Prevalence and factors associated with web-like mucus in the stomach after vonoprazan use

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Abstract. The appearance of 'web-like mucus' in the stomach is a novel phenomenon associated with vonoprazan (VPZ) usage, characterized by a descriptive mucus pattern resembling a spider web or net. The present study aimed to determine its prevalence and related factors. In this retrospective observational study, the medical records and endoscopic reports of 547 patients who underwent an esophagogastroduodenoscopy were reviewed. The overall prevalence of web-like mucus was 6% (33/547), with 97% (32/33) of these patients being VPZ users. Specifically, 19% (32/167) of VPZ users exhibited this web-like mucus pattern, which was significantly more prevalent in the VPZ group than in the control (no acid blocker intake), proton pump inhibitor, and histamine-2 receptor antagonist groups. Multivariate analysis identified that VPZ use was positively associated with web-like mucus, while open-type gastric atrophy and multiple white and flat elevated lesions were negatively associated. A retrospective analysis of endoscopic findings before initiating VPZ therapy showed that none of the 32 VPZ users with web-like mucus had exhibited the pattern previously. Furthermore, the Cochran-Armitage trend test indicated no significant association between the duration of VPZ therapy and the prevalence of web-like mucus. In conclusion, web-like mucus in the stomach is strongly associated with VPZ use but is not associated with the duration of VPZ therapy.

Introduction

The use of acid blockers, including vonoprazan (VPZ) and proton pump inhibitors (PPIs), has risen in response to the increasing prevalence of gastroesophageal reflux disease (GERD), which often requires long-term maintenance therapy with VPZ/PPI (1,2). All-age prevalence of GERD increased by 18.1% between 1990 and 2017 (3). Additionally, the implementation of *Helicobacter pylori* eradication therapy, which increases gastric acid secretion, contributes to the increased prevalence of GERD and, consequently, an increased consumption of VPZ/PPI. To prevent upper gastrointestinal bleeding, these acid blockers are persistently used in combination with low-dose aspirin (LDA) or non-steroidal anti-inflammatory drugs (NSAIDs). VPZ, a first-class potassium competitive acid blocker, has been available in Japan since 2015, and is associated with various lesions, including stardust gastric mucosal lesions (4).

However, the increase in the prolonged use of acid blockers has raised concerns among general practitioners regarding VPZ/PPI-associated gastric mucosal changes, including fundic gland polyps, gastric hyperplastic polyps, multiple white and flat elevated lesions, cobblestone-like gastric mucosal lesions and stardust gastric mucosal lesions (5). Recently, a review introduced 'web-like mucus' as a novel VPZ-associated gastric change (6). Kaneko *et al* (7) described this mucus as white and transparent with a spider web-like appearance, which is challenging to remove even with thorough endoscopic washing. This web-like mucus may represent a phenotype of excessive mucus production induced by VPZ use. However, the association between web-like mucus and long-term acid blocker use remains unclear. The present study aimed to elucidate the prevalence and associated factors of web-like mucus in the stomach.

Patients and methods

Study population and design. The present retrospective observational study included 608 consecutive patients who underwent an esophagogastroduodenoscopy (EGD) at Shinozaki Medical Clinic (Utsunomiya, Japan), a local private clinic, between December 2023 and June 2024. All EGD procedures performed using an ultrathin endoscope (EG-L580NW7; Fujifilm Corporation) were recorded. Medication histories were obtained from medical records and personal medication notebooks issued by the Japan Pharmaceutical Association, ensuring a comprehensive record

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of the prescribed medications from other medical facilities. An endoscopist had reviewed each patients' medication history before performing the EGD. Acid blockers used included VPZ, PPIs and histamine 2-receptor antagonists (H2RA). The standard endoscopic report documented the grade of gastric atrophy using the Kimura-Takemoto system (8), as well as the presence or absence of fundic gland polyps, gastric hyperplastic polyps, multiple white and flat elevated lesions, cobblestone-like gastric mucosal lesions, stardust gastric mucosal lesions and web-like mucus. An endoscopist meticulously examined these mandatory variables during the EGD and completed a standardized endoscopic report form immediately after the procedure. During each EGD session, more than 50 images, including several images of the gastric fundus, were routinely captured. *H. pylori* infection status was determined using serum anti-*H. pylori* immunoglobulin G analysis, stool antigen testing or the ^{13}C-urea breath test. Any history of *H. pylori* eradication was confirmed retrospectively through medical records or patient interviews. Web-like mucus was defined as a mucus pattern in the stomach resembling a spider web or net-like appearance, extending from the fundus to the greater curvature of the upper body (Fig. 1). This change was diagnosed solely based on endoscopic findings. The main difference between web-like mucus and general mucus adhesion is that web-like mucus forms a solid adhesion resistant to thorough washing with a syringe or water jet during endoscopy. The duration of VPZ therapy was defined as the interval between the start date of VPZ and the date of the EGD.

