Pill Esophagitis: Clinical and Endoscopic Profile

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Abstract

Background Medications can rarely cause esophageal injury and present with acute symptoms. Multiple factors, including the type of medication, comorbidity, and method of ingestion play a role in causing drug-induced or pill esophagitis (PE). We analyzed the clinical, endoscopic, and histopathological profiles of PE cases at our gastroenterology outpatient clinic.

Methods Medical records of PE cases were reviewed retrospectively over a period of 5 years at a tertiary care hospital in India from May 2017 to May 2022. The data were collected and analyzed using descriptive statistical analysis.

Results A total of 30 patients diagnosed with PE were involved in the study. A slight male preponderance of 56.7% was noted with a mean age of 40.7 years. Odynophagia was the dominant symptom (70%) with a mean duration of symptoms of 5.63 days. The most common location was at the mid-esophagus (80%) followed by the lower esophagus (10%). The majority (56.7%; 17/30) had over-the-counter (OTC) drug consumption, followed by doxycycline (33.3%; 10/30). Kissing ulcers were seen in 30% of the subjects; 90% of the patients received a combination of proton pump inhibitors and sucralfate suspension for 2 weeks along with discontinuation of the causative drug, with a 96.7% resolution rate.

Conclusion OTC medication and antibiotics such as doxycycline are the leading cause of PE. Prompt recognition and discontinuation of the causative drug are crucial in preventing complications. Patient education is vital in preventing PE regarding the usage of OTC medicines in developing countries.

Keywords
- doxycycline
- drug-induced esophagitis
- drugs
- over-the-counter
- pill esophagitis
- pill-induced esophagitis

Introduction

Pill-induced esophagitis (PE), even though common (3.9 per 100,000 population annually), is rarely reported.[1] Since first described in 1970, more than 100 drugs have been implicated in PE.[2] Most of the patients report a self-limiting symptom, but rarely serious complications such as bleeding, strictures, and perforation can develop.[3] PE usually develops due to the dissolution of caustic medicine and the release of noxious content in the esophagus due to delayed transit of drug to the stomach. Physical and chemical properties of the pill such as capsule formulation, large size, and higher acidic and alkaline content and patient factors such as position of patient and amount of water consumed along with the pill play a key role in developing PE.[4] Anatomical and motility disorders of the esophagus also predispose to PE.

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They usually present with acute-onset odynophagia, retrosternal chest pain, and dysphagia. Many clinicians fail to recognize this entity, leading to unnecessary and extensive diagnostic evaluation, and continued exposure to drugs leading to complications. In spite of accumulating literature on PE and accessibility of endoscopy centers, there is still a lack of awareness of PE among clinicians. Early recognition of PE and intervention leads to complete recovery without complication. We retrospectively analyzed clinical, endoscopic, and histopathological features of PE and their outcome.

Materials and Methods

All diagnosed patients of PE (> 18 years old) were included in this retrospective case series. PE was diagnosed based on clinical, endoscopic, and, in selected patients, histopathology. Patients' clinical, endoscopic, and histopathology data were retrieved by reviewing the electronic medical case records. Patients' detailed histories including the details of medicine, indication and presenting features, endoscopic findings, and histopathology features were recorded. Patients with upper gastrointestinal malignancies, infectious esophagitis, and gastroesophageal reflux diseases were excluded. All the patients were treated on an outpatient basis. Ethical approval was obtained from the institutional ethics committee. Details were entered in Microsoft Excel and analyzed in SPSS V25. Descriptive statistics were represented with percentages for qualitative data and mean with standard deviation (SD) or median with interquartile range for quantitative data. The Shapiro–Wilk's test was applied to find normality.

Results

A total of 30 patients were included in the study.

Demographic Data

A slight male preponderance of 56.7% (17/30) was noted with a mean age of 40.7 years (SD ± 12.99; range: 22–69 years) (►**Table 1**).

