

Case Series

Vonoprazan-Associated Gastric Mucosal Redness in Non-*Helicobacter pylori*-Infected and *Helicobacter pylori*-Eradicated Stomach

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Keywords

Vonoprazan · Stomach · Gastric mucosal redness

Abstract

Vonoprazan-associated gastric mucosal redness is rare, and its endoscopic and pathological features remain poorly described. We report 4 cases of vonoprazan-associated gastric mucosal redness, that is, 2 cases each in non-*Helicobacter pylori*-infected and -eradicated stomach. In all cases, esophagogastroduodenoscopy demonstrated spotty and linear redness newly appearing in the greater curvature of the gastric body after initiation of vonoprazan but disappearing after its discontinuation. A tissue biopsy taken from the gastric mucosa with redness revealed various pathological findings and included inflammatory cell infiltration, parietal cell protrusions, oxyntic gland dilatations, congestion, focal hemorrhage with congestion beneath the basement membrane, and vacuolar degeneration of parietal cells. To our knowledge, this is the second report describing the endoscopic and pathological features of vonoprazan-associated gastric mucosal redness.

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Introduction

Vonoprazan is a potassium-competitive acid blocker (P-CAB) recently developed and approved for use in Japan [1]. Potassium-competitive acid blockers as a class reversibly inhibit gastric acid output through K⁺-competitive ionic binding to H⁺/K⁺-ATPase [2]. Vono-



Fig. 1. Esophagogastroduodenoscopy. **a** Before initiation of vonoprazan. **b** Spotty and linear redness newly appeared in the greater curvature of the gastric body after 29 months of treatment with vonoprazan. **c** Spotty and linear redness was reduced 1 month after switching from vonoprazan to esomeprazole. **d** Spotty and linear redness disappeared 3 months after switching from vonoprazan to esomeprazole. **e** Before initiation of vonoprazan. **f, g** Spotty and linear redness newly appeared in the greater curvature of the gastric body after 20 months of treatment with vonoprazan. **h** Spotty and linear redness disappeared 5 months after switching from vonoprazan to esomeprazole. **i** Before initiation of vonoprazan. **j** Spotty and linear redness newly appeared in the greater curvature of the gastric body after 1 month of treatment with vonoprazan. **k** Spotty and linear redness disappeared 2 months after switching from vonoprazan to esomeprazole. **l** Before initiation of vonoprazan. **m** Spotty and linear redness newly appeared in the greater curvature of the gastric body after 9 months of treatment with vonoprazan. **n** Spotty and linear redness disappeared 3 months after switching from vonoprazan to esomeprazole.

prazan is shown to selectively accumulate in gastric parietal cells in the mucosal layer of the rat stomach [3], and gastric cracked and cobblestone-like mucosa has been first reported as vonoprazan-associated gastric mucosal change [4]. Very recently, we reported 4 cases of vonoprazan-associated gastric mucosal redness which was characterized as newly appearing after initiation of the drug and disappearing after its discontinuation [5]. Vonoprazan-associated gastric mucosal redness has been rarely reported with its endoscopic and pathological features poorly described. We herein report additional 4 cases of vonoprazan-associated gastric mucosal redness, that is, 2 cases each in non-*Helicobacter pylori*-infected and -eradicated stomach, as the second report.

Case Presentation

Case 1

A 76-year-old woman had received vonoprazan (20 mg) once daily for gastroesophageal reflux disease. She had no history of *H. pylori* infection and tested negative for serum IgG antibody to *H. pylori*. Esophagogastroduodenoscopy (EGD) performed 29 months after initiation of the drug demonstrated spotty and linear redness in the greater curvature of the gastric body (Fig. 1b), which had not been observed before initiation of the drug (Fig. 1a). A tissue biopsy taken from the gastric mucosa with spotty and linear redness revealed focal hemorrhage, slight congestion, mild inflammatory cell infiltration, parietal cell protrusions (PCPs), and vacuolar degeneration of parietal cells (Fig. 2a). Her serum gastrin level (SGL) was shown to be 891 pg/mL. All spotty and linear redness was shown to have diminished and disappeared on repeated EGD performed 1 and 3 months after switching from vonoprazan to esomeprazole, respectively (Fig. 1c, d). Her SGL was found to have decreased to 284 pg/mL. A tissue biopsy specimen taken from the same site revealed improvement in previous pathological findings (Fig. 2b).

