What Have We Accomplished in Endoscopic Image Analysis for Atrophic Gastritis?

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Identifying precancerous conditions such as atrophic gastritis and intestinal metaplasia (IM) has a crucial role in detecting high risk patients for gastric cancer. White light imaging (WLI) is a basic tool for diagnosing these premalignant conditions, however its low accuracy and high variability has been a serious problem in diagnosing these premalignant conditions. Several noble imaging technologies, such as magnifying endoscopy, narrow band imaging, autofluorescence imaging, and confocal laser endomicroscopy, provide us with chances of overcoming the limitations of conventional WLI. Autofluorescence images help us understand the extent of atrophic gastritis with vivid colors. Magnifying endoscopy with narrow band imaging shows microsurface structure and microvascular architecture and is able to identify the degree of intestinal metaplasia by the presence of “light blue crest” sign. Confocal laser endomicroscopy produces reliable images of goblet cells that can replace biopsy. Usefulness of the new endoscopic imaging techniques for predicting gastric cancer development needs to be validated in clinical practice. Currently, it would be practical to apply magnifying endoscopy with narrow band imaging sequentially after white light endoscopy for identifying the presence of IM and atrophic gastritis. (Korean J Helicobacter Up Gastrointest Res 2013;13:6-19)

Key Words: Atrophic gastritis; Metaplasia; Endoscopy

INTRODUCTION

An endoscope is one of the most important inventions in the history of gastroenterology. Endoscopic examination has led physicians to understand the lesion in vivo not only by abstract imagination but by vivid images also. White light image (WLI) based on all spectrum of visible ray produces natural colors and shapes that we see every day. However, it is often not enough to recognize the presence or the extent of the lesion in WLI due to obscure contrasting between the lesion and the background mucosa. Thus, engineers and endoscopists put effort to develop new technology to find out and characterize the lesions easily. Now, endoscopists can acquire diverse imaging methods based on specific spectrums of light and fluorescence, as well as visible ray. In this chapter, we describe various endoscopic image technologies which can help us understanding the presence and severity of atrophic gastritis and intestinal metaplasia (IM) that are regarded as premalignant conditions.

ATROPHIC GASTRITIS AS A PRE–NEOPLASTIC CONDITION

It is widely accepted that differentiated-type gastric cancers evolve through a multistep process starting with Helicobacter pylori-associated superficial gastritis, followed by atrophy, IM, dysplasia, and finally carcinoma. According to a large scale cohort study following more than 90,000 patients for the longest period of 14 years, the risk for developing gastric cancer increased significantly with the severity of pre-neoplastic condition at baseline: hazard ratio (95% CI) of patients with IM, mild-to-moderate dysplasia and severe dysplasia was 1.74 (1.5 ~2.1), 3.93 (3.2~4.8), and 40.14 (32.2~50.1), respect-
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Fig. 1. Endoscopic appearance of gastric atrophy in the corpus. Whitish discoloration and visible vessels, evidence of atrophy, making remarkable contrast to normal mucosa.

ATROPHIC GASTRITIS IN CONVENTIONAL WHITE LIGHT IMAGE

Although gastritis is a histological entity, continuous attempts have been made to diagnose it macroscopically during endoscopy. Advantage of endoscopy on diagnosis of atrophic gastritis over multiple biopsies is capability of evaluating distribution and quantification of atrophy or IM precisely. The WLI of atrophic gastritis includes whitish to yellowish color change, visible submucosal vessels, and absence of rugae (Fig. 1).13,15 Recently, gastric mucosal atrophy is defined histologically as the loss of appropriate glands (Fig. 2).16 In 1966, Takemoto17 described the appearance of an ‘atrophic transitional zone’ in patients with gastritis (Fig. 3), and this zone has subsequently become known as the endoscopic atrophic border.13 Endoscopic atrophic border is rather easily recognized, when it becomes familiar, by discriminating differences both in color and niveau of the mucosa (Fig. 4).13 The

