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CASE REPORT | SMALL BOWEL

Sevelamer-Induced Ischemic Enteritis

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ABSTRACT

Sevelamer, a nonabsorbable dietary phosphate binder, is essential for patients with renal impairment since hyperphosphatemia is associated with an increase in all-cause mortality. Sevelamer is generally well tolerated; however, it is rarely been documented to cause gastrointestinal mucosal injury by forming sevelamer crystals and depositing within the gastrointestinal walls. We present a 35-year-old man with end-stage renal disease on peritoneal dialysis who developed abdominal pain and hematochezia. Initial imaging and endoscopic examination were concerning for ischemic enteritis, and histopathology revealed crystalloid structures surrounded by necrosis consistent with sevelamer-induced ischemic enteritis.

KEYWORDS: sevelamer; ischemic enteritis; sevelamer crystals

INTRODUCTION

Sevelamer, a commonly prescribed phosphate binder, is crucial in managing hyperphosphatemia in patients with chronic kidney disease (CKD) and those undergoing dialysis for end-stage renal disease (ESRD). Sevelamer is reported to be relatively safe with known mild gastrointestinal side effects. Although a rare complication, sevelamer has been documented to cause gastrointestinal mucosal injury by forming sevelamer crystals (SCs) and depositing in the mucosal wall.[1] SC deposition has been associated with mucosal ulceration, bleeding, ischemia, perforation, and postinflammatory strictures.[1–6]

This case report describes a young patient with ESRD on peritoneal dialysis who developed hematochezia found to be secondary to sevelamer-induced ischemic enteritis. We aimed to highlight the patient presentation and critical findings of a common medication's rare yet clinically significant complication.

CASE REPORT

A 35-year-old man with hypertension, coronary artery disease, and ESRD on nightly peritoneal dialysis presented with 2 days of hematochezia and abdominal pain. He reported 4 months of episodic abdominal pain and diarrhea requiring several hospitalizations and endoscopic investigations. One month ago, a computed tomography angiography scan of the abdomen demonstrated multiple loops of small bowel wall thickening with stranding in the adjacent mesentery concerning for enteritis, no vascular abnormalities were identified. Push enteroscopy revealed ulcerative inflammation in D2 (Figure 1) and normal jejunum. Colonoscopy revealed inflammation in the cecum and ascending colon. The terminal ileum was visualized and appeared normal (Figure 2). Biopsies were collected and revealed reactive epithelial changes of the duodenum and focal hyperplastic changes of the colon. No biopsy was taken from the terminal ileum.

On this admission, his laboratory results were significant for white blood cell 19.02 10*3/μL (normal 3.70–10.30 10*3/μL), hemoglobin 12.3 g/dL (normal 13.7–17.5 g/dL), platelet count 112 10*3/μL (normal 155–369 10*3/μL), and C-reactive protein 42.6 mg/L (normal $<$ 8.0 mg/L). Further chemistry was consistent with that of an ESRD patient with potassium 5.6 mg/dL (normal 3.7–4.8 mmol/L), serum creatinine of 12.27 mg/dL (normal 12.27 mg/dL), BUN of 54 mg/dL (normal 7–21 mg/dL), and phosphorus 6.8 mg/dL (normal 2.1–4.7 mg/dL). Infectious workup, including *Clostridioides difficile* polymerase chain reaction

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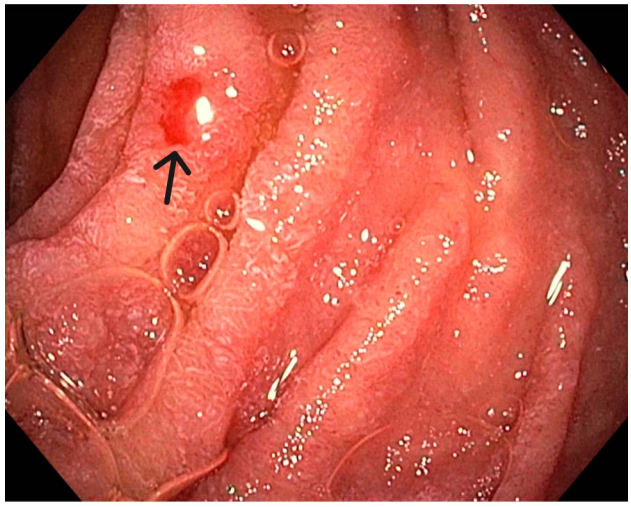

Figure 1. Endoscopic image displaying ulcerative inflammation (arrow) of D2. Biopsies of the ulcerated mucosa were performed with cold forceps.

and a comprehensive gastrointestinal polymerase chain reaction panel, was negative for acute infection. Computed tomography angiography revealed inflammation of 2 small bowel segments within the left upper quadrant and pelvis concerning for ischemia. The superior and inferior mesenteric arteries were patent, and no additional vascular abnormalities were identified.

