Pill esophagitis

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INTRODUCTION

Medications can induce esophageal abnormalities via both causing direct esophageal mucosal injury and by systemic effects. Potential systemic effects include gastroesophageal reflux and medication-induced infectious complications.

This topic will review medication-induced esophagitis from direct esophageal mucosal injury, also known as pill esophagitis. The pathophysiology of reflux esophagitis and the clinical manifestations, diagnosis, and management of other causes of esophagitis are discussed in detail separately. (See "Pathophysiology of reflux esophagitis" and "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)" and "Approach to the evaluation of dysphagia in adults".)

EPIDEMIOLOGY

Most medication-induced esophagitis is unreported and/or undetected, and only severe cases seek medical attention, making it difficult to accurately determine the incidence or prevalence [1]. Overall, the mean age at diagnosis is 41.5 years with a slightly higher prevalence in females, which is likely to be reflective of the population using culprit medications rather than a sex- or age-related increase in susceptibility [1,2]. Pill esophagitis usually occurs in the mid esophagus [3]. This corresponds to areas of extrinsic compression by the mainstem bronchus, aorta, or

cardiac atrium where pills or capsules are likely to lodge when swallowed with inadequate volumes of liquid and/or in a supine posture [4,5].

ETIOLOGY

Culprit medications — More than 100 different medications have been reported to cause pill esophagitis (table 1) [1,6-8]. Frequently prescribed medications associated with pill esophagitis include the following:

- **Antibiotics** – Antibiotics account for approximately 50 percent of reported cases of pill esophagitis and the most frequent etiology of pill esophagitis in younger adults. Tetracyclines are the most common antibiotic class implicated, but penicillins, trimethoprim-sulfamethoxazole, clindamycin, lincomycin, spiramycin, erythromycin, rifampicin, sulfamethoxypyridazine, tinidazole, zalcitabine, zidovudine, and azithromycin have all been associated with medication-induced esophagitis [9]. Esophagitis is due to the direct irritant effect of the medications on the mucosa. (See 'Pathogenesis' below.)

- **Nonsteroidal anti-inflammatory drugs (NSAIDs)** – Despite the high prevalence of aspirin and NSAID use, they account for less than 10 percent of all reports of pill esophagitis. However, they account for nearly 50 percent of all hemorrhagic complications attributable to medications. NSAID use, although less likely to cause esophagitis, is much more likely to cause hemorrhage, severe esophagitis, and/or esophageal stricture [1].

- **Bisphosphonates** – All drugs in the bisphosphonate class potentially have adverse gastrointestinal events, including pill esophagitis. In part, this is because bisphosphonates are poorly absorbed from the gastrointestinal tract, with bioavailability of less than 1 percent after oral administration [10]. Hence the recommendation to be taken after an overnight fast and to avoid eating for 30 to 60 minutes after administration. The limited bioavailability after oral administration has also prompted the development of parenterally administered bisphosphates and research into novel delivery systems. (See "Risks of bisphosphonate therapy in patients with osteoporosis".)

  In the first three years after the marketing of alendronate in 1995, 24 esophageal injuries were reported, including many cases of severe esophagitis and stricturing. This made it the most common offender for causing pill esophagitis at the time and led to strict recommendations to take the pills with at least 6 ounces of water and to remain in an upright posture for at least 30 minutes afterward. Subsequently, the frequency of reported cases diminished, and by 1999, postmarketing surveillance identified only 75 cases, which

amounted to an incidence of only 0.013 percent among the more than one-half million patients for whom prescriptions for alendronate had been written [1]. Thus, although the drug clearly has the potential to be extremely caustic to the esophageal epithelium, the incidence of pill esophagitis is minimized by cautious pill-taking habits. (See 'Precautions to decrease risk' below.)

Risk factors

- **Medication size and administration** – Patient position, the size of the medication, and the amount of fluid ingested are important determinants of the risk of medication-induced esophagitis. This was illustrated in a study that evaluated esophageal transit of six commonly used barium-impregnated medications in 121 healthy volunteers studied with fluoroscopy while controlling for the volume of liquid swallowed and body position. When the subject was in the supine position when pills were swallowed, esophageal transit delay was much more likely to occur, as was the case when swallowing only 25 mL of water compared with 100 mL. Of 726 test swallows, pill transit was delayed in 157 (22 percent). The location at which the tablets lodged were the pyriform (1 percent), aortic arch (10 percent), carina (12 percent), heart (18 percent), and cardia (58 percent). Of note, 67 percent of instances with delayed transit were asymptomatic [4]. For subjects swallowing pills while in the upright position, the quantity of water was not a significant factor with the smaller pills, but delayed esophageal transit occurred with larger tablets and small quantities of water. Similar findings were reported in a study using 6 mm barium-impregnated bread balls during concurrent fluoroscopy and esophageal manometry [5].

