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A case report of doxycycline induced esophageal and gasric ulcer

Doksisikline bağlı gelişen özofageal ve gastrik ülser gelişen bir olgu sunumu

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It is well-established that various drugs can induce esophageal and gastric mucosal injury. Generally neither motility disorder nor an anatomical stricture is found in such cases and the cause of mucosal injury is usually found to be inadequate fluid intake with medicine or consumption just prior to bedtime. Athough there are some case reports of doxycycline induced esophageal mucosal injury, doxycycline induced gastric ulcer has been reported only once in the literature.

In this case report, a 33 year old female patient who had been prescribed doxycycline for pelvic inflammatory disease is presented. She was admitted with retrosternal and epigastric pain and odynophagia, which had begun after taking the second oral dose of the drug. Endoscopic examination showed ulcers in the mid esophagus and fundus of the stomach. Histologic findings supported a drug induced etiology in these ulcers.

This is only the second case in the literature where gastric ulcer has been caused by doxycycline.

Key words: Doxycycline, pill-induced mucosal damage, esophagogastric ulcer.

İlaçların özofagus ve midede mukozal hasara yol açabildiği bilinmektedir. Olgularda genellikle motilite bozukluğu veya anatomik bir darlık saptanmamakta, ilacın yeterli miktarda suyla alınmamış olması ve/veya ilacın alındıktan hemen sonra yatılması mukozal hasarın oluşumundan sorumlu olmaktadır. İlaçlar arasında doksisikline bağlı özofageal mukozal hasar oluşan olgularla karşılaşılmaktadır. Ancak doksisiklinin neden olduğu gastrik ülser gelişimi literatürde bugüne dek yalnızca bir olguda bildirilmiştir.

Burada pelvik inflamatuar hastalık nedeniyle doksisiklin tedavisi başlanmış 33 yaşındaki bir kadın hasta sunulmaktadır. İlacın ikinci oral dozundan sonra retrosternal ağrı, epigastrik ağrı ve odinofaji semptomlarıyla başvuran hastanın endoskopik incelemesinde midözofagusta ve mide fundusunda, ilaca bağlı olabileceğini destekleyecek histolojik bulgularıyla ülserler saptanmıştır.

Doksisikline bağlı gastrik ülser gelişimi özelliğiyle bu olgu, bilgilerimize göre literatürde bildirilen ikinci olgudur.

Anahtar kelimeler: Doksisiklin, ilaca bağlı mukozal hasar, özofagogastrik ülser.

INTRODUCTION

It is well established that various drugs can cause esophageal mucosal injury, with tetracycline, doxycycline, quinidine, potassium chloride and emepronium bromide accounting for 90% of reported cases (1, 2). Severity of injury ranges from mild inflammatory changes to severe ulceration, perforation or stricture formation. In contrast to drug induced esophageal injury, drug induced gastric injury has not been well characterized. In this report a patient who developed esophageal and gastric ulcers after taking doxycycline for pelvic inflammatory disease (PID) is presented.

CASE REPORT

The patient was a 33-year old woman who had been prescribed doxycyline 100 mg b.i.d. for PID by a gynecologist. Her past medical history was not noteworthy except for a few dyspeptic symptoms. She was a nonsmoker and denied using alcohol, aspirin or non-steroidal anti inflammatory drugs (NSAIDs). She took her first dose after dinner with a glass of water and went to bed five or six hours later. In the morning she woke up without any symptoms and took the second oral dose with a glass of water after breakfast. Soon after taking the drug she went to bed again. About one hour later, she woke with severe retrosternal

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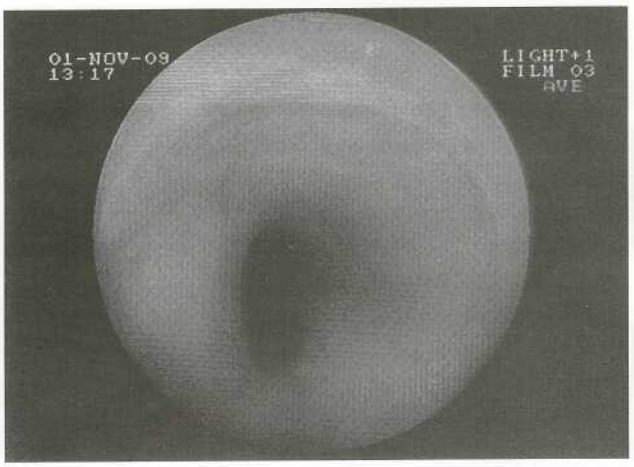

Figure 1. Doxycycline induced esophageal ulcer with a pili like membranous ring (In the mid-esophagus at the level of second physiologic narrowing, a 6-7 mm transversely oriented, fusiform ulcer is seen on the anterior wall of the esophagus). (arrows).

