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BRIEF ARTICLE

A substantial incidence of silent short segment endoscopically suspected esophageal metaplasia in an adult Japanese primary care practice

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Abstract

AIM: To determine the incidence and characteristics of endoscopically suspected esophageal metaplasia (ESEM) in a primary adult care institution.

METHODS: Eight hundred and thirty two consecutive individuals (mean age, 67.6 years) undergoing upper gastrointestinal endoscopy between January 2009 and December 2010 were included in this study. The diagnosis of ESEM was based on the criteria proposed by the Japan Esophageal Society, and was classified as long segment ESEM (3 cm or more) or short segment ESEM (< 3cm). Short segment ESEM was further divided into circumferential and partial types. Age, gender, hiatus hernia, esophagitis, gastroesophageal reflux disease (GERD)-suggested symptoms, and antacid medications were recorded as background factors. Esophagitis was graded according to the Los Angeles classification. Hiatus hernia was divided into absent and at least partially present.

RESULTS: Long and short segment ESEM were found in 0 and 184 (22.1%) patients, respectively (mean age of short segment ESEM patients, 68.3 years). Male gender and hiatus hernia were shown to be significant factors affecting short segment ESEM by both univariate (P = 0.03 and P = 9.9x10^{-18}) and multivariate [Odds ratio (OR) = 1.45; P = 0.04, and OR = 43.3; P = 1.5x10^{-7})] analyses. Two thirds of patients with short segment ESEM did not have GERD-suggested symptoms. There was no correlation between short segment ESEM and GERD-suggested symptoms.

CONCLUSION: The incidence of short segment ESEM in our community practice seems higher than assumed in Asian countries. As GERD-suggested symptoms are a poor predictor of ESEM, endoscopists should bear in mind that silent short segment ESEM does exist and, in fact, was found in the majority of our patients.

Key words: Endoscopically suspected esophageal metaplasia; Esophagitis; Gastroesophageal reflux disease; Hiatus hernia; Longitudinal vessel

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INTRODUCTION

Barrett's esophagus (BE) is a condition in which the

normal squamous epithelium of the distal esophagus is replaced by specialized intestinal metaplastic epithelium. It is one of the histological consequences of long-standing gastroesophageal reflux disease (GERD)[1] and predisposes to the development of esophageal adenocarcinomas. In Western countries, the incidence of esophageal adenocarcinomas among BE patients was 7/1000-10/1000 person-years duration of follow-up[2], which was thought to constitute a 30 to 120-fold greater risk than that in the general population[3]. An alarmingly rapid increase in esophageal adenocarcinoma has also been reported in some European[4] and Asian countries[5], and, although less marked, in Japan[6]. Accordingly, concern regarding BE as well as GERD has also increased.

Currently, BE is classified into two types according to the length of specialized intestinal metaplasia involved at the lower esophagus: traditional BE or long segment BE (LSBE), with the length being 3cm or more[7]; and short segment BE (SSBE), being less than 3cm[8]. Subsequent follow up examinations[9,10]and a metaanalysis[2] have revealed the development of dysplasia or cancer in SSBE at a substantial rate and an equivalent relative risk ratio of cancer between LSBE and SSBE, suggesting that SSBE *per se* possesses a malignancy potential similar to LSBE. In addition, the length of the columnar epithelium remained unchanged among LSBE patients[11] as well as among many SSBE patients[12], suggesting a fairly rapid evolution of BE to its full length with little subsequent change. Therefore, SSBE should not be overlooked for the early detection of subsequent neoplastic changes arising from it.

In the West, the observed incidence of LSBE and SSBE range from 0.2%-7% and 1%-17%, respectively, in asymptomatic patients[13-16], and from 1%-5% and 1%-19%,respectively, in GERD patients[14-18], while in Central and East Asia, these figures are 0.05%-1.6% and 0.38%-4.6%, respectively, even in patients with reflux symptoms[19-22], suggesting a low incidence of SSBE in Asian countries. In comparison, reports on the incidence of BE in the Japanese population are relatively scant in the literature[12,23-27]. The varying incidence of BE by geographic area might reflect a different awareness and recognition of, or different diagnostic criteria[27-30] for, this entity as well as a different and biased study population such as veterans[13], those undergoing colon cancer screening[15,16], or those seen at a gastroenterological tertiary center[14,21,22]. Therefore, the aim of this study is to elucidate the incidence and characteristics of this condition in the less selective, less biased study cohort of daily general practice. Since the Japan Esophageal Society proposed endoscopically diagnosed esophageal metaplasia (ESEM) as an endoscopic diagnosis of BE and no requirement of histological evidence[30,31], we adopted the ESEM criteria proposed by the Japan Esophageal Society and investigated consecutive adult primary care patients irrespective of reflux symptoms, including practically asymptomatic individuals undergoing an annual health check examination. Thus, our study population resembled that seen by the general practitioner.

