

Histopathological features of the gastroesophageal junction: an Eastern view

Ahrong Kim¹, Nari Shin¹, Hyung-Jeong Lee¹, Hong-Jae Jo², Joo-Yeon Kim³, Young-Keum Kim¹, Do Youn Park¹, Won-Young Park¹, Hoseok I⁴ and Gwang Ha Kim⁵

Departments of ¹Pathology, ²Surgery, ⁴Thoracic Surgery, ⁵Internal Medicine, Pusan National University Hospital and Pusan National University School of Medicine, and BioMedical Research Institute, Pusan National University Hospital and ³Department of Pathology, Haeundae Paik Hospital, University of Inje College of Medicine, Busan, Republic of Korea

Summary. The definition and features of the gastroesophageal junction (GEJ) and the histopathologic features of the cardiac mucosa remain controversial. Most reports originate from western countries, which have different prevalence of GEJ adenocarcinoma and gastroesophageal reflux disease (GERD) compared to eastern countries. Therefore, we investigated GEJ anatomic and histopathologic features by histological mapping in 30 esophagogastrectomy specimens of middle and lower esophageal squamous cell carcinoma. We measured the lengths of the cardiac mucosa, oxyntocardiac mucosa, and esophageal cardiac-type glands. We assessed the presence of intestinal metaplasia, pancreatic acinar cells, Brunner's-like glands, and submucosal esophageal gland beneath cardiac mucosa and the relationship of these features with age and the circumferential location of cardiac mucosa. The lengths of cardiac mucosa and esophageal cardiac-type glands significantly increased with age (<63 years, $2767.86 \pm 734.95 \mu\text{m}$ vs. ≥ 63 years, $5453.12 \pm 839.52 \mu\text{m}$, $P=0.025$ and <63 years, $1151.78 \pm 452.81 \mu\text{m}$ vs. ≥ 63 years, $2273.44 \pm 321.58 \mu\text{m}$, $P=0.049$, respectively) and the presence of circumferential cardiac mucosa (+, $5731.25 \pm 721.57 \mu\text{m}$ vs. -, $2625.00 \pm 356.00 \mu\text{m}$, $P=0.007$; +, $2425.00 \pm 326.13 \mu\text{m}$ vs. -, $400.00 \pm 204.80 \mu\text{m}$, $P<0.0001$ respectively). The presence of intestinal metaplasia and irregular GEJ increased with age and the circumferential location of

cardiac mucosa. The presence of esophageal submucosal glands beneath the cardiac mucosa, pancreatic acinar cells, and Brunner-like glands were seen in 8/30 (26.7%), 15/30 (50%), and 14/30 (46.7%) cases, respectively. These data indirectly suggest that cardiac mucosa originated from the distal esophagus and that the presence of cardiac mucosa may indicate GERD, in accordance with data from Western countries.

Key words: Gastroesophageal junction, Cardiac mucosa, Intestinal metaplasia, Esophageal cardiac-type glands

Introduction

The prevalence of gastroesophageal reflux disease (GERD) and gastroesophageal junction (GEJ) adenocarcinoma in Asia are lower than that in Western countries, but recent data suggested that the prevalence of GERD and GEJ adenocarcinoma are rising in Asia (Kusano et al., 2008; Park et al., 2009; Cho et al., 2010). To understand the pathogenesis of GERD, Barrett's esophagus (BE), and GEJ adenocarcinoma, the exact definition and anatomical features of the GEJ and cardiac mucosa are important to clarify. However, the exact definition and anatomic features of the GEJ and cardiac mucosa have been a controversial issue of debate. Generally, the following anatomical criteria have been used to define the GEJ: (1) incisura from the cystic stomach to the esophageal canal, (2) end of the lower sphincter muscle, or (3) distal end of the submucosal esophageal glands (Bombeck et al., 1966). However,

Offprint requests to: Do Youn Park, MD, PhD; Department of Pathology, Pusan National University Hospital and Pusan National University School of Medicine, 1-10 Ami-Dong, Seo-Gu, Busan 602-739, Republic of Korea. e-mail: pdy220@pusan.ac.kr

these criteria are difficult to apply in clinical practice such as during endoscopic procedures because the aforementioned features can only be identified after surgical resection. Endoscopically, the GEJ can be identified at the squamous-columnar junction, terminal site of the gastric fold, or terminal portion of the palisading vessels in the lower esophagus (Sharma et al., 2006). However, the definition of the location of the GEJ differs and is debated between Eastern and Western countries (Takubo et al., 2009).

