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Clinical characteristics and natural history of asymptomatic erosive esophagitis

ESOPHAGUS

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Original Article

ABSTRACT

Background/Aims: This study was designed to investigate risk factors related to asymptomatic erosive esophagitis and the natural history of both endoscopic findings and reflux-related symptoms in subjects with asymptomatic erosive esophagitis.

Materials and Methods: On a retrospective basis, data were gathered from patients with erosive esophagitis (Los Angeles classification ³A) who had undergone endoscopic follow-up at St. Vincent Hospital. Data from 313 subjects with erosive esophagitis were investigated.

Results: Most patients had mild esophagitis (grade A or B, Los Angeles classification); 198 (63.3%) had reflux symptoms, and 115 (36.7%) lacked typical or atypical symptoms. Asymptomatic erosive esophagitis was associated with non-smoking (odds ratio (OR), 2.4; 95% confidence interval (CI), 1.4-3.9) and lower body mass index (body mass index (BMI); OR, 1.5; 95% CI, 1.0-2.4), while 26% of subjects had recurring reflux-related symptoms. Younger subjects were more likely to have reflux-related symptoms ($p<0.05$).

Conclusion: Non-smoking and lower BMI are associated with asymptomatic reflux esophagitis. Most asymptomatic subjects with erosive esophagitis remained stable and exhibited unchanged endoscopic findings.

Keywords: Gastroesophageal reflux disease, esophagitis, natural course, endoscopy

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic and recurrent disease. It is common in Western countries, with 20% of the Western population experiencing typical reflux symptoms, such as heartburn, more than once a week (1,2). As the incidence of GERD is increasing, asymptomatic erosive esophagitis (EE) is thought to be increasing as well. Several studies have examined the prevalence of asymptomatic EE. A population-based study in Sweden found that 37% of patients with erosive esophagitis had no symptoms (3). In Korea, 42%-45% of affected patients in a healthy screen were asymptomatic (4,5), since patients were diagnosed as EE by chance for health examinations. Japanese patients with EE appear to be less likely to report clinical symptoms than Western patients (6). Smoking, body mass index (BMI), and gender are related to asymptomatic EE (7,8).

The natural history of GERD is still debated; typically, GERD has been approached as a disease on a continuous spectrum, emphasizing the potential progress over time of patients along the spectrum (9). In contrast to this view, some authors have proposed that patients respond in various ways to a reflux episode and develop one of 3 distinct phenotypic presentations: non-erosive reflux disease, erosive reflux disease, and Barrett's esophagus (10). It is important to know the natural history of erosive esophagitis, because a recent study showed that EE is an independent risk factor for Barrett's esophagus (11). However, Barrett's esophagus may occur in patients without typical reflux symptoms (12). Due to the lack of studies regarding the natural history of asymptomatic EE, there is no consensus on how to treat subjects with asymptomatic EE as to whether medical intervention is required. We investigated the

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risk factors related to asymptomatic EE and the natural history of both endoscopic findings and reflux-related symptoms in subjects with asymptomatic EE.

MATERIALS AND METHODS

Subjects

The present study was based on a self-reported questionnaire about reflux-related symptoms, medical history, and social habit and a biennial medical evaluation through the National Health Insurance Corporation that provides upper endoscopy. Of the subjects who underwent endoscopy in the health promotion center of St. Vincent Hospital, Catholic Medical Center, Korea, between January 2004 and December 2009, those who had follow-up endoscopy were included for the analysis. Chart reviews were conducted retrospectively on those subjects. We excluded subjects with peptic ulcer disease; stomach cancer; a history of gastrointestinal surgery; and other systemic disease, such as diabetes; or those having taken the following medications: proton pump inhibitor, histamine-2 receptor antagonists, sucralfate, anticholinergics, or other gastrointestinal (GI) medications and nonsteroidal anti-inflammatory drugs. Subjects with an ulcer scar on endoscopic findings were included. The study was reviewed and approved by the hospital's institutional review board.

