

OsmoPrep-associated Gastritis

A Histopathologic Mimic of Iron Pill Gastritis and Mucosal Calcinosis

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Abstract: We have identified 8 cases of gastritis characterized by the presence of purple to black granular deposits in the superficial mucosa associated with marked reactive epithelial changes. In each case, the patient had taken OsmoPrep, a tablet form of sodium phosphate used for bowel preparation just before upper endoscopy and had undergone concurrent colonoscopy. Endoscopic findings ranged from normal gastric mucosa to severe inflammation, congestion, and friability. No other gastrointestinal sites were noted to contain the deposits or show similar mucosal injury. On initial histologic review, the deposits raised the differential diagnosis of elemental iron and mucosal calcinosis. However, none of the patients was noted to be taking iron supplements, and none had a history of renal disease or other cause of calcium dysmetabolism. Histochemical stains revealed the deposits were negative on Perls' iron stain (8/8 cases), positive on von Kossa stain (7/8 cases), and negative on Alizarin Red stain (8/8 cases)—a histochemical profile compatible with sodium phosphate but inconsistent with mucosal calcium. A crushed OsmoPrep tablet was subjected to processing and demonstrated similar histologic features and histochemical profile. In addition, biopsies of 20 consecutive patients who did not take OsmoPrep and who underwent concurrent endoscopy and colonoscopy were reviewed, and no deposits with similar histochemical profile were identified. In summary, we have characterized a unique form of gastritis associated with OsmoPrep use. Attention to clinical history and use of a select panel of histochemical stains allow for accurate diagnosis.

Key Words: OsmoPrep, gastritis, sodium phosphate, medication, gastrointestinal

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The gastrointestinal (GI) tract is subject to unique injuries as one of the primary routes of pharmacologic therapy. Well-documented lesions have been described for an extensive list of medications including nonsteroidal anti-inflammatories, proton-pump inhibitors,^{1,2} mycophenylate,³ taxol,⁴ and colchicine.⁵ More recent additions to the list include ipalimumab,⁶ a biological used in the treatment of melanoma, the antihypertensive olmesartan,⁷ and idelalisib,⁸ a chemotherapeutic agent active against chronic lymphocytic leukemia. For the most part, these drugs have been associated with mucosal injury due to the temporal association of drug ingestion with mucosal lesions and resolution of injury upon cessation of the drug's use. Also within this category is a growing list of medications that have been associated with GI injury due not only to their temporal relationship to the mucosal lesion but also to the presence of characteristic pill residua within the biopsy specimen. These medications include iron,^{9,10} kayexalate,^{11,12} sevelamer,¹³ and yttrium-90.^{14–16} An array of histochemical stains and morphologic features, such as the presence or absence of “fish scales” help to distinguish these medications from one another and from other (likely incidental) pill fragments found in GI biopsies.¹⁷

As the number of medications approved for use increases, iatrogenic drug injury will likely increase in concert, requiring pathologists to be on alert for foreign materials as a source of tissue injury. Here we describe the histopathologic findings of an OsmoPrep-associated gastritis. In this setting, correct identification of the inciting agent can prevent clinical confusion and unnecessary additional patient work-up.

MATERIALS AND METHODS

This study was approved by the institutional review board at the University of California Davis Medical Center and by Covenant Pathology Services (Nashville, TN). Five cases were identified prospectively at Covenant Pathology Services in South San Francisco, CA. A search of the University of California Davis Medical Center electronic medical record identified 104 patients who were prescribed OsmoPrep between May 1, 2007 and August 21, 2014. Of these, 11 patients had undergone concurrent

esophagogastroduodenoscopy (EGD) with biopsy. Upper GI biopsies of these 11 patients were reviewed, and one of these biopsies contained purple-black inorganic deposits in the superficial gastric mucosa. Two additional cases were identified prospectively at the University of California Davis during the course of routine service work. As a control, GI biopsies of 20 consecutive University of California Davis patients who underwent concurrent colonoscopy and EGD with gastric biopsy and who did not use OsmoPrep for bowel cleansing were reviewed (biopsies performed between May 1, 2014 and September 1, 2014).

All stains were performed using standard histochemical protocols, and all controls performed normally.