Cardiac mucosa is generally accepted as the normal stomach mucosa, which is present from birth and composed of gastric-type surface epithelium and glands, distinct from gastric oxyntic mucosa. Recently, three reports suggested that the cardiac mucosa is actually the esophagus rather than the stomach, and the presence of cardiac mucosa itself indicates the presence of reflux disease (Chandrasoma et al., 2000a, 2010; Chandrasoma, 2005). However, these data were adapted mostly from Western populations with high incidences of GERD and GEJ adenocarcinoma, especially BE adenocarcinoma.

Therefore, the anatomical features of the GEJ may differ between eastern and western countries, and this would support a difference in the prevalences of GERD, BE, and/or BE adenocarcinoma. To this end, we investigated the histopathological features of the GEJ in a Korean population to attempt to explain the differences in the prevalences of GERD and BE between eastern and western countries.

Materials and methods

A cohort of 30 esophageal cancer patients (mean age, 63.4 years; range 48-77 years) who underwent an esophagogastrectomy with a lymph node dissection at Pusan National University Hospital in 2011 and 2012 were enrolled in this study. Patients were selected if they had the following: (1) esophageal squamous cell carcinoma without affecting the GEJ, (2) grossly and microscopically visible gastric oxyntic mucosa at the gastric resection margin, and (3) no grossly visible evidence of BE. In addition, serial mapping of the GEJ was performed (Fig. 1). First, the specimen was opened longitudinally, pinned on a corkboard, and then fixed overnight in 10% buffered formalin. Next, the GEJ was sectioned longitudinally at a thickness of 5 mm, embedded in paraffin, and stained with hematoxylin and eosin. *Helicobacter pylori* infection was identified in 3 patients among 12 who underwent gastroduo-denoscopic biopsy in the gastric antrum/body prior to surgery. The biospecimens for this study were provided in part by the Pusan National University Hospital, a member of the National Biobank of Korea, which is supported by the Ministry of Health, Welfare, and Family Affairs. All samples derived from the National Biobank of Korea were obtained with informed consent under institutional review board-approved protocols.

For the evaluation of the microscopic features of the GEJ, the type of epithelium was defined as (1) squamous

epithelium, (2) oxyntic mucosa composed entirely of parietal and chief cells without mucous cells below the foveolar region, (3) cardiac mucosa composed entirely of mucous cells without any parietal cells, (4) oxyntocardiac mucosa, which contains a mixture of mucous cells and parietal cells, (5) esophageal cardiac-type glands composed of mucous cells located in the lamina propria under squamous epithelium, or (6) columnar-lined esophagus (BE) (Chandrasoma et al., 2000b; Nakanishi et al., 2007). The length of each different type of epithelium was measured with an ocular micrometer (Fig. 1). Independent review and selection of slide for measurement of each epithelium was first performed by two of the authors (Drs Kim and Shin). Consensus measurement of each epithelium was performed at a multi-head microscope equipped with ocular micrometer by three pathologists (Drs Kim, Shin and Park) together. We use same ocular micrometer in each ocular lens with micrometer (WHN 10X-H/22 with micrometer, Olympus, Japan). In addition, the presence of a circumferential cardia (cardiac mucosa located in the entire circumference of the GEJ) was evaluated. The presence of pancreatic acinar cells, Brunner's type submucosal glands, multilayered epithelium and esophageal submucosal glands beneath the cardia were also evaluated (Fig. 2). Pancreatic acinar cells is the occurrence of small clusters or lobules of epithelial cells similar to pancreatic acinar cells in cardiac mucosa as previously described (Schneider et al., 2013). Brunner's type submucosal glands are tubuloalveolar submucosal glands composed of lobules of mucinous cells similar to Brunner's gland of the duodenum. Esophageal submucosal glands are lobular submucosal glands composed of various mixed seromucinous components. Last, the presence and severity of intestinal metaplasia in the background GEJ mucosa was evaluated based on updated Sydney system for evaluation of gastritis (Dixon et al., 1996). To perform a statistical analysis, we grouped the patients into two categories: patients under 63 years and patients aged 63 years and older. The data were analyzed for differences between groups by Student's t test, Fischer's exact tests, or the chi-squared tests. $P < 0.05$ was considered statistically significant. Statistical calculations were performed with SPSS version 10.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The mean lengths of the cardiac mucosa, oxyntocardiac mucosa, esophageal cardiac-type glands, and columnar-lined esophagus were $4200 \mu\text{m}$, $2083 \mu\text{m}$, $1750 \mu\text{m}$, and $550 \mu\text{m}$, respectively. Table 1 summarizes the relationship between age and the length of the GEJ epithelium. The length of the cardiac mucosa and esophageal cardiac type glands were significantly higher in patients aged 63 years and older (<63 years, $2767.86 \pm 734.95 \mu\text{m}$ vs. ≥ 63 years, $5453.12 \pm 839.52 \mu\text{m}$, $P = 0.025$ and <63 years, $1151.78 \pm 452.81 \mu\text{m}$ vs. ≥ 63

