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Sevelamer-Induced Gastrointestinal Mucosal Injury: A Critical Review for Clinicians

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REVIEW ARTICLE

Sevelamer-induced Gastrointestinal Mucosal Injury: A Critical Review for Clinicians

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Abstract

Sevelamer is a non-absorbable polymer used to treat hyperphosphatemia in individuals with end-stage renal disease (ESRD) undergoing hemodialysis. The deposition of sevelamer crystals in the gastrointestinal (GI) tract, especially in the colon, can cause mucosal inflammation, pseudopolyps, ulceration, ischemia, or necrosis. Owing to its rarity and lack of physician awareness, the actual incidence and prevalence of sevelamer-induced gastrointestinal mucosal injury (SIGMI) remain unknown. The current evidence is retrospective, in the form of observational studies. This systematic review of case reports provides an overview of SIGMI, with a focus on its etiology, signs and symptoms, pathogenesis, diagnosis, and management. Electronic databases, including PubMed, Embase, and Google Scholar, were searched for published case reports, case series, and abstracts from inception to August 2023. The search yielded 1239 articles that were filtered using the study design, English language, and human subjects. After screening for duplicates and irrelevant articles, only 28 articles were included in the final review. Melena and abdominal pain were the most common complaints. Sevelamer was discontinued in all patients, and 27 (75%) experienced clinical improvement or symptom resolution. Eight patients (22%) required colectomy due to colonic perforation, malignant obstruction, or extensive necrosis. SIGMI is a unique complication of sevelamer use in patients undergoing hemodialysis. Prompt diagnosis and management are crucial to prevent life-threatening complications.

Keywords: Sevelamer, Sevelamer crystals, Sevelamer-induced gastrointestinal mucosal injury, Sevelamer-induced colitis, Gastrointestinal mucosal injury, Phosphate binder, End-stage renal disease

1. Introduction

According to the 2017 US Renal Data Systems (USRDS) report, an estimated 30 million American adults have chronic kidney disease (CKD), with 500,000 patients receiving maintenance dialysis therapy.[1] As kidney function declines, it loses its capacity to excrete excess phosphorus, leading to hyperphosphatemia, which predisposes patients to renal bone disease and organopathy.[2,3] Phosphate binders, including calcium acetate, lanthanum carbonate, and sevelamer, facilitate the fecal excretion of phosphorus.[3] Sevelamer was first approved for use in the US in 1998, and its demand continues to grow due to the increasing burden of CKD.[4,5] Sevelamer is a non-absorbable polymer that is used to treat hyperphosphatemia in individuals with end-stage renal disease (ESRD) undergoing hemodialysis.[4-9] Sevelamer binds dietary phosphate within the gastrointestinal (GI) tract, impeding its reabsorption.[5-7] Generally, sevelamer is well tolerated; even so, nausea, vomiting, abdominal pain, diarrhea, excess flatulence, and constipation may occur.[4-6,9]

The deposition of sevelamer crystals in the colon can give rise to mucosal inflammation, pseudopolyps,

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ulceration, ischemia, necrosis, and luminal obstruction due to fecaliths.[4,5,8-10] Sevelamer crystals can be identified in the fibropurulent necrotic debris of ulcerated tissue, displaying a characteristic "fish-scale" pattern on histopathology.[9] **Due to its rarity and lack of physician awareness, the actual incidence of SIGMI remain unknown, and current evidence is in the form of descriptive observational studies from post marketing analysis.**[5-7,9,11] In this targeted literature review, we provide an overview of SIGMI with a focus on its etiology, signs and symptoms, pathogenesis, diagnosis, and management.

2. Methods

SIGMI is a very rare clinical entity, and the current evidence is in the form of case reports. Electronic databases, including PubMed, Embase, and Google Scholar, were systematically searched for published case reports, case series, and abstracts from inception to August 2023 (Table 1). Major keyword terms included: "Sevelamer," "Renvela," "crystal-induced colitis," "Renagel," "colitis," "lower gastrointestinal bleeding." Articles were eligible for inclusion in the study if they were in English, available as full-text, and the case report featured a patient with GI symptoms due to sevelamer use. Non-English articles, articles on non-human subjects, articles with insufficient data, and articles on GI mucosal injury due to other medications were excluded. The results obtained from the search (1239 articles) were cross-referenced for the type of study and included based on the inclusion criteria. Twenty-eight articles met the inclusion criteria and were included in this descriptive review. Statistical analysis was descriptive in the form of means, proportions, ranges, and percentages.

