

Classification of histological severity of *Helicobacter pylori*-associated gastritis by confocal laser endomicroscopy

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Abstract

AIM: To classify the histological severity of *Helicobacter pylori* (*H. pylori*) infection-associated gastritis by confocal laser endomicroscopy (CLE).

METHODS: Patients with upper gastrointestinal symptoms or individuals who were screened for gastric cancer were enrolled in this study. Histological severity of *H. pylori* infection-associated gastritis was graded according to the established CLE criteria. Diagnostic value of CLE for histological gastritis was investigated and compared with that of white light endoscopy (WLE). Targeted biopsies from the sites observed by CLE were performed.

RESULTS: A total of 118 consecutive patients with *H. pylori* infection-associated gastritis were enrolled in this study. Receiver operating characteristic curve analysis showed

that the sensitivity and specificity of CLE were 82.9% and 90.9% for the diagnosis of *H. pylori* infection, 94.6% and 97.4% for predicting gastric normal mucosa, 98.5% and 94.6% for predicting histological active inflammation, 92.9% and 95.2% for predicting glandular atrophy, 98.6% and 100% for diagnosing intestinal metaplasia, respectively. Post-CLE image analysis showed that goblet cells and absorptive cells were the two most common parameters on the CLE-diagnosed intestinal metaplasia (IM) images ($P < 0.001$). More histological lesions of the stomach could be found by CLE than by WLE ($P < 0.001$).

CONCLUSION: CLE can accurately show the histological severity of *H. pylori* infection-associated gastritis. Mapping IM by CLE has a rather good diagnostic accuracy.

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Key words: Confocal laser endomicroscopy; *Helicobacter pylori*; Gastritis; Classification; Histology

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a well accepted major etiological factor for gastric diseases, such as chronic gastritis, peptic ulcer and gastric carcinoma^[1-3]. Therefore, endos-

copists must determine the presence of *H. pylori* infection in the stomach during or after endoscopy. The updated Sydney system for classification of gastritis has established the association between *H. pylori* infection and histological evidence of gastritis^[4]. Gastric atrophy especially accompanying intestinal metaplasia (IM), which is the severest stage of gastritis and has a high risk for gastric cancer, is closely associated with *H. pylori* infection^[5]. Although the Sydney system has been widely used, multiple biopsies are rarely performed for gastritis evaluation but only for suspected lesions of cancer in clinical practice, thus leading to omission of some precancerous lesions which are difficult to find by white light endoscopy (WLE)^[6]. Therefore, *in vivo* detection of *H. pylori* infection and its related complications by endoscopy is a simple, noninvasive and inexpensive procedure. *H. pylori*-induced gastritis must be evaluated and graded especially in Eastern countries because of a high prevalence of *H. pylori* infection and a high incidence of gastric cancer^[7]. Furthermore, it can facilitate the clinical assessment and timely treatment of gastritis. The association between *H. pylori* infection and endoscopic findings has been extensively studied using modern endoscopic techniques such as magnification endoscopy and narrow-band imaging^[8-10].

Confocal laser endomicroscopy (CLE) can detect gastrointestinal diseases, such as Barrett esophagus, gastric carcinoma and colonic neoplasia^[11,12]. CLE can observe real-time histological-like cellular and subcellular conditions of gastric mucosal layer at the magnification $\times 500$ -1000. It was reported that acriflavine-aided CLE can observe *H. pylori in vivo*^[13]. In addition, gastric pit patterns of various gastropathies have been accurately classified and IM has been studied by CLE^[14,15]. However, no systematic data are available on the CLE characteristics of chronic gastritis and the classification of chronic gastritis has not been investigated by CLE.

In this study, the CLE features of gastritis mainly caused by *H. pylori* infection were compared to evaluate the accuracy of CLE in diagnosing *H. pylori* infection and the severity of gastritis.

MATERIALS AND METHODS

Patients

Consecutive patients with upper gastrointestinal symptoms or individuals who were screened for gastric carcinoma, admitted to our hospital from June to November 2009, were enrolled in this study. The following patients were excluded from the study, including those who received proton pump inhibitors, antibiotics, or bismuth subsalicylate in the previous 6 wk, those with a history of using nonsteroidal anti-inflammatory drugs and medication for *H. pylori* infection, those undergone stomach surgery, those with systematic diseases or known gastric carcinoma, pregnant or breast-feeding females, those who did not give their informed consent or had an allergy to fluorescein. All participants gave their written informed consent before endoscopy. The study was approved by the Ethics Committee of Qilu Hospital.

