Irregular arrangement of collecting venules (IRAC) provides a critical endoscopic insight in *Helicobacter pylori*-induced gastritis: A secondary publication

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Abstract. The aim of this study was to evaluate the significance of an endoscopic atrophic border and irregular arrangement of collecting venules (IRAC) in the diagnosis of *Helicobacter pylori* (*H. pylori*)-induced gastritis. Upper gastrointestinal tract endoscopy was performed on 723 patients, who were screened them for *H. pylori* infection. Any patients who had undergone *H. pylori* eradication therapy were excluded from the study. The endoscopic atrophic border and IRAC in each patient were assessed. The *H. pylori* status was determined in the patients by combination of a serological test and/or histopathological examination. The *H. pylori* infection rates were 95.4% (455/477) in the group with an endoscopic atrophic border and 22.3% (55/246) in the group without an endoscopic atrophic border. In the diagnostic validity check, presence of an endoscopic atrophic border had a sensitivity of 89.2% and a specificity of 89.7%. Furthermore, the *H. pylori* infection rates were 95.5% (506/530) in the IRAC group and 2.1% (4/193) in the regular arrangement of collecting venules (RAC) group. In the diagnostic validity check, IRAC had a sensitivity of 99.2% and a specificity of 88.7%. In conclusion, the presence of an endoscopic atrophic border and IRAC are highly indicative of an *H. pylori*-infected gastric mucosa.

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Introduction

Since the identification of *Helicobacter pylori* (*H. pylori*) in 1983 (1), the diagnosis and treatment of upper gastrointestinal diseases, such as gastritis, peptic ulcer, gastric carcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma, have undergone changes (2-7). The condition of *H. pylori*-infected gastric mucosa is characterized as acute or chronic inflammation, mucosal atrophy and intestinal metaplasia (8-10). The endoscopic features of *H. pylori*-induced gastritis include erythema and erosions, neither of which are specific. Atrophic gastritis and intestinal metaplasia are also observed secondary to *H. pylori* infection, but these findings are not easy to correctly diagnose by conventional endoscopy. In the present study, *H. pylori* infection was evaluated in atrophic gastritis and its endoscopic features to determine whether *H. pylori*-infected gastric mucosa can be diagnosed through an endoscopically superficial vascular network.

Materials and methods

Patients. This study was performed according to the principles of the Declaration of Helsinki. Upper gastrointestinal tract endoscopy was performed on 723 patients (510 males and 213 females), who had been screened for *H. pylori* infection during the past one year at Katake and Fujio Clinic, Hyogo, Japan. Any patients who had undergone *H. pylori* eradication therapy were excluded. The patients provided written informed consent for participation in the study. For the ethical procedure, linkable anonymizing method was used to ensure study blindness was maintained. Samples used in this study comprised materials for biopsy obtained for diagnosis or treatment and not for research. Medical disadvantage or risk of the patients did not increase by patient participation in this study and was obtained strictly for analysis of information as part of therapeutic intervention.

H. pylori infection status. The *H. pylori* status was determined in patients who were subjected to a combined serological test and/or histopathological examination. Serum samples were

also tested for total *H. pylori* antibodies using the Pyloriset Dry (Orion Diagnostica, Espoo, Finland) latex agglutination test. Multiple gastric biopsy specimens were removed for histopathological examination (11,12). To detect *H. pylori*, the samples were stained with hematoxylin and eosin, together with any accompanying special stains (Giemsa, Warthin-Starry) and immunohistochemical stains (Fig. 1). The biopsies were examined independently by two pathologists (K.I. and T.F.) who were unaware of the serological *H. pylori* status. If the serological test and/or histopathological examination results of *H. pylori* were positive, patients were diagnosed as being infected with *H. pylori*.

Observation by endoscopy. Endoscopic observation using high-resolution electronic endoscopy with an endoscopic video information system (Olympus Optical Co., Ltd., Tokyo, Japan and Fujifilm Corporation, Saitama, Japan) was carried out by two endoscopists (Y.K. and C.F.) who were unaware of the serological *H. pylori* status. The patients were closely observed after undergoing routine endoscopic examination. An endoscopic atrophic border was regarded as present or absent according to the Kimura-Takemoto classification (13). Following conventional endoscopy, the observed morphology of the capillary network structure was divided into two patterns: RAC, regular arrangement of collecting venules (Fig. 2) and IRAC, irregular arrangement of collecting venules (Fig. 3) (14). A RAC pattern was defined as numerous minute red points of similar size present at regular intervals throughout the viewing area. By contrast, an IRAC pattern was defined as an irregular or absent distribution of red points.