Method

We reviewed questionnaire regarding reflux symptoms and medical records, including age, sex, body mass index, smoking, and alcohol use. The questionnaire is comprised of 7 items, including 9 questions on GERD symptoms (heartburn, acid regurgitation, dysphagia, globus sensation in the throat, hoarseness, cough, and chest pain). The subjects was asked to indicate the frequency of their symptoms as 0) none, 1) less than once per month, 2) about once per month, 3) about once per week, 4) twice per week, and 5) daily. Subjects who experienced heartburn or acid regurgitation one or more times in a week during the last 3 months were defined as exhibiting typical symptoms; subjects who experienced dysphagia, globus sensation in the throat, hoarseness, cough, and chest pain once or more in a week during the last 3 months were defined as having extraesophageal reflux symptoms. Asymptomatic EE is defined as the presence of esophageal mucosal injury that is typical of GERD during upper gastrointestinal endoscopy in individuals who lack typical or atypical extraesophageal manifestations of GERD (13). EE was defined based on endoscopic findings according to the Los Angeles (LA) classification (14). Minimal changes were not included as EE. Two endoscopic specialists reviewed all gastroduodenoscopy pictures independently. We divided the symptomatic group from the asymptomatic group, according to the presence of reflux symptoms at the diagnosis of EE. We compared clinical characteristics depending on the presence of reflux-related symptoms through medical chart review and questionnaire at the time of endoscopic diagnosis.

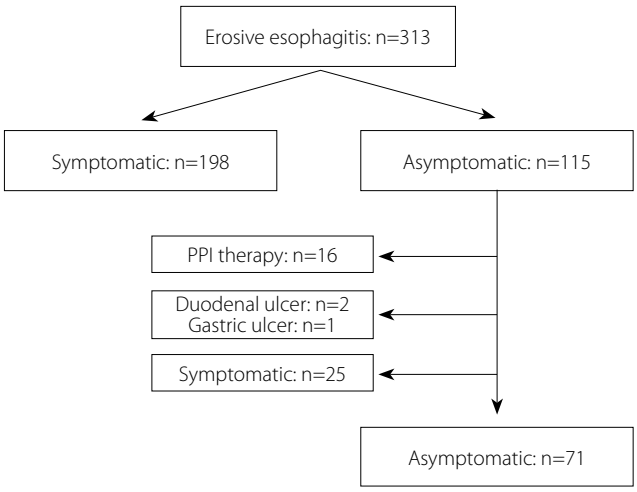

Figure 1. Summary of disease course in 313 patients with erosive esophagitis.

Statistical analysis

We used the Pearson chi-squared test to determine whether observed differences in proportions of symptoms between study groups were statistically significant. Differences in continuous data were analyzed by student's t-test. Factors that provoked symptoms in subjects with asymptomatic EE were measured by multivariate analysis using stepwise proportional hazard analysis. Symptom-free survival rates were estimated using the Kaplan-Meier method. P values less than 0.05 were defined as statistically significant. All statistical analyses were performed using SAS Staticstics software (SAS system for Windows, version 9.2; SAS Institute, Cary, North Carolina, USA).

RESULTS

We recruited 2273 subjects who had follow-up endoscopy between January 2004 and December 2009 in the health promotion center of St. Vincent Hospital. Among them, 343 (15% of 2273 subjects) subjects with erosive esophagitis were enrolled. Out of these, 30 subjects were excluded, because they had a history of a gastrointestinal surgery, a concomitant peptic ulcer disease, or a systemic disease, such as diabetes. There were 313 subjects diagnosed with EE. Most patients had mild esophagitis of LA grade A or B; 198 subjects (63.3%) had classic or extraesophageal symptoms, while 115 subjects (36.7%) had no symptoms (Figure 1). Most of the 198 symptomatic subjects had extraesophageal symptoms, such as chest pain, cough, and globus, while 10% had classic reflux symptoms, such as heartburn or acid regurgitation. Subjects with asymptomatic EE had lower body weight and body mass indices (BMIs) than subjects who had EE with symptoms. Subjects who were current smokers and who had lower body mass indices were more likely to have EE without symptoms compared to subjects with EE and symptoms (Table 1). A multiple logistic regression analysis revealed that those with a BMI less than 24 kg/m^2 and non-smokers had significant risk factors for asymptomatic EE (Table 2).

