Novel endoscopic findings as visualized by non-magnification endoscopy with linked color imaging are indicative of gastric intestinal metaplasia

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Abstract

Background: Gastric intestinal metaplasia (GIM) is generally considered to be the main mucosal background for the development of gastric adenocarcinomas. Using linked color imaging (LCI), we noticed that the color pattern in areas of GIM was purple mixed with white on the epithelium with signs of mist that were detected by the non-magnifying LCI observation. We have termed this endoscopic finding "Purple in Mist" (PIM). The aim of this study was to investigate whether PIM could be a useful optical sign for predicting GIM.

Methods: We prospectively evaluated consecutive patients undergoing endoscopy for various indications. The endoscopist used the LCI system to carefully observe the gastric antrum, body and angulus. When a PIM was identified in the surface layer, targeted biopsies were subsequently taken from this part. If the suspected area had no PIM on the surface, targeted biopsies were also taken.

Results: Sixty-three consecutive patients were included in this study. The prevalence of intestinal metaplasia (IM) was 29/63 (46%). In PIM-positive patients, the prevalence of IM was 23/26 (89%). Of these patients, 146 biopsy specimens were included in this study. For the diagnosis of IM, compared to histological assessment, the LCI finding had an accuracy of 91.1% (95%CI: 86.5%–95.7%), a sensitivity of 89.8% (95%CI: 81.3%–98.3%), a specificity of 91.8% (95%CI: 86.3%–97.2%), a positive predictive value of 84.6% (95%CI: 74.8%–94.4%), and a negative predictive value of 94.7% (95%CI: 90.1%–99.2%).

Conclusions: A positive PIM finding in a suspicious lesion on LCI would complement LCI diagnosis of possible IM because of the positive predictive value of PIM. PIM could be a novel endoscopic marker for IM.

Trial registration: ClinicalTrials.gov, No. NCT03092414; https://clinicaltrials.gov/ct2/show/NCT03092414?id=NCT03092414&rank=1

Keywords: Gastric intestinal metaplasia; Linked color imaging; Non-magnification endoscopy

Introduction

Gastric intestinal metaplasia (GIM) is a strong risk factor for differentiated gastric cancer, which makes endoscopic diagnosis of GIM important.[1,2] The diagnosis of GIM is currently performed by histologic assessment of multiple endoscopic biopsies, methylene blue chromoendoscopy, or narrow-band imaging with magnification (M-NBI).[3,4] Currently, there is still no unified standard for image enhanced endoscopy (IEE) in the diagnosis of GIM. The diagnosis of intestinal metaplasia (IM) is currently based on the histological assessment of biopsy specimens. Experts recommend mapping biopsies that are not targeted to specific lesions, although this approach may miss up to 50% of GIM cases and add to the cost and time of diagnosis.[5] While the current gold standard for the diagnosis of IM is a biopsy with subsequent histological evaluation, the newly developed optical technology IEE allows endoscopic visualization of regions of IM in the gastrointestinal tract without the need for biopsy.

Linked color imaging (LCI), a recently modified endoscopic system, has been adjusted to make the lesions more easily identified during endoscopy. Compared to narrow-band imaging (NBI), LCI emphasizes the color change of the mucosa. We previously reported that our discovery of LCI could improve the efficiency and accuracy of diagnosing gastrointestinal mucosal lesions and benefit target biopsy. We used pixel brightness in the RGB color model to evaluate the color of the endoscopic images and found that the main color characteristics of certain lesions by LCI were different. IM lesions were purple in color while those of atrophy were white in color and normal mucosa manifested as yellow.[6] However, Ono *et al*[7] observed GIM as a lavender color that is distinguishable from the circumferential mucosa without

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000172

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Chinese Medical Journal 2019;132(7)

Received: 10-12-2018 **Edited by:** Yuan-Yuan Ji

GIM by using LCI. These data support that the specific color feature of LCI images might be closely correlated with the pathology of IM. Therefore, we suggest that the special color may be a new useful optical sign of GIM by using LCI.

