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Biopsy Confirmed Doxycycline Induced Gastric Mucosal Injury

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Abstract

Doxycycline (DOX) is a tetracycline antibiotic that is prescribed for treating a variety of infections involving the skin, respiratory tract, and urogenital system. Adversely, esophageal mucosal injury due to DOX is well described; however, gastric mucosal injury is less commonly reported and may result in severe gastrointestinal hemorrhage and occasionally, perforation. In most reported cases of DOX-induced gastric lesions, patients are symptomatic upon presentation leading to endoscopic evaluation and diagnosis with biopsy. However, severe gastric insults may go unrecognized in rare cases of asymptomatic patients, increasing the risk of mortality.

Keywords

gastric mucosal injury, doxycycline, drug-induced, bleeding, gastroenterology

Background

Although esophageal injury related to doxycycline (DOX) use is commonly documented, gastric mucosal injury is rarely reported. Mucosal injury is thought to be multifactorial, attributed to direct toxicity and activation of mediators that damage the superficial vasculature and result in tissue ischemia. The majority of patients present with symptoms, such as dysphagia or epigastric pain. Characteristic endoscopic findings for these lesions include inflamed, eroded, or ulcerated mucosal tissue, often with an overlying white plaque. Histopathologic findings include eosinophilic superficial vessel degeneration with fibrin microthrombi. To our knowledge, only one case of an asymptomatic DOX-induced gastric injury has been previously reported. Given the widespread use of doxycycline for a variety of disease states and the potential for severe, asymptomatic insult, the incidence of gastric injury may be more prevalent than suggested in current literature. Here, we present the second case of an asymptomatic, biopsy-proven DOX-induced gastric mucosal lesion in an elderly patient that was recently treated for prostatitis, resulting in life-threatening gastrointestinal (GI) bleeding.

Case

A 78-year-old African American male with hypertension presented with a 1-day history of melena. He denied dysphagia, vomiting, chest pain or abdominal discomfort. He was recently diagnosed with prostatitis and was on day 10 of a prolonged course of oral DOX 100 mg BID. He denied nonsteroidal anti-inflammatory drugs (NSAID), alcohol, or tobacco use. He denied history of malignancy. He had no history of previous upper endoscopy but underwent a screening colonoscopy 9 years ago that was benign. His physical examination revealed that he was afebrile, with a heart rate of 108 and blood pressure of 85/45. His abdomen was soft and without distention or tenderness to palpation. Laboratory data included a hemoglobin (hgb) 8.1 g/dL, mean corpuscular volume 94 fL, platelets 197 000, and INR 0.9. He was treated with IV proton pump inhibitor (PPI) BID, received 2 L of normal saline, and 2 units of packed red blood cells (pRBCs). Esophagogastroduodenoscopy (EGD) revealed an oozing, mass-like lesion in the gastric fundus with an adherent white material that was biopsied and treated with placement of 2 endoclips (Figure 1A and B). Overnight, he suffered a large bloody bowel movement with associated hypotension and a drop in hgb to 6.5 g/dL. He required additional pRBCs and vasopressor support. Repeat EGD was negative for active bleeding and clips were stable. He underwent a colonoscopy

