Mid-esophageal Ulceration and Candidiasis-associated Distal Esophagitis as Two Distinct Clinical Patterns of Tetracycline or Doxycycline-induced Esophageal Injury

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Background: Tetracyclines may cause esophageal injury.

Goals: The aims of this study are to describe 2 distinct clinical patterns of esophageal injury induced by tetracycline or its derivate doxycycline and to compare these patterns with respect to demographic, endoscopic, and clinical characteristics of the patients.

Study: Forty-eight patients with the diagnosis of doxycycline- or tetracycline-induced esophageal injury by endoscopy were analyzed retrospectively. The patients were considered in 2 groups according to the type and the location of esophageal lesions (Group A: mid-esophageal ulceration, n = 18; Group B: distal esophagitis, n = 30).

Results: Patients in Group A were significantly younger than in Group B ($P = 0.0014$). In Group A, 15 patients (83%) had single ulceration, 2 (11%) double, and 1 (6%) circumferential at the mid-esophagus. In Group B, all patients had multiple micro-ulcerations in the distal esophagus. Development of mid-esophageal ulceration was induced predominantly by doxycycline, whereas distal esophagitis was induced by tetracycline. The description of drug ingestion with little or no water by patients in Group A was significantly more frequent than in Group B (94% vs. 10%, $P < 0.001$). Associated medical and benign gastric diseases and esophageal candidiasis were significantly more frequent in Group B ($P = 0.006$, $P < 0.001$, $P < 0.001$, respectively). Prompt response to medical therapy was observed in both groups with no significant difference ($P = 0.093$).

Conclusions: The type of tetracyclines used by patients may give some clues to physicians on the pattern of esophageal injury because mid-esophageal ulceration seems to be more frequently associated with doxycycline and distal esophagitis with or without candidiasis with tetracycline.

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Drug-induced esophageal ulceration as a complication of pills was first described by Pemberton[1] in 1970 in a patient receiving oral potassium therapy. To date, numerous drugs have been reported to cause either esophagitis or esophageal ulceration. Potassium chloride, tetracyclines, emepronium bromide, quinidine, acetylsalicylic acid, ferrous sulfate, praxilane, clindamycin, captopril, alprenolol, ascorbic acid, and various steroidal and nonsteroidal anti-inflammatory drugs (NSAID) are the most commonly incriminated products.[2,3] Tetracyclines, first discovered by Duggar[4] in 1948, are broad-spectrum semisynthetic antibiotics derived from streptomyces species. Because aerobic and anaerobic gram-positive and gram-negative bacteria, chlamydiae, mycoplasms, rickettsiae, spirochetes, some protozoa, and mycobacteria are sensitive to tetracyclines,[5,6] they have been widely used in the treatment of gynecologic and urinary tract infections, especially for sexually-transmitted infections such as vaginitis and nongonococcal urethritis. They are also preferred in the management of dental infections and severe acne. Although using tetracyclines was no longer in demand in 1980s, since the recognition of their adverse effects and the rising number of available safer alternatives, the interest to many of the older antibiotics including tetracycline has been renewed following the appearance of new or emerging pathogens, the increase in tick-borne infections, and the global problem of antimicrobial resistance in recent years.[5] In parallel with the increased use of tetracyclines more cases with drug-induced esophagitis and esophageal ulceration have been reported recently.[7,8]

In the present report, 2 distinct clinical patterns of esophageal lesions; mid-esophageal ulceration and distal esophagitis induced by tetracycline or its derivate doxycycline were compared with respect to demographic features, details of medical background, endoscopic findings, histopathologic results, and

response to therapy. Possible mechanism of injury was discussed.

MATERIALS AND METHODS

Forty-eight patients who had the diagnosis of doxycycline- or tetracycline-induced esophagitis and esophageal ulceration at upper gastrointestinal endoscopy at the Marmara University Institute of Gastroenterology between January 1996 and December 2002 were analyzed retrospectively with respect to age, gender, indications for antibiotic therapy, period of drug usage prior to diagnosis, endoscopic findings, pattern of esophageal lesions, histopathologic results, associated esophageal candidiasis, associated medical diseases, previous gastric surgery, type of therapy, and outcomes. The patients were considered in 2 groups according to the type and the location of esophageal lesions (Group A: mid-esophageal ulceration, Group B: distal esophagitis).

