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Drug-induced esophageal ulcers: Case series and the review of the literature

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Original Article

ABSTRACT

Background/Aims: Drugs can cause several complications in the esophagus and lead to pill esophagitis. In this paper, our purpose is to share our clinical experience in light of the literature and put forward the general characteristics of pill esophagitis.

Materials and Methods: In our clinic, between January 2008 and June 2012, by excluding other factors, 48 patients were included in the study, diagnosed as drug-induced esophagitis with their history, endoscopic view, and histopathologic evaluation.

Results: There were 34 (70.9%) female and 14 (29.1%) male patients in the study, and their average ages were 35.1 and 32.4, respectively. Clinical symptoms were odynophagia (79.1%), retrosternal pain (62.5%), and dysphagia (47.9%). The reason for these symptoms for 85.5% of the patients was related to insufficient water consumption while taking the pill, taking the pill in recumbent position, or both. Tetracycline and its variant, doxycycline, were responsible for 52% of the patients, and 62.5% of the drugs were in capsule form. Ulcers were at the proximal and middle third of the esophagus in 79.2% of the patients. In the histopathologic evaluation, nonspecific acute inflammatory changes were found in 29.1% of the cases. Various proton pump inhibitors and sucralfate were used in the treatment. While no perforation and structure were detected, 1 patient died because of repetitive arterial bleeding.

Conclusion: Almost every kind of drug, particularly doxycycline, can cause ulcer in the esophagus. Pill esophagitis can be prevented by warning patients about drinking water sufficiently and sitting up while taking the pill.

Keywords: Esophagus ulcer, doxycycline, capsule, female gender, endoscopy

INTRODUCTION

Most drugs can cause different variations of pill esophagitis (PE) and be presented in different spectrums of complications, such as mucosal inflammation, ulceration, bleeding, penetration, perforation on the esophagus, and even death (1-6). First, it was described as associated with potassium chloride tablet consumption, and then, it was reported as an etiological agent of 100 different drugs and more than 1000 cases until 1999 (7,8). Besides, considering the cases with mild clinical symptoms who were misdiagnosed or diagnosed as reflux esophagitis or unreported at all, the number and frequency of etiological agents can be said to be much higher. Although a lot of cases and case series related to different types of drugs have been reported, tetracycline and its variant, doxycycline, are still being reported as the most frequent cause of PE (9-13).

Many factors play a role in the development of the disease, such as personal factors, the drug, and the esophagus per se; however, the most important of these factors are insufficient water consumption and recumbent position while taking the drugs.

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The basic etiological factors are that doctors do not routinely give the necessary warnings about offender drugs or that patients do not take the warnings into consideration (10,14,15). Upper gastrointestinal endoscopy is the most important method for the diagnosis, differential diagnosis, follow-up, and the treatment of the complications. Histopathological evaluation is not necessary for diagnosis and has generally nonspecific findings, except that of certain agents; however, it is useful for the exclusion of malignancy (5,11,12,16).

The aim of this study is to draw attention to PE, which occurs due to almost totally preventable causes, and evaluate the general characteristics of PE in light of the literature, along with our clinic's experiences.

MATERIALS AND METHODS

Between January 2008 and June 2012, reports of 14,820 upper gastrointestinal system endoscopies were recruited, and patients diagnosed as PE were recorded. A total of 48 patients (0.32%) were included in the study. The history, endoscopic view, and histopathological evaluation of the patients were recorded. In this retrospective study, demographic features, clinical presentations, and medications taken of the patients were recorded, as well as the reason for taking the medicine; factors about the patient and the drug; the location, size, and number of ulcers on the esophagus; and the histopathological specifications of the ulcers.

Exclusion criteria were as follows:
1) Reflux esophagitis (included alcohol consumption)
2) Infectious esophagitis
3) Caustic or corrosive esophagitis
4) Malignancy presented with esophageal ulcer
5) Connective tissue disorders manifested on esophagus
6) Crohn disease manifested on esophagus

All patients who accepted the procedure had undergone upper gastrointestinal system endoscopies initially for the diagnosis and later for the recovery of PE.

The study protocol was approved by local institutional review board. Patient consents were obtained.

Statistical analysis

Statistical Package for Social Sciences (SPSS) for Windows 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All data were entered into a database and were verified by a second independent person. Data are presented as mean±SD for normally distributed variables and as median (minimum-maximum)±IQR for skewed distributed continuous variables. Categorical variables are shown as frequencies.

RESULTS

A total of 48 patients, 34 females (70.8%), have been included in the study. Median age and IQR were 35.1 (18-77) years for females and 32.8 (18-63) years for males. Clinical symptoms sorted according to frequency were odynophagia (%79.1), retrosternal pain (62.5%), dysphagia (47.9%), epigastric pain (14.5%), hematemesis (19.4%), and melana (6.2%). Symptoms appeared between 2 hours and 3 days after ingestion of drugs.