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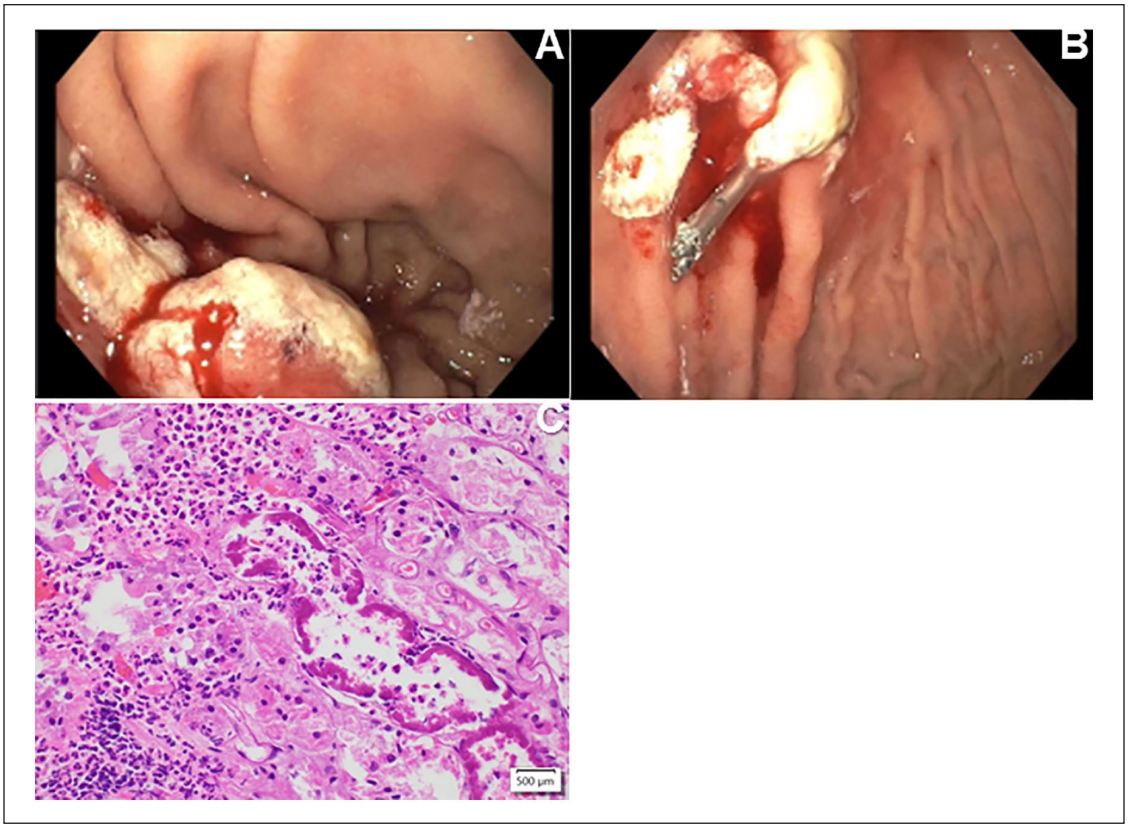

Figure 1. Initial esophagogastroduodenoscopy finding of a doxycycline induced gastric lesion. (A) Gastric fundus mucosal erosion with overlying plaque-like material. (B) Clipping of bleeding gastric lesion. (C) Gastric fundus mucosa with superficial mucosal capillaries, eosinophilic degenerative changes, and neutrophilic infiltration.

that revealed scattered diverticular disease throughout the entire colon and bright red blood but failed to visualize a source of active bleeding. Computed tomography with angiography (CTA) demonstrated brisk extravasation into the ascending colon. Coil embolization of an arterial bleed in the lateral wall of the ascending colon was successfully performed. During the procedure, he was diagnosed with an incidental pulmonary embolism and an inferior vena cava filter was placed. Repeat EGD and colonoscopy revealed a persistent gastric mass in the fundus with diminished size and oozing friable mucosa with an adherent white material, and a 3-cm ascending colon ulcer with heaped up edges but no visible vessel or active bleeding (Figure 2A and B). Pathology of the ascending colonic ulcer revealed focal adenomatous change and atrophic crypts with negative cytomegalovirus staining (Figure 2C). Histopathology of the gastric lesion from the initial EGD revealed acute erosive gastritis with classic eosinophilic capillary degeneration characteristic of DOX induced injury (Figure 1C). Staining for *Helicobacter pylori* (*H. pylori*) was negative. The patient remained stable without further bleeding events, and he was transitioned to trimethoprim-sulfamethoxazole for prostatitis and continued on oral PPI therapy upon discharge.