To interrogate the histochemical properties of OsmoPrep, crushed pill fragments were suspended in chicken egg albumen and heated briefly to denature the albumen. The denatured albumen-OsmoPrep mixture was subsequently fixed in 10% formalin and processed as per routine histology protocol. (Of note, other more conventional endeavors to adhere the crushed pill fragments

to the glass slide [eg, direct embedding of pill fragments in paraffin, use of cytology fixative] proved unsuccessful.)

RESULTS

We prospectively identified 7 cases of gastritis characterized by marked reactive epithelial changes associated with purple to black inorganic deposits in the superficial lamina propria (Fig. 1). The deposits were irregular in contour and of varying sizes (typically <100 μ m) and generally had the appearance of crushed pill fragments. Although some had a smooth, almost translucent appearance (Fig. 1B), others appeared more opaque and granular (Fig. 1D). The gastric mucosa associated with the deposits was notable for prominent mucin loss and nuclear hyperchromasia without significantly increased inflammation, compatible with reactive gastropathy. In some cases, mild superficial edema and congestion were noted adjacent to the deposits. No erosions or ulcers were identified. The deposits and the reactive changes were most frequently identified in antral

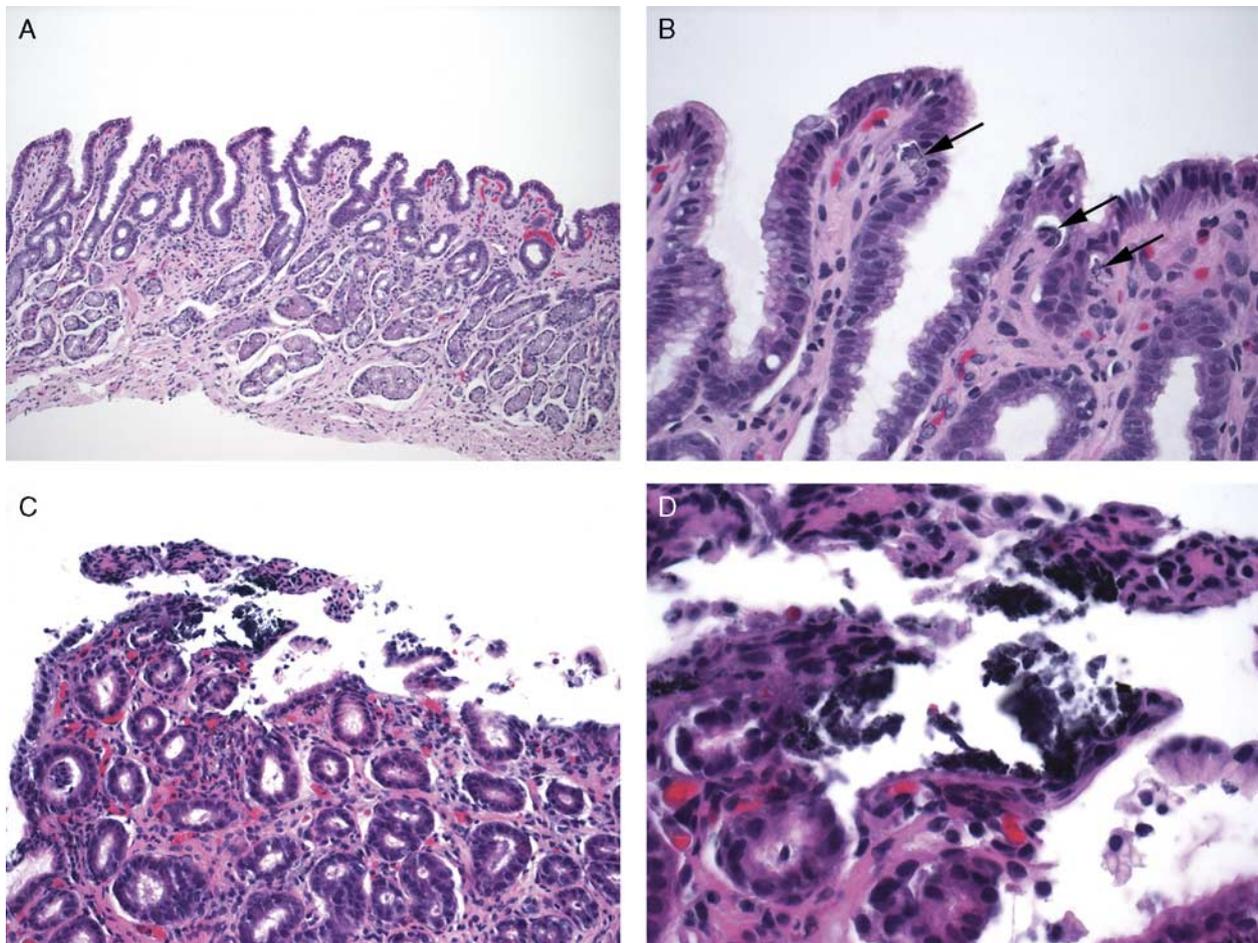


FIGURE 1. OsmoPrep-associated gastritis. Irregular purple to black deposits are present beneath surface epithelium that demonstrates mucin loss and increased nuclear chromasia. In some cases the deposits have a flat, near-translucent appearance (case #5: A, B; arrows highlight the deposits), whereas in other cases, they appear more opaque and granular (case #3: C, D).

biopsies. None of the other biopsied organs in the upper or lower GI tract of these patients showed any mucosal injury associated with similar inorganic deposits. The initial histologic differential diagnosis included iron pill gastritis and mucosal calcinosis. Histochemical stains showed the deposits were nonreactive on Perls' iron stain (all 7 cases) and positive on von Kossa stain (6/7 cases) (Table 1, cases #1 to 7). As the von Kossa stain is a histochemical preparation commonly used to detect calcium, this pattern of staining appeared to support the impression of mucosal calcinosis. However, on further investigation, none of the patients were found to have a clinical history of calcium dysmetabolism (eg, renal failure). In contrast, all were noted to have undergone concurrent colonoscopy and had taken OsmoPrep for bowel preparation. Subsequent staining of the gastric biopsies with Alizarin Red, a calcium chelating dye, showed none of the cases to be reactive, arguing against mucosal calcinosis (Figs. 2A, C, E, and G).