  Medication-induced esophagitis is frequently associated with ingestion of medication immediately prior to sleep. This is attributable to multiple risk factors: supine posture, often small volumes of water taken with the pill(s), and the minimal salivation and swallowing that occur during sleep [11].

- **Functional and anatomic risk factors** – An esophageal motility disorder or altered anatomy (eg, esophageal stricture) may also be a risk factor for pill esophagitis. This is supported by the observation of a higher incidence of pill esophagitis in patients with left atrial enlargement and following thoracic surgery. However, it is unclear if this observation is due to altered anatomy alone or if these patients are older and are therefore more likely to be taking medications associated with esophagitis. (See 'Etiology' above.)

PATHOGENESIS

It is hypothesized that pill esophagitis is usually caused by prolonged contact of the medication with the esophageal mucosa owing to delayed esophageal transit [12,13]. This hypothesis is supported by the typical esophageal lesion showing a small, punched-out ulcer in a limited area that was conceivably in contact with a high concentration of medication released from a dissolving pill (image 1). In addition, the site of injury is frequently in areas in which the esophageal lumen is compromised by the aortic arch, the carina, the esophagogastric junction, or an enlarged left atrium. The proposed mechanism of direct injury is an intense inflammatory response triggered by the high local concentration of the medication or its osmolality (eg, potassium chloride).

CLINICAL MANIFESTATIONS

Retrosternal pain and odynophagia are the most common presenting symptoms of pill esophagitis. The onset of symptoms after taking pills has not been absolutely defined but is usually within three days of the culprit ingestion, sometimes as quickly as within a few hours [14]. In some cases, the pain may be so severe that swallowing saliva is difficult. Rarely, patients may have hematemesis, abdominal pain, and weight loss [15,16].

DIAGNOSTIC EVALUATION

Diagnosis — Pill esophagitis should be suspected in patients with retrosternal pain or heartburn, odynophagia, or dysphagia and a history of ingestion of medications known to cause esophageal injury. Patients often also report swallowing a pill without water, commonly at bedtime. In such cases, a clinical diagnosis may be made by history alone.

An upper endoscopy should be performed in patients with severe symptoms, atypical symptoms (hematemesis, abdominal pain, and weight loss), or symptoms that persist for **one week** after discontinuation of the culprit medication. In such cases, an upper endoscopy with biopsy serves to establish the diagnosis and to rule out other etiologies. (See 'Differential diagnosis' below.)

Upper endoscopy and biopsy in selected patients — The most common sites of pill-induced esophageal injury are the proximal esophagus near the compression from the aortic arch or carina and the distal esophagus in patients with left atrial enlargement. The typical endoscopic appearance of pill-induced esophageal injury is of discrete ulceration or kissing ulcers in the mid esophagus with relatively normal surrounding mucosa (image 1) [3]. Ulcers may range in size from 1 or 2 mm to several centimeters. Although the typical ulcer involves only the mucosa,

deeper degrees of penetration can occur, and localized perforation has been reported [17,18]. Remnants of the offending pill may occasionally be identified at the site of injury. Esophageal strictures may be noted on upper endoscopy, especially in patients with nonsteroidal anti-inflammatory drug (NSAID)-, quinidine-, and potassium chloride-induced esophagitis [19]. The sensitivity of upper endoscopy for pill esophagitis approaches 100 percent, but the endoscopic findings of pill esophagitis are not specific [1].

Histologic features of pill esophagitis are also nonspecific and include eosinophilic microabscesses, intraepithelial pustules, and a diffuse pattern of dilated intercellular spaces, which, along with its predilection for involving the mid as opposed to the distal esophagus, can differentiate it from reflux esophagitis (image 2) [20]. The inflammatory infiltrate seen in pill esophagitis is usually dominated by T cells, followed by eosinophils.