Discussion

Doxycycline is known to cause pill-induced esophagitis, and rarely gastric injury.[1] More commonly, gastric ulceration is associated with peptic ulcer disease from NSAID use and *H. pylori*, or non-NSAID medications, such as bisphosphonates, potassium chloride, or glucocorticoids.[1,2] The first case of gastric injury secondary to DOX was documented in 1999, and to our knowledge, there are less than 20 reported cases to date. Of these cases, the majority of patients were female; however, ages varied broadly from 20 to 80 years old, and many were without significant comorbidities.[2,3] The most common symptoms on presentation were dysphagia, odynophagia, epigastric discomfort, or retrosternal chest pain, even in the absence of concomitant esophageal lesions.[2] Interestingly, symptom onset was widely variable, ranging from hours to years of DOX use.[2,4,5] Risk factors for both esophageal and gastric mucosal injury are presumably related to conditions resulting in prolonged exposure to the caustic medication, such as esophageal dysmotility, hiatal hernia, gastroparesis, small volume fluid intake, and supine positioning after ingestion.[1] Esophageal ulceration is likely more common than gastric injury, partly due to narrowing of the mid-esophagus from compression of the aortic arch and left atrium.[1] Most gastric

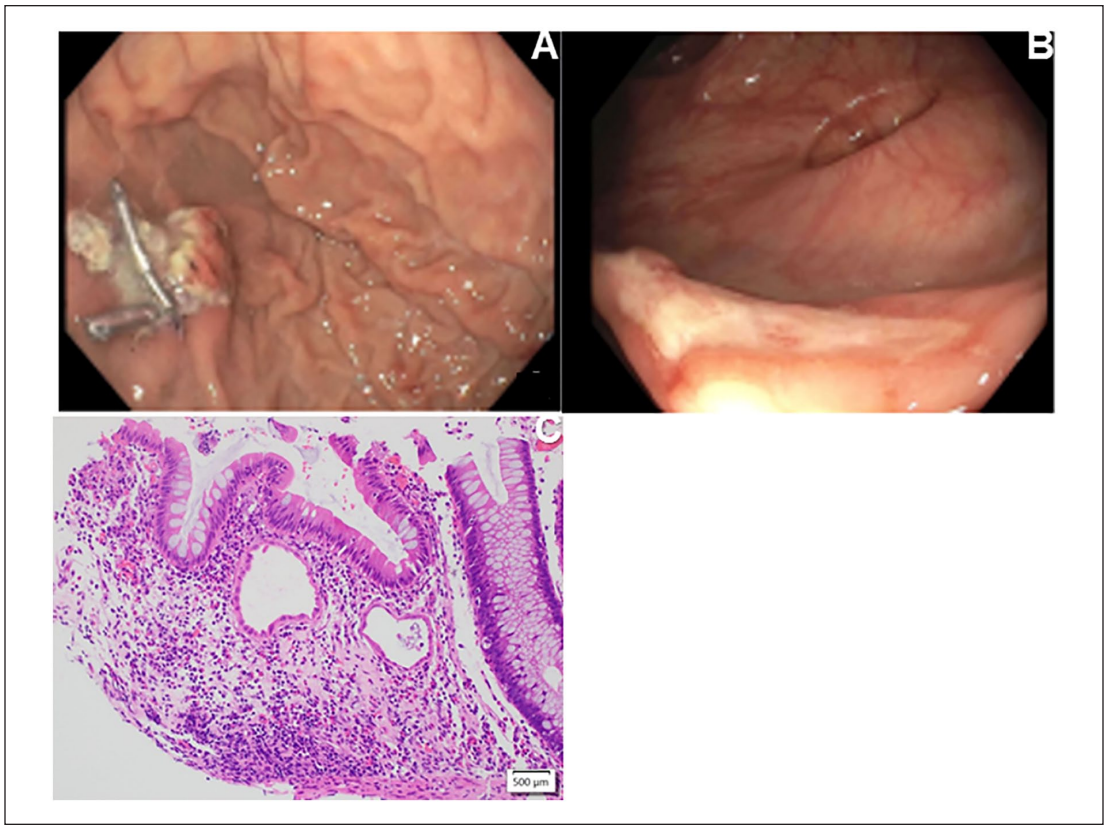

Figure 2. Follow-up esophagogastroduodenoscopy and colonoscopy findings. (A) Gastric mass in the fundus with diminished size, oozing friable mucosa with an adherent white material, and stable endoclips. (B) Three-centimeter ascending colon ulcer with no visible vessel or active bleeding. (C) Ascending colonic ulcer with focal adenomatous change and atrophic crypts.

