

[ CASE REPORT ]

## Vonoprazan-associated Gastric Mucosal Redness: A Report of Four Cases

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### Abstract:

To date, no cases of vonoprazan-associated gastric mucosal redness have been reported, and its endoscopic and pathological features remain largely unclear. We report four cases of vonoprazan-associated gastric mucosal redness. In all cases, esophagogastroduodenoscopy (EGD) demonstrated linear or spotty redness that newly appeared in the greater curvature of the middle gastric body after the initiation of vonoprazan, which disappeared after its discontinuation. A tissue biopsy taken from the gastric mucosa with redness revealed inflammatory cell infiltration, parietal cell protrusions (PCPs), and oxyntic gland dilatation. To our knowledge, this is the first report describing the endoscopic and pathological features of vonoprazan-associated gastric mucosal redness.

**Key words:** potassium-competitive acid blocker (P-CAB), vonoprazan, gastric mucosal change

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### Introduction

Vonoprazan is a potassium-competitive acid blocker (P-CAB) that was recently developed and approved for use in Japan (1). P-CABs are a class of drugs that reversibly inhibit gastric acid output through K<sup>+</sup>-competitive ionic binding to H<sup>+</sup>/K<sup>+</sup>-ATPase (2). It has been reported that P-CABs are effective for the treatment of reflux esophagitis (3), gastric and duodenal ulcer (4), post-endoscopic submucosal dissection (ESD) ulcer (5), and the eradication of *H. pylori* (6). Vonoprazan is shown to selectively accumulate in gastric parietal cells in the mucosal layer of the rat stomach (7) and a cracked and cobblestone-like gastric mucosa has been reported as a vonoprazan-associated gastric mucosal change (8). However, vonoprazan-associated gastric mucosal redness has not been reported to date and its endoscopic and pathological features remain largely unknown.

We herein report four cases of vonoprazan-associated gastric mucosal redness that newly appeared after the initiation of the drug and which disappeared after its discontinuation.

### Case Reports

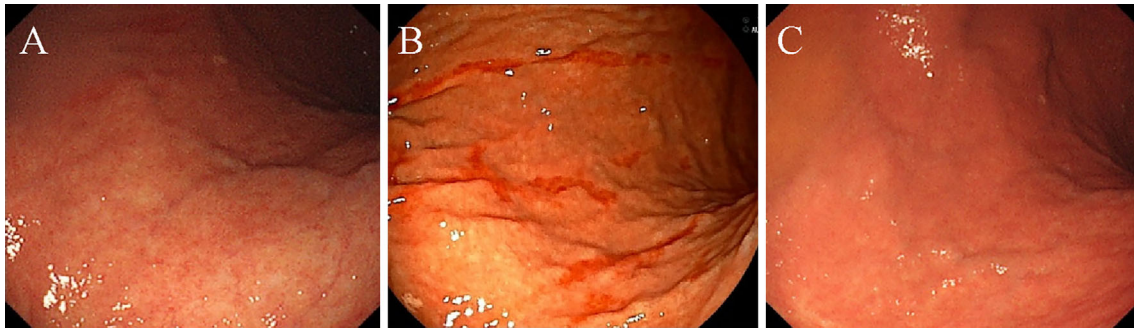
#### Case 1

Screening esophagogastroduodenoscopy (EGD) revealed a gastric ulcer in the lesser curvature of the pylorus in a 76-year-old man. He had a history of *H. pylori* eradication. The background mucosa of the gastric body showed an atrophic mucosal change due to past *H. pylori* infection. Gastric mucosal redness was not observed in the greater curvature of the middle gastric body on white light imaging (WLI) (Fig. 1A). He received vonoprazan (20 mg) once daily for his gastric ulcer for 5 months. EGD performed 5 months later demonstrated the new appearance of linear redness in the greater curvature of the middle gastric body on WLI (Fig. 1B), which had not been observed before the initiation of the drug. A tissue biopsy taken from the gastric mucosa site with linear redness revealed inflammatory cell infiltration, parietal cell protrusions (PCPs), and oxyntic gland dilatation (Fig. 2A). His serum gastrin level (SGL) was shown to be 664 pg/mL. All linear redness was shown to have dis-

