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Doxycycline-Induced Esophageal Ulcers: Two Cases Report

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1. Abstract

Drug-induced esophagitis or esophageal ulcers is considered when retrosternal chest pain or painful swallowing occurs after ingestion of a suspected drug. Various drugs have been reported to induce esophageal ulcers. Here we reported two female patients who presented with severe dysphagia and retrosternal chest pain, both with a history of doxycycline use. Esophagogastroduodenoscopy was performed and showed irregular ulcers in esophagus. Biopsies were performed and revealed inflamed granulation tissue and ulcers without infection and malignancy. Therefore, doxycycline-induced esophageal ulcer was diagnosed based on the clinicopathologic report and history of drug administration. Esophageal inflammation and ulcers were disappeared after 2-3 weeks of discontinuation of doxycycline. This study highlights a detrimental risk of doxycycline in inducing esophageal ulceration, and a preclinical precaution is warranted.

2. Introduction

Doxycycline, as a broad-spectrum antibiotic, has inhibitory effects on Staphylococcus aureus, Streptococcus, Salmonella, Brucella, Chlamydia, and Mycoplasma. Currently, doxycycline is commonly used for a combination therapy in acne and genital and urinary tract infections [1]. Reports of adverse reactions are not uncommon, including hepatotoxicity, teratogenicity, acute pancreatitis, and gastrointestinal discomfort [2-4]. Therefore, it is important to provide patients with guidance on proper medication administration to prevent these adverse consequences. In this report, we presented two cases of young women who developed esophageal ulcers due to improper use of doxycycline. This study has highlighted the importance of correct medication usage and the necessity of understanding its adverse reactions.

3. Descriptions

3.1. Case 1

A 33-year-old woman was admitted to the hospital with retrosternal pain with acid reflux and heartburn for 2 weeks. Two weeks ago, she experienced chest pain in the area behind the sternum without an apparent cause. The pain exacerbated after eating, accompanied by symptoms of gastric reflux and heartburn. She had also difficult swallowing and throat pain. Two weeks ago, the patient took doxycycline hyclate capsules to treat 'pelvic inflammatory disease'. In November 2019, the patient underwent a laparoscopic appendectomy at our hospital. There was no special personal or family history. Physical examination revealed no notable findings. During the baseline evaluation upon admission, the patient's blood pressure, pulse rate, and temperature were all within normal limits. During the physical examination, the patient's overall conditions were of moderate severity. There was no tenderness, rebound tenderness, or guarding in the abdomen. In the laboratory evaluation, the complete blood cell count analysis, biochemical values (e.g., liver function tests, kidney function tests, blood glucose, blood lipid profile), and autoantibody profiles (ANA, MPO, PR3, ANCA) were all within normal limits. Genetic screening for HLA-DQ2 and -DQ8, HLA-B*51, and HLA-B27 was

all normal. Serum antibodies against deamidated gliadin peptide, tissue transglutaminase, and endomysium were also negative. The initial gastroscopy revealed multiple longitudinal ulcers located at a distance of 34 cm from the incisors in the posterior wall of the esophagus (Figure 1A). Biopsies taken from the edges and center of the lesion demonstrated to be no evidence of malignant tumors or infectious causes but showed acute and chronic inflammation of the esophageal squamous epithelium (Figure 1C,1D). She was admitted for intravenous esomeprazole administration, oral rehabilitation new liquid intake, and sucralfate suspension gel application to relieve dysphagia. On the second day of treatment, her condition began to improve, and on the third day, her symptoms were completely alleviated. After starting to eat, there were no significant changes in her conditions. Two weeks later, a gastroscopy revealed an ulcer scar 34 cm from the incisors (Figure 1B), and she had no symptoms or signs during a 2-month follow-up period of observation.

