Drug-induced pathology of the upper gastrointestinal tract

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Abstract

Drugs can produce a wide range of pathology in the upper gastrointestinal tract. Often, the injury pattern is non-specific. Pill-induced oesophagitis usually affects the mid oesophagus. In the stomach, many drugs, particularly non-steroid anti-inflammatory drugs (NSAIDs), can cause ulcers, erosions or reactive gastropathy. Some drugs produce specific injury patterns that can be recognized by pathologists. Proton pump inhibitors cause parietal cell hyperplasia and fundic gland polyps. Kayexalate may cause erosions or ulcers, with 'mosaic' crystals within the exudate, but other resins may show crystals that can be confused for Kayexalate. Iron therapy, mucosal calcinosis, and mucosal lanthanum deposition share the presence of crystals in the mucosa of affected patients. Various agents can cause non-specific mucosal changes that mimic celiac disease, GVHD, or inflammatory bowel disease, such as olmesartan, idelalisib, and checkpoint inhibitors. Colchicine causes variable injury, and interference with microtubule assembly results in mitotic arrest. Hepatic arterial infusion chemotherapy may cause gastroduodenal ulcers associated with marked epithelial atypia that can be mistaken for carcinoma. Recognition of these histological patterns enables pathologists to make a diagnosis of drug-induced upper gastrointestinal injury and potentially to identify the specific agent responsible.

Keywords drugs; gastrointestinal; non-steroidal anti-inflammatory drugs; pathology; proton pump inhibitors; toxicity

Introduction

Although the number of drugs that can damage the upper gastrointestinal (GI) tract is large, these drugs produce a limited number of injury patterns. Some of these patterns are non-specific and generate a differential diagnosis, which may be resolved by clinical history. Occasionally, a specific drug can be suspected based on the findings within the biopsy. This review first describes the non-specific injury patterns, followed by a discussion of specific drugs and their injury patterns, beginning with the most commonly implicated drugs, namely non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs), and ending with less common but recognizable drug-related injury patterns. Recently described drug-induced lesions are selectively described.

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Non-specific injury patterns

Pill oesophagitis

Pill oesophagitis occurs secondary to caustic injury caused by retention of a pill in the oesophagus, often associated with failure to consume adequate amounts of liquid with tablet or capsule medications, and by taking these medications in the supine position before bedtime.[1–5] Women and the elderly are more often affected.[2–7] Most patients do not have pre-existing oesophageal dysmotility.[2,4] The most commonly reported agents include antibiotics (particularly doxycycline, tetracycline and clindamycin), NSAIDs, potassium chloride, iron supplements, ascorbic acid and alendronate.[1,2,5–10]

Most patients present with odynophagia, retrosternal pain and dysphagia.[3–5,7,8,10] Endoscopic findings include erythema, mucosal denudation, discrete ulcers or erosions, and strictures.[2,5,7,8,11,12] Remnants of the pill may also be seen.[1] Quinidine-induced oesophageal injury occasionally presents with exuberant exudates that mimic carcinoma.[4,5] The usual sites of involvement are the mid oesophagus at the level of the aortic arch (22–24 cm) and, in patients with left atrial enlargement, the distal oesophagus at 30–35 cm.[1,3–5,10] However, distal involvement with stricture can be mistaken for reflux oesophagitis.[2,5] Serious complications of pill oesophagitis include haemorrhage, oesophageal perforation and even death.[3,4,7]

Histological evaluation often shows the usual features of oesophagitis with acute inflammation, erosions or ulcers, and granulation tissue.[8,10] Polarizable crystalline material may be an important clue to the diagnosis, although it is not present in all cases (Figure 1).[8] Multinucleation of squamous epithelial cells has been reported in association with alendronate-associated oesophageal injury.[8,13] Oesophagitis dissecans superficialis has also been described with various medications such as alendronate, clindamycin, and methotrexate.[14–16]

Reactive gastropathy

Reactive gastropathy was initially believed to be related to gastric mucosal injury caused by reflux of duodenal contents into the stomach and was also known as alkaline gastritis or bile reflux gastritis.[17,18] This distinctive histological picture is now considered to be a non-specific response to a variety of gastric irritants, of which bile is one. NSAIDs and alcohol are common causes. The features of reactive gastropathy (or chemical gastritis) include hyperplastic foveolar epithelium with a 'corkscrew' appearance, surface epithelial degeneration with cuboidalization of the foveolar glandular cells, lamina propria oedema, vascular congestion, a paucity of inflammatory cells, and smooth muscle splaying in the lamina propria with a vertical orientation of the muscle fibres (Figure 2).[17,19] Small foci of atrophy with pseudopyloric or intestinal metaplasia are common, and may reflect ulcer repair.[19]

Ulceration or perforation

Numerous drugs can cause erosions or ulcers in the stomach. Potassium chloride was one of the earliest reported agents implicated in causing ulcers and strictures throughout the GI

