

# Superficial Flat-type Early-stage Gastric Signet Ring Cell Carcinoma in the Atrophic Background Mucosa: Two Case Reports

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## Research Article

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# Abstract

Gastric signet ring cell carcinoma is a rare and highly malignant adenocarcinoma, which is characterized by early metastasis, rapid progression and poor prognosis. Several studies have shown that early-stage gastric signet ring cell carcinoma may have equal or better prognosis than other types of gastric cancer. However, most of the early-stage lesions are difficult to detect by endoscopy. Two female cases of early-stage gastric signet ring cell carcinoma with atrophic background mucosa occurring in the middle and lower part of the stomach were found in our endoscopy center. The diagnosis was confirmed by upper gastrointestinal white light endoscopy combined with narrow-band imaging and endoscopic biopsy, both lesions less than 2.0cm in diameter were surgically removed and identified as intramucosal adenocarcinoma. Through these two cases, we aim to illustrate the difficulty of early detection of gastric signet ring cell carcinoma with mucosal atrophy. We can roughly identify the demarcation of the lesion by combining white light endoscopy and narrow-band imaging, and slightly irregular microsurface and microvascular pattern of the lesion were found via magnifying endoscopic observation, but the demarcation can hardly be accurately identified.

## Introduction

Gastric signet ring cell carcinoma (SRCC) originates from stem cells that lie in the isthmus and upper neck of gastric glands in the lamina propria<sup>[1]</sup>. Despite the decrease in the incidence of gastric cancer in recent years, the incidence of signet ring cell carcinoma of stomach is increasing<sup>[2,3]</sup>. SRCC is a highly aggressive tumor which is characterized by its early metastasis, peritoneal metastasis, rapid progression and poor prognosis<sup>[4]</sup>. With the research progressing, several studies have shown that early-stage gastric SRCC may have an equal or better prognosis than other types of gastric cancer<sup>[5]</sup>. Therefore, early detection of gastric SRCC is of great significance and benefits to patients<sup>[6,8]</sup>. SRCC shows a destructive, diffuse and invasive growth, The majority of SRCCs found by endoscopy can be classified as type 0-IIc or 0-III, however, most of the early-stage lesions are macroscopically identified as type 0-IIb, with the lesion surface covered by non-cancerous epithelium, making it difficult to detect by endoscopy, SRCC is usually found in non-atrophic fundic gland area. Due to the absence of angiogenesis, it is usually found that the mucosa of the tumor area shows a whitish color<sup>[9]</sup>. If it occurs in the atrophic background mucosa, the difficulty of detection will be greatly increased. Hereby, we report two cases of gastric SRCC with atrophic background mucosa which are difficult to detect.

## Case Presentation

### Case 1

A 57-year-old woman underwent gastroscopy in our center on April 16, 2020 due to a physical examination, 15 years after receiving H. pylori eradication therapy. White light endoscopy showed that the gastric body mucosa was red and white, with white as the main color. The capillary network was visible,

suggesting the degree of atrophy was classified as O-3 according to Kimura-Takemoto classification. A piece of area was found in the anterior wall of the middle part of stomach with a whiter mucosal surface than the surrounding mucosa, and the surface was slightly rough (Figure 1A). Narrow-band imaging (NBI) showed a whitish lesion about 2.0\*2.0 cm in size (Figure 2A) with less clear demarcation, and the biopsy specimen revealed SRCC. A biopsy scar in the discolored area was found by endoscopy, and the lesion was type 0-IIb. The demarcation of the lesion cannot be identified after spraying with indigo carmine dye. Magnifying endoscopy with narrow-band imaging (ME-NBI) showed that the distance between the glandular ducts and crypts was slightly widened. The irregularity of microsurface pattern (MSP) and microvascular pattern (MVP) were slight (Figure 3A), and the demarcation cannot be clearly determined. The enhanced CT of the abdomen (dual source) showed: 1. Splenic calcification; 2. Poor gastric filling, no obvious space-occupying Lesion. Please combine the findings of gastroscopy. Preoperative diagnosis: early-stage gastric signet ring cell carcinoma (cT1a). The patient underwent a laparoscopic-assisted radical distal subtotal gastrectomy (Billroth-I anastomosis) on April 28, 2020. Postoperative pathology revealed gastric SRCC, the tumor was 1.5×1.4cm in size, classified as superficial flat type (type 0-IIb), and limited to the mucosal layer. Postoperative pathology showed that the signet ring cells were all located in the upper or middle layer of the mucosa, the structure of gastric pits was lost partly, and the proper glands were intact (Figure 4A). After formalin fixation, the color of the type 0-IIb lesion area was extremely similar to that of the normal mucosa, the demarcation was not clear, and the lesion area corresponded to the tissue strip (Figure 5A). After comparing the endoscopic picture (Figure 6A) with the pathological section, it was found that the range of the lesion was consistent with that of the discolored area under white light and non-magnifying NBI endoscopy.