3.2. Case 2

A 22-year-old woman presented with a 4-day history of vague retrosternal and epigastric pain. She was diagnosed with bacterial vaginosis 5 days ago, treated with oral doxycycline and cefadroxil tablets. Five days ago, after taking doxycycline and cefadroxil tablets orally, she experienced mild chest and upper abdominal pain, which was more pronounced during breathing and eating, and occasionally intensified. She stopped taking the medication, but the symptoms persisted. There was no acid reflux or heartburn. She denied experiencing vomiting, alterations in gastrointestinal transport, gastrointestinal bleeding, fever, or weight loss. The initial comprehensive blood test did not detect any anomalies, and the electrocardiogram did not indicate any ischemic changes in the heart. The gastroscopy revealed multiple ulcerative lesions (Figure 2A). Histopathology of the biopsy specimen revealed show acute and chronic inflammation of the squamous epithelial mucosa (Figure 2B,2C). We stopped doxycycline and started rehabilitation solution, lidocaine, and dexamethasone sodium oral preparations. She was able to tolerate liquids in 1 day and solids in 2 days, and her symptoms disappeared after 2 months of follow-up. We diagnosed her with severe doxycycline-induced esophagitis and advised her to avoid this medication further.

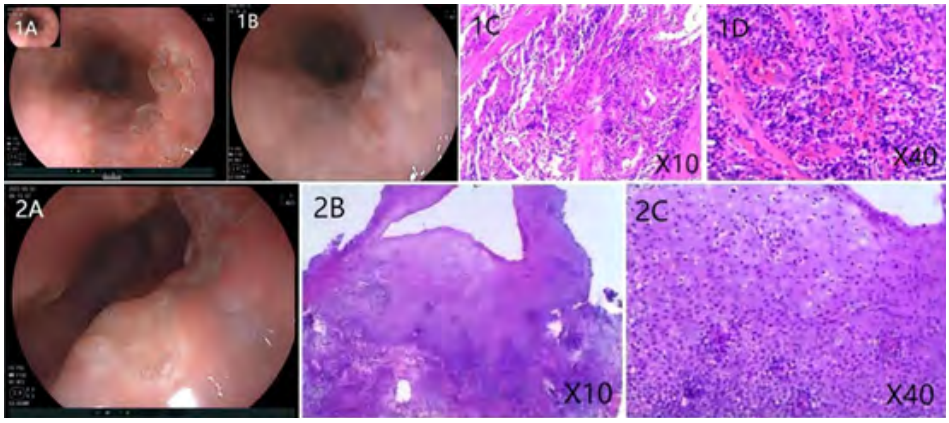

Figure 1A: shows multiple longitudinal ulcers with clear boundaries, brittle quality, and easy bleeding on the posterior wall of the esophagus 34 cm from the incisors.

Figure 1B: highlights the presence of ulcer scarring.

Figure 1C: (x10) and **1D**(x40) Hematoxylin and eosin staining show acute and chronic inflammation of the esophageal squamous epithelium.

Figure 2A: shows multiple ulcerative lesions of varying sizes were identified about 25cm from the incisors, with the larger ones measuring around 0.7*0.8cm in diameter. The ulcers were shallow and had a broad base with a small amount of white plaque visible on their surface. The surrounding mucosa was raised, and approximately three-quarters of the cavity was affected.

Figure 2B: (x10) and **2C**(x40) Hematoxylin and eosin staining show acute and chronic inflammation of the squamous epithelial mucosa.

4. Discussion

Drug-induced esophageal ulcers are esophageal mucosal injuries caused by the administration of routine doses of certain drugs. More than 100 drugs have been reported to induce esophageal disease, with an estimated annual incidence of 3.9 cases per 100,000 people [5]. Due to the limited clinical experience of medical professionals, misdiagnosis and underdiagnosis are common of esophageal ulcers, so it is critical to analyze the causes of esophageal ulcers.