Colonoscopy and push enteroscopy on day 3 revealed ulcerative inflammation in D4 and the terminal ileum 6 cm proximal to the ileocecal valve, both concerning for ischemia (Figures 3 and 4). Biopsy results of D4 revealed mucosal necrosis and inflammation, and the terminal ileum revealed mucosal necrosis with crystalloid structures consistent with pill-associated mucosal ischemia (Figure 5). Further history revealed that he

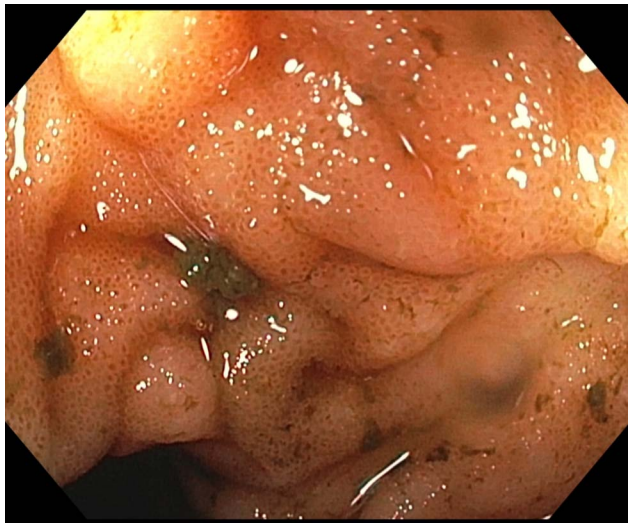

Figure 2. Endoscopic image displaying a normal appearing terminal ileum 1 month before the findings visualized in Figure 3.

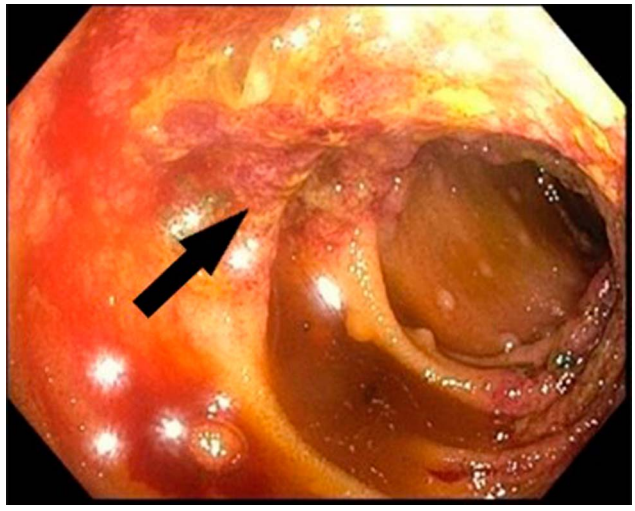

Figure 3. Endoscopic image displaying diffuse ulcerations, edema, erythema, and friability of the terminal ileum mucosa concerning for ischemia. Biopsies of the ulcerated mucosa (arrow) were performed with cold forceps.

started sevelamer 2,400 mg 3 times daily 1 month before the symptom onset. Sevelamer was discontinued on day 6, and his abdominal pain and hematochezia resolved by discharge on day 10. He missed his 1-month follow-up, but 5 months later reported continued resolution of symptoms.

DISCUSSION

Sevelamer, a calcium-free phosphate binder, is a nonabsorbable resin that binds to dietary phosphate, preventing absorption and lowering serum phosphate levels.[7] Reducing phosphate levels in patients with ESRD is important as hyperphosphatemia has been linked to an increase in all-cause mortality.[8] Studies suggest sevelamer, compared with other

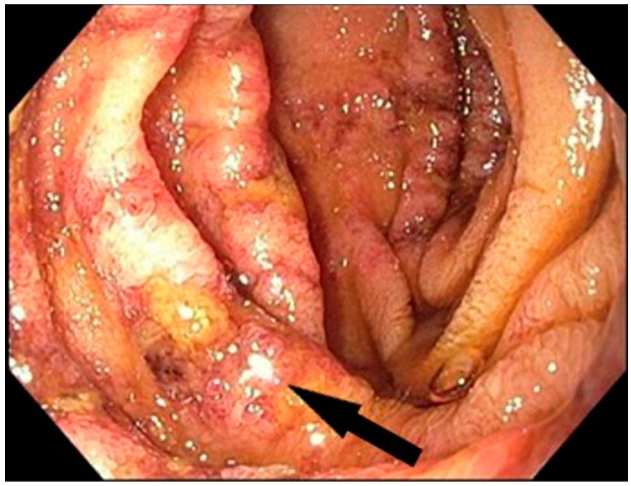

Figure 4. Endoscopic image displaying edematous and friable mucosa with diffuse ulceration in the fourth segment of the duodenum concerning for ischemia. Biopsies of the ulcerated mucosa (arrow) were performed with cold forceps.

