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The Usefulness of Magnifying Endoscopy Using a Narrow-band Imaging System for Detecting Barrett's Mucosa

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ABSTRACT

The usefulness of magnifying endoscopy and a narrow-band imaging (NBI) system for detecting Barrett's mucosa was investigated on the basis of the clinicopathologic assessment of superficial Barrett's esophageal carcinoma. Specialized columnar epithelium (SCE) was observed in the background mucosa of all patients with superficial Barrett's esophageal carcinoma, a finding that supports the theory that SCE is the original site of carcinogenesis in this condition. Magnifying endoscopy and NBI revealed the characteristic "spiral pattern," i.e., a spiral image of the capillary vessels of the superficial mucosal layer characteristic of SCE, indicating that SCE can be detected by means of magnifying endoscopy and NBI. Thus, magnifying endoscopy with NBI shows promise in the diagnosis and treatment of Barrett's mucosa. (Jikeikai Med J 2004 ; 51 : 55-66)

Key words : Barrett's mucosa, adenocarcinoma, magnifying endoscopy, narrow-band imaging system, specialized columnar epithelium

INTRODUCTION

The incidence of gastroesophageal reflux disease has increased in Japan with the westernization of lifestyles, including dietary habits, and the aging population, as had happened earlier in Western countries[1]. As a consequence, the incidence of Barrett's mucosa is also expected to increase. Recently, adenocarcinoma originating from Barrett's mucosa has occasionally been diagnosed[2,3].

In Japan, Barrett's mucosa has been defined as "columnar epithelium continuing from the stomach mucosa into the esophagus"[4]. The association of intestinal metaplasia of the columnar epithelium has recently been emphasized in the definition of Barrett's mucosa in Western countries, and Barrett's mucosa without associated intestinal metaplasia has often been called "columnar-epithelium-lined esophagus (CLE)"[5]. Thus, to diagnose Barrett's mucosa according to this definition, mucosal biopsy is essential ; however, biopsy has limitations, such as when specimens are obtained from sites not showing intestinal metaplasia, and lead to incorrect diagnoses.

Magnifying electron endoscopy (maximum magnification, ×80) has become a routine endoscopic technique[6], for which a narrow-band imaging (NBI) system has also been developed. The information provided by these endoscopic procedures equals or exceeds that obtained with dye-spraying endoscopy. Magnifying endoscopy with NBI allows clear visualization of the microstructure of the mucosal surface, especially the capillaries[7]. We have previously reported the usefulness of this technique for the diagnosis of early gastric cancer[8].

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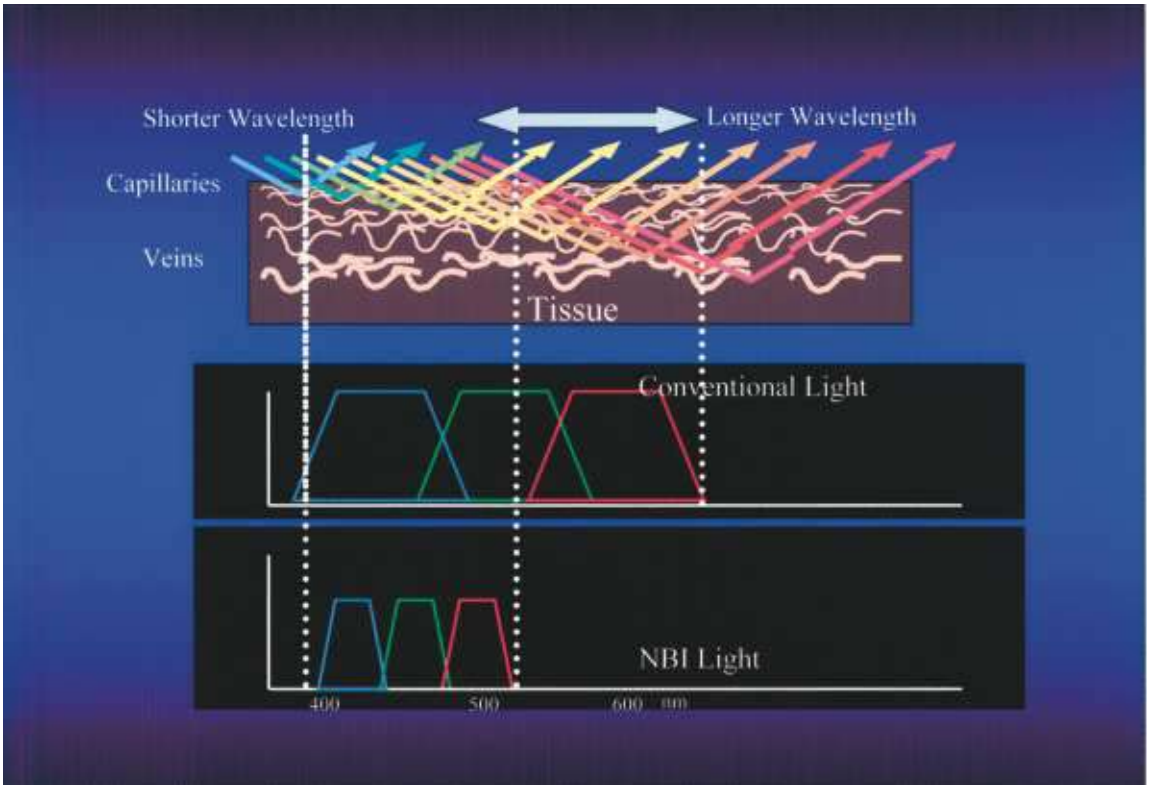