MATERIALS AND METHODS

The study population consisted of consecutive patients who underwent a referral (n = 400) or screening (n = 432) upper gastrointestinal endoscopy for a variety of clinical reasons or as a part of their annual medical examination in our Unit between January 2009 and December 2010. Our Unit is independent of gastroenterological tertiary centers and the patients were residents in the neighboring district to our institution with easy access to us. The clinical indications of referral endoscopy included GERD symptoms (n = 305) listed in the published questionnaires[32-35] (heartburn, regurgitation, dysphagia, odynophagia, epigastralgia, belching, nausea and vomiting, and non-cardiac chest pain) or other gastrointestinal symptoms such as abdominal pain (n = 6), or loss of appetite with or without a clinically important weight loss (n = 48). Other conditions unrelated to gastrointestinal symptoms but accepted indications for endoscopy included abnormalities of laboratory findings (n = 29), positive fecal occult blood test (n = 10), and other miscellaneous factors (n = 2). Histamine 2 receptor antagonists or proton pump inhibitors were regarded as antacid medications. The symptoms and antacid medications at the time when submitted for the first endoscopy were recorded. The patients who underwent therapeutic or urgent endoscopies, or who had undergone previous gastric or esophageal surgery including antireflux surgery were excluded, while those having undergone previous endoscopic mucosal resection were permitted. For patients undergoing multiple endoscopies during this study period, only the endoscopic data attained during the first endoscopy were used in this study.

The definition of ESEM was based on the anatomical criteria proposed by the Japan Esophageal Society[30,31]. Before the fiberscope was inserted into the stomach, the squamocolumnar junction (SCJ), diaphragmatic hiatus, and, if present, longitudinal vessels at the lower esophagus were recognized with only minimal air inflation. The SCJ was recognized as a distinct difference in color between a reddish-orange velvety gastric epithelium and a whitish-gray smooth esophageal epithelium. The diaphragmatic hiatus appeared endoscopically as a narrowing or notch of the lower end of the esophagus where the tubular esophagus flared to become the sack-like stomach. The gastroesophageal junction (GEJ) was defined at the distal margin of the longitudinal vessels; thus, the columnar epithelium on the longitudinal vessels, if present, was diagnosed as ESEM and was further categorized according to its length: long segment ESEM when circumferentially recognized with a minimal length of 3cm or more, or short segment ESEM for length less than 3 cm[27]. In the cases of severe esophagitis, which hindered correct recognition of longitudinal vessels, the GEJ was defined at the proximal margin of the gastric fold[36]. These measurements were recorded using the

Table 1 Demographic and endoscopic characteristics of 832 patients with or without short segment ESEM

		Total (%) (n = 832)	Short segment ESEM(+) (%) (n = 184)	ESEM(-) (%) (n = 648)	P value
Age (yr), mean ± SD		67.6 ± 12.9	68.3 ± 12.2	67.4 ± 13.0	0.41
Age (yr), decennium	80-	139 (16.7)	31 (16.8)	108 (16.7)	0.92
	70-79	266 (32.0)	63 (34.2)	203 (31.3)	
	60-69	249 (29.9)	51 (27.7)	198 (30.6)	
	50-59	97 (11.7)	21 (11.4)	76 (11.7)	
	40-49	52 (6.2)	13 (7.2)	39 (6.0)	
	-39	29 (3.5)	5 (2.7)	24 (3.7)	
Age (yr), dichotomy	70-	405 (48.7)	94 (51.1)	311 (48.0)	0.46
	-69	427 (51.3)	90 (48.9)	337 (52.0)	
Gender	Male	339 (40.7)	88 (47.8)	251 (38.7)	0.03
	Female	493 (59.3)	96 (52.2)	397 (61.3)	
Antacid therapy	(+)	196 (23.6)	52 (28.3)	144 (22.2)	0.09
	(-)	636 (76.4)	132 (71.7)	504 (77.8)	
GERD-suggested symptoms	(+)	305 (36.7)	68 (37.0)	237 (36.6)	0.92
	(-)	527 (63.3)	116 (63.0)	411 (63.4)	
Esophagitis	(+)	45 (5.4)	10 (5.4)	35 (5.4)	0.73
	(-)	787 (94.6)	174 (94.6)	613 (94.6)	
Hiatus hernia	(+)	621 (74.6)	182 (98.9)	439 (67.7)	9.9×10^{-18}
	(-)	211 (25.4)	2 (1.1)	209 (32.3)	

