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Autofluorescence videoendoscopy system using the SAFE-3000 for assessing superficial gastric neoplasia

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Abstract

Background: Autofluorescence (AF) videoendoscopy has an advantage over ordinary videoendoscopy in the diagnosis of gastric neoplasias, and the aim of the present study was to evaluate the effectiveness of using the SAFE-3000 videoendoscopy system to diagnose superficial gastric neoplasias.

Methods: Ordinary videoendoscopy, AF videoendoscopy, and chromoendoscopy (CE) were used to diagnose the tumor existence and extent in 14 patients with gastric adenoma, 40 patients with intestinal-type early gastric cancer (EGC) (10 protruded, and 30 depressed), and nine patients with diffuse-type EGC. The diagnostic accuracies of the three kinds of images were evaluated by comparison with the results of histopathological assessment of resected specimens.

Results: For gastric adenomas the diagnostic accuracy between the AF images and white light (WL) images did not differ significantly, and for protruded intestinal-type EGCs and diffuse-type EGCs the diagnostic accuracy did not differ significantly between any of the types of images. For depressed intestinal-type EGCs, the diagnostic accuracy of AF images tended to be higher than that of the WL images ($P < 0.05$) and it was not significantly different from that of the CE images. The detection rate of pink or orange color in AF images was significantly higher for protruded intestinal-type EGCs than gastric adenomas ($P = 0.005$), depressed intestinal-type EGCs ($P < 0.001$), and diffuse-type EGCs ($P = 0.027$).

Conclusions: Autofluorescence videoendoscopy using the SAFE-3000 system for gastric neoplasias might be useful for diagnosing depressed intestinal-type early gastric cancers. The detection of orange or pink color in AF images may be efficacious in discriminating protruded intestinal-type early gastric cancers from gastric adenomas.

Introduction

Early stage gastric cancers (EGCs) are sometimes hard to diagnose during routine esophagogastroduodenoscopy (EGD), and more sensitive endoscopic methods need to be used for the targeted biopsy required for accurate histological diagnosis. Recently developed autofluorescence (AF) endoscopy systems for inspecting the gastrointestinal (GI) tract *in vivo* use exogenous fluorophores such as 5-aminolevulinic acid[1] and endogenous fluorophores such as collagen, nicotinamide, adenine dinucleotide, flavin, and porphyrins.[2-10] When tissues are illuminated with blue excitation light, green AF light is emitted by endogenous fluorophores in the submucosa. The thick mucosa, abnormal vessels, inflammation, fibrosis, and change of endogenous fluorophores associated with the tumor tissues decrease the intensity of this green fluorescence, making the tumors appear dark. Light-induced fluorescence endoscopy (LIFE) for the GI tract has been reported since 2001[3-5] but has failed to provide sufficient image quality and maneuverability because it uses a fiberoptic endoscope and a heavy image-intensifying camera.

The autofluorescence imaging system (AFI, Olympus Medical Systems Corp., Tokyo, Japan) is a videoendoscopy system using a combination of AF and reflectance imaging to visualize lesions of the GI tract and has been used in studies of early neoplasias in the esophagus,[6-8] stomach,[8,9] and colon.[10] The SAFE-3000 system (HOYA Corporation, Tokyo, Japan), on the other hand, is the first AF videobronchoscopy system for detecting bronchial lesions,[11-13] and AF videobronchoscopy has been reported to detect central-type early stage lung cancer better than conventional videoendoscopy does.

The aim of the present study was to evaluate for superficial gastric neoplasias, the diagnostic accuracy of AF images obtained using the SAFE-3000.

Methods

Instruments of the SAFE-3000

The SAFE-3000 is a videoendoscopy-based AF system containing a full color charge-coupled device (CCD). Two light sources are available in the SAFE-3000: a xenon lamp for white light (WL) images and a 408 nm (i.e. blue) diode laser providing excitation light for AF images. Infrared light is eliminated by an infrared-cut filter and WL is collected by the lens and transmitted to the objects through the light guide of the videoendoscope. In the AF mode the excitation light is reflected by a beam splitter and is collected and transmitted by the light guide. The excitation light is shone on the target from the tip of the scope. The objective lens eliminates the wavelength of excitation light and captures only AF (430–700 nm) from the object. The SAFE-3000 permits easy and quick switching between WL images and AF images by means of a control button on the endoscope. Because it can alternate WL and excitation light at high speed and can capture and record both images separately through one full-color CCD, it also allows for dual ('twin mode') real-time imaging in which both WL and AF images of the target are displayed simultaneously, facilitating their comparison.

Patients

From May 2005 to December 2007, 49 patients with EGC and 14 patients with gastric adenoma were enrolled in this study (47 men, 16 women; mean age 68.0 ± 9.5 years) (Table 1). Forty had intestinal-type EGC, and nine had diffuse type EGC. Ten of the 40 intestinal-type EGC lesions were protruded (type 0-IIa or 0-I) and were pathologically well-differentiated adenocarcinomas. The other 30 were depressed (type 0-IIc), 28 being well-differentiated adenocarcinomas and two being moderately-differentiated adenocarcinomas. Of the nine diffuse-type EGC lesions, eight were depressed and one was depressed and protruded. Seven were poorly-differentiated adenocarcinomas and two were signet-ring cell carcinomas. All patients were known from previous biopsy specimens to have EGC or gastric adenoma and were referred to our endoscopy unit for assessment of the extent and the depth of their lesions and for treatment. Patients were premedicated by intravenous injection of 0.4 mg of flunitrazepam and/or 35 mg of pethidine hydrochloride as well as either 20 mg of scopolamine butylbromide or 1 mg of glucagon. After ordinary videoendoscopy (WL mode) was carried out by an endoscopist who could easily switch from WL to AF mode or twin mode by using a handswitch, chromoendoscopy (CE) was carried out with 0.2% indigo carmine. All procedures were recorded on videotape.

Criteria for diagnosing superficial gastric neoplasia in WL, AF, and CE images

White light images and CE images were deemed to show a lesion if a neoplasia was recognized by its color and appearance. AF images were deemed to show a lesion if they contained a region with a defined circumferential margin whose color differed from that of the surrounding mucosa. The videotaped endoscopic images of the lesions were assessed by three blinded endoscopists who were required to agree as to which modality was correct in the diagnosis of superficial gastric neoplasias. The diagnostic accuracy of each image of a tumor was evaluated by histopathological assessment of biopsy specimens and resected specimens obtained by endoscopic submucosal dissection (ESD) or gastrectomy.

The study protocol was conducted in accordance with the tenets of the revised Declaration of Helsinki (1989), which was approved by the institutional review board at our institution, and informed consent was obtained from all patients.

Histopathology

Biopsy specimens were fixed in 10% formalin, and resected specimens immersed in formalin were pinned flat onto a corkboard with adequate tension. Both kinds of specimens were embedded in paraffin, serially sectioned, stained with hematoxylin and eosin, and evaluated by an experienced gastrointestinal pathologist who had no knowledge of the endoscopic findings. Lesions diagnosed as low-grade neoplasms of category 3 according to the revised Vienna classification[14] were classified as gastric adenomas, and lesions diagnosed as category 4 were classified as gastric carcinomas.

Statistical analysis

The statistical significance of differences was examined using Fisher's exact test and Bonferroni correction, and a difference was considered significant when $P < 0.01$. Quantitative data are summarized as mean ± standard deviation (SD).

Results

Tumor characteristics are listed in Table 1. Fourteen patients with gastric adenoma and 40 patients with intestinal-type EGC underwent ESD, and nine patients with diffuse-type EGC underwent gastrectomy.

For all lesions the diagnoses in WL images, AF images, and CE images were consistent between three endoscopists.

Table 1 Clinical features of the gastric adenomas and early gastric cancers

Histology	*n*	Size (mm) (mean ± SD)	Tumor depth (M/SM)
Gastric adenoma	14	5–20 (10.6 ± 3.9)	14/0
Protruded intestinal-type EGC	10	5–30 (15.9 ± 9.0)	10/0
Depressed intestinal-type EGC	30	5–25 (10.6 ± 5.2)	27/3
Diffuse-type EGC	9	8–50 (27.0 ± 14.0)	6/3

EGC, early gastric cancer; M, mucosal; SD, standard deviation; SM, submucosal.

Eight of 14 gastric adenomas (57%: 95% confidence interval [CI] 28–87%) were correctly diagnosed in AF images (Table 2), and the spreading area of the tumor lesion in all of them was diagnosed in the AF images. The diagnostic accuracy did not differ significantly between the AF images and WL images, but the diagnostic accuracy of the AF images was significantly lower than that of the CE images. Seven of the eight correctly diagnosed adenomas appeared well-contrasted dark in the AF images (Fig. 1) and one appeared orange.

