Sevelamer Induced Necrotizing Ileitis: A Case Report

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Abstract
The prevalence of chronic kidney disease (CKD) has surged globally over the past two decades. Sevelamer, a non-calcium phosphate binder, has gained popularity due to its relatively good safety profile for treating hyperphosphatemia in CKD patients. However, recent reports have identified a novel side effect of sevelamer: deposition in the gastrointestinal (GI) mucosa, leading to injury. Symptoms range from nonspecific abdominal discomfort to severe complications such as ulceration and gangrene. Demonstration of characteristic sevelamer crystals in biopsies is diagnostic. To date, 40 reports of sevelamer-induced GI complications exist in the literature. An elderly male suffering from end-stage renal disease presented with sub-acute intestinal obstruction. He failed to respond to initial conservative measures and upon exploration was found to have necrotising ileitis due to sevelamer-induced inflammation with mass formation. In CKD patients presenting with abdominal pain, clinicians should maintain a high index of suspicion for Sevelamer-induced intestinal injury.

Keywords: Ileitis/etiology; Renal Insufficiency, Chronic/drug therapy; Sevelamer/adverse effects

What's already known about this topic?
- Since its introduction in 2000s, sevelamer has been accepted as a safe drug to reduce hyperphosphatemia in CKD patients. It acts by binding to dietary phosphate in the gut, thus preventing absorption.
- The usual reported gastrointestinal side effects of sevelamer include nonspecific complaints like nausea, vomiting, flatulence, constipation, abdominal pain and rarely diarrhoea. The mechanism of these side effects is poorly understood and usually managed with symptomatic medications.
- A new concerning side effect of this drug has been briefly described in a few reports in recent years. Considered to be secondary to its deposition in the GI mucosa, Sevelamer crystals lead to inflammation and in rare occasions bleeding, ulceration and gangrene.
- The core histologic feature classic of sevelamer deposition is the finding of non-birefringent material displaying an internal fish scale pattern with rusty brown exterior and pink interior, and purple coloured scales in the mucosa.
- Some studies concluded that sevelamer-mediated mucosal injury appears to be dose dependent.

What does this study add?
- With this description, we add on to the literature about a severe form of sevelamer-induced mucosal injury.
- Physicians worldwide treating CKD patients would benefit from the knowledge of this relatively under-recognized side effect of sevelamer.

Learning points/Take home messages
- Sevelamer, a phosphate binder used for hyperphosphatemia in CKD, can cause gastrointestinal mucosal injury.
- Surgeons and Nephrologists should consider Sevelamer-induced GI complications in CKD patients presenting with abdominal pain.

INTRODUCTION
The global prevalence of chronic kidney disease (CKD) is 14.3% and in India is 16.8%.[1] Hyperphosphatemia is an inevitable consequence of reduced kidney function. It leads to secondary hyperparathyroidism, cardiovascular calcification & renal osteodystrophy. Phosphate binders, which include calcium-based, aluminum-based,

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and non-calcium-based agents, are vital in managing hyperphosphatemia.

Non-calcium-based phosphate binders, such as sevelamer, are preferred for end-stage renal disease (ESRD) patients on maintenance hemodialysis. Sevelamer binds phosphate in the intestine, reducing its absorption. Although generally well tolerated, Sevelamer can cause GI side effects ranging from nausea, vomiting, and abdominal pain to severe complications like GI bleeding and perforation.

Many recent meta-analyses have conflicting conclusions on the utility of phosphate binders in reducing mortality and other systemic complications.

Differential diagnosis is necessary for surgeons who usually manage acute abdominal pain and associated symptoms. The management of these surgical complications remains the same. However, once the causative role has been attributed to sevelamer, the drug can be discontinued to prevent further complications. Although there exist many reports of sevelamer-induced gastrointestinal (GI) injury, only 40 previously reported cases of sevelamer-induced GI complications exist in literature.[2] Here we present a case of Sevelamer-induced ileitis resulting in bowel gangrene.

CASE REPORT

A 61-year-old male presented with a 3-day history of bilious vomiting and colicky abdominal pain. He had not passed flatus for two days. He was a known case of stage 5 chronic kidney disease (CKD) on maintenance hemodialysis twice weekly. He had a history of hypertension, well-controlled for the past three years with Amlodipine and Metoprolol. His treatment regimen included Sevelamer carbonate 1200 mg per day, administered in three divided doses for hyperphosphatemia. Aside from these conditions and medications, there was no other significant medical or drug history.

On examination, the patient was conscious and cooperative. He exhibited tachycardia (pulse rate: 106 beats/min) but had normal blood pressure. The abdomen was distended with diffuse tenderness, without rebound tenderness. Bowel sounds were increased. Digital rectal examination was normal. A clinical diagnosis of sub-acute intestinal obstruction (SAIO) was made, and further investigations were conducted.