Table 1. A summary of our search strategy.

Items	Specification
Search date	Databases searched up to August 31st, 2023,
Electronic Databases	PubMed, Embase, Google Scholar
Search terms	Sevelamer, Renvela, Renagel, crystal-induced colitis, colitis, lower gastrointestinal bleeding
Timeframe	From inception to August 2023
Inclusion and Exclusion criteria	Inclusion: - Case reports, image articles, case series and conference abstracts on sevelamer-induced gastrointestinal pathology (colitis/ulceration/bleeding/obstruction) - Reports written in English language - Articles available as full-texts Exclusion criteria - Non-English language articles - Non-human subjects - Non-case reports articles - Articles with insufficient information - GI mucosal injury due to other medications

3. Results

In total, our search stratagem yielded 1239 articles, which were filtered to 228 articles using the study type. Twenty-eight articles comprising 36 patients were included in the review, after screening for duplicates and irrelevant articles. The PRISMA flow diagram represents the search strategy and results (Fig. 1). There were six conference abstracts, three image articles, 17 case reports, and two case series. Of the 36 patients, 21 (58%) were female and 15 (42%) were male. The patients' age ranged from 17 to 83 years, with an average age of 52.25 years. Eighteen patients (50%) presented with GI bleeding (melena, hematochezia, or both), 17 (47%) presented with abdominal pain, and seven patients (20%) presented with both abdominal pain and GI bleeding. Sevelamer was discontinued in all the patients, and 27 (75%) experienced clinical improvement or symptom resolution. One patient required sevelamer dose reduction, one required aggressive lavage, and one required prophylaxis with diphenoxylate/atropine. One patient required hemoclip placement and coil embolization because of persistent GI bleeding. Eight patients (22%) required colectomy due to colonic perforation, malignant obstruction, or extensive necrosis.

4. Discussion

4.1. Epidemiology

Sevelamer is a complex molecule made of a backbone polyallylamine chloride cross-linked with epichlorohydrin, which is not absorbed in the GI tract.[12,13] This structure allows the molecule to act as a non-specific anion binder when reduced by the acidic pH of the stomach.[12,13] Sevelamer is not absorbed in the GI tract but instead binds phosphate, displacing it from previously bound bile acid, reducing its GI absorption.[5,12,13] The only indication for sevelamer approved by the Food and Drug Administration (FDA) is the control of serum phosphorus in adults and children aged 6 years and older with chronic kidney disease (CKD) on dialysis.[13] Sevelamer is also hypothesized to lower