Fig. 1. Spectrum data

Table 1. The characteristics of the 8 patients with superficial Barrett's esophageal adenocarcinoma

No.	Age Sex	CLE (mm)	Type	Size (mm)	Depth	Histology	Dysplasia	Therapy
1.	70 M	30	0-IIc	65×26	sm2	tub2	+	Open surgery
2.	63 M	75	0-IIa	23×13	m	tub2	+	Open surgery
3.	60 M	150	0-IIc	2×5	m	tub1	+	EMR
4.	60 M	60	0-IIa+IIc	30×45	sm3	tub1	−	Open surgery
5.	45 M	10	0-IIa	5×4	m	tub1	+	EMR
6.	48 M	20	0-IIc+IIb	15×8	m	tub1	+	EMR+ Open surgery
7.	71 M	10	0-IIa+IIc	10	sm3	Neuroendocrine cell Ca	−	Open surgery
8.	58 M	20	0-IIc	8×3	m	tub1	−	EMR

In the present study, we investigated the usefulness of magnifying endoscopy with NBI for detecting Barrett's mucosa, based on a clinicopathologic study of Barrett's esophageal adenocarcinoma.

PATIENTS AND METHODS

The subjects were 8 patients with superficial Barrett's esophageal cancer and 32 patients with CLE in whom diagnoses were made at Department of Endoscopy of the Jikei University School of Medicine Hospital from April 1997 through January 2003. For the diagnosis of CLE, the lower end of the fine, long branching vessels in the lower part of the esophagus was regarded as indicating the gastroesophageal junction, and the presence of columnar epithelium to the

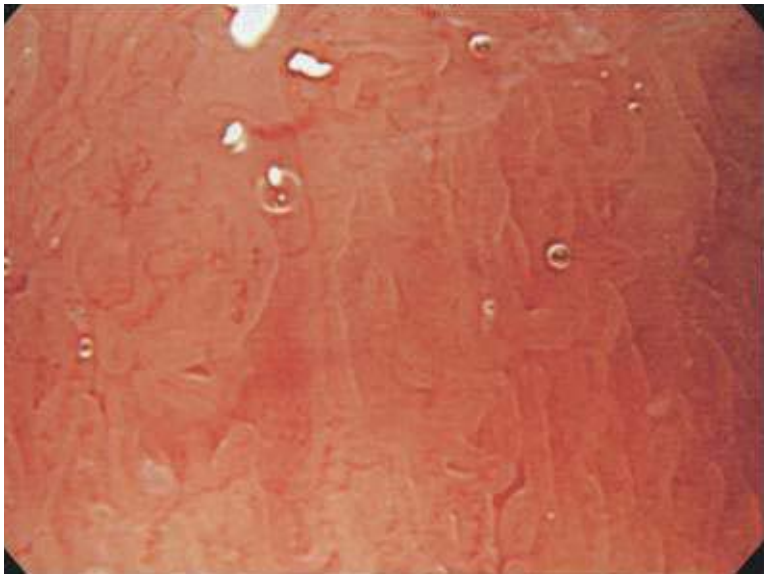

Fig. 2a

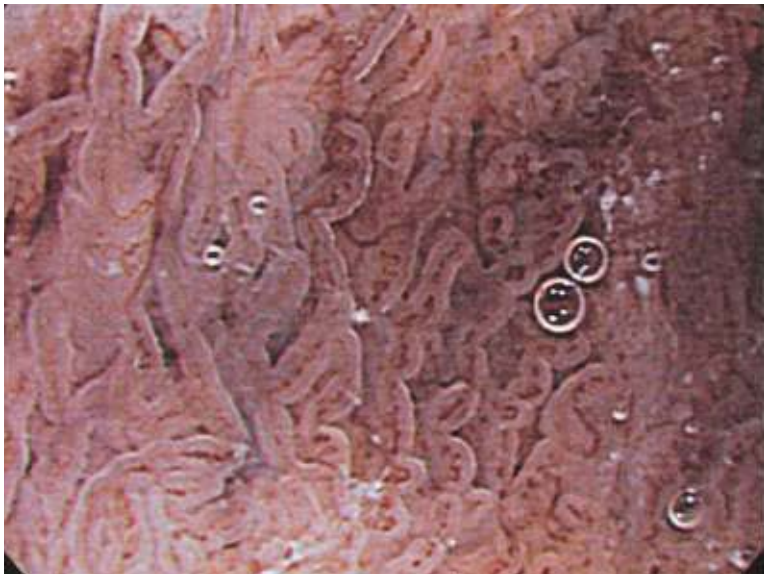

Fig. 2b

Fig. 2. Images of SCE obtained with magnifying endoscopy.
2a. Image obtained with conventional magnifying endoscopy : A chain-like pit pattern is observed.
2b. Image obtained with magnifying endoscopy and NBI : Spiral capillaries are distinctly observed in the chain-like pit pattern.