Table 1 Demographics

Variable	Number (%)
Age	40.70 ± 12.99
Gender	
Male	17 (56.7)
Female	13 (43.3)
Comorbidity	
CKD	5 (16.7)
CAD	3 (10)
Bronchial asthma	1 (3.3)
Depression	1 (3.3)
DM	1 (3.3)
HIV	2 (6.7)
Thyroid disorder (hypothyroidism or hyperthyroidism)	1 (3.3)
Symptoms	
Odynophagia	21 (70)
Dysphagia	6 (20)
Heartburn	13 (43.3)
Chest pain	6 (20)
Causative agent	
Clopidogrel	1 (3.3)
Doxycycline	9 (30.0)
Doxycycline + NSAID	1 (3.3)
NSAIDs	1 (3.3)
Steroid	1 (3.3)
Unknown	17 (56.7)

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.

Clinical Profile

Twenty-one (70%) patients presented with odynophagia, making it the most common symptom in our series. Odynophagia was observed as an individual symptom and associated with other symptoms such as heartburn (43.3%) and chest pain (20%). Dysphagia was seen in six patients (20%). All patients had symptom onset within 24 hours of consuming the offending drug, and the mean duration of presentation to the hospital was 5.63 days (SD ± 3.82; range: 2–14 days). Most patients ($n = 17$, 56.7%) consumed an over-the-counter (OTC) medicine. These included either nonsteroidal anti-inflammatory drugs (NSAIDs) or antibiotics or a combination of both which were self-medicated by the patient without a prescription from a registered medical practitioner/doctor. Attempts were made to enquire about the inciting agent (drug) such as enquiring about a written prescription and a photograph of the drug package. If both are unavailable, the patient was asked if he/she can recall the "name" of the drug. The indications for these self-administered medications were respiratory tract infections, skin infections, and generalized body aches. Doxycycline-induced PE was seen in 10 patients (33.3%), NSAIDs caused PE in one patient individually and one in combination with doxycycline. Other drugs such as clopidogrel and prednisolone were causative agents in one patient each; 16.7% ($n = 5$) had chronic kidney disease (CKD) as a comorbidity followed by coronary artery disease (CAD) in three patients (10%). A few other risk comorbid conditions were bronchial asthma, hypothyroidism, depression, diabetes mellitus, and human immunodeficiency virus ($n = 2$).

Endoscopic Profile

All patients (100%) underwent endoscopy in the outpatient endoscopy suites. Kissing ulcers were the most common endoscopic finding and were seen in 30% ($n = 9$) of the study population. Erosions were the next common (26.6%) followed by circumferential ulcers (16.6%, $n = 5$) and linear ulcers (13.3%, $n = 4$). Multiple ulcers as well as

Table 2 Endoscopic findings and biopsy

Variables	Number (%)
Ulcer type	
Circumferential ulcers	5 (16.7)
Kissing ulcers	9 (30)
Linear ulcer	4 (13.3)
Multiple ulcers	2 (6.6)
Semicircumferential ulcers	2 (6.6)
Small superficial ulcers/erosions	8 (26.7)
Additional findings	
Barrette esophagus	1 (3.3)
Candida	2 (6.7)
Location of ulcer	
Lower	3 (10)
Middle	24 (80)
Upper	1 (3.3)
Upper middle	2 (6.7)
Biopsy obtained	16 (53.3)

semicircumferential ulcers were observed during endoscopy in two patients each (6.6%). Mid-esophagus was involved in PE most commonly (80%, $n = 24$), followed by the lower esophagus (10%, $n = 3$), two patients had esophagitis at both upper and middle levels (6.7%), and only one patient (3.3%) had upper esophageal involvement. Endoscopic biopsies from ulcers were performed on approximately half of the study population (53.3%, $n = 16$). Additional endoscopic findings include coating with drug material ($n = 2$), candida infection ($n = 2$), and Barret's esophagus ($n = 1$) (►**Tables 2** and **3**) (►**Figs. 1** and **2**).

Histopathology

Sixteen patients (53.33% of study population) underwent endoscopic biopsies from the ulcers, 62.5% had a necroinflammatory type of infiltrate on microscopy ($n = 10$) followed by 18.75% of granulomatous infiltrate ($n = 3$) without any features of caseating granulomas, 12.5% of lymphoplasmacytic infiltrate ($n = 2$), and 6.25% of eosinophilic infiltrate ($n = 1$). All patients had an ulcerated esophageal mucosa on histopathological examination (►**Fig. 3**).

