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Drug-induced esophagitis: Incidence, clinical and endoscopic findings, and management

İlaca bağlı özofajit: İnsidans, klinik ve endoskopik bulgular ve yönetimi

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Background and Aims: *Drug-induced esophagitis is a rare condition, which presents with varying severity in terms of clinical and gastroscopic findings. This study aimed to investigate the incidence, clinical and endoscopic findings, and management of the disease in a prospective 1-year follow-up period.* ***Materials and Methods:*** *Overall, 4185 patients underwent esophagogastroduodenoscopy at the Endoscopy Unit of Erzurum Education and Research Hospital between February 2010 and February 2011. Among these, the patients diagnosed with drug-induced esophagitis were followed up prospectively.* ***Results:*** *Among patients who underwent esophagogastroduodenoscopy, 1926 (46%) were males with a mean age of 47.8±18.1 years (range, 12–100 years). In total, 760 patients (18%) were diagnosed with esophagitis, of which five had drug-induced esophagitis (0.012% of gastroscopies, 0.65% of esophagitis). All patients presented with symptoms of retrosternal pain, odynophagia, and dysphagia. Four patients were young women, whereas the remaining patient was an elderly man; based on the medical history and esophagogastroduodenoscopy findings, patients diagnosed with esophagitis were using doxycycline, tetracycline, and tramadol hydrochloride capsules. Drugs that were considered to be the causative agents of esophagitis were discontinued, and proton pump inhibitors were administered parenterally or orally. The patients recovered without any complications.* ***Conclusion:*** *Drug-induced esophagitis is considered to be a rare condition, presenting with varying esophagogastroduodenoscopy findings and severe esophagitis in some cases. Discontinuing the causative agent and administering proton pump inhibitors are sufficient to manage the condition.*

Anahtar kelimeler: *Drug-induced esophagitis, incidence, treatment*

Giriş ve Amaç: *İlaca bağlı özofajit nadir görülen bir antite olup, değişik derecede klinik ve özofagogastroduodenoskopik bulgularla prezente olur. Bu çalışmada bir yıllık periodda görülme sıklığı, klinik ve gastroskopik özelliklerin incelenmesi amaçlanmıştır.* ***Gereç ve Yöntem:*** *Şubat 2010-Şubat 2011 yılları arasında Erzurum Eğitim ve Araştırma Hastanesinde gastroskopisi yapılan 4185 hastada, ilaca bağlı özofajit saptanan hastalar prospektif olarak takip edildi.* ***Bulgular:*** *Özofagogastroduodenoskopi yapılan hastaların yaş ortalaması 47.8±18.1 (dağılım 12-100) yaş olup, 1926 (%46)'sı erkekti. Hastaların 760 tanesinde (%18) özofajit saptandı. Hastaların 5 tanesinde (özofagogastroduodonoskopi yapılanların %0.012'si, özofajitlerin %0.65'i) ilaca bağlı özofajit tesbit edildi. Tüm hastaların retrosternal ağrı, disfaji ve odinofaji yakınmaları vardı. Bu hastaların 4 tanesi genç kadın, 1 tanesi yaşlı erkek olup, hastalara doksisiklin, tetrasiklin ve tramodol hidroklorür alım hikayeleri ve gastroskopi bulguları ile tanı konuldu. Tanı konulduktan sonra sebep olan ilaçlar kesilerek, enteral veya parenteral proton pompa inhibitörü başlandı. Takiplerde hiçbir hastada komplikasyon gelişmedi.* ***Sonuç:*** *İlaca bağlı özofajit sık görülen biri klinik antite olmayıp, hastalar değişik derecelerde özofagogastroduodenoskopik bulgularla, bazen ciddi özofajitle prezente olur. Sebep olan ilacın kesilmesi ve proton pompa inhibitörü tedavisi yeterli olmaktadır.*

Keywords: *İlaca bağlı özofajit, insidans, tedavi*

INTRODUCTION

Since 1970, >650 cases of drug-induced esophagitis caused by >30 drugs were reported worldwide. Approximately 50% of causative agents include tetracycline, doxycycline, and clindamycin (1-6). Esophageal lacerations are observed 22-fold more commonly among patients using capsules than in those using tablets because capsule formulations show easier adherence to the esophageal surface (7). In literature, numerous esophagitis cases caused by tetracycline and doxycycline use have been reported (7-11). No cases of tramadol-induced esophagitis have been reported in literature.