ESEM: Endoscopically suspected esophageal metaplasia; GERD: Gastroesophageal reflux disease.

markings of the endoscopic shaft. The shapes of the short segment ESEM were categorized as circumferential or partial types. The hiatus hernia was determined by subtracting the area of ESEM from the area between the SCJ and diaphragmatic hiatus, and then divided into absent or at least partially present. Reflux esophagitis was endoscopically scored as grade A, B, C, or D according to the Los Angeles classification[37].

For univariate analysis, Fisher's exact tests were used to compare categorical data. An unpaired Student t test was used for the comparison of two mean values. For multivariate analysis, a logistic regression method was employed to investigate the factors affecting the presence of short segment ESEM. P values of less than 0.05 were considered significant.

This study followed the principles of the declaration of Helsinki.

RESULTS

This study comprised 832 patients (mean age 67.6 years old, 40.7% male). Long and short segment ESEM wereidentified in 0 and 184 (22.1%) patients,respectively. Thus, the subsequent analyses focused on short segment ESEM (n = 184) and non ESEM patients (n = 648).

Overall, 405 (48.7%) patients were aged 70 years or older, while 81 (9.7%) patients were < 50 years old (Table 1). Univariate analysis showed that short segment ESEM was correlated with male gender (P = 0.03) and hiatus hernia (P = 9.9 $\times 10^{-18}$) (Table 1). Surprisingly, GERD-suggested symptoms were negative in 63% of short segment ESEM patients and did not correlate with short segment ESEM, indicating that approximately two thirds of short segment ESEM patients were silent. Patients with (n = 305) or without (n = 527) GERD-suggested symptoms exhibited almost the same incidence of short segment ESEM (22.3% and 22.0%, respectively). Logistic regression analysis also showed that male gender (P = 0.04) and hiatus hernia (P = 1.5 $\times 10^{-7}$) were significant factors affecting short segment ESEM (Table 2). Again, GERD-suggested symptoms did not correlate with short segment ESEM. Among the 184 patients with short segment ESEM, a partial type was observed in 129 (70.1%) patients. The types of short segment ESEM did not correlate with any of the background factors.

Grades A, B, C, and D esophagitis were observed in 17, 19, 3, and 6 patients, respectively. Neither endoscopically suspected dysplasia nor adenocarcinoma arising from the ESEM that required biopsy was documented.

DISCUSSION

The merit of our study is its application to consecutive individuals in a community practice irrespective of GERD-suggested symptoms. In sharp contrast to the reported incidence of LSBE (0.05%-1.6%), or SSBE (0.4%-4.6%), or even endoscopically diagnosed BE (ESEM) (1.5%-10%) in Asian countries[19-22], we have demonstrated that long and short segment ESEM were observed in 0% and 22.1%,respectively, of the study population, rates in accordance with (0.2%-0.5% and 20%-43%)[12,25-27] or even higher than (0.2%-0.6% and 12.0%-15.1%)[23,24] those reported from Japan. Our results suggest that the incidence of short segment ESEM is greater than assumed in Asian countries irrespective of tertiary or primary care institutions.These differences among geographic areas might reflect different levels of awareness and recognition of this entity, diagnostic criteria (biopsy proven or endoscopically), or a different study population (GERD patients or asymptomatic individuals). In addition, age of the study population may account for the differences. As compared with the incidence of short segment ESEM in the present study, a lower or similar incidence of SSBE was respectively reported in a cohort with a mean age younger than (47-61 years old)[13-15,20-24] or similar to (66-69 years old)[12,26] those in our study population. Further more, a substantially high incidence of short segment ESEM in the present study may only be an approximation of the real incidence due to the easily accessible gastrointestinal unit. Since no universally accepted definition of BE currently exists[27-30], the diagnostic criteria for this condition in the West and in Japan should be first compared and discussed.

