Case Report

Ischemic Colitis in Association with Sevelamer Crystals

Abstract

Sevelamer is an important drug used to lower serum phosphate levels in advanced kidney disease and in patients on dialysis. This drug is generally well tolerated but some patients report mild gastrointestinal distress as a side effect. Although regulatory agencies, such as Food and Drug Administration, list bowel ischemia and necrosis as potential and rare side effects, there are few case reports describing these adverse effects. We present a 35-year-old HIV patient with end-stage renal disease on hemodialysis who developed colonic hemorrhage and perforation. Imaging showed ischemic gangrene of bowel wall. Histopathology was consistent with transmural ischemic necrosis with deposition of fibrin thrombi and sevelamer crystals.

Keywords: *Sevelamer associated bowel ischemia, sevelamer associated gastrointestinal bleeding, sevelamer crystals*

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Introduction

Sevelamer is very commonly used non-calcium-phosphate-binding agent in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients to lower blood phosphate levels.[1,2] It was first approved for use in 2000. Currently, it is available as sevelamer hydrochloride and sevelamer bicarbonate. Use of this medication has been increasing due to its efficacy with phosphate lowering and the proposed lack of hypercalcemia and associated vascular calcification.[3]

Most commonly reported side effects of sevelamer are noted to be nausea, vomiting, constipation, flatulence, and diarrhea. Although regulatory agencies such as Food and Drug Administration and the drug label list bowel perforation and ischemia as some of the more serious adverse reactions, there is insufficient literature in support of these effects.

In this case report, we describe a 35-year-old African-American female patient who was treated with sevelamer hydrochloride who presented with acute abdominal pain caused by ischemic colitis and hemorrhage. Biopsy of the right colon tissue revealed fibrinoid necrosis and deposition of crystals, whose description was consistent with sevelamer crystals.

Case Report

This is a 35-year African-American female patient with ESRD due to idiopathic focal segmental glomerular sclerosis on hemodialysis. Significant medical history included HIV and seizure disorder. Seizure disorder was been well controlled on phenytoin. HIV status is monitored by HIV clinics at our institution. Her recent CD4 count was within normal limits and the viral load undetectable. Maintenance medication regimen included sevelamer 4.8 g/day, calcitriol, darbepoetin, cholecalciferol, clopidogrel, abacavir, lamivudine, and phenytoin. Notably, she was on sevelamer 1600 md three times a day.

Our patient presented to the hospital with hematochezia, bright red bleeding per rectum and right lower quadrant abdominal pain. At the time of presentation, BP was 114/70, temperature was 98.5°F, and heart rate was 124/min. Blood chemistries were that of an ESRD patient with potassium of 5 mg/dl, serum creatinine of 6.92 mg/dl, and BUN of 41 mg/dl. Contrast CT scan of abdomen and pelvis showed cecal and colon dilatation (15–16 cm), intraluminal hemorrhage, and fat stranding. Lack of bowel wall enhancement was suggestive of ischemic colitis. Due to the above findings, patient underwent exploratory laparotomy and right hemicolectomy which was later followed by ileocolic anastomosis.

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The excised tissue was promptly subjected to pathological analysis. Histopathology of the right colonic tissue showed patchy transmural ischemic necrosis with vascular fibrin thrombi and presence of sevelamer crystals at the necrotic bed and site of perforation [Figures 1 and 2]. These crystals demonstrated broad and curved "fish scale" like morphology. The scales intersected at curved points and displayed a 2-toned pink linear accentuation against a rusty yellow background.

Discussion

Sevelamer is an anion exchanger free of calcium and other metals. This polymeric resin has multiple amines on a carbon backbone. Amines in the polymer exist in a protonated form in the GI tract. Due to their charge, they bind phosphate anion decreasing the overall absorption of phosphorus from the GI tract.[4]

Mucosal injury caused by other sequestering agents such as sodium polystyrene sulfate has been reported but little data exist on sevelamer-associated gastrointestinal injury.[5-7]

Sevelamer crystal-associated GI injury was first reported in 2008.[8] In this case report, stercoral ulceration due to fecaloma formation lead to lower intestinal bleeding. The severe constipation was attributed to sevelamer use. However, they did not report sevelamer crystal deposition on histopathology.

