Pathology of Resin-Induced Gastrointestinal Damage: Report of 15 Cases and Review of Literature

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ABSTRACT

Objective: Medication resins such as Kayexalate and Sevelamer used in the setting of chronic kidney disease for the correction of hyperkalemia and hyperphosphatemia are associated with gastrointestinal mucosal injury. In this study we describe the clinico-pathological features of Resin-induced gastrointestinal mucosal injury highlighting the histo-morphological appearances and differential diagnoses. The aim of this study is to increase the awareness of pathologists and clinicians alike to an under-reported etiology and pattern of intestinal mucosal injury related to medical resin therapy which may at times pose a clinical emergency.

Material and Method: The archives of the Department of Histopathology, Mubarak Al Kabir hospital were analyzed for cases of resin-induced gastrointestinal mucosal injury between 2013 and 2018.

Results: Of the 15 cases, Kayexalate crystals were identified in 7 cases, Sevelamer in 5 cases and both together were seen in 3 cases. Resin crystals were identified in the gastric antrum&duodenum (3 cases), colon (9 cases in the left colon, 2 cases in the right colon) and anal canal (1 case). The histological tissue reactions included mucosal necrosis (1 case), inflammatory polyps (2 cases), mucosal ulcerations with granulation tissue formation (10 cases), perforation (1 case) and luminal crystals (1 case).

Conclusion: Accurate and timely recognition of the resin crystals in biopsy samples with clinical correlation is mandatory to avoid serious complications.

Key Words: Resins, Kayexalate, Sevelamer, Gastrointestinal tract injury

INTRODUCTION

The gastrointestinal tract (GIT) is a target of several types of medical drugs including nonsteroidal anti-inflammatory drugs, iron pills, Taxol, Cellcept, bisphosphonates, colchicines and oral resins used in renal failure patients (1).

Resins which include Kayexalate, Sevelamer and bile acid sequestrant agents are non-absorbable medications that facilitate ion exchange. Their main therapeutic effect is exerted within the lumen of the GIT. Reported clinical adverse effects related to the GIT include constipation, nausea, diarrhea and vomiting. In addition, mucosal ulceration including wall perforation and post-inflammatory stricture formation are among the serious complications which may present as a clinical emergency (2-12).

Pathologists are increasingly required to identify such resin-induced damage in small biopsies. This however, can be very challenging since changes reported overlap with those seen in inflammatory bowel disease, ischemic colitis, infectious colitis as well as microscopic colitis. One of the

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main distinctive features of resin mucosal damage is the identification of resin crystals. This is reported in roughly in 75% of cases according to a study by Gonzalez et al. (13). It is logical to think that familiarity of the reporting pathologist with the different morphological appearances of such resins coupled with a high index of suspicion with clinical correlation is crucial.

In the current study, we present a series of 15 cases encountered in our teaching hospital in which resins were identified in various types of surgical and biopsy material of the GIT with discussion of their pathological features and correlation with other inflammatory disorders of the GIT.

MATERIALS and METHODS

A retrospective review of our archives between 2013 and 2018 uncovered 15 cases where resins were identified in biopsy materials. The Hematoxylin and Eosin (H&E) stained sections were evaluated for general morphology. This was complemented by examination of two additional ancillary stains: Periodic Acid-Schiff with diastase (PAS/D)

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and Zeihl-Neelsen Acid-Fast Bacillus (AFB) stain. The following patient details were extracted from the electronic file: age, sex, type of specimen, clinical history provided on the request forms; patient clinical data from the case files were retrieved in addition to other laboratory results at the time of admission. These were correlated with the type of crystal seen and the associated tissue reactions in the biopsy.

Kayexalate crystals were identified by their mosaic pattern of rectangular shaped "fish scales" showing perpendicular points of intersection; they appeared purple on H&E (Figure 1A, B), turned magenta on PAS/D (Figure 1C) and stained black with acid-fast stains (Figure 1D) (8,13,14). These crystals were refractile but did not polarize.

Sevelamer crystals were non-polarizable with broad, curved, and irregularly spaced "fish scales" and displayed a

2-toned color imparted by bright pink linear accentuations and a rusty yellow background (Figure 2A,B). They acquired a violet color on PAS/D and maintained their internal structure (Figure 2C) and magenta color on AFB stain (Figure 2D) (8).