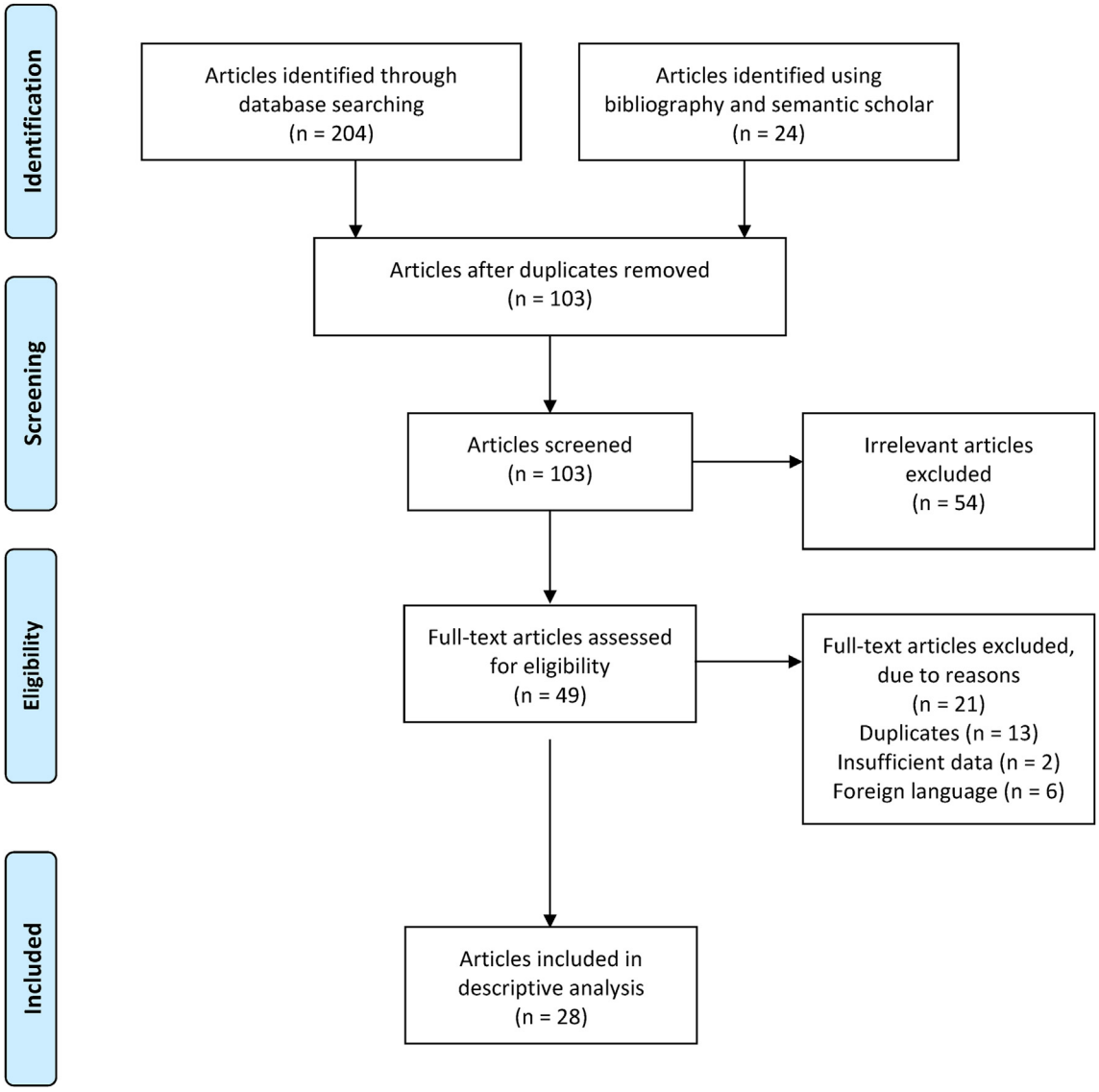

Fig. 1. PRISMA flow diagram showcasing the search strategy and results.

serum cholesterol, proinflammatory mediators, and uremic toxins, such as p-Cresol, which are inadequately eliminated via dialysis.[13] Sevelamer carbonate is available as a tablet or powder, and the initial dose is 800 mg or 1600 mg administered orally three times a day with meals.[14] Sevelamer hydrochloride (Renagel) on the other hand, exists only in tablet formulation but has the same dosing schedule as Renvela. In pediatric patients, sevelamer dosing is titrated based on the body surface area.

Sevelamer causes mild GI symptoms such as nausea, vomiting, abdominal pain, and constipation.[2,4-6,13,15-23] Rare complications such as obstruction, mucosal injury, bleeding ulceration, necrosis, and perforation have also been reported.[4,5,13,20] Despite its known association with GI injury, little research has been conducted on its mechanism.[2] The current data is retrospective in the form of case reports and conference proceedings. In 2008, Madan et al.[17] reported the first case of SIGMI in a patient who presented with rectal bleeding and was diagnosed with stercoral ulcers during colonoscopy. Since then, 27 additional cases have been reported (Table 2); however, prospective studies evaluating GI complications of sevelamer in patients with ESRD are still lacking.

4.2. Pathogenesis

There is a paucity of data on SIGMI and the mechanism of injury is not completely understood. The spectrum of mucosal injury ranges from acute

Table 2. Summary table of sevelamer-induced gastrointestinal mucosal injury cases published in the literature.

