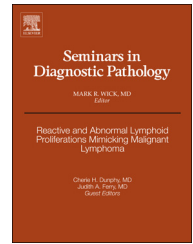


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## Drug-induced injury in the gastrointestinal tract

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### ABSTRACT

Abnormalities of the gastrointestinal tract due to drug-induced injuries are common and often have important clinical consequences. Medications may cause damage by direct corrosive effects on mucosae or by alter processes, mucosal immunity, and local environmental conditions. The aim of this review is to guide practicing pathologists in the identification of drug-related injuries in gastrointestinal mucosal biopsies and resection specimens. Common causes of injury and their gross, endoscopic, and microscopic features are presented.

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### Introduction

A growing number of medications adversely affect the gastrointestinal tract. Factors such as medication dose, mechanism of action, drug interactions, and patients' underlying states of health influence the type and severity of these effects. Some medications produce characteristic histologic changes, but most cause non-specific patterns of injury that display considerable overlap with pathologic findings caused by other drugs, infections, and immune-mediated diseases. Evaluation of patients with drug-induced gastrointestinal illness often includes upper and lower endoscopy with biopsy to facilitate distinction between these entities. Familiarity with general and specific patterns of drug-mediated gastrointestinal injury is an invaluable tool to pathologic interpretation of specimens from these patients. This review summarizes the clinical, gross, and histologic features of common drug-related gastrointestinal injuries. Differential diagnoses and potential interpretative challenges are emphasized.

### General patterns of drug-related injury in the gastrointestinal tract

More than 100 medications have been reported to cause esophageal injury. Drug toxicity may result from a therapeutic

drug action or injury related to direct mucosal contact. For example, smooth muscle relaxants promote gastroesophageal reflux disease, medication-induced immunosuppression increases opportunistic infection risk, and antibiotic-related alterations in flora may result in *Candida* infection. Local, or topical, injury to the mucosa (pill esophagitis) results from pill stasis, usually in areas of esophageal narrowing. Common sites of impaction include those affected by external compression, such as where the esophagus rests against the left main stem bronchus, the gastroesophageal junction, and sites of previous injury. Patients with left atrial enlargement may also develop injury at this location. Symptoms of pill esophagitis include sudden onset of dysphagia, odynophagia, and retrosternal chest pain.<sup>1</sup> Several drugs cause direct mucosal injury, namely anti-inflammatory analgesics, quinidine, potassium chloride, emepronium bromide, alendronate, tetracyclines, clindamycin, ferrous sulfate, and phenytoin.<sup>2–7</sup> Of these, alendronate is perhaps the most common. Elderly patients are particularly at risk, since they are more likely to ingest pills with inadequate amounts of water or lie in the recumbent position during, or shortly after, taking medications. Most injuries heal after withdrawal of the offending drug, although severe damage may require endoscopic or surgical intervention. Erosions, ulcers, erythema, and mucosal friability are typical, but strictures and circumferential wall thickening may simulate malignancy in some cases.<sup>8</sup>

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Intact squamous mucosa, adjacent to erosions and ulcers, displays neutrophil-rich infiltrates and reactive epithelial changes, including enlarged, hyperchromatic nuclei and multinucleation. Clear, refractile crystalline material may be seen in many cases in association with a foreign body giant cell reaction. This material represents the cellulose filler used in numerous prescription and over-the-counter medications and is not specific for any agent.<sup>9</sup>

Pill esophagitis may simulate the endoscopic appearance of severe gastroesophageal reflux disease, although gastroesophageal reflux disease tends to present more insidiously. Pill esophagitis that is limited to the narrowing of the mid-esophagus is less likely to be confused with gastroesophageal reflux, which invariably involves the distal esophagus. Biopsies from patients with gastroesophageal reflux disease reveal eosinophilic, rather than neutrophilic, inflammatory infiltrates, except in areas of erosion or ulcer. Viral infections, such as herpes and cytomegalovirus, also cause esophageal ulcers, but tend to occur in immunosuppressed patients. Well-sampled viral ulcers often reveal characteristic inclusions.

Medication-induced injury to the gastric mucosa is most commonly encountered in the antrum, although patchy or diffuse gastropathy may be seen. Endoscopic features include erythema, edema, and erosions. Hemorrhage or contact bleeding is sometimes associated with NSAID or corticosteroid administration. The most common histologic pattern of injury is chemical gastropathy, which is characterized by mucin-depleted epithelium and elongated, tortuous gastric pits. The lamina propria contains dilated and congested mucosal capillaries, associated with edema and fibrosis in the case of healed erosions. Inflammatory infiltrates are minimal, but neutrophils reflect the presence of erosions and ulcers.<sup>10,11</sup> Chemical gastropathy may also be related to ingestion of alcohol, acidic and alkaline substances, and reflux of bile and other duodenal contents into the stomach.