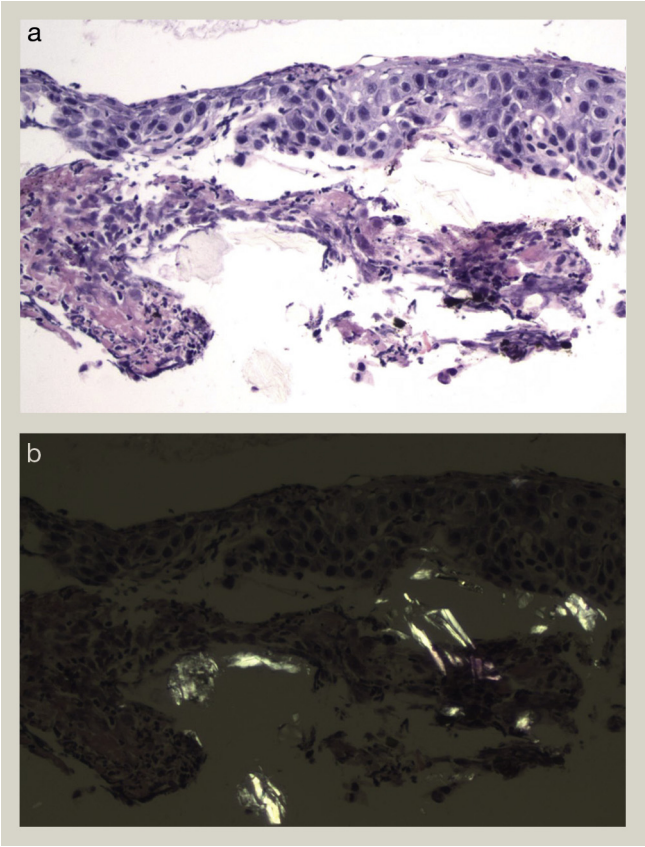

Figure 1 (**a**). Pill oesophagitis demonstrating reactive squamous epithelium accompanied by ulcer exudate. (**b**). Polarizable material is seen within the ulcer exudate, consistent with pill fragments.

tract, including the stomach.[20,21] Certainly the most common drugs to result in gastric ulcers are NSAIDs.[22] These drugs not only damage the mucosa, but they also retard ulcer healing.[23] Gastrointestinal perforation is strongly associated with NSAID use.[24] Other drugs associated with gastrointestinal ulcers include alendronate, doxycycline, chemotherapy, corticosteroids, iron, Kayexalate and colchicine.[1,9,21,25–27]

Specific agents and their injury patterns

Non-steroidal anti-inflammatory drugs

NSAIDs are the most widely prescribed drugs in the world, and are well known to cause a wide spectrum of upper GI tract injury, including oesophagitis and oesophageal strictures; gastric, oesophageal and duodenal ulcers; gastrointestinal bleeding; and perforation.[28–32] The relative risk of developing serious GI complications in patients exposed to NSAIDs is five to six times higher than in the non-exposed population.[33] However, the risk of serious complications seems to be declining somewhat, perhaps due to the introduction of safer NSAIDs, the use of proton pump inhibitors and the reduction in dose of NSAIDs.[34]

Up to 45% of patients who consume NSAIDs will develop chemical gastritis or reactive gastropathy.[35,36] NSAID erosions are usually in the gastric body and heal within days, whether or not the NSAID is continued, whereas NSAID ulcers are often large and multiple, more commonly in the gastric antrum than in the duodenum, and painless.[32,37]

Although the prevalence of *Helicobacter pylori* infection is similar in patients who ingest NSAIDs compared to those who do not, it is typically absent in patients who have well-developed patterns of reactive gastritis.[36,38] Possibly, the changes caused by NSAIDs induce a local microenvironment hostile to the organism, or the inflammation caused by the infection masks NSAID-related gastritis. Whether *H. pylori* infection increases the risk of developing NSAID-related complications is controversial.[39,40] Some evidence suggests that the risk of NSAID injury is paradoxically greater in *H. pylori*-negative patients, perhaps because *H. pylori* infection increases the prostaglandin level in gastric mucosa.[23] Other studies suggest that *H. pylori* significantly increases the risk of ulcer in NSAID users and that eradication of *H. pylori* before starting NSAID therapy markedly reduces the incidence of ulcers.[37]

The mechanism of NSAID-induced gastric injury is multifactorial. First, as NSAIDs are weak acids, in the strong acid environment of the stomach, they are protonated, rendering them electrically neutral, and able to cross cell membranes. Once inside the cell, they are ionized and trapped within the cell ('ion trapping') where they cause damage.[41,42] Second, NSAIDs also uncouple oxidative phosphorylation within cells and deplete ATP.[41,42] A third mechanism by which NSAIDs cause injury is by inhibition of prostaglandin synthesis via inhibition of cyclo-oxygenase.[41,43] Although some prostaglandins are responsible for inflammation, others are involved in mucosal protection and mucosal blood flow, and it is the decrease in the latter prostaglandins that results in mucosal injury.[41,43] The recognition that cyclo-oxygenase exists as two isoforms, one of which (COX-2) is responsible for the synthesis of inflammatory cytokines and the other (COX-1) for mucosal protection, has led to the introduction of selective COX-2 inhibitors. Two major studies, the Celecoxib Long-Term Arthritis Safety Study (CLASS)[44] and the Vioxx Gastrointestinal Outcomes Research Trial (VIGOR)[45] demonstrated that these agents are associated with a significantly lower incidence of upper GI events (perforations, ulcers, bleeding) than non-selective NSAIDs, although their cardiovascular risks limit their utility in some patients.

Proton pump inhibitors

Proton pump inhibitors (PPIs) are widely used in the treatment of reflux oesophagitis and peptic ulcer disease. These agents block gastric acid production by binding the H+, K+-ATPase on the canalicular surface of the parietal cell membrane and are quite effective in reducing gastric acidity. However, there have been concerns, exacerbated by reports in the media, about their long-term safety due to their possible association with cardiovascular events, dementia, fractures, C. difficile colitis, and hypomagnesaemia.

PPIs may aggravate gastritis and atrophy in the gastric corpus, almost exclusively among *H. pylori* infected individuals.[46–51] Typically, *H. pylori* colonizes the gastric antrum more effectively than the corpus, possibly related to acid production by the corpus.[48] Suppression of gastric acidity may allow the organisms to redistribute to the corpus, enable better contact between the organisms and the corpus foveolar epithelium, or reduce buffering of the ammonia produced by the organism.[48] The result may be increased corpus gastritis and atrophy in some patients.[46–54]