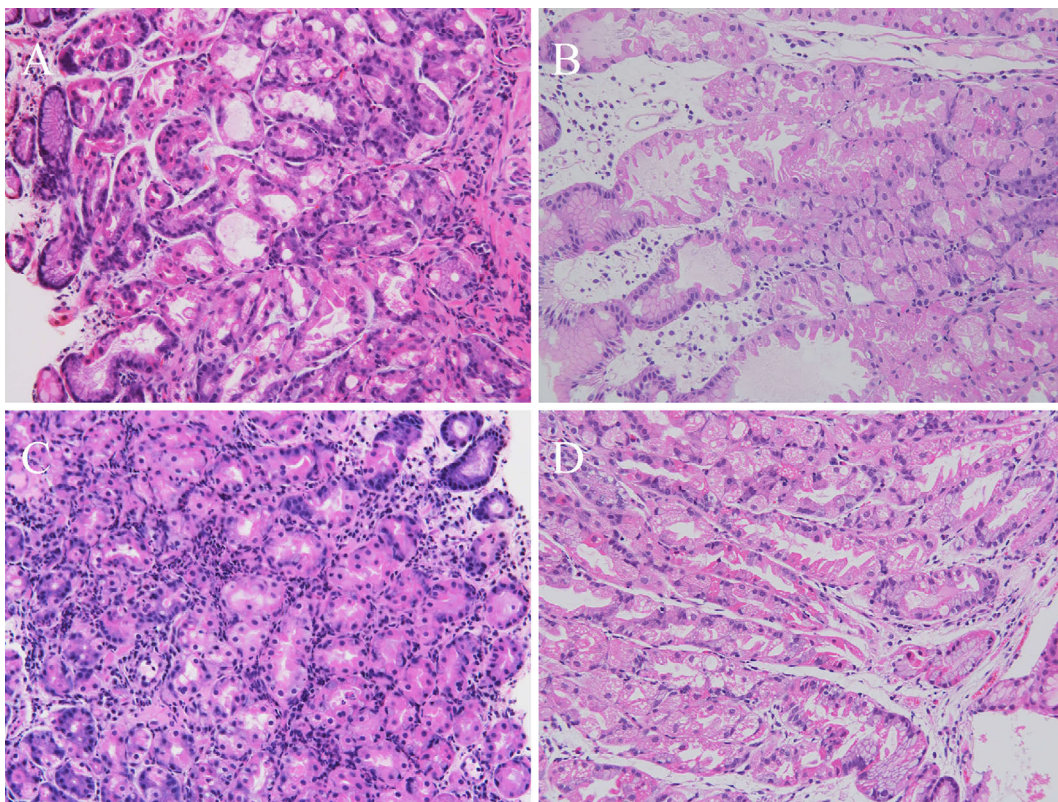
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**Figure 1.** Esophagogastroduodenoscopy. (A) Before the initiation of vonoprazan. (B) Linear redness newly appeared in the greater curvature of the middle gastric body after 5 months of treatment with vonoprazan. (C) The linear redness disappeared 1 year after switching from vonoprazan to esomeprazole.



**Figure 2.** Findings from a histopathologic examination of specimens from sites of gastric mucosal redness. (A) Case 1. The histological examination showed inflammatory cell infiltration, parietal cell protrusions (PCPs), and oxyntic gland dilatation. (B) Case 2. The histological examination showed inflammatory cell infiltration, PCPs, and oxyntic gland dilatation. (C) Case 3. The histological examination showed inflammatory cell infiltration and PCPs. (D) Case 4. The histological examination showed inflammatory cell infiltration and PCPs.

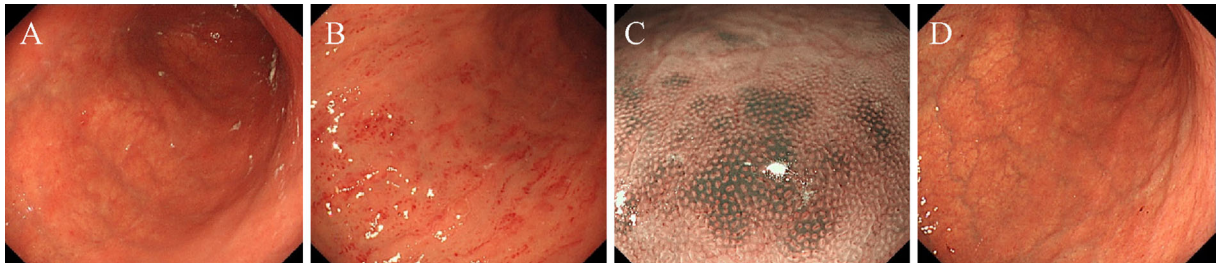
appeared on repeated EGD performed 1 year after switching from vonoprazan to esomeprazole (Fig. 1C). His SGL was found to have decreased to 559 pg/mL.

