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Leading article

Diagnosis of *Helicobacter pylori*-related chronic gastritis, gastric adenoma and early gastric cancer by magnifying endoscopy

Nei SOMA

Department of Gastroenterology, Medical Center, Beijing Tsinghua Changgung Hospital, Medical Center, Tsinghua University, Beijing, China

Evaluating the prevalence and severity of gastritis by endoscopy is useful for estimating the risk of gastric cancer (GC). Moreover, understanding the endoscopic appearances of gastritis is important for diagnosing GC due to the fact that superficial mucosal lesions mimicing gastritis (gastritis-like lesions) are quite difficult to be detected even with optimum preparation and the best technique, and in such cases tissue biopsy is often not very accurate for the diagnosis of gastric epithelial neoplasia. Magnifying endoscopy is a highly accurate technique for the detection of early gastric cancer (EGC). Recent reports have described that various novel endoscopic markers which, visualized by magnifying endoscopy with image-enhanced system (ME-IEE), can predict specific histopathological findings. Using ME-IEE with vessels and surface classification system (VSCS) may represent an excellent diagnostic performance with high confidence and good reproducibility to the endoscopists if performed under consistent conditions, including observation under maximal magnification. The aim of this review was to discuss how to identify high-risk groups for GC by endoscopy, and how to detect effectively signs of suspicious lesions by conventional white light imaging (C-WLI) or chromoendoscopy (CE). Furthermore, to characterize suspicious lesions using ME-IEE using the criteria and classification of EGC based upon VSCS.

KEY WORDS: *Helicobacter pylori*-related chronic gastritis, early gastric cancer, magnifying endoscopy with image-enhanced endoscopy, vessels and surface classification system.

INTRODUCTION

There are usually no or non-specific symptoms of gastric cancer (GC) at the early stage; however, the presence of symptoms, especially alarm symptoms, suggests that GC is of a quite advanced stage, for which curative surgical resection is often impossible.[1]

Correspondence to: Nei SOMA, Department of Gastroenterology, Medical Center, Beijing Tsinghua Changgung Hospital, Tsinghua University, No.168 Litang Road, Changping District, Beijing 102218, China. Email: xmna01183@btch.edu.cn

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Preventing the occurrence and development of GC involves both primary and secondary preventive strategies. As a primary preventative strategy, *Helicobacter pylori* (*H. pylori*) eradication is theoretically promising, acting by reducing gastric inflammation and its subsequent mucosal changes such as gastric atrophy and intestinal metaplasia (IM).[2–8] For secondary prevention, the policy is to detect GC at early stage so that it can be cured by appropriate treatments.[6]

However, endoscopic diagnosis of early gastric cancer (EGC) is indeed difficult because of the variety of background gastric mucosa and the complicated histology of GC. Endoscopists need to familiarize themselves with systematic techniques and current knowledge on GC.[9–11] Magnifying endoscopy with image-enhanced

endoscopy (ME-IEE) has become an essential tool for the diagnosis and treatment of EGC, but training is required for both interpreting endoscopic images and developing skills to obtain maximal resolution, and thus to improve the diagnostic ability of the operators by using ME-IEE with the vessels and surface classification system (VSCS).[12–15]

In this study, I aimed to explain how to evaluate whether risk factors for GC were present in the background mucosa, such as *H. pylori*-associated gastritis, gastric atrophy or IM using endoscopic inspection alone. Moreover, I aimed to discuss how to detect suspicious lesions and characterize them to make an accurate diagnosis using magnifying endoscopic observation following by VSCS for the differential diagnosis of EGC. In addition, I aimed to introduce various novel endoscopic markers visualized by ME-IEE that could predict specific histopathological findings.

ENDOSCOPIC EVALUATION OF HIGH-RISK GROUP FOR GC

During the endoscopic examination several specific findings indicate an increased risk of dysplasia and should be followed up with a thorough inspection by the endoscopists. A well-known hypothesis posits that GC develops through a cascade of precursor lesions (chronic non-atrophic gastritis→atrophic gastritis→IM→dysplasia) after *H. pylori* infection.[16,17] The adjusted relative risk (RR) of GC in patients diagnosed with severe fundal atrophy has been reported to be higher than in those with little or no fundal atrophy. Similarly, IM has been implicated as a precancerous lesion. In Japan, the severity of atrophic gastritis is commonly evaluated to assess the risk of developing GC in the individuals. The detection of early neoplastic lesions is under particular scrutiny in these cases.