lesions are found in the gastric fundus; however, few cases of antral and duodenal lesions have been reported, as well. Aside from our patient, only one case of an asymptomatic, incidental DOX-induced gastric lesion found on EGD for esophageal varices surveillance has been documented.[4]

Given the bulk of patients with DOX induced gastric injury are symptomatic, suspicion is usually based upon the patient's history and high clinical suspicion, warranting further evaluation with EGD, especially after severe complications are ruled out with radiographic imaging and the etiology remains unclear. Grossly, these gastric mucosal injuries may appear as a single or clusters of ulcers, erosions, or erythematous tissue.[2] Additionally, several reports have described adherent white plaques overlying the injury, consistent with our patient's EGD. Microscopically, the pattern of gastric mucosal injury found on biopsy is diagnostic. Characteristic histopathologic findings of DOX-induced gastric injury are described as neutrophilic infiltration of the lamina propria and eosinophilic superficial capillary degeneration with fibrin microthrombi, resulting in ischemic tissue injury.[2,3,4] Altogether these characteristic gross and microscopic findings and location of injury aids to differentiate DOX-induced injury from similar gastric lesions found in gastric antral vascular ectasia, portal hypertensive gastropathy and peptic ulcer disease.[5] DOX is thought to induce these injuries by a variety of factors. First, patients may have difficulty swallowing gelatinous capsules, which can become lodged in the mid-esophagus resulting in pill breakdown and direct caustic effect from the acidic formulation.[1,2] Additional studies have suggested DOX-induced superficial vascular damage by suppression of matrix metalloproteinases and subsequent downregulation of angiogenesis.[6,7] Unfortunately, these lesions may lead to severe complications, such as stricture formation, upper GI hemorrhage and gastric perforation.[2] Treatment by discontinuation of DOX and initiation of PPI therapy has been proven successful and several studies involving follow-up EGD in these patients revealed normal appearing gastric mucosa 4 months later.[3,4] Few cases of life-threatening GI bleeding requiring endoscopic intervention due to DOX induced gastric injury are noted in the current literature, and our case is the first to our knowledge of successful treatment with endoclip placement. The development of this severe gastric lesion with a relatively short course of DOX is alarming and further emphasizes the variability in the time-to-injury.

Our patient likely had 2 bleeding events; an indolent bleed at presentation from the DOX-induced gastric injury and potentially the colonic ulcer, followed by a brisk bleed secondary to colonic diverticula or a Dieulafoy lesion. Our case is the second reported finding of an asymptomatic DOX-induced gastric injury confirmed by biopsy and raises

concern, given the lack of subjective complaints prior to the onset of melena in our patient. Additionally, patients presenting with complicated comorbidities, the use of multiple offending medications, poor health literacy, and non-specific complaints may lead to unnecessary laboratory and radiographic workup or inappropriate treatment regimens, resulting in delayed diagnosis and financial burden. Although there are no current guidelines regarding treatment of these lesions or recommendations for follow-up EGD, it is reassuring that treatment of uncomplicated lesions remains simple in many cases, by discontinuing the insulting medication and initiation of oral PPI therapy. Furthermore, the use of endoclips for complicated DOX-induced gastric lesions, such as those with active hemorrhage or deep ulcers with exposed vessels, was proven safe and effective in our patient.

Conclusion

It is highly probable that the incidence of gastric injury is underreported considering these asymptomatic cases and the widespread use of DOX. Physicians must be cognizant of this potentially life-threatening adverse effect of DOX and consider safe alternatives in patients concurrently prescribed multiple offending agents, prior history of GI hemorrhage, or determined high risk for upper GI bleeding.

Authors' Note

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Author Contributions

Hannah Gaulden wrote the manuscript and is the article guarantor. William Dungan, John Romano, and Ira Willner revised the manuscript for intellectual content.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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