The Ever-Changing Landscape of Drug-Induced Injury of the Lower Gastrointestinal Tract

Esmeralda Celia Marginean, MD

**Context.**—There is an ever-growing armamentarium of pharmacologic agents that can cause gastrointestinal (GI) mucosal injury, the most common symptoms being diarrhea, constipation, nausea, and vomiting. These are often self-limiting and without serious sequelae, but some symptoms are of greater concern, like drug-induced mucosal ulceration that can manifest as GI hemorrhage, stricture formation, and even perforation. Histologically, there is significant overlap between drug-induced injuries and various disease entities. A single type of medication may cause multiple patterns of injury, which can involve the entire GI tract or just some parts of it.

**Objective.**—To review the most common drug-induced injury patterns affecting the colon, which may be recognized by the surgical pathologist on colonic mucosal biopsies. This review does not address the injuries occurring in the upper GI tract.

**Data Sources.**—A PubMed review of English-language literature, up to December 2015, on drug-induced injury of GI tract was performed.

**Conclusions.**—There are numerous drugs that damage the colonic mucosa. The most common drugs are included in this review according to their histologic pattern of injury. It is important for the pathologist to keep in mind that a single drug type can induce many histologic patterns of mucosal injury that can mimic many disease entities. Although there are some histologic clues helpful in the diagnosis of drug-induced colonic injury, correlation with clinical history and especially medication history is essential to improve diagnostic accuracy.


An ever-increasing number of pharmacologic agents are known to cause gastrointestinal (GI) injury, with diarrhea, constipation, nausea, and vomiting being the most common symptoms. The potential damaging power of a drug is essentially determined by its pharmacologic properties and the mode of drug administration. The GI injuries manifest as nonspecific and overlapping histologic changes, making a definitive diagnosis of medication-induced injury challenging. For a correct diagnosis, it is important to establish a temporal relationship between drug administration and symptom onset, to demonstrate stomatic improvement with drug withdrawal or aggravation on reexposure, and to rule out other etiologies with similar histologic features. The role of the pathologist is mostly to maintain a high index of suspicion for a possible medication-induced pathology and to rule out underlying diseases. Microscopic patterns of injury associated with medications may mimic common entities (Table 1), like mucosal erosions/ulcerations, inflammatory bowel disease (IBD), ischemic colitis, infectious colitis, microscopic colitis, or graft-versus-host disease (GVHD). More importantly, a single drug can be associated with several patterns of injury (Table 2). This review intends to provide a practical guide for the general surgical pathologist for recognition and diagnosis of most common medication-induced injuries of the colon, classified according to the pattern of histologic mucosal injury.

**MOST COMMON DRUG-INDUCED HISTOLOGIC PATTERNS OF INJURY IN COLON**

**Mucosal Ulcerations, Erosions, and Strictures**

The most common drugs presenting with an ulcerative/erosive mucosal injury pattern are nonsteroidal anti-inflammatory drugs (NSAIDs), a heterogeneous class of medications, including salicylates, propionic and acetic acid derivatives, and selective cyclooxygenase 2 (COX2) inhibitors. Nonsteroidal anti-inflammatory drugs are among the most commonly used classes of medications worldwide, and their use has been associated with potentially serious dose-dependent GI complications. Toxicity of NSAIDs to GI mucosa has 2 pathogenetic mechanisms: irritation via direct mucosal contact and injury from actual direct drug action. Nonsteroidal anti-inflammatory drug injury can occur anywhere in the GI tract, mostly in the stomach and small intestine, mostly due to contact irritation. However, with the increased use of enteric-coated, slow-release preparations and enemas, lower GI tract involvement has become more common. In the colon, not only can NSAIDs cause direct
mucosal injury, but they can also aggravate preexisting conditions (ie, diverticulitis, IBD) and significantly increase the risk of injury by other concurrently administered medications. In the colon, NSAIDs cause toxicity mostly by inhibition of COX2 and reduced production of prostaglandins rather than contact irritation. Nonsteroidal anti-inflammatory drug–induced colonic ulcerations are mainly right-sided, in the ileocecal region and ascending colon, but may also be found in the rectum associated with use of NSAID-containing suppositories or enemas.