Case 2

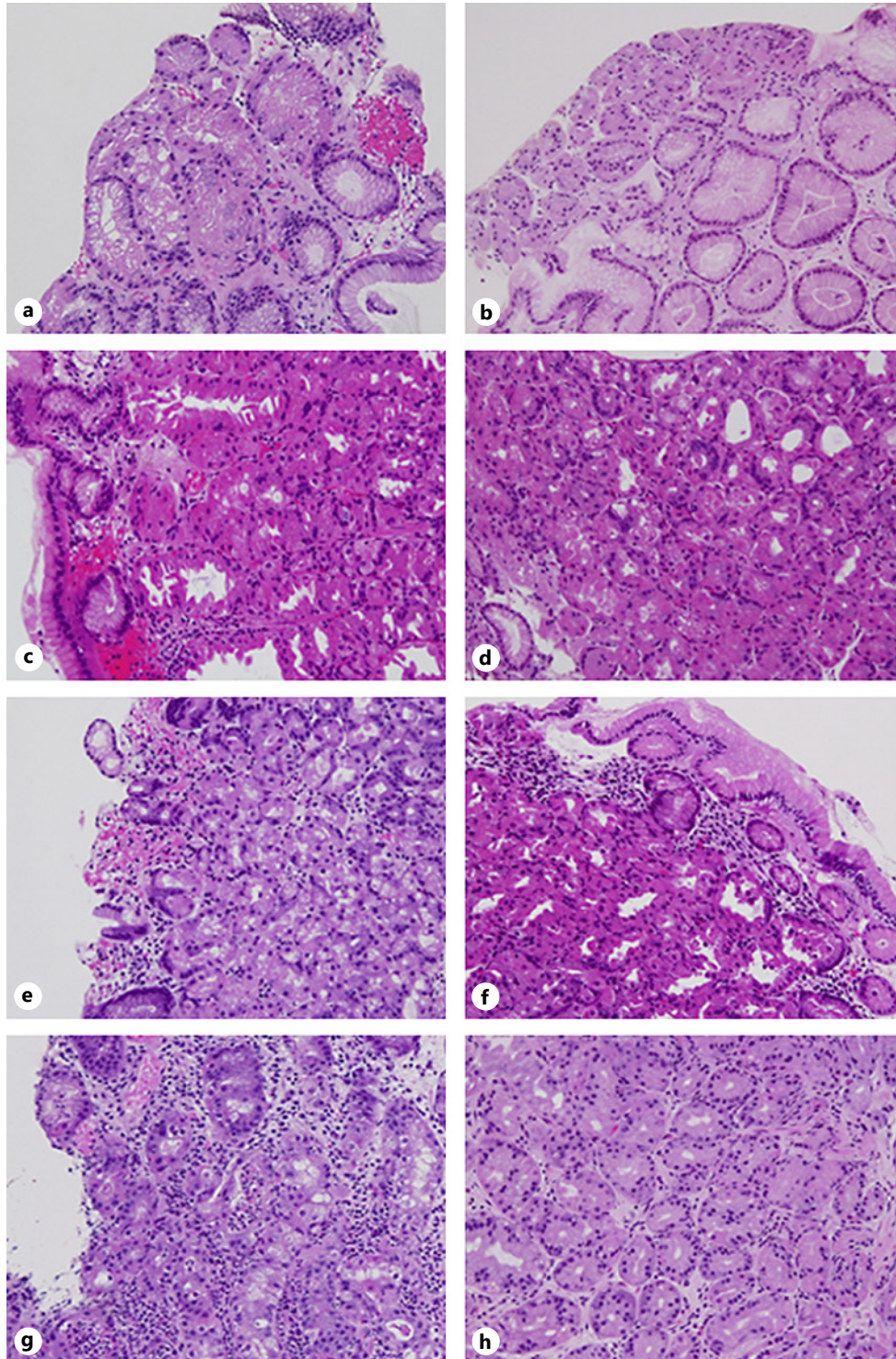
An 80-year-old woman visited a nearby clinic complaining of epigastric pain. EGD revealed normal gastric mucosa (Fig. 1e). Stool *H. pylori* antigen and ³C-urea breath test were all negative, suggesting noninfection of *H. pylori*. She had received vonoprazan (20 mg) once daily for treatment. EGD performed 20 months later demonstrated spotty redness newly appearing in the gastric body (Fig. 1f). The patient was referred to our hospital for further examination and treatment. EGD confirmed spotty and linear redness in the greater curvature of the gastric body (Fig. 1g). A tissue biopsy taken from the gastric mucosa with spotty and linear redness revealed focal hemorrhage and congestion beneath the basement membrane, mild inflammatory cell infiltration, PCPs, and oxyntic gland dilatation (Fig. 2c). Her SGL was 3,280 pg/mL. All spotty and linear redness was shown to have disappeared on repeated EGD performed 5 months after switching from vonoprazan to esomeprazole (Fig. 1h), and her SGL was shown to have decreased to 864 pg/mL. A tissue biopsy specimen taken from the same site revealed improvement in hemorrhage and congestion beneath the basement membrane but no change in inflammatory cell infiltration, PCPs, and oxyntic gland dilatation (Fig. 2d).