In 2014, Swanson *et al*. reported a spectrum of GI mucosal injury associated with sevelamer crystal deposition in a case series of 15 patients.[9] Also, the crystal deposition was reported in esophagus, small bowel, and colon. This series described that sevelamer crystals demonstrated broad and curved "fish scale" like morphology. The scales intersected at curved points and displayed a 2-toned pink linear accentuation against a rusty yellow background. They stained eosinophilic to brown on hematoxylin and eosin (H and E) stain and violet on periodic acid-Schiff staining with diastase. To confirm the validity of their findings, they crushed sevelamer tablets and subjected to routine H and E and PAS staining. The crystals in tables demonstrated identical crystal structure to those seen in patient specimens.

Since the publication of this study, there have been reports on sevelamer-associated sigmoidal bleeding,[10] sigmoid colon perforation,[11] and GI mucosal injury causing sigmoid colon mucosal injury with bleeding.[12]

In our case, the resected bowel was subjected to routine histopathological analysis. Pathology revealed patchy transmural ischemic necrosis [Figure 1] with vascular fibrin thrombi along with sevelamer crystal deposition. The crystals on H and E stained exhibited broad and curved fish scales with two tones against a yellow-brown background. The histopathological description of these crystals is similar to what was described by Swanson *et al*. Possibility of kayexalate can be raised but the patient had not ingested kayexalate prior around this event. Moreover, kayexalate crystals have narrow rectangular fish scales and are usually exhibit a single color.

Despite visualization of sevelamer crystals at the site of necrosis, the regular causes of bowel ischemia must always be considered. Given the duration of dialysis, vascular calcification and resultant ischemia put these patients at a very high risk of vascular events. Mesenteric ischemia due to invasive fungi throughout the gastrointestinal tract has been reported in dialysis patients.[13,14] Another consideration is beta-2 microglobulin amyloidosis. This has been reported to cause ischemic insult throughout the GI tract.[15]

Conclusion

Although a rarely described entity, the awareness that sevelamer may be associated with intestinal ischemia is important. However, one must always consider and rule out the common causes of mesenteric ischemia such as

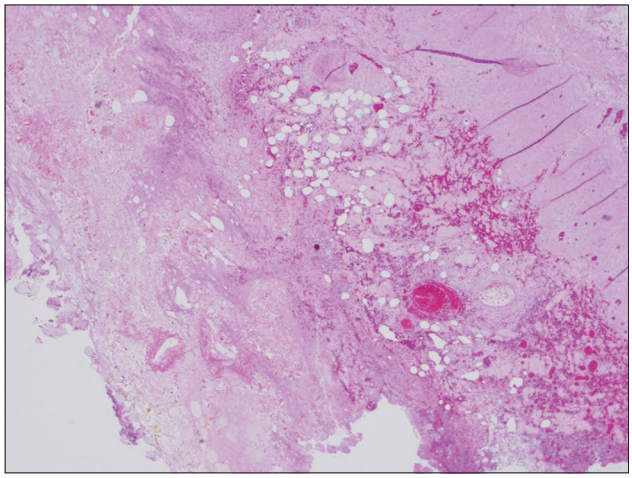

Figure 1: Fibrinoid necrosis (H and E)

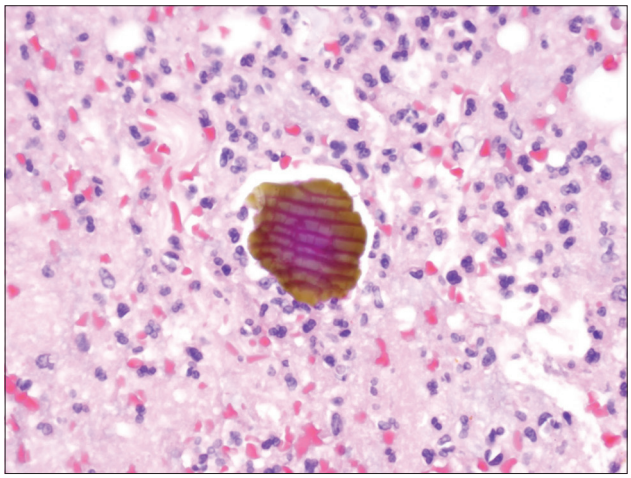

Figure 2: Sevelamer crystals displaying broad and curved 2-toned fish scales

atherosclerosis and vascular calcifications along with less common conditions associated with angioinvasive fungal infections and beta-2 microglobulin amyloidosis. More studies are needed to establish if sevelamer is a mere association versus if it causes ischemic injury on its own.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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