### Case 2

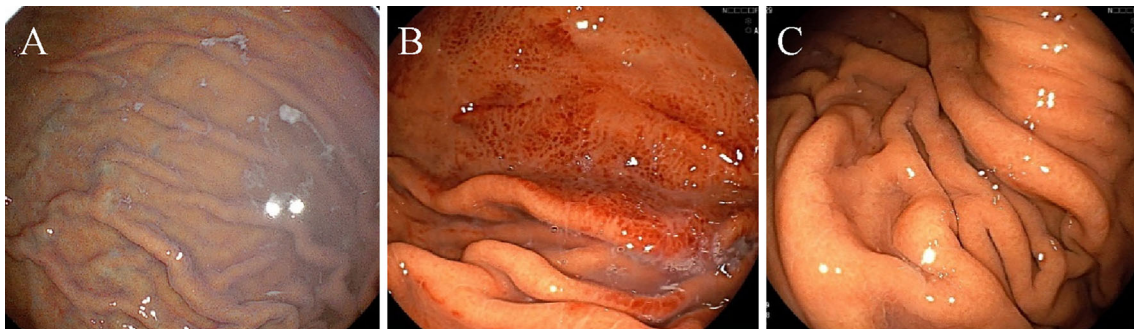
The patient was an 88-year-old man who had been diagnosed with early gastric cancer and undergone ESD. He had received vonoprazan (20 mg) once daily for the treatment of post-ESD ulcer for 4 months. He had a history of *H. pylori*

eradication. The background mucosa of the gastric body showed an atrophic mucosal change due to previous *H. pylori* infection. EGD performed 4 months later demonstrated the new appearance of spotty redness in the greater curvature of the middle gastric body on WLI (Fig. 3B), which had not been observed before the initiation of the drug (Fig. 3A). Magnifying endoscopy with narrow-band imaging (NBI) showed an oval crypt opening and diffuse redness of the surrounding mucosa (Fig. 3C). A tissue biopsy taken

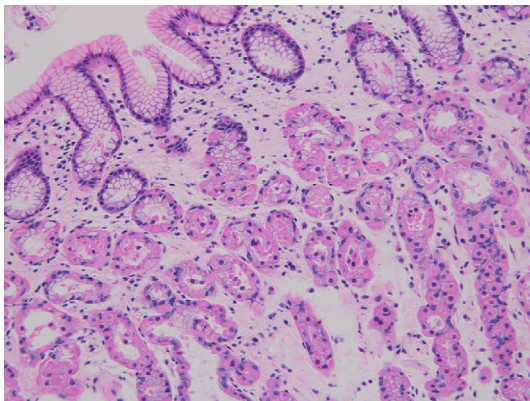




**Figure 3.** Esophagogastroduodenoscopy. (A) Before the initiation of vonoprazan. (B) Spotty redness newly appeared in the greater curvature of the middle gastric body after 4 months of treatment with vonoprazan. (C) Magnifying endoscopy with narrow-band imaging showed spotty redness. (D) The spotty redness disappeared 3 months after discontinuation of vonoprazan.



**Figure 4.** Esophagogastroduodenoscopy. (A) Before the initiation of vonoprazan. (B) Spotty redness newly appeared in the greater curvature of the middle gastric body after 2 months of treatment with vonoprazan. (C) The spotty redness disappeared 3 months after the discontinuation of vonoprazan.



**Figure 5.** Findings from the histopathologic examination of a specimen of a site of the mucosa in case 3, from which spotty redness had disappeared. A histological examination revealed improvement in inflammatory cell infiltration but no change in PCPs.