We identified an eighth case of gastritis associated with reactive epithelial changes, purple-black inorganic deposits, and OsmoPrep use by searching the University of California Davis Medical Center electronic medical record for patients prescribed OsmoPrep from years 2007 through 2014. Histochemical stains performed on this gastric biopsy showed an identical pattern as that seen in the 7 other cases (ie, nonreactive on Perls' iron stain, reactive on von Kossa stain, and nonreactive on Alizarin Red stain) (Table 1, case #8).

For comparison, we retrospectively reviewed the upper and lower GI biopsies of 20 consecutive patients who presented for concurrent EGD and colonoscopy and who had not taken OsmoPrep for bowel preparation. Histologic findings in the gastric biopsies were varied and ranged from normal mucosa to *Helicobacter* gastritis to

mucosal calcinosis and included intestinal metaplasia and a fundic gland polyp with low-grade dysplasia. No mucosal deposits with a similar staining pattern as that seen in the other group were identified. In the 1 case of mucosal calcinosis, the patient was known to have chronic renal disease, and histochemical staining revealed the deposits to be reactive on von Kossa and Alizarin Red stains and nonreactive on Perls' iron stain (Figs. 2B, D, F, and H).

To directly examine the histochemical properties of OsmoPrep, we obtained an OsmoPrep tablet and subjected pill fragments to hematoxylin and eosin, von Kossa, Alizarin Red, and Perls' iron stains (Fig. 3). Although the hematoxylin and eosin—stained pill fragments were more eosinophilic than those seen in the gastric biopsies, the histochemical profile was identical to that of the OsmoPrep-associated gastritis cases.

Review of the patient demographic and clinical information revealed that 7 patients were female and 1 was male, ranging in age from 19 to 66 years. No history of renal disease, other cause of calcium dysmetabolism, or use of oral iron supplements was elicited. Upper GI symptoms that had brought the patient to endoscopy included gastroesophageal reflux, dysphagia, epigastric pain, and anemia. Findings at endoscopy ranged from normal mucosa to diffuse erosions, erythema, and friability (Fig. 4). None of the patients reported experiencing any preendoscopic exacerbation of their upper GI symptoms, and none reported any postprocedure complications.

DISCUSSION

We have identified 8 cases of gastritis associated with superficial inorganic deposits and OsmoPrep use.