## Case 2

A 37-year-old woman underwent gastroscopy in our center on May 21, 2020 due to a physical examination, 3 years after receiving H. pylori eradication therapy. White light endoscopy showed that the gastric body mucosa was red and white, with white as the main color. the background mucosa indicated the degree of atrophy was classified as C-3 according to Kimura-Takemoto classification. A whitish mucosal area about 1.5\*1.5cm in size was found in the greater curvature on the anterior wall of the lower gastric body (Figure 1B). NBI showed that the lesion area was whiter than the surrounding mucosa (Figure 2B). Two biopsies showed few signet ring cells in the lamina propria of the mucosa. Gastroscopy showed two biopsy scars in the discolored area, and the lesions were type 0-IIb. The demarcation of the lesions cannot be identified after spraying with indigo carmine dye. The whitish area almost disappeared due to the biopsies. ME-NBI indicated no irregular microvessels, but the distance between the crypts was slightly widened (Figure 3B). The enhanced CT of the abdomen (dual source) showed 1. Hemangioma of the left lateral lobe of the liver; 2. Possible thickening of the gastric wall in the antrum; 3. a small amount of pelvic fluid. Preoperative diagnosis: early-stage gastric signet ring cell carcinoma (cT1a). The patient underwent a laparoscopic-assisted radical distal subtotal gastrectomy (B-I anastomosis) on May 29, 2020. Postoperative pathology revealed gastric signet ring cell carcinoma, the tumor was 1.2×1.0cm in size, classified as superficial flat type (type 0-IIb), and limited to the mucosal layer. Postoperative pathology showed that the signet ring cells were all located in the upper or middle layer of the mucosa,

and the proper glands were intact (Figure 4B). After formalin fixation, there was no significant difference between the color of the type 0-IIb lesion area and the normal mucosa. The demarcation was unclear and the lesion area corresponded to the tissue strip (Figure 5B). After comparing the endoscopic picture with the pathological section, it was found that the range of the lesion was consistent with that of the discolored area under white light and non-magnifying NBI endoscopy. (Figure 6B).

## Discussion

Early-stage gastric signet ring cell carcinoma originates from undifferentiated stem cells at the neck of the gland in the lamina propria. It can spread widely through the mucosal layer, but generally invade into the submucosa at a low speed, therefore, the treatment effect is better when it is limited to the mucosal layer. However, once breaking through to the submucosa, it will quickly spread and metastasize. The early detection of the disease is extremely significant, suggesting that better awareness to find the lesion, a better ability to make endoscopic diagnosis and standard operation are required. And this is the only way that SRCC can get treatment at an early-stage. Early-stage of signet ring cell carcinoma is classified as undifferentiated type. According to previous reports, its endoscopic findings are mainly based on the destruction of the glands and typical microvessels found under ME-NBI<sup>[10]</sup>. Professor Yagi summarized its typical microvessels into three types: raimon vessels, wavy microvessels and corkscrew pattern<sup>[11,12]</sup>. Phalanusitthepha *et al.*<sup>[13]</sup> reported that the typical endoscopic finding of early-stage signet ring cell carcinoma is a widened intervening part (IP), which is called "stretch sign". The two cases of signet ring cell carcinoma found in our center were both due to physical examinations and asymptomatic, and both were type 0-IIb lesions with mucosal atrophy after eradication of *H. pylori* infection. It is difficult to find a whitish lesion in whitish atrophic mucosa. We combine the white light endoscopy and image enhancement endoscopy (IEE) (such as NBI) to make it easier to highlight the difference in hue to help with the diagnosis. Demarcation of such type 0-IIb lesions cannot be highlighted accurately after spraying with the indigo carmine dye. Magnifying endoscopic observation found that the MSP of the lesion is mainly characterized by the elongated and widened glands<sup>[14]</sup>, and no typical raimon vessels, wavy microvessels or corkscrew pattern can be seen. It is difficult to identify a clear demarcation with ME-NBI. Size of the lesion determined by pathological results is consistent with that of the whitish area under NBI. We believe that the demarcation can be determined by white light endoscopy and non-magnifying NBI. If necessary, biopsies can be performed. We are also convinced that the depth of invasion of type 0-IIb flat lesion less than 2cm in size is within the mucosa, especially within the upper or middle layer of the lamina propria. The depth of invasion of early gastric cancer is limited to the mucosa or submucosa, but only when undifferentiated cancer is limited to the mucosal layer (cT1a) can endoscopic treatment be considered. Early-stage gastric signet ring cell carcinoma is classified according to the location of cancer cells in the lamina propria as the middle layer type, superficial layer type, and whole layer type which can be determined according to MVP and MSP under ME-NBI<sup>[15,16]</sup>. Endoscopic submucosal dissection (ESD) is widely accepted as a minimally invasive treatment for early intramucosal gastric cancer, with almost no risk of lymph node metastasis<sup>[17-19]</sup>. According to the "Guidelines for Gastric Cancer ESD/EMR (First Edition)" of Japanese Gastroenterological Endoscopy Society (JGES), UL0 cT1a undifferentiated-type