Nine of the 10 protruded intestinal-type EGC lesions (90%: 95% CI 67–100%) were diagnosed in the AF images, and the spreading area of all nine was diagnosed in the AF images. Three of the nine appeared well-contrasted dark and six appeared orange or pink (Figs 2,3). The mean size of the three dark ones was 21.7 ± 14.4 mm, and that of the six orange or pink ones was 12.3 ± 5.0 mm. The size difference between these two groups was not significant ($P = 0.17$). With the protruded intestinal-type EGC lesions there were no significant differences between the diagnostic accuracies of the WL images, AF images and CE images. With the 30 depressed intestinal-type EGC lesions, on the other hand, 29 (97%: 95% CI 90–100%) were diagnosed in AF images and the spreading area of all 29 was diagnosed in AF images, but only 23

Table 2 Comparison of diagnostic accuracy in white-light images, autofluorescence images and chromoendoscopic images of gastric adenomas and early gastric cancers

Histology	WL	AF	CE
Gastric adenoma ($n = 14$)	10 (71%: 95% CI 42–92%)	8 (57%: 95% CI 28%–87%)	14 (100%: 95% CI 100%)*
Protruded intestinal-type EGC ($n = 10$)	8 (80%: 95% CI 50–100%)	9 (90%: 95% CI 67%–100%)	10 (100%: 95% CI 100%)
Depressed intestinal-type EGC ($n = 30$)	23 (77%: 95% CI 61–93%)	29 (97%: 95% CI 90%–100%)†	30 (100%: 95% CI 100%)‡
Diffuse-type EGC ($n = 9$)	8 (89%: 95% CI 63–100%)	8 (89%: 95% CI 63%–100%)	9 (100%: 95% CI 100%)

*$P < 0.01$ versus AF, †$P < 0.05$ versus WL, ‡$P < 0.01$ versus WL.

AF, autofluorescence; CE, chromoendoscopy; CI, confidence intervals; EGC, early gastric cancer; WL, white light.

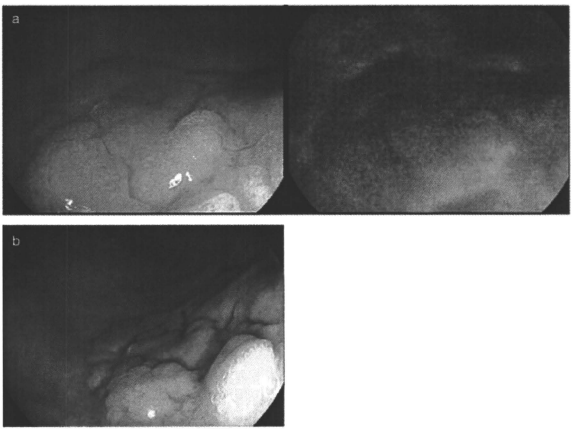

Figure 1 (a) White-light (WL) (left side) and autofluorescence (AF) (right side) images of a gastric adenoma lesion observed simultaneously in the twin mode. The lesion appeared dark in the AF image. (b) Chromoendoscopic (CE) image showing the lesion.

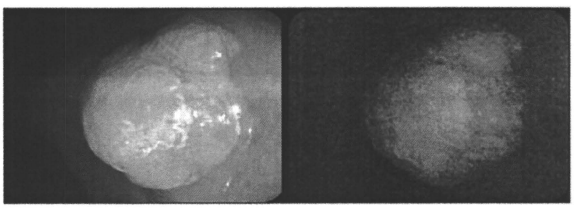

Figure 2 White-light (WL) (left) and autofluorescence (AF) (right) images of the protruded intestinal-type early gastric cancer lesion. The lesion appeared bright and orange in the AF image.

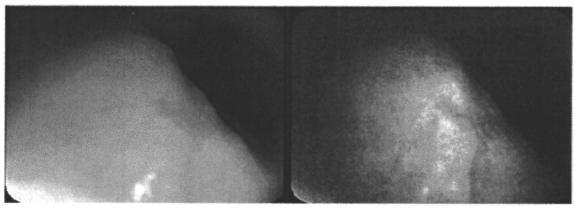

Figure 3 White-light (WL) (left) and autofluorescence (AF) (right) images of the protruded intestinal-type early gastric cancer lesions. The lesion appeared pink in the AF image.

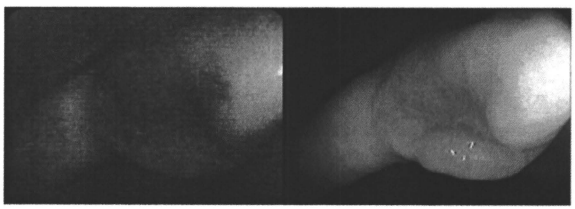

Figure 4 White-light (WL) (right) and autofluorescence (AF) (left) images of a depressed intestinal-type early gastric cancer lesion. The lesion appeared dark green in the AF image.

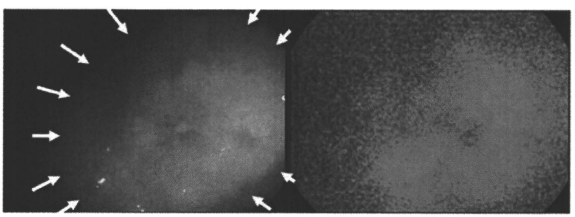

Figure 5 White-light (WL) (left) and autofluorescence (AF) (right) of the diffuse-type early gastric cancer lesion. Only some parts of the lesion appeared dark green in the AF image.

(77%: 95% CI 61–93%) were diagnosed in WL images. Diagnostic accuracy of the AF images tended to be higher than that of the WL images ($P < 0.05$), and it was not significantly different from that of the CE images. Twenty-seven of the 29 depressed intestinal-type EGC lesions diagnosed in AF images appeared well-contrasted dark (Fig. 4) and two appeared orange or pink. Eight of the nine diffuse-type EGC lesions (89%: 95% CI 63–100%) were diagnosed correctly in the AF images. There were no significant differences between the diagnostic accuracies of WL images, AF images, and CE images of the diffuse-type EGC lesions, but only part of the tumor lesion area could be detected in the AF images of four of eight diffuse-type EGC lesions (Fig. 5). Seven of the eight lesions appeared well-contrasted dark, and the other appeared orange.

The detection rate of pink or orange color in the AF images of protruded intestinal-type EGCs was significantly higher than that in the AF images of gastric adenomas ($P = 0.005$), depressed intestinal-type EGCs ($P < 0.001$), and diffuse-type EGCs ($P = 0.027$) (Table 3).

Table 3 Comparison of the number of gastric adenomas and early gastric cancers in which orange or pink color was detected in autofluorescence images

Histology	*n*	*P*-value (compared with protruded intestinal-type EGC)
Gastric adenoma ($n = 14$)	1	$P = 0.005$
Protruded intestinal-type EGC ($n = 10$)	6	
Depressed intestinal-type EGC ($n = 30$)	2	$P < 0.001$
Diffuse-type EGC ($n = 9$)	1	$P = 0.027$

EGC, early gastric cancer.

Discussion

Several groups of investigators have reported clinical studies in which AF videoendoscopy was used for diagnosis of superficial

gastric neoplasia,[8,9] but that technique is less sensitive than chromoendoscopy and has low specificity for gastric neoplasias. This study is the first report of AF images of gastric neoplasias acquired using the SAFE-3000 system.

In our study, protruded and depressed intestinal-type EGC lesions were diagnosed accurately in AF images equal to WL images and depressed intestinal-type EGC lesions tended to be diagnosed more accurately in AF images than in WL images. Ohkawa *et al.*[3] reported high sensitivity (100%) for AF endoscopy when using the LIFE system for gastric cancers including 17 intestinal-type EGC lesions and 14 diffuse-type EGC lesions. On the other hand, Kato *et al.*[9] reported that sensitivity of AF endoscopy using AFI for gastric neoplasias, which had indication for ESD, was 69.2% and that 18 of 26 depressed gastric neoplasias (69.2%) were detected. The SAFE-3000 system uses for excitation lights a diode laser with narrowly specified wavelength (408 nm) and observes AF images themselves, whereas the LIFE system uses for excitation light a blue metal halide light with broad wavelength range (400–450 nm) and makes pseudocolor images that combine green and red fluorescence intensities. AFI uses the split light of wavelength 390–470 nm and green light of wavelength 540–560 nm. The different detection rates seem to be due to the different systems. Uedo *et al.*[8] reported that the limitations of diagnosis of EGCs were due to ulcerations or inflammation that caused overdiagnosis in the AF observation. In our study, four of the 30 depressed intestinal-type EGC lesions had ulcerations, but all four of them could be detected. The different detection rates seem to indicate that none of them had any severe ulcerations or inflammation.

