IATROGENIC GASTROINTESTINAL TRACT INJURY

E. MONTGOMERY

Iron

In our patient population, mucosal iron (ferrous sulfate) is found in about 1% of patients undergoing upper tract endoscopic biopsies. Iron is well recognized for its capacity to cause corrosive injury in the esophagus and, in a hospital population, it is not uncommon to find iron associated with an esophageal ulcer or erosion. While it can be argued that such a phenomenon results from a prior injury in which an iron tablet became embedded, the corrosive and toxic nature of iron itself suggests that just having the pill lodge in the esophagus caused the injury. Either way, it is worth learning to recognize “iron pill esophagitis,” and to encourage the patient to ingest the medication in a crushed form with soft food (such as applesauce or yogurt). Using our material at The Johns Hopkins Hospital, where we have a busy endoscopy service, Abraham et al. (1) studied the clinical and histologic features of 36 upper gastrointestinal tract biopsies from 33 patients (24 gastric, nine esophageal, one gastroesophageal junction, and two duodenal) containing characteristic brown crystalline iron material, and evaluated the amount and tissue distribution of the iron. They also investigated the prevalence of iron-associated mucosal injury on the endoscopic examinations. The biopsies typically displayed luminal crystalline iron adjacent to the surface epithelium, or admixed with luminal fibrinoinflammatory exudates. Most biopsies (83%) showed crystalline iron deposition in the lamina propria: either covered by an intact epithelium, subjacent to small superficial erosions, or admixed with granulation tissue. Three biopsies (8%) demonstrated iron-containing thrombi in mucosal blood vessels. Erosive or ulcerative mucosal injury was present in the majority of biopsies (83%). The amount of iron accumulation in tissue with mucosal injury was greater than in tissue without mucosal injury. Iron medication (usually ferrous sulfate) was confirmed in 25 of 33 patients (76%). However, as an argument for iron-causing injury as a secondary event, half of the patients (17 of 33, 51%) also had underlying infectious, mechanical, toxic, or systemic medical conditions that could have initiated or exacerbated tissue injury.

In order not to miss iron injury in the esophagus (or stomach for that matter), it is worthwhile to pay attention to material in ulcer beds. On H&E stains, the oxidized iron has a readily recognizable bluish brown color that can be highlighted with iron stain. The same stain can highlight iron embedded in cells deep to the ulcer that is inapparent on H&E stain. Whereas in the stomach iron must be distinguished from mucosal calcinosis, since calcinosis seems not to be encountered in the esophagus, esophageal iron-associated injury can be diagnosed without special stains.

Kayexalate

The use of kayexalate (sodium polystyrene sulfonate) for the management of hyperkalemia was approved for use in the United States in 1975. Kayexalate is a cation-exchange resin that can be instilled into the lower gastrointestinal tract, as an enema preparation, or into the upper gastrointestinal tract, either orally or by nasogastric tube. When administered orally or by nasogastric tube, sodium cations are released from the resin and exchanged for hydrogen ions in the acidic milieu of the stomach. As the resin passes through the intestines, hydrogen is exchanged for potassium, which is then eliminated in the feces along with the remainder of the altered resin, thereby lowering the serum potassium concentration.

In the early use of kayexalate, the resin was typically administered as a suspension in water. Although it was generally well-tolerated, some patients were reported to develop gastric and bowel opacifications as a result of concretions of crystalline resin. Therefore, it became
increasingly popular to administer kayexalate in a suspension with hypertonic sorbitol. This solution reduces both the frequency of kayexalate bezoar formation and colonic impaction by promoting an osmotic diarrhea. In 1987, Lillemoe et al. (2) reported five uremic patients who developed colonic necrosis, temporally associated with the use of kayexalate in sorbitol, which contributed to the death of four of the five patients. That study also provided experimental evidence implicating sorbitol as the agent responsible for colonic necrosis in a rat model.