A routine blood panel revealed multiple organ failure as shown in Table 1.

Table 1. Derangements in routine blood tests

Hemoglobin	8.3 g/dL
Total leukocyte count	19630 cells/µL
Neutrophils	89%
S. creatinine	6.85 mg/dL
BUN	85.18 mg/dL
Sodium	129 mmol/L
Potassium	6.8 mmol/L
Calcium	7.1 mg/dL
Parathyroid hormone	5.1 pg/mL
Phosphorus	8.2 mg/dL
Prothrombin time	20.9 seconds
INR	1.55
pH	7.14
PCO2	12 mmHg
PO2	81 mmHg
HCO3	4.1 mmol/L
SBEc[standard base excess]	-24.9 mmol/L
Lactate	0.9 mmol/L

He was admitted to the Intensive care unit due to mixed pattern acidosis, hyperkalemia, hypocalcaemia and leukocytosis. There were multiple air fluid levels on abdominal X-ray (Fig. 1). Conservative management of SAIO (sub-acute intestinal obstruction), including Ryle's tube insertion and hemodialysis, was initiated. Despite correction of acid-base and electrolyte disorders, abdominal symptoms worsened. A computed tomography (CT) scan revealed dilated jejunal and ileal loops with multiple air-fluid levels, without a clear transition point (Fig. 2). There were no features suggestive of intestinal ischemia on CT.

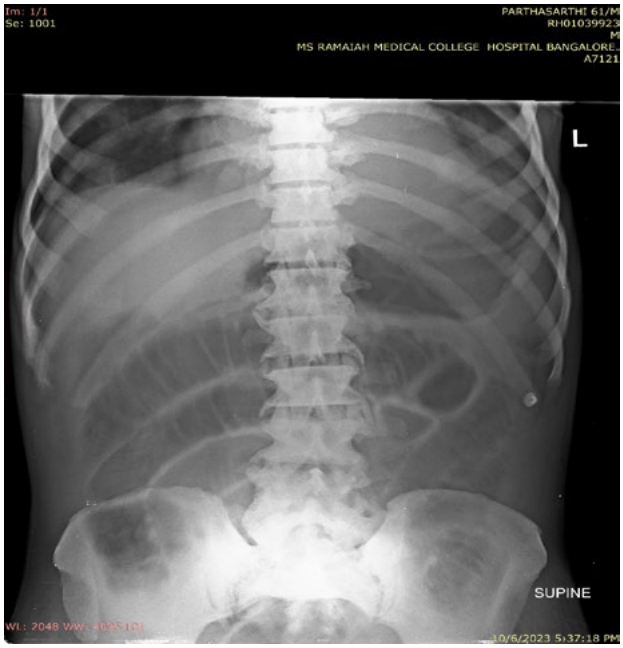


Figure 1. Erect X-ray of abdomen showing multiple air fluid levels

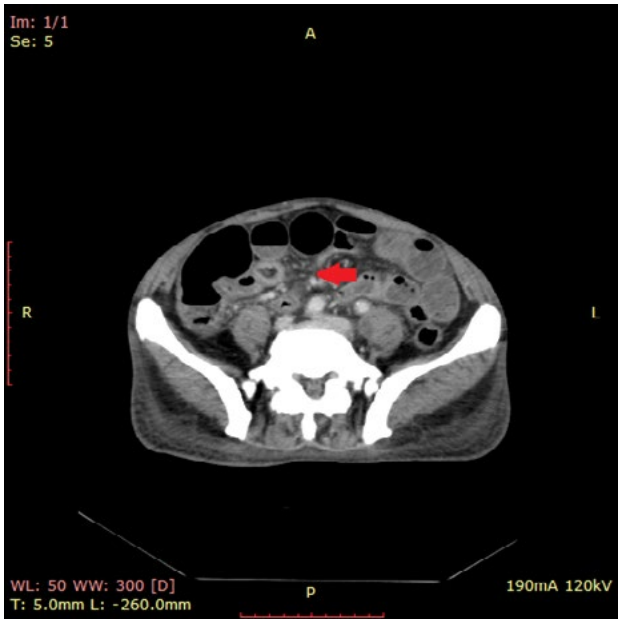


Figure 2. Axial section of CT abdomen showing dilated jejunal and ileal loops with transition at distal ileum