gastric mucosa on the border itself and on the fundic gland side has neutrophil and mononuclear cell infiltra-
tion but no atrophy or IM. By contrast, on the pyloric side of the border, the mucosa shows atrophy of the fundic glands with or without IM.18 Therefore, the endo-
scopic atrophic border marks the furthest front of the extent of atrophic gastritis in the stomach. The problem of diagnosis of atrophy and IM by conventional WLI is high inter-observer variability19 and a poor correlation with histological findings.20,22 The sensitivities of submu-
cosal vessel visibility and disappearance of rugae were low: 48% and 67% respectively.15 Ash-colored nodular change was specific (98∼99%) for identifying histological IM, but sensitivity was extremely low (6∼12%) (Fig. 5).

These are because IM also appeared in flat mucosa and shows few morphologic changes.21 The low sensitivity and high inter-observer variability of WLI has driven endoscopists to develop more sensitive and specific endoscopic methods beyond WLI.

ATROPHIC GASTRITIS IN CHROMOENDOSCOPIC IMAGE

Chromoendoscopic evaluation enabled us to evaluate extent of atrophic gastritis that is inflammation, atrophy and distribution of IM, and contributes identification of
Fig. 2. (A) Normal mucosa of the stomach antrum (H&E, ×100). (B) Nearly disappeared mucosal glands and hyperplasia of the fibrous tissue in the severe gastric atrophy of the antrum (H&E, ×100). (C) Intestinal-type epithelium with numerous goblet cells (stained blue with the Alcian blue stain) replaces the gastric mucosa and represents gastric atrophy. Mild chronic inflammation is observed in the lamina propria (Genta stain, ×200).

Fig. 3. Classification of the endoscopic atrophic pattern proposed by Kimura and Takemoto. C indicates closed-type gastritis, and O indicates open-type gastritis. C-1 represents highly localized antral gastritis; subsequent lines represent increasing extension through the lesser and greater curvatures. O-3 represents extensive atrophic gastritis, affecting almost the entire stomach. Atrophic gastritis develops initially in the antrum, mainly extending proximally (pyloro-cardial extension), with some occurring in the cardia extending distally (bipolar extension). The speed of extension of atrophic gastritis is faster on the lesser curvature than that on the greater curvature (Adapted from the article of Mihara et al. Helicobacter 1999;4:40-4852).

High-risks for developing gastric cancer. Congo red is a pH-sensitive indicator that changes from red to dark blue or black in acidic conditions. When Congo red is sprayed on the gastric mucosa, the normal fundic mucosa that secretes acid turn black, whereas the mucosa that lost acid secretion due to atrophy or IM remain red. Accordingly, the extent of atrophic gastritis of the corpus can be observed as “non-discolored” areas where Congo red does not change color (Fig. 6). The efficacy of using vital staining with methylene blue to help identify areas
Fig. 4. The endoscopic atrophic border (yellow line) in a patient with gastritis. The area to the lesser curvature side of the border shows whitish to pale yellow color change compared to the anterior and posterior wall sides to the border: Kimura-Takemoto classification C-3.

Fig. 5. Multiple ash-colored ovoid cobblestone-like lesions were noticed at the lesser curvature side of the antrum.

Fig. 6. An area of color shift from red to black presents acid secretion reacting to Congo red.

Fig. 7. Methylene blue dye selectively stains multiple foci of intestinal metaplasia of the stomach.

ATROPHIC GASTRITIS IN AUTOFLUORESCENCE IMAGING

Extent of atrophic gastritis including atrophy and IM in the corpus can be diagnosed as green mucosa of the gastric corpus in autofluorescence imaging (AFI). The basic principle of AFI is showing differences in the color between premalignant and normal mucosa by illuminating target sites with excitation light (390–470 nm) and green light that is well absorbed by hemoglobin (540–560 nm).
**Fig. 8.** Principle of the autofluorescence imagings. AFI, autofluorescence imaging; CCD, charge coupled device.