Table 1. Etiological agents causing esophageal ulcer

Etiological Agents	Number
Doxycycline	24
Tetracycline	1
Cyproterone acetate, ethinylestradiol	3
Escitalopram	2
Citalopram HBr	1
Ibuprofen	2
Naproxen	2
Aspirin	1
Ciprofloxacin	2
Alendronate sodium	1
Ornidazole	1
Dobesilate calcium	1
Methylprednisolone	1
Ferrous glycine sulfate	1
Phenytoin sodium	1
Clindamycin	1
Rifampicin	1
Radioactive I^{131}	1
Lansoprazole	1

Of the patients, 41.6% had a history of drug consumption with insufficient water, 22.9% described recumbent position while taking the drug or taking it shortly before going to bed, 25% had a history of drinking insufficient water and in recumbent position, and 14.5% had neither of these factors. For 48 cases, a total of 19 different drugs that caused esophageal ulcers was determined as the etiology.

Of patients, 25 (52%) were associated with tetracycline consumption, and 24 of 25 were doxycycline-related. The second cause of PE was non-steroid anti-inflammatory drugs (NSAIDs), with a ratio of 10.4%. Capsule form was the most frequent shape for the drugs, with a ratio of 62.5%. The most frequent primary diseases that required medication were various urinary system diseases (USDs) and acne vulgaris. The drugs causing PE and underlying primary diseases are given in Table 1 and Table 2. Detected by endoscope, ulcers were located at the proximal, middle, and distal third of the esophagus with a ratio of 18.7%, 47.9%, and 20.8%, respectively, while 12.5% of the cases had both proximal and middle esophageal ulcers. Endoscopic views of the ulcers were round, geograph-

Table 2. Primary diseases requiring treatment

Primary Diseases	Number
URD (vaginitis, cervicitis, endometritis, salpingitis, urethritis)	13
Acne vulgaris	11
Menstrual disorders, contraception	3
Depressive disorder, anxiety	3
Migraine	2
Sinusitis	2
Urinary system infection	2
Osteoporosis	1
Brucellosis	2
Seborrheic dermatitis	1
Hemorrhoids	1
Pemphigus vulgaris	1
Anemia	1
Epilepsy	1
Gingivitis	1
Tuberculosis	1
Papillary thyroid Ca	1
Gastritis	1

ical shaped, irregular, superficial, deep, surrounding the lumen, or kissing ulcers. The sizes of the ulcers varied between 0.5 to 6 cm, and their numbers were between 1 to 5.

Due to refusal of the patients, control endoscopy could only be performed in 47.9% of the cases. Clinical and full mucosal recoveries were detected after 2 or 5 weeks in the patients who performed endoscopy. Ulcer, subepithelial abscess formation, or acute inflammatory changes were detected in 29.1% of the patients who had a histopathological evaluation. No specific histopathological evidence or malignancy was detected. The endoscopic and histopathological views of doxycycline-induced esophageal ulcers are shown in Figure 1, and the endoscopic view of the esophageal ulcer in the patient who both had hemodialysis and took clindamycin capsules with insufficient water is shown in Figure 2. Several proton pump inhibitors (PPIs) and sucralfate were used in different periods and doses. While no penetration, perforation, and stricture were seen, one patient died because of repetitive arterial bleeding. Four patients were hospitalized because of bleeding, deep ulcer, or insufficient oral nourishment.

DISCUSSION

In our study, we found that the offender drug for PE was doxycycline for half of the cases, and PE was seen more often in the female gender or patients using the capsule form of the drug. In addition, we also found that causes of PE were almost always associated with a history of drinking insufficient water

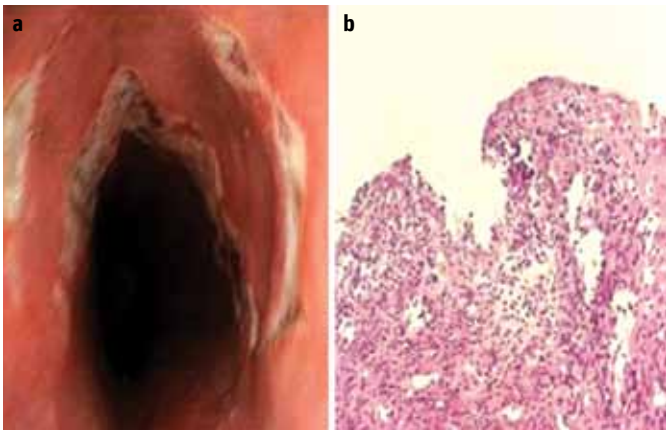

Figure 1. a, b. Ulcer at the middle third of esophagus due to doxycycline **(a)**. Histopathological view of picture **(b)**.

while taking drugs and/or recumbent position after ingestion the drug, all of which are preventable factors. PE is seen more frequently in female gender in case series of the literature (2,9,11-13,16). In our study, remarkably, female gender dominance was seen (70.9%). In the literature, most of the cases ranged between ages 20 to 40, while PE can be seen in different ages with different drugs (9,11,13,17). Most of our patients were young individuals, less than 40, and in their reproductive age, and they used doxycycline for indications, such as USD and acne vulgaris.

