



Correlation between Endoscopically Suspected Esophageal Metaplasia and Barrett's Esophagus: A Single Center Experience

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Authors' contributions

This work was carried out in collaboration between all authors. Author CLL designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author SCH managed the literature searches, analyses of the study. Author SHH approved the pathology part of this study. Authors CCT and CHW collected and performed some of the endoscopy exams. All authors read and approved the final manuscript.

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ABSTRACT

Background: Barrett's esophagus (BE) is defined as a suspect endoscopic finding followed by pathologically proven specific intestinal metaplasia as opposed to the normal squamous epithelium of the esophagus. A new BE classification, the Prague C and M criteria, was proposed in 2006 to define the extent of BE based on the circumference (C) and maximum diameter (M) of the lesion.

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AIM: In this study, we adopted Prague C and M criteria to record endoscopically suspected esophageal metaplasia (ESEM); biopsies were subsequently taken to determine any correlation between ESEM and histologically proven BE. The risk factors of BE were also investigated.

Methods: This was an observational study. From June 2006 to June 2009, 62 cases of ESEM were enrolled with subsequent standardized random biopsies (four pieces were taken every 2 cm from the four quarters of the esophagus). BE was defined by histological verification of specialized intestinal metaplasia (SIM). Data were analyzed to identify correlations between ESEM and BE. Logistic regression models were used to investigate the relationship between age, gender, hiatal hernia, long-segment metaplasia (LS defined as maximal extension greater than 3 cm from the SCJ), and BE. A multi-variate regression model was also used.

Results: A total of 6836 subjects who underwent endoscopic examination were enrolled from June 2006 to June 2009. Of these, 42 BE subjects were confirmed among 62 ESEM cases; the prevalence of BE among cases that received endoscopy was 0.61%. Long-segment ESEM was more prevalent than short segment (LS: SS = 43:19). Several factors such as age, gender, hiatal hernia, and LS were analyzed using a regression model; this model revealed that only LS ESEM predicted BE with borderline significance ($p = 0.07$). However, a multi-variate regression model including all the factors revealed that males with ESEM were significantly associated with BE ($p = 0.015$).

Conclusion: This study was performed in single center and used Prague C and M criteria to record ESEM. The use of Prague C and M criteria to record ESEM yielded a histological verification of BE rate of 67.7%. A standardized random quadruple biopsy to validate BE should be routinely performed. LS metaplasia was a single predictor of BE with borderline significance and male sex was a significant predictor of BE.

Keywords: Barrett's esophagus; endoscopically suspected esophageal metaplasia.

1. INTRODUCTION

Barrett's esophagus (BE) is a well-recognized premalignant condition detected in the majority of patients with esophageal and gastroesophageal adenocarcinoma [1], it carries a 30–125-fold higher risk than the general population [2,3]. BE is a metaplastic change of the lining of the esophageal mucosa, such that the normal squamous epithelium is replaced with specialized or intestinalized columnar epithelium [4,5].

The development of BE has also been associated with gastroesophageal reflux disease (GERD) [6]. BE is diagnosed in approximately 10–15% of patients with reflux who undergo endoscopy; it has also been reported in patients without chronic reflux symptoms, with a prevalence of 5.6% in one endoscopic screening report. In previous studies, the prevalence of BE was considered to be lower in Asia than in the West [7,8], with a range of 0.3–2% in the general population and 6.3–13.6 % [9–15] in patients with GERD.

Histologically, BE is a metaplastic change of the lining of the esophageal mucosa, such that the normal squamous epithelium is replaced with specialized or intestinalized columnar epithelium. However, BE diagnosis requires initial

examination using upper gastrointestinal endoscopy to reveal that the squamocolumnar junction no longer coincides with the gastroesophageal junction, which indicates cephalad displacement of the former. For this first step, there was no consensus-based guidance method until a new classification of BE, the Prague C and M criteria [16], was introduced by the International Working Group for the Classification of Oesophagitis (IWGCO), based on the circumference (C) and maximum diameter (M) of the lesion.

This study aimed to investigate the prevalence of endoscopically suspected esophageal metaplasia (ESEM) and BE in a Taiwanese population undergoing diagnostic endoscopy with histologic confirmation and to assess the utility of the Prague C and M criteria in correlating ESEM with BE.

2. MATERIALS AND METHODS

2.1 Design Overview

This was an observational study that included unselected patients presenting with upper abdominal symptoms (e.g., nausea, vomiting, acid regurgitation, heartburn, epigastric pain, abdominal fullness, occult gastrointestinal

bleeding, and / or other dyspeptic symptoms). Written informed consent was obtained from all patients. This study was performed according to good clinical practice and the Declaration of Helsinki; furthermore, the study protocol was approved by the ethics institutional review board of our hospital.