Author(s)	Year	Patient	Presentation	Intervention/Outcome	Endoscopy	Pathology	Article
Prlic et al.[1]	2023	74F	Rectal bleeding, colonic perforation, shock	Total colectomy & ileostomy Sevelamer discontinued.	Large ulceration in the transverse colon	Mucosal injury with "fish-scale" crystals	Case report
Pant et al.[2]	2023	77F	SOB, fatigue, and weakness	Sevelamer discontinued	Ulcers in the cecum and ileocecal valve,	Active colitis with ulceration and granulation tissue, SC	Case report
Deshmukh et al.[3]	2022	66M	Hematochezia	IVF and PPIs. Sevelamer discontinued. Colitis resolved	Friable, erythematous mucosa and ulcerations in the colon	Necrotic debris, acute inflammation & ulceration "Fish-scale" crystals	Abstract
Yamada et al.[4]	2022	24F	Abdominal pain & melena	Sevelamer discontinued. Started on ferric citrate	Ulcerations in the cecum	Crystalline material consistent with sevelamer	Abstract
Hryzak et al.[5]	2022	67M	Abdominal pain, nausea, & vomiting	Hemi-colectomy due to bowel necrosis		Crystalline resin within lumen & stoma ulceration consistent with sevelamer crystals	Abstract
Cockrell et al.[6]	2021	65F	Abdominal pain and hematochezia	Sigmoid colectomy and end colostomy due to large bowel obstruction	Multiple non-bleeding sigmoid diverticula	Pericolonic abscess and sevelamer crystals	Case report
Schoot et al.[7]	2021	67F	Rectal bleeding	Stopped Sevelamer. Rectal bleeding decreased/resolved	Multiple deep ulcers & diffuse edematous mucosa in sigmoid and rectum	Ulcerated mucosa	Case report
Al-Qaisi et al.[8]	2020	71M	Hematochezia	Sevelamer discontinued. Colitis resolved	Ulcerations, mucosal erythema & nodularity in rectum & rectosigmoid colon	Crypt distortion, fragments of resin consistent with sevelamer	Abstract
Lai et al.[9]	2020	47M	Crampy abdominal pain	Sevelamer switched to calcium carbonate. Symptoms improved	Circumferential ulceration in the colon	Ragged colonic mucosa with ulcerative debris and non-polarizing crystalline material	Case report
Keri et al.[10]	2019	35F	Abdominal pain, rectal bleeding, and hematochezia	Right hemicolectomy followed by ileocolic anastomosis		Patchy transmural ischemic necrosis with vascular fibrin thrombi and sevelamer crystals	Case report
Uy et al.[11]	2018	33M	Hematochezia & periumbilical pain	Sevelamer switched to lanthanum carbonate. Hematochezia resolved	Non-bleeding ulcerated colonic mucosa	Sevelamer crystals	Case report
Nambiar et al.[12]	2018	56F	Rectal bleeding, syncope, and shortness of breath	Emergent hemi-colectomy	Erythema and ulceration near hepatic flexure without active bleeding	Colonic mucosa with inflammation & ulceration. Clusters of "fish-scale" crystals	Case report
Okwara et al.[13]	2018	70M	Copious hematemesis, rectal bleeding, SOB, dizziness	Hemostatic clips Coil embolizations: distal R gastroepiploic artery, gastroduodenal artery, gastrohepatic trunk	EGD: ulcerated mass at pylorus	Sevelamer crystal-associated chronic, focally active gastritis	Case report/ Image article
Brahmbhatt et al.[14]	2017	40F	Diarrhea and LLQ abdominal pain	Sevelamer switched to calcium acetate.	Fungating, non-obstructing, circumferential, 6 cm mass in the proximal sigmoid colon	Necro-inflammatory debris with embedded crystalline fragments	Abstract

(*continued on next page*)

Table 2. (continued)