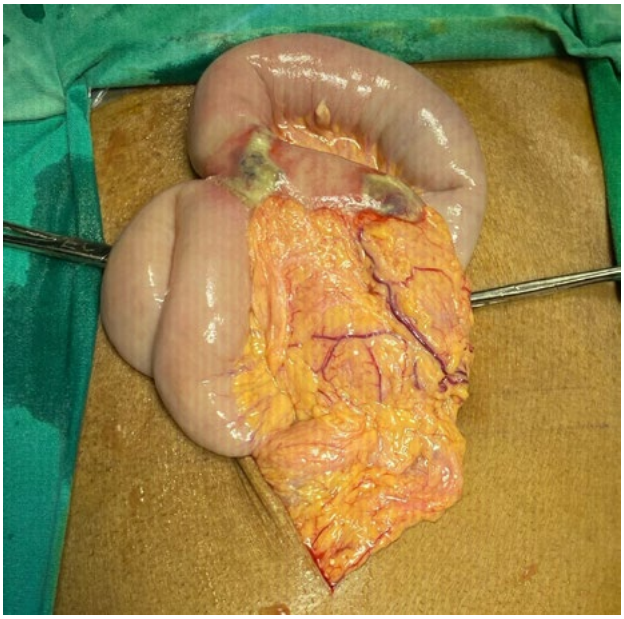


Figure 3. Intraoperative image showing multiple coin shaped patchy transmural necrosis in terminal ileum

On laparotomy, small bowel loops were dilated. The terminal ileum, around 40 cm from the ileo-caecal junction, was wrapped with omentum, forming a phlegmon. Ileum and jejunum proximal to this mass were dilated. The inflammatory mass was opened and multiple coin--shaped necrotic patches with inter-bowel adhesion were seen (Fig. 3). The pathology-bearing ileal segment was resected and an end-to-end ileal anastomosis was performed. Histopathological examination of the resected segment showed patchy transmural necrosis with dense inflammatory cell infiltrates (predominantly neutrophils). Amidst the patchy necrosis non non-birefringent material displaying an internal fish scale pattern with rusty brown exterior and pink interior, and purple coloured scales were seen (Fig. 4). These findings confirmed sevelamer-induced ileitis with ulceration and gangrene.

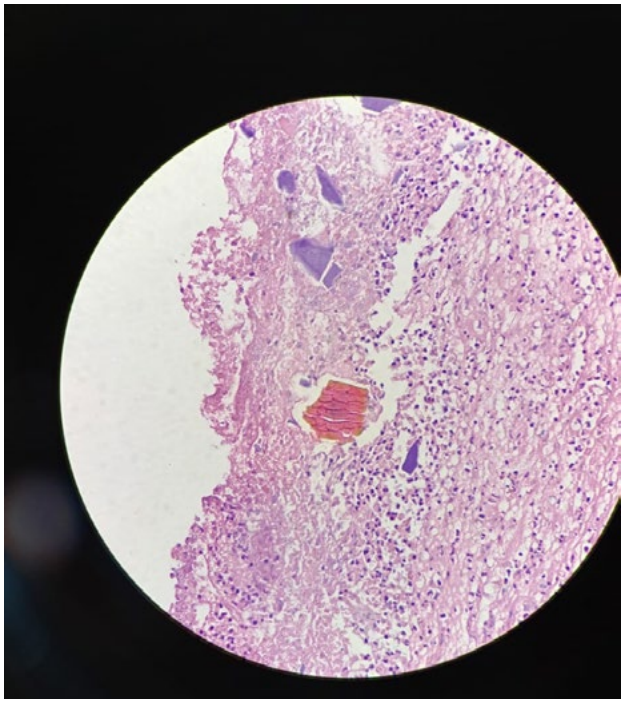


Figure 4. Microscopic image showing transmural necrosis with dense inflammatory cell infiltrates and the characteristic sevelamer crystals.

Postoperatively, the patient showed symptomatic improvement. He passed flatus on post-operative day 2 and had bowel movements by day 3. Ryle's tube was removed, and a liquid diet was initiated. The abdominal drain was removed on day 5. However, on day 7, during regular hemodialysis, the patient experienced sudden cardiac arrest.

Despite resuscitation and management for acute coronary syndrome, he succumbed to a second cardiac arrest.

DISCUSSION

CKD is defined as persistently reduced kidney function or damage for more than 3 months, irrespective of the cause. 21st century has seen an increase in the prevalence non non-communicable diseases (NCD) - diabetes, hypertension, obesity and cardiac disease. These NCD are recognized drivers in the increase in prevalence of CKD. The Global prevalence of CKD 14.3% of which 90% are in early stages not requiring hemodialysis.[1] The prevalence in India is 16.8 %.[1]

Long-term aims in CKD are preventing or slowing disease progression and avoiding complications arising from reduced kidney function. A wide range of disorders may develop as a consequence. Indeed, Hyperphosphatemia is a common complication of CKD. A tendency toward phosphate retention begins early in kidney disease due to the reduction in the filtered phosphate load. Although this problem is initially mild, with hyperphosphatemia being a relatively late event, phosphate retention is intimately related to the common development of secondary hyperparathyroidism. Dietary phosphate restriction and oral phosphate binders may limit the development of secondary hyperparathyroidism in patients with CKD.[3] There are three main types of phosphate binders available – calcium-containing binders and aluminium-containing binders and the new non-calcium-based binders (such as sevelamer and lanthanum).[4] Calcium carbonate is the most common form of phosphate binder prescribed, particularly in non-dialysis chronic kidney disease.[4] The newer non-calcium-based binders – sevelamer and lanthanum are usually reserved for dialysis patients.[4] Although calcium-based binders are effective and cheap, hypercalcemia and accelerated vascular calcification are major drawbacks. Sevelamer, being calcium-free free is devoid of these complications but poses GI side effects.