Differential diagnosis — The differential diagnosis of pill esophagitis includes other causes of esophagitis, retrosternal pain, and/or dysphagia and can be distinguished from them by upper endoscopy and biopsy (table 2). The evaluation of patients with dysphagia is also discussed in detail, separately. (See "Approach to the evaluation of dysphagia in adults", section on 'Symptom-based differential diagnosis'.)

MANAGEMENT

General measures

Discontinuation of offending medication — The initial step in management is to discontinue the offending medication. Most cases of medication-induced esophageal injury heal without intervention within a few days of discontinuing the culprit medication [14]. In the vast majority of cases and in those uncomplicated by stricture, symptoms usually resolve within 7 to 10 days, but in some patients symptoms persist for many weeks after the culprit medication has been discontinued. Patients with persistent symptoms one week after discontinuation of the culprit medication require additional evaluation with upper endoscopy if not already performed to establish the diagnosis. (See 'Upper endoscopy and biopsy in selected patients' above.)

Acid suppression — We use standard-dose proton pump inhibitors until symptoms have resolved as gastroesophageal reflux disease may be exacerbating or perpetuating the pill-induced injury. Although the use of other acid suppressive medication (eg, antacids, histamine receptor antagonists) and surface agents (eg, sucralfate, and local anesthetic agents) are all commonly advised, it is unclear if they are effective in treating pill esophagitis. (See "Medical

management of gastroesophageal reflux disease in adults", section on 'Severe or frequent symptoms or erosive esophagitis'.)

Supportive care — Patients with severe odynophagia who are unable to eat or drink may require short-term parenteral hydration or alimentation. (See 'Clinical manifestations' above.)

Prevention of recurrence

Medication resumption — In patients without an apparent predisposition to esophageal injury (eg, a large left atrium), the culprit medication may be resumed after symptoms resolve. Pills implicated in causing frequent or severe pill esophagitis should be avoided in bed-ridden patients or those with esophageal motility disorders. In patients predisposed to recurrent injury who need to continue the culprit medication, a liquid formulation should be prescribed if possible. (See 'Etiology' above and 'Precautions to decrease risk' below.)

Addressing predisposing factors — To minimize the risk of recurrence, the underlying predisposing factors should be addressed. This may require additional evaluation (eg, air contrast barium study in patients in whom extrinsic esophageal compression is suspected or esophageal manometry evaluation for an underlying motility disorder) or treatment (eg, endoscopic dilation in patients with an esophageal stricture or optimizing management of gastroesophageal reflux). (See "Approach to the evaluation of dysphagia in adults", section on 'Approach to diagnostic testing' and "Endoscopic interventions for nonmalignant esophageal strictures in adults", section on 'Endoscopic dilation'.)

Precautions to decrease risk — We suggest the following measures to minimize the risk of medication-induced esophagitis:

- Patients should take all pills in an upright posture.
- Patients should drink at least 4 ounces of fluid with any medication and 8 ounces with medications that are strongly associated with pill esophagitis (eg, tetracycline, alendronate, potassium chloride, or quinidine).
- Patients should remain upright for at least 10 minutes after taking any pills and for at least 30 minutes with pills that are strongly associated with pill esophagitis.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading

level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Esophagitis (The Basics)" and "Patient education: Upper endoscopy (The Basics)")
- Beyond the Basics topic (see "Patient education: Upper endoscopy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Etiology** – Medications can cause direct esophageal mucosal injury, commonly referred to as pill esophagitis. More than 100 different medications and supplements have been reported to cause pill esophagitis (table 1). (See 'Etiology' above.)
- **Pathogenesis** – Pill esophagitis is likely caused by prolonged contact of the medication with the esophageal mucosa owing to delayed esophageal transit. The size of the medication, position of the patient, and amount of fluid ingested with the medication all affect the rate of esophageal transit. (See 'Risk factors' above and 'Pathogenesis' above.)
- **Symptoms** – Patients with pill esophagitis often present with the sudden onset of odynophagia, dysphagia, or retrosternal pain. The onset of the symptoms usually occurs within a few hours to three days after ingestion of the drug. (See 'Clinical manifestations' above.)
- **Diagnosis** – Pill esophagitis should be suspected in patients with retrosternal pain or odynophagia and a history of ingestion of medications known to cause pill esophagitis. In these cases, a clinical diagnosis may be made by history alone. We perform an upper endoscopy with biopsy in patients with severe symptoms, atypical symptoms (hematemesis, abdominal pain, and weight loss), or persistent symptoms one week after discontinuation of culprit medications. In such cases, an upper endoscopy with biopsy

serves to establish the diagnosis and to rule out other etiologies (image 1 and image 2). (See 'Diagnostic evaluation' above and 'Differential diagnosis' above.)