When the clinical presentations of the patients are taken into consideration, odynophagia, retrosternal pain, and dysphagia are the most encountered symptoms reported, with varying frequencies (2,6,8,11,13). In our study, the most frequent symptom was odynophagia, while hematemesis and melana were rarely primarily the reason for the application.

Various factors relating to the drug, person, and esophagus play a role in developing PE. The most important drug-induced causes are the chemical structure and pharmaceutical form of the drug, because the capsule form can adhere to the esophagus and pose a higher risk than the tablet form (5,13,14,18). Capsule forms of drugs, such as doxycycline, tetracycline, clindamycin, calcium dobesilate, rifampicin, radioactive I^{131}, and lansoprazole, account for 62.5% of our cases. The most important patient-related factors are insufficient water consumption and taking drugs in recumbent position (14). These two factors together or separately played a role in 85.5% of our patients. The factors related to the esophagus are mostly associated with motility disorders or regions of anatomical narrowness (14). We detected esophageal varices in only one patient, which can be regarded as a predisposing factor for PE because of the negative impact on esophageal motility.

Although every kind of drug can lead to mucosal damage of the esophagus in different ways, the most common agents in the literature are tetracycline and more frequently its variant, doxycycline (27-50%) (9,12,19,20). Doxycycline can damage

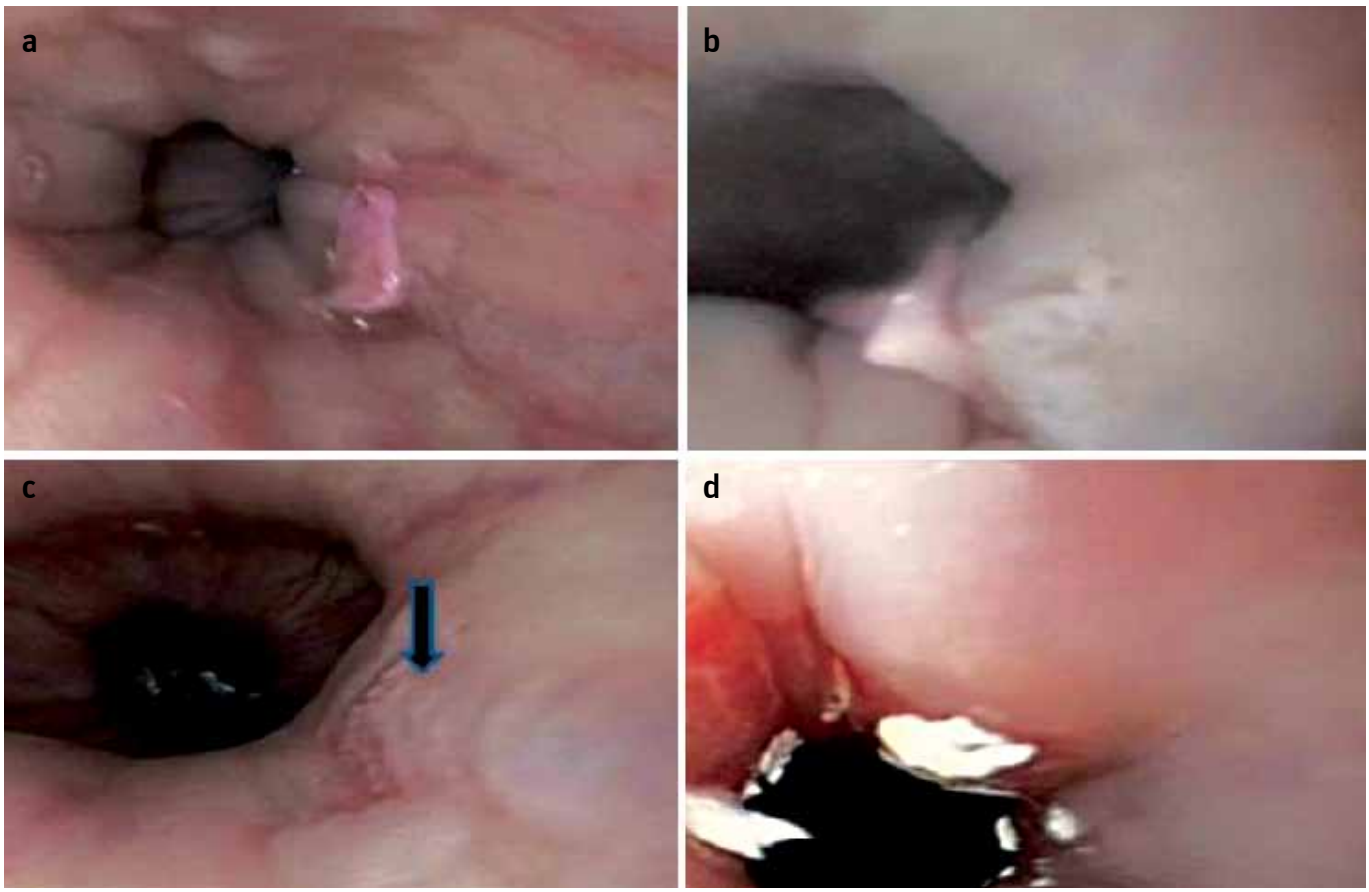

Figure 2. a-d. Clindamycin in gelatin capsule form adhering to distal esophagus **(a)**. Washing the capsule with water during endoscopy **(b)**. The superficial ulcerous area under the capsule (arrow) **(c)**. The white colored content of the drug's capsule adhering to mucosa in the distal esophagus **(d)**.

the esophageal mucosa by its acidic structure, with a direct local caustic effect, and it also accumulates in the epithelial cells and causes damage, with an inhibiting effect on protein synthesis (20,21). In our study, doxycycline, used widely for indications, such as USD, acne, and brucellosis, was the most frequent offending drug (50%); besides, 19 different drugs leading to esophageal ulcer were identified.

Upper gastrointestinal system endoscopy is the golden standard for PE diagnosis. Allowing detection of the mucosal changes, taking biopsy sampling, and intervening in bleeding and other complications of the esophagus, upper endoscopy is the first choice for both diagnosis and the treatment (2,5,11,18). In the upper endoscopy, we found that most of the ulcers were located in the middle third of the esophagus, which is compatible with the literature (2,13). Although the histopathological examination of PE is rarely pathognomonic, it is