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years, $2273.44 \pm 321.58 \mu\text{m}$, $P=0.049$, respectively). Table 2 shows the relationship between the pathologic features of the GEJ and the two age groups. Among these pathologic features, the presence of severe intestinal metaplasia (moderate, marked) ($P=0.003$) was also increased in the older age group (Table 2). In addition, cardiac mucosa was present in all cases and circumferentially in 20 (66.7%) cases, and a patchy distribution was found in 10 (33.3%) cases. These data indicate that 33.3% of cases showed focal areas of direct continuity of the gastric fundic mucosa with the esophageal squamous epithelium (Fig. 1).

Table 3 describes the relationship between the presence of circumferential cardiac mucosa and the length of the GEJ mucosa. The mean length of the

cardiac mucosa and esophageal cardiac-type glands was significantly higher in cases with circumferential cardia than that of cases without circumferential cardia

Table 1. Relationship between age and length of the gastroesophageal junction mucosa in 30 patients who underwent esophagectomy for squamous cell carcinoma.

	Age (years)		P value
	<63	≥63	
Cardiac mucosa	2767.86±734.95	5453.12±839.52	0.025
Oxyntocardiac mucosa	1642.85±229.54	2468.75±527.81	0.183
Esophageal cardia gland	1151.78±452.81	2273.44±321.58	0.049
Columnar-lined esophagus	625.00±250.68	484.37±159.29	0.631

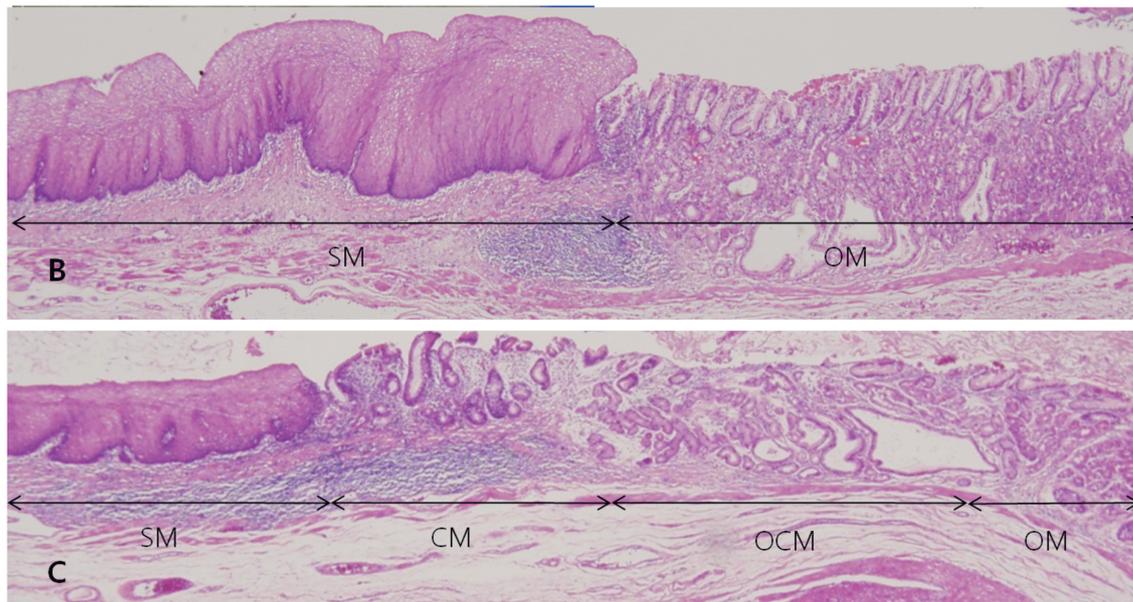
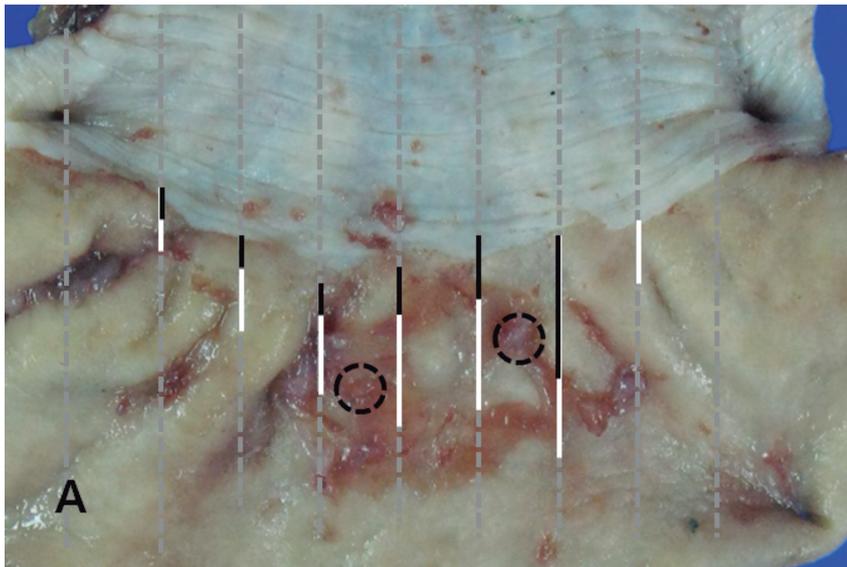