oral aspect of this junction was considered diagnostic for CLE. The 8 patients with superficial Barrett's esophageal carcinoma underwent clinicopathologic examinations to determine the length of the Barrett's mucosa, the macroscopic type, histological type, size, and depth of the invasion of the tumor, and the type of background mucosa.

The 32 patients with CLE underwent routine magnifying endoscopy or magnifying endoscopy with NBI. A magnifying electron endoscope (GIF-Q240Z, Olympus Optical Co., Ltd., Tokyo, Japan) equipped with a transparent hood, an NBI system (Olympus Optical Co., Ltd.), and a digital stationary image recorder (Olympus Optical Co., Ltd.) were used. In

Fig. 3. Image of SCE obtained with magnifying endoscopy and NBI. A spiral pattern of capillaries, as in Fig. 4, is observed.

the conventional area-sequential electroscope, fast rotation of a turret to which red, blue, and green filters are applied to the anterior surface of a white light source was used to induce time-series irradiation with the 3 colored lights. Thus, the images obtained are successively treated by signal processing for color image formation. The NBI system is a light source system using narrow-band filters for the red, blue, and green filters, whose wavelengths differ from the conventional ones (Fig. 1). The system was designed to improve the visualization of lesions with the area -sequential electroscope. In the present study, red, blue, and green filters, with wavelengths adjusted to 485 to 515 nm, 400 to 430 nm, and 430 to 460 nm, respectively, were used. The enhancement of the blue band, which has a strong affinity for hemoglobin in the living body, enables clear observation of the capillaries of the superficial mucosal layer. Biopsies were performed at sites showing the characteristic findings, and the endoscopic images were analyzed in relation to the histologic findings.

Immunohistochemical studies of the biopsy specimens were also performed. Three-dimensional (3-D) images of capillaries were constructed with a confocal laser scanning microscope (LSM) and compared with images obtained with magnifying endoscopy performed with NBI. The biopsy specimens were treated as follows. After fixation in a 4% paraformaldehyde solution at 4°C for 30 minutes, the specimens were rinsed with 0.1 M phosphate-buffered saline (PBS) and treated at 4°C for 30 minutes with the surfactant Triton X-100 diluted to 0.5% with 0.1 M PBS. The specimens were then allowed to react with a murine anti-human endothelial cell monoclonal antibody (CD34 : anti-human progenitor cell antigen-2 ; BD Biosciences Immunocytometry Systems, San Jose, CA, USA) diluted 1 : 40 as the first antibody at room temperature for 60 minutes, and then at 4°C for 24 hours. Then, the specimens were allowed to react with a fluorochrome (fluorescein isothiocyanate) -labeled goat anti-murine IgG antibody (molecular probe) diluted 1 : 100 at room temperature for 60 minutes. A confocal LSM 410 (Carl Zeiss, Oberkochen, Germany) was used for observation, and an argon laser at a wavelength of 488 nm was used to excite the fluorescein isothiocyanate.

RESULTS

Assessment of superficial Barrett's esophageal carcinoma

All patients were men aged 45 to 71 years (mean, 59.4 years). Cancer developed from Barrett's esophagus in 4 patients and from the so-called short segment