Management

All the patients after endoscopic confirmation of PE were treated on an outpatient basis with discontinuation of the causative drug. The majority (90%) were prescribed both oral proton pump inhibitors (PPI) and sucralfate suspension for 2 weeks. Only three patients (10%) received PPI alone without sucralfate; 96.7% ($n = 29$) had a resolution of symptoms after 2 weeks of therapy, and only one patient (3.3%) had persistent symptoms which required long-term treatment.

Discussion

Many drugs have been reported to cause PE including antibiotics, NSAIDs, bisphosphonates, potassium chloride, ferrous sulfate, ascorbic acid, dabigatran, chemotherapeutic agents, and antihypertensive medications.

Our study had a modest study population size of 30 compared with other retrospective studies by Kim et al ($n = 78$) done in South Korea, Dağ et al ($n = 48$) in the Turkish population, and Abid et al ($n = 92$) in Pakistan.[4–6] To our knowledge, this is one of the few studies done on PE from India. In comparison to our study which had a slight male preponderance, a review of the literature by O'Neill and Remington showed PE is more frequent in females with a mean age of 41.5 years.[7] PE presents with acute-onset odynophagia, which is the hallmark symptom. It is associated with or without additional symptoms such as chest pain, heartburn, and/or dysphagia.[8] Chest pain is typically constant, retrosternal, and exacerbated with swallowing. Similar to several case reports and series, odynophagia is the most common symptom in our study (70%). Boyce described PE as drug-induced esophageal damage which can manifest within a few hours to 10 days after consumption of the offending

Table 3 Causative agent and ulcer location

Pill/drug	Esophageal location						*p*-Value
	Lower		Middle		Upper		
	Count	%	Count	%	Count	%	**0.015**[a]
Clopidogrel	0	0.0%	0	0.0%	1	100.0%	
Doxycycline	0	0.0%	9	100.0%	0	0.0%	
Doxycycline + NSAID	0	0.0%	0	0.0%	1	100.0%	
NSAIDs	0	0.0%	1	100.0%	0	0.0%	
Steroid	0	0.0%	1	100.0%	0	0.0%	
Unknown/OTC	3	17.6%	13	76.5%	1	5.9%	
Total	3	10.0%	24	80.0%	3	10.0%	

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; OCT, over-the-counter.
Note: Doxycycline and OTC medications were significantly associated with pill-induced esophagitis. Concerning the location, the number of injuries was more in the mid-esophagus compared with the lower and upper esophagus.
[a]statistically significant.

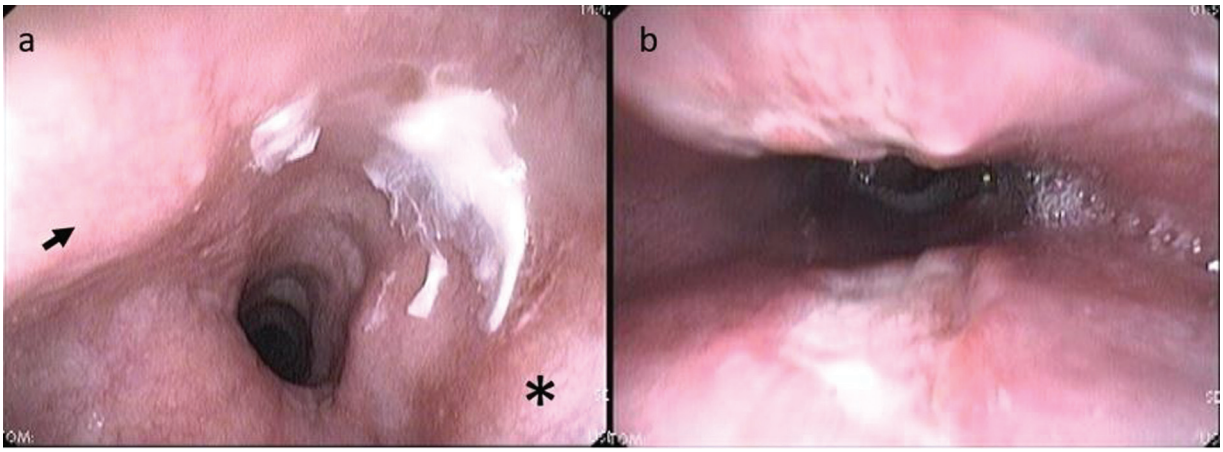

Fig. 1 (**a**) Pill esophagitis with white medication coating in the mid-esophagus. Note the aortic arch (arrow) and vertebral body (asterisk) compressions. (**b**) Classical kissing ulcers that are opposite to each other.

