Drug-induced Esophagitis

Pande Made Juniarta[*], *I Dewa Nyoman Wibawa*[**]
*Department of Internal Medicine, Faculty of Medicine
Universitas Udayana/Sanglah General Hospital, Bali
**Division of Gastroentero-hepatology, Department of Internal Medicine
Faculty of Medicine, Universitas Udayana/Sanglah General Hospital, Bali

Corresponding author :
I Dewa Nyoman Wibawa. Division of Gastroentero-hepatology, Department of Internal Medicine, Sanglah General Hospital. Jl. Diponegoro Dauh Puri Klod Denpasar Indonesia. Phone/facsimile: +62-361-244177. E-mail: agusbobwibawa@yahoo.com

ABSTRACT

Esophageal injury could be caused by a various etiology, such as drug administration. Drug-induced esophagitis is a spectrum of esophageal lesions due to drugs that can cause complications of ulceration, perforation and stricture of the esophagus. More than one hundred drugs have been identified to cause damage to the esophageal wall, such as antibiotics, nonsteroidal anti inflammatory drugs (NSAID), alendronate, potassium chloride, anti-hypertension, quinidine, etc. Symptoms of drug induced esophagitis might appear as retrosternal pain, heartburn, odynophagia, dysphagia, weight loss, gastrointestinal bleeding, which also found in other cases of gastrointestinal lesions so they are often misdiagnosed in daily clinical practice. Endoscopic procedure is the first choice in diagnosis of drug-induced esophagitis. The lesion may appear as erosion, bleeding, ulcers, strictures, kissing ulcers, and residual drugs fragment on endoscopy. Management of drug-induced esophagitis are by stopping suspected drugs and educating about the proper drug administration. In severe cases, adequate fluid hydration and parenteral nutrition can be given. Sucralfat forms a protective layer in the area of the lesion, thus accelerates wound healing process. Acid-lowering agents can be considered in cases of reflux esophagitis. Therapeutic endoscopic may indicated in strictures cases, active bleeding due to esophageal ulcers, and retrieval remaining drug fragments that are lodged in the esophagus. While surgery should be reserved for patients with severe complications such as erosion of the mediastinal organs, heart and large blood vessels

Keywords: *drug-induced esophagitis, diagnosis, treatment*

ABSTRAK

Kerusakan lapisan esofagus dapat disebabkan oleh berbagai sebab, salah satunya adalah akibat penggunaan obat-obatan. Drug-induced esophagitis merupakan spektrum lesi esofagus akibat obat-obatan yang dapat menimbulkan komplikasi ulserasi, perforasi dan striktur esofagus. Sampai saat ini lebih dari seratus jenis obat telah teridentifikasi dapat menimbulkan kerusakan pada dinding esofagus, seperti golongan antibiotik, nonsteroidal anti inflammatory drugs (NSAID), alendronate, potassium klorida, anti hipertensi, quinidine, dan sebagainya. Keluhan drug-induced esophagitis seperti nyeri retrosternal, rasa terbakar (heartburn), odinofagia, disfagia, penurunan berat badan, perdarahan saluran cerna, sering didapatkan pada kasus lesi gastrointestinal lainnya sehingga sering salah didiagnosis pada praktek klinis sehari-hari. Penegakan diagnosis melalui pemeriksaan endoskopi menjadi pilihan utama pada kasus drug-induced esophagitis. Lesi esofagus dapat bervariasi meliputi erosi, perdarahan, ulkus, striktur, kissing ulcers, dan sisa obat yang tampak pada endoskopi. Prinsip dasar tatalaksana drug-induced esophagitis dengan menghentikan obat-obatan yang dicurigai

serta edukasi tentang cara pemberian obat yang benar. Pada kasus yang berat dapat diberikan hidrasi cairan yang adekuat dan nutrisi parenteral. Pemberian sucralfat bertujuan untuk membentuk lapisan proteksi pada area lesi sehingga mempercepat proses penyembuhan luka. Acid-lowering agents dapat dipertimbangkan pada kasus-kasus dengan penyakit dasar refluks esofagitis. Tindakan endoskopi terapeutik diindikasikan pada kasus striktur, perdarahan aktif akibat ulkus esofagus, dan pengambilan sisa fragmen obat yang tersangkut dalam esofagus. Sedangkan tindakan pembedahan dilakukan pada kasus dengan komplikasi berat seperti erosi pada organ mediastinum, jantung dan pembuluh darah besar.