In the West, the diagnosis of LSBE and SSBE is

Table 2 Logistic regression analysis of association between short segment ESEM and background factors

		Odds ratio	95% Confidence interval	*P* value
Age		1.01	0.99-1.02	0.28
Gender	Female	1	-	
	Male	1.45	1.02-2.06	0.04
Antacid therapy	(-)	1	-	
	(+)	1.23	0.83-1.84	0.3
GERD-suggested symptoms	(-)	1	-	
	(+)	1.08	0.75-1.57	0.67
Esophagitis	(-)	1	-	
	(+)	0.74	0.35-1.58	0.44
Hiatus hernia	(-)	1	-	
	(+)	43.3	10.6-176.1	1.5×10^{-7}

GERD: Gastroesophageal reflux disease; ESEM: Endoscopically suspected esophageal metaplasia.

based on multiple, systematic, and targeted biopsies confirming specialized intestinal metaplasia[28] or a columnar-lined epithelium[29]. In order to determine the optimal site of biopsy, precise recognition of the GEJ is a prerequisite; however, current difficulties include a lack of endoscopic landmarks for the GEJ. Although the GEJ is defined as the proximal margin of the gastric folds in the West, its appearance changes from moment to moment under live endoscopy, depending on inspiration, peristaltic activity, and gagging reflux with a transient prolapse of gastric folds up into the esophagus. In addition, gastric mucosal atrophy and air overinflation with the subsequent disappearance of gastric folds hamper identification of the "true" proximal margin of the fold. Furthermore, intestinal metaplasia can exist at the SCJ even in individuals without BE[38], suggesting a false positive diagnosis of BE. On the other hand, failure to detect intestinal metaplasia in 20% or more of BE patients[39,40] suggests a false negative diagnosis of BE.

It is widely accepted in Japan that the distal margin of the palisade-shaped longitudinal capillary vessels corresponds to the GEJ. Therefore, longitudinal vessels emanating from the SCJ, if they locate in the area of reddish-orange velvety mucosa distally to the SCJ, can be considered ESEM, and histological evidence of goblet cells is not mandatory[30,31]. The rationale for these criteria is supported by several anatomical and molecular biological findings. The longitudinal vessels are specifically located in the lamina propria of the esophagus[41]. Analyses of protein[42] or gene[43] expression have provided phenotypic evidence of intestinal differentiation in the endoscopically defined SSBE or in the metaplastic but nongoblet esophageal columnar lined epithelium. Patients with a columnar-lined epithelium with or without specialized intestinal metaplasia carry a similar risk of developing esophageal adenocarcinoma[44]. Furthermore, the Japanese criteria have merit due to the endoscopic diagnosis accompanied by atraumatic procedures with lower cost and ease, readily allowing general practitioners to adopt this technique and thus facilitating the endoscopic description of BE, especially for those with conditions liable to bleeding such as liver cirrhosis, coagulopathies, or anticoagulant therapies. Indeed, Western experts have also emphasized the value of the Japanese criteria[45] and Western endoscopists have actually been able to recognize the distal margin of the longitudinal vessels similar to Japanese endoscopists[46].

In the present study, 36.7% of patients showed GERD-suggested symptoms. This incidence seems to be higher than those reported from Asia (2.5%-4.8%) and the West (16%-28%)[47]. However, such a comparison requires caution because the incidence of GERD is influenced by many factors including disease awareness as well as diagnostic criteria such as symptomatology and its frequency threshold. In the present study, we did not use precise questionnaires and did not consider symptom frequency for the consideration of GERD because, in consideration of ESEM and efforts toward its detection, we believe that GERD or other gastrointestinal symptoms *per se* by which the patients are willing to undergo endoscopy are more important for the initiation of endoscopy. It is noteworthy that, when symptom frequency was not taken into account, the incidence of GERD was higher both in Japan (15.8%-44.1%)[48-50] and in Asian countries (32.3%-41.2%)[51-53], which is consistent with the findings in the present study.