**Fig. 9.** Color differences in autofluorescence image of the tumor according to their morphology (elevated tumor as purple and depressed tumor as green). The autofluorescence image represents normal pyloric gland mucosa as green, and the normal gastric body mucosa as purple.
Fig. 10. Classification of the extent of atrophic fundal gastritis according to autofluorescence imaging color AF-C-1, the entire gastric body appears purple to dark green; AF-C-2, a color border on the lesser curvature was observed at a lower part of the gastric body; AF-C-3, a color border on the lesser curvature at an upper part of the gastric body; AF-O-1, a color border between the lesser curvature and the anterior wall; AF-O-2, a color border between the anterior wall and the greater curvature; and AF-O-3, a color border on the greater curvature proximal to the lower gastric body (Adapted from the article of Inoue et al. J Gastroenterol 2010;45:45-5122).

Fig. 11. The gastric corpus mucosal patterns identified on magnifying endoscopy. (A) The type 1 pattern comprises a honeycomb-type subepithelial capillary network (secn) with a regular arrangement of collecting venules and regular, round pits. The sensitivity and specificity of type 1 for predicting an *Helicobacter pylori*-negative gastric mucosa were 92.7% and 100%. (B) The type 2 pattern comprises a honeycomb-type secn with regular, round pits, but with loss of collecting venules. (C) In the type 3 pattern, there is loss of the normal SECN and collecting venules, with enlarged white pits surrounded by erythema. The sensitivity and of the combination of type 2 and type 3 for predicting an *H. pylori* infected stomach were 100% and 92.7%. (D) The type 4 pattern is characterized by loss of the normal SECN and round pits, with irregular arrangement of the collecting venules. The sensitivity and specificity for predicting gastric atrophy were 90% and 96% (Adapted from the article of Aragnostopoulos et al. Endoscopy 2007;39:202-207).
As an elevated lesion generates weak autofluorescence, it represents as purple color, while a depressed lesion looks green due to strong autofluorescence (Fig. 9). In the AFI images, normal mucosa in the digestive tract looks green, whereas that in the gastric corpus looks purple. The reason why the gastric corpus shows unique color is probably because thick fundic mucosa reduces autofluorescence from the submucosa. Because the autofluorescence intensity depends on the mucosal height associated with fundic gland atrophy, the extent of atrophic gastritis in the corpus can be simply estimated by AFI as greenish mucosa. Inoue et al. revealed that AFI could diagnose the extent of chronic atrophic fundic gastritis with higher reproducibility compared with WLI: the intra-observer agreement was substantial ($\kappa = 0.67$) for AFI, but only moderate ($\kappa = 0.56$) for the WLI (Fig. 10). Authors also found that the diagnostic accuracy of green areas in the gastric corpus of the patients in atrophy and IM was 88% and 81% respectively.

Magnifying endoscopy enables us to evaluate detailed morphological feature of the superficial gastric mucosa that corresponds to histological findings. Its resolution power is 7.9 μm, so it is possible to visualize the capillaries and even the red blood cells in the gastric mucosa. Anagnostopoulos et al. classified gastric corpus mucosal patterns into four types and revealed that each pattern showed extremely high sensitivity and specificity for specific histologic findings (Fig. 11). Inter- and intra-observer agreement in predicting were high also: $\kappa = 0.864$ and 0.913 respectively. Magnifying images with methylene blue closely associate with histological findings and is useful not only for detecting gastric IM, but also for assessing its extent.

Narrow band imaging (NBI) system is obtained by using the specific filter that passes narrow banded blue and green lights, which are different from conventional red-green-blue filters (Fig. 12). Combining the NBI and magnifying endoscopy (M-NBI) visualized contrasted micromucosal structures and microvascular architecture of
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**Fig. 13.** Typical cases of 1 normal and 3 abnormal gastric mucosal patterns in the corpus seen with magnifying narrow band imaging endoscopy. (A) Normal pattern: small, round pits surrounded by subepithelial capillary networks (SECNs) (black arrows), which are regularly interspersed with collecting venules (blue arrows). (B) Type 1: slightly enlarged, round pit with unclear or irregular SECNs. (C) Type 2: obviously enlarged, oval or prolonged pit with increased density of irregular vessels. (D) Type 3: well-demarcated, oval or tubulovillous pit with clearly visible coiled or wavy vessels (Adapted from the article of Tahara et al. Gastrointest Endosc 2009;70:246-253).38