Kata kunci: *drug-induced esophagitis, diagnosis, tatalaksana*

INTRODUCTION

Drugs are chemical compounds with certain substances used as a therapeutic and diagnostic process of an illness. Use of drugs may cause therapeutic or adverse effects in both normal and sensitive people to substances in drug content. Inflammation or damage to esophageal layer could be caused by variety of reasons, such as drug administration. Drug-induced esophagitis is one of esophageal lesions spectrum due to drugs that caused complications of ulceration, perforation and stricture of the esophagus.

Drug-induced esophagitis is a preventable cause of morbidity but it is likely underdiagnosed in clinical practise for several reasons. The incidence of drug-induced esophagitis estimated about 3.9 per 100,000 population per year, and more common in elderly.[1] Nowadays, more than one hundred drugs have been identified cause esophageal injury, such as antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), alendronate, potassium chloride, anti-hypertension, quinidine, etc.[2]

Clinical symptoms of drug-induced esophagitis are vary and not specific. Retrosternal pain, heartburn, odynophagia, dysphagia, weight loss, hematemesis, are often found in cases of other gastrointestinal lesions which they are often misdiagnosed in daily clinical practice.[3] This could be worsen the symptoms due to delay of drugs discontinuation. Work up diagnosis by endoscopy is the main choice in drug-induced esophagitis cases. The spectrum of esophageal lesions may vary in endoscopic finding, such as erosion, bleeding, ulcers, strictures, kissing ulcers, and residual drugs fragment on endoscopy. In late stages, lesions of the esophageal wall can develop into perforations and strictures which can cause disruption of the swallowing process.[4]

DEFINITION

Drug-induced esophagitis is defined as inflammation of the esophagus which is characterized by the symptoms (heartburn, retrosternal pain, odinophagia or dysphagia) in less than 2 weeks due to ingestion of drugs.[1,4]

EPIDEMIOLOGY

The incidence of drug-induced esophagitis is unknown and more often reported as a case report in literature. Study in Sweden reported the incidence of drug-induced esophagitis was 4 cases per 100,000 population per year, whereas another study by Wright reported about 3.9 cases per 100,000 population.[5,6] However, these does not reflect the actual number caused by subclinical and misdiagnosed cases. Drug-induced esophagitis is more common in women and occur in ages ranging from 18-70 years, which commonly appear in elderly.[7]

ETIOLOGY

Since it was published in 1970 by Pemberton, more than 100 drugs have been identified as the cause of drug-induced esophagitis. Antibiotics, antiviral drugs, bisphosphonates, chemotherapy, non-steroidal anti-inflammatory drugs (NSAIDs), quinidine, ferrous sulphate, ascorbic acid, potassium chloride, and teophyline have been widely reported as causes of drug-induced esophagitis.[4]

Table 1 Etiology of drug-induced esophagitis[3]

Antibiotic	Clindamycin
	Doxycycline
	Penicillin
	Rifampin
	Tetracycline
Antiviral	Nefinavir
	Zalcitabine
	Zidovudine
Biphosponate	Alendronate
	Etidronate
	Pamidronate
Chemotherapy	Bleomycin
	Cytarabine
	Dactinomycin
	Daunorubicin
	5-Fluorouracil
	Methotrexate
	Vincristine

