenolate typically leads to resolution of symptoms within 20 days, with over 80% of cases experiencing endoscopic improvement.[3,4] However, mycophenolate can persist in the serum for $>$ 6 weeks in patients with kidney and liver impairments. Tacrolimus, contrarily, is an accepted treatment of autoimmune enteritis/colitis; however, paradoxical GI injury has been reported.[5] Hissong et al[5] found that in 20 patients receiving tacrolimus monotherapy, 85% had GI symptoms, 55% had colitis, and 15% had ulcers and/or erosions. Everolimus is believed to be associated with GI injury as well; however, the incidence, extent, and severity is not well-reported.[6] Abdel-Rahman and Fouad[6] conducted a large meta-analysis consisting of 18 clinical trials and 8,143 patients. They found that the relative risk of diarrhea was 3.49, but did not further characterize the endoscopic or histopathologic effects. Therefore, one might expect that the combination of these 3 agents could have synergistic effects in producing GI injury, although data examining these combinations are limited. This perfect storm of agents may have accounted for the severity and extensive presentation observed in our patient.

In conclusion, we present a case of immunosuppressant-induced GI injury due to a combination of mycophenolate, tacrolimus, and everolimus. While there have been cases documenting immunosuppressant-induced GI injury, most of the available data look at the effects of individual agents. Our case serves to increase recognition of tacrolimus and everolimus-induced GI injury and to increase awareness of the potential risk that can arise when multiple immunosuppressants are combined.

DISCLOSURES

Author contributions: J. Karan and D. Aintabi were responsible for analyzing and interpreting the case, drafting large portions of the case, as well as reviewing and revising the case before publication. K. Choi was responsible for reviewing and revising the critically important informational content. J. Berinstein was responsible for drafting portions of the case, primarily the case presentation section; reviewing and revising large portions of the case before publication; and made the final approval of the version to be published. All parties agreed to be responsible for all aspects of the work in ensuring that questions related to the

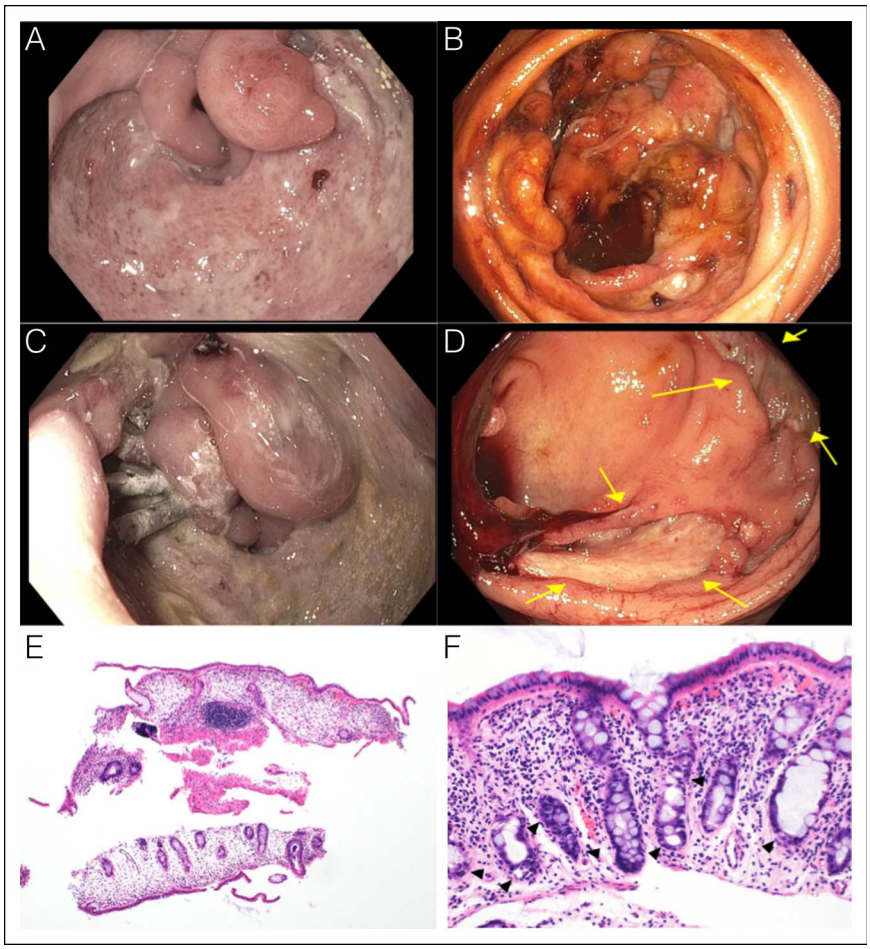

Figure 2. Endoscopic and histologic images. (A) Upper endoscopy demonstrating ulcerated gastric antrum. (B) Colonoscopy depicting ulcerated mucosa of the cecum and ileocecal valve. (C) Upper endoscopy demonstrating the ulcerated mucosa in the gastric antrum with the pulsating bleeding vessel treated with hemostatic clips placement. (D) Random colon biopsies with features suggestive of drug-induced injury, such as colonic mucosa with foci of crypt loss and injury. Hematoxylin and eosin stain, 40× magnification. (E) Random colon biopsies with injured and dilated crypts lined by attenuated epithelium and many crypt apoptosis (arrowheads). Hematoxylin and eosin stain, 200× magnification.

accuracy or integrity of any part of the work are appropriately investigated and resolved. J. Berinstein is the article guarantor.

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