carcinomas with a long diameter 2 cm or less is an expanded indication for ESD. After communicating the pros and cons of surgical and endoscopic treatment with the patients and their families, both patients finally chose surgical treatment. No recurrence or lymph node metastasis was found in the follow-up. In 2020, according to the "Guidelines for Gastric Cancer ESD/EMR (Second Edition)" [20] of JGES, UL0 cT1a undifferentiated-type carcinomas with a long diameter 2 cm or less has been classified as an absolute indication for ESD. Strict pathological evaluation and curative evaluation should be carried out afterwards. In addition, whether H. pylori-negative or H. pylori-positive signet ring cell carcinoma are given the same diagnosis strategy is worthy of our further study and discussion.

## Declarations

### Author contributions

JC: study concept and design, data interpretation and technical support. WW: manuscript draft, data interpretation. YY: manuscript revision, data acquisition and analysis. QX and SW: data acquisition and analysis. LZ and RY: data acquisition and analysis, technical support. JH: technical support. JC: final approval of the version to be published.

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### Informed Consent

Written and informed consent was obtained from the patient to publish his data.

### Conflict of Interest

The authors declare no competing interests.

## References

1. Humar B, Fukuzawa R, Blair V *et al*. Destabilized adhesion in the gastric proliferative zone and c-Src kinase activation mark the development of early diffuse gastric cancer. *Cancer Res* 2007; 67(6): 2480-9.
2. Bamboat ZM, Tang LH, Vinuela E *et al*. Stage-stratified prognosis of signet ring cell histology in patients undergoing curative resection for gastric adenocarcinoma. *Ann Surg Oncol* 2014; 21: 1678-85.
3. Henson DE, Dittus C, Younes M *et al*. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. *Arch Pathol Lab Med* 2004; 128: 765-70.

4. Kwon KJ, Shim KN, Song EM *et al.* Clinicopathological characteristics and prognosis of signet ring cell carcinoma of the stomach. *Gastic Cancer*, 2014; 17: 43-53.
5. Jiang CG, Wang ZN, Sun Z *et al.* Clinicopathologic characteristics and prognosis of signet ring cell carcinoma of the stomach: results from a Chinese mono-institutional study. *J Surg Oncol* 2011; 103: 700-3.
6. Ajani JA, Bentrem DJ, Besh S *et al.* Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw* 2013; 11: 531-46.
7. Isobe Y, Nashimoto A, Akazawa K *et al.* Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. *Gastric Cancer* 2011; 14: 301-16.
8. Li C, Du XH, Chen L Status quo of gastric cancer metastatic lymph node ratio. [Academic Journal of Chinese Pla Medical School](#) 2014; 35: 634-6.
9. Yao K, Nagahama T, Matsui T *et al.* Detection and characterization of early gastric cancer for curative endoscopic submucosal dissection. *Dig Endosc* 2013; 25: 44-54.
10. Okada K, Fujisaki J, Kasuga A *et al.* Diagnosis of undifferentiated type early gastric cancers by magnification endoscopy with narrow-band imaging. *J Gastroenterol Hepatol* 2011; 26: 1262-9.
11. Nakayoshi T, Tajiri H, Matsuda K *et al.* Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology(including video). *Endoscopy* 2004; 36: 1080-1084.
12. Okada K, Fujisaki J, Kasuga A *et al.* Diagnosis of undifferentiated type early gastric cancers by magnification endoscopy with narrow-band imaging. *J Gastroenterol Hepatol*. 2011; 26: 1262-9.
13. Phalanusitthepha C, Grimes K L, Ikeda H *et al.* Endoscopic features of early-stage signet-ring-cell carcinoma of the stomach. *World J Gastrointest Endosc* 2015; 7: 741-6.
14. Yamamoto Y, Fujisaki J, Omae M *et al.* *Helicobacter pylori*-negative gastric cancer: Characteristics and endoscopic findings. *Digestive Endoscopy* 2015; 27: 551–61.
15. Horiuchi Y, Fujisaki J, Yamamoto N *et al.* Accuracy of diagnostic demarcation of undifferentiated-type early gastric cancers for magnifying endoscopy with narrow-band imaging: endoscopic submucosal dissection cases. *Gastric Cancer*, 2016; 19: 515-23.
16. Horiuchi Y, Fujisaki J, Yamamoto N *et al.* Accuracy of diagnostic demarcation of undifferentiated-type early gastric cancer for magnifying endoscopy with narrow-band imaging: surgical cases. *Surg Endosc* 2017; 31: 1906-13.
17. Gotoda T, Yanagisawa A, Sasako M *et al.* Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; 3: 219-25.
18. Ono H, Kondo H, Gotoda T *et al.* Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; 48: 225-9.
19. Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; 10: 1-11.

