

Clinical and endoscopic characteristics of doxycycline induced esophageal ulcers: Retrospective observational study

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ABSTRACT

Introduction: Doxycycline usage takes an essential place in drug-induced esophageal ulcers. The study aims to investigate the clinical and endoscopic features of doxycycline-induced esophageal ulcers.

Materials and Methods: Patients who were treated with doxycycline for several reasons between 2014 and 2021 and who were diagnosed with esophageal ulcer after evaluation of their clinical complaints were included in the study. Patients were evaluated retrospectively in terms of demographic characteristics, clinical complaints, biopsy rate, indications for doxycycline use, endoscopy findings, and ulcer type.

Results: The study includes thirty patients. About 70% of the patients were female. Biopsy was performed in 13.3% of the patients. The most common indication for the use of doxycycline was acne vulgaris (53.3%). The most common clinical complaint was dysphagia (43.3%). Esophageal ulcers were most common in the middle esophagus, with 73.3%. In the endoscopic evaluation, the most common ulcer shape was circumscribed form (56%), and most ulcers were single (60%).

Conclusion: Esophageal ulcer diagnosis should be considered in patients with complaints such as dysphagia, odynophagia, and chest pain during doxycycline usage.

Keywords: Doxycycline, endoscopy, esophageal ulcer

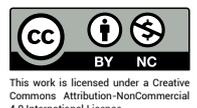
Introduction

Fifty years after the first drug-induced esophageal injury was reported, nearly 1000 cases due to nearly 100 different drugs have been reported in the world literature.^[1] Antibiotics account for almost 50% of all cases, while only doxycycline covers 27%.^[2] It may be suspected for diagnosis in patients with retrosternal pain, dysphagia, and odynophagia after doxycycline usage. Upper gastroin-

testinal system endoscopy is essential to confirm the diagnosis.^[3] Many cases have been reported of doxycycline-induced esophageal ulcers (DIEU).^[4-7] However, as far as we can determine, there are very few studies in the literature that only deal with the characteristics of DIEU.^[8,9] The study aims to investigate the clinical and endoscopic features of DIEU.



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Materials and Methods

Patients diagnosed with esophageal ulcers during doxycycline capsule treatment between 2014 and 2021 years in Sakarya Medar Hospital were included in the study. Inclusion criteria were patients being 18 years old and older, no history of digestive system disease or previous history of drug allergy, no history of medication or gastrointestinal system symptoms for at least 1 month before starting oral doxycycline treatment, history of oral doxycycline use prior to gastroscopy, having an esophageal ulcer confirmed by gastroscopy, having a complete medical history, including clinical data and endoscopy reports. Patients who did not meet the inclusion criteria or did not have sufficient clinical and follow-up data were excluded from the study. Patients were evaluated retrospectively in terms of demographic features, doxycycline use indications, clinical complaints, endoscopy findings, and esophageal ulcer features. Ethics committee approval no. E-71522473-050.01.04-32209-326 was obtained from the Clinical Research Ethics Committee of Sakarya University Faculty of Medicine. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or the national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Thirty patients were included in the study. The mean age of the patients was 31 (16–52) years. 70% of the patients were female (n=21), and 30% were male (n=9). Biopsy was performed on four patients (13.3%). The results are shown in Table 1. The patients had a history of doxycycline use due to acne vulgaris (53.3%), cystitis (20%), vaginitis (23.3%), and pneumonia (3.3%). All patients were taking Doxycycline 100 mg, as oral capsules twice daily. The most common complaint was dysphagia (43.2%). Esophageal ulcers were most frequently located in the mid esophagus with 73%. Complaints and ulcer localization rates are shown in Figure 1. The number of esophageal ulcers seen mostly in endoscopy was single with 60% and the most common type of ulcer was circumscribed with 56%. Structural features of esophageal ulcers are shown in Table 2. The other shapes of ulcers revealed in endoscopy were half-moon (23.3%), kissing ulcer (13.3%), linear (6.7%), and oval (23.3%).