Within the colon, NSAIDs may cause a variety of nonspecific histologic features, and these include superficial erosions and ulcers, strictures, and increased apoptosis. In the elderly or after long-term use, perforation and the formation of diaphragms may occur. Nonsteroidal anti-inflammatory drug–induced ulcers are discrete, sharply demarcated mucosal defects bordered by normal mucosa on both sides, with no evidence of chronic features (architectural crypt distortion, basal plasmacytosis, Paneth or pyloric metaplasia). There may be an increase in mucosal eosinophils, a feature common to most drugs (Figure 1, A and B). In the rectum, isolated mucosal ulceration must be differentiated from solitary rectal ulcer, radiation-induced changes, ischemia, and infections, especially tuberculosis and amebiasis.

Diaphragm disease is very rare and is considered to be pathognomonic to NSAIDs. Originally described in terminal ileum, it has also been reported in right colon. The diagnosis is straightforward on endoscopy and gross examinations of resected specimens. Histologically, elongated plicae (diaphragms) with submucosal fibrosis are seen, often eroded at the tip. In these areas the mucosa shows architectural distortion and hamartoma-like changes, with a mixture of smooth muscle, nerves, ganglion cells, and blood vessels, and mild acute inflammation. Diaphragm disease can progress to significant strictures and bowel obstruction, which may necessitate endoscopic or surgical intervention.
Figure 1. Nonsteroidal anti-inflammatory drug-induced mucosal ulceration. A, The image shows a discrete ulceration at the bottom right, sharply demarcated from adjacent normal colonic mucosa. B, The ulcer bed composed of granulation tissue only partially covered by surface epithelium (hematoxylin-eosin, original magnifications ×20 [A] and ×100 [B]).

Figure 2. Mycophenolate acid–induced colonic injury with increased apoptosis. A, The colonic mucosa shows abundant eosinophils in lamina propria (>25 per 10 high-power fields) and one central damaged crypt containing eosinophilic debris. The crypt epithelium shows mucin depletion and marked nuclear regenerative atypia. B, The colonic mucosa shows increased apoptosis at the crypt base (circle). C, A few single cells or small clusters of endocrine cells can be seen in lamina propria and base crypts in graft-versus-host disease. D, Ipilimumab-induced colonic injury. The colonic mucosa shows preserved crypt architecture, and marked and diffuse lymphocytic inflammatory infiltrate in lamina propria, with occasional plasma cells and eosinophils and increased apoptosis in the crypts (circle in inset) (hematoxylin-eosin, original magnifications ×100 [A and D] and ×200 [B]; chromogranin A immunostain, original magnification ×100 [C]). Photo courtesy of Giovanni De Petris, MD, associate professor, Colorado Springs, Colorado.
Table 3. Comparison of Histologic Features in Mycophenolate Acid (MFA)-Induced Colitis and Graft-versus-Host Disease (GVHD)

<table>
<thead>
<tr>
<th>Histologic Features</th>
<th>MFA-Induced Colitis</th>
<th>GVHD</th>
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<tr>
<td>Lamina propria</td>
<td>Numerous (&gt;15 per 10 HPF)</td>
<td>Rare</td>
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<tr>
<td>eosinophils</td>
<td>Rare</td>
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<tr>
<td>Lamina propria</td>
<td>Absent</td>
<td>Frequent*</td>
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<tr>
<td>endocrine cell aggregates</td>
<td></td>
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<tr>
<td>Crypt distortion</td>
<td>Absent or mild</td>
<td>Frequent*</td>
</tr>
<tr>
<td>Neutrophilic abscesses</td>
<td>Rare or absent</td>
<td>Frequent*</td>
</tr>
<tr>
<td>Eosinophilic abscesses</td>
<td>Rare</td>
<td>Frequent*</td>
</tr>
<tr>
<td>Acute cryptitis</td>
<td>Rare</td>
<td>Frequent*</td>
</tr>
<tr>
<td>Apoptoses</td>
<td>Frequent</td>
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<tr>
<td>Apoptotic</td>
<td>Absent</td>
<td>Frequent</td>
</tr>
<tr>
<td>microabscesses</td>
<td>Present</td>
<td>Frequent*</td>
</tr>
<tr>
<td>Hyper eosinophilic (degenerated) crypts</td>
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Abbreviation: HPF, high-power field.
*Features associated with increased disease severity, and therefore more numerous in GVHD grades 3–4.

Nonsteroidal anti-inflammatory drugs can also induce different patterns of colitis, including microscopic colitis (lymphocytic or collagenous), focal active colitis, IBD-like colitis, or ischemic colitis (discussed in subsequent sections).