Accordingly, in this study, we examined the color pattern and accuracy of the diagnosis using LCI. The aim of the study was to investigate LCI endoscopic findings for the prediction of IM and to clarify the diagnostic efficacy of LCI for the detection of IM.

Methods

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local ethics committee of the Institutional Review Board of the Affiliated Hospital of Academy of Military Medical Sciences, and was registered at ClinicalTrials.gov (No. NCT03092414). Informed written consent was obtained from all patients prior to their enrollment in this study.

Color changes with distance under LCI

Under normal conditions, the color of the gastric mucosa changes with distance. To observe whether the color changes with distance using the LCI light source, we used edible dye (yellow, purple and red, Sugarman, Co. China; each 10 mL) to spray the mucosa of the gastric antrum and lesser curvature at different distances (4 cm, 3 cm, 2 cm, and 1 cm) and observe the changes in the color of the mucosa at the vertical (gastric antrum) and tangent (gastric lesser curvature) regions at different distances. The distance to the mucosa was estimated using the scale for comparison when taking images (HEAL, Shanghai, China) [Figure 1]. MatLab software (MathWorks, Natick, MA, USA) was applied to analyze the LCI images and compare the RGB value as previously described.[8]

Definition of "Purple in Mist"

After endoscopist observation and Matlab analysis, the color pattern of the IM area was purple mixed with white. We have termed this endoscopic finding the "Purple in Mist" (PIM), defined as white color mixed with purple on the epithelium with signs of mist detected by the non-magnifying LCI observation. Because of the white color, it is easier to determine the boundaries of the surrounding area and to distinguish the color surround PIM. In magnified LCI, PIM was characterized by an enclosing white band on purple mucosa.

The endoscopist used white light (WL), LCI, blue-laser imaging (BLI), BLI-bright, and linked color imaging-magnify endoscopy (LCI-ME) modes to observe the PIM and recorded all the images. When PIM was identified in any part of the lesion, the lesion was assessed as PIM-positive.

