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| Title            | Endoscopic ultrasonography features of gastric mucosal cobblestone-like changes from a proton-pump inhibitor                                              |
| Author(s)        | Miyamoto, Shuichi; Kudo, Takahiko; Kato, Mototsugu et al.                                                                                                 |
| Citation         | Clinical journal of gastroenterology, 10(3), 220-223<br><a href="https://doi.org/10.1007/s12328-017-0724-5">https://doi.org/10.1007/s12328-017-0724-5</a> |
| Issue Date       | 2017-06                                                                                                                                                   |
| Doc URL          | <a href="https://hdl.handle.net/2115/70647">https://hdl.handle.net/2115/70647</a>                                                                         |
| Rights           | Clinical journal of gastroenterology                                                                                                                      |
| Type             | journal article                                                                                                                                           |
| File Information | ClinJGastroenterol10_220.pdf                                                                                                                              |



**Endoscopic ultrasonography features of gastric mucosal cobblestone-like changes from a proton-pump inhibitor**

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## Abstract

A 68-year-old man with no symptoms presented to Hokkaido University Hospital for esophagogastroduodenoscopy screening. He had a history of *Helicobacter pylori* eradication. Initial esophagogastroduodenoscopy showed no gastric cobblestone-like mucosa or gastric cracked mucosa. After 1 year, he received esomeprazole (20 mg) once daily for heartburn at another hospital. Esophagogastroduodenoscopy was performed after 2 years of esomeprazole administration. Endoscopic findings showed that after *H. pylori* eradication, according to the Kyoto classification, gastric cobblestone-like mucosa presented in the gastric body area. Dilation of the oval crypt opening and intervening part in the gastric cobblestone-like mucosa was detected by endoscopy with narrow band imaging. Endoscopic ultrasonography revealed a thick gastric second layer and sporadic small anechoic lesions in the low-echoic thickened second layer in the gastric cobblestone-like mucosa. The gastric cobblestone-like mucosa biopsy specimen showed parietal cell protrusions and oxyntic gland dilatations. Recently, we reported that gastric mucosal changes such as gastric cracked mucosa and gastric cobblestone-like mucosa were caused by proton-pump inhibitors; however, the gastric cobblestone-like mucosa was not examined by endoscopic ultrasonography. In this case, endoscopic ultrasonography findings suggested that oxyntic gland dilatations caused the elevated gastric mucosa, such as gastric cobblestone-like mucosa, from the use of proton-pump inhibitors.

**Keywords**

endoscopic ultrasonography, cobblestone-like changes, proton-pump inhibitor

## Introduction

Proton-pump inhibitors (PPIs) strongly inhibit the function of  $H^+/K^+$ -ATPase in gastric parietal cells and suppress the secretion of gastric acid. PPIs are widely available for acid-related disorders such as gastric or duodenal ulcers and gastroesophageal reflux disease. The use of PPIs is increasing [1]. In addition, high rates of long-term PPI use are reported [1, 2]. The long-term use of PPIs is related to some side effects such as enteric infections [3] and fractures [4]. In addition, the development of fundic gland polyps results from a trophic effect on parietal cells with PPI use [5, 6]. In addition, it was reported that gastric black spots and white flat elevated lesions appeared in a patient taking PPIs [7, 8]. Pathologically, parietal cell protrusions and oxyntic gland dilatations occur in patients using PPIs [9, 10]. Recently, we reported that gastric mucosal changes such as gastric cobblestone-like mucosa (GCSM) and gastric cracked mucosa (GCM) were caused by PPIs [11]. GCSM is defined as gastric mucosa that has a cobblestone-like appearance and is endoscopically detected as multiple smooth elevated mucosa. GCM is defined as gastric mucosa that has a crackled-like appearance and is endoscopically detected as multiple depressed lines. GCSM and GCM were detected in 9.1% and 24.4% of patient receiving PPIs. These mucosal changes appeared only in the gastric corpus area and were associated with oxyntic gland dilatations. It was assumed that oxyntic gland dilatations led to mucosal elevation and that slight oxyntic gland dilatations in the gastric mucosa appeared to be GCM and that more substantial dilatations appeared to be GCSM. However, endoscopic ultrasonography (EUS) of the GCSM has not been reported. In this case, we examined the GCSM by EUS.

## Case Report

A 68-year-old man with no symptoms presented to Hokkaido University Hospital for esophagogastroduodenoscopy (EGD) screening. He had a history of *Helicobacter pylori* eradication. Initial EGD showed no GCSM or GCM (Figure 1a, 1b). After 1 year, he received esomeprazole (20 mg) once daily for heartburn at another hospital. EGD was performed after 2 years of esomeprazole administration. Endoscopic findings showed that after the eradication of *H. pylori* according to the Kyoto classification [8], i.e., atrophic changes in the antrum (Figure 2a), there was no regular arrangement of collecting venules in the gastric angle (Figure 2b) and no atrophic changes in the body area (Figure 2c). The patient was negative for all *H. pylori* tests, including the <sup>13</sup>C-urea breath test (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), rapid urease test (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), *H. pylori* IgG E-plate (Eiken Chemical Co., Ltd., Tokyo, Japan), and culture. For histological examination, gastric biopsy tissues of the antrum showed moderate atrophy; however, tissues of the body area showed no atrophy. Both tissues showed no *H. pylori*. Serum gastrin level was 678 pg/ml, serum pepsinogen (PG) I level was 222 ng/ml, and serum PGII level was 36.2 ng/ml. In this patient, GCSM presented in the gastric body area (Figure 2d, 2e). Endoscopic findings with narrow band imaging (NBI) showed dilation of the oval crypt opening and the intervening part in the GCSM (Figure 2f). EUS using a 20-MHz probe (UM-G20-29R; Olympus Co, Tokyo Japan) with an ultrasound processor (EU-ME1; Olympus Co, Tokyo Japan) for the GCSM revealed a thick gastric second layer and sporadic small a-echoic lesions in the low-echoic thickened second layer (Figure 3). GCSM biopsy specimen showed parietal cell protrusions (PCPs) and oxyntic gland dilatations (Figure 4a, 4b). There was no fibrosis, hypervascularity, or inflammatory cell infiltration.