Author(s)	Year	Patient	Presentation	Intervention/Outcome	Endoscopy	Pathology	Article
Bansal et al.[15]	2017	42F	LLQ abdominal pain & watery diarrhea	Sevelamer discontinued	6 cm, fungating, oozing mass sigmoid colon	Necrotic debris and eosinophilic "fish-scale" crystals	Image article
Modi et al.[16]	2017	60F	Diffuse abdominal pain and watery diarrhea	Restarted on sevelamer with diphenoxylate/atropine, PRN	Solitary 14-mm ulcer with surrounding erythema in distal rectum	Colonic mucosal inflammation and crystal foreign material	Image article
Sy et al.[17]	2017	69M	Abdominal pain	Aggressive lavage	35-mm mass lesion in the cecum	Benign inflamed colonic mucosa and sevelamer crystals	Image article
Yuste el.[18]	2017	51F	Hematochezia	Sevelamer switched to calcium carbonate	DRE: big anal fissure. Large ulcer in the ileocecal valve	Focal erosion with bacterial material mixed with sevelamer crystals	Case series
		53M	Painless rectal bleeding	PPIs. Sevelamer dose reduced	Pseudopolyps and inflammation of the colon	Chronic colitis with low inflammatory activity and sevelamer crystals	
		76F	Lower GI bleeding and severe anemia	Symptoms resolved with the discontinuation of sevelamer	Chronic gastritis, diverticulosis, several gastric and colonic polyps	Superficial sevelamer crystals surrounded by mucus and detritus	
Nandiraju et al.[19]	2016	67M	Symptomatic anemia, hematochezia, and melena	Symptoms resolved with the discontinuation of sevelamer	Large ulceration at the splenic flexure and indeterminate diffuse colitis and polyps	Rare surface crystals with "fish-scales" consistent with sevelamer crystals	Abstract
Desai et al.[20]	2016	45F	Intermittent abdominal cramping and hematochezia	Symptoms resolved with the discontinuation of sevelamer	Healing linear ulcerations at the flexures, transverse, and sigmoid colon Anal verge stricture, and inflamed and friable colonic mucosa	Acute inflammation, ulceration, and granulation tissue associated with fragments of crystal material	Case report
Tieu et al.[21]	2016	74F	Constipation, abdominal discomfort, rectal pain & hematochezia	Sevelamer switched to calcium acetate.	Recto-sigmoid ulcers	Pill fragments consistent with sevelamer crystals	Case report
Kim et al.[22]	2016	17F	Acute-onset abdominal pain and emesis	Hemi-colectomy with colostomy. Sevelamer discontinued	11-cm stricture and high-grade obstruction at the junction of the descending colon and sigmoid colon	Sevelamer crystals with adjacent ischemic change of the colonic mucosa	Case report
Yamaguchi et al.[23]	2016	66M	Abdominal pain	Hemi-colectomy with colostomy creation for colonic perforation		Sevelamer crystals	Case report
Subramanian & Roorda[24]	2016	65F	Abdominal pain and rectal bleeding	Symptoms resolved with the discontinuation of sevelamer	Pseudomembrane and nodularity in rectosigmoid region	Sevelamer crystals in an area of ulceration	Case report
Hudacko et al.[25]	2015	83F	Mixed shock and abdominal distension	Subtotal colectomy for diffuse bowel necrosis and perforation of transverse colon		Mucosal ischemic injury with ulcers, transmural necrosis, and acute serositis Sevelamer crystals	Case report

Chintamaneni et al.[26]	2014	61F	Painless hematochezia and thrombosed AVF	Symptoms resolved with the discontinuation of sevelamer	5-cm ulceration in sigmoid colon	Sevelamer crystals embedded in colonic mucosa	Case report
Swanson et al.[27]	2013	59F	Anuric, dyspepsia,	Small bowel resection Symptoms resolved with the discontinuation of sevelamer	Unknown	Small bowel ischemia, necrosis & sevelamer crystals	Case series
		68M	Screening colonoscopy	Unknown	Normal colon	Inflammatory polyps with acute inflammation, sevelamer crystals	
		38M	Screening colonoscopy	Unknown	Colon polyps	Acute colitis & sevelamer crystals	
		49F	Dyspepsia	Symptoms resolved with the discontinuation of sevelamer	Diffuse peptic changes	Extensive esophageal ulceration, sevelamer crystals	
		53M	Screening colonoscopy	Unknown	Colon polyp	Mucosal prolapse, sevelamer crystals	
		66M	Rectal bleeding	Symptoms resolved with the discontinuation of sevelamer	Hyperpigmented mucosa in duodenum, antrum, body. Colon polyps	Fragments of tubular adenoma	
		81M	Dysphagia, odynophagia, vomiting	Symptoms resolved with the discontinuation of sevelamer	Extensive esophageal ulcerations and eroded mucosa, plaque-like white exudates	Extensive ulceration	
Madan et al.[28]	2008	62F	Rectal bleeding	Symptoms resolved with the discontinuation of sevelamer	Stercoral ulcers in rectum	Denuded mucosa with acute and chronic inflammation	Case report