Endoscopy and Histopathologic Evaluation

All upper gastrointestinal endoscopies were performed under sedation with intravenous midazolam (Dormicum, Roche, Istanbul, Turkey) and topical pharyngeal anesthesia with lidocaine 10% (Xylocain, Eczacibasi, Istanbul, Turkey). All esophageal ulcerations were biopsied and sampling biopsy was performed in patients who had esophagitis with or without candidiasis. The histopathologic slides were re-evaluated by the same pathologist (O.K.Y.).

Statistical Analysis

The Mann-Whitney *U* test was used to compare age, duration of drug usage prior to diagnosis, and interval until symptom relief following therapy. χ^2 test was used to analyze the distribution of gender and Fisher exact test for the analysis of drugs causing 2 distinct patterns of esophageal injury, associated medical diseases, ongoing steroid therapy, previous gastric surgery, drug ingestion habit with little or no water, associated esophageal candidiasis, associated benign gastric diseases, and the need for hospitalization. A result was considered statistically significant if the *P* value was less than or equal to an alpha-level of 0.05.

TABLE 1. Indications of Doxycycline or Tetracycline Usage in Both Groups

Indications	Group A n (%)	Group B n (%)
Vaginitis	8 (45)	10 (33)
Nongonococcal urethritis	4 (22)	13 (43)
Dental infection	2 (11)	7 (23)
Severe acne	4 (22)	0

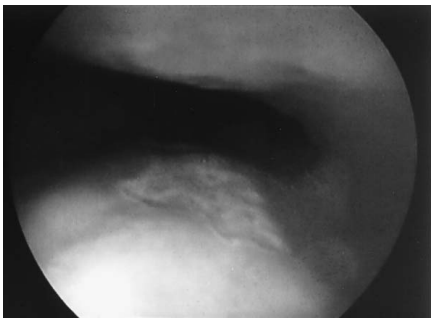


FIGURE 1. Endoscopic view of doxycycline-induced mid-esophageal ulceration.

RESULTS

There were 6 men (33%) and 12 women (67%) with a median age of 40.5 (20–75) years in Group A and 16 men (53%) and 14 women (47%) with a median age of 64.5 (17–84) years in Group B. There was no difference with respect to gender between 2 groups ($P = 0.178$). Patients in Group A were significantly younger than in Group B ($P = 0.0014$). The distribution of patients according to indication of antibiotic usage is shown in Table 1. In Group A, 15 patients (83%) had single ulceration, 2 (11%) double, and 1 (6%) circumferential at the mid-esophagus (Fig. 1). In Group B, all patients had multiple micro-ulcerations, usually 2–3 mm in diameter, in the distal esophagus, immediately above the gastro-esophageal junction (Fig. 2). All the patients in Group B and 3 (17%) patients in Group A had received tetracycline, whereas 15 (83%) patients in Group A were on doxycycline treatment. Development of mid-esophageal ulceration was induced predominantly by doxycycline, whereas distal esophagitis was mainly induced by tetracycline (100% in Group A vs. 91% in Group B, $P < 0.001$). The median duration of drug usage prior to diagnosis was 5 (2–25) days in Group A and 4 (3–18) days in Group B with no significant difference ($P = 0.148$). Ingestion of drug with little or no water was significantly more frequent in Group A as compared with Group B (94% vs. 10%, $P < 0.001$).

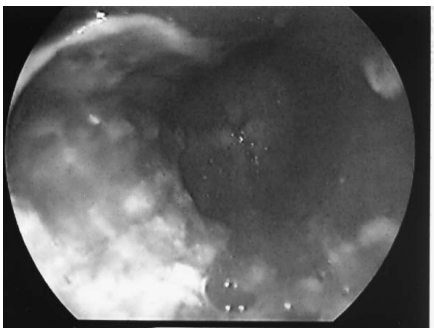


FIGURE 2. Endoscopic view of candidiasis associated tetracycline-induced distal esophagitis.

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Acute inflammation and superficial or deep necrosis with the formation of granulation tissue were observed especially in Group A (Fig. 3). The biopsies from patients of Group B revealed classic features of esophagitis, such as inflammatory cells in epithelial layer, hyperplasia of basal zone exceeding 20% of epithelium, and elongation of lamina propria papillae with erosion or mild ulceration associated with candidiasis or not (Fig 4 and 5).