Statistical analysis. The sensitivity, specificity, positive and negative predictive values, likelihood ratios and accuracy were calculated with standard formulas (15).

Results

H. pylori infection and endoscopic atrophic border. The *H. pylori* infection rates were 95.4% (455/477) in the group that had an endoscopic atrophic border [mean age ± standard deviation (SD), 57.3±12.4 years] and 22.3% (55/246) in the group without an endoscopic atrophic border (mean age ± SD, 42.6±11.8). In the diagnostic validity check, presence of an endoscopic atrophic border had a sensitivity of 89.2 and a specificity of 89.7%. The positive predictive value was 95.4, while the negative predictive value was 77.6%. The positive likelihood ratio was 8.638, while the negative likelihood ratio 0.120. The accuracy was found to be 89.3% (Table I).

H. pylori infection and capillary network patterns. The *H. pylori* infection rates were 95.5% (506/530) in the IRAC group (mean age ± SD, 56.2±13.2) and 2.1% (4/193) in the RAC group (mean age ± SD, 48.9±12.9). In the diagnostic validity check, IRAC had a sensitivity of 99.2% and a specificity of 88.7%. The positive predictive value was 95.5%, while the negative predictive value was 97.9%. The positive likelihood ratio was 8.805, while the negative likelihood ratio was 0.009. The accuracy was found to be 96.1% (Table II).

Table I. Correlation between *Helicobacter pylori* infection and endoscopic atrophic border.

	Helicobacter pylori infection		
	Positive	Negative	Total
Atrophic border			
Present	455	22	477
Absent	55	191	246
Total	510	213	723

Sensitivity 89.2%, Specificity 89.7%, positive predictive value 95.4%, negative predictive value 77.6%, positive likelihood ratio 8.638, negative likelihood ratio 0.120, accuracy 89.3%.

Table II. Correlation between *Helicobacter pylori* infection and capillary network patterns.

	Helicobacter pylori infection		
	Positive	Negative	Total
IRAC	506	24	530
RAC	4	189	193
Total	510	213	723

Sensitivity 99.2%, specificity 88.7%, positive predictive value 95.5%, negative predictive value 97.9%, positive likelihood ratio 8.805, negative likelihood ratio 0.009, accuracy 96.1%. IRAC, irregular arrangement of collecting venules, RAC, regular arrangement of collecting venules.

Discussion

It would be useful to diagnose *H. pylori* status on the basis of endoscopic appearance alone in patients with *H. pylori*-related diseases such as gastritis, peptic ulcer, gastric carcinoma and MALT lymphoma (2-7). There has been some debate over whether *H. pylori* status can be diagnosed by endoscopy before biopsies and serological tests are performed (16-18). Previous studies have demonstrated that the extent of atrophic gastritis is a valuable endoscopic finding that helps in the diagnosis of *H. pylori* infection (8-10). Previously, Yagi *et al* (14,19) reported that RAC in the gastric corpus seen by close observation essentially excluded *H. pylori* infection. There were also several reports that supported their seminal study (20-24). Moreover, it has been reported that magnifying narrow-band imaging (NBI) is useful for predicting *H. pylori* infection (25).

H. pylori infection can be diagnosed by two main methods. Invasive tests that require endoscopy and non-invasive or minimally invasive tests that do not require endoscopy. The invasive tests include rapid urease tests, culture, histopathological examination including immunohistochemistry and polymerase chain reaction (PCR)-based methods, while the non-invasive tests include serology, *H. pylori* stool antigen test and urea