Methotrexate is an immunosuppressive agent widely used in the treatment of neoplasms and in many autoimmune diseases, including IBD, psoriasis, and rheumatoid arthritis. The adverse effects of methotrexate, such as renal or liver impairment, bone marrow toxicity, and GI mucosal injury, may be related to peak dosage, and they can often be avoided by dose reduction or combined use with folic acid. Nonspecific mucosal ulcerations can be seen in esophagus, stomach, duodenum, and colon. Rarely, extensive mucosal necrosis can be seen, which can be complicated by life-threatening superimposed bacterial infections. If the pathologist is not aware of the patient’s medical history, the etiology of the ulcer may be unclear; therefore, in the absence of any identifiable cause of ulcer, drug injury should always be included in the differential diagnosis.

Increased Epithelial Apoptosis

Apoptotic cells are rare in normal intestinal mucosa, and then they are confined to the surface epithelium because of normal cell turnover. Increased crypt apoptosis should prompt the pathologist to look for associated histologic findings and request detailed clinical history.

Mycophenolate acid (MFA) is available in 2 forms: mycophenolate mofetil (MMF; CellCept, Roche, Nutley, New Jersey) and mycophenolate sodium (Myfortic, Novartis, East Hanover, New Jersey). Mycophenolate acid is an immunomodulator used to prevent rejection in both solid organ transplants (liver, kidney, heart) and bone marrow/ peripheral stem cell transplants. Mycophenolate acid prevents rejection by preventing proliferation of T and B lymphocytes and the formation of antibodies from B lymphocytes. Mycophenolate acid is comparable in efficacy with other immunosuppressive agents, such as tacrolimus, cyclosporine, and azathioprine, but with fewer side effects.

In addition to preventing acute allograft rejection, MFA is also used to treat autoimmune disorders, like lupus, psoriasis, rheumatoid arthritis, myasthenia gravis, and autoimmune uveoretinitis. The combination of MMF and tacrolimus has been approved as a salvage therapy for steroid-resistant chronic graft-versus-host disease (GVHD). Mycophenolate acid–induced side effects include neutropenia and leukopenia, neurologic abnormalities, and GI toxicity, including diarrhea unresponsive to antibiotics or steroids, abdominal pain, nausea, vomiting, and gastritis. Some patients show severe toxicity, which requires drug discontinuation.

Bone marrow transplant patients receiving MMF for GVHD prophylaxis are at risk of developing both true GVHD and MMF–induced colitis, and the need to differentiate these two entities on morphologic grounds is extremely important given the therapeutic implications. Specifically, in MMF–induced colitis, a decreased dose of MMF (ie, reduced immunosuppression) is prescribed, whereas in GVHD, increased immunosuppression with corticosteroids and/or other immunosuppressants is given.

Mycophenolate acid–associated colitis has been reported to show patterns of colonic mucosal injury that mimics several conditions, including GVHD (with increased apoptosis), ischemic colitis, acute self-limited colitis, and IBD. The most common pattern is the one mimicking mild GVHD (grades 1–2). In both entities, the colonic mucosa shows increased apoptosis at the crypt bases, normal or mildly distorted crypt architecture, mild epithelial regenerative atypia, and occasional “damaged crypts” (dilated crypts with flattened epithelium and eosinophilic luminal debris; Figure 2, A and B). However, in MFA–associated colitis, the lamina propria shows significantly more eosinophils within the lamina propria compared with GVHD, but no significant increase in lymphocytes, plasma cells, neutrophils, or mast cells. In GVHD there is a selective sparing of enterochromaffin cells in colon, and single or small clusters of endocrine cells can be seen in lamina propria (Figure 2, C). Compared with GVHD, MMF colitis appears to lack apoptotic microabscesses and the aggregates of endocrine cells within lamina propria. One recent study showed that more than 15 eosinophils per 10 high–power fields, combined with a lack of endocrine cell aggregates and lack of apoptotic microabscesses, revealed sensitivity, specificity, and positive and negative predictive values of 76%, 93%, 81%, and 90%, respectively, for differentiating MMF colitis from GVHD. A summary of histologic features that may distinguish between MMF colitis and GVHD is provided in Table 3.