CLE system

A confocal laser endomicroscope (Pentax ISC-1000, Pentax, Tokyo, Japan) was used in this study. It is novel digestive endoscope with a confocal laser microscope integrated into the distal tip, can realize a histological-like examination during routine endoscopy and accurately diagnose gastrointestinal diseases at the magnification $\times 1000$. CLE was performed to scan the gastric mucosa from the top layer to 250 μm beneath the surface. The CLE and white-light endoscopy (WLE) images were captured and stored.

CLE procedure

CLE was performed by an endoscopist experienced with the system. All patients received oral chymotrypsin (20000 U) to eliminate the slime layer of the stomach for better visualization. One mL of 2% fluorescein (a contrast agent) was intravenously injected before endoscopy. After a first WLE of the stomach, 10 mL of 10% fluorescein was intravenously injected, and CLE images could be seen after a few seconds. Five standardized sites (2 from the lesser and greater curvatures of the antrum about 2-3 cm near the pylorus, 2 from the middle portion of the lesser and greater curvatures of the corpus about 8 cm from the cardia, and 1 from the angulus), as recommended by the updated Sydney system, were examined separately on CLE images. Shallow-deep CLE images were captured at each site and stored as digital files for further analysis. At the standardized locations, real-time image assessment and targeted biopsies were performed by CLE for histopathology. For *H. pylori* testing, 2 specimens were taken from the greater curvature of the antrum and corpus, respectively. If necessary, other scanning and biopsies were performed for lesions such as those with color changes or erosions, polyps, ulcers, or abnormal folds.

CLE classification of *H. pylori* infection-associated gastritis severity

In our study, the severity of gastritis was divided into 6 levels by CLE: normal mucosa, *H. pylori*-associated active inflammation (3 levels), glandular atrophy and IM.

CLE criteria for normal gastric mucosa and *H. pylori*-associated active inflammation: The published CLE classification of gastric pit patterns was used for one part of our classification of *H. pylori*-associated active inflammation^[14]. In addition, a new marker, fluorescein leakage, was introduced to define the active inflammation in stomach on CLE images (Figure 1). Each of the 5 standardized sites was assigned to a confocal gastritis score (CGS) and a corresponding histologic gastritis score (HGS). The CGS for normal mucosa, and mild, moderate and marked active inflammation was 0, 1, 2 and 3, respectively. The severity of histological activity and chronic inflammation was also defined as normal, mild, moderate and marked with a score of 0-3, respectively. Finally, the mean CGS and HGS (mCGS and mHGS) were calculated for specimens from each stomach.