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Table 1. Characteristics of symptomatic and asymptomatic groups

	Symptomatic group (n=198)	Asymptomatic group (n=115)	p value
Age (years)	46.9±9.2	45.7±9.6	0.269
Sex (male/female), n (%)	174 (87.9) / 24 (12.1)	93 (80.9) / 22 (19.1)	0.091
BMI (kg/m^2)	25.3±2.5	24.5±2.5	0.015
Smoking (Y/N), n (%)	89 (44.9) / 109 (55.1)	30 (26.1) / 85 (73.9)	0.001
Alcohol (Y/N), n (%)	156 (78.8) / 42 (21.2)	83 (72.2) / 32 (27.8)	0.184
LA-A/LA-B, n (%)	163 (82.3) / 35 (17.7)	103 (89.6) / 12 (10.4)	0.084
Hernia (Y/N), n (%)	48 (24.2) / 150 (75.8)	23 (20.0) / 92 (80.0)	0.388

BMI: body mass index; LA: Los Angeles classification of esophagitis

Table 2. Independent factors associated with asymptomatic esophagitis identified on multivariate analysis

	Estimated value	Standard error	Odds ratio	95% CI	p value
BMI (>24 kg/m^2/≤24 kg/m^2)	0.433	0.217	1.54	1.01-2.36	0.046
Smoking (Yes/No)	0.857	0.259	2.36	1.41-3.91	0.001
LA classification (LA-A/LA-B)	0.654	0.366	1.92	0.93-3.94	0.074

CI: confidence interval; BMI: body mass index; LA: Los Angeles classification of esophagitis

Nineteen out of 115 subjects who had asymptomatic EE were excluded. Of these, 16 had taken medications, such as acid reducers, NSAIDs, and aspirin, during the 3 months before endoscopic follow-up. Three subjects had peptic ulcer on follow-up endoscopy (Figure 1). Ninety-six subjects with asymptomatic esophagitis were followed up. In terms of symptoms, 25 subjects (21.7%) experienced symptoms (9 with classic and 16 with extraesophageal symptoms), while 71 subjects (78.3%) had no symptoms. Endoscopy was followed up for a mean interval of 33.5 months (range, 11-69). The frequency of endoscopy was 2.6 examinations (range: 2-5). Endoscopic characteristics remained unchanged in 82 subjects (85%) and had reverted back to regression in 12 subjects. Two subjects progressed to grade B disease from grade A.

We used Cox's proportional hazard regression model to investigate which factors significantly correlated with occurrence of reflux symptoms and found that age was the most important factor. Kaplan-Meier symptom-free survival rates depending on age in 96 patients with asymptomatic erosive esophagitis revealed that subjects younger than 40 years were more likely to have symptoms without undergoing medical treatment; this was statistically significant (Figure 2).

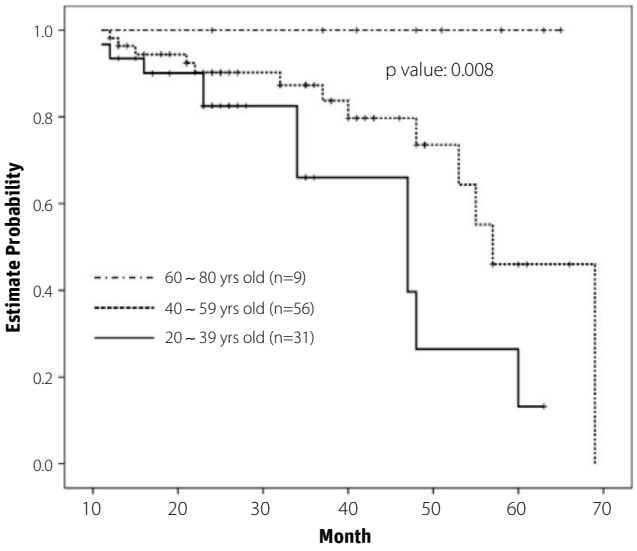

Figure 2. Kaplan-Meier symptom-free survival rates for 96 patients with asymptomatic erosive esophagitis depending on age.