It has subsequently become apparent that kayexalate also can be associated with severe mucosal injury in the upper GI tract, and a series of such cases has been reported by Abraham et al. (3). In most instances, kayexalate is easy to recognize in endoscopic biopsies and the clinician can be alerted if there is associated ischemic GI tract disease or erosive lesions.

Kayexalate crystals are lightly basophilic on hematoxylin and eosin stain red on PAS/AB and acid-fast stains, and blue on Diff-Quik staining. However, occasionally they seem to absorb bile and can thus be bile-pigmented, although this feature is encountered in kayexalate in intestinal biopsies and not in esophageal biopsies. The crystals display a characteristic mosaic pattern that resembles fish scales. The pattern is faintly present in many cases on routine hematoxylin and eosin stain, but is better demonstrated on acid-fast, PAS/AB, and Diff-Quik stains. It is this mosaic pattern that distinguishes kayexalate crystals from histologically similar cholestyramine crystals. Kayexalate crystals are refractile but not polarizable. 

Renvela/Sevelamer-associated injury

Swanson et al (4) have recently described the appearance of sevelamer crystals (Renagel and Renvela, Genzyme; phosphate-lowering agents) in the gastrointestinal tract. Finding these crystals was associated with chronic mucosal damage, acute inflammation, an inflammatory polyp, extensive ulceration, ischemia, and necrosis. In general, sevelamer crystals displayed broad, curved, and irregularly spaced "fish scales" with a variably eosinophilic to rusty brown color on hematoxylin and eosin (H&E) staining and violet color on periodic acid-Schiff-alcian special staining with diastase (PAS/D). In contrast, Kayexalate has narrow, rectangular "fish scales" and is violet on H&E and magenta on PAS/D; cholestyramine lacks internal "fish scales," is bright orange-red on H&E, variably gray or hot pink on PAS/D, and is unassociated with mucosal injury. Further study is required to determine whether sevelamer plays a causal role in these injuries; however, its crystal is an important mimic of both Kayexalate and cholestyramine.

Taxol Effect, Colchicine Toxicity

Taxol, an antineoplastic agent with a novel mechanism of action, can be associated with striking mitotic arrest associated with epithelial necrosis and ulceration of the esophagus. As a class of drug, taxane chemotherapeutic agents are commonly used to treat malignancies of the esophagus, breast, and lung. Paclitaxel (Taxol®) chemotherapy has been associated with dramatic GI mucosal changes, accompanied by an increase in apoptosis(5). Taxol, as reviewed by Rowinsky et al.(6), induces these GI mucosal changes by binding to microtubules, thus promoting polymerization and inhibiting depolymerization. Electron microscopy has shown this central core of polymerized microtubules surrounded by dispersed chromatin, resulting in a “ring” structure during metaphase(5). Taxanes have been shown to induce unique histologic changes within epithelium of the GI tract associated with cell necrosis in the GI tract(5). As referenced by Hruban et al., in preclinical trials, taxol had been associated with gastritis and duodenal necrosis in mice and with colonic necrosis in dogs(5). Reported human drug-related GI effects have included vomiting, diarrhea, mucositis, and neutropenic enterocolitis(6).
Since the mitotic arrest is associated with bundling of intermediate filaments secondary to accumulation of polymerized microtubules, the histologic correlate is the presence of arrested mitoses with ring forms. With taxol, the findings tend to be striking in the esophagus, whereas, in colchicine toxicity, the small bowel is more likely to be severely altered. The ring mitoses are accompanied by prominent apoptosis in all gastrointestinal tract sites and, regardless of the site, the alterations are found in the proliferative compartment. Thus, in esophageal squamous mucosa, they are encountered in the basal layer, whereas they are encountered in the gastric pits rather than the deeper glands. In the small bowel, the epithelial changes are found in the mid crypt but they are in the deep crypts in the colon. The surface cells are uninvolved in all sites. It was initially believed that finding this pattern of injury in a patient taking taxol indicated clinical toxicity. However, this is not necessarily the case. The medication is administered intravenously on an outpatient basis. If the patient happens to have a gastrointestinal tract biopsy or resection within 4 days of the administration of the medication, the histologic changes are encountered even in asymptomatic patients (7).

