

*Case report*

## **Doxycycline Hyclate-Induced Esophageal Injury Associated with Inappropriate Drug Use**

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### **SUMMARY**

**Introduction.** Drug-induced esophageal injuries are rare in clinical practice. Doxycycline is the most common antibiotic that can damage the esophagus.

**Case report.** We present a 26-year-old woman who visited a gastroenterologist because of difficulty swallowing and pain during swallowing. After laparoscopic treatment of endometriosis, the gynecologist prescribed her doxycycline capsules of 100 mg daily, in duration of five days, in order to prevent infection. The patient took a doxycycline hyclate capsules with a small amount of water, at night, before going to bed. After the third day of therapy, the patient developed difficulty swallowing, which progressed to odynophagia until the end of therapy. A performed endoscopy showed ulceration involving almost the entire circumference of the esophageal lumen in the middle part of the esophagus, which was suspected malignant neoplasm. Virological analyzes and tumor markers were within normal limits. Pathohistological examination of ulceration biopsy was without any signs of malignancy. After a month of proton pump inhibitors (PPIs) therapy, the patient was symptom free at the control examination, and the endoscopic finding was normal.

**Conclusion.** It is difficult to distinguish endoscopically extensive doxycycline-induced esophageal ulcerations caused by esophageal cancer. In addition, the pathological finding is not specific. The anamnesis of inadequate use of the drug is important and all patients taking doxycycline must be given detailed instructions about the appropriate administration methods.

**Keywords:** doxycycline, esophagus, ulcer, endoscopy

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## INTRODUCTION

Drug-induced esophageal injuries are rare in clinical practice. However, about 100 types of medications that can cause esophageal injuries have been described in the reference literature (1). Doxycycline is the most common antibiotic that can damage the esophagus (2), especially in the mid-esophageal segment (3). Esophageal lesions caused by doxycycline mostly appear as mild esophagitis and sometimes as ulceration with a generally benign course. However, extensive ulcerations after doxycycline intake have been reported so far (4). It is difficult endoscopically to distinguish extensive doxycycline-induced esophageal ulcerations from esophageal cancer. A few cases of doxycycline-induced ulceration mimicking esophageal cancer have been described in the literature (2, 4).

Older people are more prone to drug-induced esophageal injuries as a result of decreased esophageal motility and saliva production, cardiac enlargement, and multiple drugs intake (1, 2). However, doxycycline-related esophageal injury frequently occurs in young women with no history of esophageal dysfunction. The reason is an incorrect intake of doxycycline with a small amount of water or just immediately before going to sleep (5, 6).

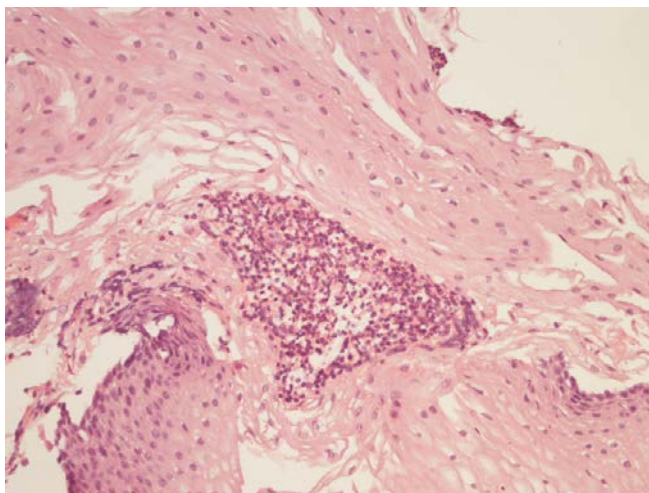
## CASE REPORT

We present a case of a recently treated 26-year-old woman who visited a gastroenterologist