Associated medical diseases in patients in Group B were significantly more frequent than in Group A (50% vs. 11%, $P = 0.006$, Table 2). One patient in Group A and 3 patients in Group B were under long-term steroid therapy at the time of diagnosis and the distribution was not significant (6% vs. 10%, $P = 0.516$).

The most frequent complaint was retrosternal pain, seen in all patients in both groups, followed by odynophagia (78% in Group A and 56% in Group B) and dysphagia (63% in Group A and 47% in Group B). Two patients in each group had previous gastric surgery for peptic ulcer disease; 1 subtotal gastrectomy & gastro-jejunostomy and 1 total gastrectomy & Roux-Y esophago-jejunostomy in Group A and 2 cases with subtotal gastrectomy & gastro-jejunostomy in Group B. There was no significant difference in the frequency of previous gastric surgery (11% in Group A vs. 7% in Group B, $P = 0.484$). Two cases (7%) in Group B had been receiving chemotherapy for leukemia and breast cancer.

Associated esophageal candidiasis in Group B was significantly more frequent than in Group A (73% vs. 0%, $P < 0.001$). Of the 22 cases with esophageal candidiasis in Group B, 14 (64%) had an associated medical disease. Additionally, in 19 patients (63%) in Group B, endoscopy revealed some associated benign gastric diseases; hiatus hernia and gastroesophageal reflux disease in 13 patients, gastritis in 4, and peptic ulcer disease in 2. Associated benign gastric diseases in Group B were significantly more frequent than in Group A (63% vs. 6%, $P < 0.001$).

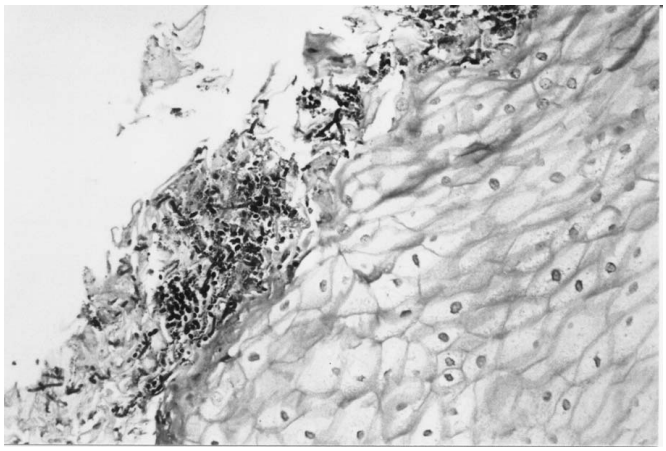


FIGURE 4. The budding yeast-like cells and pseudohyphae of candida at the superficial portion of the squamous epithelium within a necrotic background, PAS, ×400.

Fifteen patients (83%) in Group A and 20 (67%) in Group B received medical therapy at home (Table 3). No significant difference was observed in the number of patients who needed hospitalization for severe odynophagia (17% vs. 33%, $P = 0.179$). Four patients in Group A (22%) and 9 in Group B (30%) receiving oral medication at home were able to get liquids orally, whereas 3 in Group A (17%) and 10 in Group B (33%) needed intravenous fluid support. Oral lidocaine solution was instituted in patients who were hospitalized for severe odynophagia. Following the discontinuation of the drug, prompt response to medical therapy consisting of sucralfate and proton pump inhibitors was observed within a median of 5 (3–6) days in Group A and 4 (2–6) days in Group B with no

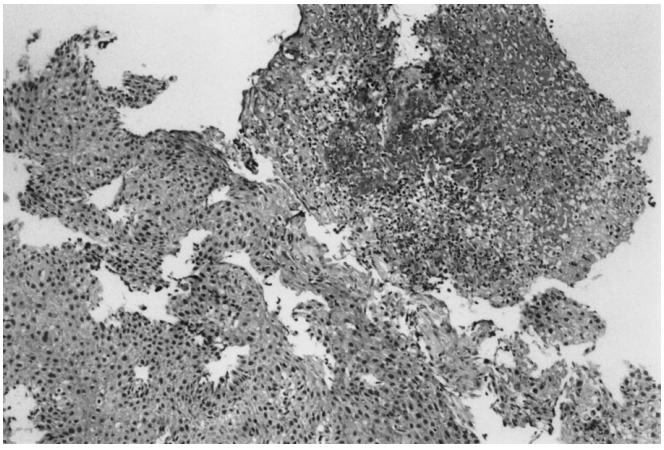


FIGURE 3. Fibrinopurulent exudate containing degenerated and necrotic squamous epithelial cells (on the top-right) next to the squamous epithelium (bottom-left) which is infiltrated by polymorphonuclear leukocytes, PAS, ×100.