Ipilimumab (Yervoy, Bristol–Myers Squibb, Princeton, New Jersey) is a humanized monoclonal antibody against cytotoxic T–lymphocyte antigen 4 (CTLA–4), used to treat advanced melanoma as well as renal, ovarian, and prostate cancer. CTLA–4 blockade with ipilimumab can cause dysregulation of GI mucosal immunity, resulting in GI toxicity. Patients may present with diarrhea, abdominal pain, blood in stools, increased stool frequency, nausea, vomiting, or constipation, with or without fever. Diarrhea and/or colitis can become life threatening, with reports of ipilimumab–induced fatal bowel perforation and sepsis. Extensive ulcerations observed by colonoscopy indicate severe cases. However, biopsies with unexpectedly severe inflammation often occur in the presence of mild endoscopic changes.

Colonic biopsies show 2 patterns: a focal active colitis pattern, subsequently discussed in the section on drugs causing focal active/self–limiting colitis, and a pattern resembling GVHD. The latter shows increased apoptosis...
in the crypts; increased intraepithelial lymphocytes; marked and diffuse lymphocytic inflammatory infiltrates in lamina propria, with occasional plasma cells and eosinophils; and rare foci of acute cryptitis without chronic features like basal plasmacytosis or crypt distortion (Figure 2, D).

Other drugs associated with GVHD-like features (increased crypt apoptosis, cystically dilated crypts lined by flattened and degenerated epithelium and luminal apoptotic debris) include antimetabolites (methotrexate, capecitabine), and tumor necrosis α inhibitors (etanercept and infliximab). The patients present with transitory watery diarrhea, which improves upon drug discontinuation. Most of these patients, however, are not biopsied, and only case reports have been published.11

Idelalisib (Zydelig, Gilead, Foster City, California) is an inhibitor of the phosphatidylinositol-3-kinase d (PI3Kδ) isoform approved for the treatment of patients with relapsed chronic lymphocytic leukemia/small cell lymphoma, follicular lymphoma, and indolent non-Hodgkin lymphoma. Many patients develop gastrointestinal symptoms during idelalisib therapy; however, histologic findings in colonic biopsies have only recently been described. The mucosal biopsies showed a “triad” of intraepithelial lymphocytosis, epithelial cell apoptosis, and neutrophilic cryptitis12,13 (Figure 3). Awareness of the histologic features of idelalisib-associated enterocolitis is important to distinguish it from potential mimics, particularly GVHD, other drug-induced injury (especially MFA), autoimmune enteropathy, and infections, like cytomegalovirus/infectious enterocolitis. Most of these entities can be excluded on clinical grounds and medication history.

**IBD-like Pattern**

In addition to the GVHD-like pattern described above, MFA use can be associated with an IBD-like, especially Crohn-like, histologic pattern. The colonic mucosa shows mild to moderate crypt distortion, with branching, shortening, and crypt dropout, increased inflammatory cells within lamina propria, increased epithelial apoptosis, and occasional crypt dilatation (“dilated damaged crypt pattern”) with luminal eosinophilic debris. The lamina propria inflammation is typically less intense in MFA-associated colitis than in true IBD. Differentiating MFA-induced changes from IBD requires an adequate clinical history. In favor of IBD are a clinical history of chronic diarrhea, bloody diarrhea, a typical endoscopic appearance, and no history of transplant or MFA use.

Rare patients may develop abdominal pain and bloody diarrhea a few days after initiation therapy with ipilimumab. Endoscopic findings vary from normal to segmental to diffuse erythema and ulceration that can mimic IBD.14 Again, clinical history and especially medication history are helpful in arriving to the correct diagnosis.

Rituximab (Rituxan, Biogen Idec, Cambridge, Massachusetts, and Genentech, San Francisco, California) is an anti-CD20 monoclonal antibody used to treat B-cell non-Hodgkin lymphomas resistant to other chemotherapy regimens, as well as to treat multiple myeloma, rheumatoid arthritis, and other autoimmune disorders, mostly off-label. In rare cases it has been associated with new onset or exacerbation of ulcerative colitis,15 or even colonic perforation.16

**Ischemic Colitis**

Classic ischemic colitis is seen in elderly patients in the watershed area of the colonic splenic flexure, in those who...
usually have right-sided heart failure and a low–blood flow state. If accumulating to toxic levels (but not on therapeutic levels), digitals may predispose to ischemic colitis due to shunting of blood away from the mesenteric vasculature. The characteristic histologic pattern includes small, withered crypts, hyalinized lamina propria with few inflammatory cells, fibrin thrombi in small vessels, surface ulceration and granulation tissue, and occasionally pseudomembranes formation (Figure 4).