TABLE 1. Clinical, Endoscopic, and Histologic Features of Osmoprep-associated Gastritis

Case	Sex	Age (y)	Symptoms	EGD Gastric Findings	Biopsy Site	Histologic Findings	Osmoprep Confirmed?	Renal Disease?	Iron Pill?	Iron Stain	von Kossa	Alizarin Red
1	F	60	GERD	Diffuse erosions, erythema, friability	Antrum	Reactive gastropathy, mild lamina propria hemorrhage	Yes	No	No	Neg	Pos	Neg
2	F	51	GERD, dysphagia	Diffuse severe inflammation, congestion, friability	Antrum	Reactive gastropathy, congestion, edema	Yes	No	No	Neg	Neg	Neg
3	F	66	Epigastric pain, dysphagia	Erythema	Antrum	Reactive gastropathy	Yes	No	No	Neg	Pos	Neg
4	F	19	Abdominal pain	Moderate diffuse inflammation	Body	Reactive gastropathy	Yes	No	No	Neg	Pos	Neg
5	F	62	GERD	Normal	Antrum	Reactive gastropathy	Yes	No	No	Neg	Pos	Neg
6	F	62	GERD	Edema, erythema of antrum	Antrum	Reactive gastropathy, chronic gastritis	Yes	No	No	Neg	Pos	Neg
7	M	64	GERD, history of gastric leiomyoma	Mild erythema of body	Body	Reactive gastropathy	Yes	No	No	Neg	Pos	Neg
8	F	61	Epigastric pain, GERD, anemia	Moderate gastritis of body and fundus	Antrum	Reactive gastropathy	Yes	No	No	Neg	Pos	Neg

F indicates female; GERD, gastroesophageal reflux; M, male; Neg, negative; Pos, positive.