2.2 Settings and Participants

Between June 2006 and February 2009, consecutive patients, either presenting with epigastric discomfort or acid regurgitation who received an esophagogastroduodenoscopy (EGD), were enrolled for evaluation. EGD was performed by three experienced endoscopists using the Olympus Q260 scope (Tokyo, Japan) together with narrow-band imaging and high-definition TV for better visualization and recognition of ESEM.

EGD was performed following topical anesthetization of the oropharynx with xylocaine spray and included examination of the duodenal bulb, the second portion, stomach, and esophagus. Particular attention was given to the gastroesophageal junction and mid-lower section of the esophagus. According to the Prague C and M criteria, the endoscopic gastroesophageal junction is defined as the proximal margin of the gastric folds. Lesions were judged as ESEM if they showed morphological resemblance to BE, or were detected on endoscopic examination as a columnar-lined distal esophagus. The circumference and maximum diameter of BE were rated according to the Prague C and M criteria. The extent of ESEM was recorded as C x M y (x and y represent the values of circumferential (C) and maximum diameter (M), respectively). Furthermore, long-segment n Prague C and M criteria when M wBE (LSBE) was defined by the value of "M" as ≥ 3 cm. If "M" was < 3 cm, the lesion was classified as short-segment BE (SSBE).

A standardized endoscopic biopsy protocol (random biopsy from four quadrants, taken every 2 cm separately, a total of eight pieces) was performed at sites with ESEM, which usually appeared as a reddish discoloration in an otherwise relatively whitish esophageal mucosa with palisading vessels. Biopsy samples were formalin-fixed, embedded in paraffin, and stained with hematoxylin and eosin, HID-Alcian blue at pH 2.5, or modified Giemsa stain to be interpreted by an alimentary pathologist (S.H.

Huang). Histological parameters for the diagnosis of BE were specialized intestinal metaplasia (SIM) having the appearance of goblet cells of the esophagus, and gastric metaplasia (GM) according to the Montreal definition and classification. The histological parameter for determining the severity of BE was the grading of dysplasia according to the Vienna classification of epithelial neoplasia of the digestive tract [5].

Quantitative variables were given as means \pm SD, and *p*-values < 0.05 were considered significant. All the calculations were performed using STATA version 11 software (Stata Corporation, Texas, USA).

3. RESULTS

3.1 Demographic Characteristics

Over the three year period, a total of 6836 (Male: 3325, M:F = 1:1.06; mean age: 53.6 y) subjects who underwent general endoscopy examination were enrolled; 62 cases were recorded as ESEM following observation of a red, columnar-lined esophagus mixed with or without palisading vessels extending downwardly from the squamocolumnar junction.

Compared with our findings, the pathologist confirmed 42 patients as BE (Table 1). As shown in Table 2, the prevalence rates of ESEM were 2.27% (1/44) in the group < 20 y old, 0.80% (3/373) at age 21–30 y, 1.01% (8/791) at age 31–40 y, 0.998% (11/1102) at age 41–50 y, 0.57% (10/1753) at age 51–60 y, 1.19% (21/1423) at age 61–70 y, 0.794% (4/1008) at age 71–80 y, and 1.17% (4/342) in the group aged > 80 y. The overall prevalence of ESEM among patients who received an EGD examination was 0.9% (62/6836) and BE was confirmed in 0.6% (42/6836).

3.2 ESEM with Prague C and M Criteria

For the correlation between ESEM and BE, our study revealed a 0% (0/1; BE/ESEM) correlation in the group < 20 y old, 66.7% (2/3) correlation at 20–30 y, 37.5% (3/8) correlation at 30–40 y, 81.8% (9/11) at 40–50 y, 80% (8/10) at 50–60 y, 58.8% (10/17) at 60–70 y, 87.5% (7/8) at 70–80 y, and 75% (3/4) at > 80 y old. The best correlation (87.5%) was observed in the 70–80 y age group.

Table 1. Brief results of the study population

Male:Female	45:17
Age	Mean: 55.7±16.8 (18–91)
Hiatal hernia	35.5% (22/62)
Short segment	69.4% (43/62)
Dysplasia (low grade)	25.8% (16/62)

Table 2. Age distribution of the study population

	Cases	ESEM	Hiatal hernia	BE
<20	44	1	0	0
21~30	373	3	0	2
31~40	791	8	1	3
41~50	1102	11	2	9
51~60	1753	10	6	8
61~70	1423	21	8	10
71~80	1008	4	2	7
>80	342	4	3	3
Total	6,836	62	22	42

The mean age of patients with ESEM was 55.7±16.8 y (18–91 y). Males predominated (72.6%, 45/62) as ESEM patients. As for ESEM classified by Prague C and M criteria, the ratio of short/long-segment ESEM was 2.26 (43/19). Following endoscopic observation, hiatal hernias were present in 35.5% (22/62) of ESEM patients. Sixteen subjects (25.8%) had BE coexistent with dysplasia according to the Vienna classification. All of them were low-grade dysplasia and none had high-grade dysplasia or invasive adenocarcinoma.