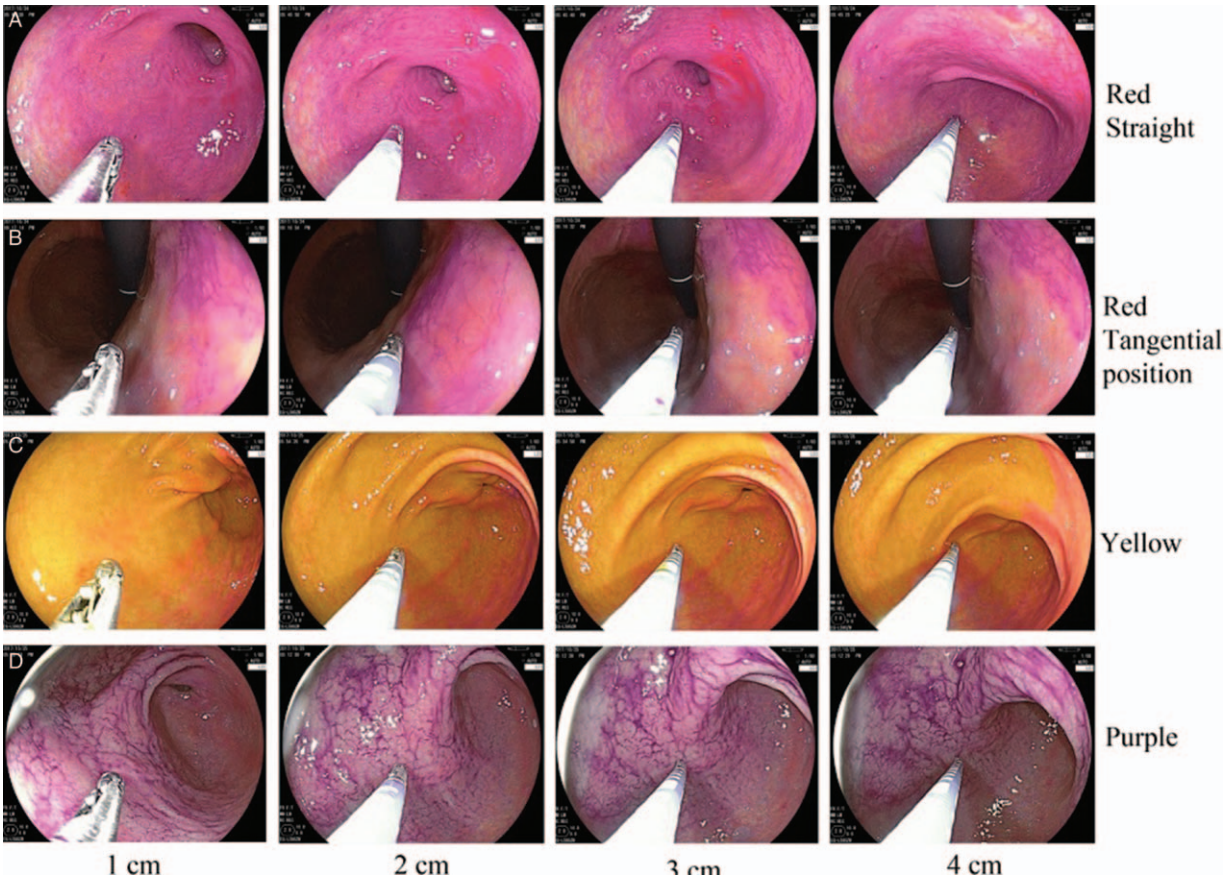

Figure 1: Typical endoscopic LCI images for edible dye (yellow, purple, and red) spray at different distances. A: Straight red; B: Tangential red; C: Yellow; D: Purple; LCI: Linked color imaging.

Study design and participants

This study was a single-center, blinded, prospective study and was performed in consecutive patients who were 40 years or older and required endoscopic examination at the Affiliated Hospital to Academy of Military Medical Sciences from May to July 2017. Exclusion criteria were patients who were receiving nonsteroidal anti-inflammatory drugs, pump inhibitors (PPI) or antibiotics in the last 3 weeks, severe uncontrolled coagulopathy, prior history of gastric surgery, and pregnancy and lactation. All participating patients were supplied with an explanation of the study and provided their written, informed consent.

Endoscopic procedures and biopsy

All procedures were performed with a high-definition GF-L590WR endoscope that was part of the LASEREO endoscopic system (FUJIFILM Co., Tokyo, Japan). The LCI technique used in the present study is a novel image enhanced mode based on BLI-bright image with additional image processing that enhances the color separation of red colors, allowing more vivid visualization of red and white colors.

We selected the gastric antrum, body and angulus for examination in this study. First, after routine observation, the endoscopist used an LCI system to carefully observe the gastric antrum, body and angulus. When a PIM area was detected during non-magnifying observation with LCI imaging, targeted biopsies were subsequently taken from the area. If the suspected area had no PIM on the surface, targeted biopsies were also taken. Currently, there are no standard criteria for GIM in LCI or WL; therefore, any abnormal mucosal change, such as localized discoloration and rough areas, was considered to be indicative of a GIM lesion and biopsies were taken.

Histological evaluation

All biopsy specimens were immersed in formalin and then embedded in paraffin. Sections were cut from the paraffin blocks and stained with hematoxylin and eosin. All specimens were evaluated by a single experienced pathologist who was unaware of the endoscopic findings. Histological diagnosis was reported according to the updated Sydney Classification for chronic gastritis and the modified Vienna criteria for neoplasia.

Statistical analysis

All statistical analyses were conducted using SPSS 17.0 software (Chicago, IL, USA). The agreement of the G/(R+B) ratios between the endoscopic images of different distances was evaluated by using F test. Mean values were compared using Student's t test. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for detection of IM compared to no IM. A P value of <0.05 was considered statistically significant.