Patients were excluded from the current retrospective analysis based on the following criteria: i) A current *H. pylori* infection; ii) the current use of acid blockers for <1 year; iii) a history of esophageal or gastric surgery; and iv) concurrent use of LDA and/or NSAIDs. Consequently, 61 patients were excluded and the remaining 547 patients were analyzed. These patients were categorized into four groups: Control (no acid blocker intake; n=308), VPZ (n=167), PPI (n=49) and H2RA (n=23) groups. This study protocol was approved by the Institutional Review Board of Shinozaki Medical Clinic (approval no. 31-R001), and written informed consent was obtained from all patients.

Statistical analysis. Categorical data were compared using either the χ^2 test or the Fisher's exact tests for expected counts of <5. Continuous data were compared using the Mann-Whitney U test. Factors for multivariate analysis using a logistic regression model were selected based on their clinical significance in univariate analysis. The aforementioned statistical analyses were performed using Statflex version 7.0 (Artech Co., Ltd.). The trend in the duration of VPZ use and the prevalence of web-like mucus was evaluated using the Cochran-Armitage trend test with BellCurve for Excel software (Social Survey Research Information Co., Ltd.). P<0.05 was considered to indicate a statistically significant difference.

Results

Prevalence of web-like mucus. The baseline characteristics of the 547 patients are presented in Table I. The mean age of the cases was 64.2 years (standard deviation, 14.3; range, 16-88 years), with 44% of the patients being male. Approximately one-half of the patients (47%) had a history of *H. pylori* eradication. For most patients, the indication for EGD was screening. Open-type gastric atrophy was less common among patients with web-like mucus compared with that in patients without this finding (P=0.02). Hiatal hernia, gastric hyperplastic polyps and stardust gastric mucosal lesions were significantly more frequent in the web-like mucus group compared with those in the no web-like mucus group. The mean duration of VPZ therapy in the VPZ group (n=167) was 4.3±2.1 years. The overall prevalence of web-like mucus was 6% (33/547), with 97% (32/33) of these patients using VPZ. Specifically, 19% (32/167) of VPZ users exhibited web-like mucus. At the time of EGD, the daily doses of VPZ administered were either 10 mg (n=147) or 20 mg (n=20). The prevalence of web-like mucus was 18% (26/147 patients) in the 10-mg group and 30% (6/20 patients) in the 20-mg group. There was no significant difference in the prevalence of web-like mucus between the two dosage groups (P=0.189).

Factors associated with web-like mucus. To minimize confounding variables, a multivariate analysis was performed to identify factors associated with web-like mucus (Table II). VPZ use was identified as a significant positive factor (P<0.001), while open-type gastric atrophy and multiple white and flat elevated lesions were identified as significant negative factors (P=0.019), after adjusting for potential confounders.

Presence or absence of web-like mucus before starting VPZ. A back-to-back analysis of the EGD findings before the initiation of VPZ was conducted among the 32 patients with web-like mucus who were undergoing long-term VPZ therapy. EGD images of the gastric fundus before starting treatment with VPZ were obtained for all patients, and none of these patients had exhibited web-like mucus before starting VPZ (0%) (Fig. 1C).

Duration of VPZ therapy and prevalence of web-like mucus. The association between the duration of VPZ therapy and the prevalence of web-like mucus was evaluated (Fig. 2). No significant increase in prevalence was observed over time. The Cochran-Armitage trend test indicated no significant association between the duration of VPZ therapy and the prevalence of web-like mucus (P=0.884).

Discussion

The present retrospective observational study demonstrated a significant association between web-like mucus and the use of VPZ, a finding supported by the multivariate analysis. Severe gastric atrophy and multiple white and flat elevated lesions were identified as significant negative factors for web-like mucus. In back-to-back analyses, no instances of web-like mucus were observed before initiating VPZ therapy. Furthermore, the duration of VPZ therapy did not influence the prevalence of web-like mucus.

The relationship between mucin production and acid blockers has been explored in previous studies. A double-blind study involving asymptomatic volunteers found that rabeprazole increased gastric mucin by 41%, while pentagastrin increased it by 160% (9). Additionally, rabeprazole and

Table I. Characteristics of the 547 included patients.