The mucosal border surrounding the ulcers seen during endoscopy was normal. There was no evidence of fungi or malignancy in pathological findings. Endoscopy findings are shown in Figure 2. Based on the current endoscopy findings, the patients were diagnosed with a doxycycline-

Table 1. Demographic features and characteristics of patients

Age/year min-max (median) Mean±SD	16-52 (31)	31.167±9.025
Gender n(%)		
Male	9	30
Female	21	70
Biopsy/n (%)		
No biopsy	26	86.7
Biopsy done	4	13.3
Complaint n (%)		
Chest pain	8	26.7
Dysphagia	7	23.3
Odinophagia	1	3.3
Chest pain and dysphagia	7	23.3
Dysphagia and odinophagia	4	13.3
Chest pain and odinophagia	2	6.7
Dysphagia and stomach pain	1	3.3
Medical treatment indication n(%)		
Vaginitis	7	23.3
Acne Vulgaris	16	53.3
Cystitis	6	20
Pneumonia	1	3.3

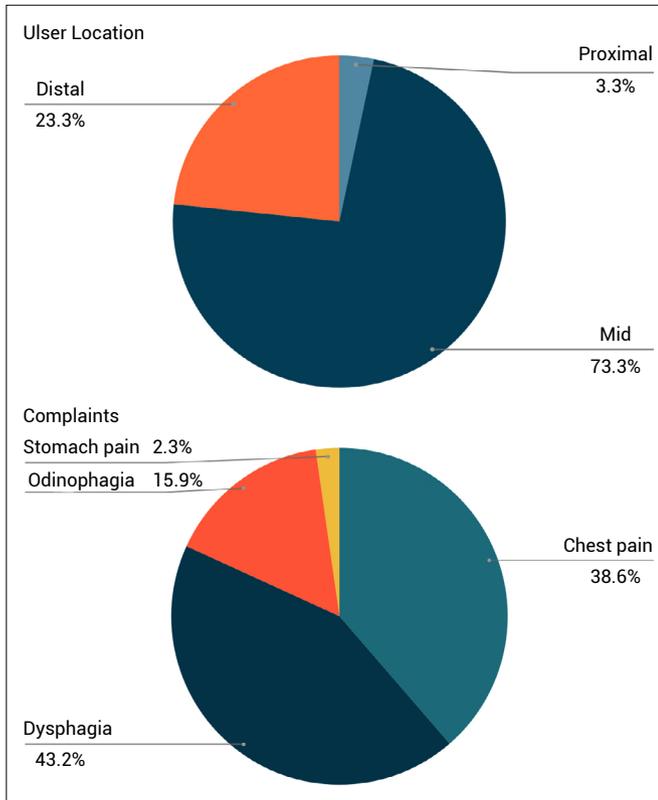


Figure 1. Ulcer location and complaints of patients.

induced esophageal ulcer. Hence, doxycycline treatment was discontinued. All the patients were prescribed proton pump inhibitors (20-30-40 mg capsule, once daily, in the morning, on an empty stomach) and a mucosal coating agent (aluminum carbonate chewable tablet, twice daily, or sucralfate oral suspension, 3 times daily). Symptoms of

discomfort were relieved in all patients after 3–7 days of ulcer treatment, and patients were able to resume a regular diet without any dysphagia.

Discussion

Mucosal damage in DIEU depends on numerous pharmacological factors. Long-term mucosal contact with pill content plays an important role and can be affected by pill size and pill formulation.^[10,11] Large pills get stuck in the esophagus more often than small pills.^[12] Sustained-release pills sometimes damage the esophagus more than the tablet form of the same drug.^[2] Gelatin capsules are hygroscopic and may become sticky by adhering to the esophageal mucosa, delaying pill passage. In the experimental study of Carlborg et al., doxycycline capsules adhered to the esophagus 3 times more often than doxycycline tablets and were associated with more esophageal damage accordingly.^[13] In our study, all patients were using doxycycline capsules too. Doxycycline may accumulate in the basal layer of the squamous epithelium and may cause cell toxicity by inhibiting protein synthesis, cell transformation, and repair.^[14] It produces a pH<3.0 when it comes in contact with saliva and may cause ulceration by damaging the esophageal mucosa.^[15] For these reasons, the transit time of the pills in the esophagus is relatively important. Posture has been demonstrated to be important in transmitting the oral tablet to the stomach.^[16,17] Drug transit may be delayed due to physiolog-

