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Endoscopic finding of hematin represents strong gastric acidity

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Abstract

Background Hematin is a state in which hemoglobin, as petechiae, is discolored to a brown coffee color by gastric hydrochloric acid. Given the nature of hematin, a close relationship between hematin and acidity has been suggested, but has not been confirmed. We investigated the clinical significance of endoscopic finding of hematin with respect to gastric acidity.

Methods A total of 501 patients were assessed for both hematin and fasting gastric juice pH by endoscopy. Endpoints were as follows: 1) the relationship between the presence of hematin and the fasting gastric juice pH; and 2) the diagnostic performance of endoscopic hematin. In addition, we performed a supplementary *in vitro* study to clarify the relationship between hematin formation and various acid pH levels.

Results The prevalence of hematin was 31.1% (142/206), 4.6% (5/109) and 45.2% (84/186) in the *H. pylori*-uninfected, -infected and -eradicated groups, respectively. The mean pH of fasting gastric juice in the hematin-positive cases was significantly lower than the hematin-negative cases (mean pH 1.2, 95% confidence interval [CI] 1.1-1.3 vs. 2.7 95%CI 2.5-3.0; P<0.001). The sensitivity, specificity, positive predictive value and negative predictive value of hematin for predicting strong acidic condition (pH 1 or 2 for fasting gastric juice) were 36.0%, 98.1%, 98.7% and 29.3%, respectively. Interobserver agreement was categorized as "excellent" (κ=0.88). Supplementary *in vitro* results showed that hematin formation was only observed at a pH=1.

Conclusion Endoscopic finding of hematin represent strong gastric acidity.

Keywords Hematin, gastric acid, fasting gastric juice, gastritis classification, endoscopy

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Introduction

Gastric acidity is closely related to various types of upper gastrointestinal disorders, including gastroesophageal reflux disease (GERD) and peptic ulcer in *Helicobacter pylori* (*H. pylori*) infection status [1]. Therefore, it is very important to evaluate the gastric acid condition in diagnosing these diseases and considering treatment strategies or management. However, the techniques for the estimation of gastric acid secretion are time-consuming and are not readily available in routine clinical practice. Therefore, it would be highly desirable to determine the endoscopic findings predicting gastric acidity.

With respect to determining the intragastric acidity endoscopically, we have recently reported the clinical significance of a white opaque substance (WOS) by magnification endoscopy with narrow band imaging (M-NBI) [2,3]. Briefly, the presence of a WOS within intestinal metaplasia observed by M-NBI was shown to be closely associated with hypochlorhydria following *H. pylori* infection [2,3], and thus could be a novel endoscopic marker of gastric acidity [2,3]. However, little is known about endoscopic findings under strongly acid conditions.

Hematin, or "acidic hematin", as the name suggests, has the potential to be one of the predictors of endoscopic findings suggestive of strong gastric acid. Hemoglobin is converted into hematin by hydrochloric acid in the stomach [4]. The color of hematin changes from bright red to a brown coffee color, while

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Conflict of Interest: None

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it is also altered to a completely different chemical structure from hemoglobin [4]. Therefore, given the nature of hematin itself, it is logical that there is a close relationship between endoscopic hematin and acidity. The first report on endoscopically visualized hematin was introduced as a finding in the Forrest classification [5,6]. Hematin has been proposed as one of the findings of hemorrhagic ulcer (Forrest IIc), but its relationship with gastric acid has not been discussed [5,6]. Recently, the Japan Gastroenterological Endoscopy Society proposed the Kyoto classification as a new classification system for endoscopic gastritis based on *H. pylori* infection status [7] and gastric cancer risk [8,9]. In this classification, hematin was proposed as one of the frequently observed findings in *H. pylori*-negative patients (no gastritis) and patients previously infected with *H. pylori* (inactive gastritis) [7], but it has not been discussed in terms of gastric acidity. Interestingly, Hatta *et al* recently reported that endoscopic hematin and antral erosion have a potential as endoscopic findings associated with hyperchlorhydria status [10].