Characteristic	Web-like mucus (n=33)	No web-like mucus (n=514)	P-value
Mean age ± SD, years	65±15	64±14	0.487
Sex, male, n (%)	13 (39.4)	229 (45.5)	0.563
History of *H. pylori* eradication, n (%)	13 (39.4)	242 (47.1)	0.390
Indication, n (%)			0.094[a]
Screening	32 (96.9)	468 (91.1)	
Symptoms	0 (0.0)	41 (7.9)	
Abnormal gastrointestinal series	1 (3.0)	2 (0.3)	
Anemia	0 (0.0)	3 (0.5)	
Hiatal hernia, n (%)	6 (18.2)	35 (6.8)	0.016
Gastric atrophy, n (%)			0.037[a]
No atrophy	16 (48.5)	220 (42.8)	
Closed-type	13 (39.4)	134 (26.1)	
Open-type	4 (12.1)	160 (31.1)	
Gastric ulcer scar, n (%)	0 (0.0)	18 (3.5)	0.274
Duodenal ulcer scar, n (%)	3 (9.1)	23 (4.5)	0.201[a]
Fundic gland polyp, n (%)	13 (39.4)	142 (27.6)	0.145
Gastric hyperplastic polyp, n (%)	6 (18.2)	24 (4.7)	0.006[a]
Multiple white and flat elevated lesions, n (%)	5 (15.2)	117 (22.7)	0.308
Cobblestone-like gastric mucosal lesions, n (%)	3 (9.1)	35 (6.8)	0.492[a]
Stardust gastric mucosal lesions, n (%)	19 (57.5)	102 (19.8)	<0.001
Acid blocker, >1 year, n (%)			<0.001[a]
None	1 (3.0)	307 (59.7)	
Vonoprazan	32 (97.0)	135 (26.2)	
Proton pump inhibitor	0 (0.0)	49 (9.5)	
Histamine-2 receptor antagonist	0 (0.0)	23 (4.5)	

[a]Fisher's exact test.

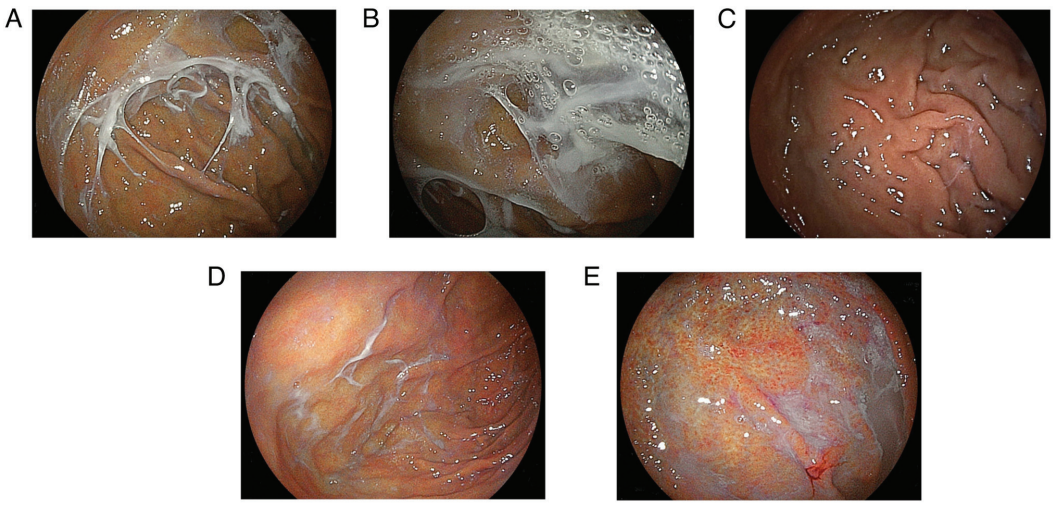

Figure 1. Endoscopic images of web-like mucus. (A) Distant view along the greater curvature of the upper body and fundus of the stomach in a patient undergoing prolonged vonoprazan therapy on linked color imaging (LCI). (B) Close-up view showing white and transparent mucus in a former patient on LCI. (C) Gastric fundus without web-like mucus before starting vonoprazan in a former patient on white light imaging. (D) Web-like mucus in a patient not receiving acid blockers on LCI. (E) General mucus adhesion of the gastric fundus on LCI.

pentagastrin administration elevated gastric juice viscosity (9). Web-like mucus may develop due to excessive mucin (mucus glycoprotein) production stimulated by gastrin or prostaglandin, potentially exacerbating by acid blockers. Although

Table II. Factors associated with web-like mucus.