Drug-induced esophagitis is a rare condition (12), which presents with varying severity in terms of clinical, endoscopic, and histopathological findings (13). The most common symptoms are retrosternal pain, dysphagia, and odynophagia (9,12). This study aimed to investigate the incidence, clinical and endoscopic findings, and management of esophagitis in patients referred to the Endoscopy Unit of Erzurum Education and Research Hospital in a 1-year progressive follow-up period.

MATERIALS and METHODS

Patients referred to the Endoscopy Unit of Erzurum Regional Education and Research Hospital underwent esophagogastroduodenoscopy (EGD) between February 2010 and February 2011, forwarded from emergency and normal outpatient units, other outpatient units and wards, and other hospitals in Erzurum and peripheral hospitals. Endoscopic evaluations were performed for all reasons, most frequently for dyspepsia

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followed by reflux, hematemesis, melena, malignity, or anemia. Accordingly, patients diagnosed with drug-induced esophagitis were determined and prospectively followed up.

The procedure was performed by experienced gastroenterologists using Fujinon video endoscopes. During the procedure, the esophagus, Z line, cardia, fundus, corpus, antrum, pylori, bulbus, and second segment of the duodenum were evaluated.

The procedure was performed after solid food and fluid restriction for 10 and 5 h, respectively. *Xylocaine* was used as premedication. No sedation was implemented during the procedure.

Endoscopic staging of esophagitis was based on Los Angeles (LA) classification (14).

The SPSS 13 statistical program was utilized for statistical analysis. Quantitative variables were presented as mean±standard deviation (SD).

RESULTS

Between February 2010 and February 2011, 4185 patients underwent EGD in the Endoscopy Unit of Erzurum Regional Education and Research Hospital; of these, 1926 patients were males (46%) with a mean age of 47.8±18.1 years (range, 12–100 years). In total, 760 patients (18%) were diagnosed with esophagitis, with 5 cases of drug-induced esophagitis (0.012% of all patients, 0.65% of esophagitis cases). Common symptoms observed in all patients were retrosternal pain, odynophagia, and dysphagia.

Four patients diagnosed with drug-induced esophagitis were females (80%), and the remaining patient was male, with a mean age of 35.4±18.24 years (range 20–67 years). LA grade D esophagitis was observed in three patients (60%), whereas LA grade B was detected in two patients (40%).

Causative agents were doxycycline in 2 patients, tetracycline in two patients, and tramadol HCl in one patient. Drugs that were considered to be causative agents for esophagitis were discontinued followed by appropriate fluid–electrolyte treatment and parenteral or oral proton pump inhibitor (PPI) administration, according to disease severity. Improvement of symptoms in patients was observed in 3–10 days, and no complications were observed in any patient. The last patient was lost to clinical follow-up because of transfer to another hospital. Clinical and endoscopic findings of patients were as follows:

Case 1

A 30-year-old female patient was referred to our outpatient clinic with complaints of retrosternal pain, dysphagia, and odynophagia; EGD evaluation revealed severe esophagitis with denudation (LA grade D), beginning at 30 cm from the incisors and extending to the Z line (38 cm), surrounding almost the entire lumen with patchy necrosis and ulcerations with a diameter of approximately 4×8 cm (Figure 1). Except for erythema, no significant characteristic was observed in the corpus and antrum. Investigation regarding drug history revealed tetracycline use for 2 weeks at a dose of 4×500 mg as treatment for pelvic inflammatory disease; furthermore, the patient stated that she ingested the drug without any water. She was hospitalized; oral intake was discontinued, and antacid (esomeprazole 40 mg 2×1 IV, alginic acid 6×20 ml) and fluid–electrolyte treatment was initiated. Upon improvement of symptoms, oral intake was rearranged and oral treatment was initiated; she was discharged and requested to visit for follow-up.

