

## Caustic Injury and Stricture of the Esophagus After Long-Term Phenytoin Use

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### Abstract

A 50-year-old man with a history of epilepsy controlled with phenytoin presented for evaluation of dysphagia. History revealed the patient was taking his phenytoin daily without water. Barium esophagram showed severe stricturing of the mid-esophagus. Upper endoscopy revealed diffuse gross mucosal abnormality with a thick stricture and occasional exudate. Biopsies were consistent with a drug-induced injury with lymphocytic infiltration and epithelial cell necrosis.

### Introduction

Many medications are known to cause pill-induced esophageal injury. Preventative measures such as taking pills with copious water and avoiding the supine position prevent most esophageal injury. While pill-induced esophagitis is common, caustic injury is induced by only a few medications whose dissolution pH is outside the range of physiological esophageal pH values. Phenytoin is significantly alkali with a pH >10 when dissolved in water.<sup>1</sup>

### Case Report

A 50-year-old male with epilepsy presented with a 5-year history of dysphagia. Since temporal lobectomy 12 years prior, his seizures were well controlled on 6 tablets daily of phenytoin 100 mg. His dysphagia was insidious, progressive, and most notable with solids such as bread, rice, and meats. The patient reported no difficulty swallowing liquids. He had the sensation of the pills feeling “stuck” in his chest when taking phenytoin without water. Additionally, he had chest pain and heartburn partially relieved with a proton pump inhibitor. The patient denied alcohol or tobacco use, radiation exposure, or a history of cancer.

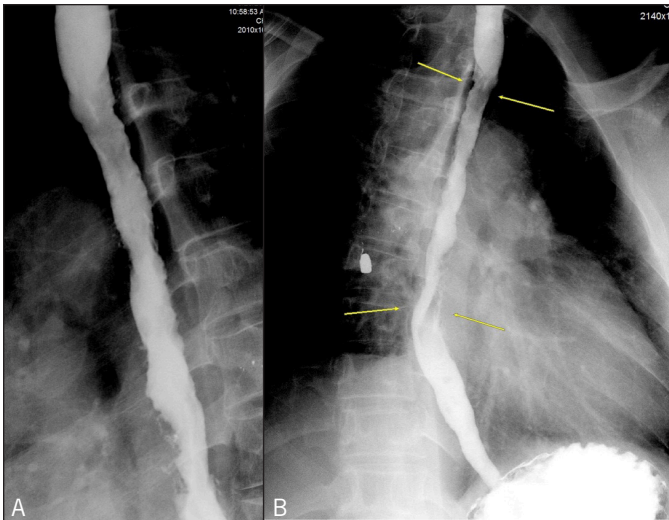
Barium esophagram exhibited a fixed, irregular, long-segment, mid-esophageal stricture. Multiple small (<2 mm) outpouchings filled with barium contrast were scattered throughout the proximal esophagus. The 13-mm barium pill failed to traverse the stricture (Figure 1). Upper endoscopy revealed an abnormal esophagus with the exception of the proximal and distal 5 cm. The mucosa appeared pale and thick with pitting and scars (Figure 2). The mid-esophagus from 28 to 35 cm from the incisors had a thick stricture

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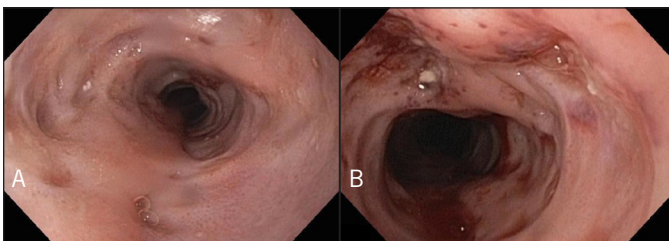


**Figure 1.** (A) Mid-esophageal irregular stricture with multiple small outpouchings filling with oral contrast. The neck for each outpouching is imperceptible, resulting in an extraluminal appearance of each pseudodiverticulae. (B) A 13-mm barium pill failed to pass through the proximal portion of the stricture involving the entire mid-esophagus (arrows).