The presence of ischemic colitis in young patients should always raise the possibility of drug involvement, especially oral contraceptives, cocaine, and migraine medication, like ergotamine derivatives and potentially sumatriptan. Oral contraceptives produce a hypercoagulable state and may cause mesenteric vein fibrosis. Ergotamine causes localized ischemia due to vasospasm, usually leading to shallow rectal ulcers. Rare perforations and strictures have also been recorded. Cocaine is a potent vasoconstrictor that can cause localized or diffuse intestinal ischemic changes, sometimes requiring surgical resection of the ischemic bowel segment.

Other drugs that may induce ischemic colitis include nonabsorbable drugs, which exert their effects in the lumen of the GI tract. Sodium polystyrene sulfonate (Kayexalate, Sanofi Aventis, Bridgewater, New Jersey) is a cation–exchange resin routinely used in the treatment of hyperkalemia. Its action is primarily in the colon, where the sodium ions are partially released and replaced by potassium ions. The excess potassium is then evacuated along with the stool. Because Kayexalate can induce constipation, original formulations of Kayexalate included 70% sorbitol, an osmotic laxative, which was implicated in the early reports of terminal ileum and colonic necrosis and ischemia. However, lower concentrations, and even the absence of sorbitol in other formulations, failed to eliminate the ischemic side effects, proving that Kayexalate itself is toxic. Kayexalate may induce ischemic necrotizing lesions in small intestine and colon, with mucosal ischemia and numerous crystals entrapped in the injured mucosal surface or admixed with the superficial inflammatory exudate. The crystals are basophilic or violet on hematoxylin–eosin stain (H&E), and gray or pink on periodic acid–Schiff special staining with diastase, resembling broken glass (Figure 5, A). In uremic, posttransplantation, or postoperative patients, Kayexalate may induce fissuring, deep ulcerations (Figure 5, B), or even transmural necrosis with perforation, with a mortality rate of approximately 33%. Rare cases of colonic mucosal necrosis were described in patients using calcium polystyrene sulfonate (Kalinate, Kowa, Nagoya, Japan), an analogue of Kayexalate without sorbitol. The crystals found in the inflammatory exudates are very similar to the Kayexalate crystals.

Other resins include the bile sequestrants cholestyramine (Questran, Par Pharmaceutical Inc, Spring Valley, New York), colestevelam (Welchol, Daiichi Sankyo, Parsippany, New Jersey), and colestipol (Colestid, Cholestabyl, Pfizer, New York, New York), used to lower high levels of cholesterol in the blood, especially low-density lipoprotein. The bile acid sequestration properties of colestipol and cholestyramine, but not colestevelam, have the ability to remove the offending agents of bile acid–mediated pruritus in cholestatic liver disease. The bile sequestrant resins can also be used to sequester other agents, including excess thyroid hormone, bacterial toxins, and digoxin, rendering them useful in the treatment of symptomatic hyperthyroidism, medication-resistant Clostridium difficile, and digoxin overdose, respectively. Patients using the bile sequestrant resins may present with diarrhea.

The colonic biopsies may be entirely normal, or rarely may show chronic injury, erosions, ulcerations, or increased crypt apoptosis, with associated characteristic crystals floating on the mucosal surface or embedded in the mucosa. Colesevelam, colestipol, and cholestyramine crystals display identical morphology to each other but can be distinguished from Kayexalate crystals. Colesevelam, colestipol, and cholestyramine crystals are rhomboid, bright orange and opaque on H&E, and gray or pink on periodic acid–Schiff special staining with diastase, with a more homogeneous appearance (Figure 5, C). In general, the crystals are considered innocent bystanders, entrapped in mucosal injured due to previous inflammatory conditions, and not the actual cause of mucosal injury.

Sevelamer (Renvela, Genzyme, Cambridge, Massachusetts) is a resin used to bind excess phosphate in dialysis patients with hyperphosphatemia. Sevelamer crystals are broad and curved, with irregularly spaced “fish scales” that intersect at curved points (as opposed to the narrow, regularly spaced, rectangular “fish scales” of Kayexalate), a 2-tone rusty brown color on H&E (Figure 5, D), and a violet color on periodic acid–Schiff special staining with diastase. Sevelamer is usually associated with mucosal ulceration, ischemia, or necrosis.

Glutaraldehyde may induce iatrogenic ischemic colitis, within minutes or hours after colonoscopy. Used to disinfect endoscopes, glutaraldehyde may remain on improperly rinsed endoscopes, inciting a local irritant effect and possibly producing mucosal injury resembling usual ischemic colitis, but this is usually self-limited.