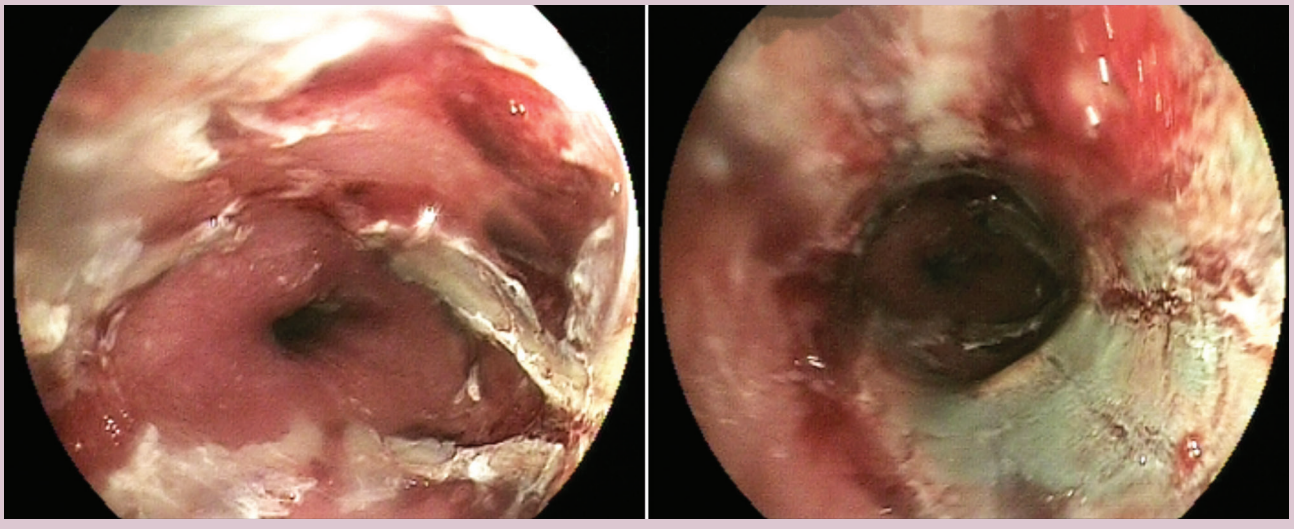

Figure 1. Tetracycline-induced esophagitis (Case 1, proximal–distal)

Case 2

A 28-year-old female patient was referred to our outpatient clinic with complaints of retrosternal pain, dysphagia, and odynophagia; EGD revealed esophagitis beginning at 28 cm from the incisors and extending through 3–4 cm of the segment, exhibiting erosive lesions of 0.3–0.6 cm, with a clear surface and perforated appearance (LA grade B; Figure 2). Millimetric erosions were found in the corpus and antrum. Drug history of the patient revealed tetracycline use for 3–4 days as treatment for urethritis at 4×500 mg. Tetracycline was discontinued, and treatment with oral PPI (esomeprazole 40 mg 1×1) and alginic acid 4×10 ml was initiated; she was followed up as an outpatient through regular visits.

Case 3

A 20-year-old female patient was referred to our outpatient clinic with symptoms of retrosternal pain, dysphagia, and odynophagia; upon EGD evaluation, esophagitis was detected, beginning at 26–30 cm from the incisors and extending through approximately 4 segments with superficially ulcerated, erosive lesions with a diameter of 0.4–0.8 cm (LA grade B; Figure 3). Hyperemia, edema, and nodular appearance were observed in the fundus, corpus, and antrum. Drug history of the patient revealed doxycycline capsule use for 7 days as treatment for acne at a dose of 1×100 mg; she mentioned that the drug was occasionally ingested without water, and doxycycline was discontinued 3 days prior to admission. She was