drug.[9] The duration of symptoms before presentation to our outpatient clinic ranged from 2 days to 2 weeks with a mean of 5.6 days, this was similar to the case series by Kadayifci et al where the presentation ranged from 3 to 4 days.[10]

Hey et al demonstrated that the position of the patient, the size of the medication, and the volume of fluid consumed are important factors that determine the risk of PE.[11] Supine position, consuming less than 100 mL of water and large

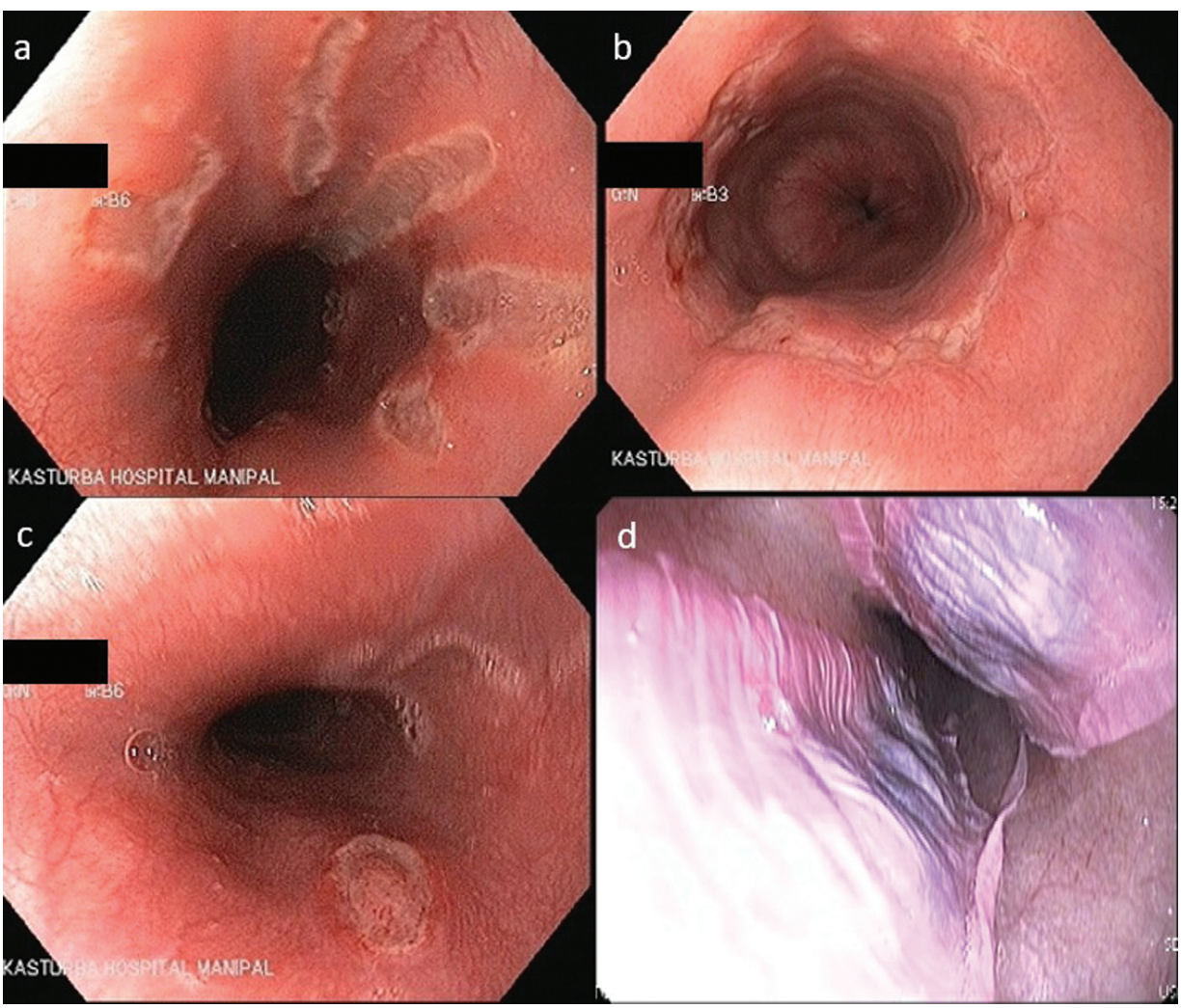

Fig. 2 Various shapes and sizes of ulcers in PE. (**a**) Multiple linear ulcers; (**b**) circumferential ulcers; (**c**) isolated punched-out ulcer; (**d**) PE with pinkish-blue medication coating. PE, pill esophagitis.