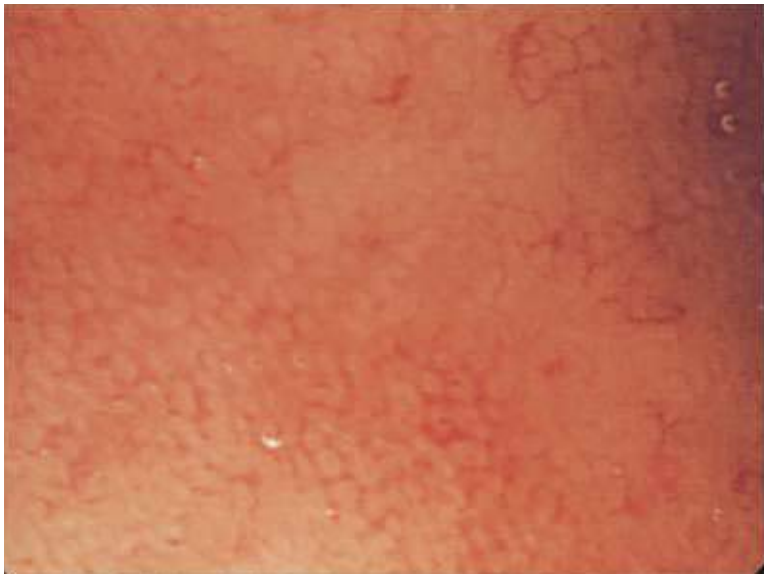

Fig. 4a

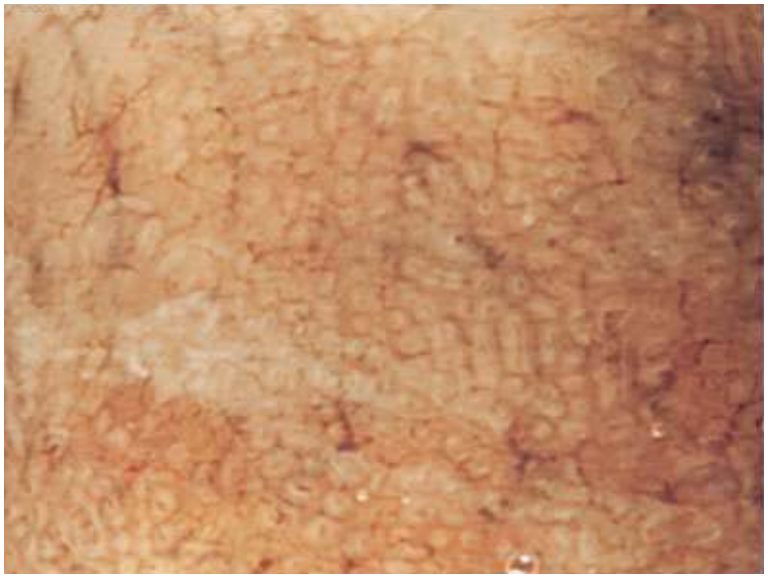

Fig. 4b

Fig. 4. Images of fundic type epithelium obtained with magnifying endoscopy.
4a. Image obtained with conventional magnifying endoscopy : A fine oval-pit pattern is observed.
4b. Image obtained with magnifying endoscopy and NBI : The pit pattern is more distinct.

Barrett's esophagus (SSBE)[9], where the length of the Barrett's mucosa is 3 cm or less, in the remaining 4 patients. The length of Barrett's mucosa was 30 to 150 mm (mean, 78.8 mm) in patients with Barrett's esophagus and 10 to 20 mm (mean, 15.0 mm) in patients with SSBE. Seven of the 8 patients had differentiated adenocarcinoma. Specialized columnar epithelium (SCE) was observed in the background mucosa in all 8 patients, and dysplasia was observed in 6 of 8 patients. Endoscopic mucosal resection (EMR) was performed in 4 patients, 1 of whom also underwent open resection. The remaining 4 patients underwent open resection (Table 1).