Results

Standard color analysis of LCI images

Pixel brightness for the red, yellow, and purple colors from the endoscopic images was investigated in the same gastric antrum and lesser curvature region [Figure 1]. The RGB pixel brightness results for these colors are presented in Table 1. The RGB values for the same color at different distances were not significantly different ($P>0.05$). These results suggest that the colors do not change at different distances using the LCI light source, and its fidelity is good.

Clinical characteristics

From May to July 2017, 63 consecutive patients were included in this study. The clinical characteristics and demographic characteristics of the patients are shown in Table 2. The patients were referred to our hospital mainly because of gastro-oesophageal reflux disease and/or dyspepsia symptoms (41%); 33% underwent the endoscopic

Table 2: Baseline characteristics of patients who underwent endoscopic examinations ($n=63$).

Characteristics	Values
Age (years)	54.2±13.1
Males	36 (57)
Indication	
Symptoms	26 (41)
Screening	21 (33)
Others	16 (25)
PIM	
Present	26 (41)
Absent	37 (59)
PIM location	
Antrum	10 (39)
Angulus	11 (42)
Body	5 (19)

Values were shown as mean±standard deviation or n (%). PIM: Purple in Mist.

Table 1: Pixel brightness for red, yellow, and purple was calculated for LCI images at different distances.

Items	1 cm	2 cm	3 cm	4 cm	F	P
Straight red	0.252±0.013	0.251±0.015	0.248±0.010	0.251±0.012	2.18	0.12
Tangential red	0.246±0.006	0.259±0.014	0.251±0.009	0.252±0.009	0.14	0.94
Yellow	0.553±0.012	0.543±0.012	0.532±0.024	0.539±0.013	2.09	0.13
Purple	0.345±0.015	0.345±0.017	0.340±0.007	0.357±0.013	2.33	0.10

LCI: Linked color imaging.

procedure for screening. The remaining patients were referred for other indications. The prevalence of IM was 29/63 (46%). In PIM-positive patients, the prevalence of IM was 23/26 (89%). PIM was observed in the antrum of ten patients (39%), in the angulus of 11 patients (42%) and five patients in the body (19%).

Endoscopic and histological findings

Endoscopic image in WL shows ash-colored nodular changes [Figure 2A]. Endoscopic image in LCI shows PIM in lesser curvature [Figure 2B]. Magnifying endoscopy with LCI showed PIM in Figure 2C (magnification × 80). Histopathological appearance with hematoxylin and eosin (H&E) staining showed IM in Figure 2D. IM in the gastric pylorus under M-BLI and LCI mode was shown in Figure 3A and 3B. Magnifying endoscopy with M-BLI showed light-blue crests (LBC) at the edge of the marginal crypt epithelium [Figure 3C]. When switched to the magnifying LCI, LBC turns to bright-white lines visible on the epithelial surface and appears more visible than BLI images due to the white enhanced [Figure 3D].

One hundred and forty-six biopsy specimens (61 in the lesser curvature, 57 in the antrum and 28 in the gastric body) were included in this study. Fifty-two of the 146 specimens were PIM positive, of which 44 showed histological evidence of IM. Among the 94 biopsy samples taken from non-PIM mucosa in the suspected IM patients, 89 showed no evidence of IM. In our study, in the eight false cases (PIM-positive), LCI images of five cases showed the present of submucosal vessels appears purple [Figure 4].

Primary endpoint

For the diagnosis of IM, compared to histological assessment, the LCI finding had an accuracy of 91.1% (95%CI: 86.5%–95.7%), a sensitivity of 89.8% (95%CI: 81.3%–98.3%), a specificity of 91.8% (95%CI: 86.3%–97.2%), a positive predictive value of 84.6% (95%CI: 74.8%–94.4%), and a negative predictive value of 94.7% (95%CI: 90.1%–99.2%).