20. Ono H, Yao K, Fujishiro M *et al.* Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). *Dig Endosc*, 2021; 33: 4-20.

## Figures

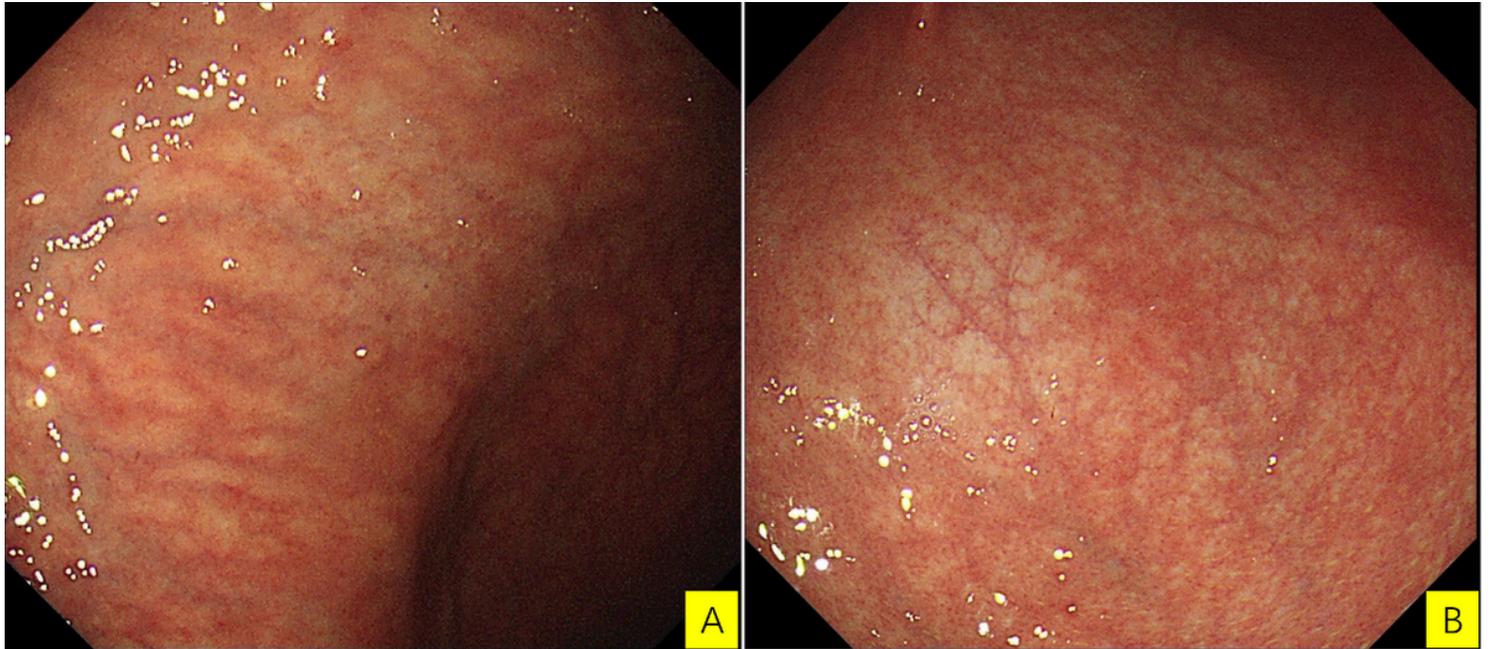
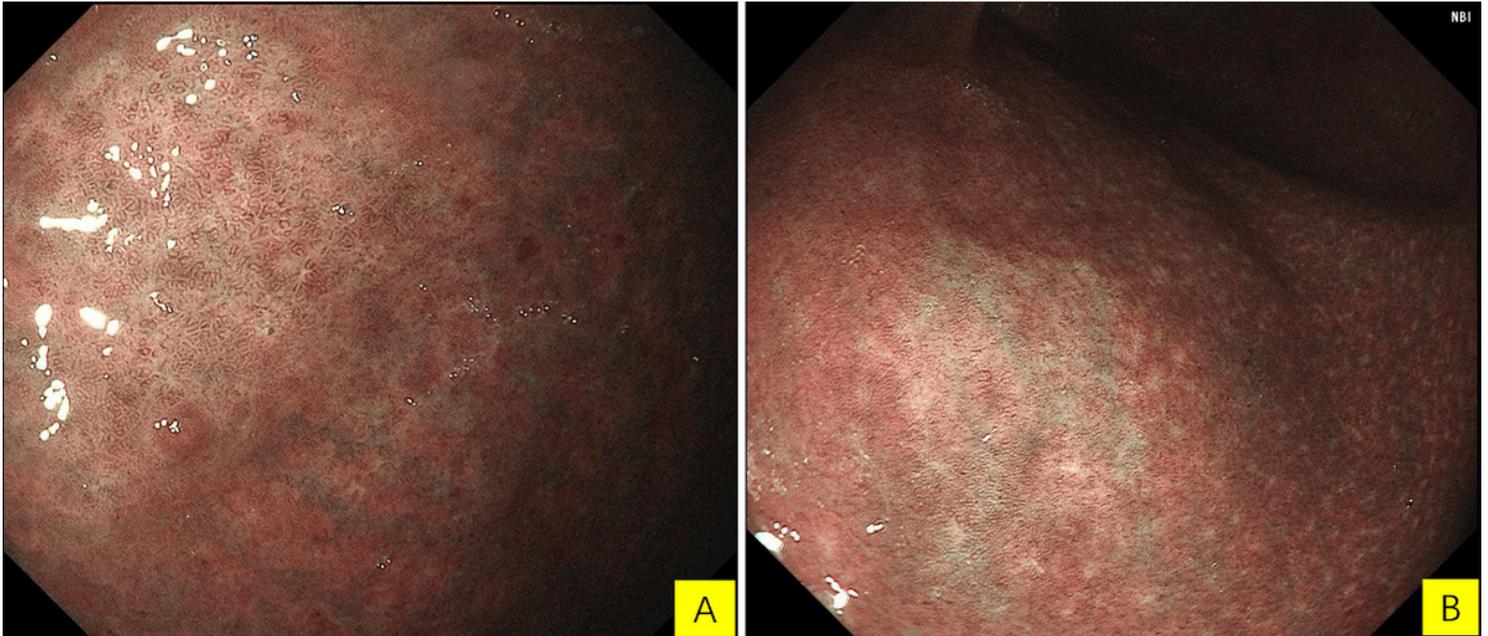