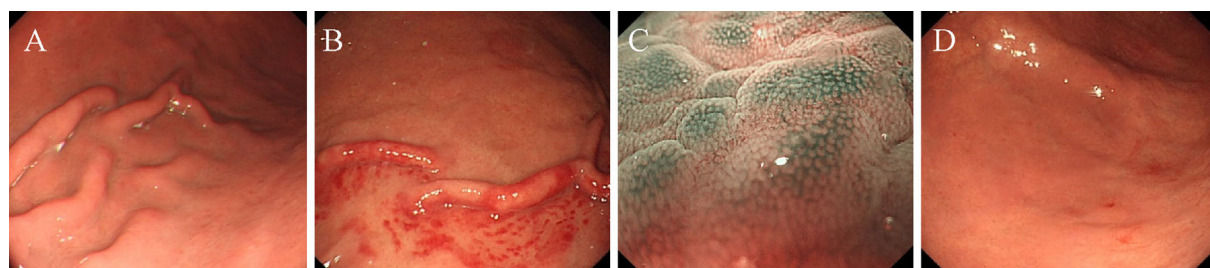
from a gastric mucosa site with spotty redness revealed inflammatory cell infiltration, PCPs, and oxyntic gland dilatation (Fig. 2B). His SGL was 1,720 pg/mL. All spotty redness was found to have disappeared on repeated EGD performed 3 months after the discontinuation of the drug (Fig. 3D) and his SGL was found to have returned to the normal range (143 pg/mL).

### Case 3

The patient was a 72-year-old man who had been diagnosed with recurrent esophageal cancer and who had undergone argon plasma coagulation (APC). He had received vonoprazan (20 mg) once daily for the treatment of post-APC ulcer for 2 months. He had a history of *H. pylori* eradication. The background mucosa of the gastric body showed an atrophic mucosal change due to earlier *H. pylori* infection. EGD performed 2 months later demonstrated the new appearance of spotty redness in the greater curvature of the middle gastric body on WLI (Fig. 4B), which had not been observed before the initiation of the drug (Fig. 4A). A tissue biopsy specimen taken from a gastric mucosa site with spotty redness revealed inflammatory cell infiltration and PCPs (Fig. 2C). His SGL was 161 pg/mL. All spotty redness was found to have disappeared on repeated EGD performed 3 months after the discontinuation of the drug (Fig. 4C). A tissue biopsy specimen taken from the same site revealed improvement in inflammatory cell infiltration but no change in the PCPs (Fig. 5). His SGL was 67 pg/mL.

### Case 4

The patient was a 79-year-old woman who had been diagnosed with early gastric cancer and undergone ESD. She



**Figure 6.** Esophagogastroduodenoscopy. (A) Before the initiation of vonoprazan. (B) Spotty redness newly appeared in the greater curvature of the middle gastric body after 6 months of treatment with vonoprazan. (C) Magnifying endoscopy with narrow-band imaging showed spotty redness. (D) The spotty redness disappeared 3 months after switching from vonoprazan to esomeprazole.

**Table 1.** Patient Characteristic.

Case	Age	Sex	Background mucosa		Medical history			Medication	
			<i>H. pylori</i>	Atrophy	Portal hypertension	Antithrombotic drugs	NSAIDs	Prior history of PPI use	
1	76	M	Previously infected	(O-1)	(-)	(-)	(-)	Rabeprazole	
2	88	M	Previously infected	(O-1)	(-)	(-)	(-)	Esomeprazole	
3	73	M	Previously infected	(O-1)	(-)	(-)	(-)	(-)	
4	79	F	Previously infected	(O-3)	(-)	(-)	(-)	Esomeprazole	

**Table 2.** Clinical Course.

Case	Vonoprazan dose	Appearance of redness			Disappearance of redness	
		Time after vonoprazan administration	SGL	Time after vonoprazan discontinuation	SGL	
1	20 mg	5 months	664 pg/mL	12 months	559 pg/mL	
2	20 mg	4 months	1,720 pg/mL	3 months	143 pg/mL	
3	20 mg	2 months	161 pg/mL	3 months	67 pg/mL	
4	20 mg	6 months	232 pg/mL	3 months	98 pg/mL	