RESULTS

A total of 15 cases were analyzed for this study. The clinicopathological features are summarized in Table I. Of the 15 cases, 3 were surgical resections and 12 were biopsy samples. The patients were 10 males and 5 females and the age range was 41- 82 years. Kayexalate crystals were identified in 7 cases, Sevelamer in 5 cases and both together were seen in 3 cases. Resin crystals were identified in the upper GIT (duodenum & gastric antrum, 3 cases) (Figure 1A) and colon (11 cases of which 9 were in the left side of the colon and 2 cases in the right side) (Figure 2A; 3A).



Figure 1: A) Gastric antral biopsy with ulceration and purplish Kayexalate crystals (H&E; x50). **B)** Purplish Kayexalate crystals with rectangular shaped fish-scales (H&E; x400). **C)** Magenta colored Kayexalate crystals (PAS/D; x200). **D)** Black colored Kayexalate crystals (Acid Fast stain; x200).

Table	I: Sun	nmary of clinical de	tails, site of biopsy and	histological features.			
Patien Age	t Sex	Type of Specimen	Site	Clinical History Provided	Type of Crystals	Associated Tissue Reaction	Background Renal Disease/ History of Drug Intake
82	Μ	Biopsy	Duodenum	Endoscopy: Large duodenal ulcer	Kayexalate	Ulcer and granulation tissue	CKD, hyperkalemia; history of oral intake of Calcium polystyrene sulfonate
72	Μ	Biopsy	Rectosigmoid colon	Colonoscopy: Large ulcerations	Kayexalate	Severe colitis with ulcerations	CKD, Hyperkalemia, history of calcium polystyrene sulfonate 30 gm enema
73	Μ	Surgical resection	Sigmoid colon	Intestinal obstruction	Kayexalate	Concomitant colonic adenocarcinoma and luminal crystals	AKI on top of CKD, Hyperkalemia; history of oral intake of calcium polystyrene sulfonate
41	ц	Biopsy	Duodenum, Gastric antrum	Endoscopy:Irregular duodenal folds, antral gastritis	Kayexalate	Active duodenitis and gastritis	AKI on top of CKD, Hyperkalemia; history of oral intake of calcium polystyrene sulfonate
71	ц	Biopsy	Stomach, caecum, ascending, transverse and descending colon	Anemia; extensive longitudinal ulcerations? ischemic	Kayexalate	Mucosal ulcerations with granulation tissue	AKI, Hyperkalemia; History of oral intake of calcium polystyrene sulfonate
61	Μ	Biopsy	Sigmoid colon	Mucosal ulcerations	Kayexalate	Mucosal ulcerations with granulation tissue	AKI on top of CKD, Hyperkalemia; history of intake of calcium polystyrene sulfonate
48	ц	Biopsy	Peri-anal soft tissue	Peri-anal fistula	Kayexalate	Inflammatory granulation tissue	No history available
65	ц	Biopsy	Transverse colon	Colonoscopy: Colonic polyp	Sevelamer	Inflammatory polyp	CKD, hyperphosphatemia; History of Sevelamer hydrochloride 800mg intake.
68	Μ	Biopsy	Transverse & Rectosigmoid colon	Colonoscopy: Mucosal ulcerations	Sevelamer	Moderate to severe pancolitis	Renal stone disease, hyperphosphatemia; history of intake of Sevelamer hydrochloride 800 mg
45	Μ	Surgical resection	Rectosigmoid colon	Diverticular disease	Sevelamer	Diverticular perforation, abscesses and diverticulitis	No history available
75	Μ	Biopsy	Sigmoid colon	Ulcerated polypoid lesion	Sevelamer	Inflammatory polyp, acute colitis with ulceration	CKD, ESRD, History of intake of Sevelamer hydrochloride 800mg
60	Μ	Right hemicolectomy	Caecum, transverse colon	Melena, bowel peforation	Sevelamer	Colonic mucosal ulcerations	AKI on top of CKD, hyperphosphatemia, history of Sevelamer hydrochloride 800 mg intake
77	ц	Biopsy	Caecum, hepatic flexure colon	Mucosal ulcerations ?ischemic	Kayexalate &sevelamer	Acute colitis with ulceration	CKD; hyperkalemia & hyperphosphatemia; history of Sevelamer hydrochloride & calcium polystyrene sulfonate treatment
64	Μ	Biopsy	Caecum	Cecal ulcers? ischemic	Kayexalate &sevelamer	Ulcer and granulation tissue	CKD; hyperkalemia & hyperphosphatemia; history of Sevelamer hydrochloride 800 mg & calcium polystyrene sulfonate treatment
53	Μ	Biopsy	Anal canal	Anal pain & bleeding	Kayexalate & Sevelamer	Extensive tissue necrosis with ulceration and inflammation	CKD; hyperkalemia & hyperphosphatemia; history of Sevelamer hydrochloride & calcium polystyrene sulfonate treatment
AKI: Ac	ute kic	lney injury, CKD: Chi	ronic kidney disease, ESR	D: End stage renal disease.			