The diagnostic accuracy of AF images of gastric adenomas was not high because it seems that gastric adenomas have fewer abnormal vessels and different endogenous fluorophores than intestinal-type EGCs have. Ohkawa *et al.*[3] however, reported a high sensitivity (87.5%) of AF endoscopy when using the LIFE system for gastric adenomas. Because Kato *et al.*[9] did not separate the sample into superficial gastric cancers and gastric adenomas, the sensitivity for only gastric adenomas had therefore not been made apparent.

Furthermore, Ohkawa *et al.*[3] reported high sensitivity (100%) of AF endoscopy using the LIFE system for not only intestinal-type EGC lesions but also diffuse-type EGC lesions. Although in our study all but one of the eight diffuse-type EGCs were detected in AF images, only parts of the lesions could be seen in the AF images of four of them. Abe *et al.*[5] reported different detection rates due to different histopathologic findings, such as 82% for differentiated cancer and 61% for undifferentiated cancer, indicating that the diffuse-type EGCs were diffusely spread and had not caused any structural changes in the mucosa or submucosa. The diffuse-type EGCs are also thought to have thinner lateral margins and fewer vessels than the intestinal-type EGCs.

As the SAFE-3000 system contains a full color CCD and provides AF images not combined with reflectance images, it can detect orange or pink colors in AF images. Orange or pink color was found more frequently in AF images of protruded intestinal-type EGC lesions than in AF images of gastric adenomas or either depressed intestinal-type or diffuse-type EGC lesions. This might mean that more than half of protruded intestinal-type EGC lesions have distinctive endogenous fluorophores such as protoporphyrin, because under 408 nm excitation, the main emission peak of protoporphyrin is at 630 nm. It has been reported that, as a result of downregulation of ferrochelatase mRNA expression, protoporphyrin IX (PpIX) generally accumulates more in cancerous colon cells than in normal colon cells,[15] but in the present study of gastric neoplasias we did not measure the concentration of PpIX. Moreover, the presence of orange or pink colors in the AF images of protruded intestinal-type EGC lesions was not correlated with tumor size or pathological findings.

As the SAFE-3000 has a twin mode that can display WL images and AF images simultaneously, it facilitates the comparison of WL images and AF images. AF videoendoscopy using the SAFE-3000 system, however, yields lower-resolution and darker images than ordinary videoendoscopy does, because the intensity of the AF itself is weak and the signal-to-noise ratios in the AF imaging system are low. It is therefore necessary to bring the videoendoscope close to lesions to observe them in AF images. More improvement of this system is needed. As some benign erosions and redness also appeared dark, specificity for gastric neoplasias were not evaluated in the present study.

In conclusion, this study is the first report that autofluorescence videoendoscopy using the SAFE-3000 system for gastric neoplasias might be useful for diagnosing intestinal-type early gastric cancers. The detection of orange or pink color in AF images may be efficacious in discriminating protruded intestinal-type early gastric cancers from gastric adenomas.

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Competing interests: None.

Disclosure

The SAFE 3000 system was provided by Hoya Co, Ltd.

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Serum lipid levels are positively associated with non-erosive reflux disease, but not with functional heartburn

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Abstract

Background *Metabolic syndrome and obesity are known risk factors for gastro-esophageal reflux disease (GERD), especially for erosive esophagitis. Although non-erosive reflux disease (NERD) is probably associated with obesity or other metabolic syndrome, there is little direct evidence to support this assertion.* ***Methods*** *Workers in Keio University who underwent a general health examination between September 2006 and August 2007 were enrolled. Reflux symptom questionnaires were administered and metabolic parameters were obtained. The severity of gastro-esophageal reflux (GER) was scored using a validated scale of videoesophagography.* ***Key Results*** *Two hundred and eighty-three subjects (243 men and 40 women; mean age 49.8 ± 6.9 years) with no radiographic evidence of erosive esophagitis were enrolled. The severity of GER was worse among men than among women, whereas the severity of reflux symptoms was worse among women. The severity of GER was associated with age and serum triglyceride levels in men, and with the serum low-density lipoprotein cholesterol levels in women. The severity of reflux symptoms, however, was not associated with metabolic parameters. There were more women than men with reflux symptoms but without GER ('presumed' functional heartburn group), compared with subjects with neither GER nor reflux symptoms. In men, the presence of both reflux symptoms and GER ('presumed' NERD group) was associated with the serum triglyceride levels.* ***Conclusions & Inferences*** *While NERD is associated with serum lipid levels, functional heartburn is not. The prevalence of GER was greater among men; conversely, the prevalence of functional heartburn was greater among women.*

Keywords *dyslipidemia, functional heartburn, metabolic syndrome, NERD.*

INTRODUCTION

Metabolic syndrome is a cluster of metabolic abnormalities defined as the presence of three or more of the following factors: abdominal obesity (increased waist circumference), elevated triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), high blood pressure, and high fasting plasma glucose.[1,2] Metabolic syndrome helps to identify individuals at high risk for cardiovascular diseases, diabetes mellitus, and other chronic diseases.

Gastro-esophageal reflux disease (GERD) develops when reflux of gastric contents into the esophagus leads to troublesome symptoms, with or without mucosal damage, and/or complications.[3] Gastro-esophageal reflux disease is common with an estimated prevalence of 10–40% in Western countries and is increasing dramatically in Asian countries, including Japan.[4–7] Gastro-esophageal reflux disease adversely affects health-related quality of life;[8] however, the majority of patients (~60%) with typical reflux symptoms have no evidence of erosive esophagitis.[9] Such patients are usually considered to have non-erosive reflux disease (NERD) if there is evidence that their symptoms are due to acid reflux, for example a positive correlation between the symptoms and abnormal acid

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exposure on 24- or 48-h ambulatory esophageal pH measurement, or a symptomatic response to therapeutic acid suppression.[10] According to the Rome III criteria, the spectrum of NERD should not include patients with 'functional heartburn (FH)' (normal endoscopy, and no correlation of symptoms with acid exposure).[11] Studies using both endoscopy and ambulatory pH monitoring to objectively establish evidence of GERD indicate that FH represents more than 10% of patients with heartburn.[12]

It has been generally accepted that obesity is associated with erosive esophagitis and GERD symptoms.[13–18] Some studies demonstrated that the metabolic syndrome is also associated with erosive esophagitits.[5,19,20] Although NERD may be associated with obesity and the metabolic syndrome, there is little direct evidence to support this assertion.[21,22] Moreover, if the definition of NERD is further refined to exclude FH, there have been no epidemiological studies evaluating this association.[22]

To distinguish FH from NERD, pH or impedance monitoring are usually used. However, these techniques are difficult to be performed in general health examination especially for the non-symptomatic population. In Japan, it is common for an upper gastrointestinal barium meal study (upper GI series) to be performed as a part of the annual health examination. Barium esophagography can simultaneously evaluate esophageal motility, gastro-esophageal reflux (GER), and morphologic abnormalities in the esophagus.[23] Double-contrast esophagography has a sensitivity approaching 90% for the diagnosis of erosive esophagitis.[24,25] In addition, the authors have reported that the predominant mechanism of reflux, such as increased frequency of transient lower esophageal sphincter relaxation, hiatus hernia, impaired esophageal clearance, and reduced lower esophageal sphincter pressure, can be examined and scored using videoesophagography.[26]

In this study, we used reflux symptom questionnaires, the findings of videoesophagography, and various metabolic parameters among persons undergoing annual health examinations to examine the epidemiology of NERD and FH in Japan, and to determine whether there was a significant association between these entities and the metabolic syndrome.

MATERIALS AND METHODS

Study subjects

The protocol of this cross-sectional study was approved by the Ethics Committee of Keio University School of Medicine (No.18-30(2)), and registered with the UMIN Clinical Trials Registry (UMIN 000000616). Forty- to 65-year-old workers at Keio University who underwent a general health examination between September 2006 and August 2007 and provided informed consent were enrolled in this study. Subjects completed the two kinds of reflux symptom assessment systems; the Japanese version of the Carlsson-Dent self-administered questionnaire (QUEST)[27] and the frequency scale for the symptoms of gastro-esophageal reflux disease (FSSG).[28] The grade of GER was assessed using videoesophagography.