Fig. 2. Histopathologic examination. Case 1. A histopathologic examination of gastric mucosal redness revealed focal hemorrhage, slight congestion, mild inflammatory cell infiltration, PCPs, and vacuolar degeneration of parietal cells (**a**); and an examination of the mucosa from which redness had disappeared revealed improvement in previous pathological findings (**b**) (×100). Case 2. A histopathologic examination of gastric mucosal redness revealed focal hemorrhage and congestion beneath the basement membrane, mild inflammatory cell infiltration, PCPs, and oxyntic gland dilatation (**c**); and an examination of the mucosa from which redness had disappeared revealed improvement in hemorrhage and congestion beneath the basement membrane but no change in inflammatory cell infiltration, PCPs, and oxyntic gland dilatation (**d**) (×100). Case 3. A histopathologic examination of gastric mucosal redness revealed focal hemorrhage, congestion, mild inflammatory cell infiltration, PCPs, vacuolar degeneration of parietal cells, and oxyntic gland dilatation (**e**); and an examination of the mucosa from which redness had disappeared revealed improvement in hemorrhage, congestion, and vacuolar degeneration of parietal cells but no change in inflammatory cell infiltration, PCPs, and oxyntic gland dilatation (**f**) (×100). Case 4. A histopathologic examination of gastric mucosal redness revealed focal hemorrhage and congestion, marked inflammatory cell infiltration, PCPs, and oxyntic gland dilatation (**g**); and an examination of the mucosa from which redness had disappeared revealed improvement in previous pathological findings (**h**) (×100). PCPs, parietal cell protrusions.

(For figure see next page.)

Case 3

An 88-year-old man had received vonoprazan (20 mg) once daily for gastric ulcer. 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 1 month later demonstrated spotty and linear redness newly appearing in the greater curvature of the



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Table 1. Patient characteristics

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	F	Uninfected	(-)	(-)	(-)	(-)	(-)
2	80	F	Uninfected	(-)	(-)	(-)	(-)	(-)
3	88	M	Previously infected	(O-1)	(-)	(-)	(-)	(-)
4	83	M	Previously infected	(C-0)	(-)	(-)	(-)	Esomeprazole

gastric body (Fig. 1j), which had not been observed before initiation of the drug (Fig. 1i). A tissue biopsy specimen taken from the gastric mucosa with spotty and linear redness revealed focal hemorrhage, congestion, mild inflammatory cell infiltration, PCPs, vacuolar degeneration of parietal cells, and oxyntic gland dilatation (Fig. 2e). His SGL was 243 pg/mL. All spotty and linear redness was shown to have disappeared on repeated EGD performed 2 months after switching from vonoprazan to esomeprazole (Fig. 1k), and his SGL was shown to have decreased to 133 pg/mL. A tissue biopsy specimen taken from the same site revealed improvement in hemorrhage and congestion and vacuolar degeneration of parietal cells but no change in inflammatory cell infiltration, PCPs, and oxyntic gland dilatation (Fig. 2f).