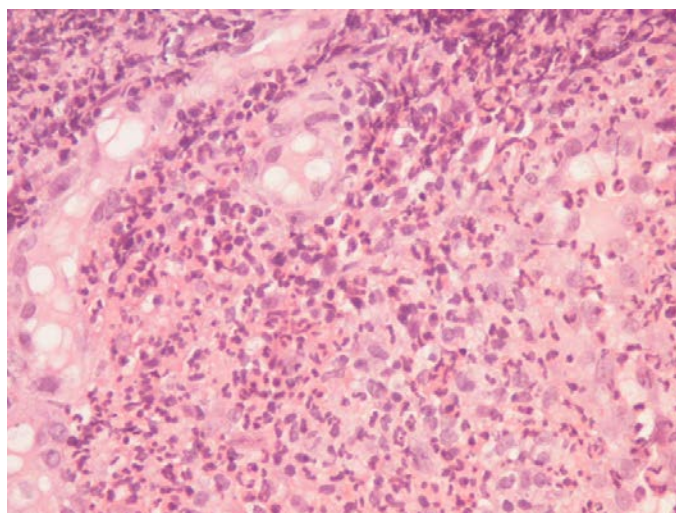
due to difficult and painful swallowing. Two weeks before, the patient underwent laparoscopic treatment for endometriosis due to infertility. The gynecologist prescribed her doxycycline hyclate capsules of 100 mg daily, in duration of five days, to prevent infection. The patient took a doxycycline capsules with a small amount of water, at night before going to bed. After the third day of therapy the patient developed difficulty swallowing, which progressed to odynophagia until the end of therapy. Physical examination, blood count and laboratory analysis were within normal limits. Proximal endoscopy showed ulceration involving almost the entire circumference of the esophageal lumen (Figure 1) in the middle part of the esophagus, suspected of malignant neoplasm. Cold and liquid diet and proton pump inhibitors (PPIs) two times a day were prescribed. Virological analyzes were performed since viral esophagitis gives a similar clinical and endoscopic picture. Anti-herpes simplex virus antibodies, anti-varicella-zoster virus antibody and anti-cytomegalo virus antibody were negative. Due to an endoscopic finding similar to esophageal cancer, tumour markers were checked. The levels of the carcinoembryonic antigen (CEA), squamous cell cancer antigen (SCC-Ag), CA 19-9, CA 125 were within normal limits. Pathohistological examination of ulceration biopsy specimens stained with standard haematoxylin-eosin (HE) indicated squamous epithelium with mixed inflammatory infiltrate, granulation tissue with numerous neutrophils and eosino-



**Figure 1.** Endoscopic appearance of the ulcer at the level of the mid-esophagus. An upper endoscopic examination revealed deep ulceration at the level of the mid-esophagus



**Figure 2.** *Squamous epithelium with inflammatory infiltrate (HE x 100)*



**Figure 3.** *Granulation tissue with numerous neutrophils and eosinophilic leukocytes (HE x 200)*

philic leukocytes, without any signs of malignancy (Figure 2 and 3).

After a month of PPIs therapy at the control examination, the patient was symptom free, and the endoscopic finding was within normal limits.

## DISCUSSION

Approximately 100 types of medications are reported to cause esophageal injuries (2). Drug-induced esophageal injuries are classified by their etiology into four categories: (I)—injury resulting from acidic antibiotics; (II)—chemical esophagitis caused by bisphosphonates such as alendronate; (III)—hyperosmotic injury caused by potassium chloride or quinidine, and (IV)—distal esophagitis associated

with non-steroidal anti-inflammatory drugs in patients with gastroesophageal reflux disease (5). Tetracyclines are a group of bacteriostatic antibiotics that provide a broad-spectrum of activity against both Gram-positive and Gram-negative infections (7). Doxycycline hyclate is the most common antibiotic that can damage the esophagus—it contributed to 27% of all cases reported in the world literature (6). A frequent use of doxycycline hyclate capsules cause more damage to esophageal epithelium than the same drug taken in tablets. This is also more common with the use of doxycycline hyclate compared to doxycycline monohydrate (8).