	Univariate analysis			Multivariate analysis		
Factor	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age, >60 years	1.127	0.524-2.421	0.759			
Male	0.809	0.394-1.661	0.563			
History of *H. pylori* eradication	0.731	0.356-1.500	0.392			
Hiatal hernia	3.041	1.178-7.855	0.021	1.567	0.512-4.791	0.430
Open-type gastric atrophy	0.305	0.106-0.883	0.028	0.252	0.082-0.773	0.015
Fundic gland polyp	1.703	0.825-3.514	0.149			
Gastric hyperplastic polyp	4.537	1.712-12.027	0.002	1.781	0.561-5.649	0.327
Multiple white and flat elevated lesions	0.606	0.229-1.604	0.313	0.285	0.099-0.820	0.019
Cobblestone-like gastric mucosal lesion	1.369	0.398-4.708	0.618			
Stardust gastric mucosal lesions	5.482	2.659-11.302	<0.001	0.884	0.367-2.129	0.783
Vonoprazan use	89.837	12.158-663.827	<0.001	119.420	15.091-945.033	<0.001

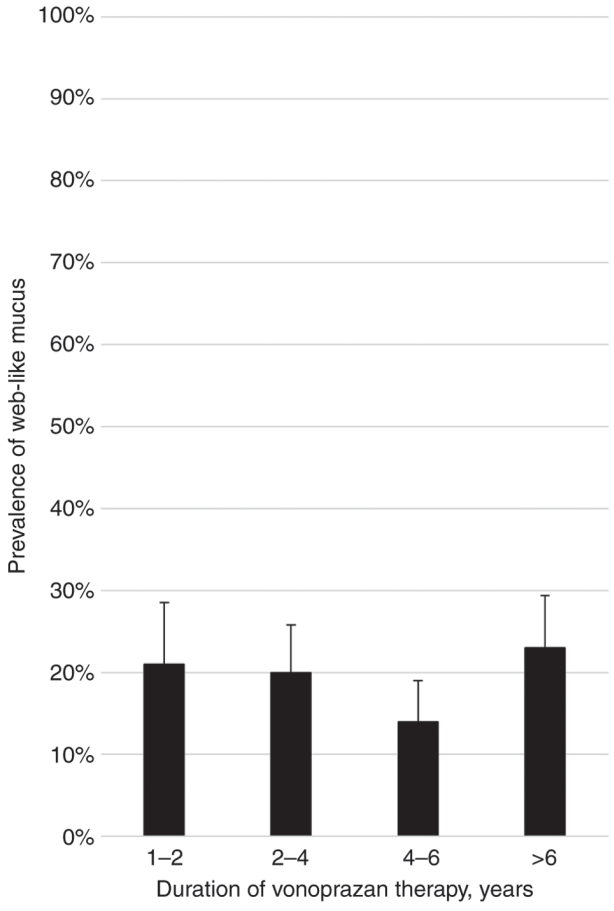

Figure 2. Association between the prevalence of web-like mucus and duration of vonoprazan therapy.

both VPZ and PPIs induce hypergastrinemia, VPZ induces significantly higher levels than PPIs (10). Further studies are needed to investigate the effects of VPZ/PPI on the development of web-like mucus.

While VPZ/PPI-related gastric mucosal changes are commonly discussed in relation to hypergastrinemia, several conditions, such as fundic gland polyps, multiple white and flat elevated lesions, and cobblestone-like gastric mucosal changes, are not related to hypergastrinemia (5). Conversely, the present multivariate analysis did not establish significant associations between these lesions and web-like mucus, although gastric hyperplastic polyps and stardust gastric mucosal lesions may be related to hypergastrinemia. Additionally, the present study identified open-type gastric atrophy as a negative factor for web-like mucus, which contradicts our previous findings linking it to hypergastrinemia during prolonged VPZ therapy (11). In patients with severe gastric atrophy, the number of mucus-producing cells may be reduced, leading to diminished mucus production. Although hypergastrinemia is more predominant among females than males, regardless of the acid suppression therapy (11,12), no sex-specific predominance in the prevalence of web-like mucus was observed in the present study. In addition to hypergastrinemia, we speculate that VPZ-specific mechanisms, which remain unidentified, may contribute to the development of web-like mucus.