- **Management**

  - **General measures** – The initial step in management is to discontinue the offending medication. Most cases of medication-induced esophageal injury heal without intervention within a few days of discontinuing the culprit medication. We use acid suppression with a standard-dose proton pump inhibitor until symptoms have resolved as gastroesophageal reflux may be exacerbating or perpetuating the pill-induced injury.

  - **Prevention of recurrence** – In patients without an apparent predisposition to esophageal injury, the culprit medication may be resumed after symptoms resolve, with careful instructions on how to take the medication. In patients predisposed to recurrent injury who need to continue the culprit medication, a liquid formulation should be prescribed if possible. (See 'Management' above and 'Precautions to decrease risk' above.)

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Topic 2255 Version 19.0

GRAPHICS

Selected medications implicated in pill-induced esophageal injury[1,2]

Antiarrhythmics, antihypertensives, and vasodilators

Antiarrhythmics:

- Mexiletine
- Quinidine

Antihypertensives:

- Captopril
- Nifedipine

Vasodilators:

- Naftidrofuryl (nafronyl)*

Antimicrobials

Lincosamides:

- Clindamycin
- Lincomycin

Macrolides:

- Azithromycin[1]
- Clarithromycin
- Erythromycin
- Spiramycin*

Penicillins:

- Amoxicillin
- Ampicillin
- Penicillin
- Pivmecillinam*

Sulfonamides:

- Sulfamethoxypyridazine*
- Trimethoprim-sulfamethoxazole

Tetracyclines:

- Doxycycline
- Minocycline
- Oxytetracycline*
- Tetracycline

Other:

- Cephalexin
- Emepronium*
- Metronidazole

- Rifampin (rifampicin)
- Tinidazole
- Zidovudine

Bisphosphonates

- Alendronate
- Etidronate*
- Ibandronate
- Pamidronate

NSAIDs

- Aspirin
- Diclofenac
- Ibuprofen
- Indomethacin
- Naproxen
- Piroxicam

Vitamins and supplements

- Ascorbic acid
- Calcium dobesilate*
- Iron preparations (eg, ferrous sulfate)
- L-arginine
- Multivitamins
- Potassium chloride

Other

- Acetaminophen
- Caffeine
- Clomethiazole (chlormethiazole)
- Estramustine
- Glucocorticoids
- Glyburide (glibenclamide)
- Oral contraceptives
- Phenytoin
- Pinaverium*
- Retinoic acid derivatives (eg, isotretinoin)
- Theophylline/aminophylline
- Warfarin

This table includes a selection of commonly used medications implicated in direct esophageal mucosal injury. This is not a complete list; other medications, including others within the drug classes above, combination drugs containing these ingredients, and others may also cause esophageal injury.

NSAIDs: nonsteroidal anti-inflammatory drugs.

* Not available in the United States.