As *H. pylori* infection-related gastric atrophy and IM are considered as risk factors for GC, it is important to assess their severity. Currently, the gold standard for diagnosing gastric atrophy and IM is the histological findings of gastric mucosa, but the invasive nature of this method precludes its use for population screening. Moreover, biopsy cannot be performed during every gastroscopic procedure. In Japan, atrophic gastritis under endoscopic examination is classified according to the Kimura–Takemoto classification as closed type (C-1, C-2 and C-3), and open type (O-1, O-2 and O-3).[18] The atrophic border crosses the angulus on the lesser curvature in the C-1 pattern, the lower and middle parts of the corpus in the C-2 pattern, and the upper part of the corpus in the C-3 pattern. The atrophic border, which is parallel to the vertical axis of the stomach, is on the lesser curvature in the O-1 pattern, on the anterior and posterior walls in the O-2 pattern, and on the greater curvature in the O-3 pattern. The C-1 pattern represents highly localized antral atrophy, with subsequent lines representing increasing extension through the lesser and greater curvatures. The O-3 pattern represents extensive atrophy, affecting almost the entire stomach. The Kimura–Takemoto endoscopic classification, as a simple and useful modality that has been widely applied, correlates with histological findings and serum pepsinogen level in the

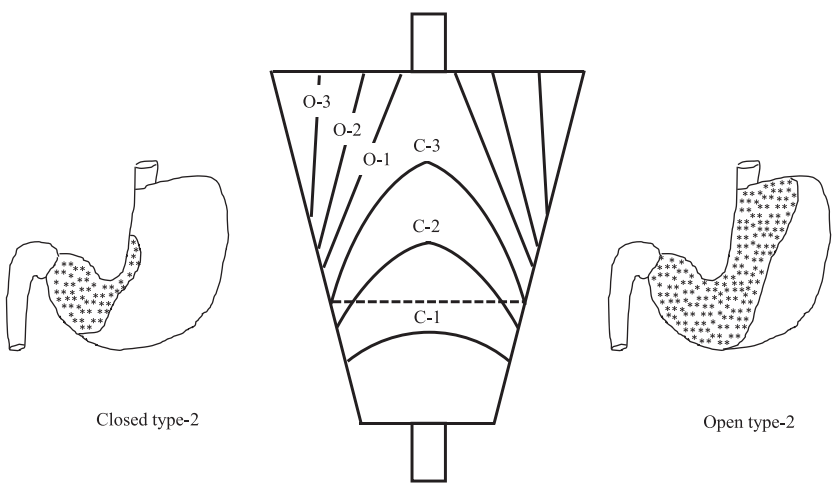

Figure 1. Kimura–Takemoto classification for the diagnosis of the extent of gastric atrophy by conventional endoscopy, which evaluates the location of the endoscopic atrophic border. The closed (C) type is classified as C-1, C-2 and C-3, and the open (O) type is classified as O-1, O-2 and O-3.

evaluation of atrophy (Fig. 1). Kono *et al.* reported that the strength of agreement between endoscopic and histological atrophy, as assessed by cancer risk-oriented grading, was reproducible, with the κ value of 0.81 (95% confidence interval [CI] 0.75–0.87).[19]

Advanced endoscopic techniques, such as chromoendoscopy (CE), image-enhanced endoscopy (IEE), and high-definition and high-magnification endoscopy, are likely to improve the accuracy of the endoscopic diagnosis of gastric atrophy. Endoscopic Congo red test was developed in the 1970s to determine the extent of atrophy;[20,21] however, this test requires gastrin injection to stimulate acid secretion and to observe the changes in color. Autofluorescence imaging (AFI) is useful in the diagnosis of mucosal atrophy.[22,23] Loss of fundic glands through atrophy increases the intensity of AFI, with the mucosa appearing green and the atrophic border more reproducibly identified. AFI in combination with narrow band imaging (NBI) also improves the detection of precancerous lesions. [24] However, some of these techniques extend the procedural time of the endoscopy, generate additional workload and may reduce the patient tolerance of the procedure. A great number of attributes must be considered, with the increase in the modalities employed for diagnosis, making it more difficult for endoscopists to agree on a standard workable protocol. Thus, their routine use cannot always be recommended. In contrast, conventional endoscopy diagnoses atrophy based only on the Kimura–Takemoto classification. Therefore, the newest endoscopes might not be needed.

Recent reports have shown a potential usefulness of ME-NBI for the diagnosis of *H. pylori* infection as well as the evaluation of the degree of histological gastritis and IM.[25–29] The clear visualization of fine mucosal and capillary patterns, as obtained by ME-NBI, allows the prediction of the histological condition, in greater details without biopsy. It may also be useful for the less invasive and cost-effective endoscopic surveillance of GC and the prediction of *H. pylori* eradication.

The regular arrangement of collecting venules (RAC) and round crypt openings (CO) that are surrounded by a network of subepithelial capillaries represent the predictive appearance of a normal corpus mucosa that is negative for *H. pylori* (Fig. 2).[30,31] In contrast, the normal antral mucosa shows a ridged or papillary microsurface pattern that encases coiled subepithelial capillaries. As atrophic gastritis progresses, the corpus mucosa, exhibiting round CO, transforms into the ridged/papillary mucosa that is similar to the antral mucosa. The identification of ridged/papillary mucosa with a light-blue crest or white opaque substance represents the predictive appearance of IM (Figs. 3, 4).[28,32,33]

Detection and characterization of signs of suspicious lesions using conventional white light imaging (C-WLI) or CE

Among gastric mucosal cancers, the depressed type is the predominant morphology. The detection of mucosal cancers of 20 mm in diameter is ideal, because they are curable using minimally invasive treatments such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Accordingly, we need to be aware of the key signs for detecting superficial mucosal neoplasia.[34,35] The two distinct markers are surface and color changes (Fig. 5). Other markers are the changes in light reflection and spontaneous hemorrhage.

