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Sevelamer-associated gastric erosions in a hemodialysis patient: A case report and brief literature review

Simella Provatopoulou, Irini Pathiaki, Paraskevi Polyzou, Apostolia Vogiatzi, Dimitrios Lazarou

ABSTRACT

Introduction: The use of sevelamer as a phosphate binder in chronic kidney disease patients with hyperphosphatemia is typically associated with mild gastrointestinal adverse events. However, recent reports indicate that its effect may be considerably more damaging. **Case Report:** We describe the incidental finding of sevelamer crystals in the gastric mucosa of a 55-year-old female patient on maintenance hemodialysis. The patient was subjected to gastroscopy as part of anemia investigation which revealed mild gastritis and presence of linear mucosal erosions at the pyloric antrum. Pathology reported extended granulomatous foreign body response in the gastric mucosa. Giant cell histiocytes were identified containing crystalline material with irregularly shaped fish scales. Pathology findings were consistent with lesions described in recent literature as induced by sevelamer crystals. Sevelamer administration was immediately stopped and a follow-up gastroscopy after 12 months showed improvement of the lesions. **Conclusion:** A thorough literature review reveals that sevelamer-associated mucosal injury has been identified as the underlying cause of several acute gastrointestinal events as well as chronic persistent symptomatology. Currently, its prevalence in hemodialysis patients is largely unknown due to lack of routine endoscopic assessment, however it may be significantly higher than expected. Therefore, timely diagnosis and appropriate management of sevelamer-associated injury require a high index of clinical suspicion, especially for patients with a history of long-term sevelamer use.

Keywords: Crystalline material, Fish scales, Mucosal injury, Sevelamer crystals

Simella Provatopoulou[1], Irini Pathiaki[2], Paraskevi Polyzou[3], Apostolia Vogiatzi[4], Dimitrios Lazarou[5]

Affiliations: [1]MD, PhD(c), Nephrologist, Department of Nephrology, General Hospital of Lamia, Lamia, Greece; [2]MD, Pathologist, Department of Pathology, General Hospital of Lamia, Lamia, Greece; [3]MD, Director of Gastroenterology, Department of Gastroenterology, General Hospital of Lamia, Lamia, Greece; [4]MD, Microbiologist, Department of Microbiology, General Hospital of Lamia, Lamia, Greece; [5]MD, MSc, Nephrologist, Department of Nephrology, General Hospital of Lamia, Lamia, Greece, dimlazarou75@gmail.com

Corresponding Author: Provatopoulou Simella, End Papasiopoulou Str. 35 100, Lamia, Greece; Email: simellap@gmail.com

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INTRODUCTION

Sevelamer is a commonly prescribed medication indicated for the treatment of hyperphosphatemia in patients with renal disease. Owing to its proven effectiveness and favorable safety profile, it is considered first-line therapy for over two decades. The use of sevelamer as a phosphate-binder is typically associated with mild gastrointestinal (GI) adverse events. Common side effects include vomiting, nausea, diarrhea, dyspepsia, flatulence, constipation, and rarely bowel obstruction [1]. Several recent findings indicate that the effect of sevelamer on the GI tract may be considerably more damaging. More specifically, a rapidly growing number of published and anecdotal records have identified severe lesions in the colonic mucosa induced by deposition of sevelamer

pill fragments resulting in ulceration, perforation, and occasionally life-threatening hemorrhage [2–5]. We describe a unique case of gastric erosions associated with sevelamer crystals (SCs) that were incidentally diagnosed in a hemodialysis patient, aiming to contribute to the existing knowledge regarding this entity.

CASE REPORT

A 55-year-old female hemodialysis patient was found severely anemic during her regular monthly workout (blood hemoglobin levels decreased from 11.2 to 8.0 g/dL during the previous month). Anemia type was hypochromic microcytic and standard laboratory testing was unremarkable with normal iron stores. The patient was asymptomatic and reported no recent blood loss. Her medical history included end-stage renal disease on maintenance hemodialysis over the last 11 years, type 2 diabetes mellitus, dyslipidemia, and epileptic seizures. Her medication consisted of vildagliptin 50 mg, simvastatin/ezetimibe 10/20 mg, levetiracetam 1500 mg, and sevelamer carbonate 4000 mg daily, prescribed consistently for several years with sustained clinical efficacy. She was administered intravenous erythropoietin 3000 IU per dialysis session and appropriate iron supplementation with no recent dose modifications. It was confirmed that the patient had been compliant with her medication and routine dialysis sessions. Moreover, the medical prescription had been correctly executed by the dialysis staff. Notably, the patient had been subjected to a routine upper and lower GI endoscopy three years ago during pretransplant evaluation that was only remarkable for enlarged hemorrhoids.