Fig. 1. Serial mapping of the gastroesophageal junction (GEJ). **A.** Representative serial sections of the GEJ (black line, cardiac mucosa; white line, oxyntocardiac mucosa; black circle, sites of esophageal submucosal glands beneath the gastric cardiac mucosa) showed non-circumferential location of the cardiac mucosa. **B.** GEJ mucosa showed direct continuity of the gastric oxyntic mucosa (OM) and esophageal squamous mucosa (SM). **C.** Cardiac mucosa with intestinal metaplasia is present between the SM and oxyntocardiac mucosa (OCM). Hematoxylin & eosin stain). B, C, $\times 20$

(5731.25±721.57 vs. 2625.00±356.00 μm , $P=0.007$; 2425.00±326.13 μm vs. 400.00±204.80 μm , $P<0.0001$).

The relationship between circumferential cardia and the histopathological features of the GEJ are summarized in Table 4. The presence of severe intestinal metaplasia, and increased age were significantly associated with circumferential cardiac mucosa ($P<0.0001$, $P<0.0001$ and $P=0.019$, respectively). Also, presence of multilayered epithelium was related with circumferential cardiac mucosa ($p=0.056$). Interestingly, esophageal-type submucosal glands beneath the cardiac mucosa were seen in 8 cases (26.7%), demonstrating the esophageal origin of cardiac mucosa (Fig. 2). In addition, pancreatic acinar cells and Brunner's type glands were seen in 15 cases (50.0%) and 14 cases (46.7%), respectively, and were not associated with increased age or circumferential cardiac mucosa (Fig. 2).

Discussion

In the present study, we demonstrated that the length of the cardiac mucosa and esophageal cardiac-type glands was increased in the older age group, and severe intestinal metaplasia, and circumferential location of the cardiac mucosa were also increased in the older cases. These data indirectly suggest that cardiac mucosa may have originated from the distal esophagus. Moreover, the presence of cardiac mucosa in our population suggests that the histopathologic features of GEJ adenocarcinoma and GERD are similar to those observed in western countries. Western gastroenterologists can define the GEJ as the proximal limit of the gastric rugal folds; however, Japanese gastroenterologists have defined the GEJ as the terminal portion of the palisading vessels in

Table 2. Relationship between age and pathologic features of the GEJ in 30 patients who underwent esophagectomy for squamous cell carcinoma.