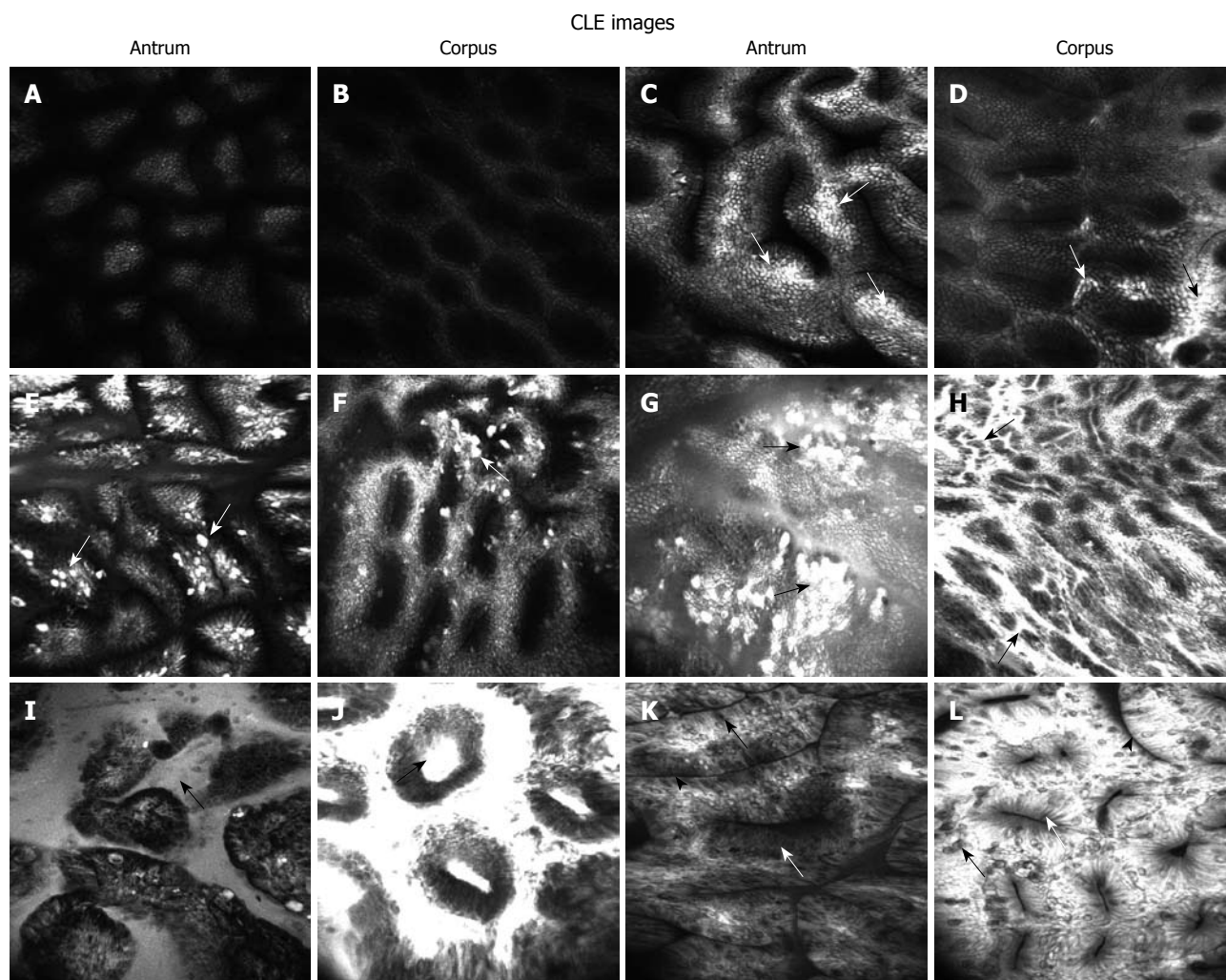


Figure 1 Confocal laser endomicroscopy classification of *Helicobacter pylori*-associated gastritis severity in gastric antrum and corpus. A, B: Normal mucosa with normal antral and corporal pits, and free of fluorescein leakage; C, D: Active inflammation (mild) with slightly distorted pits and intact epithelium, scattered focal fluorescein leakage (arrows); E, F: Active inflammation (moderate) with more distorted pits and partly destroyed epithelium (arrows), and more fluorescein leakage; G, H: Active inflammation (marked) with markedly distorted pits and dilated opening, destroyed epithelium (arrows), and widespread fluorescein leakage; I, J: Glandular atrophy with decreased gastric pits and markedly dilated opening (arrows); K, L: Intestinal metaplasia with villous-like gastric pits and goblet cells (black arrows), absorptive cells (white arrows) and brush border (arrowheads) appearing. CLE: Confocal laser endomicroscopy.

CLE criteria for glandular atrophy and IM: Glandular atrophy and IM are the severest stage of chronic gastritis. The CLE classification of glandular atrophy and IM was defined as decreased gastric pits with a dilated opening and as villous-like gastric pits with goblet cells, absorptive cells and brush border, respectively (Figure 1). To assess the CLE images, the mean number of gastric pits on each grade image was calculated and compared, except for that on IM images. The clinical values for IM features on CLE images were assessed by calculating their mean ratio present in each IM site on CLE images.

Final diagnosis of *H. pylori* infection

Rapid urease testing and Giemsa staining confirmed *H. pylori* infection. If only one test was positive for *H. pylori* infection, ^{13}C -urea breath test was performed for further confirmation. The *H. pylori* infection was classified into Hp (-), Hp (+), Hp (++) and Hp (+++).

Histopathology

All specimens were fixed in 10% formalin. An experienced histopathologist analyzed the histological features of each sample with hematoxylin and eosin staining and made the diagnosis according to the updated Sydney classification. The histological parameters assessed in this study included histological activity, chronic inflammation, glandular atrophy and intestinal metaplasia, which were identified blinding to the results of CLE or WLE.

Statistical analysis

Data were collected from CLE images and histological examination. analysis of variance and box-plot analysis of mCGS were used in pairwise comparison of mCGS among the 4 *H. pylori* test groups [Hp (-), Hp (+), Hp (++) and Hp (+++)]. $P < 0.05$ was considered statistically significant. The efficacy of CGS for predicting *H. pylori* infection was evaluated by area under the receiver oper-

Table 1 Characteristics of patients enrolled in this study

Patients	118
Gender	
Female	44
Male	74
Age (yr), median (range)	49.8 (19-67)
<i>H. pylori</i> infection (mCGS, mean \pm SD)	
Positive	41
+	15 (1.11 \pm 0.53)
++	15 (1.68 \pm 0.51)
+++	11 (2.42 \pm 0.45)
Negative	77 (0.61 \pm 0.39)
Indication for CLE	
Upper GI symptoms	87
Screened for gastric cancer	31
Endoscopic diagnosis	
Normal stomach	6
Gastritis	92
Peptic ulcer	5
Polyps	13
Early gastric cancer	2