**Fig. 14.** Areae gastricae (AG) pattern in chromoendoscopy. The AG are defined as small, slightly elevated polygonal areas of the gastric mucosa 1–5 mm in diameter that was subdivided by the system of intersecting furrow on the mucosal surface. (A) Polygonal area gastricae that looked reddish in chromoendoscopy were arranged in the corpus lesser curvature, and there was an int-area gastricae appeared bluish. (B) The area gastricae were indicated as light gray and the int-area gastricae was indicated as dark gray in schematic images (Adapted from the article of Kanzaki et al. Helicobacter 2012;17:224-231).39

...the superficial mucosa.37 Tahara et al.38 classified M-NBI images of the gastric mucosa into four groups and showed that sensitivity and specificity of the type 3 pattern for IM were 73.3% and 95.6%, respectively (Fig. 13). The sensitivity and specificity of type 3 for the prediction of severe histological atrophy (50.0% and 96.3%) was also better than those of serum pepsinogen test (41.7% and 96.3%) and standard endoscopy (66.7% and 72.0%).38 Recently, Kanzaki et al.39 excavated the concept of areae gastricae and interestingly correlated it...
Fig. 15. Suggested progression pattern of chronic atrophic fundic gastritis in image-enhanced endoscopy. As the extent of chronic atrophic fundic gastritis widened, areae gastricae (int-AG) increased, instead of a reduction in areae gastricae (AG). A white square in the scheme of autofluorescence imaging indicated a region-of-interest for the micro-mucosal evaluation. CAFG, chronic atrophic fundic gastritis (Adapted from the article of Kanzaki et al. Helicobacter 2012;17:224-23139).

Fig. 16. Micro-mucosal structure pattern in magnifying endoscopy with narrow band imaging system. White squares in (A) and (C) indicate the magnified area taken for images in (B) and (D), respectively. The foveola type was characterized as mucosa with round, oval, or linear foveolae (gastric pits) in chromoendoscopic images, whereas the groove type was characterized by mucosal crests that were divided by continuous grooves. On narrow band imaging, the gastric pits and adjacent epithelia appear as light brown areas, and these were surrounded by dark brown subepithelial capillaries in the foveola type. The dark brown subepithelial capillaries were surrounded by light brown gastric pits and epithelium in the groove type (Adapted from the article of Kanzaki et al. Helicobacter 2012;17:224-23139).
with M-NBI findings (Fig. 14). They revealed that as the extent of atrophic gastritis widened, the size of the areae gastricae decreased, compared with a proportional increase in intervening part of the areae gastricae at the corpus lesser curvature (Fig. 15). In M-NBI, most areae gastricae showed a foveola-type micromucosal structure (82.7%), while intervening part of areae gastricae had a groove-type structure (98.0%). Groove-type mucosa had a higher grade of atrophy and IM compared with foveola type (Fig. 16). This study illustrated how the microsurface structure changes according to the progress of the atrophic gastritis and how we can understand different microsurface structures nearly at the same area from the view of micro-topographic changes. Moreover, they suggested that only two micromucosal patterns: foveola and groove types are enough to understand M-NBI finding of atrophic gastritis.

One of the most well known endoscopic sign in the NBI image for IM must be light blue crest (LBC). The LBC was defined as a fine, blue-white line on the crests of the epithelial surface/gyri (Fig. 17). The appearance of LBC correlated with histological evidence of IM with a sensitivity of 89%, a specificity of 93%, a positive predictive value of 91%, a negative predictive value of 92%, and an accuracy of 91%. The NBI system has the advantage that it does not require complex preparation procedures or the administration of any substances to the patient.