Findings of videoesophagography were scored using the radiological severity score for gastro-esophageal reflux (XRSS) (Fig. S1). Firstly, a subject swallowed 40 mL barium sulfate in the spinal right anterior oblique (RAO) position. Gastro-esophageal barium reflux was scored from 0 to 2 (0, none; 1, to middle esophagus; 2, to upper esophagus). The size of hiatus hernia was measured as the maximum distance between the gastro-esophageal junction and the esophageal hiatus and scored from 0 to 2 (0, none; 1, 0–2 cm; 2, ≥2 cm). Subsequently, a patient swallowed a gas-producing agent and 150 mL more barium while standing. The frequency of belching was scored from 0 to 2 (0, none; 1, occasionally; 2, often). The size of hiatus hernia was also scored. Finally, a patient was repositioned in the spinal RAO, and gastro-esophageal barium reflux was scored again. The XRSS, ranging from 0 to 10, was calculated by adding the individual scores. Detailed methods of videoesophagography and scoring XRSS has already been reported.[26] The XRSS is useful to evaluate the severity of mechanical GER conveniently as compared with 24-h pH monitoring.

Subjects' height, weight, and waist were measured and their body mass index (BMI) (weight/height^2) was calculated. Measurement of waist circumference was made at the level of the navel during minimal respiration. History of the alcohol consumption, smoking status, previous diseases, and medication were obtained during a study interview. Blood samples were obtained for biochemical analyses including fasting plasma glucose, triglyceride (TG), HDL-C, low-density lipoprotein cholesterol (LDL-C), and high moleculer weight adiponectin.

Patients who were diagnosed to have esophagogastroduodenal disease, such as erosive esophagitis or peptic ulcer, by upper GI series were excluded, as were patients with a history of drug use. Subjects whose serum TG levels were over 600 mg dL^{-1} were excluded as outliers for analysis.

Definition of NERD, FH, and silent reflux group

A minimum value indicating the presence of GER symptoms for the QUEST score was set at six points, and for the FSSG total score was set at eight points, according to the previous reports.[27,29] Based on videoesophagography, the presence of GER was defined as subjects with XRSS of more than one point.

Using these definitions, subjects were divided into four groups as follows: control, the 'presumed' NERD, the 'presumed' FH, and the 'presumed' silent reflux group. Subjects with both reflux symptoms and GER were defined as the 'presumed' NERD group. Subjects with reflux symptoms but without GER were defined as the 'presumed' FH group. Subjects with GER but without reflux symptoms were defined as the 'presumed' silent reflux group. Subjects with neither reflux symptoms nor GER were defined as the control group.

Statistical analysis

Analyses were conducted for each gender separately. The data were expressed as mean ± SD. The difference between genders was evaluated using unpaired Student's *t*-test. The correlations among QUEST, FSSG, and XRSS were evaluated using Pearson's

correlation. The associations of QUEST, FSSG, and XRSS with the other measured values were evaluated using linear regression analysis. The associations of the presence of the 'presumed' NERD, FH, and silent reflux with the other measured values were evaluated using logistic regression analysis. All statistical analyses were conducted using the SPSS Statistics version 17.0 for Windows software (SPSS Japan, Tokyo, Japan). A two-sided P value of <0.05 was considered statistically significant.

RESULTS

Although reflux was worse in men, reflux symptoms were worse in women

Among 2562 workers at Keio University, 283 (243 men and 40 women; mean age 49.8 ± 6.9 years) were analyzed. Study population in this study was shown in Fig. 1. Among 283 subjects, six subjects were obese (BMI of more than 30 kg m^{-2}), and 64 subjects were overweight (BMI between 25 and 30 kg m^{-2}).

Average FSSG scores were significantly higher in women than in men, whereas average XRSS were significantly higher in men than in women (Table 1). Average QUEST scores trended higher in women than in men, but this was not statistically significant. Levels of metabolic parameters and alcohol consumption were significantly different between genders (Table 1). Alcohol consumption was greater in men than in women. BMI, waist circumference, serum TG, and serum LDL-C levels were higher in men than in

Table 1 Subject characteristics

	Men (n = 243)	Women (n = 40)	P value
QUEST	2.55 ± 3.46	3.18 ± 3.79	0.30
FSSG	5.81 ± 4.68	**7.50 ± 4.75**	0.01
XRSS	**1.65 ± 2.10**	0.90 ± 1.66	0.01
Age (year)	50.1 ± 7.0	48.3 ± 6.2	0.14
Smoking Status			
Presence	23 (9.5%)	3 (7.5%)	0.69
Absence	220 (90.5%)	37 (92.5%)	
Alcohol consumption status			
Presence	**61 (25.1%)**	3 (7.5%)	0.001
Absence	182 (74.9%)	37 (92.5%)	
BMI (kg m^{-2})	**23.7 ± 2.9**	22.1 ± 2.9	0.001
Waist circumference (cm)	**82.6 ± 7.4**	76.6 ± 7.9	<0.001
Fasting plasma glucose (mg dL^{-1})	94.1 ± 19.7	90.2 ± 13.6	0.23
TG (mg dL^{-1})	**114.7 ± 68.4**	76.4 ± 41.6	<0.001
HDL-C (mg dL^{-1})	60.1 ± 14.3	**68.8 ± 15.5**	<0.001
LDL-C (mg dL^{-1})	**127.5 ± 28.6**	115.5 ± 28.6	0.02
Adiponectin (μg mL^{-1})	3.24 ± 2.00	**7.88 ± 6.02**	<0.002

BMI, body mass index; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Bold values – difference between genders at $P < 0.05$ significance using unpaired Student's t-test.

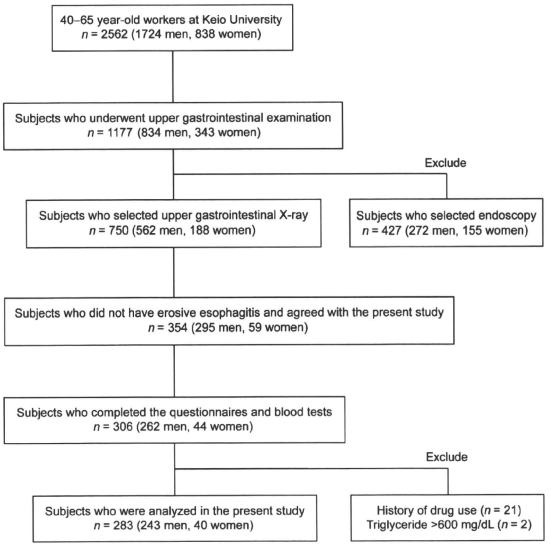

Figure 1 Diagram of inclusion of the study population.

Table 2 The correlations among QUEST, FSSG score and XRSS

	Men (n = 243)		Women (n = 40)	
	r*	P value	r	P value
QUEST *vs* FSSG	**0.518**	<0.001	**0.393**	0.01
QUEST *vs* XRSS	0.034	0.60	0.056	0.73
FSSG *vs* XRSS	−0.004	0.95	0.045	0.78

*Pearson product-moment correlation coefficient; Bold values – correlation at $P < 0.05$ significance.

women. Serum HDL-C and adiponectin levels were higher in women.

The FSSG score significantly correlated with the QUEST score in both genders (Table 2). However, GER defined by XRSS did not correlate with either QUEST or FSSG scores. This suggests that in the case of subjects without morphologic abnormalities of the esophagus, the severity of reflux symptoms did not correlate with the severity of GER.

Although reflux was associated with serum lipid levels, reflux symptoms were not

The results of a linear regression model revealed that age and serum TG levels were positively associated with XRSS in men (Table 3). Multivariable linear regression with adjustment for age and TG confirmed that both age and serum TG level were independently associated with XRSS in men. In women, serum LDL-C levels were positively associated with XRSS using univariate linear regression model, as was age ($P < 0.1$). Multivariable linear regression with adjustment for age and LDL-C revealed that serum LDL-C level was associated with XRSS in women ($P < 0.1$). On the other hand, the severity of reflux symptoms was associated with neither age nor serum lipid levels.