The histologic findings associated with colchicine toxicity are essentially the same as those encountered in patients taking taxol but are only seen in patients who have clinical toxicity (8). Since it is impossible to separate the effects of the two medications with certainty on histologic examination, it is our practice to contact the submitting clinician caring for the patient to correlate with medication history and determine the need for intervention (colchicine toxicity can require supportive care). That noted, colchicine toxicity is typically encountered in the antrum and small bowel.

Mycophenolate

Mycophenolic acid (MPA) is a fermentation product of Penicillium brevicompactum and related fungi. It was isolated in 1898(9, 10). It is an immunosuppressive drug used mainly in patients with solid organ transplants (kidney, liver, heart, lung) to maintain their grafts, but this medication is also administered to patients with a wide range of other conditions including but not limited to nephritis, uveitis, vasculitis, and pemphigus (11-17). In the US, there are two available preparations for this compound: mycophenolate mofetil (MMF; Cellcept; Roche Pharmaceuticals) and mycophenolate sodium (Myofortic, Novartis Inc.). The principal difference between the two preparations is that Myofortic is an enteric coated drug (18) while MMF is not. Thus Myofortic is absorbed in the intestine while MMF is absorbed in the stomach. The efficacy of preventing rejection in transplanted patients and the side effects of the two preparations are similar (10, 18).

MPA exerts its immunosuppressive properties by inhibiting the de novo pathway of purine synthesis, namely inhibiting guanosine synthesis for DNA synthesis and cell division (9). Specifically, MPA inhibits inosine monophosphate dehydrogenase (IMP dehydrogenase) which is a key enzyme of the de novo pathway. In general, almost 100% of B and T lymphocytes depend on the de novo pathway for purine synthesis, while this dependency is lower for enterocytes (about 50%). Therefore, by inhibiting guanosine synthesis in lymphocytes, cytotoxic T-lymphocytes responsible for cellular rejection and antibody production by B-lymphocytes are suppressed in transplanted patients. Although the dependency of enterocytes on the de novo pathway for purine genesis is lower than that of lymphocytes, MPA can inhibit the proliferation of enterocytes, leading to epithelial injury.

The side effects of MPA predominantly involve the gastrointestinal (GI) tract and hematopoiesis and include diarrhea, nausea, vomiting, gastritis, ulcers, opportunistic infections,
and anemia(10, 19). Since the main side effect of MPA is diarrhea, it is not surprising that colonic injury related to MPA has been documented(20, 21). Papadimitriou et al. characterized a colonic MPA-induced injury pattern similar to that of graft-versus-host-disease (GVHD), including increased crypt apoptosis, crypt distortion, cellular reparative changes, and increased neuroendocrine cells(20, 21). The first histologic description of upper GI tract MPA-associated damage was documented by Ducloux in 1998 who described villous blunting and crypt hyperplasia in the duodenum of a kidney transplanted patient taking mycophenolate mofetil(22). Parfitt et al. described upper GI tract injury caused by MPA and noted the following features: active esophagitis with ulceration or erosion; chemical gastropathy and Crohn-like features in the stomach; and GVHD-like changes and Crohn-like features in the duodenum(23). We have further studied the pathologic features of the upper GI tract in patients taking MPA and noted that clinical symptoms tended to correlate with apoptotic counts. In the esophagus, >2 apoptotic bodies per 10 high power fields is in keeping with mycophenolate injury and can be diagnosed as such(24). Of course finding apoptosis is not specific for mycophenolate-associated injury and the findings are essentially identical to those of graft-versus-host disease such that clinical correlation is always required. Essentially when prominent apoptosis is encountered in mucosal biopsies from patients who have had transplants, those with bone marrow transplants are likely to have graft-versus-host-disease, whereas those who have had solid organ transplants are likely to have mycophenolate-associated mucosal damage. Additionally, cytomegalovirus infection (and other viral infections) is also associated with apoptosis.