generally nonspecific and includes mostly benign ulcer and acute inflammatory changes (12,16,22-24). However, histological evaluation should be performed for differential diagnosis, especially in cases where malignancy and infectious pathologies are suspected. From 29.1% of our cases, biopsy was taken endoscopically; in the rest, typical clinical presentation, history of drug usage, and endoscopic appearance were sufficient to establish the diagnosis. While no infectious or malignant changes were seen, benign changes, such as acute inflammation and ulcer, were detected in all samples.

The most efficient method for the treatment seems to be prevention of the development of PE. In most cases, drugs are discontinued first, and supportive treatments, such as PPI and sucralfate, are introduced, and thus, rapid clinical and mucosal recoveries are achieved. PPIs are found to be very effective with their acid-inhibiting properties, while sucralfate has local protective barrier and cytoprotective effects (11,12,23,25). In our cases, the offender drug was immediately stopped, and supportive treatment was started, along with PPIs and/or sucralfate in different doses and periods. Thus, rapid clinical (3-8 days) and mucosal recovery (2-5 weeks) was achieved for all patients General characteristics of PE in light of the literature, along with our study results, can be listed as follows:

1) Female gender, 2) young-middle age (especially for patients using tetracycline or doxycycline), 3) a history of oral drug use, 4) development of symptoms, such as odynophagia, retrosternal chest pain, or dysphagia, within hours or days following the drug intake, 5) acute clinical presentation, 6) absence of alarm symptoms suggestive of malignity, 7) a history of drinking insufficient water and taking drugs in recumbent position, 8) use of tetracycline and its variant, doxycycline, 9) almost every drug

is a potential risk for PE, 10) greater risk in capsule form of drugs, 11) endoscopy is golden standard for diagnosis, differential diagnosis, and follow-up, 12) histopathological examinations for mostly nonspecific benign ulcer and acute inflammatory changes, and 13) rapid clinical recovery by stopping the offender drug.

In conclusion, almost every kind of drug, especially the doxycycline variant tetracycline, can cause ulcer in the esophagus. Diagnosis of PE can be performed easily with a typical history, clinical presentation, and endoscopic view. Histopathological evaluation is generally unnecessary, unless high suspicion of malignancy or infectious etiology exists. PE can be prevented to a large extent by warning the patients about drinking water sufficiently and sitting up while taking the pill, which are the major predisposing factors.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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