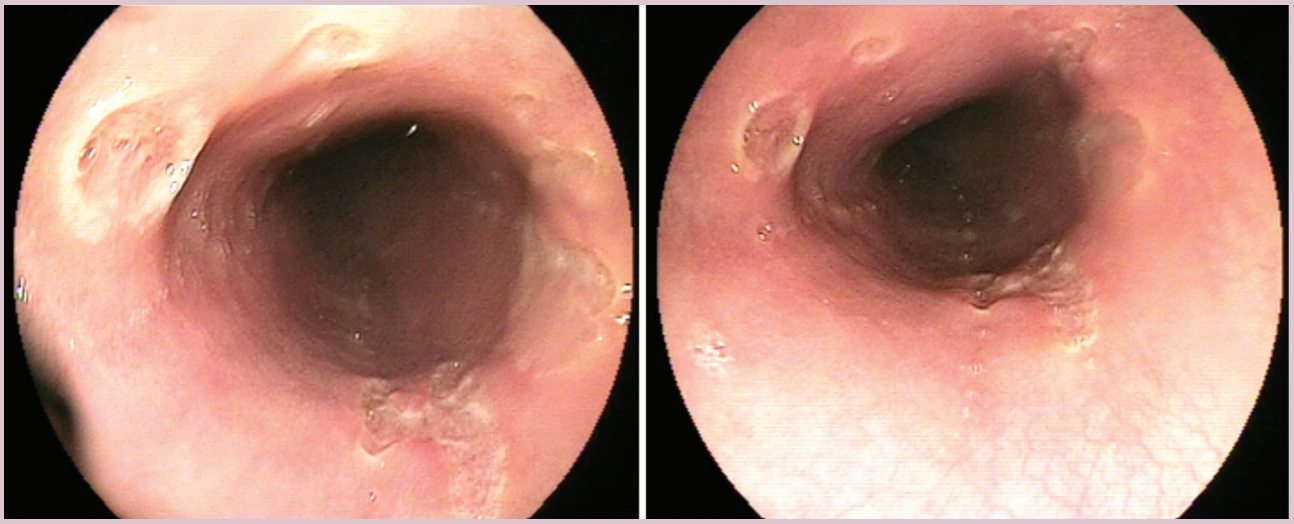

Figure 2. Tetracycline-induced esophagitis (Case 2)

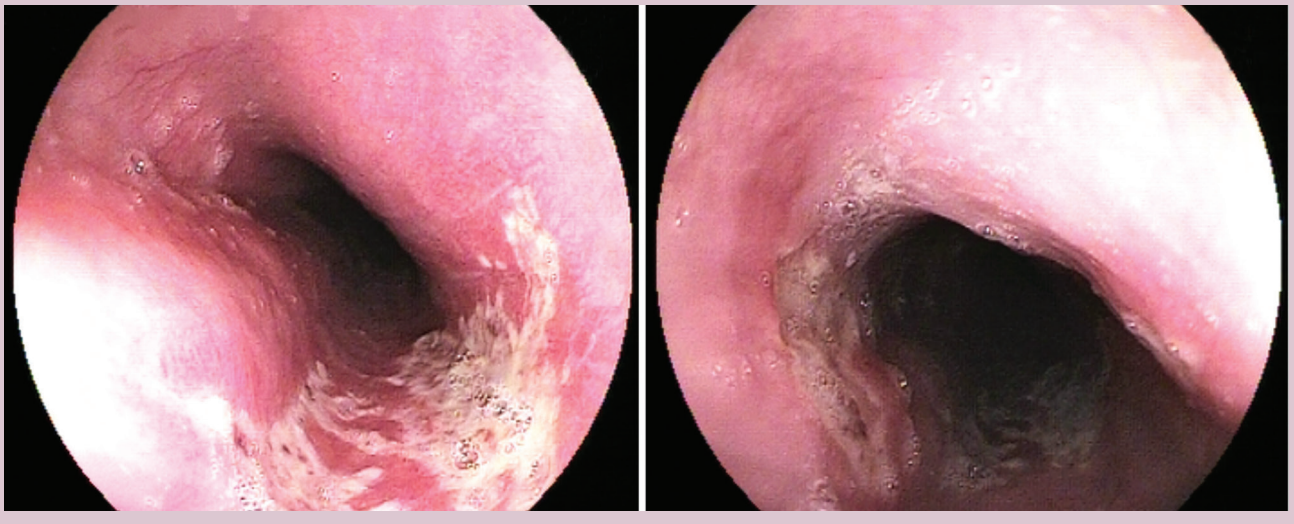

Figure 3. Doxycycline-induced esophagitis (Case 3)

advised against reinitiating doxycycline, and she was treated with oral PPI (esomeprazole 40 mg 1×1) and alginic acid 4 × 10 ml; she was followed up as an outpatient through regular visits.

Case 4

Similarly, a 32-year-old female patient was referred to outpatient clinic with symptoms of retrosternal pain, dysphagia, and odynophagia; EGD revealed esophagitis beginning at 23–30 cm from the incisors and extending through approximately 4 cm along the segment with superficially ulcerated, erosive, and hemorrhagic lesions; the first lesion covered two-third of the lumen, and the second one surrounded the lumen with a diameter of 1.5–2 cm (LA grade D; Figure 4). Hyperemia and edema were detected in the antrum, and food residues were detected in the lumen. The patient mentioned that she used doxycycline capsules for 1 month as treatment for acne at a dose of 1×100 mg, occasionally ingesting the drug without water, and discontinued treatment 5 days prior to admission. At referral, she was not using doxycycline. Treatment with oral PPI (esomeprazole 40 mg 1×1) and alginic acid 4×10 ml was initiated, and she was followed up as an outpatient through regular visits.