The etiological analysis of drug-induced esophageal ulcers may be related to several factors, such as the nature of the drugs, esophageal factors, and individual adverse medication habits [6]. (1) Different qualities of pathogenic drugs have different mechanisms of incidence. Antibiotics and non-steroidal anti-inflammatory drugs, as well as antibacterial and anti-inflammatory agents, are the main types of drugs that cause direct esophageal injury. Some drugs have direct local toxicity to the esophageal mucosa, usually being corrosive (acidic or alkaline) or hypertonic, such as doxycycline and tetracycline. When corrosive drugs fail to descend smoothly and stay on the esophageal wall, and contact directly with the esophageal mucosa for a long time, it is easy to cause esophageal mucosal damage [7, 8]. Besides, other drugs, like potassium chloride, may cause mucosal dryness, damage

to blood vessels, esophageal injury, and if not detected in a timely manner, could lead to a high incidence of complications, such as esophageal stenosis, fatal bleeding, and invasion of the chest vessels. Different drug dosage forms can also have an impact, with capsules or tablets usually delaying when passing through the esophagus[9]. (2) Esophageal factors. In this report, the esophageal ulcers of two patients occurred in the middle section of the esophagus at a distance of 25-34 cm from the incisor teeth, which may be related to the physiological contraction of the aortic arch and left atrium of the esophageal lumen, delaying drug transport. Three physiological esophageal narrowings may also cause capsule drug adherence, leading to esophageal damage. Some esophageal motor disorders are induced by external esophageal diseases, such as Parkinson's disease and multiple sclerosis, which can cause the drug to remain in the esophagus and damage the esophageal mucosa [6, 10, 11]. (3) Improper medication methods are the main inducing factors, such as taking small amounts of water and lying on one's back after taking medication [12].

The typical symptoms of drug-induced esophageal ulcer are sudden pain behind the sternum, pain during swallowing, and difficulty swallowing. In severe cases, there may be gastrointestinal bleeding symptoms such as vomiting blood or black stools. Endoscopy examination is a commonly used method for diagnosis, and most lesions are located in the middle segment of the esophagus. Erosion or ulceration is the main pathological feature, and ulcers can be single or multiple, with varying depths and sizes. However, residual pill fragments and strictures are rare [8, 12, 13]. In clinical treatment, drug-induced esophagitis is an exclusionary diagnosis that needs to be distinguished from reflux esophagitis, coronary heart disease, esophageal Behcet's disease, esophageal Crohn's disease, eosinophilic esophagitis, and infectious esophagitis [14-16]. Therefore, gastroenterologists should strengthen their understanding of these diseases, carefully and comprehensively take medical history, and make reasonable and accurate diagnoses in a timely manner.

If drug-related esophageal inflammation and ulcers is diagnosed early and managed properly, such esophageal injury can be completely cured. Generally, symptoms improve within 2-7 days after the discontinuation of the medication. Symptomatic treatment with acid suppressants, H2 receptor antagonists, proton pump inhibitors, and sucralfate is implemented, and follow-up endoscopy after 2-3 weeks shows healing of the esophageal mucosa [17, 18].

In summary, the management of drug-induced esophagitis focuses on prevention. Physicians should strictly adhere to the indications and contraindications of drugs such as non-steroidal anti-inflammatory drugs and doxycycline when prescribing them to patients, reminding patients of the major adverse reactions of the drugs, such as the risk of drug-induced esophageal ulcers, and emphasizing the need for monitoring during medication. When sudden retrosternal pain occurs, the medication should be discontinued promptly, and immediate medical attention should be sought to avoid serious adverse consequences. It is important to strengthen medication guidance and promote knowledge of proper medication practices, such as avoiding taking medication at night or before bedtime, and taking medication with at least 100 ml of water and maintaining an upright position for one hour after taking the medication [5, 9]. For patients who have already developed drug-induced esophagitis, proactive treatment measures should be taken, including protecting the esophageal mucosa, relieving symptoms, and preventing complications.

5. Conclusion

The reported cases here demonstrate the importance of proper administration of antibiotics such as doxycycline. Differential diagnosis of upper gastrointestinal ulcerative lesions should include inappropriate use of antibiotics and other drugs. Albeit rare, physicians need to be aware of this type of adverse reaction, and preclinical precaution is warranted.

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