Discussion

This study did pioneering work to show that the PIM observed by LCI imaging may be a new optical marker for

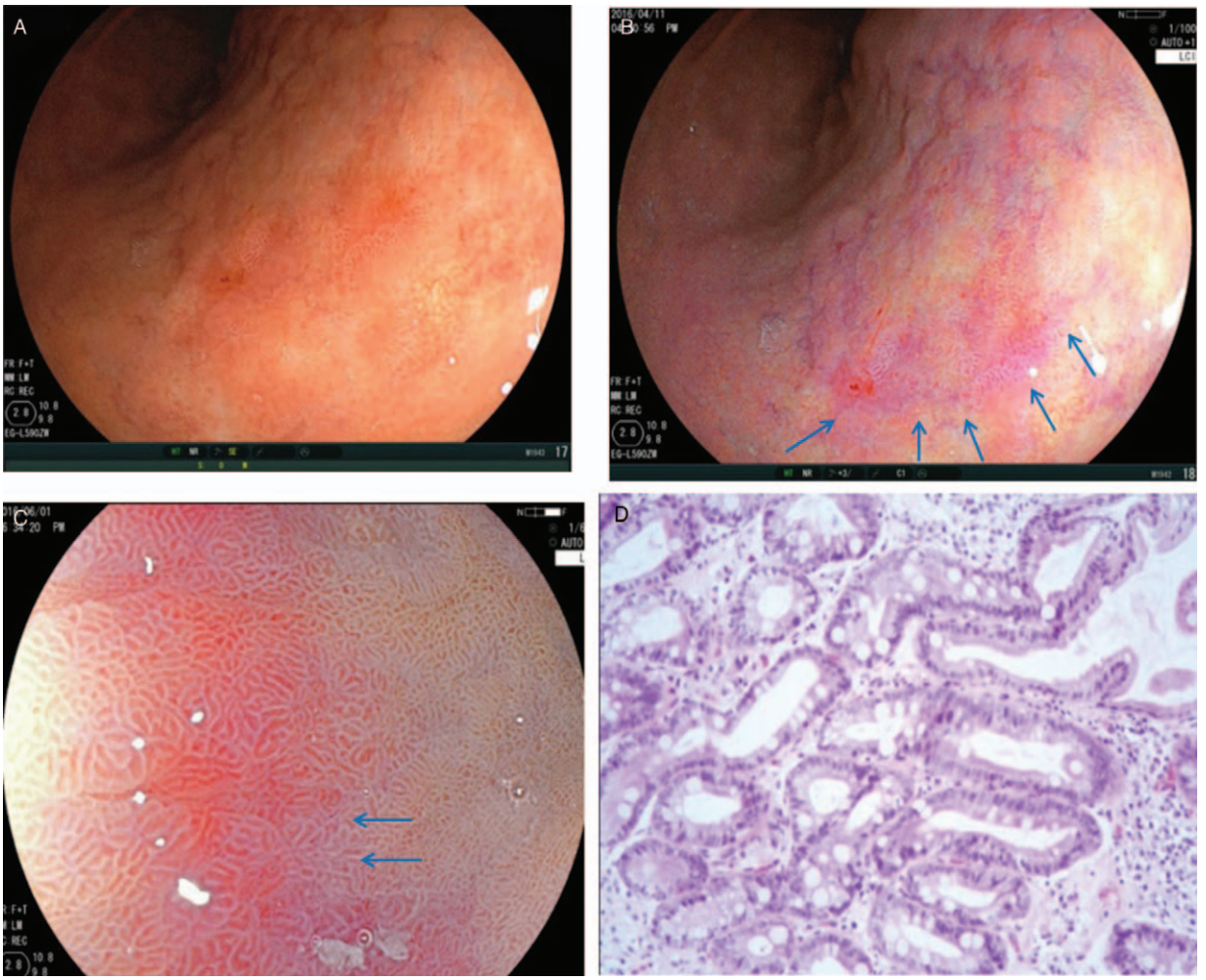

Figure 2: Appearance of intestinal metaplasia in the gastric lesser curvature under WL and LCI mode. Endoscopic image in WL shows ash-colored nodular changes (A). Endoscopic image in LCI shows PIM (blue arrows) in lesser curvature (B). Magnifying endoscopy with LCI showing PIM (C) (blue arrows) (Original magnification × 80). Histopathological appearance with hematoxylin and eosin (H&E, original magnification ×20) staining showing intestinal metaplasia (D). LCI: linked color imaging; PIM: "Purple in Mist"; WL: White light.