As mentioned above, there are very few reports of hematin and gastric acidity. However, we strongly believe that, given the nature of hematin itself, this substance may be an excellent endoscopic finding that predicts strong gastric acidity. The aim of the present study was to determine the relationship between endoscopically visualized hematin and gastric acidity.

Patients and methods

Study design and clinical study participants

This study was based on a retrospective evaluation of data accumulated in a database based on our previous study [3]. Briefly, between April 2014 and July 2016, we extracted 582 patients at Oita Red Cross Hospital who underwent upper gastrointestinal (GI) screening endoscopy and intragastric pH assessment. Subjects were excluded if they had the following: 1) a history of gastric resection; 2) severe organ failure such as liver, renal, or cardiopulmonary dysfunctions; 3) current intake of antacids (within 5 days prior to the endoscopic examination); 4) patients within 6 months of prior *H. pylori* eradication; 5) an unclear *H. pylori* status or suggestive of spontaneous *H. pylori* eradication; and 6) endoscopic images insufficient for assessment due to hemorrhage, residue, or cloudy lenses. After 81 patients had been excluded, a total of 501 patients remained for analysis in this study.

The study was approved by the Institutional Review Board of Oita Red Cross Hospital (IRB No. 273) and conducted according to the Declaration of Helsinki. All patients provided written informed consent.

Endoscopic procedure and pH measurement of fasting gastric juice

A high-resolution magnifying upper GI endoscope (GIF-Q240Z; Olympus Co. Ltd., Tokyo, Japan) or a high-definition magnifying upper GI endoscope (GIF-H260Z; Olympus Co. Ltd., Tokyo, Japan) and an electronic endoscopy system (EVIS LUCERA Spectrum; Olympus Co. Ltd., Tokyo, Japan) were used. Measurement of the fasting gastric juice pH and endoscopic examinations were carried out by specialists certified by the Japan Gastroenterological Endoscopy Society. Endoscopic studies were performed following an overnight fast of >12 h.

To prevent contamination from affecting the accuracy of the pH measurements, premedication (such as a mucolytic or deforming agent) was not administered, except for local pharyngeal anesthesia with an 8% lidocaine pump spray. After the endoscope had been inserted into the stomach, pooled gastric juice was aspirated and collected endoscopically according to a previously described technique [11]. The pH of the collected sample was immediately measured using a 14-step pH test strip (pH 1-14; AS ONE Co. Ltd, Osaka, Japan). Following this, the observer performed a routine screening endoscopy study by high-resolution white light electronic endoscopy. The endoscopic photos and the results were recorded in a digital filing system (NEXUS; Fuji Film Medical Co., Tokyo, Japan).

Definitions and evaluation of hematin

As shown in Fig. 1, we defined the presence of hematin to be when 3 or more small brown coffee color spots without an ulcer were observed by white light endoscopic image. In the present study, the evaluation of the presence of hematin in endoscopic images was retrospectively reviewed by 2 authors (MA and TU) blinded to the results of fasting gastric juice pH.

Definitions of *H. pylori* status

To detect *H. pylori* infection, the following tests were used: serum IgG antibody against *H. pylori*; 13C-urea breath test (UBT); urine antibody and stool antigen against *H. pylori*; and histologic examination. When a serum IgG antibody was used, an antibody titer <3 U/mL was considered negative and >10 U/mL was considered positive. When antibody titer was 3-10 U/mL, we added another test. A positive result for any test was diagnosed as "*H. pylori*-infected." A negative result for at least one test, without endoscopic atrophy, was diagnosed as