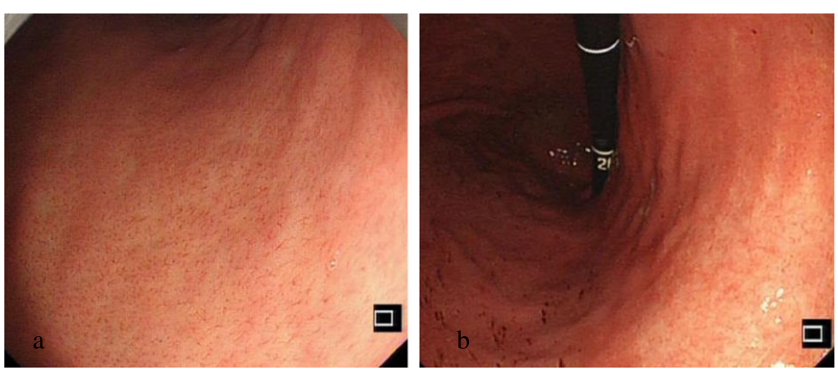

Figure 2. (a) Endoscopic findings of regular arrangement of collecting venules (RAC) showing a characteristic endoscopic feature of *Helicobacter pylori*-negative normal stomach. (b) Atrophic gastritis diagnosed as closed type (C-2) according to the Kimura–Takemoto classification. In such cases RAC is usually difficult to be observed.

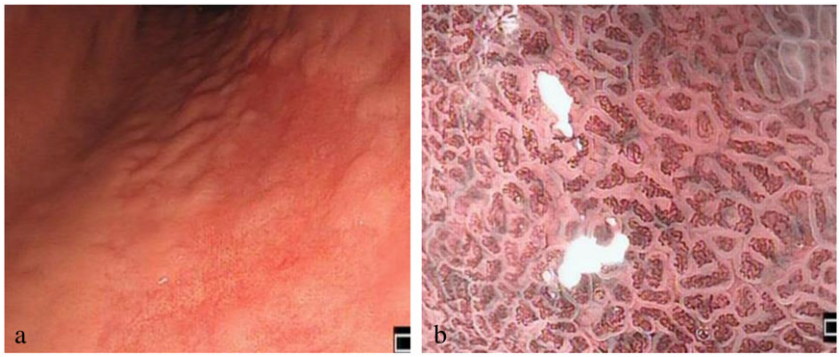

Figure 3. In atrophic gastritis (15 months after *H. pylori* eradication), the corpus mucosa transforms into a ridged or papillary mucosa under (a) conventional endoscopy and (b) magnifying endoscopy with narrow-band imaging.

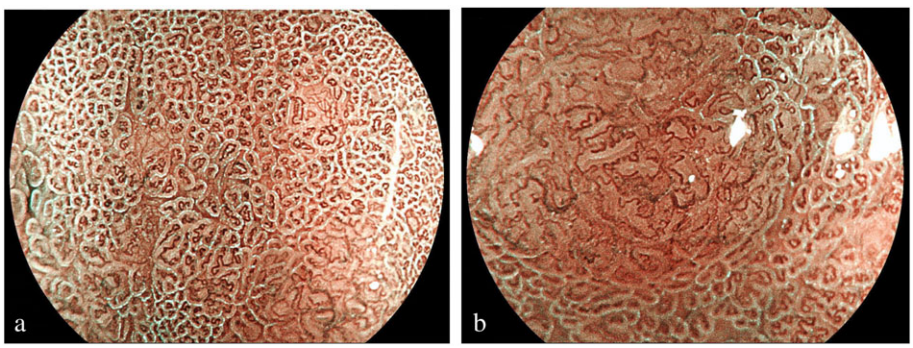

Figure 4. A ridged/papillary mucosa with (a) light blue crest or (b) white opaque substance represents predictive appearances of intestinal metaplasia using magnifying endoscopy-blue laser imaging (ME-BLI).