There are isolated reports of ischemic colitis associated with other drugs, like NSAIDs: alosetron (Lotronex, GlaxoSmithKline, Philadelphia, Pennsylvania), used for the management of severe diarrhea in irritable bowel syndrome in women only; pseudoephedrine; interferon; dopamine; and methysergide.

Mycophenolate acid has rarely been associated with ischemic changes, although it is unclear whether the changes were due to the drug or superimposed cardiovascular disease. There are some published case reports of segmental ischemic colitis associated with MMP.

**Focal Active Colitis/Self-Limited Colitis**

If acute infections, Crohn disease, and ischemia have been ruled out, drugs—most commonly NSAIDs and sodium phosphate bowel preparations—should always be considered as a potential cause of focal active colitis. Focal active colitis is a histologic pattern of injury, not a specific diagnosis; it is defined by single or multiple, isolated foci of acute cryptitis, with normal intervening mucosa and small numbers of neutrophils within lamina propria or within surface epithelium. Increased mononuclear cells in the lamina propria may accompany the crypt injury; however, no chronic features or granulomata are present (Figure 6). Oral sodium phosphate solutions can also induce a mild increase in crypt apoptosis and aphthoid erosions. These changes can typically be safely ignored in an asymptomatic patient undergoing a routine screening colonoscopy.

Mycophenolate acid use has rarely been associated with a focal active colitis pattern of inflammation, which reportedly improved after discontinuation of MFA. In this situation,
Figure 5. Mucosal damage induced by nonabsorbable drugs. A, Sodium polystyrene sulfonate (Kayexalate) crystals are seen floating in inflammatory infiltrate on the surface of colonic mucosa. The crystals are basophilic or violet on hematoxylin-eosin stain; they are nonpolarizable; they have a rectangular shape; and they resemble broken glass. They show narrow, regularly spaced, rectangular “fish scales.” B, Kayexalate-induced deep mucosal ulceration extending into submucosa. The crystals are seen floating in the surface inflammatory infiltrate. Another area showed transmural ischemic necrosis with perforation of cecum (not shown). This patient had concomitant collagenous colitis. C, Cholestyramine crystals are irregular in shape, opaque, and orange. D, Sevelamer crystals are broad and curved, with irregularly spaced “fish scales” that intersect at curved points (as opposed to the narrow, regularly spaced, rectangular “fish scales” of Kayexalate), and a 2-tone rusty brown color on hematoxylin-eosin stain. Sevelamer may be associated with mucosal ulceration, ischemia, or necrosis (hematoxylin-eosin, original magnifications ×200 [A and C], ×20 [B], and ×400 [D]).

Figure 6. Focal active colitis pattern of inflammation, which may be induced by numerous drugs, including nonsteroidal anti-inflammatory drugs, bowel preparations, mycophenolate acid, and ipilimumab. A, The colonic mucosa shows preserved crypt architecture. Lamina propria shows patchy increase in inflammatory cells, with small numbers of neutrophils and increased mononuclear cells. B, Multiple, isolated foci of acute cryptitis and small crypt abscesses, with normal intervening mucosa (hematoxylin-eosin, original magnifications ×40 [A] and ×100 [B]).
clinical correlation is of utmost importance, because the diagnosis cannot be made on histologic grounds alone.

The most common pattern of colonic toxicity associated with irinotecan use is focal active colitis, with isolated crypt destruction, loss of goblet cells and regenerative epithelium, and neutrophilic infiltrates in the crypt epithelium.33,34

Microscopic Colitis

Proton pump inhibitors, especially lansoprazole (Prevacid, Takeda, Tokyo, Japan), have been associated with developing microscopic colitis, either lymphocytic or collagenous colitis.35 Other drugs associated with microscopic colitis include an ever increasing list of drugs, like H2 receptor antagonists (ranitidine, cimetidine), ticlopidine, NSAIDs (reportedly associated with collagenous colitis), Cyclo 3 Fort (used to treat chronic venous insufficiency),36 simvastatin, carbamazepine, flutamide, paroxetine, penicillin, and selective serotonin reuptake inhibitors like sertraline. The newest drug associated with increased intraepithelial lymphocytes in colon, both in surface and crypt epithelium, is idelalisib37 (which has been described in more detail in the section Increased Epithelial Apoptosis above). However, in addition to intraepithelial lymphocytes, there are numerous apoptotic crypt cells, some quite large, “exploding,” and neutrophilic infiltrate of the crypt epithelium, which distinguish it from lymphocytic colitis.