H. pylori: *Helicobacter pylori*; mCGS: Mean confocal gastritis score; CLE: Confocal laser endomicroscopy; GI: Gastrointestinal.

ating characteristic (ROC) curve analysis. On the other hand, the sensitivity, specificity, positive and negative predictive values (PPV, NPV) of the CLE criteria for diagnosing normal gastric mucosa, *H. pylori*-associated active inflammation, glandular atrophy and IM were calculated, respectively. Correlation between mCGS and mHGS was analyzed with the coefficient of determination. SPSS v16.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

Collection of data

One hundred and eighteen patients including 74 males, at a mean age of 49.8 years (range 19-67 years) were enrolled in this study. A total of 12 243 CLE images (mean 104 images per patient) and 653 optical biopsy images (mean 5.5 biopsy images per patient) were obtained. The median endoscopy time was 23.2 min (range 15-33 min) (Table 1). The quality of over 90% of CLE images was good, while that of the remaining 10% was not satisfactory because it was difficult to fix the distal tip on the gastric angle and the artifacts were motile in gastrointestinal tract. No endoscopic complications or adverse reactions to fluorescein were observed.

CLE diagnosis of *H. pylori* infection

Association between mCGS and *H. pylori* infection:

Of the 118 patients enrolled in this study, 41 were positive for *H. pylori*. Detailed data on *H. pylori* level are shown in Table 1. The mCGS was significantly differed among Hp (-), Hp (+), Hp (++) and Hp (+++) groups ($P < 0.001$). The median mCGS was significantly higher in Hp (+) and Hp (+++) groups than in Hp (-) and Hp (++) groups ($P < 0.001$), and higher in Hp (++) group than in Hp (+) and Hp (-) groups ($P < 0.001$) (Figure 2).

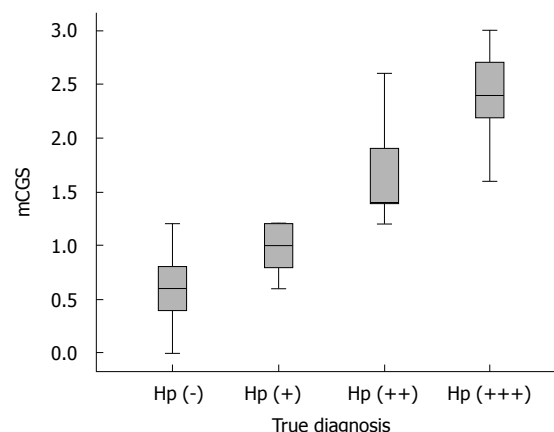


Figure 2 Box plot analysis of mean confocal gastritis score in 4 *Helicobacter pylori* test groups. mCGS: Mean confocal gastritis score.

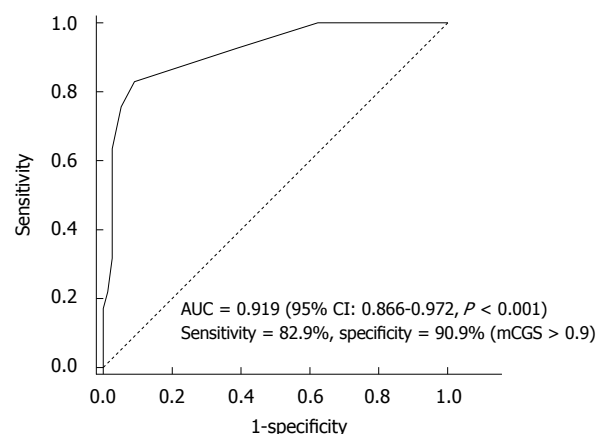


Figure 3 Receiver operating characteristic curve analysis showing the sensitivity and specificity of confocal laser endomicroscopy and mean confocal gastritis score for diagnosing *Helicobacter pylori* infection. AUC: Area under curve; mCGS: Mean confocal gastritis score.

Sensitivity and specificity of CLE for *H. pylori* detection:

The ROC curve for mCGS was plotted to determine a cut-off value of sensitivity relative to specificity for diagnosing *H. pylori* infection. The area under the ROC curve was 0.919 (95% CI: 0.866-0.972), showing an excellent accuracy (Figure 3). The sensitivity and specificity of CEL were 82.9% and 90.9%, respectively, for mCGS > 0.9 . With this cut-off value, CLE could correctly diagnose *H. pylori* infection.