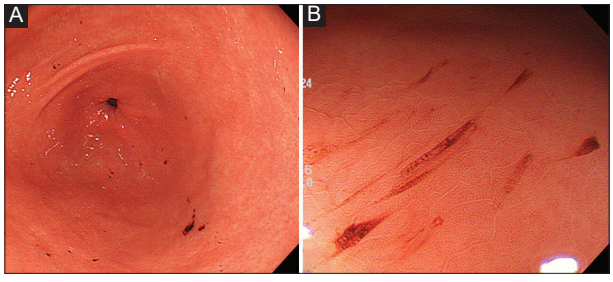

Figure 1 Definitions of endoscopic findings of hematin. (A) We defined hematin when 3 or more small brown coffee color spots without ulcers were observed by white light endoscopy. (B) High-magnification image of the hematin

"*H. pylori*-uninfected." When a UBT yielded negative results with a history of eradication therapy, a diagnosis of "*H. pylori*-eradicated" was assigned. Subjects with a negative result for at least 2 of the tests, combined with endoscopic atrophy and no history of *H. pylori* eradication suggestive of spontaneous eradication, were excluded from the study.

Endpoints for the clinical study

The endpoints of the clinical study were as follows: 1) the relationship between the presence of hematin and fasting gastric juice pH; 2) the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of hematin for predicting strong acidity (fasting gastric juice pH 1 or 2). To determine interobserver agreement for the diagnosis of hematin, 2 experienced endoscopists (MA and TU) independently assessed 100 sets of endoscopic images containing hematin-positive and -negative cases.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD) or 95% confidence interval (CI). We used the chi-square test for categorical comparison of the data. Differences in the means of continuous data were compared using Wilcoxon's rank-sum test. A P-value <0.05 was considered statistically significant. We calculated the value of the interobserver agreement using the kappa statistic to clarify the reproducibility of the endoscopic diagnosis of hematin. Kappa values (κ) between 0.81-1.00 indicated excellent, 0.61-0.80 indicated good, 0.41-0.60 indicated moderate, 0.21-0.40 indicated fair, and 0-0.20 indicated poor reproducibility [12]. All statistical analyses were performed using JMP-9 software (SAS Institute, Cary, NC, USA).

Supplementary *in vitro* study

To clarify the relationship between hematin formation and acidic levels, we conducted a supplementary *in vitro* study. We prepared 125 μL of hydrochloric acid buffer gradually adjusted in 8 steps (pH 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, and 7.0), and 5 μL of blood was added to each solution. The blood used in this study was obtained from one author (TU), collected in his health test. Then, we evaluated hematin formation after 5 min. The endpoint of the experimental study was the relationship between hematin formation and acid pH.

Results

Baseline patient characteristics

The baseline patient characteristics are summarized in Table 1. The mean age of the 501 patients was 57.2±13.4 years. The male-to-female ratio was 303:198. The *H. pylori* status of the 501 patients was as follows: 206 (41.1%) were *H. pylori*-uninfected; 109 (21.8%) were *H. pylori*-infected; and 186 (37.1%) were *H. pylori*-eradicated. Of the 501 patients, 153 were positive for hematin and 348 were negative. The prevalence of hematin was 31.1% in *H. pylori*-uninfected, 4.6% in *H. pylori*-infected, and 45.2% in *H. pylori*-eradicated groups (P<0.001). According to the Kimura-Takemoto classification system for degree of gastritis [13], 224 had no atrophy, 127 had closed-type atrophic gastritis, and 150 had open-type atrophic gastritis. The prevalence of hematin was 71 (31.7%) in the no-atrophy group, 53 (41.7%) in the closed-type atrophy group, and 29 (19.3%) in the open-type atrophy group (P<0.001). According to the Los Angeles (LA) classification system for degree of reflux esophagitis [14], 52 patients had LA-A or higher degree of reflux esophagitis. The prevalence of hematin was 131 (29.2%) in LA grade N and 22 (42.3%) in LA grade >A (P=0.0516). Eight patients had gastric ulcer and 4 patients duodenal ulcer. The prevalence of hematin was 0 (0%) in the patients with gastric ulcer (P=0.0587) and 3 (75%) in those with duodenal ulcer (P=0.0526).