NSAIDs	Aspirin
	Ibuprofen
	Naproxen
Miscelaneous	Ascorbic Acid
	Ferrous Sulphate
	Potassium Chloride
	Teophyline
	Nitrate
	Emepronium bromide
	Antagonist Calcium

MECHANISM AND RISK FACTORS

Drugs may cause damage of the esophageal layer through direct mechanism due to the caustic nature of the drugs or through indirect mechanisms that facilitate esophageal damage such as induction of acid reflux by calcium channel antagonist groups or induction of systemic reactions which can damage the esophageal mucosa. Direct damage to the esophageal mucosa can occur through various mechanism: production of acidic compound (ascorbic acid and ferrous sulphate), production of alkaline compound (alendronate), formation of hyperosmolar solutions after contact with the esophageal mucosa (potassium chloride) and direct toxic effect on the esophageal mucosa (tetracycline). Characteristics of the drug can also affect the toxicity of the esophageal mucosa such as: duration of esophageal contact, gelatin-coating, sustained-release, size and drugs form.[3,8]

Table 2 Risk factors of drug-induced esophagitis [10]

Patient Factors	Elderly
	Institutionalized
	Preexisting esophageal disorders
	Cardiomegaly
Drug/Formulation Factors	Gelatin capsules
	Extended or sustained-release
	Large or bulky size
	Acidic
	Fast dissolution rates
Administration Factors	Concurent alcohol use
	Insufficient liquid bolus
	Recumbent position
	Frequent dosing time/ polypharmacy

Disorders of esophageal motility (esophageal achalasia, esophageal stricture, esophageal reflux, esophageal diverticula, hiatal hernia, cardiomegaly) may increase the risk of drug-induced esophagitis due to decrease time clearance and lower esophageal sphincter pressure, also impair the food passage. However, drug-induced esophagitis may occur in normal esophageal function because physiologically there is narrowing area of the esophageal wall (an overlapping area between the striated and smooth muscle muscles, the crossing area between the aortic arch or the left bronchial main branch with the esophagus) which relatively statis in drug movement especially if not taken appropriately.[3] The size, shape, coating and non-medical content in capsules or tablets also affect esophageal transit time. Inappropriate drug consumption and supine position after taking medication increase the risk of drug-induced esophagitis.[9,10]

CLASSIFICATION

Drug-induced esophagitis is divided into two major groups. First, drug causing temporary damage to esophageal mucosa and has self-limiting characteristic. Several drugs included in this group are doxycycline, tetracycline, clindamycin, emepronium bromide, ascorbic acid, and ferrous sulphate. These drugs cause damage to the esophageal mucosa due to low pH profile when dissolved in water, thus caused localized discrete ulcers that heal spontaneously after discontinuation of the drug without esophageal stricture. The second group is drug caussing damage to the esophageal mucosa persistently and often associated with esophageal stricture. Drugs in this group include: quinidine, potassium chloride, NSAID.[8]

CLINICAL SYMPTOMS

Clinical symptoms may appear as retrosternal or substernal chest pain, odinophagia, dysphagia, nausea, vomiting. In severe cases, it may accompanied by gastrointestinal bleeding and weight loss. Acute symptoms start from several hours until 10 days after ingestion of suspected drugs. History taking needs to explore about supine position shortly after taking medication.[4,7]

DIAGNOSIS

Diagnosis of drug-induced esophagitis is based on clinical symptoms related to suspected drugs and supported by objective findings from esophagogastroduodenoscopy (EGD), barium esophagography and histopathological examination.[1,8]

ENDOSCOPY

Endoscopy evaluation is indicated in cases which is not respond to therapy or the suspected drug cannot be stopped. Endoscopy findings may ranging from superficial erythema, mucous denudation, esophageal erosion, esophageal ulcer, kissing ulcers. Esophageal strictures, esophagorespiratorial fistulas and esophageal perforations are commo in severe cases. Frequently,

pill fragments may be adherent to ulcerated areas and complete pills may be found intact in the esophagus superimposed over an ulcerated area of mucosa. Esophageal lesions is more common in the middle third part of esophagus, although distal and proximal lesions may be involved in some cases.[11,12] Endoscopy is more sensitive than radiological examination although studies comparing both examination have not been performed.[3]