Upon anemia investigation, a fecal occult blood test was prescribed that was found positive. Subsequently, GI imaging and endoscopy were performed that did not reveal any site of active bleeding. Gastroscopy findings included mild gastritis and presence of occasional linear mucosal erosions at the pyloric antrum resembling watermelon stomach (Figure 1). Testing for *Helicobacter pylori* was negative. As a result, the patient's anemia was attributed to either the known hemorrhoidal disease or occult upper GI blood loss. Conservative management was advised and a brief course of proton pump inhibitor was prescribed. During the following month, the patient's blood hemoglobin levels gradually increased to 10.8 g/dL without any other intervention.

Surprisingly, pathological evaluation of the gastric biopsy specimen revealed unexpected findings. More specifically, extended granulomatous foreign body response was identified in the antral and pyloric mucosa corresponding to the sites of erosion (Figure 2). Giant cell histiocytes were observed in the lamina propria containing crystalline material in their cytoplasm (Figure 3). The intracytoplasmic material had pink irregularly shaped fish scales on Hematoxylin-Eosin (H&E) stain, whereas it acquired a violet color on periodic acid–Schiff stain with diastase (PAS/D) (Figure 4). Moreover, vascular distention and congestion in the corium was observed. These findings were consistent with lesions that have been described in recent literature as induced by SCs. Following the pathology report, sevelamer carbonate was discontinued and the patient was switched to calcium carbonate as a phosphate binder. In a repeat gastroscopy of 12 months, despite significant improvement after the erosions, SCs were still microscopically detected in the gastric mucosa.

DISCUSSION

It is commonly accepted that medication resins can be damaging to the GI tract. Resin-associated mucosal injury has been thoroughly described by pathologists in

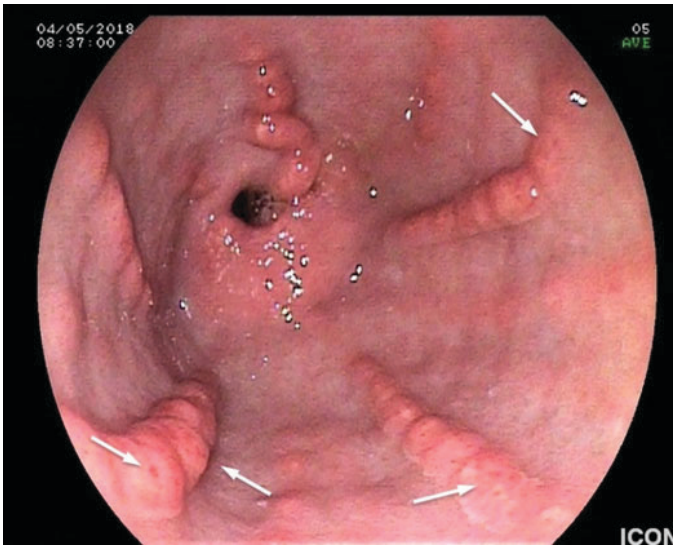

Figure 1: Gastroscopy image. Linear erosions at the pyloric antrum without signs of active hemorrhage (white arrows).

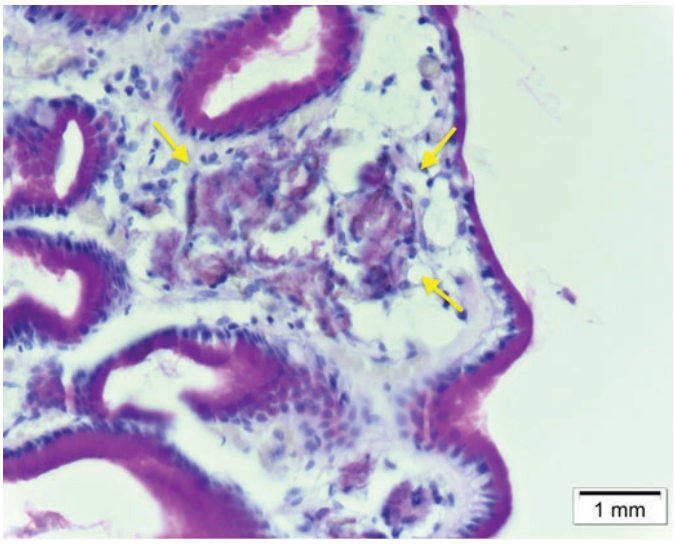

Figure 2: Granulomatous foreign body response (yellow arrows) in the antral and pyloric mucosa surrounding pink crystalline material (H&E).