Relationship between presence of hematin and pH of fasting gastric juice

The mean pH (95%CI) of fasting gastric juice was significantly lower in the hematin-positive cases than in the hematin-negative cases (mean pH 1.2, 95%CI 1.1-1.3 vs. 2.7, 95%CI 2.5-3.0; P<0.001; Fig. 2).

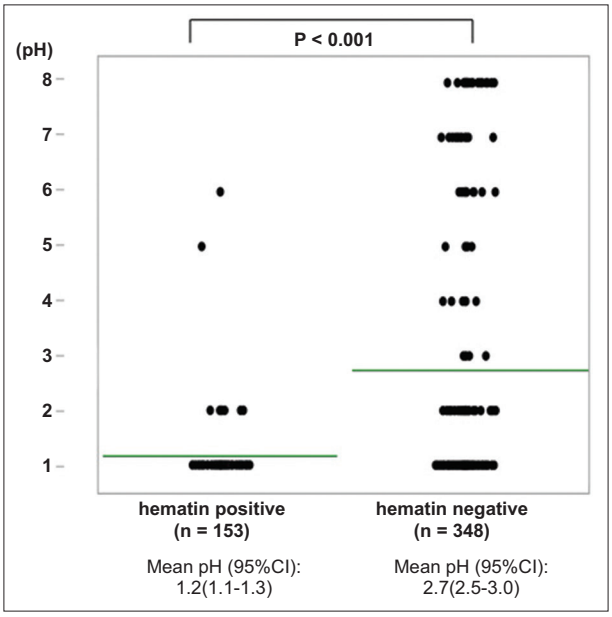

Figure 2 Relationship between the presence of hematin and the pH of fasting gastric juice. The mean pH level (95% confidence interval [CI]) of fasting gastric juice was significantly lower in the hematin-positive cases than in the hematin-negative cases (mean pH 1.2, 95%CI 1.1-1.3 vs. 2.7, 95%CI 2.5-3.0; P<0.001)

Diagnostic performance of endoscopic hematin

The sensitivity, specificity, PPV, and NPV of hematin for predicting a strong acidic condition (pH 1 or 2 for fasting gastric juice) were 36.0%, 98.1%, 98.7%, and 29.3%, respectively. Interobserver agreement was categorized as "excellent" (κ=0.88).

Relationship between hematin formation and acid pH in the *in vitro* study

In the *in vitro* study, of the 8 pH levels (pH 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, and 7.0), hematin formation was only observed at pH=1 at 5 min (Fig. 3).

Discussion

In this study, we clarified the clinical significance of endoscopic findings of hematin with respect to gastric acidity. First, endoscopic hematin findings were closely associated with a lower fasting gastric juice pH. The mean pH of fasting gastric juice was significantly lower in hematin-positive cases than in hematin-negative cases (mean pH 1.2, 95%CI 1.1-1.3 vs. 2.7, 95%CI 2.5-3.0; P<0.001). In addition, a supplemental *in vitro* study showed that hematin formation was only observed at a pH=1. Hence, these clinical and experimental findings indicated that the endoscopic findings of hematin represent strong gastric acidity (approximately pH=1 for fasting gastric juice). Although methods of estimating gastric acid secretion status differ from our study, a previous report form Hatta *et al*, showing that endoscopic hematin is related to hyperchlorhydria status by endoscopic gastrin test, supports our results [10].

With respect to the diagnostic performance of endoscopic hematin in this study, the sensitivity, specificity, PPV, and NPV of hematin for predicting strong gastric acidity (fasting gastric juice is pH 1 or 2) were 36.1%, 98.1%, 98.7%, and 29.3%, respectively. This diagnostic performance of endoscopic hematin showed excellent interobserver agreement (κ=0.88). Given this high specificity, high PPV, and excellent interobserver agreement, hematin can be a very useful finding in our daily clinical practice. We can accurately and reliably predict a strong gastric acidity when hematin is positive, without performing time-consuming acid secretion tests.

