Sevelamer-Associated Appendicitis

UC DAVIS HEALTH

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Background:
This 34 year old woman presented to our institution with a history of acute abdominal pain, nausea, and non-bilious, non-bloody vomiting. She had a history of lupus nephritis for which she was treated with peritoneal dialysis. She was found to have a polymicrobial bacterial peritonitis and positive blood cultures, with negative CT and vaginal ultrasound scans. She was treated with antibiotics and her peritoneal catheter was removed. Her abdominal pain diminished and her white cell count decreased.

She then developed acute right lower quadrant abdominal pain and leukocytosis. Her pain increased and became refractory to narcotics, and a third CT a week later showed intraperitoneal free air and thickening of the ascending and descending colon. Exploratory surgery revealed a gangrenous perforated appendix with diffuse peritonitis and a pelvic floor abscess. Her appendix was removed, and her recovery was complicated by additional intraperitoneal fluid collections (requiring IR drainage), fluid overload (requiring an ICU stay), and C. difficile colitis.

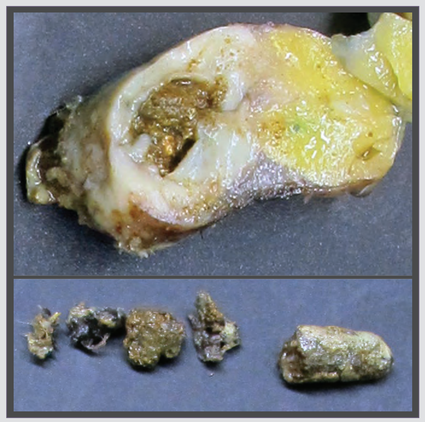

Figure 1: *Gross appearance of the cut surface of the appendix, with fibrinopurulent exudate and granular brown luminal contents.*

Findings:
Grossly, her appendix was gangrenous and perforated with marked fibrinopurulent exudate (see **Figure 1**). The lumen was distended and filled with a granular brown material. Histologic sections revealed innumerable crystalline bodies within the appendiceal lumen and invested within the inflamed epithelium (see **Figure 2**). The crystals show a characteristic shape and two-tone coloration that is consistent with published reports of sevelamer.

Review of her medical record showed treatment for hyperphosphatemia with 1600 mg of Renagel (sevelamer HCl; Sanofi, Paris) three times daily with meals.

Discussion:
Sevelamer is a non-absorbable anion-exchange hydrogel polymer approved by the FDA in 1998 designed to bind phosphate within the GI lumen into an insoluble compound that is passed in the stool.[1] It is composed of ammonia fixed on a carbon backbone and associated with an anion in the solid form (e.g. hydrochloride).[2]

Previous studies have shown that the crystals of sevelamer are morphologically distinct from other ion-exchange resins (e.g. kayexalate, cholestyramine). They can be distinguished histologically by the characteristic "fish scale" cracked appearance with curved intersecting lines. On H&E, they show two-toned coloration with outlines highlighted in pink and the interior of the crystals orange-yellow.[2] Notably, reports have suggested that crystals embedded within areas of mucosal ulceration or ischemia, or within necrotic debris, can show a deep “rusty” brown color (See **Figure 2,** left).[2]

Kayexalate (sodium polystyrene sulfonate) crystals, by contrast, have a more rectangular shape with perpendicular intersecting lines and show a characteristic violet color.[1,2]