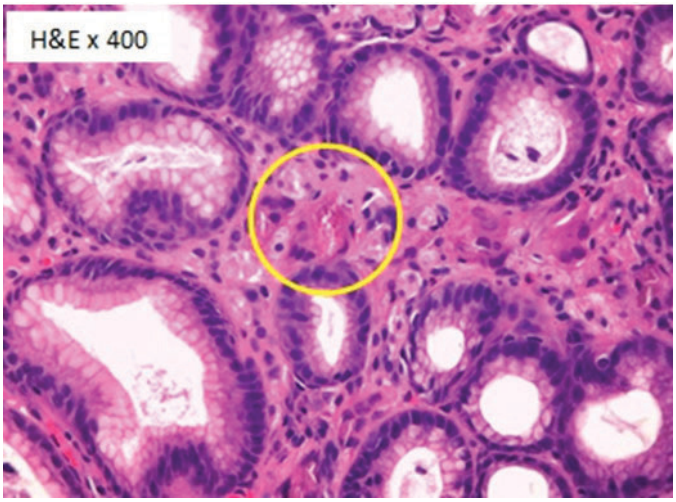

Figure 3: Pyloric mucosa with the presence of giant cell histiocytes in the lamina propria containing pink crystalline material (yellow circle) (H&E ×400).

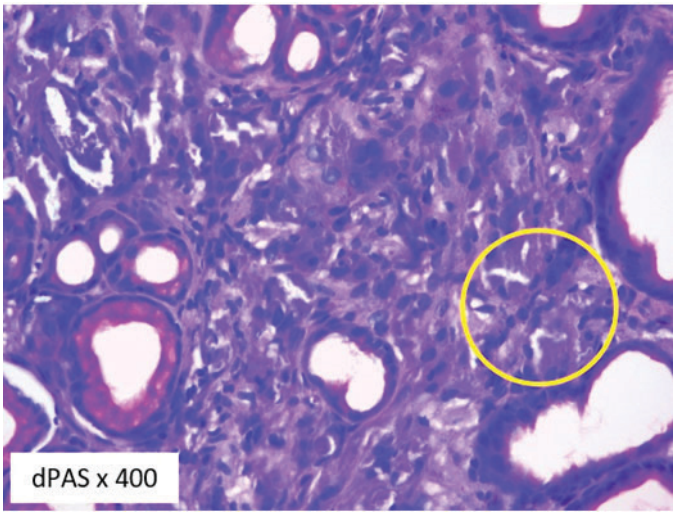

Figure 4: Intracytoplasmic crystalline material of violet color (yellow circle) in the giant cells (PAS/D ×400).

terms of histological features and differential diagnosis [6]. The identification of resin-induced mucosal injury in a biopsy specimen may pose a clinical emergency and prompt enhanced attention and careful monitoring, hence increased clinical suspicion and provision of detailed medical history is warranted [3, 7]. Several medications have been identified as capable of causing mucosal injury through crystalline formation, such as sodium polystyrene sulfonate (Kayexalate), bile acid sequestrants (Cholestyramine), and more recently sevelamer.

Sevelamer is an insoluble non-absorbed polymer used as a phosphate binder in patients with hyperphosphatemia due to chronic kidney disease (CKD). It contains multiple amines that become partially protonated in the stomach and interact with phosphate ions in the small intestine, thus preventing their absorbance. In animal studies, the presence of eosinophilic crystalline material inside the intestinal lumen was attributed to increased intraluminal osmotic pressure and subsequent submucosal edema at high doses of sevelamer [1]. In hemodialysis patients, crystallization inside the lumen may be enhanced by the relative dehydration due to reduced water consumption. Furthermore, it has been postulated that GI dysmotility, or abnormal secretion and absorption due to chronic uremia could be implicated in the crystallization process [3]. Nevertheless, the potential mechanisms of crystallization cannot adequately explain the affinity of SCs for GI mucosa nor the severity of the resultant injury.