CLE classification of histological gastritis severity

Normal gastric mucosa: A good correlation was found between normal mucosa detected by CLE and histology. The sensitivity, specificity, PPV and NPV of CLE were 94.6% (95% CI: 91.9%-97.4%), 97.4% (95% CI: 95.8%-99.1%), 96.5% (95% CI: 94.2%-98.7%), and 96.1% (95% CI: 94.1%-98.1%), respectively, for predicting gastric normal mucosa lesions (Table 2).

Chronic active inflammation: The CLE criteria correlated well with the active inflammation detected by histology. The sensitivity, specificity, PPV and NPV of CLE

Table 2 Sensitivity, specificity, positive predictive values and negative predictive values of confocal laser endomicroscopy for the diagnosis of normal mucosa, *Helicobacter pylori*-associated active inflammation, glandular atrophy and intestinal metaplasia (per specimen) [% (95% CI)]

CLE classification	Sensitivity	Specificity	PPV	NPV
Normal mucosa	94.6 (91.9-97.4)	97.4 (95.8-99.1)	96.5 (94.2-98.7)	96.1 (94.1-98.1)
Active inflammation	98.5 (97.2-99.8)	94.6 (91.9-97.4)	95.9 (93.7-97.9)	98.0 (96.3-99.7)
Glandular atrophy	92.9 (87.0-98.9)	95.2 (93.3-97.0)	72.5 (63.4-81.7)	98.9 (98.1-99.9)
Intestinal metaplasia	98.6 (95.7-100.0)	100 (100.0-100.0)	100 (100.0-100.0)	99.8 (99.4-100.0)

CLE: Confocal laser endomicroscopy; PPV: Positive predictive value; NPV: Negative predictive value.

Table 3 Confocal laser endomicroscopy and white-light endoscopy in predicting histological changes

Biopsy sites	CLE normal sites ¹	CLE abnormal sites ¹			
		Inflammation	Atrophy	IM	Early cancer
WLE normal sites	216	173	41	45	0
WLE abnormal sites ²	31	83	25	23	2

¹The normal and abnormal sites on confocal laser endomicroscopy (CLE) images were confirmed by histology; ²Abnormal sites include erythema, erosion, nodules and petechiae, etc., with no noticeable lesions such as ulcers or polyps on white light endoscopy (WLE) images. IM: Intestinal metaplasia.

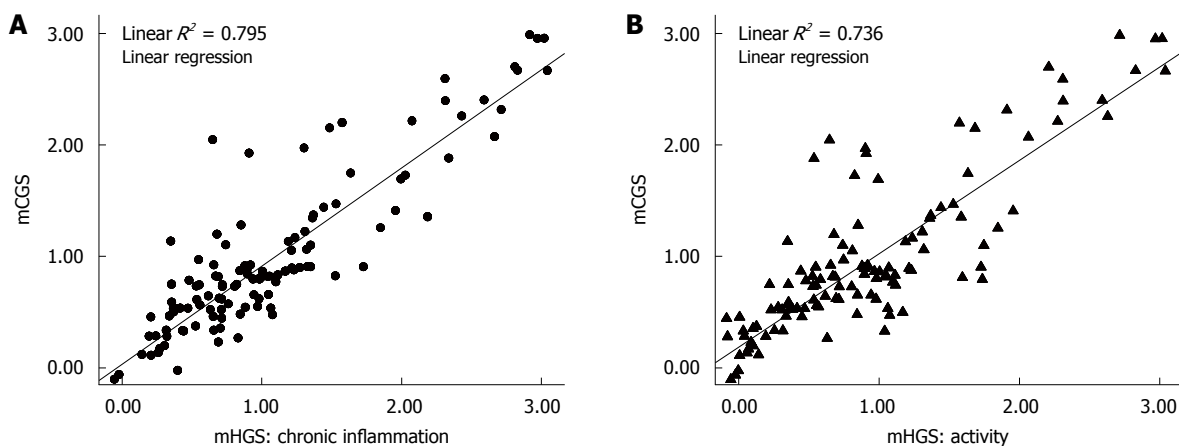


Figure 4 Correlation between mean confocal gastritis score and mean histologic gastritis score for histological chronic inflammation ($R^2 = 0.795$, A) and activity ($R^2 = 0.736$, B). mCGS: Mean confocal gastritis score; mHGS: Mean histologic gastritis score.

were 98.5% (95% CI: 97.2%-99.8%), 94.6% (95% CI: 91.9%-97.4%), 95.9% (95% CI: 93.7%-97.9%), and 98.0% (95% CI: 96.3%-99.7%), respectively, for predicting active inflammation detected by histology (Table 2). In particular, the histological activity and chronic inflammation were significantly differed among the 3 levels of active inflammation on CLE images, based on the evidence that histological activity and chronic inflammation were positively and linearly correlated with the mCGS ($R^2 = 0.795$, $R^2 = 0.736$, $P < 0.001$) (Figure 4).