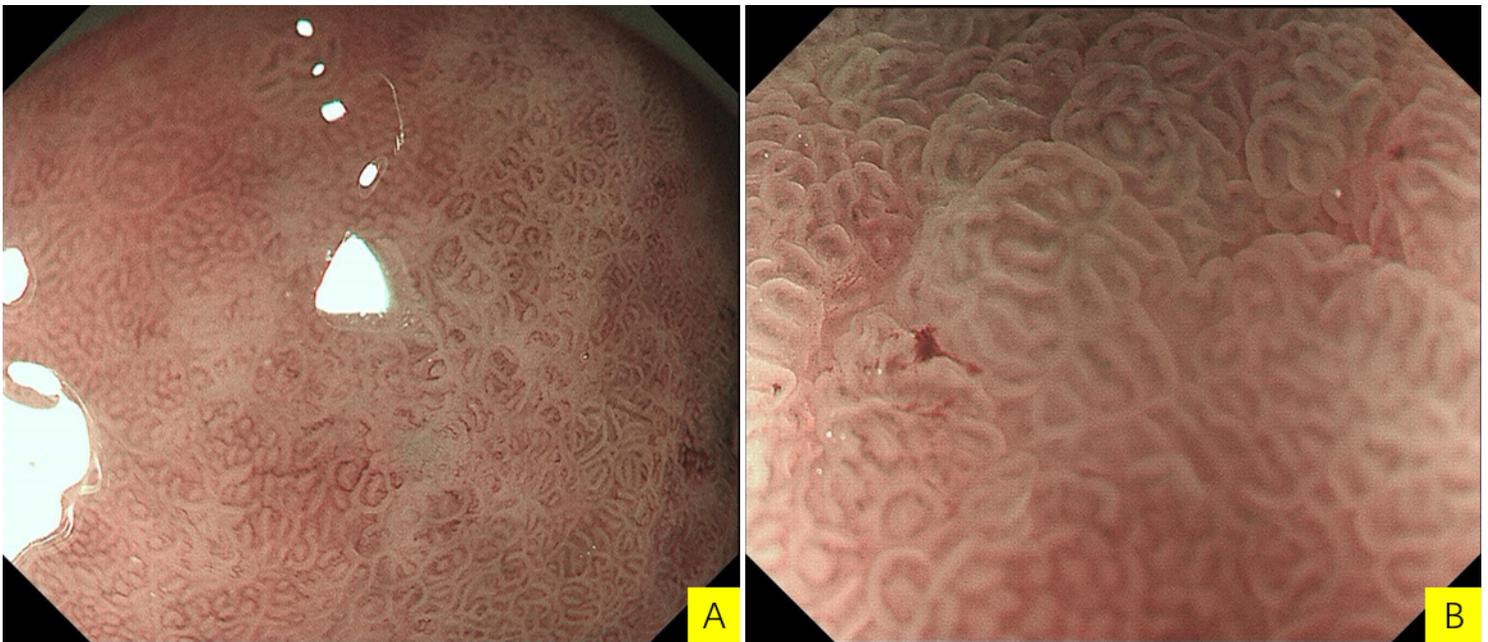
Figure 1

**white light endoscopy** The atrophic background mucosa after *H. pylori* eradication. No ulcer was found, the demarcation was less clear, and the lesion area showed a more whitish color than the surrounding mucosa. A: a discolored type 0-IIb lesion with a long diameter of 2.0cm in case 1 is was found oinn the anterior wall of the middle part of the stomach. B: a discolored type 0-IIb lesion with a long diameter of 1.5cm in case 2 is was found adjacent to the anterior wall and located in the greater curvature at the border of gastric body and antrum.