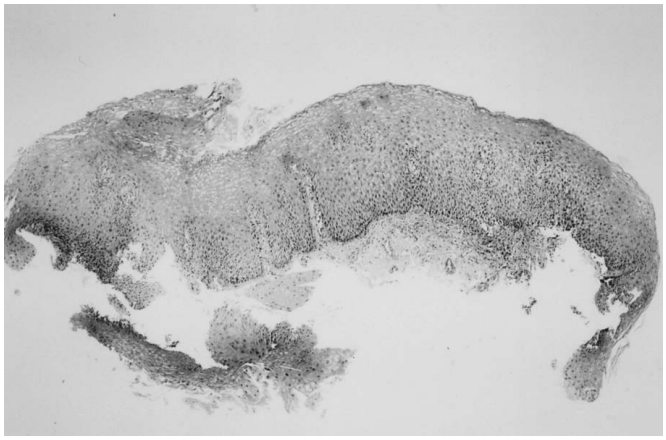


FIGURE 5. Squamous epithelium showing basal zone hyperplasia and the presence of inflammatory cells with elongation of lamina propria papillae, H + E, ×40. (Note the absence of ulceration and fungal organisms).

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TABLE 2. Distribution of Associated Medical Diseases at the Time of Diagnosis in Patients of Both Groups

Associated Disease	Group A n (%)	Group B n (%)
Gastric tumor	1 (6)	3 (10)
Cirrhosis	0	4 (13)
Chronic renal failure	0	2 (7)
Leukemia	1 (6)	0
Lymphoma	0	1 (3)
Breast tumor	0	1 (3)
Pancreatitis	0	1 (3)
Cerebro-vascular accident	0	1 (3)
Ankylosing spondylitis	0	1 (3)
Idiopathic thrombocytopenic purpura (ITP)	0	1 (3)
Total	2 (11)	15 (50)

significant difference ($P = 0.093$). Ketoconazole was added to the regimen in Group B patients whose esophageal candidiasis was documented.

Follow-up endoscopy was performed in 2 cases in Group B, whose complaints were not completely resolved despite a course of 4-week-therapy; however, endoscopy showed complete healing of esophageal ulcer in these hiatus hernia-associated patients. Additionally, in 12 other patients who underwent further upper gastrointestinal endoscopy for irrelevant gastric complaints in the first year following therapy, complete healing was observed either in esophageal ulcers and candidiasis associated esophagitis in Group B.

DISCUSSION

The exact incidence of drug-induced esophageal injury is unknown, because many cases are undiagnosed or not reported.[7] In 1983, Kikendall[9] reported the incidence as 3.9 cases per 100.000 population per year. The current incidence may be estimated to be much higher than the past because of the widespread use of endoscopic examinations. More frequent use of drugs that have the potential to cause esophageal injury results in an increase in the number of cases having drug-induced esophagitis diagnosed at endoscopy. In addition, its development has a close relation with some patient-related factors such as habit of drug ingestion and associated medical diseases.

To date, more than 70 drugs have been reported to cause esophageal injury.[2] Tetracyclines are the most commonly implicated drugs.[2,3,9] Although tetracyclines are generally well tolerated, they have certain adverse effects such as yellow discoloration of teeth and growth retardation by deposition in the skeleton in children, gastrointestinal complaints, hepatotoxicity, nephrotoxicity, photosensitivity reactions, lupus-like syndrome, vertigo, fungal superinfection, and rarely pseudotumor cerebri.[10–13] Gastrointestinal side effects are the most common complications.[5] On the other hand, esophageal ulceration induced by the tetracycline or its derivates, most frequently by doxycycline, has been reported since the 1970s as sporadic cases. Doxycycline, a second-generation agent of tetracyclines, has wide antimicrobial spectrum of activity, superior pharmacokinetic profile, and low cost. Therefore, it has been more frequently prescribed recently, especially in the clinics of gynecology, urology, dermatology, and dental medicine.