3.3 Statistical Analysis

Under uni-variate logistic regression analysis, none of the following factors: age (increasing), sex, hiatal hernia, or long-segment ESEM showed a significance for predicting BE (Table 3); however, multi-variate logistic regression revealed male sex as a significant predictor of ESEM to BE ($p = 0.015$).

Table 3. Logistic regression

	Uni-variate	Multi-variate
Male sex	0.131	0.015
Age	0.122	0.09
Hiatal hernia (+)	0.086	0.09
Long segment	0.072	0.09

4. DISCUSSION

This observational study identified the prevalence of ESEM to be 0.9% and BE to be

0.6% in a group of unselected patients presenting with upper abdominal symptoms.

As we know from other studies, the prevalence of BE has been considered to be lower in Asia than in the West. A multi-center prospective study from Korea reported a BE prevalence of 0.3%, while another study performed in Japan showed a prevalence of 0.6% [17,18]. These studies had a slightly lower prevalence than our results because both studies only identified LSBE and did not perform standard biopsies, factors that might contribute to the relatively lower prevalence [19]. More recently, the Asian Barrett's Consortium conducted a review of published studies on BE from Asia to assess the current status of BE research there. Differences in study design, enrolled population, and the endoscopic biopsy protocols used led to a substantial variability in the reported BE prevalence (0.06%–19.9%) across Asia [20]. As for other Taiwanese data, a previously published study also reported the prevalence of BE among referral endoscopy patients, screening endoscopy, and overall to be 1.06%, 0.35%, and 0.85%, respectively [21]. One study from Taiwan [22] focused on the discussion on the prevalence of BE among GERD patients where they reported a 3.8% frequency of BE. Hiatal hernia and prolonged GERD duration were also significant risk factors in this study.

Several investigations have identified the clinical features and characteristics of patients with BE; age over 40 y, male gender, more frequent reflux episodes, increased BMI, and increased abdominal circumference have been associated with BE [23–25]. However, in this observational study, only male gender in a multi-variate model revealed a significant risk factor of ESEM patients developing BE. This study's drawback was the relatively small number of ESEM cases (only 62) among 6836 subjects, which led to an insignificant uni-variate analysis among age (increasing), gender, hiatal hernia, and long-segment ESEM.

Histologically identifiable BE has been detected in 25–32% of cases of SS suspected columnar-lined esophagus and in 55% of cases of LS suspected columnar-lined esophagus in random biopsies [26,27]. The number of biopsies also affects the likelihood of detection. Harrison et al. reported that goblet cells were detected in 68% of endoscopies when eight biopsies were taken, compared to 35% if only four biopsies were analyzed [28]. In our study, a standardized

endoscopic biopsy protocol (random biopsy from four quadrants taken every 2 cm separately, giving a total of eight pieces) was performed, which met the requirement and accuracy demanded for the diagnosis of BE displaying SIM.

Limitation of the study: owing to an observational study, we retrospectively enrolled the consecutive patients, either presenting with epigastric discomfort or acid regurgitation who received an esophagogastroduodenoscopy (EGD), which means we didn't separate GERD patients with other patients who had upper GI problems. In addition, we did not collect complete baseline informations such as BMI, smoking history and alcohol consumption to analyze these as risk factors to be BE. Thus, this observational study focused mainly on endoscopically suspected ESEM to be BE.

Most importantly, BE patients should be informed of their increased risk of developing of esophageal adenocarcinoma, although this risk is low. Acid-suppressive therapy (proton-pump inhibitors), antireflux surgery, or both, are useful in controlling symptoms of reflux and healing erosive esophagitis in BE patients, but there is currently no conclusive evidence that such therapies reduce the risk of neoplastic progression.

5. CONCLUSION

In conclusion, from our single center experience, the use of Prague C and M criteria to record ESEM yields a histological verification of BE rate of around 67.7% and 25.8% of low-grade dysplasia, which indicates that it is worthwhile performing a standardized random quadruple biopsy to validate BE, and male gender carries higher risk to be BE than female gender; patients should subsequently be closely monitored.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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