Fosamax

The bisphosphonates (BPs) prevent osteoclast-mediated bone reabsorption. Therefore, they have been found to be effective in the treatment of osteoporosis, Paget disease, and the hypercalcemia of malignancy (25). The commercially available bisphosphonates in clinical use include the following:

- Alendronate (Fosamax®)
- Etidronate (Didronel®)
- Clodronate (Bonefos®, Clasteon®, Difosfonal®)
- Pamidronate (Aredia®)
- Ibandronate (Boniva®)
- Risedronate (Actonel®)
- Zolendronate (Zometa®, Zomera®, Aclasta®, Reclast®)

Ingestion of alendronate sodium (Fosamax) and related medications by osteoporotic patients has been associated with esophagitis and esophageal ulcer as well as with gastroduodenal ulcers(26-28). Alendronate can damage the esophagus both by toxicity from the medication itself and by nonspecific irritation, secondary to contact between the pill and the esophageal mucosa (“pill esophagitis”). Abraham and colleagues reported ten patients who experienced erosive/ulcerative esophagitis while ingesting alendronate (29). Biopsies from all patients showed inflammatory exudates and inflamed granulation tissue as characteristic of any ulcer site (e-Fig. 42). Polarizable crystalline foreign material was present in six of ten biopsies (60%). Multinucleated giant cells, within the inflammatory exudates, were near the crystalline foreign material in three of ten biopsies (30%). Adjacent squamous epithelium typically showed active inflammation and a reactive appearance with enlarged, hyperchromatic nuclei. Multinucleated squamous epithelial giant cells were present in two of ten cases (20%). Micro-organisms were unusual; scattered fungi and/or viral inclusions were present in only two of ten biopsies (20%).
Although there is no specific histologic finding, it is worthwhile to be aware of this complication with such medicines and relay that concern appropriately to the clinician. There have been reports of esophageal mucosal injury in patients taking all of the bisphosphonates, but it is likely that many of the patients had additional risk factors. In a study that adjusted for the risk of esophagitis, esophageal ulcers, and esophageal perforations before and after initiation of the bisphosphonates, only alendronate, and etidronate were associated with an increased risk of esophageal damage. These agents (i.e., alendronate sodium and related medications) should be avoided in patients with achalasia and other motility disorders of the esophagus, esophageal stricture, or pre-existing severe reflux esophagitis. However, patients with reflux disease can probably be treated with a proton pump inhibitor (PPI) and then safely have bisphosphonate therapy with continued concomitant use of the PPI.

The Food and Drug Administration has also received reports of esophageal cancers developing in patients taking alendronate. However, when this issue is studied with proper controls, there seems to be no causal association between bisphosphonate use and esophageal carcinomas.

Although bisphosphonates are classically associated with esophageal injury, other medications can lodge in this area and induce similar damage. Like with bisphosphonates, pill fragments may be evident microscopically.

**ESOPHAGITIS DISSECANS SUPERFICIALIS/“THERMAL INJURY”/“SLOUGHING ESOPHAGITIS”**

These terms have all been used to describe a characteristic pattern of injury consisting of an unaltered basal layer and “mummification” of the superficial squamous epithelium, such that there are “ghost” nuclei (displaying poor uptake of hematoxylin stain) and the mucosa sloughs. The condition is uncommon but produces a dramatic endoscopic picture and a blister-like appearance on histologic evaluation that has overlap with skin disorders, especially pemphigus.

The full name for this condition is esophagitis dissecans superficialis. In early reports patients were said to have vomited large esophageal “casts” with a tubular configuration but more typically, the condition is not even suspected until an endoscopist notices whitish strips or streaks (“pseudomembranes”) of peeling esophageal mucosa during an endoscopic examination performed for reasons that may be unrelated to the esophagus, although some patients have dysphagia or even strictures. The condition is associated with “polypharmacy”, skin conditions, heavy smoking, physical trauma (including ingesting hot liquids), immunosuppression, and impaired mobility but the pathogenesis remains unknown. It may be a topical allergic response (similar to the blistering after skin exposure to poison ivy).