	Case No.	Age (years)		P value
		<63	≥63	
Intestinal metaplasia				
None, mild	15	11	4	0.003
Moderate, Marked	15	3	12	
Pancreatic acinar cells				
Absent	15	7	8	1.000
Present	15	7	8	
Brunner's gland-like gland				
Absent	16	9	7	0.299
Present	14	5	9	
Esophageal submucosal gland				
Absent	22	9	13	0.295
Present	8	5	3	
Multilayered epithelium				
Absent	13	8	5	0.153
Present	17	6	11	

GEJ, gastroesophageal junction

the lower esophagus from endoscopic findings (Takubo et al., 2009). Histologically, the GEJ is defined as the distal limit of the squamous epithelium that can be ideally matched with the squamo-columnar junction. However, differences between the GEJ and the squamo-columnar junction have been found in an autopsy study using western data (Bombeck et al., 1966). In Japan, Shimoda et al. (2004) reported that the GEJ and squamo-columnar junction were well matched in most Japanese individuals. In contrast to the above data, Chandrasoma et al. (2006) suggested that the GEJ should be defined as the proximal limit of the gastric oxyntic mucosa. In addition, the cardiac mucosa is not considered a normal structure and provides pathological evidence of esophageal injury from reflux (Chandrasoma et al., 2000b, 2010, 2011). Therefore, the definition of the GEJ is highly associated with the existence of cardiac

Table 3. Relationship between the circumferential gastric cardiac mucosa and length of the gastroesophageal junction mucosa in 30 patients who underwent esophagectomy for squamous cell carcinoma.

	Circumferential cardiac mucosa		P value
	Absent	Present	
Cardiac mucosa	2625.00±356.00	5731.25±721.57	0.007
Oxyntocardiac mucosa	1500.00±190.02	2375.00±438.86	0.182
Esophageal cardiac gland	400.00±204.80	2425.00±326.13	0.000
Columnar-lined esophagus	275.00±275.00	687.50±160.05	0.177

Table 4. Relationship between circumferential cardiac mucosa and histopathologic features of the GEJ in 30 patients who underwent esophagectomy for squamous cell carcinoma.

	Case No.	Circumferential cardiac mucosa		P value
		Absent	Present	
Age (years)				
<63	14	8	6	0.019
≥63	16	2	14	
Intestinal cardia metaplasia				
None, mild	15	10	5	0.000
Moderate, marked	15	0	15	
Pancreatic acinar cells				
Absent	15	4	11	0.439
Present	15	6	9	
Brunner's gland-like				
Absent	16	6	10	0.709
Present	14	4	10	
Esophageal submucosal gland				
Absent	22	5	17	0.078
Present	8	5	3	
Multilayered epithelium				
Absent	13	7	6	0.056
Present	17	3	14	

GEJ, gastroesophageal junction

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mucosa. De Hertogh et al. (2003) reported that cardiac mucosa is present from gestation (embryos, fetuses, and infants). Furthermore, Kilgore et al. (2000) reported that

cardiac mucosa was present in all cases of pediatric autopsy. However, Park et al. (2003) reported that no pure mucous cells (cardiac mucosa) were found in a fetal