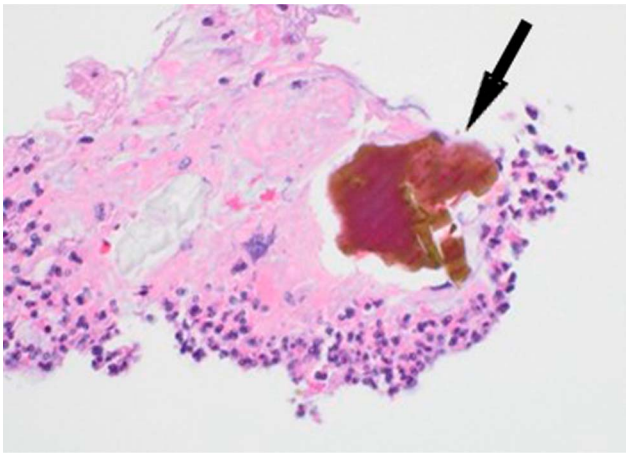

Figure 5. Histopathology of biopsied small bowel stained with hematoxylin and eosin showing sevelamer crystals displayed as violet fish scales in a yellow-brown necrotic and inflamed background. Magnification 400×.

phosphate binders, may have greater efficacy in lowering lipid levels, reducing the progression of vascular calcification, and decreasing cardiovascular events.[9] Sevelamer is generally well tolerated. Common side effects include nausea, vomiting, diarrhea, flatulence, and constipation.[5]

Although rare, emerging evidence suggests an association between sevelamer use and GI mucosal injury.[1–6] Of the cases reported, sevelamer injury has been distinguished by the histologic presence of SC deposition within the intestinal wall.[1] The first histologic description of SCs in the GI tract was described in 2013 by Swanson et al. They collected 15 histologically identical crystal specimens from patients with CKD using sevelamer. SCs were characterized as having a pink to violet fish-scale pattern with a rusty yellow-brown background (Figure 5).[1] Their presence was associated with mucosal inflammation, ulceration, polyps, ischemia, and necrosis.[1]

The pathophysiology of mucosal injury is not fully understood; however, it is believed that the nonabsorbable sevelamer resin forms crystals that can deposit within the gastrointestinal wall and cause direct mucosal toxicity.[1,5] Studies suggest diabetics are at increased risk of developing mucosal injury, likely secondary to their increased risk of gastroparesis predisposing to SC deposition.[5] Constipation is also thought to increase the risk of SC deposition.[3] Furthermore, patients with ESRD on dialysis are at increased risk of hypotension and vascular events making them more susceptible to mesenteric ischemia.[4,8,9] In such cases, the weakened intestinal mucosa could predispose patients to sevelamer injury.[4]

Most patients present with abdominal pain and lower gastrointestinal bleeding.[5] A review by Yuste et al examined 16 published case reports in which sevelamer caused GI mucosal injury. SCs were present in 15 of 16 patients, and lesions were found in all parts of the GI tract from the esophagus to the colon.[5] In 25% of cases, like ours, more than one GI segment were affected.[5] The histological lesions described were ulcerations in 9 patients, necrosis in 6 patients, acute inflammation in 5 patients, and ischemic injury and inflammatory polyps in 3 patients.[5] There have been no studies correlating sevelamer dose with the risk of mucosal injury.[5] Since SCs can deposit anywhere within the gastrointestinal tract, patients taking sevelamer that present with GI bleeding without an identifiable source on standard upper endoscopy and colonoscopy, video capsule endoscopy, or push enteroscopy should be considered for further evaluation.

This patient was neither diabetic, nor constipated, and had no evidence of vascular abnormalities on imaging. Based on our imaging and endoscopic examination concerning for ischemia, combined with the histological findings, we believe his picture is most consistent with a diagnosis of sevelamer-induced ischemic enteritis.

Overall, in patients with CKD or ESRD on sevelamer who present with acute abdominal pain or gastrointestinal bleeding, it is essential to recognize that sevelamer could be causing GI mucosal injury and to stop the sevelamer immediately. If sevelamer is not stopped, complications such as ischemia, ulceration, acute anemia, stricture formation, and perforation may occur.[1–6]

DISCLOSURES

Author contributions: H. Darnell and A. Brenner reviewed literature, provided endoscopic images, drafted and revised the final manuscript. C. Kern and D. Flomenhoft reviewed literature, drafted and revised the final manuscript. E. Lee conducted the histological analysis of tissue samples and provided photos of the pathological findings. Deborah Flomenhoft MD is the article guarantor.

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Informed consent was obtained for this case report.

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