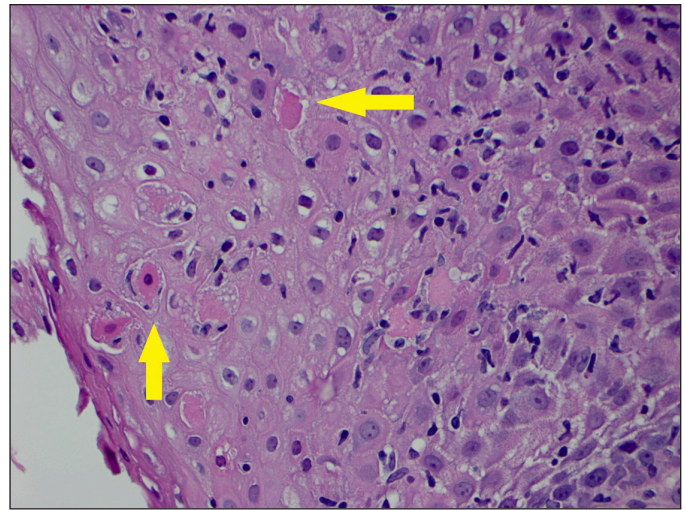
with multiple intramural pseudodiverticuli and occasional white punctate exudate (Figure 2). Savary dilation to 14 mm was performed with moderate resistance to allow passage of the scope.

Biopsies from the proximal, mid, and distal esophagus showed severe mucosal injury consisting of extensive chronic inflammation with scattered neutrophils with extensive intracellular edema. Scattered throughout the mucosa, primarily near the surface, were numerous dyskeratotic and necrotic squamous cells (Figure 3). The histologic changes were akin to those seen in drug reactions of the skin but otherwise compatible with a toxic injury to the mucosa. Based on the findings, the esophageal injury was attributed to administration of phenytoin tablets.

The patient was switched from phenytoin tablets to a liquid preparation to prevent further injury. He was instructed to take medication with a copious amount of water while in an upright position to prevent further damage, and to continue to take a proton pump inhibitor. His dys-



**Figure 2.** Upper endoscopy showing (A) thick stricture and multiple intramural pseudodiverticuli and (B) thickened, scarred mucosa after Savary dilation.



**Figure 3.** H&E stain at 40x magnification showing mucosa with marked intracellular edema, associated inflammatory infiltrate, and scattered dyskeratotic and necrotic squamous cells (arrows).

phagia improved after dilation and we intend to perform serial dilations of the stricture.

### Discussion

Esophageal clearance of pills is dependent on the volume of liquid ingested and the posture assumed following administration. Clearance can be further affected by esophageal dysmotility or structural abnormalities. Pills commonly lodge in the mid-esophagus near the crossing of the aorta or carina due to extrinsic compression from these structures,<sup>2</sup> and this can lead to pill-induced esophagitis.

Drug-induced injury is related to the inherent caustic properties of the medication, including the pH, dissolution time, and time in contact with the esophageal mucosal surface. One study found that only 3 drugs (ascorbic acid, aspirin, and phenytoin) had a statistically significant dissolution pH outside the range of physiological esophageal pH values (pH 4–7).<sup>1</sup> Phenytoin, the only statistically significant alkali, produced a pH of 10.16±0.11 when dissolved in artificial saliva. However, the average dissolution time was 30 minutes, precluding esophageal injury if pills pass rapidly. Underlying esophageal anatomical obstruction or dysmotility delays pill transit, increasing esophageal mucosa exposure to the resultant alkaline pH after pill dissolution, creating esophageal injury.<sup>1</sup>

In caustic alkali injury, tissue damage occurs rapidly as alkalis combine with tissue proteins causing liquefactive necrosis and saponification. Absorption leads to thrombosis in blood vessels, impeding blood flow to already damaged tissue.<sup>3</sup> Subsequently, tissue remodeling occurs followed by collagen deposition and scar retraction. Scar retraction

can continue for months, resulting in stricture formation and impairment of gastroesophageal sphincter pressures, which further increases reflux and accelerates stricture formation.<sup>4,5</sup>

The presence of esophageal intramural pseudodiverticulis can provide a barrier for pill or bolus transit. The etiology and pathogenesis of esophageal intramural pseudodiverticulis (EIPD) is not well understood, but is thought to be associated with risk factors such as diabetes mellitus, chronic alcoholism, candidiasis, and reflux esophagitis. Potential complications of EIPD include stenosis, strictures, perforation, bleeding, and fistula formation.<sup>6</sup> The mainstay of management is treatment of the underlying condition and esophageal dilation.

There has only been 1 previously reported case of benign esophageal stricture secondary to phenytoin. The patient failed endoscopic therapy with dilation and ultimately required sleeve resection of the esophagus.<sup>7</sup> We describe the first case of long-term phenytoin use inducing caustic injury to the esophagus that was adequately treated without requiring surgical intervention. This case demonstrates the importance of patient education when prescribing medications with inherent caustic properties such as phenytoin.

## Disclosures

Author contributions: KK Nelson drafted the manuscript and is the article guarantor. SB Clayton, AL Champeaux, JC Feldman, and JE Richter contributed to and edited the final manuscript.

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Informed consent was obtained for this case report.

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