The mechanism of esophageal mucosal injury may be explained by doxycycline acidic effect, gelatinous sticky capsules, increased mucosal concen-

trations and intracellular toxicity (1, 9, 10). Also, dissolved doxycycline molecules can cause an inhibition of protein synthesis, which further leads to esophageal epithelial injuries, such as ulcers (11, 12). Endoscopy is considered as a method of choice for detecting drug induced esophageal injuries. Doxycycline-induced esophageal ulceration varied in size, depth, and number. Those are usually discrete, confluent, linearbroad band-formed and butterfly-shaped ulcers partially covered with pseudomembranes (1). Doxycycline hyclate tends to cause the damage in mid-esophageal segment in 66% of cases (3, 6). There has been reported one case of doxycycline-induced esophageal ulcers and tissue fragility mimicking esophageal cancer simultaneously in the lower and mid-esophageal segment (4). Extensive ulcerations may cause endoscopists to suspect esophageal cancer and may be the reason for many additional analyses. In such cases, it is necessary to exclude esophageal carcinoma by histology. Pathological findings on endoscopic biopsies specimens are not specific.

We used the Naranjo probability scale, which can indicate a probable adverse drug reaction (13). The score was 8, which is indicative of probable adverse drug reaction. The adverse effect associated with doxycycline treatment may contribute to poor infection treatment outcomes and development of bacterial resistance.

All patients taking doxycycline must be given detailed instructions about the adequate medication administration to prevent esophageal injury. It is recommended to swallow doxycycline capsule whole, with at least 100 ml of water, while sitting or standing (upright for at least 90 seconds after swallowing). Doxycycline is best taken in the morning, if

possible, or at least one hour before bedtime. It is important that the patient remain in the upright position for at least 30 minutes after taking doxycycline to prevent the irritation of the throat and esophagus. Recommendation is to substitute doxycycline monohydrate for doxycycline hyclate to prevent irritation of esophagus and start taking a PPI, which can be helpful in blocking the acid that can cause further irritation and prevent healing.

## CONCLUSION

We presented a case of an uncommon doxycycline hyclate-induced extensive esophageal ulceration mimicking esophageal cancer. Esophageal injury was serious and adverse effect was caused by inappropriate use of doxycycline. Therefore, it is important that all patients taking doxycycline must be given detailed instructions about the appropriate administration methods and their adherence to prescribed regimens. Doxycycline monohydrate has an advantage over doxycycline hyclate in the prevention of irritation of the esophagus.

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## Conflict of interest

The authors declare that they did not have any competing interest.

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## Oštećenje jednjaka izazvano neadekvatnom upotrebom doksiciklin-hiklata

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### SAŽETAK

**Uvod.** Oštećenja jednjaka izazvana lekovima retka su u kliničkoj praksi. Antibiotik koji najčešće može dovesti do oštećenja jednjaka jeste doksiciklin.

**Prikaz slučaja.** U ovom radu je predstavljen slučaj dvadesetšestogodišnje žene koja se javila gastroenterologu zbog otežanog gutanja i bolova pri gutanju. Nakon laparoskopskog lečenja endometrioze ginekolog joj je propisao terapiju kapsulama doksiciklina od 100 mg dnevno u trajanju od pet dana, kako bi se sprečila pojava infekcije. Bolesnica je uzimala kapsule doksiciklin-hiklata sa malom količinom vode uveče pre spavanja. Posle trećeg dana terapije došlo je do pojave otežanog gutanja, koje je do kraja terapije prešlo u odinofagiju. Prilikom endoskopije uočena je ulceracija koja je zahvatala skoro čitav lumen srednjeg dela jednjaka; sumnjalo se da je reč o malignoj neoplazmi. Virusološke analize i tumor markeri bili su u granicama normale. Patohistološki pregled biopsije ulceracije nije pokazao znakove maligniteta. Nakon mesec dana terapije inhibitorima protonske pumpe (IPP), bolesnica na kontrolnom pregledu nije pokazivala nikakve simptome, a endoskopski nalaz je bio normalan.

**Zaključak.** Endoskopski je teško razlikovati ekstenzivne ulceracije jednjaka izazvane doksiciklinom od maligne neoplazme jednjaka. Takođe, patološki nalaz nije specifičan. Veoma je važna anamneza o neadekvatnoj upotrebi leka. Svim bolesnicima koji uzimaju doksiciklin treba dati detaljna uputstva o odgovarajućem načinu primene leka.

**Ključne reči:** doksiciklin, jednjak, ulceracija, endoskopija