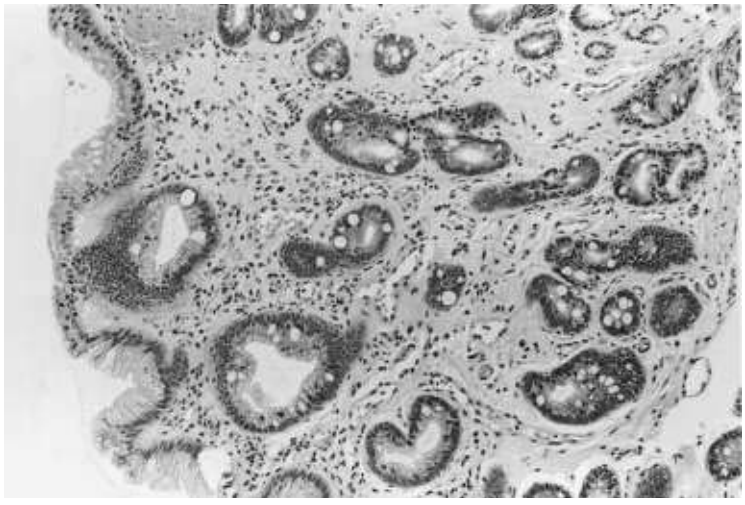

Fig. 5a

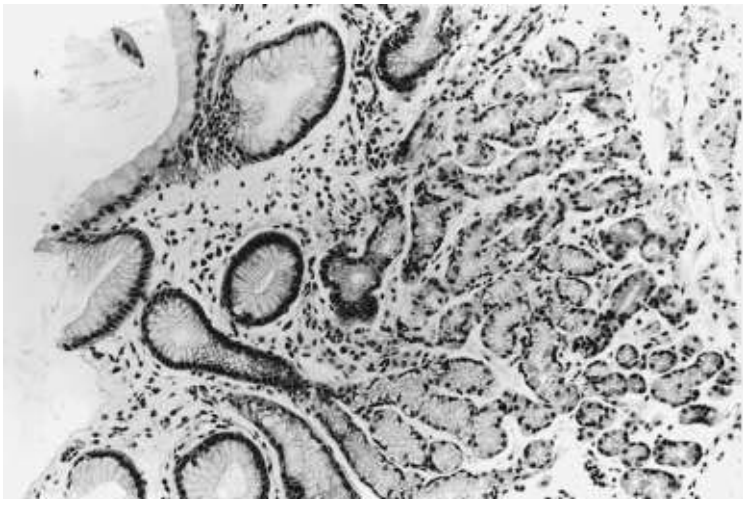

Fig. 5b

Fig. 5. Images obtained with magnifying endoscopy and NBI, and histologic findings of biopsy specimens
5a. SCE was confirmed with histologic examination of biopsy specimens obtained from the site where the spiral pattern was observed.
5b. Fundic type epithelium was confirmed with histologic examination of biopsy specimens obtained from the site where the fine oval-pit pattern was observed.

Magnifying endoscopy with NBI for CLE

CLE is observed as uniform columnar epithelial mucosa with conventional endoscopy, and the presence or absence of intestinal metaplasia is difficult to diagnose on visual inspection alone. In the present study, two characteristic features of CLE were observed with magnifying endoscopy with NBI : a spiral image of capillaries in a chain-like pit pattern. The chain-like pit pattern was observed with conventional magnifying endoscopy, which, when combined with NBI, revealed a more distinct chain-like pit pattern in which the spiral image of the capillaries (Fig. 2a, 2b) was evident (which we refer to as "the spiral pattern" ; Fig. 3). Biopsy specimens from this site showed intestinal metaplastic mucosa, consistent with the diagnosis of SCE (Fig. 5a). The spiral pattern was observed over a wide field to the oral aspect of the GE junction in all 11 patients with CLE extending over 30 mm or more of the entire circumference. In other patients, the spiral pattern either was observed over a relatively wide field involving the oral aspect or was scarcely observed.

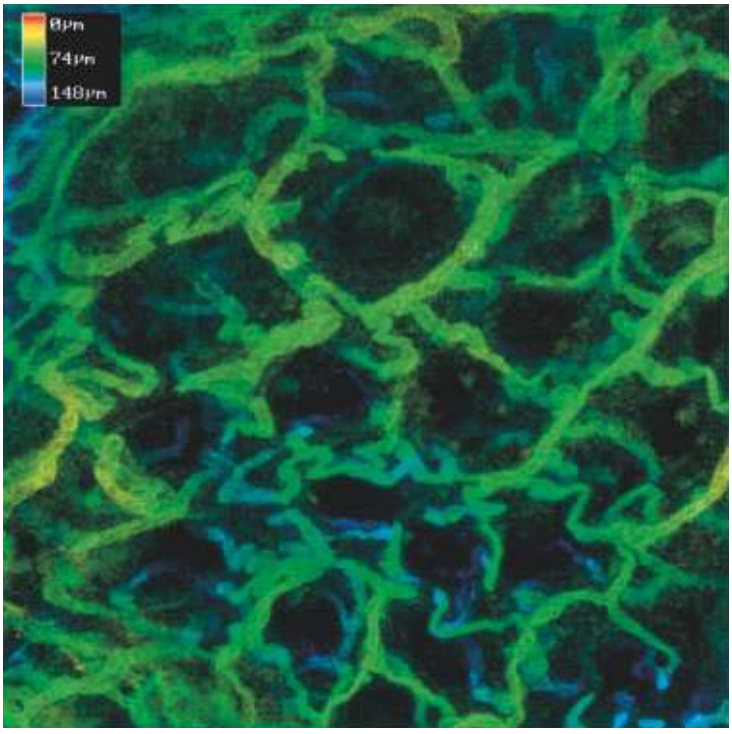

Fig. 6. 3-D image of capillaries reconstructed with LSM.
Biopsy specimens were immunostained with CD34. Subsequently, 3-D images of spiral blood vessels, as seen with NBI, were constructed.

Table 2. The characteristics of patients with CLE and the rate of identification of SCE by biopsy and NBI

	age (years)	length (mm)			SCE	
			min.	max.	biopsy	NBI spiral pattern
A $n=11$	64.1±5.1	97.8±48.0	30	160	11/11 (100%)	11/11 (100%)
B $n=21$	52.7±6.6	14.8±8.4	5	40	10/21 (47.6%)	17/21 (81.0%)

A : CLE≧30 mm B : CLE<30 mm

In contrast, a pattern of fine oval pits was observed mainly on the side of the stomach (Fig. 4a, 4b). Adeniform epithelium of the fundus was confirmed by biopsy of this site (Fig. 5b). Some sites also showed a mosaic of both the pattern of fine oval pits and the spiral pattern.