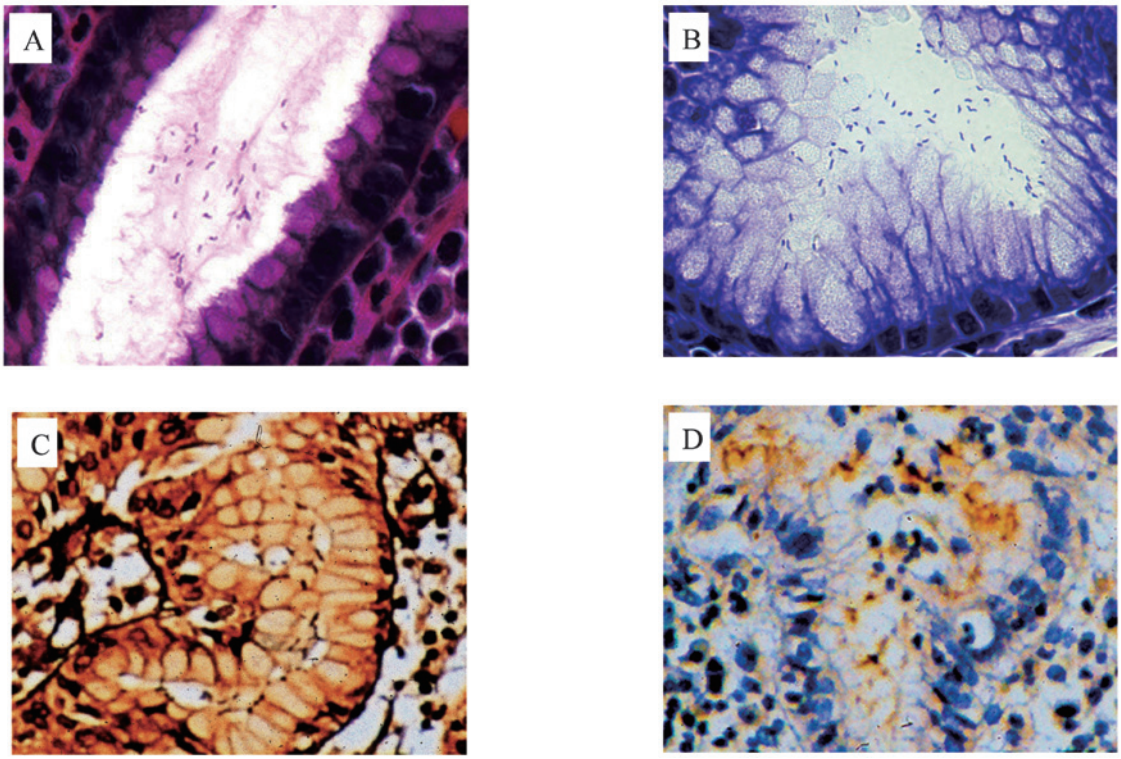

Figure 1. Histopathological detection of *H. pylori* in gastric biopsy specimen is shown. The organisms in the surface of gastric mucosa [(A), hematoxylin and eosin stain; (B), Giemsa stain; (C), Warthin-Starry stain]. (D), Immunohistochemical stain is focally positive.

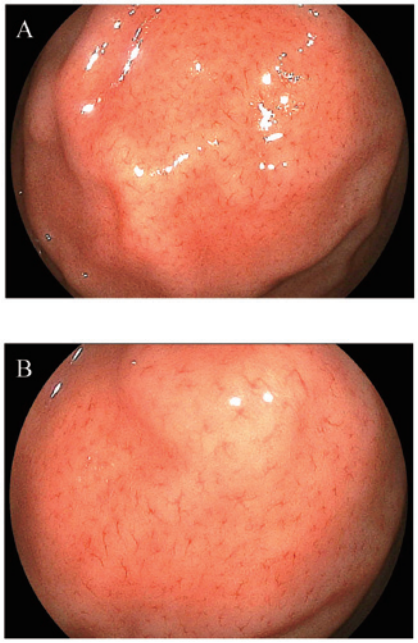

Figure 2. Typical endoscopic view of the regular arrangement of collecting venules (RAC) by high-resolution endoscopy [(B) was increased by magnification of (A) to obtain a more detailed view]. Courtesy of Dr C. Fujio, Fujio Clinic, Kobe, Hyogo.