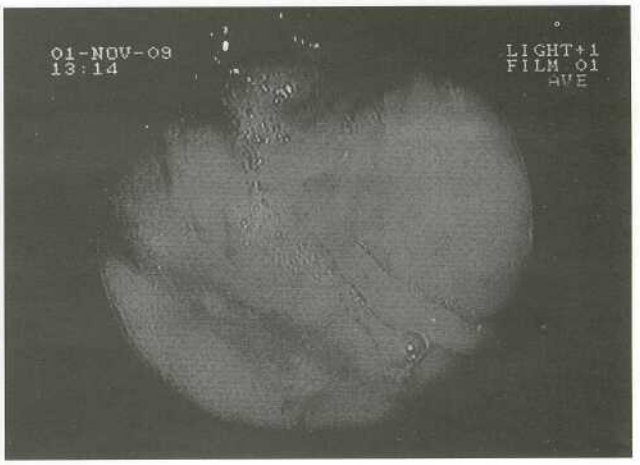

Figure 2. Doxycycline induced gastric ulcerations (There are two superficial ulcerations 4-5 mm in diameter lying together in the fundus, on an erythematous and oedematous mucosa just at the level of gastric pool of great curvatura). (arrows).

pain, which was radiating to her back. A serious odynophagia started and she experienced pain even while swallowing her own saliva. After a few hours epigastric pain, which was not as severe as the retrosternal pain, began. She thought that her symptoms were caused by the doxycycline and stopped taking it after the second dose.

In spite of taking famotidine 40 mg/day, liquid antacids and anticholinergics, she was able to take only liquids, and was admitted to our unit on the seventh day of her symptoms. An esophagogastroduodenoscopic examination was performed and a 6-7 mm transversely oriented, fusiform ulcer was seen on the anterior wall of the mid-esophagus (Figure 1), about 28-cm from the incisor teeth, at the level of second physiologic narrowing, where aortic pulsation was seen. The edges of the ulcer were elevated and its base was smooth and white in colour. In addition, a pili like membranous ring about 1 mm in height, starting from one edge of the ulcer surrounding the esophagus circularly and ending at the other end, was seen. There were also two superficial ulcerations 4-5 mm in diameter lying together in the fundus, on an erythematous and oedematous mucosa just at the level of the gastric pool of great curvatura (Figure 2). Biopsies were taken from both the esophageal and gastric lesions. An obstructive esophageal lesion was not seen and hiatus hernia was not present. No other gastroduodenal lesion other than as described above was seen. Histologic examination of the biopsies taken from the esophageal and gastric lesions were reported as acute erosive esophagitis and acute erosive gastritis respectively. No H. pylori or fungus and tumor cells were seen (Figures 3 and 4). A double dose of proton-pump inhibitor together with liquid food was prescribed and her symptoms gradually disappeared within a 10 day period. Follow-up endoscopic examination after six weeks was normal.

DISCUSSION

Drug induced esophageal and gastric mucosal injury is uncommon but may result in considerable morbidity, depending on the severity of injury. Both drug and patient factors play a role in mucosal damage (3). Drug related factors that affect toxicity include the chemical nature of the drug, its solubility and its contact time with the mucosa. Pills coated with gelatinous material, like capsules, can stick to the esophageal mucosa, especially when taken with too little water (4). Esophageal motility disturbances, esophageal strictures and taking pills with little fluid or just before going to bed should be taken into consideration when evaluating the most common patient related factors. However, among the reported cases of pill-induced injury, the proportion of the patients having a motility disorder such as achalasia and scleroderma or an anatomical narrowing such as tumor or stricture is low (3). Esophageal damage mostly occurs at the aortic arch level or

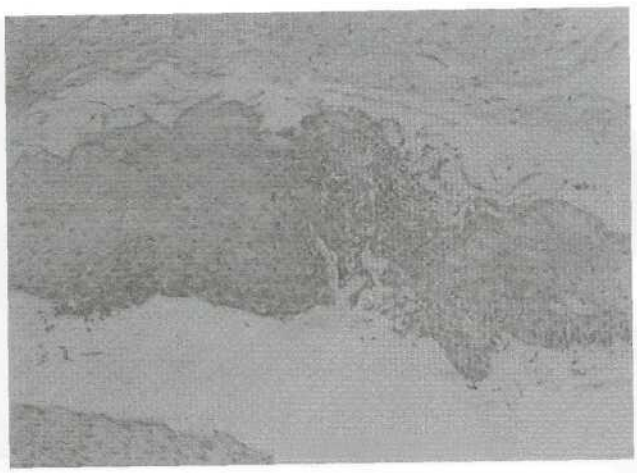

Figure 3. Epithelial destruction and dense polymorphonuclear leucocyte infiltration in the focal area of the surface epithelium (Hematoxylin & eosin X 100). (arrows)