Two cases showed crystals in the perianal soft tissue associated with fistula and the other in the anal canal associated with extensive tissue necrosis (Figure 3B). Among the gastrointestinal cases, three cases had concomitant pathology such as ulcerative colitis, diverticular disease and colonic adenocarcinoma. The remainder of the cases presented as ulcerations endoscopically.

None of the pathology request forms had any relevant clinical history such as background of chronic kidney disease (CKD) or any history of intake of these resins. Retrieval of data from case files showed up background of CKD and relevant drug history in 13 cases. No supporting clinical histories were obtained in two cases.

DISCUSSION

Kayexalate is a non-absorbable ion-exchange resin consisting of sodium polystyrene sulfonate (SPS). It is mainly used for treating hyperkalemia in chronic renal failure and can be administered orally or locally as an enema. An osmotic laxative (Sorbitol) is usually added to reduce the risk of constipation and impaction. The gastrointestinal complications are seen more frequently in uremic patients and in post-transplant patients (2,4,5). Both Kayexalate crystals and the hyperosmotic sorbitol diluent used are considered to cause marked mucosal injury (3).

Overall, the clinicopathological features associated with Kayexalate crystals in the current report are similar to



Figure 2: A) Colonic ulceration with acute inflammatory exudate and Sevelamer crystals (H&E; x50). **B)** Sevelamer crystals with a 2-toned color imparted by bright pink linear accentuations and a rusty yellow background and irregularly spaced fish-scales (H&E; x400). **C)** Sevelamer crystals with violet hue (PAS/D; x200). **D)** Magenta colored Sevelamer crystals (AFB; x200).

those in the literature. Ulcerations were identified in 7 of the gastrointestinal biopsy cases and were associated with inflamed granulation tissue (Figure 1A, 3A). In one of the cases with concomitant adenocarcinoma, Kayexalate crystals were noted in the lumen but without any inflammatory tissue reaction.

Sevelamer, the newest in the family of resin medications, is a phosphate binding anion-exchange resin which is used to treat and prevent hyperphosphatemia caused by chronic renal failure. It is a cross-linked polymeric amine that also binds bile acids and is not systemically absorbed.

The histopathology of Sevelamer crystals in the GIT was described by Swanson et al. They noted that their presence was associated with mucosal abnormalities such as inflammation, ulceration, ischemia and necrosis (8). Though limited, a literature search has revealed 16 case reports of Sevelamer-induced gastrointestinal complications such as recto-sigmoid ulcerations, mass forming lesions, and diverticular rupture (9-12). Our cases also showed mucosal necrosis (Figure 3B), mucosal ulcerations with granulation tissue formation (Figures 2A; 3C,D) and perforation. The mode of injury is theorized to be linked to CKD associated gastrointestinal dysmotility, abnormal secretion and absorption which potentially increase the risk of Sevelamer crystallization and deposition in tissue (8,12). However larger studies are warranted for elucidating the exact mechanism of injury.

Of note, the histological tissue reactions seen in resininduced gastrointestinal injury significantly overlap with other gastrointestinal pathologies such as acute infective colitis, ischemic colitis, inflammatory bowel disease,



Figure 3: A) Colonic biopsy with Kayexalate induced ulceration and granulation tissue formation (H&E; x50). **B)** Anal canal mucosal necrosis with Sevelamer crystals (H&E; x200). **C)** Gross pathology of colonic resection with mucosal ulcerations smeared with exudates. **D)** Ulcerated colonic mucosa with Sevelamer crystals and acute inflammatory exudate (H&E; x50).

etc. Most of our cases had a clinical and/or endoscopic diagnosis of either ischemic colitis or inflammatory bowel disease. In this scenario, morphological recognition of the crystals supported by the clinical history helps in clinching the diagnosis.