Recently, the need to evaluate gastric acid status is increasing in Japan. Indeed, the prevalence of *H. pylori* has been decreasing in Japan [15]. In addition, patients with *H. pylori* eradication have been increasing since the Japanese government approved eradication treatment for patients with *H. pylori*-associated chronic gastritis under the National Health Insurance System in February 2013. The number of patients with acid-related diseases is increasing as a result of maintained or restored acid secretion. Generally, the pH of fasting gastric juice is at a pH=1 and pH=6-7, thus, showing bimodality [16,17]. *H. pylori* infection is an important biological factor that can alter gastric acid secretion. In the *H. pylori*-uninfected state, the pH of fasting gastric juice has strong acidity. Persistence of *H. pylori* infection leads to corpus-predominant gastritis, which can induce hyposecretion of acid [18,19]; however, most patients after *H. pylori* eradication therapy contribute to restoring acid secretion, not only in the intact stomach, but also in the remaining gastric stump after gastrectomy [20,21]. In this study,

Table 1 Baseline patient characteristics

Characteristics	Total (n=501)	Hematin-positive (n=153)	Hematin-negative (n=348)	P-value
Mean age ± SD (years)	57.2±13.4	59.2±13.3	56.3±13.4	0.0162
Male/female, n	303/198	100/53	203/145	0.1385
Helicobacter pylori status				
Uninfected, n (%)	206	64 (31.1)	142 (68.9)	
Infected, n (%)	109	5 (4.6)	104 (95.4)	
Eradicated, n (%)	186	84 (45.2)	102 (54.8)	

SD, standard deviation

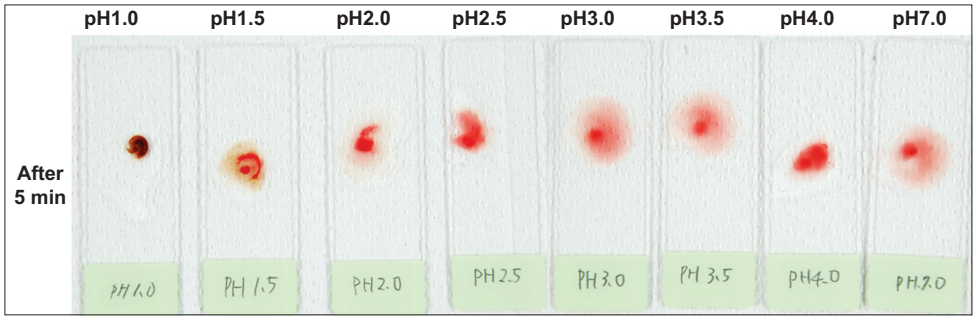

Figure 3 Relationship between hematin formation and acid pH from the *in vitro* study. Of the 8 pH levels (pH 1, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 7.0), hematin formation was only observed at pH=1 at 5 min

hematin was observed less frequently in the *H. pylori*-infected group (4.3%) than in the *H. pylori*-uninfected (31.0%) and *H. pylori*-eradicated groups (45.0%). Considering the acidic status of the stomach, as described above, the difference in the prevalence of hematin among the *H. pylori* infection status is quite reasonable. Hematin was observed less frequently in low acidity (*H. pylori*-infected group) than high acidity (*H. pylori*-uninfected and *H. pylori*-eradicated groups). We believe that the appearance of hematin is strongly related to the gastric acid condition and petechiae due to surface mucosal damage, rather than the difference in the *H. pylori* status. Of course, damage to the superficial mucosa can be caused by persistent gastritis from *H. pylori* infection. However, hematin appears less in the *H. pylori*-infected group, which has the most mucosal damage. We believe that the reason is that the *H. pylori*-infected group is not in the high acidity condition. Thus, the presence of hematin strongly reflects gastric acidity, rather than the difference in *H. pylori* status. In other words, we can predict the gastric acidity based on hematin findings, regardless of the *H. pylori* infection status.