SGL: serum gastrin level

had received vonoprazan (20 mg) once daily for the treatment of post-ESD ulcer for 6 months. The background mucosa of the gastric body showed an atrophic mucosal change due to previous *H. pylori* infection. EGD performed 6 months later revealed the new appearance of spotty redness in the greater curvature of the middle gastric body on WLI (Fig. 6B), which had not been observed before the initiation of the drug (Fig. 6A). Magnifying endoscopy with NBI showed oval crypt openings and diffuse redness of the surrounding tissue (Fig. 6C). A tissue biopsy specimen taken from the site with spotty redness revealed inflammatory cell infiltration and PCPs (Fig. 2D). Her SGL was 232 pg/mL. All spotty redness was found to have disappeared on repeated EGD performed 3 months after switching from vonoprazan to esomeprazole (Fig. 6D). Her SGL returned to normal (98 pg/mL).

All four patients were asymptomatic and none had a history of portal hypertension or non-steroidal anti-inflammatory drug (NSAID) use (Table 1). Only one patient had taken low-dose aspirin (LDA), clopidogrel, and ethylcosapentate as antithrombotic drugs. Furthermore, with the

exception of vonoprazan, no drugs-including drugs for the eradication of *H. pylori*-were used during the observation period.

## Discussion

Our cases have two important clinical implications. First, gastric mucosal redness presented as a vonoprazan-associated change in the gastric mucosa. The endoscopic and pathological features of vonoprazan-associated gastric mucosal redness remain largely unclear, with no reports available in the literature.

The profile of our four patients is summarized in the Tables. None of the four patients had a history of portal hypertension and no patients had taken NSAIDs that might have caused redness (Table 1). Additionally, *H. pylori* eradication treatment was not performed during the observation period. In our cases, gastric redness, which had not been previously observed, newly appeared at least two months after the initiation of vonoprazan, but disappeared at least three months after the discontinuation of the drug (Table 2). Thus, the

**Table 3. Lesion Characteristics.**

Case	Location	Endoscopic findings	NBI findings	Pathological findings
1	Greater curvature of the middle gastric body	Linear redness	(-)	Inflammatory cell infiltration, PCPs, oxyntic gland dilatations
2	Greater curvature of the middle gastric body	Spotty redness	Oval crypt openings and diffuse redness of the surrounding mucosa	Inflammatory cell infiltration, PCPs, oxyntic gland dilatations
3	Greater curvature of the middle gastric body	Spotty redness	(-)	Inflammatory cell infiltration, PCPs
4	Greater curvature of the middle gastric body	Spotty redness	Oval crypt openings and diffuse redness of the surrounding mucosa	Inflammatory cell infiltration, PCPs

NBI: narrow-band imaging, PCP: parietal cell profusion

redness was thought to have been induced by the administration of vonoprazan. The SGL was shown to have returned to normal in three of the patients after the discontinuation of vonoprazan (Table 2). Additionally, the redness observed in the greater curvature of the middle gastric body on WLI was spotty in three cases and linear in one (Table 3). On NBI, the lesion was depicted as oval crypt openings and diffuse redness of the surrounding mucosa (Table 3). To our knowledge, this is the first report describing vonoprazan-associated gastric mucosal redness.

The second implication of our cases is that vonoprazan-associated gastric mucosal redness may be pathologically characterized as inflammatory cell infiltration. Our study confirmed that PCPs and oxyntic gland dilatation were recognized in our cases, which is in agreement with an earlier report showing that PCPs and oxyntic gland dilatation were induced by the use of vonoprazan (8). It also suggested the involvement of inflammatory cell infiltration as a new finding. In one case, a tissue biopsy specimen taken from the site from which spotty redness had disappeared revealed improvement in inflammatory cell infiltration but no change in PCPs. Thus, we hypothesized that the gastric mucosal redness was caused by inflammation and not PCPs.

To the best of our knowledge, this is the first report describing the endoscopic and pathological features of vonoprazan-associated gastric mucosal redness that newly appeared after the initiation of the drug and which disappeared after its discontinuation. This new lesion may represent an additional adverse event associated with vonoprazan. While its clinical significance remains unclear, it appears to cause no symptoms.

**The authors state that they have no Conflict of Interest (COI).**

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