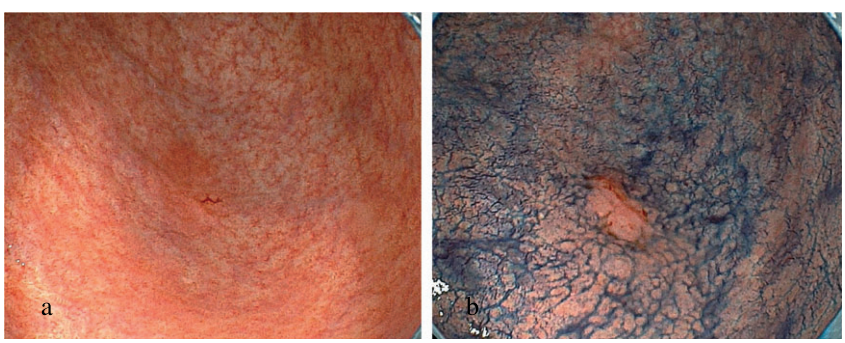

Figure 5. Endoscopic findings of superficial elevated (0–IIa) type of early gastric cancer at the gastric antrum. Histological type: differentiated (intestinal) type. (a) Conventional white light imaging shows a reddish lesion and spontaneous bleeding. (b) Indigo carmine chromoendoscopy shows a well-demarcated superficial elevated (0–IIa) lesion with an irregular surface appearance.

After the detection of suspicious lesions, cancerous and non-cancerous lesions should be differentiated. Usually, superficial mucosal lesions mimic gastritis (gastritis-like lesions), especially small depressed cancers (10 mm in diameter), which are more difficult to be distinguished from benign abnormalities (such as inflammation) than elevated-type cancers even with optimum preparation and using the best technique.[35–38] For characterization, two distinct markers, namely color and surface morphology, should be applied to the interpretation of endoscopic findings using C-WLI. CE by using indigo carmine is efficient in enhancing the surface pattern (Fig. 6). Although CE using indigo carmine contributes to an improvement in the diagnosis of gastric mucosal cancers, there is no evidence of its superiority over C-WLI.

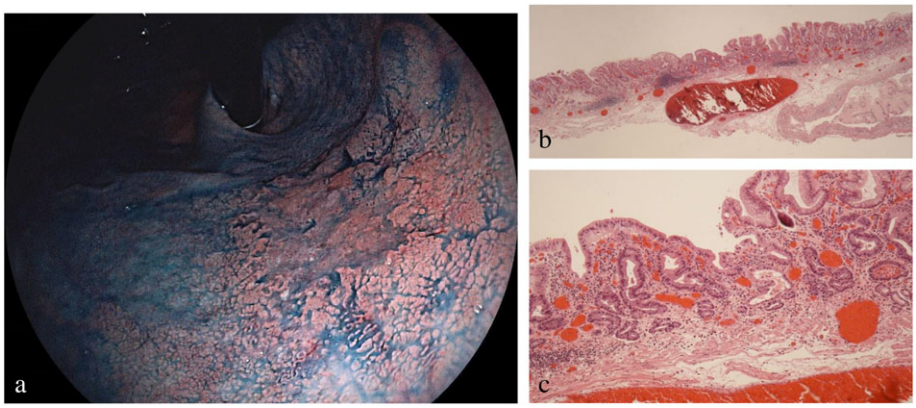

Figure 6. (a) Indigo carmine chromoendoscopy delineates a well-demarcated superficial depressed (0–IIc) type lesion with an irregular margin at the upper gastric body. (b,c) The pathological diagnosis is tubular adenocarcinoma, well-differentiated type more than moderately differentiated type of 12 mm × 18 mm in size with pathological classification of pT1a(M), ly0, v0, pHM0, pVM0. HE stain, magnification: (b) ×10; (c) ×40.

Therefore, C-WLI remains the standard imaging modality. However, it is difficult to correctly diagnose minute (≤5 mm) or superficial flat (0–IIb) GC using C-WLI endoscope or CE, because these lesion types yield only non-specific findings using conventional endoscopy alone. In such cases, the following advanced imaging is efficient in differentiating between small/flat cancers and focal gastritis.[13,14,36]

The Application of ME-NBI for the Characterization of Gastritis-Like Lesions

The NBI system consists of a sequential electronic endoscope system and a source of light equipped with new narrow band filters yielding clear images of microvessels on mucosal surface. After detecting a suspicious lesion using C-WLI endoscope, the next step is to identify a demarcation line between the suspicious lesion and background mucosae by ME-NBI. Finally, verifying an irregular microvascular pattern or microsurface pattern can help to diagnose a suspicious lesion as EGC. Several diagnostic criteria have been developed to guide endoscopists in the optical diagnosis of EGC by ME-NBI. Yao *et al.* first proposed a simple classification system called the 'VSCS', in which an irregular microsurface or microvascular pattern with a demarcation line, or both, strongly indicate EGC (Figs. 7, 8).[13,14] However, the definition of the irregularity of microvascular pattern described in VSCS remains ambiguous and is sometimes difficult to decide. Therefore, the dilatation, heterogeneity, varying thickness and winding about the microvascular pattern reported by Nakayoshi *et al.* have being used extensively in clinical practice (Fig. 9).[39] The latter authors classified the microvascular patterns into three groups, a fine network, a corkscrew and an unclassified pattern, and compared them with histological findings. Among 109 cases with a differentiated adenocarcinoma, the fine network microvascular pattern was observed in 72 (66.1%). Among the 56 cases with undifferentiated adenocarcinoma, the corkscrew pattern was observed in 48 (85.7%), which was more common than the fine network pattern ($P = 0.0011$). While ME in combination with the NBI system is not sufficient to replace conventional histology, it is capable of predicting the histological characteristics of GC.