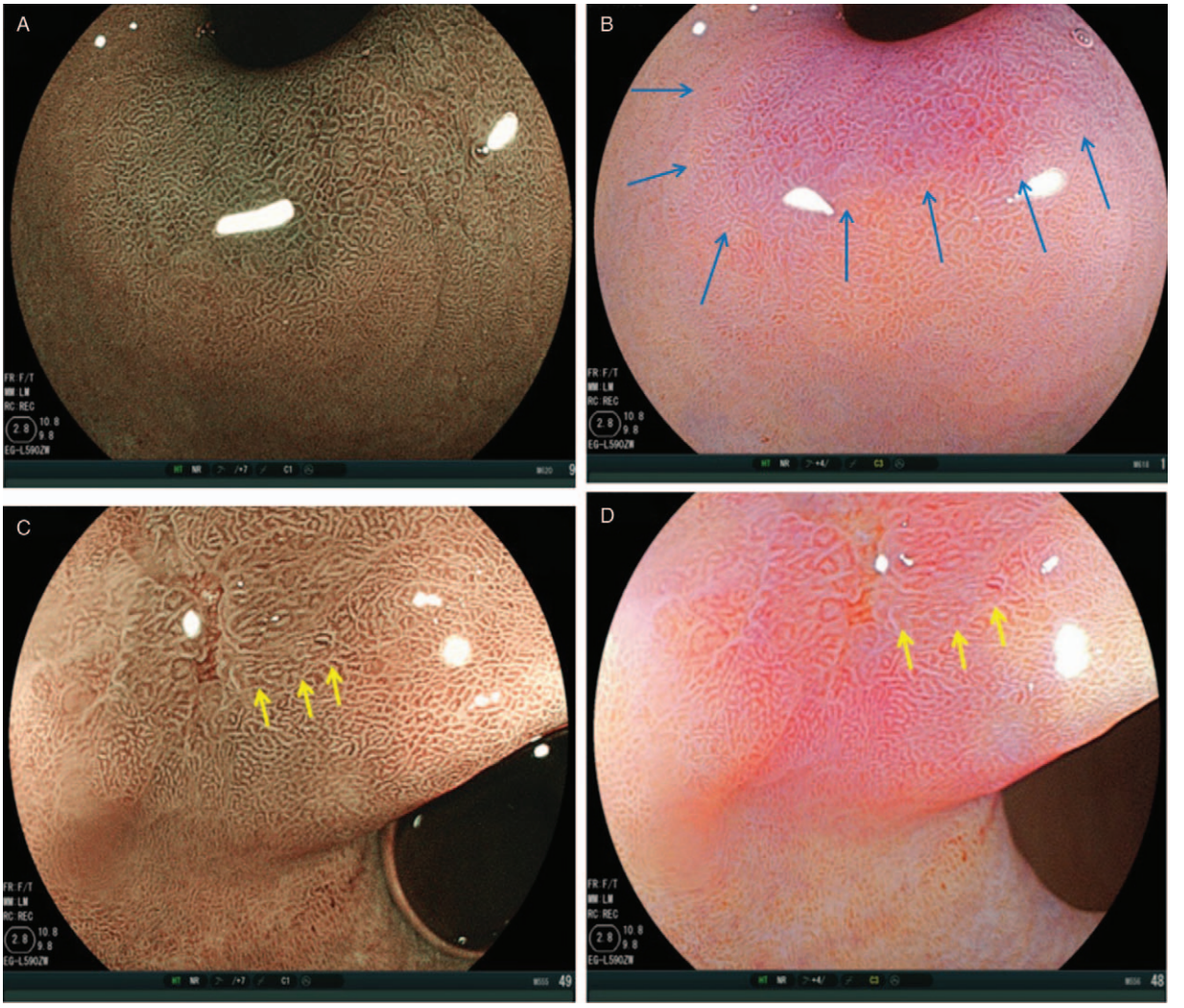

Figure 3: (A) Magnifying endoscopy with blue-laser imaging (M-BLI) of IM exhibit as bluish-whitish areas (Original magnification × 60). (B) When switched to the magnifying LCI (M-LCI), PIM was pointed with blue arrows (Original magnification × 60). (C) M-BLI showing LBCs at the edge of the marginal crypt epithelium (yellow arrows) (Original magnification × 80). (D) When switched to the M-LCI, LBC turns to bright-white lines visible on the epithelial surface (yellow arrows) (Original magnification × 80). IM: Intestinal metaplasia; LBC: Light-blue crests; LCI: Linked color imaging; PIM: "Purple in Mist".

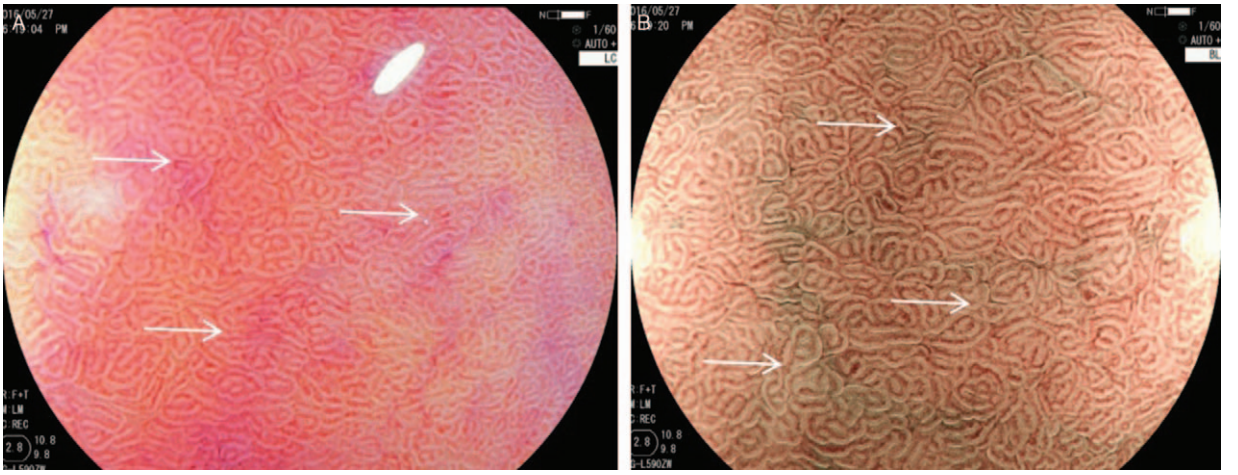

Figure 4: (A) Magnifying endoscopy with LCI showing submucosal vessels appear purple (white arrows). (B) When switched to the magnifying BLI, submucosal vessels appear deep green (white arrows). BLI: Blue-laser imaging; LCI: Linked color imaging.

the prediction of histology in GIM. Our results showed through routine gastric observation by LCI that PIM detection was an important optical sign for predicting IM. The accuracy was as high as 91.1%.

GIM exhibits few macroscopic morphological changes, and as a result, GIM may often be missed with random biopsy sampling. Many studies have investigated the use of magnifying endoscopy to overcome the diagnostic limitations of IM with conventional endoscopy.[9-11] LBC and white opaque substance (WOS) are two features of IM in the stomach that can be observed with M-NBI.[12,13] Previous studies have demonstrated that LBC and WOS both showed a high specificity and positive predictive value for the diagnosis of IM.[14,15] However, even though these special markers are useful for the identification of IM, they are not widely used in clinical practice because of a lack of availability or high cost. To obtain the markers, an institution must currently have available equipment for optical magnification endoscopy. Thus, there is a high rate of interobserver variability in the identification of these markers, and the endoscopic findings correlate poorly with histological findings. In our study, by using magnifying LCI (M-LCI), we found LBC turns to bright white lines visible on the epithelial surface and appears more visible due to the white enhanced. Meanwhile, we can predict IM by using non-magnifying LCI to identify PIM.