The distributions of age and gender of patients with tetracycline-induced esophageal injury reflect the population group more likely to receive these drugs. Although there was a female predominance in the mid-esophageal ulceration group compared with esophagitis group in the present study, the difference was not significant and was more likely to be related to patients' behavior of pill ingestion with little or no water just before lying down. Mid-esophageal ulceration was seen in younger patients, probably due to the same reason.

Esophageal candidiasis may develop in patients who are under broad-spectrum antibiotherapy.[14] The more frequent association of esophageal candidiasis with tetracycline-induced esophagitis is considered as the result of the underlying systemic disease such as cancer or cirrhosis in Group B patients. Candida easily colonizes in the injured esophageal mucosa in an environment where the flora has already been changed by tetracycline usage. In addition, in 2 patients receiving chemotherapy for leukemia and breast cancer in Group B, associated esophageal candidiasis was likely to have occurred secondary to immunosuppression.

The results of present study showed that tetracyclines may cause esophageal injury in 2 distinct patterns by different possible mechanisms. The first type of esophageal injury was mid-esophageal ulceration probably due to pill lodgment in the thoracic esophagus at the level of aortic arch, the region that is known as the second anatomic narrowing of the esophagus. This area is characterized by external compression from the arch itself, a transition from striated to smooth muscle, and by physiologic reduction in amplitude of the esophageal peristaltic waves.[3,9] Most of the reported drug-induced esophageal ulcers are in this area.[7,15,16] Because all patients in Group A in the present study described the same drug ingestion habit, which was to take medications with a small amount of water or

TABLE 3. Type of Therapy

Type of Therapy	Group A n (%)	Group B n (%)
Oral at home	11 (61)	11 (37)
Intravenous at home	4 (22)	9 (30)
Need of hospitalization	3 (17)	10 (33)

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without water immediately before bedtime, it is very likely that the mechanism of ulcer development in the mid-esophagus is related to the local cytochemical effects of doxycycline, which produces an acid environment when mixed with water.[17,18] Morris and Davis[7] have suggested the mechanism by which doxycycline induces esophageal injury as to be a direct injury secondary to prolonged contact between the medication and the esophageal mucosa. A combination of drug-specific factors, including the pH of doxycycline in solution; the intrinsic caustic nature of the drug; the dissolution rate; the drug dose; the dose form; and individual patient conditions, may be involved in this mechanism.[7] Acid injury alone, as a result of doxycycline dissolved in water with a pH of 2.5 to 3, is not enough to be responsible for developing of esophageal ulceration with the knowledge of physiologic reflux of gastric juice, with a pH of less than 4, does not cause an ulcer in the esophagus. On the other hand, the pH of doxycycline when dissolved in artificial saliva is 4.48, well within the normal physiologic range as stated by Morris and Davis[7]. In a French study evaluating 81 patients with esophageal injury induced by tetracycline, esophageal ulcer was detected in 79%, whereas 11% had esophagitis.[8] Most of the cases (96%) with mid-esophageal ulceration in this series had ingested doxycycline as tetracycline. This observation supports the fact that esophageal ulcerations tend to occur more frequently in patients receiving doxycycline.

There are some differences in the pharmacokinetics of tetracycline and doxycycline: the latter has higher bioavailability, longer half-life, and higher lipid solubility that results in excellent tissue penetration. Doxycycline also obeys concentration-dependent kinetics while it is eliminated by time-dependent kinetics.[5] However, these distinctions are unlikely to play a major role in the location of injury.

A finding by O'Meara,[19] which was further confirmed by the results of an experimental study examining the local ulcerogenic effects of 6 different tetracycline capsules and tablets in a cat-model, was that exudates at the base of the ulcer had the same color as the capsule in a case of doxycycline-induced esophageal ulceration. This finding suggests that the logged capsule at the mid-esophagus was responsible for the mucosal injury by direct contact following its adhesion and dissolution at that point.

Dissolution rate of drugs seems to be a contributing factor in the development of esophageal ulcer. Early dissolved capsules may result in longer contact with the esophageal mucosa. Doxycycline dissolves in artificial saliva within 10 minutes.[7] Doxycycline and minocycline, the second-generation tetracyclines, have high lipid solubility resulting in excellent tissue penetration.[20] This pharmacokinetic feature may enhance the accumulation of these drugs in the esophageal mucosa and result in an acute esophageal ulceration. Rapid dissolution rate and high lipid solubility of doxycycline may be considered as the possible relevant factors.