The major clinical applications of the ME-NBI technique following VSCS are as follows. At first, as a routine screening endoscopy to differentiate between small EGC and focal gastritis, it is very difficult to accurately diagnose a small-sized EGC using C-WLI endoscope alone. Ezoe *et al.*[36] investigated the real-time diagnostic performance of C-WLI in comparison of ME-NBI in a multicenter prospective randomized controlled trial including patients with undiagnosed small depressed lesions identified at esophagogastroduodenoscopy (EGD) and concluded that the diagnostic value for ME-NBI was superior to that of C-WLI (accuracy: 90.4% *vs* 64.8%, $P < 0.001$; sensitivity: 60.0% *vs* 40.0%, $P = 0.034$; specificity: 94.3% *vs* 67.9%, $P < 0.001$).[36] The combination of ME-NBI and C-WLI significantly enhanced the diagnostic performance compared with C-WLI alone. In fact, the median value of accuracy was increased from 64.8% to 96.6% ($P = 0.001$), sensitivity from 40.0% to 95.0% ($P = 0.001$), and specificity from 67.9% to 96.8% ($P = 0.001$). This study demonstrated that ME-NBI was extremely useful as a routine screening

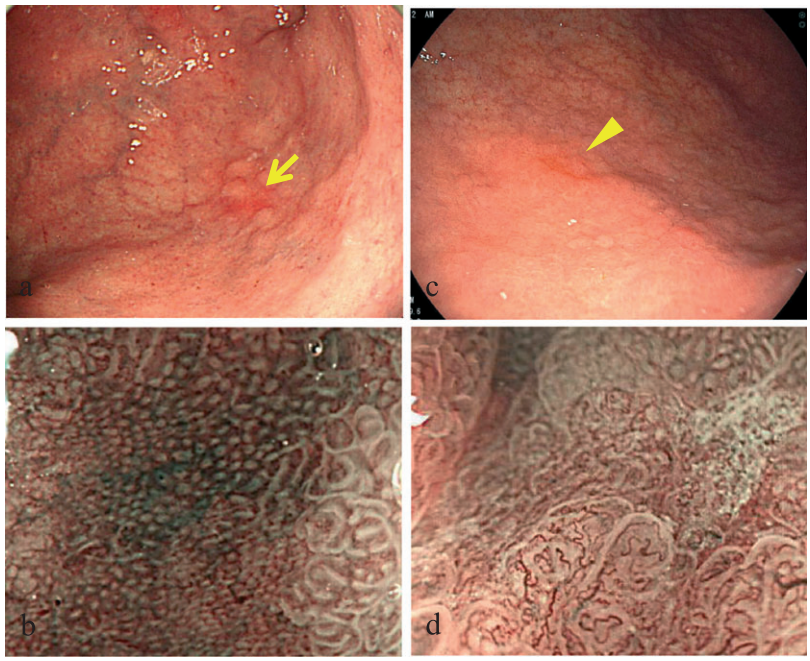

Figure 7. Differential diagnosis of (a,b) gastritis and (c,d) early gastric cancer by magnifying endoscopy with narrow-band imaging (ME-NBI) followed by vessels plus surface classification system (VSCS). (a,c) Conventional white light imaging (C-WLI) showing a slightly depressed well-demarcated lesion with irregular margins which is suspicious of cancer by C-WLI alone (arrow). However, (b) ME-NBI shows a regular microvascular pattern and a regular microsurface pattern with a demarcation line, which enable us to accurately diagnose this as a non-cancerous lesion. (d) ME-NBI shows an irregular microvascular pattern and irregular microsurface pattern with a clear demarcation line. According to the VSCS, these findings meet the criteria for a cancerous lesion.

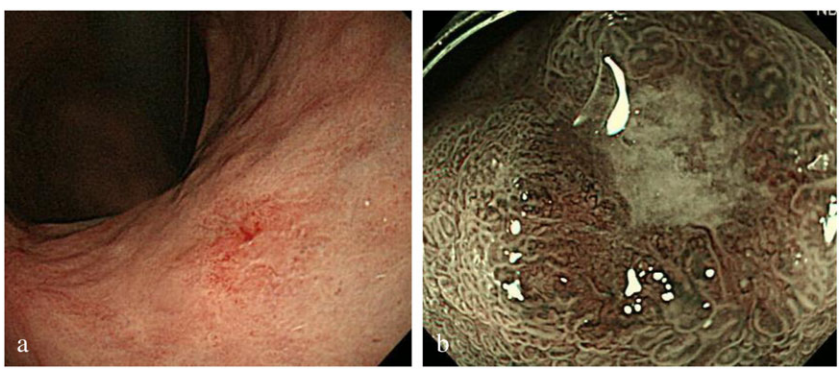

Figure 8. A gastritis-like superficial lesion. (a) Conventional white light imaging shows a slightly depressed type (0–IIc) as an erosive lesion. (b) Magnifying endoscopy with narrow-band imaging shows an irregular microvascular pattern and an absent microsurface pattern with well-demarcated line. According to the vessels plus surface classification system, this lesion is diagnosed as a cancerous lesion on the lesser curvature. Pathological diagnosis: well-differentiated tubular adenocarcinoma, endoscopic submucosal dissection 0–IIc, 10 mm × 9 mm, pT1a(M), tub0, ly0, v0, pHM0, pVM0.