inflammation, tissue ischemia and necrosis, pseudopolyps, and ulceration to fecaliths.[5,15,20,24] Sevelamer crystal deposits are thought to be directly cytotoxic to mucosal cells, but this effect is yet to be verified.[15] It is postulated that these crystals can aggregate intraluminally and precipitate into a mass leading to bowel obstruction or perforation.[2,19] Although the etiopathogenesis of SIGMI remains unclear, temporality, dose-response relationship, and biological plausibility have been established in reported observational studies that further strengthen the causation hypothesis.[5,15]

4.3. Clinical manifestations

GI bleeding is the most commonly reported complaint, presenting as frank blood per rectum, hematochezia, or melena.[2,5,17] In our review of published cases of SIGMI, hematochezia was the most common complaint, followed by abdominal pain and diarrhea.[2,4,7,18,19,22,25,26] Sevelamer crystals can be deposited at unique sites such as the esophagus and stomach, resulting in esophageal ulceration, vomiting, hematemesis, dysphagia, odynophagia, gastric ulceration, and abdominal distension.[15,20,22,23,27] Unique patient presentations, such as symptomatic anemia, shock, and syncope, have also been observed.[13,15,22,23]

4.4. Diagnosis

Owing to its rarity and non-specific presentation, SIGMI may be mistaken for ischemic colitis, infectious colitis, inflammatory bowel disease, or other medication-induced colitis. A temporal relationship has been observed between sevelamer use and the onset of GI symptoms. In patients presenting with GI bleeding, bloodwork may be significant for acute blood loss anemia or leukocytosis due to inflammation. Routine imaging studies may be non-specific; however, intraluminal hemorrhage, colonic dilation, and fat stranding have been observed.[17] Endoscopy with biopsy can be both diagnostic and therapeutic. Colonoscopic findings include colonic ulcers, friable and erythematous mucosa, pseudopolyps, masses, anal fissures, anal strictures, pseudomembranes and nodularity, and colonic polyps (Fig. 2).[5-7,9,11,15,16,20,24,26-28] Gastritis, esophageal ulcers, gastric polyps, and ulcerated pylorus have been observed on upper endoscopy.[15,20,22,29] Some patients had normal endoscopic evaluations despite having melena, hematochezia, or signs of obstruction.[4,15,23]

The histopathology of SIGMI varies from active colitis, ulceration and granulation tissue, crypt distortion, eosinophilia, necrotic debris, inflammatory

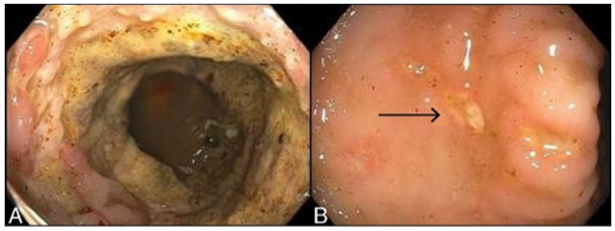

Fig. 2. Endoscopic image showing the descending colon (A) and sigmoid colon with continuous non-bleeding ulcerated mucosa. Used with permission from Uy et al.[7]

polyps, to crystals.[4,5,9,11,13,15,16,18,20,24] Examination of the sevelamer crystals will reveal a non-polarizable "fish-scale" pattern that stains pink centrally and yellow/orange peripherally with hematoxylin and eosin (H&E) stain (Fig. 3).[5,7] Polystyrene sulfonate and cholestyramine are known to cause medication-induced colitis and must be considered in the differential diagnosis of SIGMI.[20] Polystyrene sulfonate crystals share a similar architectural pattern with sevelamer crystals; however, they will stain purple with H&E stain.[5,13,20] Cholestyramine has a unique structure from sevelamer and stains orange when exposed to an H&E stain, which further distinguishes it from sevelamer crystals.