For the clinical application of this hematin finding associated with strong acid, we believe it will be useful in diagnosis, treatment strategy, or management for various types of gastric acid-related upper gastrointestinal disorders. For example, patients with GERD can develop esophageal erosion caused by the high acidity of gastric juice [22]. If hematin is positive in GERD patients despite proper treatment with proton pump inhibitors (PPIs), we should consider that gastric acidity has not yet decreased. In addition, we have to speculate that the effectiveness of PPIs may be reduced by CYP2C19 gene polymorphisms [23].

We have recently reported that qualitative diagnosis of gastric epithelial neoplasia detected after *H. pylori* eradication was difficult because of the effects of restoration of acid secretion [24,25]. In that report, we speculated that gastric neoplasms, especially intestinal-type adenomas, might be more strongly influenced by the recovered acidity and are unable to reveal their original characteristics, because we have more frequently experienced difficulty in the qualitative diagnosis of gastric adenomas detected after *H. pylori* eradication [24,25]. Therefore, if the presence of hematin predicts strong gastric acidity, we recommend reassessment after neutralizing gastric acid with PPI or potassium-competitive acid blocker for accurate diagnosis of gastric adenomas detected after *H. pylori* eradication [24,25]. Furthermore, we have recently clarified the clinical significance of the WOS, which signifies "absorbed lipid droplets" in intestinal metaplasia, and its limitations with respect to intragastric acid conditions [2,3]. In brief, the presence of WOS in intestinal metaplasia was closely related to the condition of hypochlorhydria after *H. pylori* infection, and WOS was not observed in intestinal metaplasia after acid recovery following eradication of *H. pylori* [2,3]. Therefore, if the presence of hematin predicts strong gastric acidity, WOS findings could not be used as an appropriate endoscopic indicator of intestinal metaplasia, suggesting an increased risk of gastric cancer. For these reasons, the acidic environment of the stomach is very important, not only for determining the therapeutic effect of antacids in gastric acid-related diseases, but also for the qualitative diagnosis of gastric neoplasia and non-neoplastic lesions.

The current study had several limitations. First, the study had a retrospective design and was conducted at a single center. Second, gastric acid conditions were only evaluated by fasting gastric juice pH level. Although pH measurement of fasting gastric juice may not be the perfect method for evaluation of acid secretion, the pH of fasting gastric juice provides reliable information regarding gastric acidity [1,11]. Moreover, its noninvasiveness made it suitable for this study. Third, we did not disclose whether there were other endoscopic findings based on the Kyoto classification of gastritis associated with acidity of the stomach. We are currently planning further research. The first is a confirmatory study of hematin (UMIN 000040962) and the second is to find the most reliable endoscopic findings associated with strong acidity in the Kyoto classification of gastritis (UMIN 000040999). We hope that the results of these studies will solve the current problem.

In conclusion, the present study clarified the potential of hematin as a novel endoscopic marker for predicting strong gastric acidity. Using this endoscopic hematin finding, we can accurately and reliably predict strong gastric acidity, without the need for time-consuming acid secretion tests.

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Summary Box

What is already known:

- Gastric acidity is closely related to various types of *Helicobacter pylori* (*H. pylori*) infection
- It is very useful to know the gastric acid secretion status for assessing the pathophysiology of the intragastric environment
- However, the techniques for estimation of gastric acid secretion are time-consuming, and are not readily available in routine clinical practice

What the new findings are:

- Hematin has potential as an endoscopic marker for predicting strong gastric acidity
- The presence of hematin strongly reflects gastric acidity, rather than a difference in *H. pylori* status
- The finding of hematin can predict strong gastric acidity without the need for time-consuming acid secretion tests

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