In international literature, sevelamer-associated mucosal injury has been documented in more than 40 cases so far, therefore it can be regarded as a distinct clinical and pathologic entity. It is characterized by foreign body response and subsequent granulation tissue formation in the GI mucosa. Mucosal abnormalities range from focal inflammation and edema to ulceration, pseudoinflammatory polyp formation, ischemia, and necrosis. The pathognomonic feature of sevelamer-induced injury is the presence of irregularly spaced, broad, nonpolarizable crystals with a fish scale pattern. They can be differentiated from other crystals with H&E stain, as are usually two-toned with a pink center and rusty yellow edges, whereas Kayexalate crystals are purple and Cholestyramine crystals are orange [2]. Furthermore, SCs are stained violet on PAS/D, contrary to Kayexalate crystals that are magenta or Cholestyramine crystals that are gray-pink [2, 4]. Sevelamer crystals have been identified in biopsy specimens from the bowel lumen, the affected mucosa, the submucosal area, or the ulcer bed and exudate [2, 3, 7, 8]. Their unique pattern has been reproduced ex vivo by crushing and processing sevelamer tablets [2].

The etiological association of SCs with mucosal injury is yet to be determined. Originally it was postulated that, at least in some cases, SCs were incidentally detected within mucosal injury induced by an unrelated, usually chronic comorbid process [2]. It has also been suggested that the increased frequency of mesenteric ischemia in CKD patients renders them more susceptible to intestinal necrosis and perforation in the presence of constipation [7]. An indirect mechanism of injury has been described involving a SC-containing fecal mass with subsequent superficial erosion, stercoral ulceration, or bowel obstruction [4, 9, 10]. Most researchers agree that SCs have a direct damaging effect on the GI mucosa, but a disruption in mucosal integrity is probably required for the process to initiate [6, 11].

In the vast majority of reported cases, mucosal injury was located in the colon and predominantly the rectosigmoid. Fewer incidents have been reported with ulcers on the ileocecal valve, duodenal, and esophagus, while some patients had multiple ulcers throughout the GI tract. Interestingly, SCs have been detected in unexpected sites such as the bronchi [12]

and perirenal soft tissue [13]. It is unclear why SCs are more commonly found in certain locations, but it may be related to anatomic differences in the GI tract, sevelamer pharmacokinetics and presence of previous GI trauma or surgical sites. Our patient had a rare gastric location of SCs. To our knowledge, gastric location of sevelamer-associated injury has been described in only one other patient whose presenting symptom was hematemesis and endoscopy revealed SC-induced chronic, focally active gastritis in the antral mucosa [11].

In most described cases, clinical presentation was acute ranging from abdominal pain to severe hemorrhage and subsequent hemodynamic instability [5, 7, 11]. Less frequently, presenting symptoms were those of chronic obstruction, bowel distention, or intermittent hematochezia [4, 8, 10]. Absence of clinical symptoms has been reported in three cases in which endoscopy was performed for screening purposes and revealed SC-containing inflammatory colon polyps [2]. Diagnosis was based on histologic examination of biopsy material that was collected either endoscopically or surgically, although some cases were diagnosed as sevelamer-associated in retrospect [4]. In all patients, sevelamer administration was discontinued after the identification of the crystals and further management was directed by the location and severity of mucosal injury. Immediate enterectomy was required in patients presenting with acute abdomen [7], whereas the remaining was managed conservatively with subsequent clinical improvement [4, 10].

The clinical course and prognosis of sevelamer-associated mucosal injury have not been systematically evaluated. Endoscopic follow-up of the lesions has been reported in very limited cases. However, where available, it was consistent with repair of mucosal injury [8, 10]. In our patient, sevelamer-associated injury of the gastric mucosa caused epithelial erosions with no accompanying symptoms. After 12 months of follow-up, there was no recurrence of anemia and endoscopic reevaluation affirmed that mucosal injury had significantly subsided. Despite that fact, SCs were still present in the gastric mucosa.

CONCLUSION

The spectrum of sevelamer-associated mucosal injury is expected to broaden as diagnostic endoscopy becomes widely implemented. In the CKD population, whose unique nature is accompanied by frequent GI discomfort, the probability of overlapping symptomatology or covert SC-induced pathology should not be overseen. Therefore, increased awareness is warranted until large-scale studies are able to elucidate the clinical characteristics of this condition.

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Author Contributions

Simella Provatopoulou – Conception of the work, Design of the work, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved

Irini Pathiaki – Acquisition of data, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Paraskevi Polyzou – Acquisition of data, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Apostolia Vogiatzi – Design of the work, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Dimitrios Lazarou – Design of the work, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.