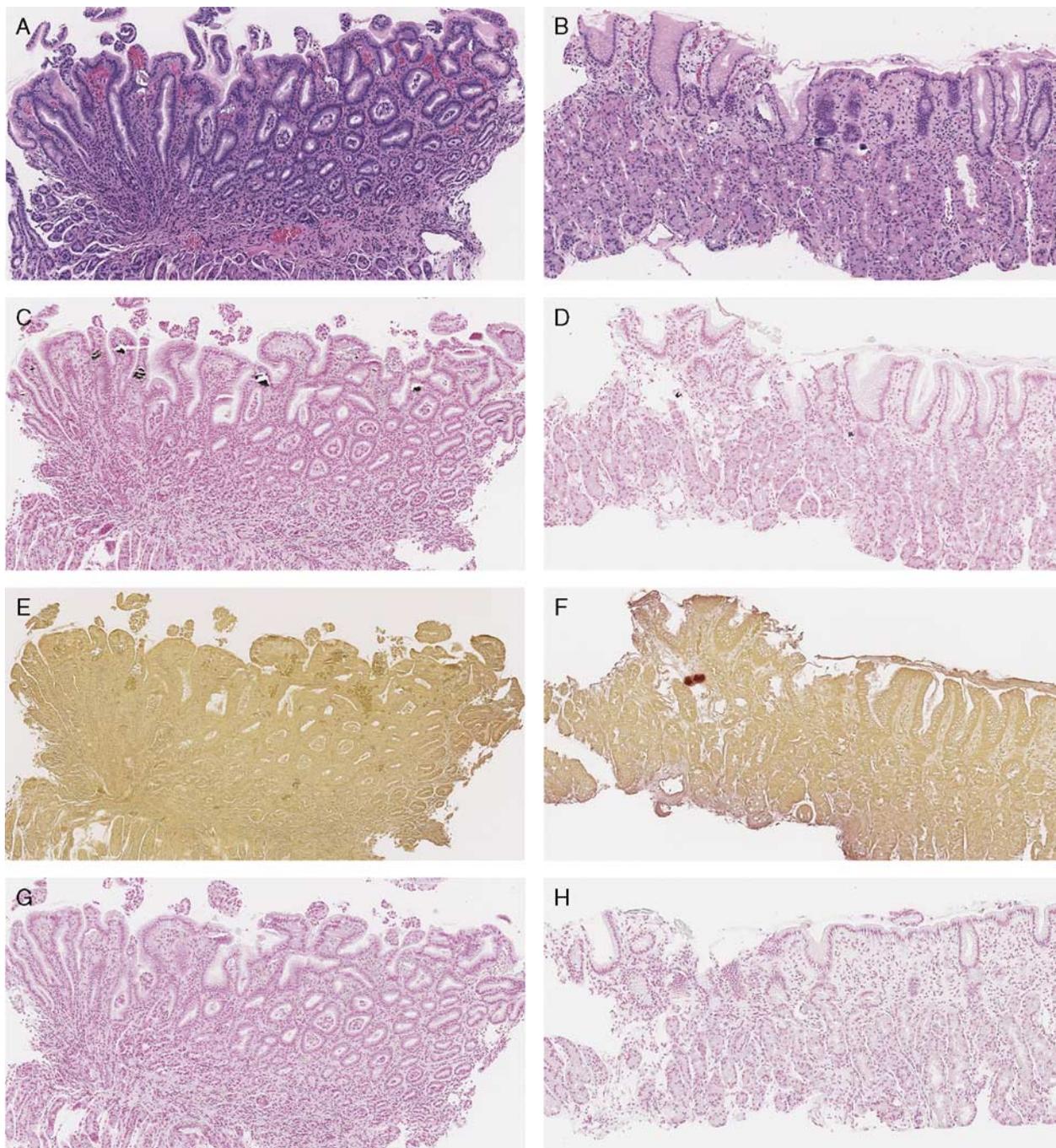


FIGURE 2. Differences in histochemical staining pattern of OsmoPrep-associated gastritis (A, C, E, and G) versus mucosal calcinosis (B, D, F, and H). The deposits of OsmoPrep-associated gastritis are positive on von Kossa stain (C) and negative on Alizarin Red (E) and Perls’ iron (G) stains. In contrast, the deposits of mucosal calcinosis are positive on von Kossa (D) and Alizarin Red (F) stains and negative on Perls’ iron stain (H). A and B, hematoxylin and eosin stain. All images digitally scanned.

Overall, the deposits were reactive on von Kossa stain and nonreactive on Alizarin Red and Perls’ iron stains. Importantly, while von Kossa staining is commonly used to detect tissue calcium, it is actually a chemical reaction of the phosphate or carbonate moiety of the calcium salt.^{18,19} Thus, it is phosphate (or carbonate) that the von Kossa stain highlights, not calcium itself. As sodium

phosphate is the active ingredient in OsmoPrep, this explains the histochemical staining pattern of the deposits in our cases, as well as that of the crushed OsmoPrep pill. In contrast, Alizarin Red is a dye that directly binds calcium,^{18,19} and as such is a more specific test for calcium deposition. In regard to case #2 which did not appear to be reactive on von Kossa stain, we note this gastric biopsy