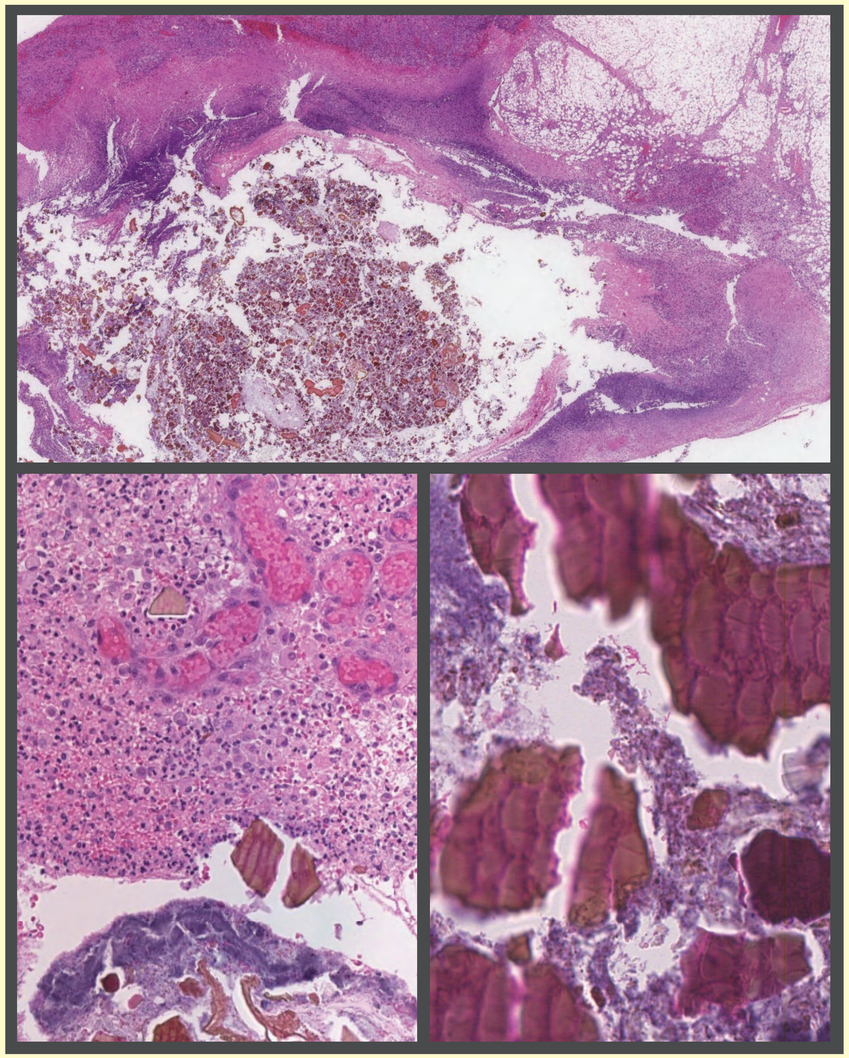

Figure 2: *Histologic examination of the resected specimen. A low power view **(top)** shows the lumen of the appendix filled by innumerable crystalline structures with transmural appendicitis and serositis. A high power view **(left)** shows mixed inflammatory infiltrate with granulation tissue, bacterial overgrowth, and crystals intimately associated with the residual mucosa. These crystals show a “rusty” brown color. Examination of the crystals **(right)** shows two-toned pink to orange colored fragments with characteristic fracture lines creating a “fish scale” appearance. The lines intersect at curved points rather than at perpendicular angles.*

Cholestyramine crystals lack internal lines, have a solid single-tone color (typically eosinophilic), and a smooth texture.[1,2] Studies have suggested that cholestyramine crystals lack the ability to cause mucosal injury, though they may be associated with areas of injury in patients taking multiple resins.[2] Crystals seen in this case are morphologically consistent with sevelamer; the patient was not taking any other ion-binding resins.

Previous reports have implicated sevelamer use as a risk factor for mucosal-associated GI tract injuries. The risk is thought to increase with GI dysmotility and with increasing doses of sevelamer.[2] Prior reports have included both upper and lower GI injuries ranging from esophageal ulcerations[2,3]; chronic gastritis[3]; duodenal mucosal ulcerations[4]; inflammatory pseudopolyps of the ileocecal valve[3]; ascending, transverse, and descending colonic mucosal ulcerations[5,6]; sigmoid colonic strictures[7]; colonic mass-like inflammatory lesions[8]; hematochezia[9]; and rectal stercoral ulcers,[10] lesions which span almost the entirety of the GI tract. Limited data have suggested that up to 25% of patients have lesions involving more than one area of the GI tract at presentation.[3] To our knowledge, this is the first reported case of acute appendicitis tied to sevelamer use.

There is inadequate data to definitively determine sevelamer to be the cause of the appendicitis in this case; however, the rich abundance of crystals within the appendiceal lumen leaves no doubt that sevelamer was a contributing factor. No other cause of her appendicitis has been identified.

Conclusion:
Our patient eventually recovered after a nearly month-long hospitalization. She was transitioned back to peritoneal dialysis and subsequently discharged. She remains on sevelamer to prevent hyperphosphatemia and has not presented with further sequelae.

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