## Discussion

We performed EUS for the GCSM and examined the gastric mucosa. EUS showed sporadic small a-echoic lesions in the low-echoic thickened second layer. Histologically, PCPs and oxyntic gland dilatations were detected in the tissue of the GCSM.

PCPs and oxyntic gland dilatations result from PPI use [9]. PPIs increase the number of parietal cells by expressing aquaporin-4, which forms membrane water channels [12]. Therefore, these histological changes might be caused by the movement of water from the interstitial space toward the lumen of oxyntic glands. Kumar *et al.* demonstrated that oxyntic gland dilatation is associated with PPI use only in patients without *H. pylori* infection [9]. Similarly, fundic gland polyps developed from long-term PPI use in a patient without *H. pylori* infection [5]. Recently, we reported that gastric mucosal changes such as GCM and GCSM result from the use of PPIs in a patient without current *H. pylori* infection [11].

In our case, the patient had a history of *H. pylori* eradication and tests for *H. pylori* were all negative. Endoscopically and histologically, atrophic changes presented in only the gastric antrum area. Therefore, oxyntic glands remained in the body area and were dilated by PPIs. Endoscopic findings with NBI showed dilation of the oval crypt opening and intervening part. In addition, EUS showed a thick second layer and sporadic small low-echoic lesions. Histologically, many dilated fundic glands with PCPs were detected, and the major axis of the lumen of the most dilated fundic gland was 360  $\mu\text{m}$ . The normal fundic glands exhibit no PCPs and are not dilated. The major axis of the lumen of the normal fundic gland is usually <50  $\mu\text{m}$  [11]. Large-size oxyntic gland dilatations were detected by EUS as sporadic small a-echoic lesions. Therefore, these NBI and EUS

findings suggest that oxyntic gland dilatations caused the elevated gastric mucosa.

A limitation of this case is that features of EUS findings were compared only with those of biopsy specimens.

In conclusion, we presented the EUS features of GCSM, such as small a-echoic lesions in the low-echoic thickened second layer. These EUS findings support PPI use as the cause of GCSM development. In addition, given that the number of patients taking anticoagulants has been increasing, EUS is helpful for diagnosing the GCSM in case of biopsy difficulties.



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## **Figure legends**

### **Figure 1**

Endoscopic images before esomeprazole administration.

- (a) Endoscopic image of the lesser curvature of the gastric corpus showing no gastric cobblestone-like mucosa (GCSM).
- (b) Endoscopic image of the greater curvature of the gastric corpus showing no GCSM.

### **Figure 2**

Endoscopic images after 2 years of esomeprazole administration.

- (a) Endoscopic image of the gastric antrum area showing an atrophic change.
- (b) Endoscopic image of the gastric angle showing no regular arrangement of collecting venules.
- (c) Endoscopic image of the gastric body area showing gastric cobblestone-like mucosa (GCSM), no atrophic change and no diffuse redness.
- (d) Endoscopic image of the GCSM.
- (e) Endoscopic image of the GCSM after indigo carmine spray.
- (f) Magnifying endoscopic image with narrow band imaging of the GCSM.

### **Figure 3**

Endoscopic ultrasonography (EUS) for the gastric cobblestone-like mucosa.

EUS with a 20-MHz probe showed mucosal elevation in the thick second layer (red color arrows) and sporadic, small a-echoic lesions (yellow color arrows) in the second layer.

### **Figure 4**

The gastric cobblestone-like mucosa biopsy specimen showed parietal cell protrusions and oxyntic gland dilatations.

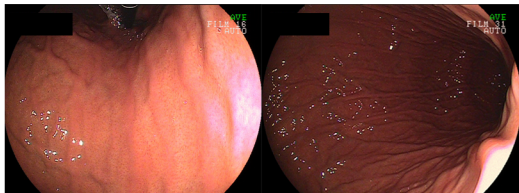
(a) Hematoxylin and eosin, original magnification, 100×, Scale bars, 500  $\mu\text{m}$ .

(b) Hematoxylin and eosin, original magnification, 400×, Scale bars, 50  $\mu\text{m}$ .

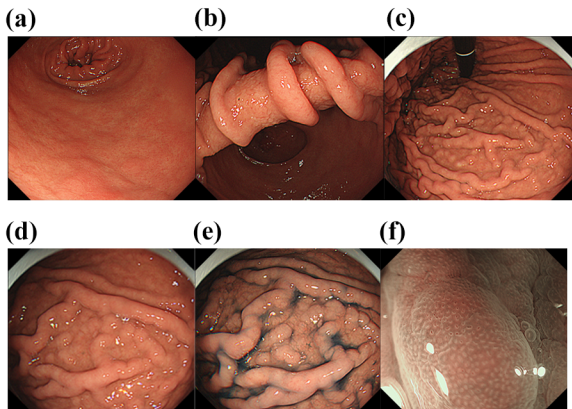
# Figure 1

(a)

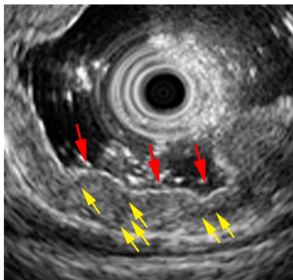
(b)



**Figure 2**



**Figure 3**



**Figure 4**

**(a)**

**(b)**