Infectious/Necrotizing Colitis

Several medications may render the GI tract more susceptible to infections, including numerous chemotherapy drugs, corticosteroids, and antibiotics.

Chemotherapy Drugs.—A significant, life-threatening complication of high-dose chemotherapy in immunocompromised patients is neutropenic enterocolitis, or typhilitis. It has been reported initially in children following induction therapy for acute leukemia, but later has been described with chemotherapy for acute myeloid leukemia; multiple myeloma; aplastic anemia; myelodysplastic syndromes; breast, lung, and testis solid tumors; AIDS; and transplants.37 The hematologic agents implicated include cytosine arabinoside, vincristine, doxorubicin, methotrexate, cyclophosphamide, etoposide, daunomycin, and prednisone; the agents for solid tumors include vinorelbine, docetaxel, paclitaxel, carboptatin, cisplatin, gemcitabine, and 5-fluorouracil. Neutropenic enterocolitis has also been reported as an unusual38 and, rarely, fatal complication39 of hepatitis C treatment with pegylated interferon and ribavirin. The disease appears to be the result of a combination of factors, including direct mucosal injury by cytotoxic drugs, neutropenia, and impaired host defense to intestinal organisms, with bacterial invasion of the bowel wall and production of bacterial endotoxins, resulting in necrosis and hemorrhage. The cecum is always involved, probably because of its distensibility and limited blood supply40, sometimes terminal ileum, and right and left colon may be involved. The colon appears markedly edematous, with mucosal ulcerations, hemorrhage, mucosal or transmural necrosis, and bacterial colonies. An important diagnostic clue is the paucity of inflammatory cells and lack of mucosal neutrophils in the ulceration (Figure 7). The bacteria most commonly involved include Gram-negative rods, Gram-positive cocci, enterococci, Clostridium septicum, Candida spp (as secondary infections), and cytomegalovirus. Neutropenic enterocolitis should be suspected in any patient with absolute neutrophil count lower than 500/µL, fever, and abdominal pain, 10 to 14 days after initiation of cytotoxic chemotherapy. Mortality is very high, approaching 100% because of recurrent or persistent malignancy, sepsis, or bowel perforation, as well as ischemia and necrosis.40

Corticosteroids.—Corticosteroid use has been associated with perforation of inflamed sigmoid diverticula.41 High-dose corticosteroid therapy decreases the clinical manifestation of peritonitis to the point that recognition, and therefore treatment, of GI perforation was markedly delayed. Risk of diverticula perforation has been described also with NSAIDs and opioids.32 Rare cases of malaco- laksia have been described after corticosteroid use in treatment of IBD.42 Malaco- laksia is a form of chronic granulomatous inflammatory reaction due to defective inflammatory response to Gram-negative bacterial infections that rarely affects the GI tract. Histologically it is characterized by a diffuse infiltration of the colonic mucosa by sheets of large macrophages with eosinophilic granular cytoplasm and characteristic cytoplasmic calciospherites (Michaelis-Gutmann bodies), which are typically positive with Prussian blue and von Kossa stains. There are rare case reports of malaco- laksia after immunosuppression for transplants.44

A special type of infectious colitis is pseudomembranous colitis following antibiotics use, or previously called “antibiotics colitis.” Pseudomembranous colitis is a descriptive term for colitides defined by the presence of pseudo-membranes on the colonic or, rarely, small intestinal mucosa. Antibiotics, especially penicillins, clindamycin, cephalosporins, and trimethoprim-sulfamethoxazole, are most commonly implicated, and they render the colon of hospitalized patients susceptible to colonization by Clostridium difficile by altering the bowel flora.45 The mucosal damage is due to toxin A produced by Clostridium difficile in bowel lumen, not by tissue invasion by bacteria. Recently, evidence showed that proton pump inhibitor use is associated with community-acquired Clostridium difficile colitis, which may have significant public health implications.46 By suppressing gastric acid production, proton pump inhibitors increase gastric pH, a major defense mechanism against ingested pathogens; they have also been shown to affect leukocyte function, which may contribute to the reported associations with an increased risk of respiratory tract infections and enteric infections, including hospital-acquired and nursing home-acquired Clostridium difficile colitis.