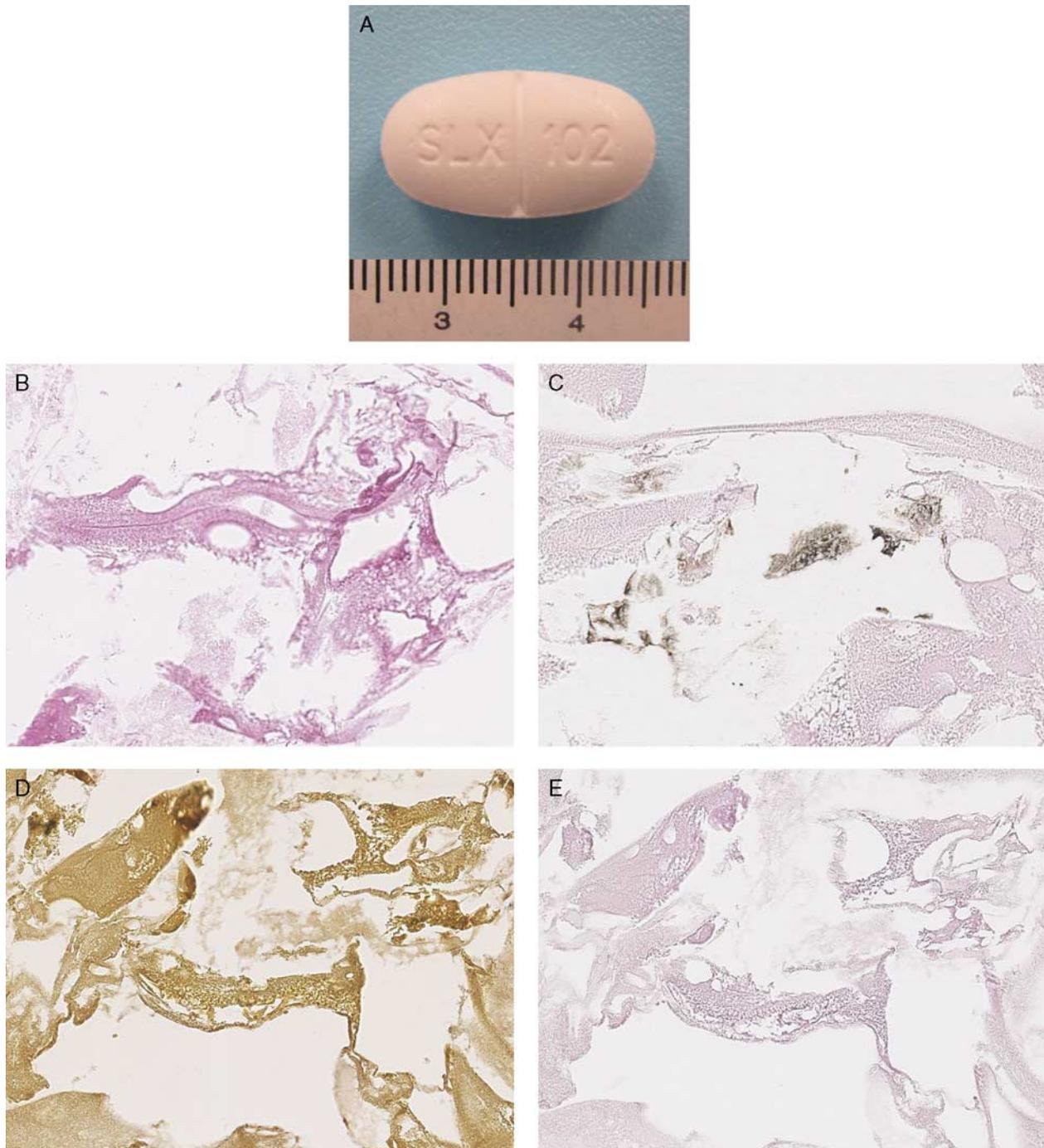


FIGURE 3. OsmoPrep. A, Whole pill (800 mg). B, Hematoxylin and eosin stain. The crushed tablet demonstrates a finely granular appearance with irregular contours and eosinophilic hue in contrast to the purple to black tinctorial quality of tissue-associated OsmoPrep. C–E, Similar to the deposits in the gastric mucosa, the crushed OsmoPrep tablet is reactive on von Kossa stain (C) and nonreactive on Alizarin Red (D) and Perls' iron (E) stains. All images digitally scanned.

had very small superficial deposits, and it is conceivable these deposits did not survive the histochemical staining process.

We also observed that the albumen-embedded OsmoPrep pill fragments lacked the purple to black hue seen in the gastric biopsies and demonstrated relatively focal

reactivity on von Kossa stain. The cause of these differences is not known; however, it is possible that environmental factors specific to the stomach, such as low pH and/or the presence of gastric mucus, contributed to the dye reaction. Alternatively, because egg albumen contains ovalbumin, a protein well-known to bind a large number



FIGURE 4. Erythema was the most commonly reported endoscopic finding in cases of OsmoPrep-associated gastritis. In case #1 (shown here), the gastroenterologist reported diffuse erosions, erythema, and friability.

of small molecules, it may have modified the dye reaction. (While ovalbumin may also chelate iron and thus interfere with the Perls' iron reaction, we did not observe even focal reactivity on the Perls' iron stain.) Furthermore, previous studies demonstrating the histologic and histochemical properties of oral medications have demonstrated alternative staining characteristics of the medication when processed directly from the crushed pill as compared with that derived from tissue biopsy.¹³