At low magnification, unusually long, detached fragments of superficial epithelium can be seen. Most cases have some degree of intraepithelial splitting at varying degrees above the basal layer and in a few cases a distinct bulla is apparent. Most cases show fragments of necrotic epithelium with minimal or no inflammation, in some cases with bacterial colonies. Parakeratosis is common.

Nonsteroidal anti-inflammatory drugs
Nonsteroidal anti-inflammatory drugs (NSAIDs) are well-known to be associated with mucosal damage in the small intestine. They may even lead to a peculiar form of strictures called “diaphragm disease,” based on their macroscopic appearance(43-45). The typical injury consists of ulcers, which may lead to strictures. Unfortunately, the histologic features of NSAID-associated ulcers are not specific, although they are usually not associated with abundant chronic inflammation.

Graft versus host disease

Patients with graft versus host disease (GVHD) present with secretory diarrhea, abdominal pain, and, at times, hemorrhage. There is also a syndrome of upper GI GVHD, presenting clinically as anorexia, dyspepsia, food intolerance, nausea, and vomiting. These syndromes were first recognized in the early 1990s(46-48) and endoscopic criteria for recognizing the lesions of GVHD are now available (49). Of course, patients who have had bone marrow transplants are prone to many infectious causes of enteritis, but many also have upper tract GVHD. The original grading criteria were published by Snover et al. (47) and are summarized as follows:

Grade 1 = increased crypt apoptosis
Grade 2 = apoptosis with crypt abscess
Grade 3 = individual crypt necrosis
Grade 4 = total denudation of areas of mucosa.

These criteria are simple to apply and correlate well with clinical findings. Unfortunately, chronic GVHD results in nonspecific features of lamina propria fibrosis, mucosal atrophy, and crypt distortion without basal plasmacytosis. When confronted with such biopsies, we attempt to grade the active component and note the features of the chronic component. We also compare the biopsies to any prior ones.

Ipilimumab-associated injury

Monoclonal antibodies (mAbs) against the cytotoxic T lymphocyte antigen-4 (CTLA-4) molecule are used as an adjuvant to experimental tumor immunization protocols in the treatment of a growing number of malignant neoplasms (for example melanomas, ovarian carcinomas, and pancreatic carcinoma). Among adverse effects associated with these medications, severe gastroenteritis has been reported. Oble et al have reported their observations of 5 patients who developed severe gastrointestinal toxicity affecting the gastric, small intestinal, and colonic mucosa(50). The endoscopic findings were variable, ranging from normal to diffusely erythematous and ulcerated mucosa. The constant histologic findings included a lymphoplasmacytic expansion of the lamina propria with increase in intraepithelial lymphocytes, and prominent apoptosis. Samples displayed cryptitis and glandular inflammation in the colon, ileum, and stomach, whereas villous blunting was present in the ileal and duodenal mucosa. Immunohistochemical analysis revealed a marked increase of all T-cell subsets (CD3+, CD4+, and CD8+) and of CD4+CD25+ regulatory T cells. The authors pointed out that the findings resembled those seen in autoimmune enteropathy (discussed below).

Olmesartan-associated Injury

This medication can be associated with a celiac disease-like pattern of injury(51). Olmesartan (trade name Benicar) is, an angiotensin II receptor antagonist commonly prescribed for treatment of hypertension. Colleagues at Mayo clinic reported 22 patients with unexplained chronic diarrhea and enteropathy while taking olmesartan. Celiac disease was ruled out in all cases. To be included in the study, the patients also had to have clinical improvement after suspension of olmesartan. Intestinal biopsies showed both villous atrophy and variable degrees of mucosal...
inflammation some with marked subepithelial collagen deposition (collagenous sprue). Collagenous or lymphocytic gastritis was documented in some patients, and microscopic colitis was documented in others. Clinical response was demonstrated in all cases. Histologic recovery or improvement of the duodenum after discontinuation of olmesartan was confirmed in all patients who underwent follow-up biopsies.

References


