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CASE REPORT | COLON

Sevelamer-Associated Rectosigmoid Ulcers in an End-Stage Renal Disease Patient

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ABSTRACT

Sevelamer carbonate is a commonly prescribed anion-exchange resin administered orally to prevent hyperphosphatemia in patients with chronic kidney disease. We present a rare case of a 33-year-old man with end-stage renal disease and diabetic gastroparesis on sevelamer carbonate, who presented with hematochezia and was found to have rectosigmoid ulcers induced by sevelamer crystals. His hematochezia resolved after switching from sevelamer carbonate to lanthanum carbonate. Clinicians and pathologists must be aware of the possibility of drug-induced mucosal ulceration associated with sevelamer use as a potential etiology of a gastrointestinal bleed.

INTRODUCTION

Medications associated with gastrointestinal (GI) tract injuries are common, yet some causes are underrecognized due to decreased awareness. With only around 19 reported cases published in literature, GI injuries due to sevelamer carbonate are rare.[1-4] Two classic examples of medications known to cause GI mucosal injuries are nonsteroidal anti-inflammatory drugs and bisphosphonates, which can lead to mucosal erosions, and proton pump inhibitors, which can cause microscopic colitis.[5] Novel causes of crystal-induced mucosal ulcerations and bleeding, such as non-absorbable anion-exchange resin (e.g., sevelamer, sodium polystyrene sulfonate, cholestyramine), have been identified recently.[1]

CASE DESCRIPTION

A 33-year-old, African-American man with diabetes mellitus type 1 with gastroparesis, end-stage renal disease on hemodialysis, hypertension, and coronary artery disease with stents on dual antiplatelet therapy, presented with a 1-day history of recurrent episodes of hematochezia with periumbilical pain. He had no prior history of GI bleeding but had chronic constipation and abdominal discomfort associated with his diabetic gastroparesis.

On exam, he was afebrile and hemodynamically stable with periumbilical tenderness and dark red blood with mucus on rectal exam. Laboratory results were significant for hemoglobin 7.8 g/dL, platelet 425,000/μL, white blood cell count 22,000/μL, and international normalized ratio of 1.2. Stool studies were negative for *Clostridium difficile*, *Salmonella*, *Shigella*, *Campylobacter*, and fecal leukocytes. Computed tomography showed a moderate amount of stool throughout the colon with no evidence of colonic wall thickening. Colonoscopy revealed a continuous area of nonbleeding ulcerated mucosa 45 cm proximal to the anus, but the study was stopped due to the extent of ulcerations and poor bowel preparation (Figure 1). Targeted ulcer biopsies were obtained. While waiting for the pathology report, the patient continued to present hematochezia with persistent reduction in hemoglobin to 6 g/dL, requiring transfusion of 6 units of packed red blood cells. A surgical approach for bleeding control was considered, but the patient was deemed a poor surgical candidate given his multiple comorbidities. On the eighth hospital day,

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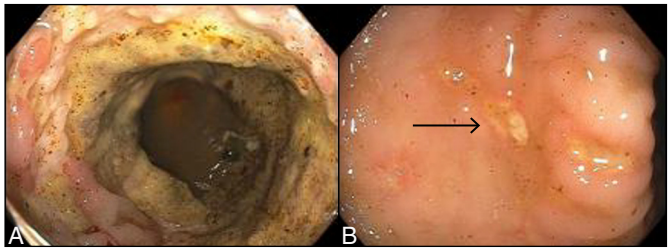

Figure 1. (A) Descending colon and (B) sigmoid colon with continuous nonbleeding ulcerated mucosa.

histopathology revealed sevelamer crystals without signs of tissue ischemia (Figure 2). On further investigation, the patient was found to be on sevelamer carbonate (2,400 mg by mouth 3 times daily for 2 years), and was receiving the medication as an inpatient. The sevelamer carbonate was switched to lanthanum carbonate. On the eleventh hospital day, his hematochezia resolved, and the patient was discharged on fifteenth hospital day with instructions to resume dual antiplatelet therapy in 1–2 weeks. The patient was lost to follow-up and passed away 1 year later from non-GI–related causes.

DISCUSSION

Sevelamer is one of the orally administered anion-exchange resins that are used in the treatment of hyperphosphatemia among patients with chronic kidney disease. Sevelamer exerts its effect by binding and forming an insoluble complex with dietary phosphorus to prevent its reabsorption from the GI tract.[6] The most common GI side effects include vomiting, nausea, diarrhea, gastroesophageal reflux, dyspepsia, abdominal pain, and constipation.[5] Known contraindications to sevelamer use include history of intestinal obstruction and swallowing disorders.[5] The characteristic histologic features of sevelamer crystals include broad, curved, and irregularly spaced "fish scales" of varying colors, with its most characteristic color being prominent linear bright pink accentuations surrounded by a rustic yellow background on hematoxylin and eosin stain.[5]