OsmoPrep is a tablet form of bowel preparation produced by Salix Pharmaceuticals (Raleigh, NC) and approved for use in the United States in 2006. The active ingredient is sodium phosphate, which functions as an osmotic laxative. It is an infrequently used colon preparatory agent due primarily to the associated risk of acute phosphate nephropathy.²⁰ Patients may opt for this form of colon preparation if they cannot tolerate the large volume of chalky fluid that constitutes the more commonly prescribed liquid sodium phosphate agent. However, OsmoPrep prescribing instructions are nevertheless quite demanding: the patient must take 4 large tablets with 8 ounces of clear liquid every 15 minutes for 1 hour (total of 20 tablets in 1 hour) on the evening before the colonoscopy and 4 large tablets with 8 ounces of clear liquid every 15 minutes over a period of 30 minutes (total of 12 tablets in 30 min) the morning of the procedure. Thus, consumption of a large volume of fluid over a short interval remains obligatory. GI signs and symptoms, including abdominal bloating, nausea, abdominal pain, and vomiting, are the most common side effects. Contraindications include a history of acute phosphate nephropathy (biopsy-proven), GI obstruction, gastric bypass or stapling surgery, bowel perforation, toxic colitis, toxic megacolon, and hypersensitivity to any component of OsmoPrep.

GI mucosal injury was initially reported with OsmoPrep in the premarket clinical trial period; however, the injury was thought to be restricted to the colon, and no specific gastric lesions were documented.²⁰ Subsequently, in 2010 French investigators reported 6 cases of endoscopically identified gastric mucosal injury associated with the use of Colokit (an analogous tablet-based sodium phosphate colon preparatory agent made by the French pharmaceutical company Mayoly Spindler—Chatou, France).²¹ Histologic findings revealed ulceration, necrosis, and edema, but no pill fragments were noted. The colon preparatory agent was implicated based on the temporal relationship of upper GI symptoms with the initiation of medication ingestion and subsequent resolution of symptoms after endoscopy. More recently, other investigators tested the effects of direct exposure of sodium phosphate tablets on gastric mucosa in a porcine model.²² Their findings confirmed the existence of a medication-induced injury but did not reveal any functional deficit in mucosal integrity, with lesions grossly resolving within 72 hours. Although histologic sections were examined, pill fragments with related tissue response were not identified.

In contrast to sodium phosphate tablets, oral sodium phosphate solutions have been in use as bowel preparatory agents for >2 decades and are well documented to cause colonic aphthous-type erosions and focal acute cryptitis.^{23–26} More recently, a large Korean study found that the incidence of hemorrhagic gastritis was significantly increased in patients presenting for EGD when undergoing concurrent colonoscopy with sodium phosphate solution bowel preparation as compared with those presenting for EGD alone.²⁷ Interestingly, their data showed associations of hemorrhagic gastritis with male sex, body mass index <20, certain medications, and duodenal ulcers. In our case series, the female predominance of the gastritis was striking and mirrored that of the French case series, which reported a Colokit-associated gastritis in 4 females and 2 males. Although the majority of our cases were identified outside of the University of California Davis, it is noteworthy that 73% of the 104 patients prescribed OsmoPrep at the University of California Davis were female, suggesting a selection bias. Other (as yet unknown) factors certainly may exist as well. Finally, the differences in our findings as compared with the Korean study may reflect the different forms of oral sodium phosphate administered.

Given that the prescribing frequency of OsmoPrep is quite low and concurrent upper endoscopy is not uniformly performed in those instances, it is not entirely clear how often this type of iatrogenic gastritis occurs. Of the 11 cases that met inclusion criteria from the University of California Davis patient database, only 1 was found to have inorganic deposits compatible with OsmoPrep. Thus, it is likely that only a small fraction of patients who take OsmoPrep will demonstrate gastric mucosal injury related to OsmoPrep use. More importantly, despite the dramatic endoscopic and histologic findings that can be seen, no long-term complications have been noted in any of the patients.

In summary, our series is the first to document histologic evidence of mucosal deposits associated with gastric mucosal injury and OsmoPrep use. Because the mucosal deposits demonstrate a histochemical staining pattern that is both consistent with sodium phosphate and also identical to that seen with OsmoPrep pill fragments, the findings strongly support the existence of an OsmoPrep-associated gastritis. Although neither major complication nor specific therapeutic intervention has been reported subsequent to these cases, this pattern of mucosal injury is a potential diagnostic pitfall and another factor in the consideration of Osmoprep use.

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