DISCUSSION

We demonstrated that non-smoking and lower BMI are associated with asymptomatic EE. Male sex, old age (>65 years old), hiatal hernia, smoking, alcohol, Caucasian race, and obesity are independent risk factors associated with asymptomatic esophagitis (8,15-17). Atrophy, *Helicobacter pylori* infection, and peptic ulcer are not considered to be risk factors for provoking asymptomatic EE, while there are varying reports of association between BMI and asymptomatic EE (7,8,18).

Our findings differ from the results of previous studies with regard to smoking. These studies suggested that cigarette smoking was associated with isolated and subtle cognitive difficulties among very healthy individuals and that smoking was an independent risk factor of silent RE (19). This was based on the fact that the anti-nociceptive effect of smoking appeared to be mediated by nicotinic and mu-opioid receptors (20,21). However, being a non-smoker was associated with asymptomatic EE in our study. The difference could due to our inclusion criteria. We defined asymptomatic subjects as subjects who lacked both typical and atypical extra-esophageal manifestations, such that many smokers were included in a group having reflux-related symptoms. BMI effects varied according to ethnicity. Lower BMI was related to asymptomatic erosive esophagitis in this study, consistent with previous work (7). A prospective study will be needed to clarify this issue.

Gastroesophageal reflux symptoms, which are either typical or atypical, were reported by 63.3% of patients with endoscopy-proven reflux esophagitis in our study. Only 10% of symptomatic patients had typical weekly symptoms; these subjects had a mild form of reflux esophagitis of LA grade A or B. In previous studies, the prevalence of endoscopy-proven reflux esophagitis was 11.8%-27.4%, and 37% of EE had typical symptoms (3,15,22-27). In Japan, the prevalence of EE in symptomatic patients was 10.6%-13.8% (15,27) and was 7.1%-7.8% in subjects who had undergone a medical checkup (27,28). The prevalence of EE in Chinese and Taiwanese populations was 3.6%-12%, with 35%-50% not having typical reflux symptoms and 87% with mild reflux esophagitis of LA grade A or B (16-18,29). Differences in prevalence among these studies may be due to whether extraesophageal symptoms were included or not. We defined subjects with extraesophageal symptoms as symptomatic, because extraesophageal symptoms are associated with GERD (30).

In this study, we demonstrated that most asymptomatic subjects with EE remained stable and exhibited unchanged endoscopic findings. These results correspond well with those of other studies. In previous studies, the progression rate from mild to severe is around 10% (6%-12.5%), although most studies were retrospective (31-37). In a prospective multicenter open cohort study, most GERD patients remained stable or improved over a 5-year observation period under current routine clinical care (38). Among those subjects, 10%-81% had unchanged symptoms and 19%-84% had reverted to normal or regressed. In a Japanese study, 105 patients with LA grade A or B esophagitis (A, 57; B, 48) on initial endoscopy performed after 4 weeks without acid suppression were followed up with annual endoscopy for a mean duration of 5.5 years (35). The risk factors that were more highly associated with progression were female gender, older age, severity of symptoms at diagnosis, presence of hiatal hernia, and endoscopic atrophy of the stomach. In the present study, younger subjects tended to have symptoms during the follow-up period, since older patients are thought to have a higher pain threshold (39). The limitations of our study are the retrospective manner and small sample size. Because of data showing that 25% of cases of Barrett's esophagus and 40% of esophageal adenocarcinomas occur in patients without, or with only minimal, prior reflux symptoms, we should carefully follow up the asymptomatic EE patients (12,40).

The strength of this study is that we investigated the natural history of silent esophagitis. Because our hospital is not a tertiary center, the study may represent esophagitis in the general population, even though the subjects were visitors at a healthcare center. However, this was a retrospective study. Another limitation is the small sample size of asymptomatic EE.

In conclusion, non-smoking and lower BMI are factors associated with asymptomatic reflux esophagitis. Most asymptomatic subjects remained stable or were unchanged on endoscopy findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the institutional ethics committee.

Informed Consent: N/A.

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