Case 5

A 67-year-old male patient, hospitalized at Chest Diseases Hospital with a diagnosis of lung cancer, was referred to our clinic for EGD evaluation because of symptoms of retrosternal

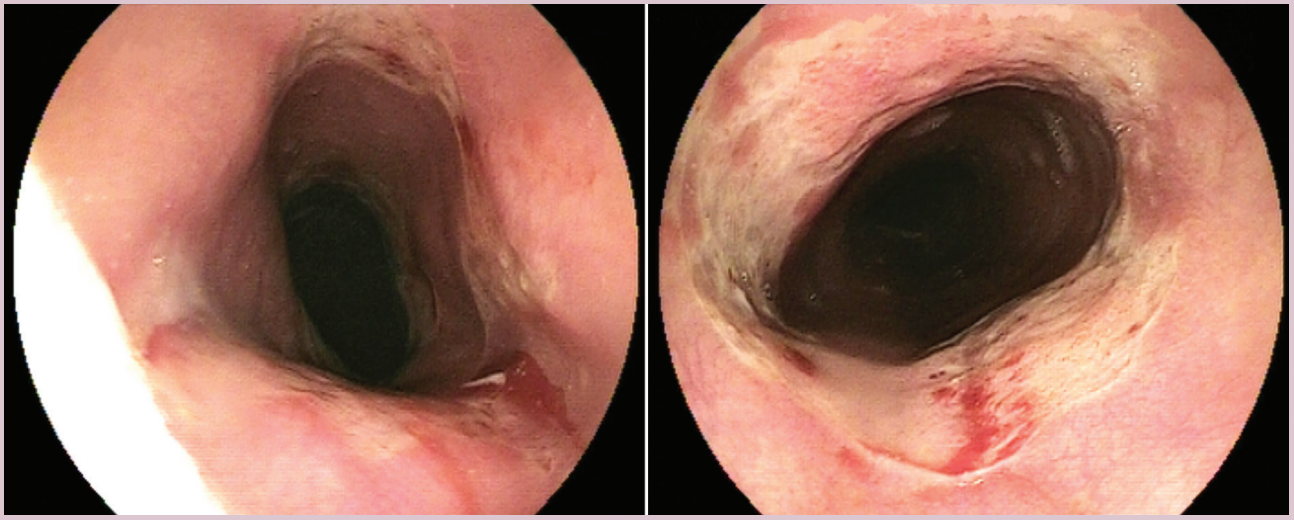

Figure 4. Doxycycline-induced esophagitis (Case 4)

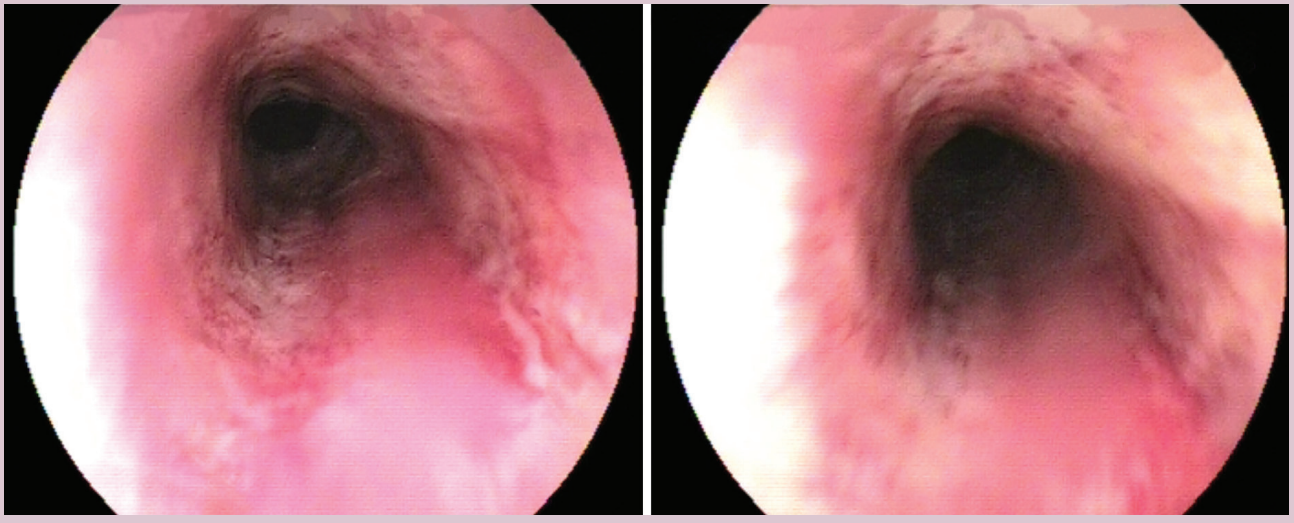

Figure 5. Tramadol HCl-induced esophagitis (Case 5)