Reconstructed 3-D images of capillaries obtained with LSM showed a spiral image of capillaries of the superficial mucosal layer in biopsy specimens from sites where the spiral pattern was observed ; the findings were consistent with those of the spiral pattern (Fig. 6).

Table 2 shows the rate of identification of SCE with magnifying endoscopy and NBI. Patients with CLE extending over 30 mm or more of the entire circumference were assigned to group A, and the remaining patients were assigned to group B. In the 11 patients of group A, the length of CLE was 30 to 160 mm (97.8±48.0 mm, mean±SD), and the spiral pattern was observed with magnifying endoscopy and NBI in all of them. The presence of SCE was confirmed with biopsy. In the 21 patients of group B, the length of CLE was 5 to 40 mm (14.8±8.4), and 17 (81.0%) of the 21 patients showed a spiral pattern on magnifying endoscopy with NBI. SCE was confirmed with biopsy in 10 (47.6%) of the 21 patients.

Case report (patient 8 in Table 1)

A 58-year-old man was suspected, on the basis of a checkup at his workplace, of having reflux esophagitis and was referred to our hospital. Because conventional endoscopy revealed Barrett's mucosa approximately 20 mm long, we decided to monitor the

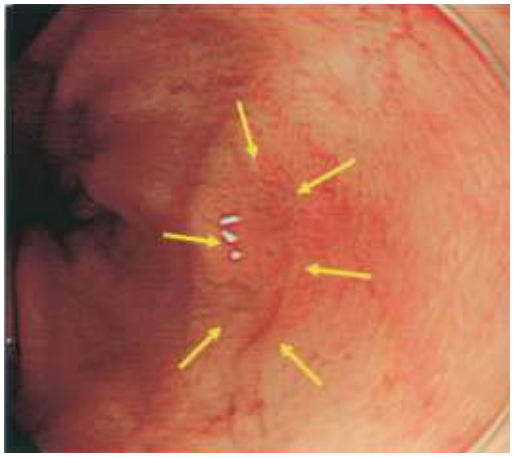

Fig. 7a

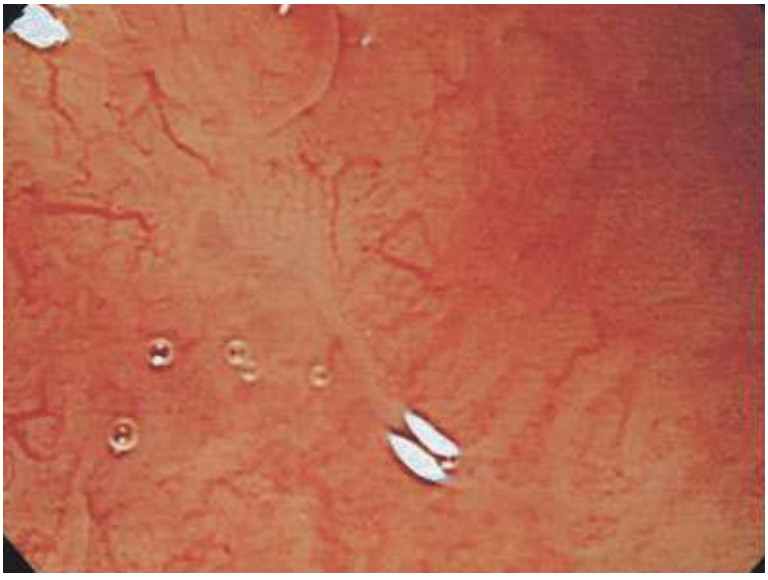

Fig. 7b

patient's course by means of annual examinations with magnifying endoscopy and NBI. Approximately 2 years later, a depressed lesion with slight rubor, approximately 8 mm in diameter, was observed in the Barrett's mucosa, which extended over a length of approximately 20 mm on conventional endoscopy (Fig. 7a). Magnifying endoscopy with NBI revealed an irregular mesh-like pattern of blood vessels which was distinct from the background mucosa (Fig. 7b, 7c). The spiral pattern was observed in the mucosa surrounding the depressed site. Biopsy of the surface of the depressed lesion showed well-differentiated adenocarcinoma, with the depth of invasion limited to the mucosa, as revealed by endoscopic ultrasonography (Fig. 7d), and EMR was performed. Because the lesion was a well-differentiated adenocarcinoma (Fig. 8a, 8b) with mucosal invasion and a negative stump, we decided to montior the patient's course.