Glandular atrophy and IM: The sensitivity, specificity, PPV and NPV of CLE were 92.9% (95% CI: 87.0%-98.9%), 95.2% (95% CI: 93.3%-97.0%), 72.5% (95% CI: 63.4%-81.7%) and 98.9% (95% CI: 98.1%-99.9%), respectively, for glandular atrophy (Table 2). Furthermore, a post-CLE analysis of CLE images showed that the mean number of gastric pits in glandular atrophy was significantly

less than that in IM on CLE images ($P < 0.001$) (Figure 5).

The sensitivity, specificity, PPV and NPV of CLE for IM were 98.6% (95% CI: 95.7%-100.0%), 100% (95% CI: 100.0%-100.0%), 100% (95% CI: 100.0%-100.0%), and 99.8% (95% CI: 99.4%-100.0%), respectively, for predicting IM (Table 2). Of the IM features on CLE images, goblet cells and absorptive cells were more common and easier to note than the other features ($P < 0.001$) (Figure 6).

CLE and WLE for predicting histological conditions:

In our study, 54.5% (259/475) normal sites were found to be abnormal on WLE by CLE (173 inflamed sites, 41 atrophic sites and 45 IM sites). In contrast, of the 164 abnormal sites on WLE images, 18.9% (31/164) were found to be normal on CLE images. All the findings on CLE images were confirmed by histology, indicating that CLE can show more histological lesions than WLE ($P < 0.001$) (Table 3).

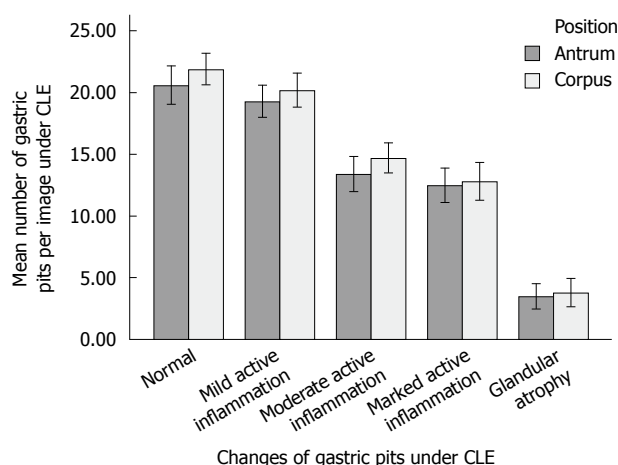


Figure 5 Gastric pits on confocal laser endomicroscopy images. CLE: Confocal laser endomicroscopy.

DISCUSSION

Conventional endoscopy is not frequently correlated with histological alterations, WLE is not accurate for predicting histological gastritis with nonspecific erythema, prominent area gastrica, nodularity, or erosions, *etc.*^[16], and gastroscopy without biopsy is incomplete in routine clinical practice. In recent years, novel endoscopies, such as magnification endoscopy and narrow band imaging, have been evaluated for gastric pathologic conditions with a good accuracy^[17]. High resolution, magnification and advanced electronic dye techniques, can identify the mucosal and vascular details of *H. pylori* infection and its related complications, with a high diagnostic sensitivity and specificity^[18].

More details of gastric pits can be clearly observed on CLE images at the magnification $\times 1000$. Zhang *et al.*^[14] reported that CLE can reveal inflamed pits with marked morphological alterations. The sensitivity and specificity of type B'+D' pits are 81.9% and 99.3%, respectively, for predicting moderate to severe active inflammation. In our study, *H. pylori* infection was positively correlated with progressively increasing changes in gastric pits due to direct injury caused by *H. pylori* and inflammatory infiltration. CLE could accurately distinguish normal mucosa from *H. pylori*-infected mucosa in the stomach. ROC curve analysis showed a high sensitivity (82.9%) and specificity (90.9%) of mCGS for diagnosing *H. pylori* infection. The mCGS cut-off value was 0.9, indicating an accurate and balanced result. Fluorescein leakage can classify active inflammation in ulcerative colitis^[19] and fluorescein leakage into crypt lumen is positively correlated with histological active inflammation, because of increased colonic permeability. Fluorescein leakage is often present in the stomach, which contributes to the diagnosis of *H. pylori*-associated gastritis. When normal gastric mucosa is observed on CLE images, the fluorescence is confined to beneath the subepithelium and evenly distributed, epithelial cells are clearly visible and well-demarcated, showing a uniform gray cytoplasm and black border (Figure 1A and B). However, in *H. pylori*-infected mucosa, fluorescein easily leaks