Inflammation and ulcers due to medications occur throughout the small intestine and colon, but are particularly

common in the proximal duodenum, terminal ileum, and right colon. Ulcers may appear as well-demarcated aphthous lesions within normal mucosa or occur on a background of patchy erythema, edema, or ischemic-type changes.

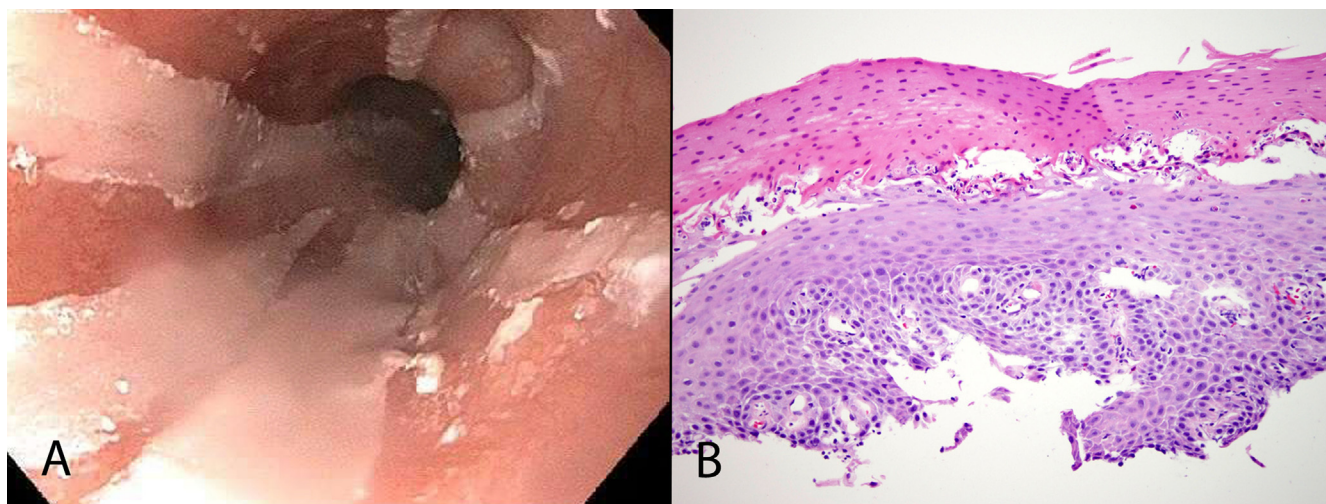
### Specific medications that cause injury to the gastrointestinal tract

#### Alendronate

Alendronate sodium is an aminobisphosphonate that selectively inhibits osteoclast-mediated bone resorption. It is used to treat disorders of bone remodeling, including osteoporosis and Paget disease. Alendronate causes pill esophagitis in <2% of patients, and gastric erosions are reported even less frequently.<sup>9</sup> Alendronate is thought to be topically corrosive due to free radicals generated from oxidation of the drug's amino acid side chain.<sup>12</sup> Rare cases of *esophagitis dissecans superficialis*, or tubular epithelial casts sloughing off of the wall of the esophagus, have also been reported in patients taking alendronate (Fig. 1A).<sup>13</sup> Biopsies show intraepithelial splitting above the basal layer of the squamous mucosa, which may create the appearance of a bulla (Fig. 1B). The squamous mucosa below the split is edematous with prominent intracellular bridges and occasional dyskeratotic cells. The superficial or "sloughed" portion of mucosa shows hyperparakeratosis and necrosis without associated inflammation. *Esophagitis dissecans superficialis* is also described in association with NSAIDs, central nervous system depressants, and immune-mediated diseases.<sup>14,15</sup>

#### Tetracycline

Tetracyclines, particularly doxycycline, are the most common antimicrobial agents to cause esophagitis, accounting for up to 45% of cases (Fig. 2A). Tetracycline-induced esophageal injury is common in the adolescent population because it is



**Fig. 1** – *Esophagitis dissecans superficialis* is characterized by longitudinally oriented, white mucosal casts that slough into the esophageal lumen. The white casts alternate with healing pink areas of re-epithelialization (A). Biopsies reveal intraepithelial splitting of the squamous mucosa. A superficial layer of deeply eosinophilic keratinocytes contains pyknotic nuclei, whereas subjacent epithelium is essentially normal (B).

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