DISCUSSION

According to Paul et al.[10], the columnar epithelium of Barrett's esophagus can be classified into the following 3 types: 1) gastric fundic type, 2) junctional type, and 3) SCE. The SCE in Barrett's esophagus has been considered the most important clinically, because its incidence in Barrett's esophagus is the highest and SCE gives rise to most tumorous

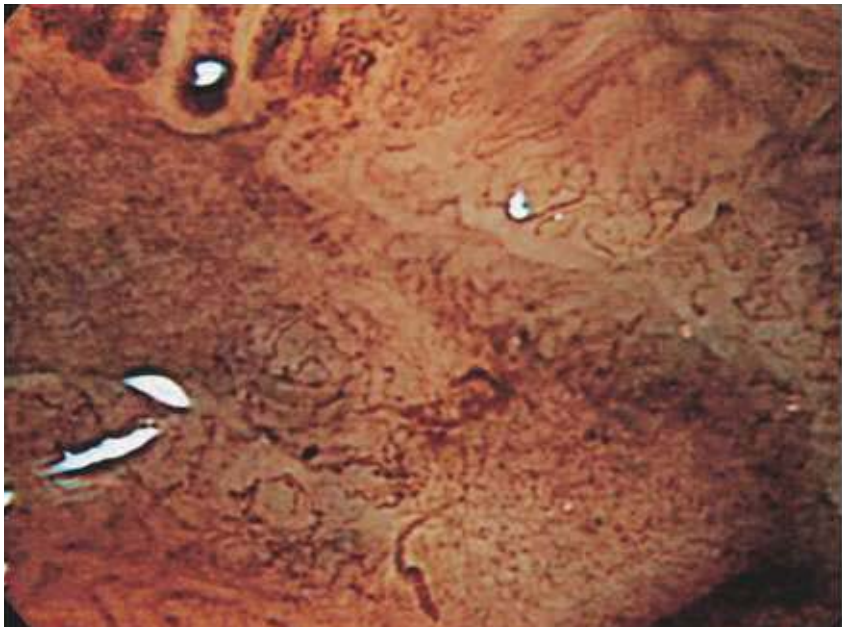

Fig. 7c

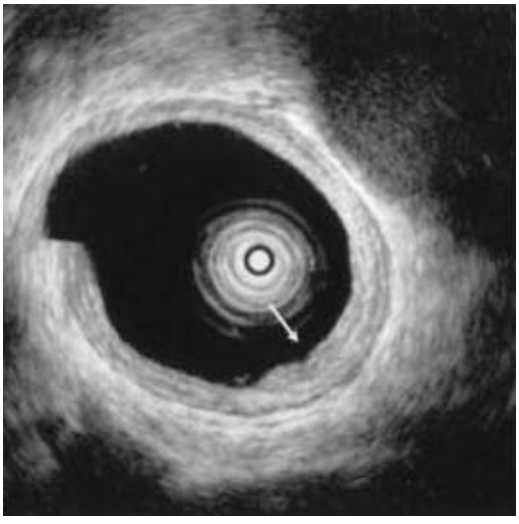

Fig. 7d

Fig. 7. Endoscopic images of superficial Barrett's esophageal adenocarcinoma (patient 8).
7a. Image obtained with conventional endoscopy
7b. Image obtained with conventional magnifying endoscopy.
7c. Image obtained with magnifying endoscopy and NBI
7d. Image obtained with endoscopic ultrasonography (with a thin 20-MHz probe)

changes, such as dysplasia and cancers[11-14]. Our finding of SCE in the background mucosa of 8 patients with superficial Barrett's esophageal carcinoma also supports this belief. Under these circumstances, the presence of intestinal metaplasia is considered essential for the definitive diagnosis of Barrett's mucosa in Western countries. However, the diagnosis of intestinal metaplasia is dependent on random biopsies, because Barrett's mucosa is difficult to differentiate from CLE on endoscopy. In addition, no endoscopic method can reliably diagnose dysplasia or superficial adenocarcinoma. For these reasons, conventional