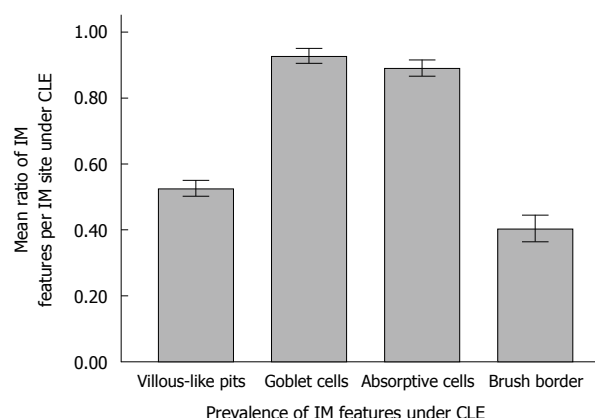


Figure 6 Prevalence of intestinal metaplasia features on confocal laser endomicroscopy images. IM: Intestinal metaplasia; CLE: Confocal laser endomicroscopy.

onto the surface through the damaged epithelium or normal epithelium with a high permeability. That is why this region is brighter than the surrounding normal epithelium. Sometimes, with a mass of the seepage, the entire field of vision can be white (Figure 1C-H). However, because fluorescein leakage is only an indirect response to mucosal damage and histological inflammation, the specificity of fluorescein is lower. In our study, fluorescein in combination with other CLE features was used to diagnose *H. pylori* infection following the active inflammation criteria defined by CLE^[4]. The CLE scoring system used in our study could offer an objective evaluation of the entire stomach. High mCGS of the stomach indicated severe *H. pylori* infection, whereas low mCGS indicated mild or no *H. pylori* infection. Because the CGS agrees with the grading of confocal images, a high score represents severely injured gastric mucosa. It was reported that *H. pylori* organisms are usually observed singly or in groups along the surface epithelium but rarely in deeper mucosa^[20]. Adherence of *H. pylori* to epithelial cells is the first step in *H. pylori* infection. When urease is secreted by *H. pylori*, and inflammatory and immune processes are activated by Vac A and Cag A toxin, the epithelium is depleted of mucin with irregular and missing cells ("drop-out cells"). In our study, similar alterations in moderate and severe active inflammation were found on CLE images, and clusters of destroyed epithelial cells (drop-out cells) on the two grade images were closely correlated with *H. pylori* infection, suggesting that CLE can display the drop-out cells because such microscopic lesions may progress to micro-erosions and precursors of gastric ulcer. However, when mCGS is less than 0.9, it can result in 7 false-positive and 7 false-negative diagnoses. False-positive cases are mainly diagnosed as mild active inflammation based on the CLE images of antrum, because normal mucosa on CLE images is sometimes misdiagnosed as mild inflammation when some fibrin or debris appears on the mucosal surface. The 7 false-negative cases are diagnosed as mild inflammation with a low *H. pylori* level and the corresponding mucosal changes are thus not obvious to be identified.

The second endpoint was to demonstrate the histologi-

cal severity of gastritis by CLE, which showed that the 6 CLE grades were well correlated with the corresponding parameters of histological gastritis. Active inflammation was classified into 3 levels by CLE. On the other hand, obvious drop-out cells were observed at the moderate and marked levels with a high risk for gastric ulcer formation and management of these groups of patients. The severity of chronic inflammation was much higher at moderate and marked levels on CLE images ($R^2 = 0.736$ and 0.795), probably because interstitial infiltration of inflammatory cells can easily squeeze the glands and damage the epithelium with an increasing severity of inflammation and *H. pylori* infection, leading to aggravated pit distortion and fluorescein leakage.

Gastric glands would be destroyed, and glandular atrophy and/or intestinal metaplasia would occur when they are infected with *H. pylori* and infiltrated with inflammatory cells. Glandular atrophy is manifested as thinner mucosa without gastric rugae but with visibly vascular pattern on WLE images^[21]. However, gastric atrophy is poorly correlated with histological atrophy on WLE images^[22]. It was reported that CLE shows a good sensitivity and specificity for gastric atrophy^[14]. In our study, the diagnostic sensitivity and specificity of CLE were 92.9% and 95.2% for glandular atrophy. A further analysis of CLE-diagnosed glandular atrophy was performed with a more objective method. The mean number of gastric pits was calculated on different CLE images, and the mean number of pits in glandular atrophy was significantly less than that in gastritis on CLE images ($P < 0.001$). However, IM on CLE images was not analyzed because the gastric pits were replaced by intestinal mucosa, which became another form of atrophy or metaplasia. Although the sensitivity and specificity of CLE were high for glandular atrophy, the PPV was relatively low (72.5%) probably due to the low prevalence of atrophy in histology (71 sites/590 sites, 12.0%), indicating that there is a certain false positive rate when CLE is used to diagnose glandular atrophy, and identification of mild glandular atrophy is a big challenge for CLE.