endoscopy for differentiating between small EGC and focal gastritis to make an accurate diagnosis based on endoscopic findings alone. And second, the ME-NBI technique is applied for preoperative assessment of the lateral extent of EGC, for curative endoscopic resection. ME enables the reliable delineation of the horizontal extent of EGC prior to ESD.[40–42] Nagahama *et al.* reported that the advantages of ME-NBI over C-WLI with dye spraying, and investigated the usefulness and limitations of ME-NBI when the horizontal extent

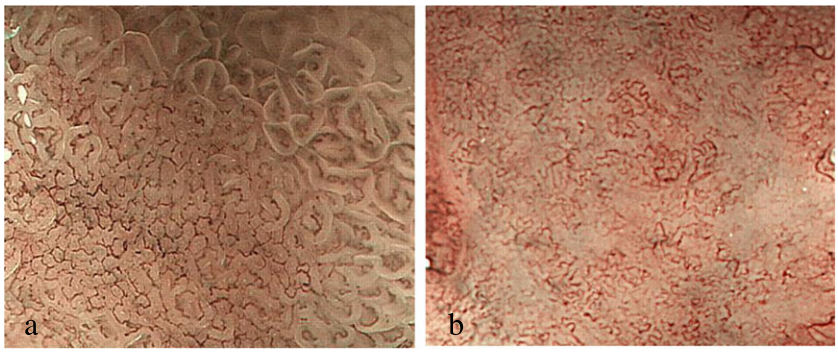

Figure 9. Magnifying endoscopic finding with narrow band imaging system in superficial depressed gastric cancer. (a) The fine network pattern appears as a mesh, and abundant microvessels are well connected with one another. (b) The corkscrew pattern has isolated and tortuous microvessels.

of EGC could not be determined by CE.[41] A series of 350 consecutive EGC resected *en bloc* using ESD were included in the study. The proportion of cancers showing unclear margins using CE was 18.9% (n = 66); of these, 62 (93.9%) were examined using ME-NBI, with the entire margins successfully delineated in 72.6% (45/62) of the lesions with unclear margins using CE. However, the diagnostic success rate for undifferentiated cancers was 0%, which was significantly lower than that for differentiated lesions ($P < 0.001$). Accordingly, ME-NBI using the VSCS is an excellent modality for identifying the entire margin of EGC when the margins are unclear using CE. It remains difficult to assess the lateral extent of undifferentiated EGC based on endoscopic findings alone; therefore, the endoscopic diagnostic strategy differs according to the histological type (Fig. 10). In difficult cases, the authors recommend that in these cases biopsy samples should be obtained from the apparently non-cancerous tissues around the lesions and then the resection margins should be determined after histopthologically confirming the absence of cancer invasion.

Differential Diangosis Between Gastric Low-Grade Adenoma (LGA) and EGC

ME-NBI can also be used for the differential diagnosis between gastric LGA and EGC. The microvascular pattern, as visualized using ME, is a reliable marker for differentiating between benign and malignant flat gastric lesions. However, in cases of gastric neoplasia of the superficially elevated type, it is sometimes impossible to visualize the microvascular pattern due to a white opaque substance (WOS) obscuring the subepithelial microvascular pattern (Fig. 11). The WOS morphology in 100% of adenomas with WOS exhibited a regular distribution; in contrast, 83% of the carcinomas with WOS showed an irregular WOS distribution.[43–47] For superficially elevated tumors with either WOS in a regular distribution or a regular microvascular pattern, the sensitivity and specificity for differentiating adenoma from carcinoma were 94% and 96%, respectively. In lesions with WOS, rather than assessing the microvascular pattern, the morphological analysis of WOS may be a new alternative visual marker for differentiating adenomas from carcinomas when using ME-NBI.

In addition, ME-NBI can visualize CO as slit-like structures in the gastric epithelial neoplasia. Kanesaka *et al.* investigated whether the visualization of CO by ME-NBI was useful for discriminating between gastric LGA and EGC retrospectively by evaluating 51 superficial elevated-type gastric neoplasia (LGA, n = 10; and EGC, n = 41).[48] They reported that visualized CO was significantly more common in the LGA group than in the EGC group (31.2 [95% CI 16.3–46.1] *vs* 6.3 [95% CI 3.6–9.0], $P < 0.001$). With a cut-off number of visualized CO of 20, the sensitivity, specificity and accuracy of dense-type CO for discriminating between LGA and EGC were 90.0%, 87.8% and 88.2%, respectively. Thus, determining the number of visualized CO in superficial elevated-type gastric neoplasia by ME-NBI appears to be useful for discriminating between LGA and EGC.