Resins have been described in unusual locations and we also found them in the peri-renal soft tissue of a graft nephrectomy case and the peri-anal soft tissue in a case of peri-anal fistula. Morphological features compatible with Kayexalate crystals were identified in the peri-anal soft tissue which clinically presented as a fistula but no supporting clinical data was available in this case. The graft nephrectomy showed both Kayexalate and Sevelamer crystals admixed with suppurative inflammation in the peri-renal soft tissue. The presence of vegetable matter signaled an underlying intestinal perforation which was masked in this case (14).

Non-classical resin morphology poses problems in the accurate recognition of these crystals on H&E. These crystals can show overlapping tinctorial qualities which are affected by the background pH (13). In one of our cases, Sevelamer crystals were purplish on routine stain and overlapping in appearance with Kayexalate but were magenta colored on AFB stain.

It should be noted that fish scale patterns can also be produced by dystrophic calcifications, gall bladder calculi, some food particles, large bile acid sequestrant fragments and even specimen ink used in grossing. Examining the entire histologic section as well as requesting multiple levels and special stains such as PAS/D and AFB stain can help in the accurate recognition of these crystals. Among the special stains, PAS/D stain is reported to provide inconsistent results (13). From a practical stand point, though non-classical in location and morphology, it is prudent to document the presence of the resins in biopsy reports. Histological mimics of these crystals include Cholestyramine, vegetable matter and Crospovidone. Cholestyramine is a bile acid sequestrant that is used to treat hyperlipidemia. Its crystals are rhomboid in shape and are smooth and glassy without a mosaic pattern. They stain bright orange-red on H&E, variably gray or hot pink on PAS/D, lack internal "fish scales," and are unassociated with mucosal injury (8).

Lanthanum carbonate, a noncalcemic phosphate binder also causes gastrointestinal mucosal injury and is characterized histologically by prominent lamina propria histiocytes containing calcium like eosinophilic mineral deposition (15).



Figure 4: A) Coral shaped purplish Crospovidone crystals (H&E; x 400). **B)** Matchstick shaped clear colored microcrystalline cellulose (H&E; x 400).

Plant or vegetable matter, which is commonly encountered in gastrointestinal biopsies, can also mimic fish-scales. However, they are usually more rectangular and often resemble "window panes". In addition, vegetable material typically will not show the characteristic colors of the aforementioned crystals.

Crospovidone and Microcrystalline cellulose can also show up in gastrointestinal biopsies but are innocent bystanders with no specific clinic-pathologic associations. They are water-insoluble, nonabsorbable pharmaceutical fillers or binders incorporated into medications (i.e. tablets) to facilitate drug delivery. Crospovidone is non-birefringent and has coral/sponge shape segments composed of a pink core and purple coat (Figure 4A). Microcrystalline cellulose is brightly birefringent, resembling cotton fibers, but with a more prominent matchstick shape and clear color (Figure 4B) (16).

Careful review of the medication history is mandatory in the definite diagnosis of these crystals. Unfortunately, usually no clinical data will be provided in the request forms. None of our cases had any clinical data and particularly drug history mentioned in the requests. Retrieval of the patient case file is helpful in these instances.

In conclusion, the aim of this study is to increase the awareness of pathologists and clinicians alike to an under-reported etiology and pattern of intestinal mucosal injury related to medical resin therapy. Resin-induced intestinal injury may at times pose a clinical emergency. Their presence in biopsy material should therefore be reported soon to the treating clinician to watch for any serious untoward consequences. The clinicians should be increasingly aware of this pattern of intestinal damage and add it to their differential diagnosis in the proper clinical setting. Pathologist must be aware of this pattern of intestinal injury and report it promptly. Availability of the complete clinical history and other laboratory tests at the time of pathological evaluation will aid in establishing the correct diagnosis.

CONFLICT of INTEREST

The authors declare no conflict of interest.

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