Until now, few prospective data are available on the diagnostic utility and accuracy of LCI for detecting IM in routine clinical practice. The results of our study were similar to those of previous studies by Japanese experts, but there were some differences. In this study, the standard color analysis of LCI images demonstrated that there was no association between color changes and the distance of the observation. Therefore, it is very important to study the color patterns in IM under LCI. According to our previous experience, we found that the reason for the variation in color reporting in IM was not due to any technical problem, such as observation distance or subjective feeling. Rather, it may be due to two provisional mechanisms. First, LCI uses blue, green, and red color information to produce color-enhanced images. Unlike WL, the captured image is output with color enhancement in its own color range by unique image processing.[16] In fact, we found that the IM mucosa was purple, but it was not accurate to categorize all purple staining as concerning because sometimes mucosal vessels were also purple or inflammation, which is typically red, could be mislabeled as purple at a certain distance. In Figure 4, we chose a typical false case which the white arrow pointed the submucosal vessel under LCI present purple may mimic PIM.

Therefore, it is necessary to use LCI to observe PIM to distinguish inflammatory red or blood vessels. Second, in our routine observation under BLI-bright mode, the villous pattern of IM is dark blue. It may appear purple after the LCI, which used red color-enhanced images. As we know, there are white zones and LBC around the IM under NBI, which are mainly related to reflection and refraction because of the microvilli structure.[14] In our study, by using M-LCI, we found LBC turns to bright white lines which appear more visible. In M-LCI, the enclosing white band on purple mucosa which defined PIM was not clear, we suspected it may have a relationship with LBC or marginal turbid band (MTB), further research needs to be combined with pathological results.

Because IM usually appears in flat mucosa and shows few morphologic changes, it is important to find suspicious areas first during screening. Kaminishi *et al*[17] defined GIM as a lesion appearing as ash-colored nodular changes, as observed in conventional WLE, were highly specific (98% ± 99%) but had a very poor sensitivity (6% ± 12%). A previous study found that LCI enabled better color discrimination when there was high IM in the surrounding mucosa.[16] The prevalence of histologically observed IM in our hospital (46%) was slightly higher than the prevalence estimated in the other studies. A possible explanation for our findings may be related to the better color discrimination achieved by using LCI. We were able to more easily distinguish IM from the normal mucosa with additional color contrast provided by LCI.

Our study showed that using LCI, PIM allowed us to detect gastric IM areas with an accuracy of 91.1%, a sensitivity of 89.8%, a specificity of 91.8%, a positive predictive value of 84.6%, and a negative predictive value of 94.7%. In our investigation, LCI underestimated the presence of IM in five patients. The false positive cases (eight patients) presented with a histological diagnosis of inflammation or atrophy. Both of these conditions may sometimes represent a confounding factor because they show endoscopic features similar to those of gastric IM.

Our study had some limitations. First, the study included only a single center. Further research including larger multicenter prospective studies is necessary to accurately assess the effectiveness of this new marker of IM. Second, as a learning curve must still be defined, regular training is mandatory to improve our findings. Third, because the endoscopic findings were analyzed by only one experienced endoscopist in this study, interobserver reproducibility could not be evaluated.

In conclusion, LCI was shown to be a valid method for IM detection. In routine clinical practice, this technique can reliably target which patients should be biopsied to evaluate IM and those who do not need biopsies. Although we were not able to explain the PIM coloring mechanism, our findings strongly suggest that PIM under LCI is a new optical marker for GIM. More data should be accumulated to confirm whether PIM is associated with GIM.

Funding

This work was supported by grants from Beijing Nova Program (No. Z171100001117090) and National Natural Science Foundation of China (No. 81470906).

Conflicts of interest

None.

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How to cite this article: Min M, Dong TH, Liu Y, Bi YL, Ma CY. Novel endoscopic findings as visualized by non-magnification endoscopy with linked color imaging are indicative of gastric intestinal metaplasia. Chin Med J 2019;132:782–788. doi: 10.1097/CM9.0000000000000172