Case 4

An 83-year-old man had received vonoprazan (20 mg) once daily for gastric ulcer. He had a history of *H. pylori* eradication. EGD performed 9 months later demonstrated spotty and linear redness newly appearing in the greater curvature of the gastric body (Fig. 1m), which had not been observed before initiation of the drug (Fig. 1l). The background mucosa of the gastric body showed no atrophic mucosal change. A tissue biopsy specimen taken from the gastric mucosa with spotty and linear redness revealed focal hemorrhage and congestion, marked inflammatory cell infiltration, PCPs, and oxyntic gland dilatation (Fig. 2g). His SGL was 1,300 pg/mL. All spotty and linear redness was shown to have disappeared on repeated EGD performed 3 months after switching from vonoprazan to esomeprazole (Fig. 1n), and his SGL was shown to have decreased to 133 pg/mL. A tissue biopsy specimen taken from the same site revealed improvement in previous pathological findings (Fig. 2h).

All 4 patients were asymptomatic and none had a history of portal hypertension or had received antithrombotic drugs and nonsteroidal anti-inflammatory drugs (Table 1). Furthermore, with the exception of vonoprazan, no drugs were used during the observation period, including those intended for *H. pylori* eradication.

Discussion/Conclusion

Our cases offer important implications for clinical practice. First, vonoprazan-associated gastric mucosal redness may occur not only in *H. pylori*-eradicated but also non-*H. pylori*-infected stomach. Vonoprazan-associated gastric mucosal redness has only rarely been reported, with its endoscopic and pathological features poorly described in the literature.

The endoscopic features of vonoprazan-associated gastric mucosal redness in the earlier report were spotty or linear redness in the greater curvature of the gastric body [5]. It had not been previously observed, newly appeared at least 2 months after initiation of the drug, and disappeared at least 3 months after discontinuation of the drug. In addition, this occurred

Table 2. Clinical course and lesion characteristics

Case	Vonoprazan dose, mg	Clinical course		Lesion characteristics			
		appearance of redness time after vonoprazan administration, months	disappearance of redness time after vonoprazan discontinuation, months	SGL, pg/mL	location	endoscopic findings	pathological findings
1	20	30	3	891	Greater curvature of the gastric body	Spotty and linear redness	Focal hemorrhage, slight congestion, mild inflammatory cell infiltration, PCPs, and vacuolar degeneration of parietal cells
2	20	20	5	3,280	Greater curvature of the gastric body	Spotty and linear redness	Focal hemorrhage and congestion beneath the basement membrane, mild inflammatory cell infiltration, PCPs, and oxyntic gland dilatation
3	20	1	2	243	Greater curvature of the gastric body	Spotty and linear redness	Focal hemorrhage, congestion, mild inflammatory cell infiltration, PCPs, vacuolar degeneration of parietal cells, and oxyntic gland dilatation
4	20	9	3	1,300	Greater curvature of the gastric body	Spotty and linear redness	Focal hemorrhage and congestion, marked inflammatory cell infiltration, PCPs, and oxyntic gland dilatation

SGL, serum gastrin level; PCPs, parietal cell protrusions.

in *H. pylori*-eradicated stomach in all cases. Similarly, in all the 4 cases reported in this study, spotty and linear redness appeared at least 1 month after initiation of the drug and disappeared at least 2 months after its discontinuation in the greater curvature of the gastric body (Table 2). The new findings in this report are that (1) vonoprazan-associated gastric mucosal redness occurred even in non-*H. pylori*-infected stomach and that (2) the process of disappearance over time of redness was clearly captured in 1 patient (case 1).

Second, vonoprazan-associated gastric mucosal redness is associated with various pathological findings. Our study confirmed the presence in our cases not only of inflammatory cell infiltration, PCPs, and oxyntic gland dilatation, in agreement with an earlier report [5], but also of congestion, focal hemorrhage with congestion beneath the basement membrane, and vacuolar degeneration of parietal cells, as new findings. A tissue biopsy specimen taken from the site from which spotty and linear redness had disappeared revealed improvement in focal hemorrhage, with congestion shown to be present in all 4 patients (100%), inflammatory cell infiltration in 2 patients (50%), and PCPs and oxyntic gland dilatation in 2 patients (50%). Thus, we hypothesized that microhemorrhage and congestion caused gastric mucosal redness. In conclusion, vonoprazan-associated gastric mucosal redness may occur in non-*H. pylori*-infected stomach and may be associated with various pathological findings.

Statement of Ethics

The study protocol was reviewed and approved by the Institutional Review Board of Hakodate National Hospital (Approval No. R3-0528001). Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose in association with this study.

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Author Contributions

K.K., N.K., R.W., M.H., M.T., M.T., and M.K. contributed equally to the study as well as to the preparation of the manuscript for publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries may be directed to the corresponding author.

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