Prevalence of FH was greater in women than in men

Two hundred and eighty-three subjects could be divided into 108 control, 35 'presumed' NERD, 75 'presumed' FH, and 65 'presumed' silent reflux subjects. There was two and a half times greater proportion of women in the 'presumed' FH group than the control group (men : women; FH 1 : 0.32, Cont. 1 : 0.13; $P < 0.05$) (Table 4). Conversely, there was no difference in the gender ratio among the 'presumed' NERD group or the 'presumed' silent reflux group. The results of the logistic regression model revealed that the serum TG level was positively associated with the prevalence of NERD, and the fasting plasma glucose was negatively associated with the prevalence of FH in

Table 3 Association of clinical factors with the symptom assessment systems (QUEST and FSSG score) or the severity of the gastro-esophageal reflux (XRSS)

	Men (n = 243)								Women (n = 40)							
					XRSS								XRSS			
	QUEST		FSSG		Univariate		Multivariate†		QUEST		FSSG		Univariate		Multivariate‡	
	β*	P value	β	P value	β	P value	β	P value	β	P value	β	P value	β	P value	β	P value
Age (year)	−0.043	0.50	−0.074	0.25	**0.169**	0.01	**0.175**	0.006	0.112	0.49	0.053	0.75	0.266	0.096	0.205	0.19
Smoking Status	0.030	0.64	0.053	0.42	−0.012	0.85			−0.140	0.39	−0.010	0.95	−0.156	0.34		
Alcohol Consumption Status	−0.026	0.69	0.075	0.25	−0.015	0.81			−0.039	0.81	0.071	0.66	−0.156	0.34		
BMI (kg m^{-2})	−0.082	0.21	−0.059	0.36	−0.023	0.72			0.086	0.60	0.041	0.80	−0.172	0.29		
Waist circumference (cm)	−0.059	0.36	−0.018	0.78	0.039	0.55			0.150	0.36	0.177	0.27	−0.062	0.71		
Fasting plasma glucose (mg dL^{-1})	−0.053	0.42	−0.104	0.11	−0.017	0.79			−0.012	0.94	−0.216	0.18	−0.247	0.13		
TG (mg dL^{-1})	−0.034	0.60	0.027	0.68	**0.158**	0.01	**0.165**	0.009	−0.029	0.86	0.172	0.29	0.204	0.21		
HDL-C (mg dL^{-1})	0.030	0.64	0.024	0.71	−0.067	0.30			0.023	0.89	−0.005	0.98	0.109	051		
LDL-C (mg dL^{-1})	−0.015	0.82	−0.025	0.70	−0.013	0.85			0.063	0.70	0.069	0.67	**0.335**	0.03	0.292	0.07
Adiponectin (μg mL^{-1})	0.033	0.61	0.024	0.71	−0.097	0.13			−0.009	0.96	−0.145	0.37	0.160	0.32		

BMI, body mass index; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol. *Standardized partial regression coefficient. †Adjustment for age and TG. ‡Adjustment for age and LDL-C. Bold values – correlation at $P < 0.05$ significance.

Table 4 Difference in a gender ratio

		Men (n = 243)	Women (n = 40)	Men : women	P value
Control	Symptom (−) Reflux (−)	95 (39.1%)	13 (32.5%)	1 : 0.13	
NERD	Symptom (+) Reflux (+)	32 (13.2%)	3 (7.5%)	1 : 0.09	0.76
Functional heartburn	Symptom (+) Reflux (−)	57 (23.5%)	**18 (45.0%)***	1 : 0.32	0.045
Silent reflux	Symptom (−) Reflux (+)	59 (24.3%)	6 (15.0%)	1 : 0.10	0.63

NERD, non-erosive reflux disease. *Difference versus the Symptom (−) Reflux (−) group, at $P < 0.05$ significance using Fisher's exact test.

Table 5 Association of clinical factors with FH or NERD

	Control (n = 95)	NERD (n = 32)			Functional heartburn (n = 57)			Silent reflux (n = 59)		
	Mean ± SD	Mean ± SD	OR	95% CI	Mean ± SD	OR	95% CI	Mean ± SD	OR	95% CI
Age (year)	49.6 ± 7.2	51.0 ± 7.0	1.03	0.97–1.09	48.7 ± 6.3	0.98	0.94–1.03	51.6 ± 7.0	1.04	0.99–1.09
Smoking status										
Presence	10 (10.5%)	3 (9.4%)	0.88	0.23–3.42	4 (7.0%)	0.64	0.19–2.15	6 (10.2%)	0.96	0.33–2.80
Absence	85 (89.5%)	29 (90.6%)			53 (93.0%)			53 (89.8%)		
Alcohol consumption status										
Presence	26 (27.4%)	9 (28.1%)	1.04	0.43–2.54	13 (22.8%)	0.78	0.37–1.69	13 (22.0%)	0.75	0.35–1.61
Absence	69 (72.6%)	23 (71.9%)			44 (77.2%)			46 (78.0%)		
BMI (kg m^{-2})	23.9 ± 3.0	23.6 ± 3.5	1.00	0.87–1.15	23.6 ± 3.5	0.97	0.87–1.08	23.4 ± 2.5	0.94	0.84–1.06
Waist circumference (cm)	82.8 ± 7.1	83.1 ± 7.2	1.01	0.95–1.07	82.3 ± 8.5	0.99	0.95–1.04	82.5 ± 6.9	1.00	0.95–1.04
Fasting plasma glucose (mg dL^{-1})	97.5 ± 24.8	95.9 ± 26.5	1.00	0.98–1.02	**89.6 ± 8.5***	0.96	0.93–1.00	92.2 ± 11.5	0.98	0.96–1.01
TG (mg dL^{-1})	109.3 ± 60.6	**143.2 ± 104.3***	1.01	1.00–1.01	106.2 ± 56.8	1.00	0.99–1.01	116.0 ± 64.0	1.00	0.99–1.01
HDL-C (mg dL^{-1})	61.1 ± 14.8	60.0 ± 18.5	1.00	0.97–1.02	60.0 ± 13.7	0.99	0.97–1.02	58.5 ± 11.4	0.99	0.96–1.01
LDL-C (mg dL^{-1})	129.2 ± 31.1	128.7 ± 34.1	1.00	0.99–1.01	121.3 ± 23.4	0.99	0.98–1.00	130.2 ± 25.4	1.00	0.99–1.01
Adiponectin (μg mL^{-1})	3.48 ± 2.41	3.38 ± 2.23	0.98	0.82–1.17	3.13 ± 1.62	0.92	0.78–1.09	2.90 ± 1.35	0.86	0.71–1.03

BMI, body mass index; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NERD, non-erosive reflux disease. *Difference versus the Symptom (−) Reflux (−) group, at $P < 0.05$ significance using univariate logistic regression model.

men (Table 5). In women, no significant association of clinical factors with the prevalence of NERD or FH could be detected; however, this was likely due to the low number of subjects in each group.

DISCUSSION

The present study revealed that the serum TG levels were associated with the severity of GER in men, and the serum LDL-C levels were associated with the severity of GER in women. In addition, the serum TG levels were also associated with the presence of the 'presumed' NERD in men. These results suggest that the severity of dyslipidemia was associated with the severity of GER and NERD, if one excludes FH. In this study, BMI and waist circumference were not associated with the presence of NERD, although few obese subjects were enrolled.

Neither QUEST nor FSSG scores correlated with XRSS, suggesting that the severity of reflux symptoms does not reflect the severity of GER in the population without erosive esophagitis. In subjects with NERD or FH, some mechanisms other than GER, such as peripheral and/or central hypersensitivity or abnormalities of mechanoreceptor-mediated pathways,[21] would play more important role as causes of reflux symptoms.

This study of a Japanese population showed that although the severity of GER was worse among men than among women, the severity of reflux symptoms was worse among women. In addition, the prevalence of FH was greater in women than in men. Previous studies have shown a greater prevalence of erosive esophagitis and Barrett's esophagus in men than in women.[30,31] This is compatible with higher grades of XRSS in men. Other studies have described a higher prevalence of NERD in women than men.[30] Note,

however, that in these studies many patients with FH would have been included in the NERD group.

In addition, the results of this study revealed a negative association between the fasting plasma glucose levels and the presence of FH. As we currently do not have a biologic basis to explain these results, further studies remain needed. The limitations of this study include: the small numbers of women and potential selection bias for receipt of the upper GI examination (barium meal study or endoscopy).

In conclusion, the epidemiology of NERD and FH in a Japanese screening population were divergent. NERD, but not FH, is associated with serum lipid levels. Moreover, mechanical GER was more prevalent in men, whereas FH was more common in women.

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AUTHORSHIP

HS and JM designed the research study, HS, EI and HY collected subjects, YS and HS performed the radiological evaluation, JM and HS analyzed the data and wrote the manuscript, and TH supervised. All authors have read and approved the paper.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Procedure of the radiological severity score for gastro-esophageal reflux (XRSS).

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CASE REPORT

PARTIAL REGRESSION OF DUODENAL LESIONS OF INTESTINAL FOLLICULAR LYMPHOMA AFTER ANTIBIOTIC TREATMENT

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A 51-year-old man was referred to our hospital because of duodenal lesions of lymphoma. Endoscopy showed multiple tiny smooth whitish granules in the second portion of the duodenum including the papilla of Vater. Biopsy specimens showed medium-sized centrocyte-like cells forming lymphoid follicles, and immunohistology showed positive staining for bcl-2 and CD10. A small bowel series showed multiple granular lesions extending from the second portion of the duodenum to the proximal jejunum and the proximal ileum. On the basis of these findings, the tumor was diagnosed as stage I follicular lymphoma (FL). Although the patient was negative for *Helicobacter pylori*, he underwent antibiotic treatment. The lesions improved 3 months after antibiotic treatment, but biopsy specimens showed residual lymphoma cells. The patient therefore received combination chemotherapy with rituximab. Endoscopy 4 months later showed regression of FL, and there was no evidence of recurrence during 3 years of follow up. The partial regression of duodenal lesions of intestinal FL may be due to the effect of antibiotic treatment.