ESOPHAGOGRAPHY

Double-contrast is recommended compared to single-contrast barium esophagography. In simple cases, esophagographic examination often shows normal findings. Whereas in other cases it may shows stricture, multiple ulcers, external compression, and esophageal motility abnormalities.[1,13] The esophageal lesions on esophagography often resembles the other causes of esophagitis, therefore a good history taking is needed.

HISTOPATHOLOGY

Although the histopathological examination of drug-induced esophagitis is rarely pathognomonic, it is generally nonspecific and includes mostly benign ulcer and acute inflammatory changes, however, histological evaluation should be performed for differential diagnosis, especially in cases where malignancy and infectious pathologies are suspected.[7] In one study which compare the histomorphological features between drug-induced esophagitis and reflux esophagitis found that the intraepithelial eosinophilic microabscess, intraepithelial pustule and diffuse pattern of dilated intercellular spaces were observed in drug-induced esophagitis, but in none of reflux esophagitis. Other significant findings of histomorphological features of the distal esophagus lesion are a diffuse pattern of intercellular spaces was observed in drug-induced esophagitis, but in none cases of reflux esophagitis and reactive atypia was observed in reflux esophagitis, but in none cases of distal drug-induced esophagitis.[14]

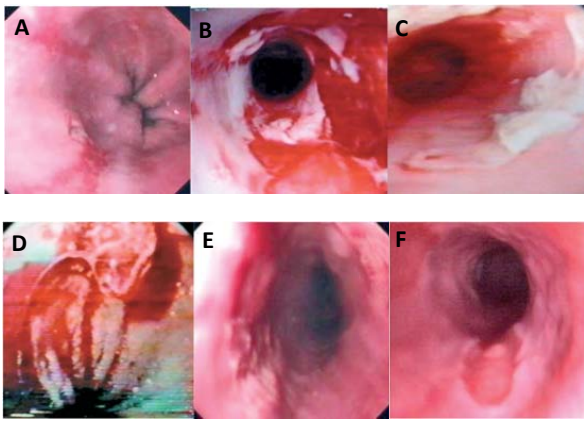

Figure 1. Endoscopic views of drug-induced esophagitis [11]

A. A small ulcer (< 5 mm) in the lower third of the esophagus, with adjacent erythematous streaks, in a 25−year-old woman who had taken a tablet of doxycycline
B. Desloughing and ulceration of the mid−esophagus, with areas of bleeding, in a 60−year−old businessman who had taken a clarithromycin
C. Extensive whitish exudates with underlying desloughed mucosa in the upper esophagus in a 52−year−old man who had taken a tetracycline
D. A vascular bleb was seen in the lower esophagus with a blood clot and active oozing from the surrounding area in a 74-year-old man who was taking aspirin and naproxen
E. Areas of mucosal ulceration in the mid−esophagus facing each other (kissing ulcers) in 66−year−old woman who was taking potassium chloride tablets
F. An area of denudation of the proximal esophageal mucosa seen in a 68−year−old who had recently started taking alendronate tablets

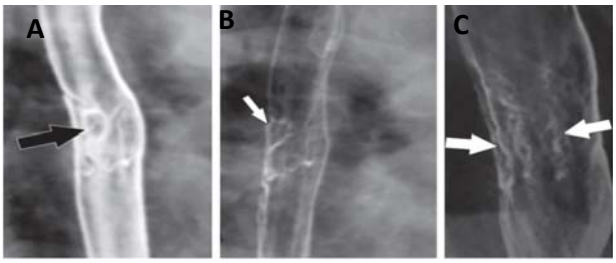

Figure 2. Barium esophagram of drug-induced esophagitis [13]