Table 2. Characteristics of oesophageal ulcers

Location (cm) min-max(median)/ Mean±SD	15-35 (30)	28.867±3.884
Location (n/%)		
Proximal	1	3.3
Middle	22	73.3
Distal	7	23.3
Number of Ulcers (n/%)		
Single	18	60
Double	5	16.7
Triple	3	10
Several	4	13.3
Ulcer Shape (n/%)		
Half moon	7	23.3
Circumscribed	10	56.7
Kissing	4	13.3
Linear	2	6.7
Oval	7	23.3

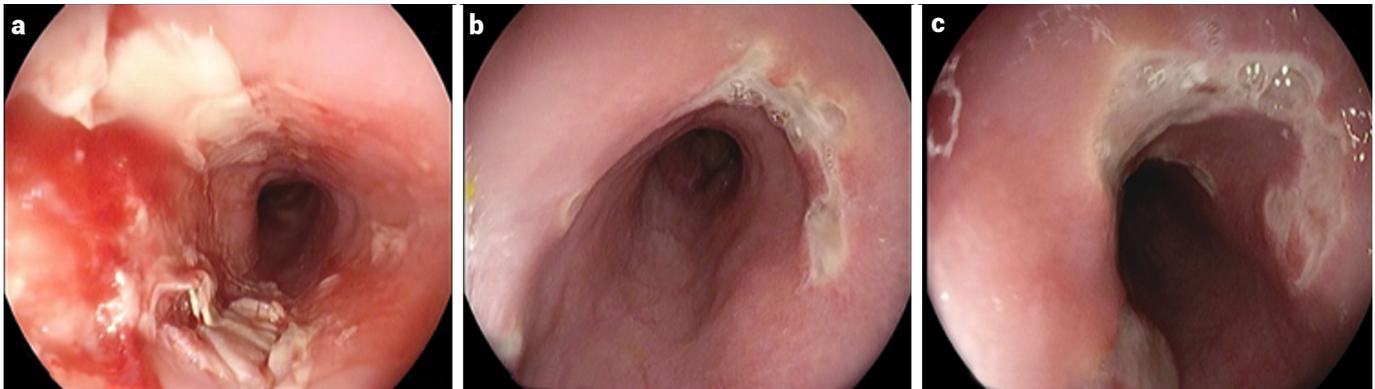


Figure 1. Endoscopic findings (a) circumscribed ulcer (b) Half-moon ulcer (c) Kissing ulcer.

ical reasons such as anatomical stenosis due to aortic arch or cardiac hypertrophy; motility disorders such as neurological dysfunction, or taking tablets with too little water in a recumbent position.^[18] As a matter of fact, in our study, recumbent position and little amount of water during medication intake were reported in the history of the patient with a proximal ulcer. When esophageal ulcers are encountered during endoscopy, if it is known that there is no clinical suspicion of other diseases (e.g., viral/fungal esophagitis, Levin tube injury, Crohn's, and radiation esophagitis), reflux esophagitis or DIEU should be considered first. Higuchi et al. reported that in the etiology of esophageal ulcers, 65.9% reflux esophagitis, 22.7% DIEI, and 11.4% other causes (viral/fungal inf., etc.) was involved.^[19]

In the endoscopy of a symptomatic patient, a definitive diagnosis can be made if pill fragments are stuck in the esophagus. However, impacted drug fragments are rarely seen. In the study, approximately $\frac{3}{4}$ of the patients had a mid-esophageal ulcer. Higuchi et al. reported that 91.4% of esophageal ulcers due to reflux esophagitis were located in the lower esophagus, and 80% of DIEU was located in the middle part of the esophagus.^[19] Other studies have also shown that drug-induced esophageal damage is frequently located in the mid-esophagus, as the middle $\frac{1}{3}$ of the esophagus is compressed by the aortic arch or the enlarged left atrium.^[8-10] In our study, the distal ulcer rate was 23%. In all these patients, the presence of esophageal ulcer was accompanied by mild, moderate cardiac-esophageal insufficiency, or sliding hiatal hernia. Alvares et al. reported in their study that the presence of hiatus hernia in patients taking doxycycline increased the risk of developing DIEU by 3.96 times.^[20]