Key words: antibiotic treatment, duodenum, follicular lymphoma, *Helicobacter pylori*.

INTRODUCTION

The stomach is the most common primary site for non-Hodgkin's lymphomas (NHL), followed by the small intestine and, less commonly, the colorectal region. The duodenum is rarely involved in NHL. Follicular lymphoma (FL), a neoplasm of follicle center B-cells, is one of the most common subtypes of NHL. Although FL of the gastrointestinal (GI) tract represents only 1–3.6% of all GI tract lymphomas, FL arising in the duodenum has been occurring with increasing frequency.[1–5]

Gastric mucosal-associated lymphoid tissue (MALT) lymphomas are associated with *Helicobacter pylori (H. pylori)* infection, and most gastric MALT lymphomas enter remission after eradication therapy for *H. pylori* infection. Some duodenal and colorectal MALT lymphomas also enter remission after *H. pylori* eradication therapy,[6,7] but few cases of duodenal FL with *H. pylori* infection have been found to respond to eradication therapy.[2–4]

We herein present a case in which the duodenal lesions of intestinal FL without *H. pylori* infection showed partial regression after antibiotic treatment.

CASE REPORT

A 51-year-old man was referred to another clinic in August 2001 because of epigastric pain and there underwent esophagogastroduodenoscopy (EGD) revealing multiple granular lesions in the second portion of the duodenum. Biopsy specimens showed lymphocyte infiltration forming lymphoid follicles, but did not show lymphoma cells. Although EGD in February 2003 showed no remarkable change, biopsy specimens showed lymphoma cells. The patient was therefore referred to our hospital.

Physical examination revealed no abnormalities, and there was no evidence of hepatosplenomegaly, peripheral lymphadenopathy, anemia, or fever. Laboratory data included normal blood counts and standard serum biochemical tests. The results of anti-*H. pylori* immunoglobulin (Ig)G antibody and urea breath test were negative.

EGD showed multiple tiny smooth whitish granules without erosions in the second portion of the duodenum including the papilla of Vater, some of which adhered to each other with the swollen folds opposite the papilla (Fig. 1).

All biopsy specimens showed medium-sized centrocyte-like cells invading the lamina propria and the submucosal layer with lymphoid follicle formations (Fig. 2a) but none showed lymphoepithelial lesions. Immunohistology showed staining for bcl-2 and CD10 (Fig. 2b) but not for CD5. On the basis of these results, the tumor was diagnosed as grade 1 FL according to the WHO classification. Histological results for biopsy specimens obtained from the stomach and duodenum were negative for *H. pylori* and other bacteria.

A small bowel series showed multiple granular lesions present from the second portion of the duodenum to the proximal jejunum and also in the proximal ileum. Colonoscopy showed no abnormal lesions in the terminal ileum or in the colon. Because computed tomography, gallium

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scintigraphy, and bone marrow aspiration showed no abnormalities, the FL was evaluated as stage I according to Lugano's stage classifications of GI lymphomas.

Although tests for *H. pylori* infection were negative, the patient wanted antibiotic treatment and was given lansoprazole (30 mg twice daily), clarithromycin (400 mg twice daily), and amoxicillin (750 mg twice daily) for 7 days. Three months later there were fewer lesions (Fig. 3), but follow-up biopsy specimens showed residual lymphoma cells. The patient wanted to receive chemotherapy for intestinal FL and was first given two courses of combination chemotherapy with cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP), and then given four courses of rituximab plus CHOP.

EGD 4 months after this chemotherapy showed regression of FL in the duodenum (Fig. 4), and histological results showed no lymphoma cells. The small bowel series also showed regression of the lesions. There was no evidence of recurrence during 3 years of follow up.

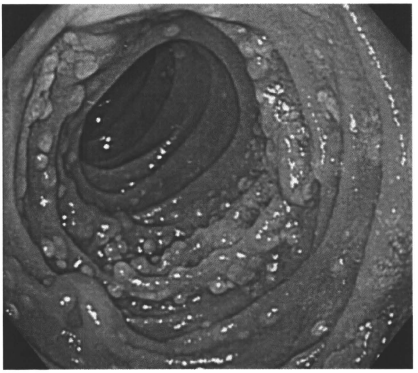

Fig. 1. Endoscopic images showing multiple whitish granular lesions in the second portion of the duodenum.

DISCUSSION

There has been increasing evidence that the incidence of FL is higher in the duodenum, especially in the second portion,

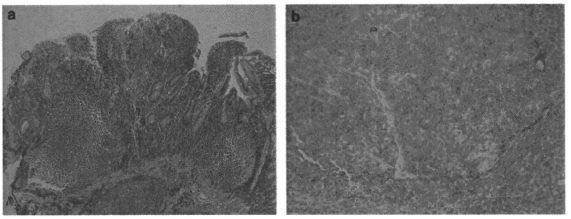

Fig. 2. Histopathological findings in biopsy specimens. (a) Lymphoma cells forming lymphoid follicles in the lamina propria and the submucosal layer (hematoxylin and eosin, ×40). (b) Lymphoma cells stained for CD10 (×400).

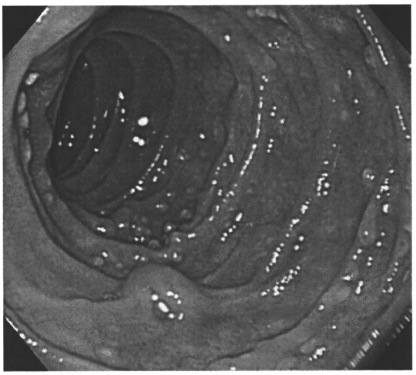

Fig. 3. Endoscopic image showing fewer lesions 3 months after eradication therapy.

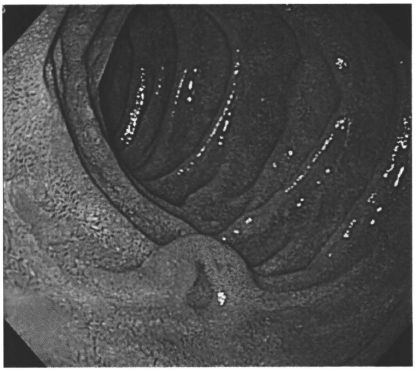

Fig. 4. Endoscopic image showing regression of follicular lymphoma in the duodenum 4 months after chemotherapy.

than in other parts of the GI tract. In an earlier study, for example, five of 13 malignant lymphomas in the duodenum were found to be FL.[1] It has recently been reported that FL in the duodenum is associated with multifocal lesions in the jejunum and/or the ileum and that the detection of these lesions is facilitated by capsule endoscopy and double-balloon endoscopy.[5]

Endoscopic findings of duodenal lesions of the intestinal FL are multiple whitish aggregated granules in the second portion, often including the papilla.[1,2,5] They are similar to those in the present case. Histology shows centrocyte-like cells forming lymphoid follicles staining for bcl-2, CD10, and CD20, but not for CD5.

Endoscopic findings of duodenal MALT lymphoma, however, are multiple erosions, ulcerations, nodular or granular mucosa, and have a polypoid appearance.[6] Histology shows centrocyte-like cells, lymphoepithelial lesions staining for bcl-2 and CD20, but not for CD10. Endoscopic findings of duodenal reactive lymphoid follicles are tiny whitish hemispheric granules mainly in the bulbus, and immunohistology shows no staining for bcl-2. The lesions in the present case were consistent with duodenal lesions of intestinal FL.

Adding an anti-CD20 monoclonal antibody (rituximab) to conventional chemotherapy, such as R-CHOP, has recently been found to improve response rates and survival times, and this combination therapy has become a standard regimen for treating patients with advanced-stage FL.[8] Patients with localized (stages I and II) FL are treated with radiation therapy and often experience prolonged survival,[9] and surgical resection, chemotherapy, and chemotherapy with radiation therapy for duodenal FL have also been reported.

In contrast, a retrospective study of 43 patients with localized FL found the outcome of deferred therapy to be similar to that of immediate treatment, and more than half of these patients remained untreated for 6 years.[9] The optimal treatment strategy for localized FL has not yet been established. It needs to be substantially considered in accordance with the localization of each intestinal FL, because FL in the duodenum sometimes has multifocal lesions in the jejunum and/or the ileum.