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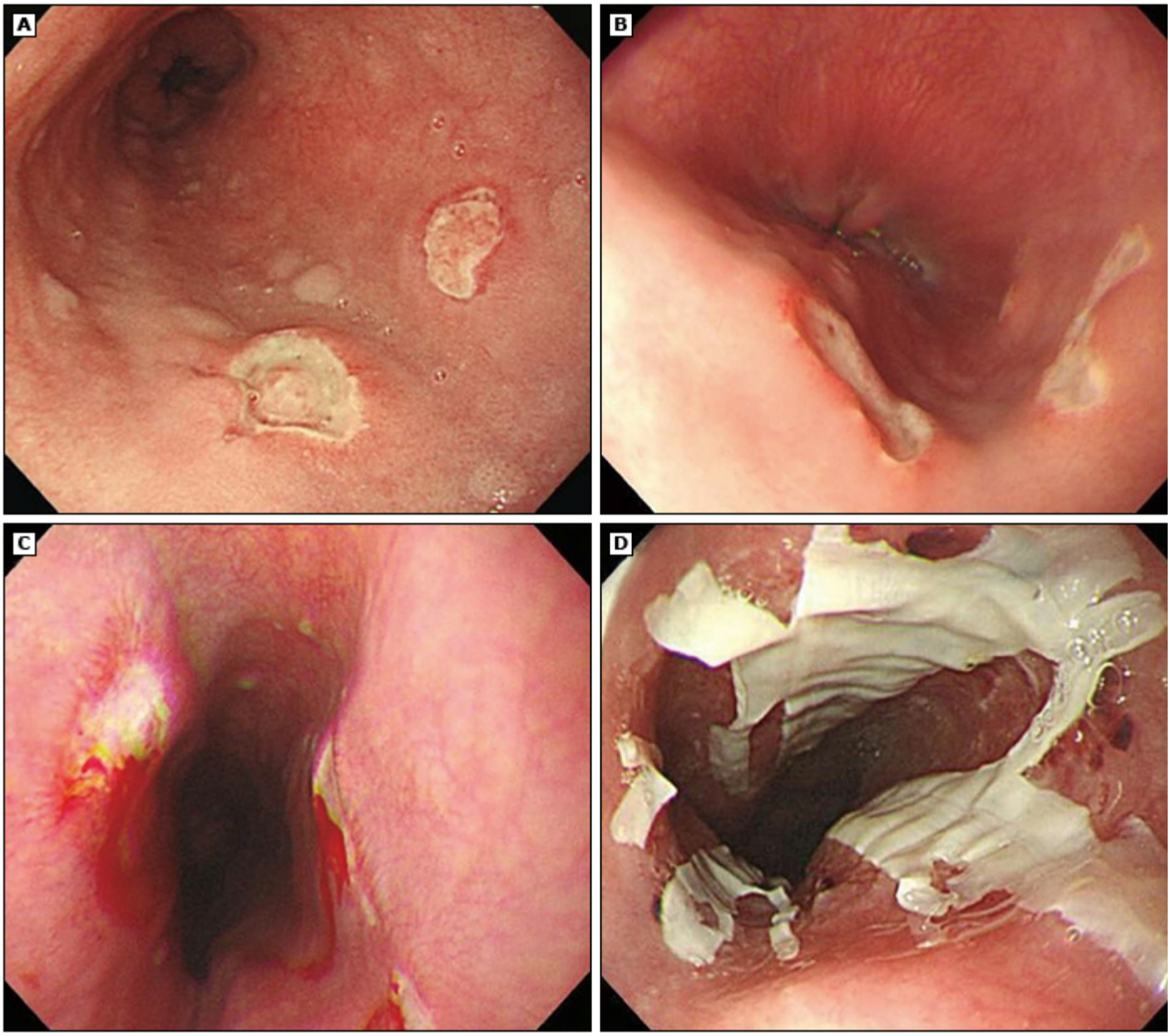
Graphic 135178 Version 2.0

Endoscopic findings of pill esophagitis



(A, B) Examples of typical kissing ulcers in the middle third of esophagus.

(C) Kissing ulcers with bleeding.

(D) Ulcerated area with coating from drug material.