A. Double-contrast esophagram in a 26-year-old woman taking tetracycline who presented with dysphagia shows a radiolucent round filling defect with a thin rim of barium (arrow). The finding represents a superficial ulcer with surrounding edema
B. Double-contrast esophagram (profile view) in a 59-year-old man taking clindamycin who presented with dysphagia shows an elongated, flat, plaquelike filling defect (arrow) consistent with an ulcer
C. Barium esophagram in a 72-year-old woman taking alendronate who presented with dysphagia shows a cluster of linear erosions (arrows) in the mid esophagus

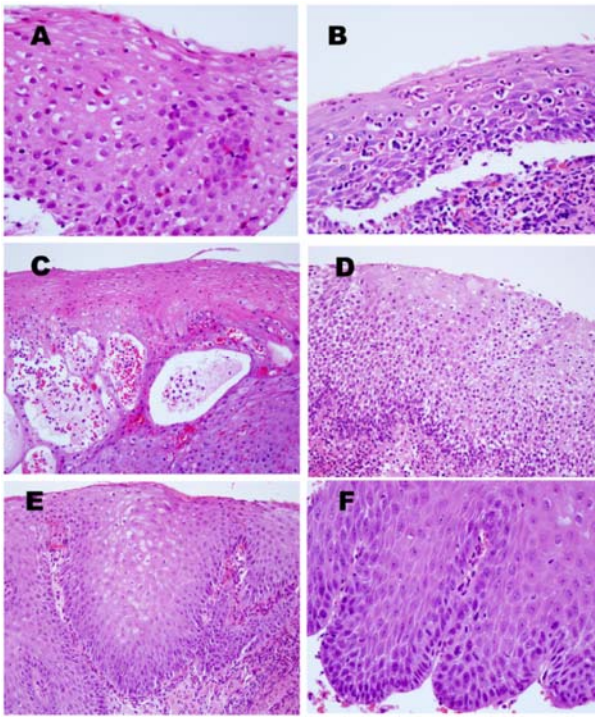

Figure 3. Histomorphological features of esophageal mucosal epithelium in drug-induced esophagitis [14]

A. Abundant intraepithelial eosinophil infiltration with eosinophilic microabscess with > 4 eosinophils found in rows
B. Mixed infiltration of eosinophils and neutrophils is observed within the squamous epithelium
C. Note intraepithelial pustules, i.e., bullae with scattered neutrophils
D. Esophageal squamous epithelium shows dilated intercellular spaces (upper part), and extensive vacuolization of squamous epithelial cells (lower part)
E. The subepithelial papillae reach upward to approximately three fourths the epithelial thickness.
F. Reactive atypia (vesicular nucleus and prominent nucleolus) of squamous epithelial cells is present.

DIFFERENTIAL DIAGNOSIS

Some diseases may show similar endoscopic findings resembling drug-induced esophagitis

Herpes Esophagitis

Herpes esophagitis is most commonly caused by type-1 herpes simplex virus and more often in immunocompromised patients although it can occur as an acute, self-limited disease in otherwise healthy patients. These patients usually present with a characteristic flu-like prodrome consisting of fever, headaches, myalgias and upper respiratory infection prior to the sudden onset of severe odynophagia on double-contrast barium esophagography, the lesions of herpes esophagitis are often difficult to distinguish from drug-induced esophagitis. However, the endoscopic features of herpes esophagitis may show ulceration with a broad pattern of distribution compared to drug-induced esophagitis. The clinical history of patients with herpes esophagitis is often associated with immunocompromised conditions due to viral infections, malignancies and previous radio-chemotherapy history.[3]