pain, dysphagia, and odynophagia. EGD revealed severe ulcerated and hyperemic esophagitis, beginning at 28 cm from the incisors and extending to 32 cm, surrounding the entire lumen and causing mild stenosis in a segment of 4 cm (LA grade D; Figure 5). Erosions were detected in the corpus and antrum. Drug history revealed irregular use of analgesic tramadol 50-mg capsules for 2 months. He was advised to discontinue the drug, and antacid (esomeprazole 40 mg 2 × 1 IV, alginic acid 6 × 20 ml) and fluid–electrolyte treatment were recommended in the hospital where he was admitted. However, the patient was lost to follow-up, with no information regarding disease progression.

DISCUSSION

In literature, the major causative agents of esophageal injuries have been identified to be tetracycline, doxycycline, and clindamycin; however, frequently used drugs such as other anti-inflammatory agents, alendronate, iron sulfate, dabigatran, and vitamin C were reported to cause similar damage (6,8,9,12,15). Telithromycin was reported to cause chemotherapy-induced esophagitis in rare cases (16,17). In this study, the causative agent was detected to be tetracycline in two cases, doxycycline in two cases, and tramadol HCl in one case. No case of esophagitis induced by tramadol HCl was identified in literature.

Numerous cases of esophagitis caused by doxycycline and tetracycline have been reported in literature, with more cases caused by doxycycline use than by tetracycline use (7-11). Among nearly 1000 cases of drug-induced esophagitis in literature, approximately one-fourth of the cases have been reported to be caused by doxycycline (10). Furthermore, pediatric cases of doxycycline-induced esophagitis have been reported (18). In our study, two cases were caused by doxycycline, and two cases were caused by tetracycline.

In a French trial evaluating 81 spontaneous esophageal injuries caused by tetracycline use between 1985 and 1992, the mean age was 29±13 years, with 73% of patients being females (19). In our patients, the mean age was 35 years, and 80% of patients were females. A relatively higher mean age was associated with the elderly male population, whereas other cases involved young female patients. This can be because tetracycline and doxycycline are frequently used as treatment for genital infections and acne.

Factors prolonging the duration of drug contact with the mucosa while passing through the esophagus, such as ingesting the drug with insufficient amount of water and entering into supine position immediately after ingesting the drug, result in serious injuries in the esophagus (2). Detailed investigation regarding the cases revealed history of ingesting doxycycline and tetracycline with insufficient or no water in three cases. Drug-induced esophagitis may be prevented by implementing simple instructional methods such as educating the patient regarding how and when to ingest the drugs.

Drug-induced esophageal injuries were reported to localize in one-third of the mid-esophagus in most cases (9,14). In a trial investigating the localization of tetracycline- and doxycycline-induced esophageal injuries, doxycycline was determined to cause injuries in the mid-esophagus in most cases, whereas tetracycline was detected to cause distal esophagitis in several cases (20). In the current study, the first patient, who was identified to have a more serious case, had distal esophagitis caused by tetracycline use. In contrast, lesions observed in the other four patients were localized in the mid-esophagus.

In literature, serious drug-induced complications and deaths were associated with esophageal injury caused by potassium ingestion (19). Most patients suffering from drug-induced esophageal injury recover within several days without any intervention. Therefore, accurate diagnosis and discontinuation of the causative agent are required for the optimal management of these cases (1). In literature, the patients who experienced symptoms were reported to recover in 2–7 days, with improvement of endoscopic findings in 3–4 weeks (9). Appropriate management of this condition involves the discontinuation of the causative drug, followed by administration of sucralfate and antacids (2). Similarly, on diagnosis of drug-induced esophagitis in the current cases, causative agents were discontinued; clinical improvement was observed in 3–10 days following treatment with oral or parenteral PPIs and alginic acid, and no complications were observed in any patient. Because recovery from the symptoms was reported in all patients, no further endoscopic control was required.

Drug-induced esophagitis is a rare condition, with an annual EGD incidence of approximately one per thousand among the total number of cases and approximately six per thousand among the esophagitis cases in our study. Endoscopically, the disease may present with various EGD findings and severe esophagitis in some cases. In patients with symptoms of retrosternal pain, dysphagia, and odynophagia, particularly among young women, tetracycline- and doxycycline-induced esophagitis should be considered and history of drug use should be thoroughly investigated. Although rare, clinicians must consider that drug-induced esophagitis may be detected in old age. Following diagnosis, discontinuation of the causative drug and symptomatic treatment are sufficient for managing these cases.

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