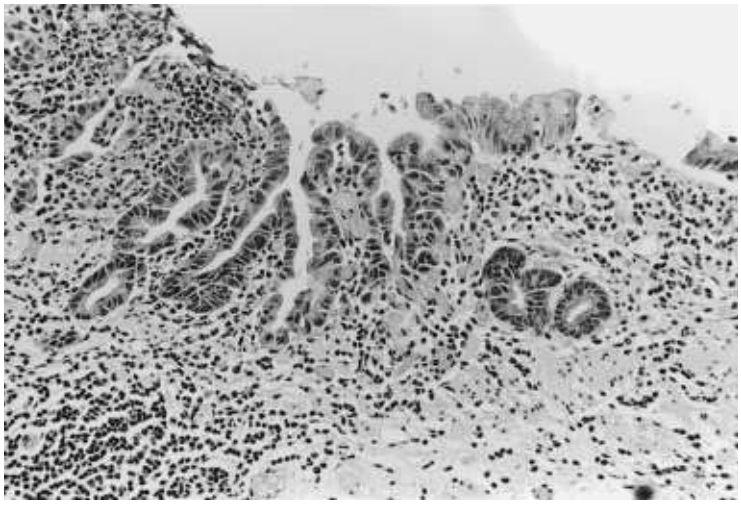

Fig. 8a

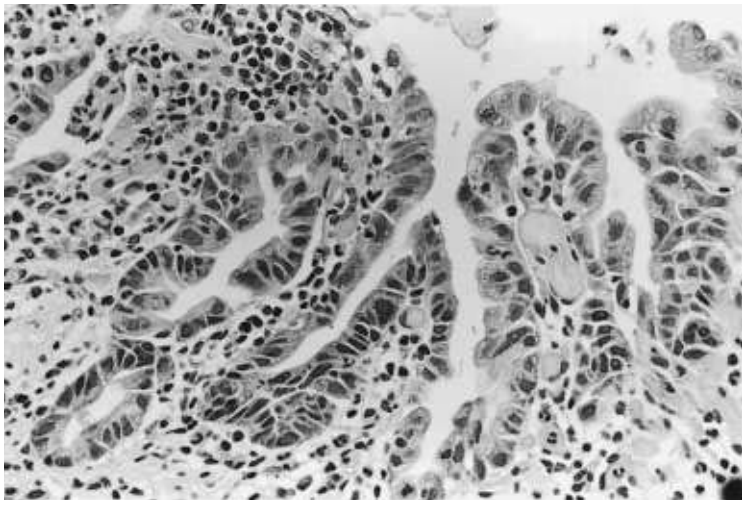

Fig. 8b

Fig. 8a, 8b. Histologic findings of the resected specimen.

endoscopy with random biopsy and dye spraying endoscopy are performed for diagnosis[15,16].

In the present study, a spiral image of blood vessels of the superficial mucosal layer (spiral pattern), characteristic of SCE, was found with magnifying endoscopy and NBI. This pattern resembled that observed in mucosa with gastric intestinal metaplasia and was extensively observed in patients with CLE extending over 30 mm or more around the entire circumference. In other patients, this pattern was observed over a relatively wide area, to the oral aspect in some and in a mosaic pattern in others. Other typical patterns were rarely or never observed in other patients. In patients with a mosaic pattern, obtaining biopsy specimens only from relevant sites is difficult. We believe this difficulty contributed to the slight difference in the numbers of patients in whom the spiral pattern was observed and of patients in whom SCE was confirmed with biopsy.

The reported incidence of SSBE in Western countries is 6% to 12%[17–20], whereas that in Japan is 5.8% to 32.9%[21–23]. We attribute this wide variation in reported incidence to differences in diagnostic criteria and differences diagnostic ability between surgeons. However, the reported incidence of SSBE in Japan is based on Japanese diagnostic criteria, which do not

consider the presence or absence of intestinal metaplasia. Therefore, some cases diagnosed as SSBE in Japan may have included CLE. Accordingly, carefully monitoring the clinical course in patients with a diagnosis of SSBE by assigning all to a group with a high risk of carcinogenesis is impractical and may cause considerable stress for patients. Magnifying endoscopy with NBI may enable the selection of high-risk patients with SCE in Barrett's mucosa, particularly those with a short length of CLE, and may increase the efficiency of endoscopy.

Methylene blue staining is considered useful for diagnosing SCE and dysplasia in Barrett's mucosa[24]. In many cases, however, obtaining clear images of absorption may be impossible, unless the mucus is adequately removed. In some cases, the surgeon's judgement may be equivocal. Accordingly, magnifying endoscopy with NBI is superior to methylene blue staining because of its simplicity. However, further studies should be done to determine any advantages, such as comparing the detection reliability of two procedures in the same patient or applying another stain (e.g., crystal violet) instead of methylene blue.

Endo et al.[25] have classified the pit patterns on magnifying endoscopy of Barrett's mucosa into 5 types (pit 1 : small round ; pit 2 : straight ; pit 3 : long oval ; pit 4 : tubular ; and pit 5 : villous). They have found that the prevalence of SCE is low in cases with patterns pit 1 and pit 2 but is high in cases with patterns pit 4 and pit 5. Endo et al. have shown that magnifying endoscopy is useful for identifying SCE.

In the present study, we detected the spiral pattern characteristic of SCE by means of magnifying endoscopy with NBI, by focusing on the capillaries of the superficial mucosal layer and the pit pattern. To our knowledge, our study is the first to report the finding of the spiral pattern on magnifying endoscopy. We also detected early superficial adenocarcinoma in several patients by monitoring the clinical course through magnifying endoscopy with NBI. In one such patient, treatment was successfully performed with EMR. In this patient, an unusual pattern of blood vessels was observed which was not observed at any other site with Barrett's mucosa. At present, the diagnosis of some cases of dysplasia and superficial carcinoma, including the case in this patient, is being investigated. We expect new diagnostic protocols to be established in the near future.

We have shown that magnifying endoscopy with NBI for the detection of Barrett's mucosa enables identification of SCE, which has been implicated as a major site of carcinogenesis. We believe the present method using magnifying endoscopy and NBI will be extremely useful for the diagnosis and treatment of Barrett's mucosa.

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