**ATROPHIC GASTRITIS IN CONFOCAL LASER ENDOMICROSCOPIC IMAGE**

Confocal laser endomicroscopic image (CLE) is the latest novel endoscopic device with high-magnification (×1,000). It is expected to acquire a real-time endoscopic analysis for histology without the need for a biopsy during the endoscopic examination. Currently, there are two different techniques: endoscopy-based confocal laser endomicroscopy (eCLE) and probe-based confocal laser endomicroscopy (pCLE). Both require an intravenous contrast injection (fluorescein) or a topical dye spray to enhance all of the vascular supplied mucosal structures. The eCLE provides a superior image quality to pCLE. However, pCLE is more flexible because it can be used with any endoscopes that accept 10 Fr size accessories. Moreover, the frame rate of the pCLE system is much faster than the current eCLE system (12 frame/second vs. ±1 frame/second). Therefore, the stream of pCLE images is closer to video output. A standard structure that contains vessels, such as a normal gastric epithelium, can be observed as a brighter object after fluorescein injection (Fig. 18). In contrast, any structure that has no vascular supply, such as mucin, will not be stained by fluorescein. Hence, mucin-containing goblet cells, indicating IM, will appear dark (Fig. 19). The sensitivity of eCLE for IM diagnosis is excellent at 98%. However, current CLE technology is still not optimal for distinguishing between mature and immature IM. The sensitivity and specificity for atrophy were reported to be 83.6% and 99.6% (Fig. 20). The use of
Fig. 18. The confocal and corresponding histologic images and the histologic features of normal mucosa with fundic glands in the stomach. (A) Round gastric pits of approximately uniform size and shape. The surface gastric pits. The gastric pit is composed of columnar cells and round opening. (B) The subsurface (below superficial epithelial cells) gastric pits. Interstitium between gastric pits can be seen. (C) The corresponding cross-sectional histologic features (H&E, ×400). (D) Diagram of normal mucosa with fundic gland (Adapted from the article of Zhang et al. Gastrointest Endosc 2008;67:843-853).59

Fig. 19. The confocal image and the histopathologic features of intestinal metaplasia (IM). (A) Villus-like appearance, interstitium in the center (blue arrow), and black goblet cells (white arrows) appearing, indicating intestinal metaplastic mucosa. The epithelial cells (red arrow) are more slender and brighter than normal gastric epithelial cells. (B) The conventional histopathologic features. Marked IM can be seen (H&E, ×200). (C) Diagram of atrophic gastritis (Adapted from the article of Zhang et al. Gastrointest Endosc 2008;67:843-853).59

CLE is promising for identifying a patient with IM, whereas the use of CLE for the other gastric findings is still limited due to poor standardization of the criteria, for which a long learning curve may be required.51 CLE can be a better alternative over a routine randomized biopsy in IM surveillance because it can reduce unnecessary
SUMMARY AND CONCLUSION

We have walked a long way in validating premalignant condition of gastric cancer. Alongside with understanding pathogenesis, endoscopic imaging technique has been developed to find out specific signs matching with histological finding, especially IM. Chromoendoscopy enhanced characteristics of lesions and brought us more reliable data. However, it was not convenient to perform in routine clinical practice. Magnifying endoscopy is so powerful in predicting histological manifestations that is sufficient to use it in clinical field. AFI enables us to understand the extent of atrophic gastritis through vivid color change but it requires a dedicated endoscope. NBI makes magnifying endoscopy more powerful in examining the microsurface structure and microvascular architecture with simply pressing a button. This M-NBI also creates special effect, “LBC”. CLE presented the plausibility to diagnose IM without histologic biopsy. If possible, it would be ideal to sequentially apply white light endoscopy, magnifying endoscopy, M-NBI, and CLE for understanding atrophic gastritis and IM. Considering actual clinical field and technologies at the forefront, however, we think that M-NBI is the most practical and reliable technique to understand the presence of IM and severity of atrophic gastritis and that AFI has potential role in evaluating the extent of atrophic gastritis. Pragmatic risk stratification and surveillance strategy based on the endoscopic finding that is relevant to clinical practice warrants to be established in the future study.

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