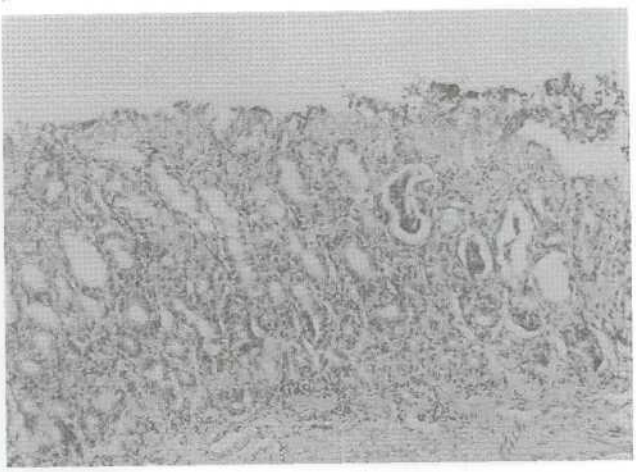

Figure 4. Figure 4: Loss of surface epithelium, fibrin and polymorphonuclear leucocyte accumulation in the fundic mucosa (Hematoxylin & eosin X 100).

above the lower esophageal sphincter, which are the physiological narrowings where the pills tend to stick (5). It may therefore be concluded that in drug induced esophagitis, taking high risk drugs with little water may predispose to the retention of the drug within the esophagus and facilitate the development of esophageal mucosal injury. Moreover, bedtime pill taking may favor retention of the pill within the esophagus, because in the supine position, effect of the gravity disappears and there is decreased salivation and swallowing during sleep, which favor pill retention.

The most common endoscopic finding is one to several discrete, clustered, shallow ulcers surrounded by normal mucosa. Ulcers are usually small but may be up to several centimeters in length. Sometimes the mucosa is focally inflamed but not ulcerated and fragments of pills may occasionally be observed near the ulcer. Deeper ulcers are occasionally encountered. Pill-induced ulcers penetrating into the mediastinum and major vessels have occasionally led to mediastinitis and exsanguinating hemorrhage respectively. In approximately 7% of reported cases, deep, circumferential ulceration results in fibrotic strictures that require dilation (3, 6).

The first step in the treatment of pill induced esophageal injury is discontinuation of the offending pill. It is also reasonable to provide empiric antireflux therapy to prevent exacerbation of the injury by acid reflux. Temporary relief of pain may be accomplished by having the patient swallow a topical anesthetic such as viscous lidocaine, but this approach is limited by possible systemic lidocaine toxicity. Severe odinophagia rarely requires parenteral hydration or, if prolonged, total parenteral nutrition. Pain subsides within days to weeks in most uncomplicated cases of pill-induced esophageal injury. Acute esophageal narrowing and dysphagia caused by inflammation and edema may resolve without esophageal bougienage, but in chronic fibrotic strictures, dilation is indicated. Esophageal perforation and hemorrhage are rare but are life-threatening complications that require immediate specific and aggressive treatment. The principles of therapy in pill-induced gastric injury do not differ from those of esophageal injury (6).

In our case the doxycycline was in capsule form. She had drunk enough water with the pill, but had gone to bed five-six hours after taking it. Thus, in the supine position, doxycycline, which is a capsule coated with gelatinous material, stuck to the mucosa at the physiological narrowing level within the thoracal esophagus. The capsule then dissolved and released the ulcerogenic drug, causing esophageal mucosal injury. About one hour later she had awoken with sharp retrosternal pain and had drunk a lot of water after standing up. It is likely that, with the help of water and an upright position, the pill then passed in to the stomach. The superficial nature of the esophageal ulcer suggests that the pill did not release all of its contents within the esophagus. The superficial

ulcers also seen on the large curvature of the fundus support this assessement that some of the pill contents caused the esophageal injury and the rest caused the gastric injury just at the place where gravity most favors. Development of epigastric pain within the same day can be evaluated as clinical evidence of drug induced gastric injury and the similarity of the histopathologic features of gastric and esophageal biopsies act as histologic evidence. In addition, anticholinergic drugs, taken by the patient for control of the pain, could increase gastric injury by slowing gastric emptying.

There are case reports of doxycycline induced esophageal mucosal injury (7 , 8, 9), but doxycycline induced gastric ulcer has been reported only once in the literature (10). To our knowledge, this is the second case report of doxycycline induced gastric ulcer.

In conclusion, drug induced gastric injury is a distinct clinical entity, which occurs in the proximal stomach at the location where the drug gravitates in a dependent manner after traversing the lower esophageal sphincter. It should be distinguished from gastric antral lesions of aspirin and other NSAIDs.

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