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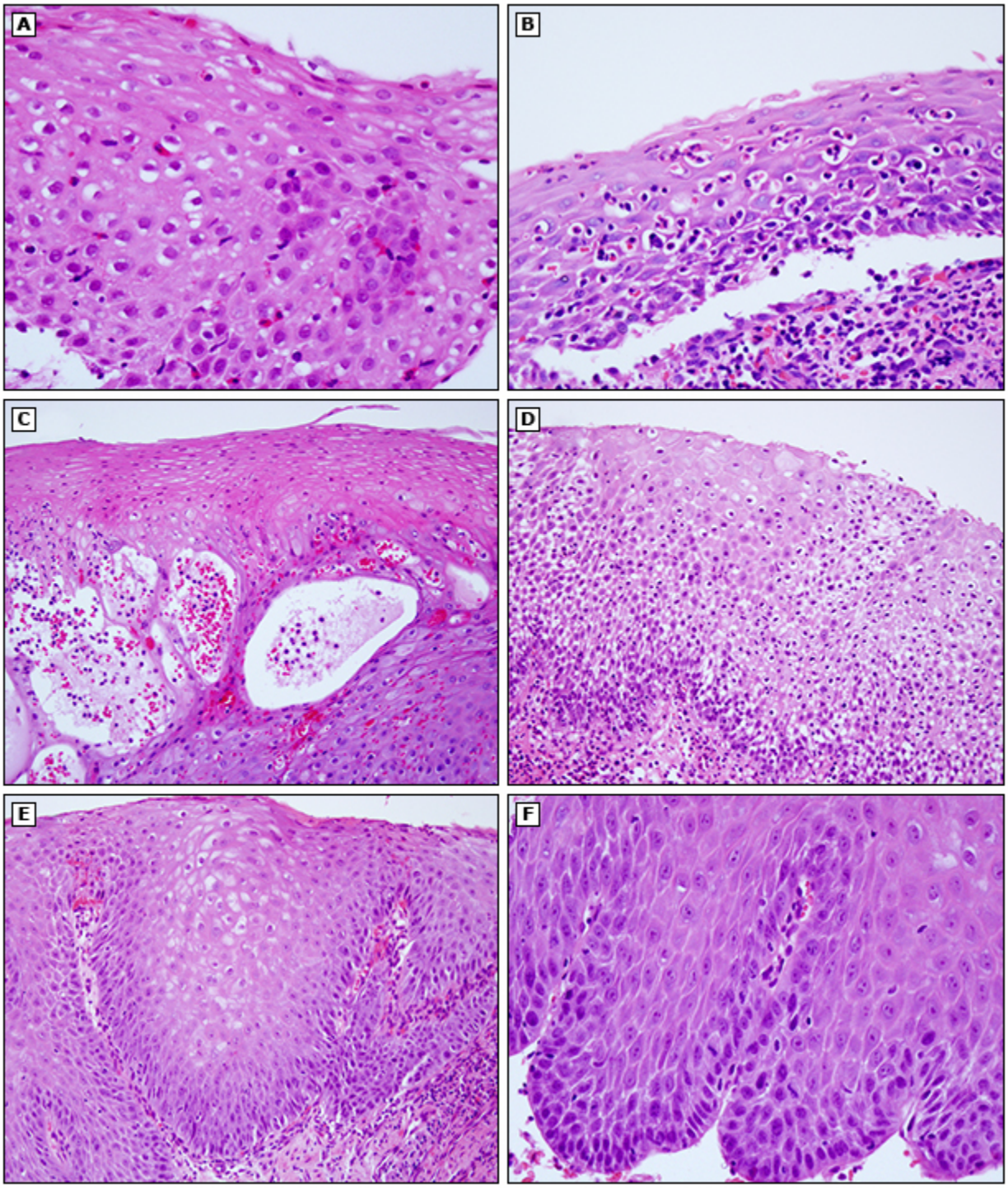
Graphic 134866 Version 2.0

Histologic features of pill-induced esophagitis and reflux esophagitis



Histologic features of esophageal mucosal epithelium in pill-induced esophagitis (A-E) and reflux esophagitis (F).

(A) Intraepithelial eosinophil infiltration with microabscess.

(B) Mixed infiltration of eosinophils and neutrophils.

(C) Intraepithelial pustules.

(D) Dilated intercellular spaces (upper), and extensive vacuolization of epithelial cells (lower).

(E) Subepithelial papillae extending three-fourths of the epithelial thickness.

(F) Reactive atypia with vesicular nucleus and prominent nucleolus (H&E stain).

Graphic 134868 Version 1.0

Causes of esophageal dysphagia

Mechanical lesions
Intrinsic
Benign tumors
Caustic esophagitis/stricture
Diverticula
Malignancy
Peptic stricture
Eosinophilic esophagitis
Infectious esophagitis
Pill esophagitis
Postsurgery (laryngeal, esophageal, gastric)
Radiation esophagitis/stricture
Rings and webs
Lymphocytic esophagitis
Extrinsic
Aberrant subclavian artery
Cervical osteophytes
Enlarged aorta
Enlarged left atrium
Mediastinal mass (lymphadenopathy, lung cancer, etc)
Postsurgery (laryngeal, spinal)
Motility disorders
Achalasia
Chagas disease
Primary motility disorders
Secondary motility disorders
Functional
Functional dysphagia

Graphic 80528 Version 5.0

Contributor Disclosures

Peter J Kahrilas, MD Patent Holder: Medtronic [FLIP panometry methods and technology]. Consultant/Advisory Boards: Ironwood [Irritable bowel]; Johnson & Johnson [Anti-reflux surgery]; Reckitt [Reflux disease]. Speaker's Bureau: Phathom [Reflux disease, H. pylori]. All of the relevant financial relationships listed have been mitigated. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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