Since its introduction in 2000s, sevelamer has been accepted as a safe drug to reduce hyperphosphatemia in CKD patients. It acts by binding to dietary phosphate in the gut, thus preventing absorption. The usual reported gastrointestinal side effects of sevelamer include nonspecific complaints like nausea, vomiting, flatulence, constipation, abdominal pain and rarely diarrhea. The mechanism of these side effects is poorly understood and usually managed with symptomatic medications.

In 2008 Madan *et al* reported a case of stercoral ulceration causing lower gastrointestinal bleed and ascribed it to sevelamer use. This was the first description of such a complication of Sevelamer use. No histological evidence was described in the case report.[5] In 2013, Swanson *et al* described the findings of histological analysis of the gastrointestinal mucosa in seven patients on sevelamer. This was the first histologic illustration of sevelamer crystals in the GI mucosa. The core histologic features of the sevelamer crystals included broad, curved, and irregularly spaced "fish scales" with a variable background colour. Whereas most crystals displayed a 2-toned colour imparted by bright pink linear accentuations and a rusty yellow background (on H&E staining), those crystals embedded in extensive ulcer, ischemia, or necrotic debris acquired a deep eosinophilia or rusty brown colour. On PAS/D, sevelamer crystals maintained their internal "fish scale" structure and acquired a violet colour. Patients in this case series had chronic mucosal injury, acute inflammation, inflammatory polyps, ischemic injury, necrosis and ulceration ranging from the esophagus to the colon from where they were biopsied. Although the authors could not establish a definitive causal relationship between sevelamer and mucosal injury, they observed that the severity of mucosal injury appeared to correlate with the dosage of sevelamer.[6] Sevelamer crystals can be reliably distinguished from their histologic mimics - kayexalate crystals and cholestyramine crystals. Cholestyramine crystals lack the characteristic internal fish scale pattern.[6] Kayexalate crystals display a narrowed "fish scale" pattern with perpendicular intersecting lines, and the crystals are violet on H&E staining. On PAS/D, Kayexalate crystals maintain their internal structure but acquire a magenta colour.[6]

There have not been many case reports of sevelamer-induced gastrointestinal injury since then. In 2024, Bathobakae *et al* conducted a review of Sevelamer-induced Gastrointestinal Injury. They note a total of 36 sevelamer-induced GI injury. Among the patients, 50% presented with GI bleeding (melena, hematochezia, or both) and 47% presented with abdominal pain. Colectomy was required in 22% of patients due to colonic perforation, malignant obstruction, or extensive necrosis, while 75% experienced clinical improvement or symptom resolution.[7]

Despite its known association with GI injury, little research has been conducted on its mechanism. The proposed pathophysiology include deposition of the sevelamer phosphate compound in the GI mucosa triggering a chronic inflammatory reaction and aggregation in the bowel lumen exacerbation constipation, leading to stercoral ulcers. Current data is mainly retrospective and comes from case reports and series. No prospective study has been published yet.

Case series demonstrating characteristic sevelamer crystals in the involved GI mucosa, dose-dependent increase in mucosal injury and symptomatic relief after interruption of sevelamer are the only current evidence of this poorly understood side effect.

The primary need to start phosphate-lowering drugs is based on the evidence that hyperphosphatemia in CKD is directly associated with increased risk of cardiovascular complications, vascular calcifications, secondary hyperparathyroidism associated with renal osteodystrophy and mortality. Conclusions from meta-analyses on the need for

phosphate binders and their resultant efficacy in lowering complications and mortality are conflicting.[8-13]Although phosphate binders reduce phosphate levels in CKD patients, it is unclear which group of binders is superior to others. Novel phosphate binders like sevelamer are being increasingly used due to the recent increase in prevalence of CKD. Discovery of sevelamer induced GI injury from recent data raise concerns on the drug's safety profile. Prospective trials comparing the adverse effect profile of sevelamer need versus benefit to be done. Need for biopsies to prove GI injury and therapeutic intervention needs to be explored.

Surgeons and Nephrologists who encounter non-specific abdominal pain in CKD patients who receive sevelamer have to be aware of the gastrointestinal side effects of sevelamer.

Ethical Disclosures

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All authors contributed to reviewing literature, data collection, drafting the article and critical reviewing of the content of the article. All authors approved the final version to be published.

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