Most gastric MALT lymphomas enter remission after eradication therapy for *H. pylori* infection, but, some may be related to infection with other bacteria, such as *Helicobacter heilmannii*. Eradication therapy is therefore also recommended for gastric MALT lymphomas that are *H. pylori* negative.[10] There have been several reports on regression of extragastric MALT lymphomas, including those of the duodenum, colon, and rectum after eradication therapy.[6,7] Antigenic stimuli other than *H. pylori* have been suggested to play a role in the pathogenesis of rectal MALT lymphoma.[7]

Few cases of duodenal FL with *H. pylori* infection have been found to respond to eradication therapy.[2-4] Toyoda *et al.* were the first to report regression of multiple yellowish-whitish granular FL of the ampulla of Vater 12 months after eradication of *H. pylori* infection not in the duodenum but in the stomach.[2] An infectious agent other than *H. pylori* has been suggested to be associated with this lesion. Nomura *et al.* reported a patient who showed no regression of duodenal FL 22 months after eradication therapy but showed spontaneous regression 3 months later.[3] Tang *et al.* reported a case with regression of gastric MALT lymphoma and persistence of duodenal FL 6 months after eradication of *H. pylori*.[4]

The present *H. pylori*-negative case experienced persistence of the duodenal lesions for 19 months and partial regression 3 months after antibiotic treatment. As the majority of gastric MALT lymphoma enters remission 3 months after eradication therapy, the duodenal lesions of intestinal FL in the present case are thought to have responded to the antibiotic treatment. Some antigenic stimuli may play a role in the pathogenesis of the intestinal FL.

It was not clear whether antibiotic treatment introduced complete regression because the present case received additional chemotherapy after partial regression. Further study will be needed to identify the molecular mechanisms of the regression of intestinal FL.

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GASTROENTEROLOGY

Clinical results of observation of the upper gastrointestinal tract by transgastrostomic endoscopy using an ultrathin endoscope

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percutaneous endoscopic gastrostomy, transgastrostomic endoscopy, ultrathin endoscope.

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Abstract

Background and Aim: Esophagogastroduodenoscopy through the oral cavity of patients who have undergone percutaneous endoscopic gastrostomy (PEG) causes some distress and puts these patients at risk of aspiration pneumonia. The aim of this study was to evaluate results for the upper gastrointestinal tract by transgastrostomic endoscopy using an ultrathin endoscope.

Methods: The study subjects were 43 patients, who underwent exchange of a PEG button or tube, 20-French or more in diameter. After PEG buttons or tubes were extracted from the gastrostomy tract, an ultrathin endoscope was inserted through the gastrostomy tract. The stomach and the duodenal bulb were observed and the esophagus was observed in retrograde passage. A new PEG button or tube was then inserted. The rate of successful insertion into the esophagus and duodenal bulb, the observation of the gastrostomy site in retroversion in the stomach, and the endoscopic findings were analyzed.

Results: Ninety-nine examinations were carried out. The esophagus could be observed in 95 (96.0%), the duodenum in 92 (92.9%) and the gastrostomy site in the stomach in all. Gastric polyps were detected in four patients, gastric erosions in two, reflux esophagitis in two, polypoid lesion at the gastrostomy tract in two, gastric ulcer scar in one, duodenal ulcer scar in one, early gastric cancer in one and recurrent esophageal cancer in one. Neither discomfort nor complications occurred during transgastrostomic endoscopy.

Conclusions: Observation of the upper gastrointestinal tract by transgastrostomic endoscopy using an ultrathin endoscope during a gastrostomy button or tube replacement may be useful and safe.

Introduction

Enteral feeding is often used to provide nutritional support for patients who are otherwise unable to take food orally because of illness or to whom eating presents unacceptable risks (e.g. aspiration). Percutaneous endoscopic gastrostomy (PEG) is a procedure that Ponsky and Gauderer developed in order to provide direct access to the lumen of the stomach.[1] PEG has become the preferred method of providing long-term enteral nutrition and some patients are able to have a long life after PEG.[2]

Aspiration pneumonia after PEG is related to swallowing disorders, reflux esophagitis (RE) and esophageal hiatal hernia (EHH).[3,4] The presence of RE and EHH is usually evaluated at the time of endoscopy during PEG; its evaluation after PEG has not been reported. Furthermore, it has been reported that massive bleeding from gastric ulcers that were in the posterior wall of the gastric body, opposite the PEG tubes, might be related to mucosal abrasion by them.[5,6] Early detection of gastric ulcers using esophagogastroduodenoscopy (EGD) after PEG is hoped to prevent bleeding from them.

Most patients who have undergone PEG have dysphagia due to neurological diseases or malignant tumors. Therefore, EGD through the oral cavity causes distress and these procedures may have a risk of aspiration pneumonia caused by the local anesthesia of the pharynx. An ultrathin transnasal videoendoscope was recently developed for various gastrointestinal (GI) conditions.[7–9] It is more comfortable for patients than a transoral videoendoscope and has fewer deleterious hemodynamic effects.[7] PEG using the transnasal endoscope has been reported.[10,11] Moreover, it has been reported that thin endoscopes have been passed through mature gastrostomy tracts to observe the upper GI tract and treat several diseases.[12–15]

The aim of this study was to evaluate the endoscopic results obtained for the upper GI tract by transgastrostomic endoscopy (TGE) using an ultrathin endoscope during a gastrostomy button or tube replacement.

Methods

The study subjects were 43 patients (27 men and 16 women), who underwent exchange of PEG buttons or tubes 20-French (Fr) or more in diameter at Keio University Hospital between August 2003 and December 2009 (One Step Button, 24-Fr, Boston Scientific, Tokyo, Japan; Ideal Button, 24-Fr, Olympus Medical Systems, Tokyo, Japan; Kangaroo Button, 20-Fr, Nippon Sharwood Medical Industries, Tokyo, Japan; PEG tube, 20- or 24-Fr, Create Medic, Tokyo, Japan). The patients ranged in age from 59 to 100 years (mean: 78). Twenty-three patients had cerebrovascular disease, eight had malignant tumor, seven had Parkinson's disease, and five had neuromotor degenerative disease. In 41 patients, the gastrostomy site was the gastric body, and in the other two it was either the anglus or the antrum.

All procedures were performed with the patient in the supine position. Lidocaine hydrochloride jelly (2%) (Astra Zeneca, Tokyo, Japan) was applied to the gastrostomy site, and some conscious patients who would be undergoing extraction and insertion of PEG buttons were given 35 mg of pethidine hydrochloride intravenously to reduce abdominal pain. Neither scopolamine butylbromide nor glucagon was administered. After a PEG button or tube was extracted from the gastrostomy tract manually, an ultrathin endoscope (GIF-XP260 5.5 mm in diameter or GIF-XP 260 N 6.5 mm in diameter, Olympus Medical Systems, Tokyo, Japan) was inserted into the stomach through the gastrostomy tract. After observation of the stomach, the endoscope was first advanced through the esophagogastric junction (EGJ) and into the upper portion of the esophagus and then was passed into the duodenal bulb. Finally, the gastrostomy tract in the stomach was observed in retroversion. After the ultrathin endoscope was withdrawn, a new PEG button or tube was inserted into the stomach through the gastrostomy tract. For most patients, TGE was performed at the first exchange of a PEG button or tube 6 months after PEG and then each year.

The frequency of successful insertion into the esophagus and duodenum and observation of the gastrostomy tract in retroversion was evaluated, and the endoscopic findings were analyzed.

The degree of abdominal discomfort and pain was assessed during the endoscopic procedure; for unconscious patients, it was assessed on the basis of their facial expression, such as an agonized look or frown.

The study protocol was conducted in accordance with the tenets of the revised Declaration of Helsinki; it was approved by the institutional review board at our institution. Informed consent was obtained from all patients or their families.

Results

Ninety-nine TGE examinations were performed in the 43 patients, and the mean number of examinations for each patient was 2.3 (range: 1–8). The follow-up periods after PEG ranged from 6 months to 8 years and 4 months (mean: 2 years and 4 months). Pethidine hydrochloride was administered in eleven examinations for four conscious patients. The mean endoscopic procedure time was 4.7 min (range: 2–10 min). The stomach could be observed in all of the 99 examinations. The esophagus could be observed in 95 of 99 examinations (96.0%), and the duodenal bulb could be observed in 92 (92.9%). The gastrostomy site in the stomach could be observed in retroversion in all of the 99 examinations and biopsy specimens could be taken if necessary.

Gastric polyps were detected in four patients (9.3%), gastric erosions in two patients (4.7%) and RE in two patients (4.7%) (Fig. 1). Gastric polypoid lesions at the gastrostomy tract were detected in two patients (4.7%) (Fig. 2), and histological examination of the biopsy specimens for both patients showed chronic gastritis with regenerative and hyperplastic changes without neoplastic changes. Gastric ulcer scar was detected in one patient (2.3%), and duodenal ulcer scar in one patient (2.3%).