Despite the higher incidence of GERD-suggested symptoms, short segment ESEM did not correlate with GERD-suggested symptoms or esophagitis. Importantly, 63% of the short segment ESEM patients in our series did not have typical reflux symptoms, suggesting the existence of silent ESEM. It is unlikely that the antacid therapy was attributable to silent ESEM because multivariate analysis found neither GERD-suggested symptoms nor antacid therapy to be significant factors for short segment ESEM. These findings are in accordance with previous studies[14,21] and a recent metaanalysis[54] which demonstrated no association between SSBE and GERD. On the other hand, we observed that short segment ESEM was strongly correlated with hiatus hernia. The higher incidence (75%) of hiatus hernia in the present study compared with those (18%-30%) in previous studies[55,56] may be ascribed partly to the different definition and classification of hiatus hernia and partly to the different age distributions. Even the presence of partial hiatus hernia was included in our study, while a hiatus hernia of only 2 cm or more was considered in most studies[56-58]. Patients aged 70 years or more comprised 49% of our study, while this figure in other studies was 27%[55,56]. Indeed, other investigators also observed that hiatus hernia was positively correlated with older age[55] and BE[57]. The inclusion criteria for hiatus hernia in the present study may have accounted for most (99%) short segment ESEM patients having hiatus hernia, which resulted in the wide range in the 95% confidence interval of the odds ratio. Although different definitions and

classifications of hiatus hernia employed by each study group undoubtedly influence the strength of the association between hiatus hernia and short segment ESEM, and hamper comparisons between publications reporting such associations, it is assumed that a hiatus hernia is likely to cause acid reflux, at least asymptomatically, and ESEM could eventually develop. Therefore, patients with short segment ESEM have backgrounds liable to cause acid reflux such as a hiatus hernia, while the majority of short segment ESEM patients are unaware that they have the condition, thus may not be diagnosed unless endoscopy is performed.

These considerations might explain our findings of no correlation between age and the incidence of short segment ESEM. In fact, there seems inconsistency in the literature concerning the correlation between older age and incidence of BE, which was positive in some reports[11,12] and neutral in another[27], the latter findings being in agreement with those of the present study. A higher incidence of hiatus hernia in the present study reflects the likely establishment of short segment ESEM regardless of age, which could provide one plausible explanation for such a neutral correlation.

The recognition of silent short segment ESEM remains a problem. Considering the paradigm that BE arises as a complication of GERD and predisposes to esophageal adenocarcinomas, asymptomatic short segment ESEM highlights the need to assess the distal esophagus carefully in all patients undergoing upper endoscopy for any indication.In this study population which had easy access to our gastrointestinal unit, our results demonstrate that short segment ESEM exists at a substantial rate even in asymptomatic patients, but can not be predicted by symptoms, a fact endoscopists should bear in mind.

COMMENTS

Background

The incidence of Barrett esophagus (BE) varies in the literature, depending on different awareness and recognition of, or different diagnostic criteria for, this entity as well as different biased study populations. Reports on the incidence of BE in the Japanese population are scantin the literature.

Research frontiers

It has been proposed that BE, even in its short segment, should not be overlooked for the early detection of subsequent neoplastic changes arising from it. The aim of this research was to clarify the incidence and characteristics of BE in the less selective, less biased study cohort of daily general practice, thus the study population resembled that seen by the general practitioner. For this purpose, the authors applied endoscopically suspected esophageal metaplasia (ESEM) as an endoscopic diagnosis of BE. The merits of the criteria used were an endoscopic diagnosis accompanied by atraumatic procedures and no requirement of histological findings, with lower cost and ease, resulting in general practitioners adopting this technique and thus facilitating the endoscopic description of BE.

Innovations and breakthroughs

The incidence of short segment ESEM in the authors' series seems higher than those reported in Asian countries. The symptoms that suggest gastroesophageal reflux disease (GERD) are a poor predictor of ESEM, suggesting that a substantial number of patients have silent short segment ESEM, a fact endoscopists should bear in mind.

Applications

Asymptomatic short segment ESEM highlights the need to carefully assess the distal esophagus in all patients undergoing upper endoscopy for any indication. This will result in the likelihood of detecting esophageal adenocarcinomas at an earlier stage since BE predisposes to esophageal adenocarcinomas.

Terminology

The definition of ESEM was based on the anatomical criteria proposed by the Japan Esophageal Society. The columnar epithelium on the longitudinal vessels emanating from the squamocolumnar junction was diagnosed as ESEM. ESEM was further categorized according to its length: long segment ESEM when circumferentially recognized with a minimal length of 3cm or more, or short segment ESEM for length less than 3 cm.

Peer review

Although this paper is a simple observational study from a single center looking at endoscopic diagnosis of esophageal metaplasia in a Japanese cohort, study population at primary adult care institution is attractive and the important findings are the presence of ESEM not related to symptoms.

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