Eosinophilic Esophagitis

Eosinophilic esophagitis are often difficult to distinguish from drug-induced esophagitis by endoscopy alone. Eosinophilic esophagitis lesions may involved proximal to distal esophagus. Esophageal abnormalties identifiable by endoscopy include esophageal ring or trachealization, whitish exudates, longitudinal furrows, edema, diffuse esophageal narrowing and confirmed by eosinophil infiltration exceeding 15 per high-power field on histopathological examination. There are history of atopy or food allergy from the history taking.[3,16]

Candida Esophagitis

Candidal organisms are the most common esophageal infection in the immunocompetent host and candida albicans accounts for the vast majority. The conditions that most predispose to candidal infection in the esophagus are those associated with severe stasis such as achalasia or scleroderma, inhaled glucocorticoid use in cases of asthma or oral fluticasone in eosinophilic esophagitis. Esophageal lesions are characterized by white pseudomembranous or plaque-like appearance adherent the esophageal mucosa. Biopsy or cytology may show the signs of inflammation, hyphae, and masses of budding yeast.[3]

Crohn's Disease

Rarely, Crohn's disease can be manifested by small aphthous ulcers in the esophagus, but these patients almost always have evidence of advanced Crohn's disease in the small bowel or colon.[2]

Reflux Esophagitis

Reflux esophagitis is a more common cause of shallow ulcers and erosions in the esophagus. However, the ulcers of reflux oesophagitis are almost always located in the distal esophagus, and supported by clinical symptoms due to regurgitation of gastric contents in the esophagus.[2,3]

Giant Esophageal Ulcer

Giant esophageal ulcers can also be caused by nasogastric intubation, endoscopic sclerotherapy, Crohn's disease, ulcerated esophageal carcinomas and infection with HIV or CMV. The correct diagnosis is

usually suggested by the clinical history. The ulcers typically appear as giant flat lesions in the esophagus.[17]

MANAGEMENT

NON-PHARMACOLOGY

The cornerstone of management of drug-induced esophagitis is by discontinuing the suspected drugs. Because most cases of drug-induced esophagitis are selflimited, mild or uncomplicated disease can be managed by simply discontinuing the medication and observing the patient. Symptomatic and endoscopic improvement is usually complete within 3 days to 6 weeks.[18] Medications should never be given at bedtime or prior to lying down, as these behaviors cause significant changes in esophageal motility. Patients should be encouraged to take their medications one pill at a time and with at least 75 to 100 mL of liquid to increase the amplitude and duration of esophageal peristalsis. For institutionalized patients, they should be as upright as possible during drug administration and remain so for at least 5–10 minutes afterward. In elderly and patients with esophageal motility disorder, liquid formulations may be preferred rather than tablet or capsule, and avoid taking gelatin-coated, large size of drugs.[2,10]

PHARMACOLOGY

In severe cases, adequate fluid hydration and parenteral nutrition can be given as supportive therapy. Topical administration of viscous lidocaine is useful for reducing pain. Sucralfate is the cornerstone of pharmacologic management of drug-induced esophagitis. One gram of sucralfate four times daily is recommended with the aim to form a protective coating over the area of inflammation in order to promote healing. In the setting of reflux diseases, giving acid-lowering agents such as histamine-2 receptor antagonists and proton-pump inhibitors may be added.[2,3]

ENDOSCOPIC THERAPY AND SURGERY

Endoscopic therapy is limited to complicated cases such as esophageal stricture, actively bleeding esophageal ulcers and endoscopic removal of impacted medications. Surgery should be reserved for patients with severe complications, such as erosion into the mediastinum, heart, or great vessels. Specific complications of surgery include anastomotic leakage, which can lead to significant morbidity and mortality. Individual procedures should be considered based on the individual case.[18]

CONCLUSION

Drug-induced esophagitis may occur at any age and with a variety of commonly used medications such as antibiotics, antivirals, NSAIDs, bisphosphonates, chemotherapy agents, ferosus sulfas, ascorbic acid, potassium chloride, theophylline, and so on. Nevertheless, drug-induced esophagitis is most likely underdiagnosed in clinical practice for several reasons. Acute onset of retrosternal chest pain, odynophagia and dysphagia that associated with a potentially injurious medication taken incorrectly strongly suggest the diagnosis. Endoscopic findings may range from erythema, erosion, kissing ulcers, signs of bleeding, perforation or strictures of the esophagus. Discontinuation of suspected drugs is the cornerstone management of drug-induced esophagitis, accompanied by giving symptomatic drug and adequate fluid hydration.