Pseudomembranous colitis has a characteristic endoscopic appearance, with discrete, numerous, very adherent mucosal yellow plaques, which histologically are formed by necrotic epithelial cells, mucus, fibrin, and neutrophils. Pseudomembranes erupt out of dilated crypts to form a mushroomlike or volcano-like cloud. The superficial lamina propria contains dense neutrophils and some capillary fibrin thrombi (Figure 7, C). Later in the course of disease, the entire crypt becomes necrotic and the features may be indistinguishable from ischemic colitis. Pseudo–signet ring cells with small bland nuclei may be seen in rare cases, confined to crypts and epithelial surface, without infiltration into lamina propria (Figure 7, D), a pitfall of signet ring carcinoma.46,47

Mimics of Dysplasia and Mitotic Arrest

Several drugs may lead to epithelial atypia mimicking dysplasia. Colchicine (Colcrys, Takeda, Deerfield, Illinois) and Taxol (paclitaxel, Bristol-Myers Squibb), although used
in different clinical settings (gout; and breast, ovarian, and lung non–small cell cancers, respectively), have similar mechanisms of action and pathologic effects in GI tract. Both drugs interfere with tubulin and inhibit its polymerization into microtubules, which causes mitotic arrest. Further, epithelial changes associated with taxanes can mimic high-grade dysplasia in nonneoplastic GI tract mucosa, especially in upper GI tract but occasionally in colon. The changes associated with colchicine are only seen in patients with toxicity. With taxane administration, these findings are not specific for toxicity, but rather reflect taxane effect. The histologic changes seen can mimic high-grade dysplasia and include glandular crowding, epithelial nuclear stratification, loss of polarization and hyperchromasia, increased apoptosis deep within crypts, and metaphase ("ring") mitoses (Figure 8).

Intravenous cyclosporine, used to treat severe ulcerative colitis, may induce colonic villous transformation and epithelial atypia mimicking dysplasia. Helpful clues to rule out true dysplasia include the presence of surface maturation and the diffuse nature of these changes.

**CONCLUSIONS**

The most common GI side effects of numerous drugs include diarrhea or constipation, nausea and vomiting, and abdominal pain. More serious side effects include bloody diarrhea, blood in stools, colonic perforation, and, rarely, death.

Histologically, drug-induced colonic injury is often nonspecific and may mimic many types of colitides, including IBD, microscopic colitis, ischemic colitis, or GVHD. It is important for the pathologist to keep in mind that a single drug type can induce many histologic patterns: NSAIDs, probably the most common medication used presently, can induce isolated mucosal erosions, ulcerations, focal active colitis, microscopic colitis (especially collagenous colitis), and, rarely diaphragm disease; MFA-induced injury may mimic GVHD, IBD, focal active colitis, and even ischemic colitis.

Figure 7. Infectious/necrotizing colitis. A and B, Neutropenic enterocolitis. The colonic mucosa shows an ulceration involving the entire mucosal thickness, covered by fibrin strands. No neutrophils are present in the granulation tissue. C, Pseudomembranous colitis induced by antibiotics. The colon is diffusely covered by pseudomembranes, composed of necrotic epithelial cells, mucus, fibrin, and neutrophils. The pseudomembranes erupt out of dilated, damaged crypts to form a "volcano-like" cloud on the surface; the lamina propria between affected crypts is relatively normal. D, Pseudomembranous colitis induced by antibiotics. Occasionally, pseudo-signet ring-like cells are seen, confined to the area with pseudomembranes, present only in the crypts and epithelial surface without infiltration of lamina propria. These cells should not be confused with signet ring carcinoma (hematoxylin-eosin, original magnifications ×40 [A], ×200 [B and D], and ×100 [C]).
Figure 8. Drugs inducing dysplasia-mimics and mitotic arrest include colchicine, taxanes, and cyclosporine administered intravenously. The colonic mucosa shows marked glandular crowding, epithelial nuclear stratification, loss of nuclear polarization and hyperchromasia, increased apoptosis deep within crypts, and metaphase (“ring”) mitoses (insert, circled) (hematoxylin-eosin, original magnification ×200).

Distinction between drug-induced injury and an established type of colitis (like IBD or GVHD) is extremely important because these entities are managed differently. Although there are some histologic clues helpful in the diagnosis of drug-induced injury, correlation with clinical history and especially medication history is essential to improve diagnostic accuracy.

Close collaboration between pathologist and clinician is extremely important in the recognition of these entities and allows us to provide the best patient care.

References


