The Many Faces of Medication-Related Injury in the Gastrointestinal Tract

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KEYWORDS

• Gastrointestinal tract • Drug toxicity • Chemotherapy • Immunomodulator • Pathologic features

Key points

- Numerous medications produce clinically significant gastrointestinal toxicity that can be identified by histologic examination
- Gastrointestinal drug toxicity can mimic other, more common inflammatory gastrointestinal disorders; a high index of suspicion is needed to establish a correct diagnosis
- Clinical correlation and careful review of the medication history are especially helpful in recognizing the presence of a drug-induced gastrointestinal injury.

ABSTRACT

Every year many new medications are approved for clinical use, several of which can cause clinically significant gastrointestinal tract toxicity. This article emphasizes the histologic features and differential diagnosis of drug-induced injury to the gastrointestinal mucosa. Ultimately, clinical correlation and cessation of a drug with resolution of symptoms are needed to definitively confirm a drug as a causative factor in mucosal injury. Recognizing histologic features in gastrointestinal biopsies, however, can allow surgical pathologists to play a key role in establishing a diagnosis of drug-induced gastrointestinal toxicity.

OVERVIEW

The Center for Drug Evaluation and Research within the Food and Drug Administration (FDA) regulates over-the-counter and prescription medications. Each year, this organization approves a large number of new drugs and biological agents. Novel drugs that have never been used in humans are classified as "new molecular entities" for purposes of regulatory review; all submitted biological products are included in this category. Many other agents are either the same as, or closely related to, previously approved agents and are intended to compete for use in clinical practice. In 2016, a total of 21 novel drugs received FDA approval for human use.[1] All proposed new medications undergo a rigorous evaluation process designed to not only assess efficacy but also determine a toxicity profile. In 2007 Congress mandated that the FDA provide safety information to the general public and medical professionals relating to medications it has approved for clinical use. For this purpose, the FDA maintains a Web site that is a valuable resource for reports of postmarket drug toxicities.[2] This review is intended to discuss the drugs that most often produce clinically significant gastrointestinal toxicity as well as recently released agents that are emerging as important new sources of mucosal injury.

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CHEMOTHERAPEUTIC AGENTS

Chemotherapeutic agents increase cell necrosis, autophagy, and/or apoptosis among cells with a high proliferative rate, which unfortunately includes the gastrointestinal epithelium. Once the epithelium is injured, loss of mucosal integrity ensues, resulting in increased permeability and susceptibility to infectious agents. Not surprisingly, a variety of chemotherapeutic agents of several classes can cause gastrointestinal mucosal damage. Platinum adducts (eg, cisplatin, carboplatin, and oxaliplatin), DNA intercalators (eg, doxorubicin), antimetabolites (eg, 5-fluorouracil, capecitabine, 6-mercaptopurine, cytarabine, and gemcitabine) and, to a lesser extent, alkylators (eg, mechlorethamine, melphalan, chlorambucil, and cyclophosphamide) are all capable of producing clinically significant diarrhea due to gastrointestinal mucosal injury.[3] Major risk factors for clinically significant toxicity include patient age (young and elderly), nutritional status, type of malignancy, method of drug delivery, and pretreatment neutropenia.[4]

Chemotherapy-induced gastrointestinal mucosal injury often produces diarrheal symptoms, although some agents may also cause odynophagia, nausea, emesis, anorexia, malabsorption, abdominal pain, and cramping. Common endoscopic findings include mucosal erythema, erosions and ulcers. Severe toxicity is uncommon but can manifest as extensive ulceration with perforation. In this situation, the possibility of individual genetic predisposition to toxicity due to a metabolic defect should be considered. Approximately 20% of patients who develop severe gastrointestinal toxicity after 5-fluorouracil administration prove to have a mutation in *DPYD*. This gene encodes dihydropyrimidine dehydrogenase, which normally promotes drug catabolism; diminished enzymatic activity results in a prolonged serum half-life and toxic drug levels (**Fig. 1**).[5,6]

Chemotherapy-induced injury can occur anywhere in the gastrointestinal tract. One hallmark feature is the presence of scattered withered crypts or glands lined by attenuated epithelial cells that show irregular nuclear spacing and acidophilic cytoplasm, often associated with necrotic epithelial cells in the lumen (**Fig. 2**). This finding is nonspecific and can be seen in other disorders, such as ischemic enterocolitis and graft-versus-host disease (GVHD). Small bowel biopsies may demonstrate villous blunting with increased apoptotic bodies. Some agents can elicit marked cytologic abnormalities that simulate dysplasia, such as cellular enlargement, bizarre and hyperchromatic nuclei, and prominent nucleoli. Affected cells, however, contain ample cytoplasm; typically contain hyperchromatic, smudged nuclei; and show minimal mitotic activity.

Some chemotherapeutic agents produce characteristic mucosal alterations. For example, taxanes inhibit tubulin polymerization into microtubules, leading to mitotic arrest in metaphase and resulting in ring mitotic figures (**Fig. 3**). This phenomenon is commonly identified in the proliferative compartment of the epithelium throughout the gastrointestinal tract.[7,8] Ring mitotic figures are accompanied by increased numbers of normal-appearing mitotic figures as well as scattered apoptotic cellular debris. Glandular crowding, loss of polarity, and nuclear stratification with hyperchromasia are common, and the combination of these features can closely simulate the appearance of dysplasia. These dramatic histologic changes do not necessarily indicate toxicity, however, because they are also seen in asymptomatic individuals who receive these drugs. Mucosal necrosis and bowel perforation reportedly occur, however, in up to 3% of patients with taxane-associated gastrointestinal toxicity.[9] Colchicine is another agent that induces mitotic arrest and produces essentially the same histologic features in mucosal biopsies. Unlike

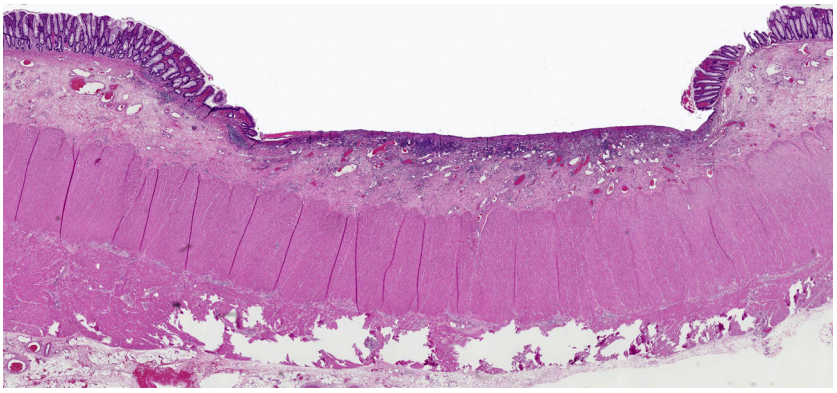

Fig. 1. Severe 5-fluorouracil toxicity produced extensive colonic ulceration in a patient with a *DPYD* mutation [H&E, original magnification ×4].