A doxycycline-induced esophageal ulcer is characterized by sudden onset of odynophagia, retrosternal burning,

dysphagia, and chest pain during treatment, and in most cases, there is no esophageal dysfunction.^[6] Zografos et al. reported the rates of the main symptoms of DIEU as chest pain, odynophagia, and dysphagia.^[21] The rate of dysphagia was found to be higher in our study compared to the case series with other drugs.^[6,11] Compared to other drugs, the relatively large size and rough surface of doxycycline may have caused an increased complaint of dysphagia. DIEU cases may be overlooked in the clinical setting for several reasons; for clinicians, more common and more severe problems such as acute coronary syndrome, pulmonary embolism, or pleurisy may usually be considered first in complaints such as chest pain, odynophagia, and dysphagia. In addition, patients can generally attribute their complaints to gastroesophageal reflux. In addition, doxycycline is a drug that has been used safely and widely for many years, and finally, DIEU is considered a rare condition as it is not routinely reported or even recognized. This is a problem because failure to recognize the active agent may result in delayed discontinuation of the drug or failure to provide recommendations to the patient to avoid continuing damage. In addition, it may lead to false and unnecessary examinations/evaluations for other pathologies. These, in turn, cause additional morbidity and increase the cost of healthcare.^[22] History and upper gastrointestinal endoscopy can be used to confirm the diagnosis of DIEU, and classic endoscopic features of esophageal ulcerations can be detected.^[23,24] In endoscopic evaluations, ulcers were reported in various shapes, such as covered with pseudomembranous, discrete, confluent, linear, broad band-formed, crescent-shaped, or oval. The size, number, and depth of ulcers were various.

When the patient population is evaluated, the elderly are more prone to develop DIEU due to their altered esophageal motility and decreased saliva production.^[11] In addition, they have more frequent cardiac morbidity and require

more cardiovascular medication.^[25,26] In younger patients, esophageal damage can be caused mainly due to antibiotics.^[2,6,27] In our study, patients were mostly young. This is to investigate the esophageal damage caused by doxycycline, an antibiotic frequently prescribed in the younger age group compared to non-steroidal anti-inflammatory drugs, antihypertensive drugs, and biophosphonates that are frequently prescribed in the elderly population. None of these patients suffered from an esophageal disease or cardiac morbidity. In addition, the literature has reported that DIEU is more common in female patients.^[4,5,8,24] Similarly, but remarkably, the number of female patients in our study is almost two and a half times more than male patients. It may be considered that this situation is caused due to use of the drug by more female patients due to the genital system or urinary system infections.

Potentially, the harmful drug's cessation will help heal esophageal damage. When assessing risk factors for DIEU, drug-related and patient-related factors should be evaluated separately. Since DIEU is preventable and treatable, it is crucial to be aware of this problem and recognize it. As a precaution, it may be recommended that patients take the drugs with at least 200 cc of water. Intake of water accelerates metabolism, and it has been reported that adequate water intake reduces the time doxycycline remains in the esophagus.^[28] Patients should stand upright for at least 30 min after taking the medication. Safer alternative drugs should be preferred in patients with a high potential for drug-induced esophageal damage, or the benefits and risks of the drug against the disease should be carefully evaluated.^[22,29] With patients in the decubitus position, the drug should be taken in a sitting position; if it is not possible to sit, the 30° recline position may assist with the force of gravity.^[30]

This study is a retrospective, observational study and lacks a control group. The mechanism by which doxycycline causes esophageal ulceration requires further investigation due to the limited number of cases, duration of exposure, and the potential selection bias of the population through sampling. In addition, since the patient group is relatively young, the correlation between age and DIEU was not investigated in this study.

Conclusion

If patients with a history of doxycycline use have complaints of odynophagia, dysphagia, and retrosternal burning, esophageal ulcer must be considered. To prevent

DIEU, the patient should be advised to swallow the pill with a large glass of water and sit still for at least 30 min. There is a need for more large-volume, cross-sectional, and controlled studies on this subject.

Disclosures

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Sakarya University Faculty of Medicine (Date: May 29, 2021; Decision No: E-71522473-050.01.04-32209-326).

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