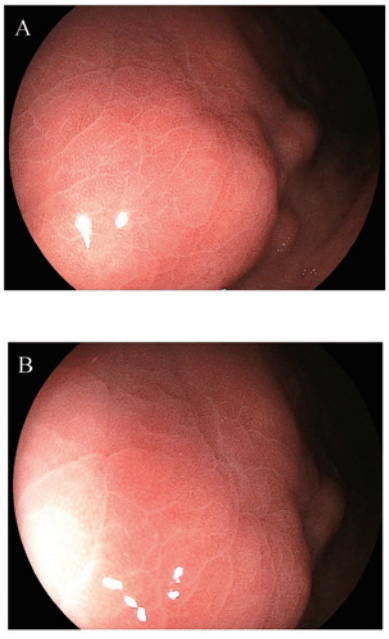

Figure 3. Typical endoscopic view of the irregular arrangement of collecting venules (IRAC) by high-resolution endoscopy; collecting venules cannot be seen [(B) was increased by magnification of (A) to obtain a more detailed view]. Courtesy of Dr C. Fujio, Fujio Clinic, Kobe, Hyogo.

breath test. With the exception of the PCR-based methods, these tests were recommended for the diagnosis of *H. pylori* infection prior and subsequent to eradication therapy in the guidelines for the management of *H. pylori* infection in Japan (26). However, the guidelines did not include a description of endoscopic findings that may be helpful in diagnosing *H. pylori* infection. The rapid urease test and histopathological examination with biopsy are accurate methods for identifying *H. pylori*. However, these methods are more invasive and expensive tests as compared to endoscopy without biopsy.

In this study, we confirmed that there was good agreement between endoscopic findings and *H. pylori* status. Our results indicate that the presence of an endoscopic atrophic border and IRAC pattern were significant indicators of an *H. pylori*-infected gastric mucosa. Thus, these findings are the most reliable criteria for the diagnosis of *H. pylori* infection. The absence of an endoscopic atrophic border and/or the presence of a RAC pattern suggests that in such cases biopsy for histopathological examination and rapid urease test to detect *H. pylori* infection would be unnecessary. Therefore, we believe that *H. pylori* screening by endoscopic examination without biopsy is an excellent test of high diagnostic accuracy and cost-effectiveness.

In conclusion, the presence of an endoscopic atrophic border and IRAC are highly indicative of an *H. pylori*-infected gastric mucosa.

Addendum

This article is based on a study first reported in the Stomach and Intestine 2002; 37: 331-336 (Japanese paper with English abstract, non-inclusion of MEDLINE). Since the definition of regular arrangement of collecting venules (RAC) was not clearly determined in the first report, it was expressed as 'red spot pattern'. Therefore, we performed a re-design of this study, and attempted a secondary publication in English according to conditions for acceptable secondary publications as stated in Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors). Additionally, the results of the re-analysis, including additional cases from the Fujio clinic, were similar to those in the first report. Therefore, a secondary version of the initial report includes content that faithfully reflects the data of the primary version, and is not a 'meat-expander' article.

Duplicate publication has been an issue for debate worldwide. However, the importance of secondary publications has been suggested, mainly in Northern Europe. The World Medical Association has adopted the Declaration of Helsinki with regard to the ethics of research. As to the ethics of publication, however, the conditions for acceptable secondary publications are described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication Updated April 2010 (http://www.icmje.org/) as follows: i) the authors have received approval from the editors of both journals (the editor concerned with the secondary publication is required to have a photocopy, reprint, or manuscript of the primary version), ii) the priority of the primary publication is respected by a publication interval of at least 1 week (unless specifically negotiated otherwise by both editors), iii) the paper for secondary publication is intended for a different group of readers; an abbreviated version is regarded as sufficient, iv) the secondary version faithfully reflects the data and interpretations of the primary version, v) the footnote on the title page of the secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part and states the primary reference. A suitable footnote might read: 'This article is based on a study first reported in the (title of journal, with full reference).' Permission for such secondary publication should be free of charge: vi) the title of the secondary publication should indicate that it is a secondary publication (complete republication, abridged republication, complete translation or abridged translation) of a primary publication. Of note, the National Library of Medicine (NLM) does not consider translations to be 'republications' and does not cite or index translations when the original article was published in a journal that is indexed in MEDLINE, vii) editors of journals that simultaneously publish in multiple languages should understand that NLM indexes the primary language version. When the full text of an article appears in more than one language in a journal issue (such as Canadian journals with the article in both English and French), both languages are indicated in the MEDLINE citation. These conditions have been accepted widely in academic journals and they would also be adopted in this journal. This report clarified conditions for acceptable secondary publication in this journal. Significance of secondary publication should be considered from an international perspective according to the rule previously described, instead of the manner as in the proverb: 'A scalded cat fears cold water', in order for a study to be appraised internationally.

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