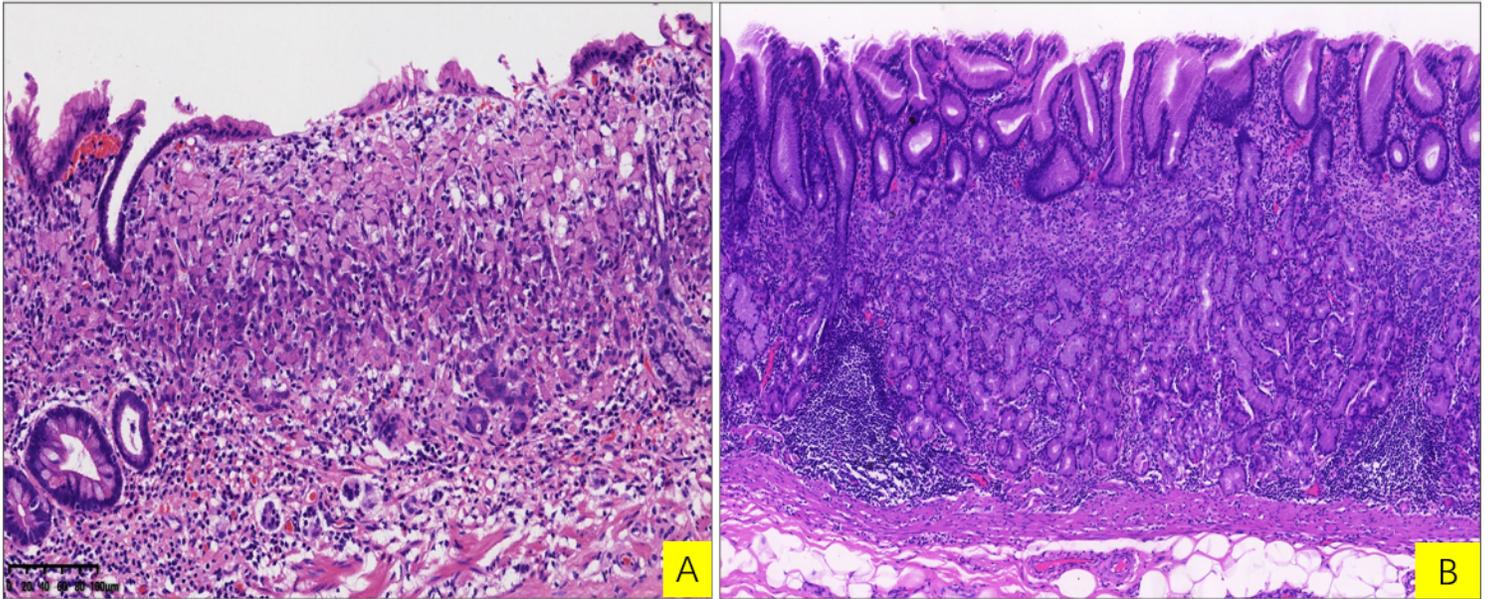
**Figure 2**

**NBI** The lesions showed a more whitish color than the surrounding mucosa, and the demarcation could be clearly identified, the image observed by NBI was clearer than that by white light endoscopy. A: NBI image of case 1. B: NBI image of case 2.



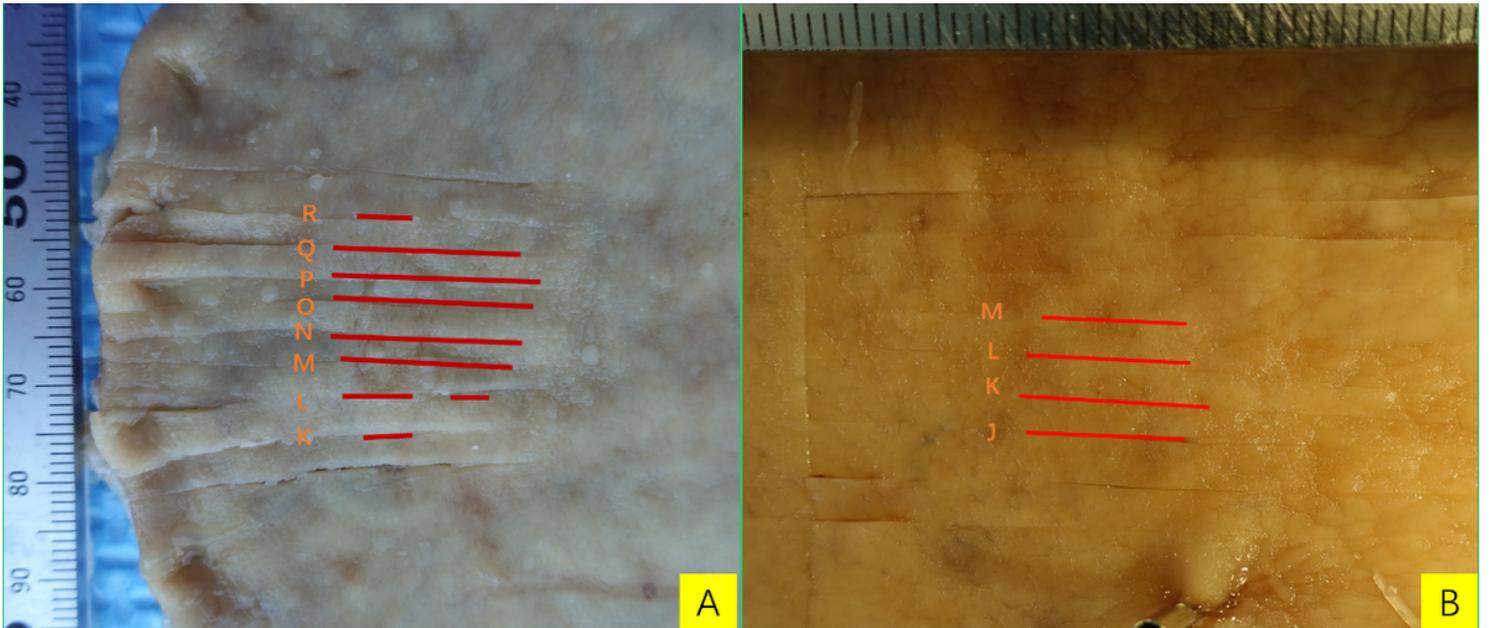
**Figure 3**

**ME-NBI** The distance between glandular ducts and crypts on the lesion surface are slightly widened, the irregularity of MVP and MSP was slight. The border between the lesion and the normal mucosa cannot be identified. A: local microvessels were slightly dilated. B: no irregular microvessels could be found on the surface.