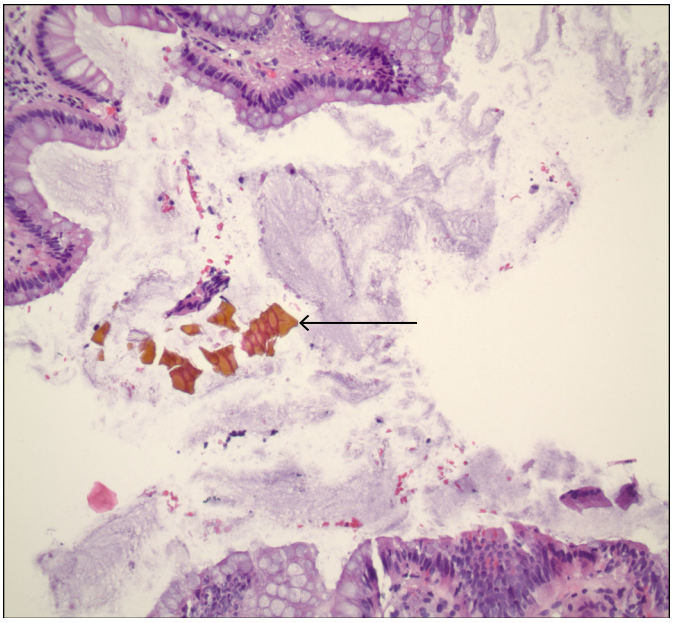

Figure 2. Colonic mucosa with nonspecific minimal reactive changes, and broad, curved, irregularly shaped "fish scales" sevelamer crystals without tissue necrosis on hematoxylin and eosin (100×).

Sevelamer crystals in the GI tract and their association with mucosal injury, which appeared to be dose-dependent, were first described in 2013.[5] However, subsequent published case reports did not find any association between the drug dose and severity of mucosal injury.[1] The exact pathophysiology of how sevelamer causes mucosal injury is still unclear. It is thought that sevelamer is directly toxic to the GI mucosa, thus leading to tissue inflammation, necrosis, ulceration, and, in a few cases, perforation. Moreover, it also predisposes to GI dysmotility including constipation, which may lead to accumulation of sevelamer crystals exerting its toxic effect on the colonic mucosa or to the development of stercoral ulcers, which are caused by pressure necrosis from hard fecal mass pushing on the colonic wall.[7]

Initially, ischemic colitis was the leading differential diagnosis for this patient's hematochezia, given his multiple medical comorbidities predisposing to colonic ischemia. Interestingly, pathology of the rectosigmoid ulcers revealed only sevelamer crystals without accompanying evidence of tissue ischemia and necrosis. There are approximately 19 cases of sevelamer-associated colorectal ulcers reported in literature, and most had evidence of mucosal ischemia or necrosis on tissue biopsy. It is likely that this patient's long-standing constipation from diabetic gastroparesis and sevelamer use led to fecal impaction, which allowed the crystals to accumulate and exert the toxic effects on the colonic mucosa, thus leading to ulcer formation. The patient's symptoms resolved after switching sevelamer to lanthanum carbonate, another anion-exchange resin used for hyperphosphatemia. Stomach acid releases a sevelamer polymer that binds phosphate in the intestine and forms crystalline aggregates. This reaction is not known to occur with lanthanum carbonate.[1]

Several recently published case reports have demonstrated the association of sevelamer crystals with ischemic colitis, colonic perforation, and pseudotumor.[8,9] Given the varying clinical manifestations of sevelamer-induced GI mucosal injury, it is important for clinicians, surgeons, and pathologists to be aware of the potential GI complications associated with sevelamer use to avoid catastrophic complications and significant patient morbidity and mortality by early withdrawal of the offending medication. Most importantly, crystal-induced

mucosal injury should be considered as one of the differentials for etiologies of GI bleeding in patients with chronic kidney disease.

DISCLOSURES

Author contributions: PP Uy wrote the manuscript and is the article guarantor. D. Guerrero Vinsard edited the revised manuscript and contributed to manuscript writing. S. Hafeez provided the histologic images and descriptions.

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Informed consent was obtained from the patient.

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REFERENCES

1. Yuste C, Mérida E, Hernández E, et al. Gastrointestinal complications induced by sevelamer crystals. *Clin Kidney J*. 2017;10(4):39–44.
2. Nambiar S, Pillai UK, Devasahayam J, Oliver T, Karippot A. Colonic mucosal ulceration and gastrointestinal bleeding associated with sevelamer crystal deposition in a patient with end stage renal disease. *Case Reports Nephrol*. 2018;2018:4708068.
3. Oka Y, Miyazaki M, Monobe Y. Sevelamer crystals found in necrotic mucosa of a perforated diverticulum. *Ther Apher Dial*. 2018. [Epub ahead of print]
4. Magee J, Robles M, Dunaway P. Sevelamer-induced gastrointestinal injury presenting as gastroenteritis. *Case Rep Gastroenterol*. 2018;12 (1):1–5.
5. Swanson BJ, Limketkai BN, Liu T-C, et al. Sevelamer crystals in the gastrointestinal tract (GIT). *Am J Surg Pathol*. 2013;37(11):86–93.
6. Grinfeld J, Inaba A, Hutchison AJ. Update and critical appraisal of sevelamer in the management of chronic renal failure. *Open Access J Urol*. 2010;2:61–70.
7. Madan P, Bhayana S, Chandra P, Hughes JI. Lower gastrointestinal bleeding: Association with sevelamer use. *World J Gastroenterol*. 2008;14;(16):5–6.
8. Hudacko R, Kaye P. Sevelamer-associated ischemic colitis with perforation. *Gastroenterol Insights*. 2015;6(1):31.
9. Okwara C, Choi C, Park JY. Sevelamer-induced colitis presenting as a pseudotumor. *Clin Gastroenterol Hepatol*. 2015;13(7):39–40.