The second type of esophageal injury was multiple micro-ulcerations, mostly associated with esophageal candidiasis, in the distal esophagus. The observation of significantly higher rate of associated benign gastric diseases, such as hiatus hernia and gastro-esophageal reflux, in patients in Group B may be possibly explained by a long exposure of distal esophageal mucosa to gastric juice containing dissolved tetracycline resulting in micro-ulcerations. However, this hypothesis is not based on results of any experimental study. In a prospective study evaluating medication induced esophageal injury (MIEI) and its relation to esophageal function, hiatus hernia was shown to increase the risk for MIEI as evidenced by the development of MIEI in 7 of 12 indomethacin or doxycycline receiving patients with hiatus hernia.[21] Furthermore, the higher frequency of esophageal candidiasis in patients with tetracycline-induced distal esophagitis in the present study may also be explained by the similar mechanism: micro-ulcerations in the distal esophagus may be the result of gastro-esophageal reflux, which may have facilitated colonization of candida in these susceptible mucosal areas where flora has already been changed under tetracycline treatment. Candidiasis in our series most frequently occurred in immunosupressed patients under chemotherapy or steroid.

The retention of tablets within the esophagus was demonstrated by the use of barium sulfate tablets similar in size to aspirin by Evans and Roberts.[22] The tablets were retained for longer than 5 minutes in 58% of patients. Moreover, esophageal scintigraphy studies have shown that while liquids emptied completely from the esophagus after 1 swallow whether the patient was supine or upright position, capsules when ingested with no water frequently remained in the esophagus for up to 2 hours without the patient having any sensation that the solid was still in the esophagus.[23] In addition, poor clearance of tablets from the esophagus in the supine position has been demonstrated by Hey et al.[24]

Drug-induced esophagitis is classified into 2 groups; transient and self-limiting esophageal injury and persistent esophagitis, often with stricture as stated by Eng and Sabanathan[3] in their review article. Whereas patients with tetracycline- and emepronium-induced esophagitis are in the first group, NSAIDs, potassium chloride, and quinidine sulfate are considered as drugs causing persistent esophageal injury. No esophageal stricture was observed in the present study; however, its development on long-term follow-up is unknown because this study was a retrospective one.

Treatment of drug-induced esophageal injury is supportive, although acid reduction is used frequently as an adjunct.[2] The purpose of control gastric acid secretion is to avoid further chemical irritation of the ulcer.[7] Proton pump inhibitors are the most preferred agents to reduce gastric acid secretion. Because sucralfate is bound selectively to diseased mucosa and to necrotic tissue in an ulcer base and stimulates mucosal generation and release of prostaglandins, it may be of help in the initial

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treatment of doxycycline-induced esophageal ulceration.[17] In patients unable to swallow fluids or even their own saliva intravenous fluid therapy should be instituted. Selected cases with associated medical diseases and suffering severe odynophagia may be hospitalized to replenish fluid and electrolytes losses in addition to nutritional support.[25]

Structural abnormalities and motility disorders of the esophagus may facilitate the development of drug-induced esophagitis.[26] Although esophageal motility test was not performed in any of our cases, neither history nor observation of esophageal dysfunction had been reported in their endoscopy records.

In conclusion, the risk of esophageal injury as an adverse effect of tetracyclines is not negligible with the increasing number of reported cases. The preference of other antimicrobial agents over tetracyclines whenever possible is the initial step in preventing esophageal injury. To reduce the risk of tetracycline-induced esophageal injury, it is recommended for the patients to take the capsules well before lying down and to drink at least 100 mL of water or to use the drug just before the meals. The type of tetracyclines used by patients may give some clues to physicians on the pattern of esophageal injury since mid-esophageal ulceration seems to be more frequently associated with doxycycline and distal esophagitis with or without candidiasis with tetracycline. Hospitalization may be needed in patients with severe odynophagia, especially if they have some associated medical diseases, whereas in the remainder the discontinuation of the relevant drug followed by supportive therapy consisting of proton pump inhibitors and sucralfate is mandatory. In cases with candidiasis, oral antimycotic agents should be added to the treatment regimen.

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