**Figure 4**

**Postoperative pathology**—Signet ring cells were located at the upper or middle layer of the mucosa, and the proper glands were intact. A—the structure of gastric pits was lost partly. B—the structure of the glands was intact, and the distance of crypts was slightly widened.



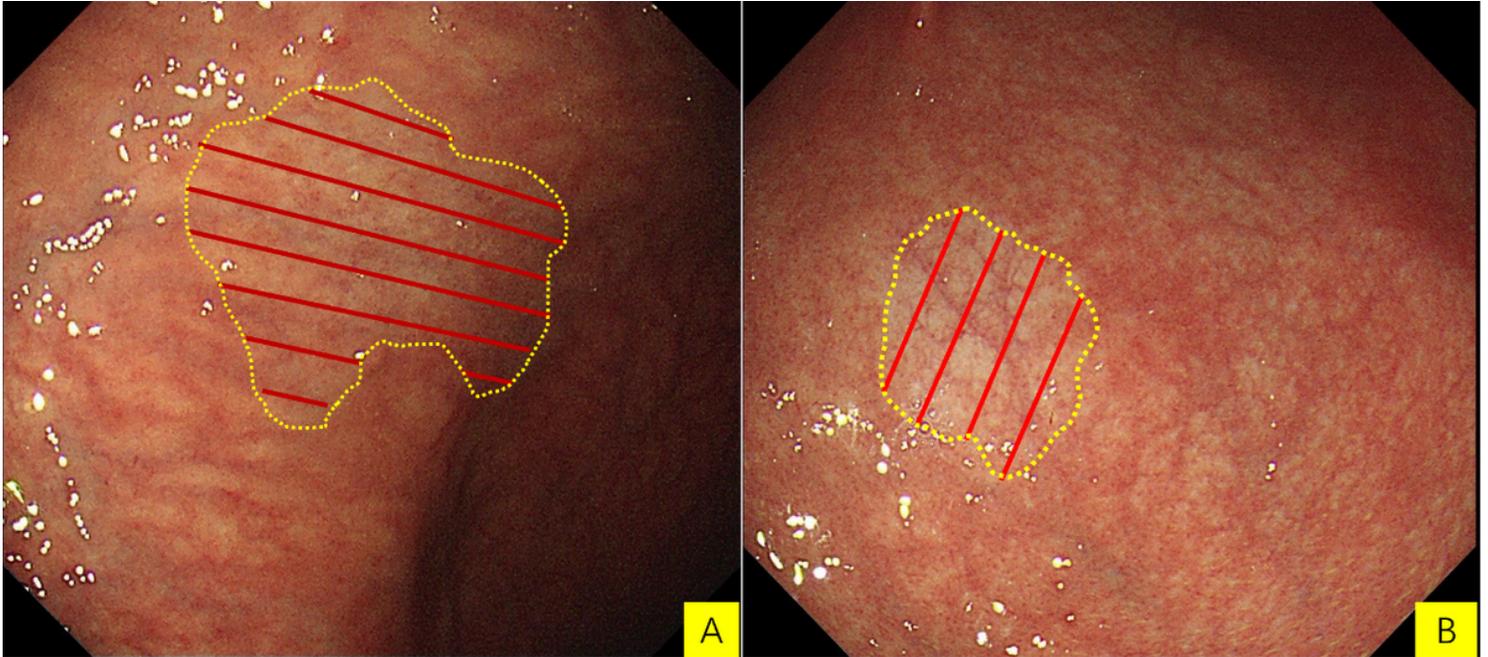
**Figure 5**

**Mapping of the specimen based on histology**—The demarcation was

not clear, and the color of the lesions was similar to that of the normal mucosa. A

signet ring cell carcinoma in case 1 distributed at superficial flat lesion measuring 1.5 cm × 1.4 cm (red line) B—signet ring cell carcinoma in case 2 distributed at

superficial flat lesion measuring 1.2 cm × 1.0 cm (red line).



**Figure 6**

**Range of the lesions based on endoscopic images** The range of both

lesions were consistent with that of the whitish areas found by white light endoscopy.