Early-stage gastric cancer was detected in one patient (2.3%) (Fig. 3), and histological examination of the biopsy specimens revealed poorly differentiated adenocarcinoma. Recurrent esophageal cancer with stenosis was detected in one asymptomatic patient (2.3%) 8 years after chemoradiation therapy, and histological examination of the biopsy specimens revealed squamous cell carcinoma (Fig. 4).

No patients had either discomfort or pain during the endoscopic procedure and no complications such as damage of the gastrostomy tract, bleeding, or aspiration pneumonia occurred.

Discussion

Patients undergoing PEG sometimes exhibit gastroesophageal reflux due to RE and EHH,[3,4] gastric ulcer bleeding[5,6] or early-stage gastric cancer.[14] Although the number of patients with these conditions in this study was small, early detection of not only gastric diseases but also esophageal and duodenal diseases by transgastrostomic endoscopy using an ultrathin endoscope is important. EGD through the oral cavity causes such patients distress and puts them at risk of aspiration pneumonia. Recently, several TGE procedures have been reported.[12–15] Adler *et al.* reported that an ultrathin endoscope (GIF-N230, 6 mm in diameter, Olympus Medical Systems) was useful for percutaneous transgastric placement of jejunal feeding tubes,[12] and Nishiwaki *et al.* reported the usefulness of TGE using a thin endoscope (GIF-XP240, 7.7 mm in diameter; Olympus Medical Systems) that could be inserted up to the upper portion of the jejunum, the oral cavity, and the pharynx.[13] Nishiwaki *et al.* also reported TGE-assisted submucosal dissection of gastric tumors using a thin endoscope (GIF-XP240).[14] Mori *et al.* reported endoscopic retrograde cholangiopancreatography through the gastrostomy tract using an ultrathin endoscope (EG530N5, 6.0 mm in diameter; Fujifilm, Tokyo, Japan).[15] We evaluated the results obtained for the upper GI tract by the TGE using an ultrathin endoscope (GIF-XP260 or GIF-XP260N) during the PEG button or tube replacement needed after PEG placement.

Adler *et al.* reported that the esophagus was examined in retrograde passage of the endoscope in some cases,[12] and Nishiwaki *et al.* reported that the esophagus could be examined in all of the patients except for two patients who had esophageal stenosis.[13] In our study, insertion into the esophagus through the EGJ in retrograde passage was also successful in all of the 99 examinations except four. It was, however, sometimes a little difficult to insert

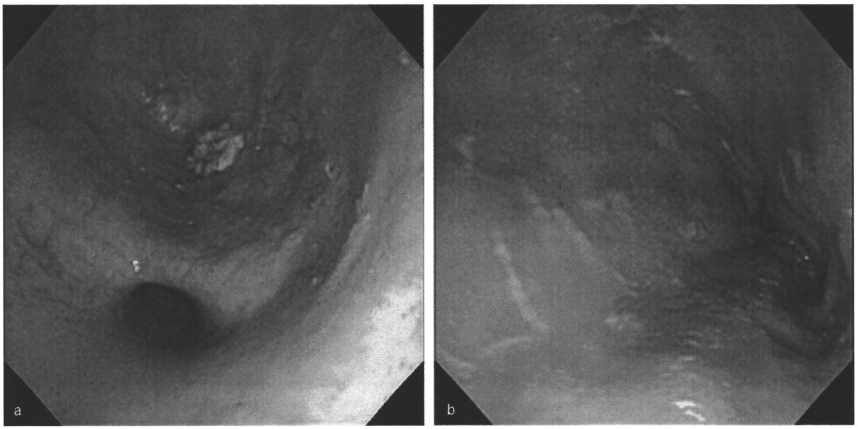

Figure 1 Transgastrostomic endoscopy showing (a) hiatus hernia without passage of endoscope and (b) reflux esophagitis with redness in lower esophagus.

Figure 2 Transgastrostomic endoscopy showing erosive and irregular polypoid lesion at gastrostomy site in retroversion.

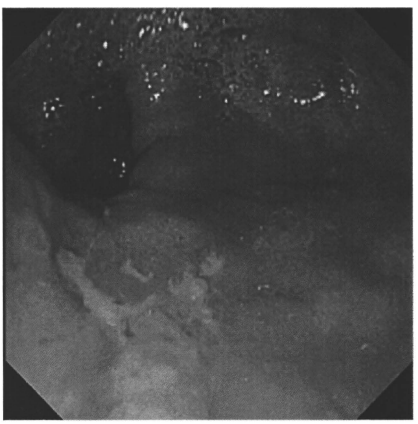

Figure 3 Transgastrostomic endoscopy showing early gastric cancer with irregular ulcer and fold convergence in posterior wall of upper gastric body.

the endoscope from the cardia into the esophagus because of the sharp angle of the EGJ. On the other hand, Adler *et al.* reported that an ultrathin endoscope could be inserted into the duodenum in all 13 of the patients in their study,[12] and Nishiwaki *et al.* reported that in 47 of 51 patients, an ultrathin endoscope could be inserted through the duodenum and into the upper portion of the jejunum.[13] In our study, an ultrathin endoscope could be inserted into the bulbus in 92 of 99 examinations. When the passage from the gastric body to the duodenum bends sharply in some cases, it might be difficult to insert the endoscope into the duodenal bulb.

Gastric ulcer bleeding in the posterior wall of the gastric body is related to mucosal abrasion by PEG tube.[5,6] In this study, only one patient, however, had gastric ulcer scar and one patient had

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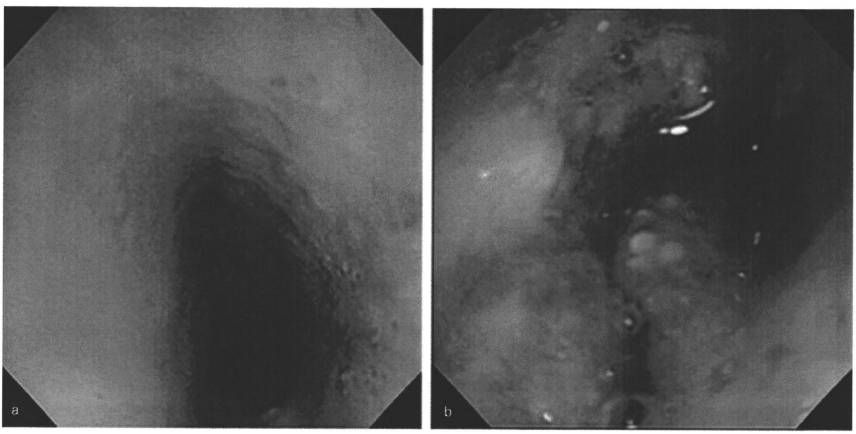

Figure 4 Transgastrostomic endoscopy during retrograde passage showing (a) no recurrence after chemoradiation therapy for advanced esophageal cancer and (b) recurrence of esophageal cancer with stenosis.

duodenal ulcer scar. It is thought that the PEG buttons that were used in most of the patients were not long enough and that they did not compress the posterior wall of the gastric body.

In our study, malignant tumors, such as early-stage gastric cancer and recurrent esophageal cancer, could be detected and they were diagnosed with biopsy specimens. Although most patients who have undergone PEG have comorbid illness, it is useful for some patients in relatively good condition to detect early-stage gastric or esophageal tumors and to treat them endoscopically as a minimally invasive treatment.[14]

It was easy to observe the gastrostomy site in the stomach in retroversion in all examinations, so all sites in the stomach could be observed. Biopsy specimens could be taken in any site in the stomach, even in the gastrostomy site. The mean operating time of the endoscopic procedure was less than 5 min, and no complications occurred. Although this procedure was performed in only a single center, observation of the upper GI tract with TGE using the ultrathin endoscope during the PEG button or tube replacement is thought to be efficacious and safe.

For unconscious patients, only local anesthesia of the gastrostomy site due to the application of lidocaine hydrochloride jelly was needed to make the PEG button replacement and the endoscopic procedure through the gastrostomy tract painless. None of the conscious patients needed intravenous pethidine to reduce abdominal pain for the endoscopic procedure, but some needed it for the PEG button replacement.

The thin endoscope Nishiwaki used requires a gastrostomy tract large enough for a 24-Fr PEG button,[13] but the ultrathin endoscope we used needs a tract large enough for a 20-Fr PEG button. As the diameter of the XP260N is smaller than that of the gastrostomy tract suitable for a 24-Fr PEG button, it is necessary to fill the gap between the endoscope and the gastrostomy tract with gauze in order to prevent leakage of air out of the stomach.

In conclusion, observation of the upper gastrointestinal tract with transgastrostomic endoscopy using an ultrathin endoscope during a gastrostomy button or tube replacement may be useful and safe.

Competing interests

The authors declare that they have no competing interests.

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