REFERENCES

1. Kikendall JW. Pill esophagitis. J Clin Gastroenterol 1999;28:298-305.
2. Jaspersen D. Drug-induced Oesophageal Disorders: Pathogenesis, Incidence, Prevention and Management. Drug Saf 2000;22:237-49.
3. Katzka DA. Esophageal Disorders Caused by Medications, Trauma, and Infection. In: Feldman M, Friedman LS, Brandt LJ, eds. Gastrointestinal and Liver Disease. 10th ed. Philadelphia 2016.p.763-71.
4. Boyce HW. Drug-induced Esophageal Damage: Diseases of Medical Progress. Gastrointest Endosc 1998;47:547-50.
5. Wright V. The oesophagus. In: Walker P, Durie JR, Hamilton JA, et al, eds. Pediatric gastrointestinal disease: pathophysiology, diagnosis and management, vol. I. Philadelphia: BC Decker Inc 1991: 375-6.
6. Carlborg B, Densert O. Medikamentella esofagus strikturer. Lakartidningen 1978;75:4609-11.
7. Dag MS, Ozturk ZA, Akin I, Tutar E, Cikman O, Gulsen MT. Drug-induced Esophageal Ulcers: Case Series and the review of the literature. Turk J Gasroenterol 2014;25:180-4.
8. Zografos GN, Georgiadou D, Thomas D, Kaltsas G, Digalakis M. Drug-induced Esophagitis. Dis Esophagus 2009;22:633-7.
9. Simko V, Joseph D, Michael S. Increased risk in esophageal obstruction with slow-release medications. J Assoc Acad Minor Phys 1997;8:38-42.
10. O'Neill JL, Remington TL. Drug-induced Esophageal Injury and Dysphagia. Ann Pharmaco Ther 2003;37:1675-84.
11. Abid S, Mumtaz K, Jafri W, Hamid S, Abbas Z, Shah HA, Khan AH. Pill-induced esophageal injury: endoscopic features and clinical outcomes. Endoscopy 2005;37:740-4.

12. Kim SH, Jeong JB, Kim JW, Koh SJ, Kim BG, Lee KL, et al. Clinical and endoscopic characteristics of drug-induced esophagitis. World J Gastroenterol 2014;20;10994-9.
13. McGettigan MJ, Menias CO, Gao ZJ, Mellnick VM, Hara AK. Imaging of drug-induced complications in the gastrointestinal system. Radio Graphics 2016;36:71-87
14. Kim JW, Kim BG, Kim SH, Kim W, Lee KL, Byeon S, et al. Histomorpological and immunophenotypic features of Pill-induced esophagitis. Plos One 2015;10:1-12
15. Seminerio J, McGrath K, Arnold CA, Voltaggio L, Singhi AD. Medication-associated lesions of the GI tract. Gastrointest Endosc 2014;79:140-51.
16. Mueller S, Aigner T, Neureiter D, Stolte M. Eosinophil infiltration and degranulation in oesophageal mucosa from adult patients with eosinophilic oesophagitis: a retrospective and comparative study on pathological biopsy. J Clin Pathol 2006;59:1175-80.
17. Craig JM, Giaffer MH, Talbot MD. Drug-induced oesophageal ulceration in a patient with acquired immunodeficiency syndrome. Int J STD AIDS 1996;7:370-1.
18. Winstead NS, Bulat R. Pill Esophagitis. Curr Treat Options Gastro 2004;7:71-6.