Although the Sydney system has suggested a definition of endoscopic intestinal metaplasia for “grey-white patches with a slight opalescent tinge and/or a villous appearance on close inspection”, studies demonstrated that these features are quite difficult to be identified by conventional endoscopy^[21,23]. The detection of IM needs multiple biopsy specimens. Tahara *et al.*^[18] reported that magnifying narrow-band imaging endoscopy can show IM with a sensitivity of 73.3% and a specificity of 95.6%. In this study, IM was further analyzed following the CLE criteria^[15]. The sensitivity and specificity of CLE were 98.6% and 100%, respectively, for IM in our study, and were higher than those reported by Tahara *et al.*^[18]. In addition, goblet cells and absorptive cells were more frequently and easily observed than other features or parameters in IM on CLE images in our study ($P < 0.001$). Because diagnosis of IM is often disregarded by naked eyes or by chromoendoscopy in clinical practice, more powerful endoscopic techniques, such as CLE and magnifying endoscopy, should be used to map IM^[24].

Microscopic examination is essential for endoscopists to make a final diagnosis of gastritis, because the term of gastritis has been used indiscriminately and whether histological inflammation is present or not. However, CLE plays a pathological role in improving the diagnostic rate of WLE. In this study, CLE could discover 54.5% of lesions missed by WLE and correct 18.9% of normal mucosal sites misdiagnosed as abnormal sites by WLE, because the micro-gastric inflammation may appear completely normal on WLE images, suggesting that the presence or absence of gastritis should not be determined only based on gross WLE images. However, CLE can detect these micro-changes.

The main limitations of our study are as follows. First, we did not establish a control group, or a follow-up group to validate our hypothesis from multiple aspects, leading some bias in determination of *H. pylori* infection and histological gastritis. Second, we did not evaluate inter- and intra-observer variability. The repeatability of our CLE criteria should be assessed in a future single study. Third, due to the scanning depth and resolution limitations of CLE, there is still some gap when compared with *in vitro* histology. Therefore, the CLE equipment needs to be constantly upgraded.

In conclusion, *H. pylori* infection is related to its related CLE image features. Histologically active inflammation can be classified by CLE. Two most accurate markers, goblet cells and absorptive cells for IM, are established. Although CLE itself still has some limitations as a novel technique, it is a promising new procedure for accurate histological assessment *in vivo*.

COMMENTS

Background

The accurate diagnosis of chronic gastritis still relies on histopathology. Confocal laser endomicroscopy (CLE) can show gastric pit patterns and epithelial cells *in vivo*, thus, contributing to an accurate diagnosis of chronic gastritis *in vivo*.

Research frontiers

CLE has been extensively investigated in cancerous or precancerous mucosa of Barrett's esophagus and its related neoplasia, early esophageal cancer, gastric intestinal metaplasia, neoplasia and early cancer, colonic neoplasia and cancer, and ulcerative colitis, *etc.*

Innovations and breakthroughs

Endoscopic diagnosis of chronic gastritis and *Helicobacter pylori* (*H. pylori*) infection is still challenge to clinical endoscopists. This study first used CLE to classify *H. pylori* infection-associated chronic gastritis, which could accurately diagnose chronic gastritis *in vivo* without multiple biopsy specimens.

Applications

By using the classification criteria for chronic gastritis established in this study, clinical endoscopists could use CLE to evaluate the conditions of the entire stomach, and calculate the abnormal mucosal sites in the entire stomach.

Terminology

CLE is novel digestive endoscope. It is a conventional white-light endoscope with a confocal laser microscope integrated into the distal tip. CLE can realize a histological-like examination during routine endoscopy and accurately diagnose gastrointestinal diseases at the magnification $\times 1000$.

Peer review

The authors established the classification criteria for chronic gastritis, and compared CLE and white light endoscopy in diagnosis of gastritis and intestinal metaplasia, thus proving a novel method for the diagnosis of gastritis and intestinal metaplasia by CLE, which has a higher sensitivity and specificity than conventional endoscopy.

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