Other Novel Endoscopic Markers Visualized by ME-NBI

White globe appearance (WGA)

Although ME-NBI is useful for the diagnosis of gastric mucosal lesions, differentiating between EGC and LGA remains challenging. During ME-NBI, Doyama

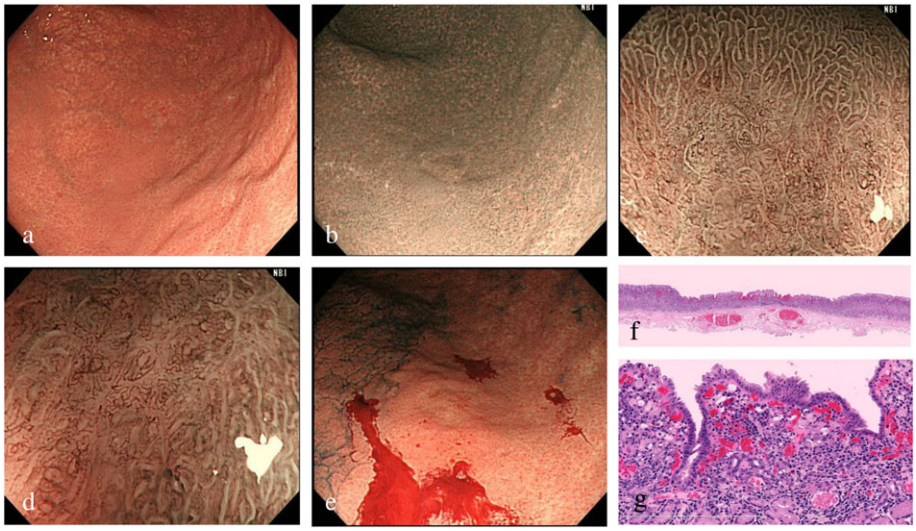

Figure 10. Undifferentiated type of early gastric cancer. (a) Endoscopic findings using conventional white light imaging showing a pale mucosal lesion. The morphology of this lesion is slightly depressed and irregularly demarcated. Endoscopic findings using narrow band imaging (NBI) (b) without, (c) with low-power and (d) high-power magnifying observations. A clear demarcation is observed at the border of the lesion. High-power magnifying endoscopy (ME)-NBI demonstrates an irregular microvascular (corkscrew) pattern and absent microsurface pattern with somehow unclear demarcation line. (e) The signet-ring cell carcinoma cells prefer growth infiltrating beneath the surface epithelium, therefore, endoscopic submucosal dissection (ESD) is performed after biopsy from the apparently noncancerous tissues adjacent to the lesion to determine the resection margins after histopthologically confirming the absence of cancerous invasion based on biopsy. (f,g) Histopathological findings of the specimen resected by ESD, showing a signet-ring cell carcinoma. Most part of this lesion invade the wall layer of mucosa, whereas at the marginal area shallowly invades the intermediate layer of the lamina propria, but does not reach the mucosal surface. HE stain, magnification: (f) ×5; (g) ×20.

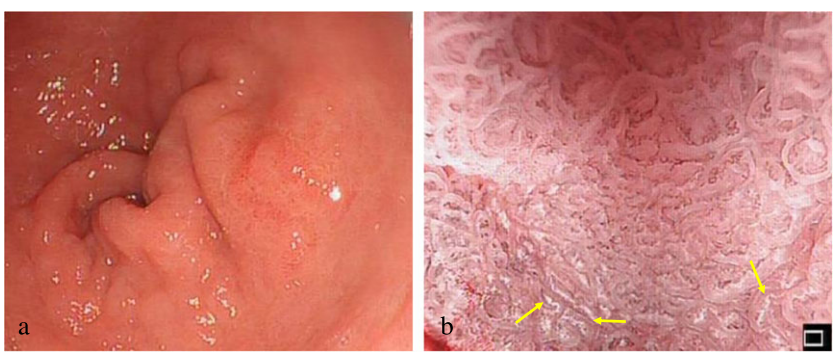

Figure 11. A slightly elevated (0–IIa) type early gastric cancer located at the gastric antrum. Histological type: differentiated (intestinal) type. (a) Conventional white light imaging shows a slightly elevated redness lesion with unclear demarcation. (b) Magnifying endoscopy with narrow-band imaging shows that the microvascular pattern is not clearly visualized due to white opaque substance (WOS; arrows) obscuring the subepithelial microvascular pattern. The WOS morphology exhibits an irregular speckled pattern. According to the vessels plus surface classification system, this lesion is diagnosed as cancerous.