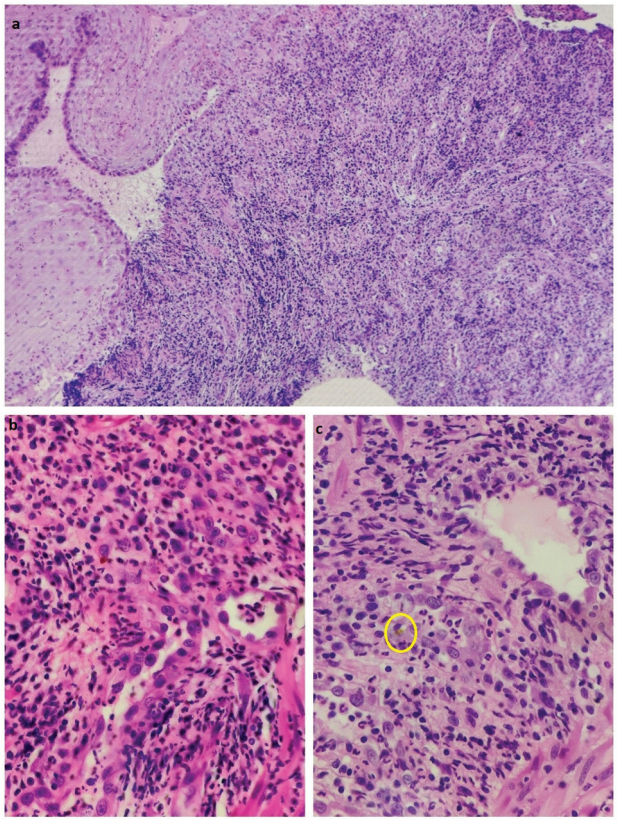

Fig. 3 Histopathology in PE. (**a**) Esophageal mucosa showing basal cell hyperplasia and intraepithelial neutrophils adjoining an ulcer; (**b**) granulation tissue composed of a dense inflammatory infiltrate of neutrophils, lymphocytes, eosinophils, plasma cells, and plump endothelial cells. All fungal special stains were negative and no viral inclusions were seen; (**c**) admixed between the inflammatory cells are a few brown foreign body materials (yellow circle) which are negative for Perl's stain (for hemosiderin) and melanin stain. PE, pill esophagitis.

round-sized tablets can lead to a delay in esophageal transit time predisposing to PE.[11] Gelatin-based capsule formulations are also a risk factor for PE as they are sticky to the esophageal wall. The highly acidic or alkaline nature of the drug can lead to esophageal inflammation on prolonged contact due to various mechanisms (e.g., osmolality). The adult esophagus measures 25 to 30 cm in length and is divided into upper, middle, and lower parts. The mid-esophagus consists of an anatomical narrowing, it is compressed by the aortic arch, left main bronchus, and vertebral bodies of thoracic vertebrae.[12] Altered anatomy of the esophagus due to strictures, rings, varices, and lesions can cause an intrinsic narrowing. Extrinsic compressions by an enlarged left atrium, mediastinal mass or nodes can narrow the lumen and predispose to PE. Other functional risk factors are any motility disorders of the esophagus. Although not much data exist on the comorbid conditions of the patients and the risk of developing PE, elderly patients with multiple comorbidities are prone to PE due to unknown reasons. CKD (16.7%) was the most common comorbidity followed by CAD (10%) in our study, whereas CAD was seen in 42% in the study by Abid et al.[6] Further observational studies are needed to better correlate comorbidity and PE.