The mucus layer of the stomach protects the gastric mucosa from acid and pepsin (13). Generally, LDA/NSAIDs reduce mucin production, compromising the gastric mucus barrier and increasing susceptibility to mucosal injury (14). This reduction in gastric mucus is caused by decreased cyclooxygenase and prostaglandin production due to LDA/NSAIDs. PPIs help reduce upper gastrointestinal bleeding associated with LDA/NSAIDs by enhancing the gastric mucosal barrier (15,16). Importantly, VPZ has demonstrated significantly better efficacy than that of PPIs in preventing LDA-associated upper gastrointestinal bleeding (17), potentially due to its superior enhancement of gastric mucus production. However, a conclusion cannot be made over whether web-like mucus represents a harmful change. VPZ is known to have a protective effect against NSAID-induced gastric mucosal damage, which we hypothesize may be related to an increased mucosal layer resulting from hypergastrinemia induced by VPZ. This excessive mucus production could contribute to the formation of web-like mucus.

Strong and sustained acid suppression therapy with VPZ leads to bacterial overgrowth possibly associated with the

development of web-like mucus. PPIs alter the normal microbiota throughout the gastrointestinal tract, and small intestinal bacterial overgrowth has been observed in 50% of patients using PPIs (18). Additionally, studies have shown that PPI users had significantly higher levels of non-*H. pylori* bacteria, including streptococci, in gastric juice compared with non-PPI users or H2RA users (19,20), and that streptococcal species are present in patients with web-like mucus (7). PPI therapy can independently lead to both bacterial overgrowth and increased gastric mucus production as a protective mechanism. It is plausible that bacterial overgrowth due to VPZ therapy may further stimulate mucus secretion. However, more targeted research is needed to elucidate this relationship.

The present study offers several novel contributions compared with previous research on web-like mucus. Firstly, a back-to-back analysis of endoscopic findings before and after initiating VPZ therapy, which was not addressed in earlier studies, clarified that none of the patients exhibited web-like mucus prior to VPZ administration, which strengthened the causal association between VPZ use and the development of web-like mucus. Secondly, the current duration-dependent analysis indicated that the prevalence of web-like mucus is not associated with the duration of VPZ use. Thirdly, the mean duration of VPZ therapy was 52 months, which was significantly longer than the 1-26 months reported in prior research (7). This extended duration provides a more comprehensive understanding of the long-term effects of VPZ. Fourthly, subjects with current *H. pylori* infection were excluded to eliminate potential confounding effects. Fifthly, the prevalence of web-like mucus among VPZ users and H2RA users was compared, which has not been previously reported. Lastly, a multivariate analysis was performed that included representative lesions associated with potassium-competitive acid blockers and PPIs, providing a more detailed assessment of factors associated with web-like mucus.

Stardust gastric mucosal lesions, another novel VPZ-associated gastric mucosal change, were reported by Yoshizaki *et al* (4) in 2021. These lesions, strongly linked to VPZ use, histologically manifest as periodic acid-Schiff stain-positive mucus pools within dilated ducts. Similar mechanisms may underlie both intraductal mucus production and web-like mucus formation due to VPZ administration. However, the present multivariate analysis did not establish a significant association between stardust gastric mucosal lesions and web-like mucus. Therefore, further investigations are warranted to elucidate the developmental mechanisms of these changes.

There are some limitations to the present study. Firstly, this was a single-center retrospective observational study. Although consecutive patients were included, there may be selection and information biases that could potentially impact the accuracy of the results. Secondly, a bacterial analysis or molecular investigation of the web-like mucus was not performed; therefore, the present study did not explore its potential pathological mechanisms. Thirdly, web-like mucus was diagnosed solely based on endoscopic findings. Fourthly, the endoscopist was not blinded to the medication history and did not evaluate the gastric mucosa using magnifying endoscopy.

In conclusion, web-like mucus is strongly associated with VPZ use, with 19% of VPZ users developing this feature after initiating VPZ therapy; however, the prevalence of web-like mucus is not associated with the duration of VPZ therapy. Further studies are needed to clarify the pathophysiology of web-like mucus and its association with potent acid suppression.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SS and HS were responsible for conception and design, data collection, data analysis and interpretation, and drafting and writing the manuscript. HO and TY were responsible for conception and design, and critical revision of important intellectual content in the manuscript. HY was responsible for data analysis and interpretation, and critical revision of important intellectual content in the manuscript. All authors read and approved the manuscript.

Ethics of approval statement and patient consent statement

This study protocol was approved by the Institutional Review Board of Shinozaki Medical Clinic (approval no. 31-R001). The Institutional Review Board waived the requirement for informed consent from participants due to the retrospective nature of the study.

Patient consent for publication

The Institutional Review Board waived the requirement for informed consent from participants due to the retrospective nature of the study.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

AI tools were utilized to enhance the readability and language of the manuscript. Subsequently, the authors revised and edited the AI-generated content, taking full responsibility for the final version of the manuscript.

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