et al. noted the presence of a small, white lesion with a globular shape underneath cancerous gastric epithelium, and have termed this endoscopic finding the WGA (Fig. 12).[49,50] By careful histological investigation, some of the WGA visualized under ME-NBI were found to correspond to intraglandular necrotic debris within markedly dilated neoplastic glands, suggesting it may be possible histological marker that is specific for cancer (Fig. 12). The WGA was evident in EGC but not in LGA. The prevalence of WGA in EGC and LGA was 21.5% (20/93) and 0% (0/18), respectively (P = 0.039). The sensitivity, specificity,

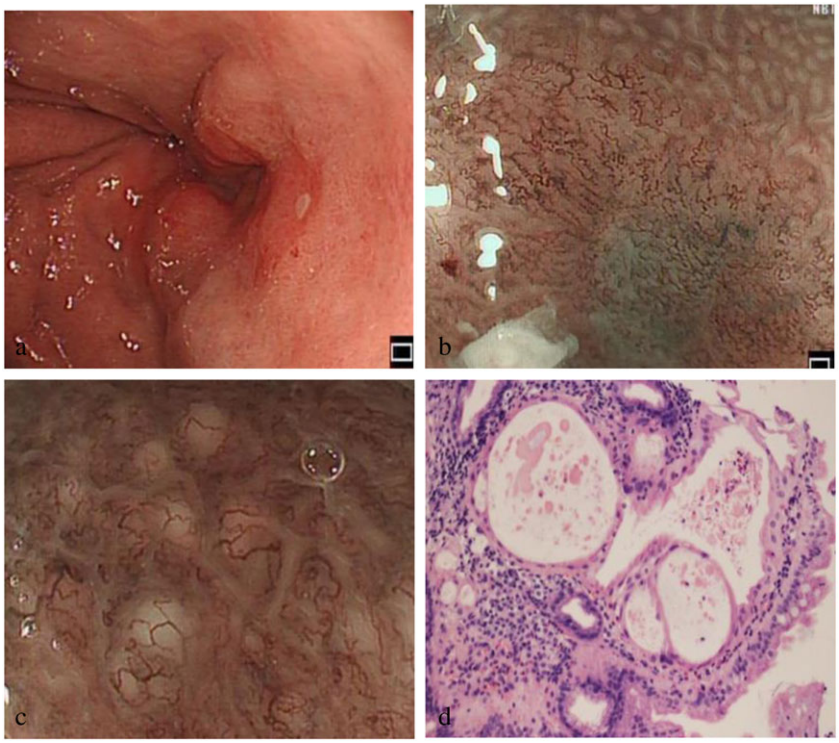

Figure 12. The white globe appearance could be a novel endoscopic marker for the extremely high specificity and positive predictive value for differentiating between early cancer and low-grade ademona. (a) Endoscopic findings of superficial depressed (0–IIc) early gastric cancer on the gastric upper body. (b) Magnifying endoscopy with narrow-band imaging (ME-NBI) shows an irregular microvascular pattern and an absent microsurface pattern with well-demarcated line. (c) Representive endoscopic image of the white globe appearance visualized by ME-NBI. (d) Representive histological image of intraglandular necrotic debris (HE stain, ×100).

positive predictive value (PPV) and negative predictive value (NPV) for differentiating between EGC and LGA, based on the presence of WGA, were 21.5%, 100%, 100% and 19.8%, respectively. Although the sensitivity and NPV were quite low, WGA could be regarded as a novel endoscopic marker for differentiating between EGC and LGA because of its extremely high specificity and PPV.

Vessels within epithelial circle (VEC) pattern

Pathological studies have indicated that the papillary adenocarcinomas are more aggressive than tubular adenocarcinomas, but a definitive diagnosis using conventional endoscopy alone is not possible. The VEC pattern visualized using ME-NBI may be a characteristic feature of papillary adenocarcinoma. Kanemitsu *et al.*[51] analyzed 35 VEC-positive lesions and 70 size- and macroscopic-type-matched VEC-negative lesions resected using ESD, showing that histologically papillary structure was observed in 94.3% (33/35) of the VEC-positive and 8.6% (6/70) of the VEC-negative lesions ($P < 0.001$). The incidence of coexisting undifferentiated carcinoma was 22.9% (8/35) of the VEC-positive and 2.9% (2/70) VEC-negative cancers ($P = 0.002$), while that of submucosal cancer invasion was 25.7% (9/35) and 10.0% (7/70), respectively ($P = 0.045$). The VEC pattern visualized by ME-NBI may be used as a promising preoperative endoscopic diagnostic marker of papillary adenocarcinoma, and the coexisting undifferentiated carcinoma and submucosal invasion were observed in approximately one-fourth of all the VEC-positive cancers.

In conclusion, ME-NBI is a reliable technique and a better diagnostic performance compared with C-WLI, and has become an essential tool for the diagnosis and treatment of EGC. In addition, it is useful for the determination of lateral spreading margins and the histological type of the cancer. Further research should focus on establishing a standard classification system and specific training of ME-NBI to reduce various biases and to improve its diagnostic accuracy.

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