Endoscopic findings include isolated or combinations of erosions, ulcers (various size and shapes), ulcers with bleed, pill fragments, and medication coatings.[13] Classical kissing ulcers are defined as ulcers which are facing each other and are described to be associated with PE but are not pathognomonic. The incidence of kissing ulcers and esophageal erosions were 30 and 26.6%, respectively, in this study. These findings were only slightly varied compared with a larger case series by Kim et al where kissing ulcers were seen in 46.7% and erosions in 17.9%.[5] Bleeding in PE is not uncommon, often it is seen along with an ulcer. Although our study had no patients with bleeding, bleeding ulcers due to PE were seen in 24.4% in the study by Kim et al and 18% in the study by Abid et al including local diluted (1:10,000) epinephrine injection done in 15% for hemostasis. Similar to earlier studies, the mid-esophagus is the most common location for PE in this series with a frequency of 80%. Although severe PE can be complicated with bleeding from ulcers and very rarely perforation of esophagus, we have encountered no such complications. Histologically, necroinflammatory infiltrate with or without micropustules is the most common finding (33.3%, $n = 10$). Less common infiltrate types were granulomatous, eosinophilic, and lymphoplasmacytic. Histology is rarely pathognomonic in PE as it is often an acute inflammatory infiltrate with nonspecific changes.[13] Hence, endoscopic biopsy is a debatable topic and it is only advised to rule out an infection or when malignancy is suspected. Like Dağ et al, several literature reviews mention endoscopic examination is the gold standard for diagnosing PE.[4]

Doxycycline is a tetracycline derivative antibiotic with high acidic content, when consumed with less volume of water or in a recumbent position can predispose to esophageal injury. Doxycycline-induced esophageal injury ranges from erosions to deep ulcers. Cumulative incidence was 35.9% among antibiotics including doxycycline by Kim et al, and 22% in studies by Patel et al and Abid et al.[10,14] A similar trend was noticed in our study as well (30%). Even in the pediatric age group, doxycycline accounted for 26% of pill-induced esophageal ulcers, as described in a Romanian series by Bordea et al.[15] Only few patients developed PE secondary to NSAIDs, clopidogrel, and steroid ($n = 1$ due to each drug). One patient developed kissing ulcers in upper and mid-esophagus due to a combination of NSAIDs along with doxycycline. An interesting observation in this study is that 56.7% of patients developed PE due to self-administration of an OTC medication. This can be due to an increasing tendency for patients to self-medicate, patients treated by quacks and liberal policies in regulating OTC drugs. According to Marathe et al, "OTC medicine can act as a double-edged sword and due consideration has to be given to safety, abuse, and patient education."[16] The recent coronavirus disease 2019 (COVID-19) pandemic has witnessed a huge surge in OTC medication (NSAIDs, steroids, antibiotics) abuse causing self-harm to patients.[17] A case series by Panigrahi et al at the All India Institute of Medical Sciences described a clear surge of doxycycline-induced PE during the COVID-19 pandemic.[18]

Our study also overlapped with the COVID-19 pandemic which started in January 2020. Possible reasons for the limited number of patients could be due to few patients reporting the symptoms at local hospitals/clinics and even fewer approaching tertiary care hospitals like our center. Another critical reason could be the limited number of diagnostic endoscopy procedures done during the COVID-19 pandemic as most gastroenterology units performed only emergency procedures.

Most patients recover well when the offending drug is discontinued and treated with PPI with or without sucralfate suspension. All patients were treated with PPI for a duration of at least 2 weeks and 90% received 5 to 10 mL (0.5–1 g) of sucralfate suspension also. The resolution rate was 96.7% ($n = 29$) in our study after receiving 2 weeks of treatment. Five patients underwent a repeat endoscopy after 4 weeks and demonstrated mucosal healing in 80% ($n = 4$), and one patient had persistent ulcers on endoscopy and required long-term treatment.

Patient education is critical in preventing PE. Consumption of 125 to 200 mL water after taking the medication in an upright position and avoiding the recumbent position immediately after should be explained in detail to patients, especially with medications prone to PE.

Conclusion

PE is increasingly recognized in clinical practice due to easy accessibility to endoscopy. In India, OTC medicines are the leading cause. Early recognition and discontinuation of causative drugs is the cornerstone of the management. Awareness among clinicians about this condition and proper education of patients regarding pill ingestion can prevent this potential complication.

Prior Publications/Presentation
Part of the study was presented as an E-poster at ENDOCON 2023, Indore, India.

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Conflict of Interest
None declared.

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