4.5. Treatment

The management of SIGMI remains a challenge due to the limited understanding of its etiopathogenesis, and the absence of established prevention strategies.[5] It is crucial for clinicians to recognize the symptoms associated with SIGMI, including hematochezia, abdominal pain, colonic ulceration, and luminal obstruction, to avoid further complications.[7] In our review of 36 patients with SIGMI, we observed that discontinuing the offending agent resulted in symptom resolution in most patients. Although the clinical improvement was immediate in some patients, it took weeks for others to experience relief. The healing time was most likely determined by the degree of GI mucosal injury. In some cases, patients received supportive management with intravenous fluids, blood transfusion, and proton pump inhibitors.[5,6,13,18,28,30] Some patients required dose reduction, whereas others required adjunctive treatment with diphenoxylate/atropine.[16,20,29] Switching patients to alternative phosphate binders has also been effective. Clinically unstable patients with colonic perforation, malignant obstruction, or extensive necrosis required exploratory laparotomy with colectomy.[2,15,19,24,25,27] Although follow-up endoscopy was performed in some cases, the benefit of relook endoscopy remains unclear. Further research is warranted to understand the etiopathogenesis of SIGMI to guide management and guidelines. **Suspected or confirmed cases on SIGMI can reported on *MedWatch*, a U.S. Food and Drug Administration's (FDA) safety information and adverse event reporting program. This program is designed to allow healthcare professionals and consumers to report adverse events, product quality problems, therapeutic inequivalence/failures, and product use errors associated with FDA-regulated products, including drugs, biologics, medical devices, dietary supplements, and cosmetics.**[31]

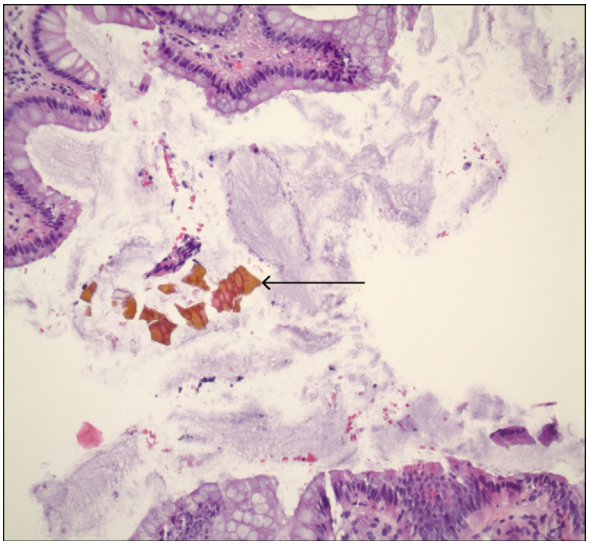

Fig. 3. Colonic mucosa with non-specific minimal reactive changes, and broad, curved, irregularly shaped "fish scales" sevelamer crystals without tissue necrosis on H & E (100x). Used with permission from Uy et al.[7]

5. Conclusion

SIGMI is a very rare clinical entity that results from the deposition of sevelamer crystals in the GI tract. Sevelamer causes mild gastrointestinal symptoms such as nausea, vomiting, diarrhea, and constipation. However, the deposition of sevelamer crystals in the GI tract may lead to mucosal injury, ulceration, tissue ischemia or necrosis, pseudopolyps, and bowel obstruction. SIGMI is often missed in clinical practice because of its rarity and the lack of physician awareness. This literature review provides an overview of SIGMI, focusing on its etiology, signs and symptoms, pathogenesis, diagnosis, and management.

Disclosure

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Ethics statement

Our institution does not require ethical approval for review articles.

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Data availability statement

The authors declare that data supporting the findings of this study are available within the article.

Conflict of interest

No conflicts of interest to declare.

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