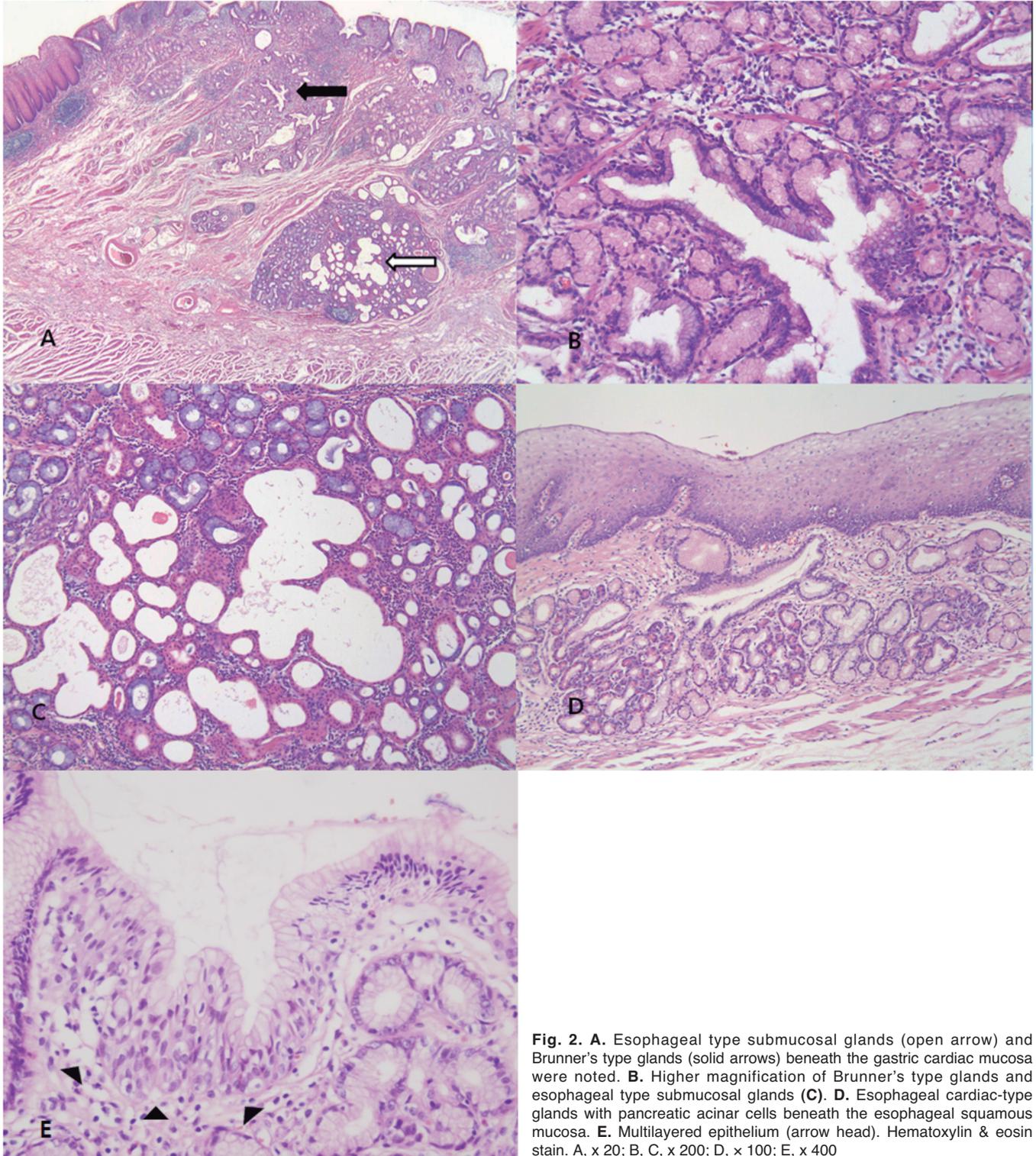


Fig. 2. A. Esophageal type submucosal glands (open arrow) and Brunner's type glands (solid arrows) beneath the gastric cardiac mucosa were noted. B. Higher magnification of Brunner's type glands and esophageal type submucosal glands (C). D. Esophageal cardiac-type glands with pancreatic acinar cells beneath the esophageal squamous mucosa. E. Multilayered epithelium (arrow head). Hematoxylin & eosin stain. A, x 20; B, C, x 200; D, x 100; E, x 400

and pediatric autopsy study on Koreans. Taken together, the GEJ can be defined endoscopically as the upper limit of the proximal gastric folds, and the cardiac mucosa may develop as a physiologic response to injury (El-Zimaity and Riddel, 2012).

In this study, cardiac mucosa was present circumferentially in 66.7% of cases. Thus, 33.3% of the cases showed direct continuity of gastric fundic mucosa and esophageal squamous mucosa. Furthermore, the presence of circumferential cardiac mucosa was significantly higher in older patients. In addition, esophageal type submucosal glands beneath the cardiac mucosa were present in 26.7% of cases. These features have reinforced hypotheses investigating the esophageal origin of the cardiac mucosa. In accordance with our data, Chandrasoma et al. (2000a) and Sarbia et al. (2002) reported that cardiac mucosa is circumferentially present only in subsets of the adult population (50% and 55.5%, respectively). Sarbia et al. (2002) reported that 25% (9/36) of cases had cardiac mucosa located over the submucosal esophageal glands, which is in accordance with our results. However, Stojic et al. (2011) reported that cardiac mucosa was circumferentially present in all cases, and the length of the cardiac mucosa was not associated with age or presence of carditis. Therefore, our data reinforces the idea that cardiac mucosa is not a normal structure in Koreans, which is similar to western datasets. In the biopsy specimen it is difficult to identify esophageal submucosal glands. Therefore, there are several reports about the importance of multilayered epithelium and duct of esophageal glands in the biopsy specimen to help diagnosis of the esophageal origin of columnar-lined epithelium (Odze, 2005; El-Zimaity and Riddel, 2012). Recently, Langner et al reported that multilayered epithelium at GEJ is a marker of GERD, frequently identified within or adjacent to ducts of esophageal glands, associated with increasing age, obesity, hiatal hernia, endoscopic diagnosis of esophagitis and Barrett's esophagus (Langner et al, 2014). And our study showed that the presence of multilayered epithelium was associated with circumferential presence of cardiac mucosa, which is similar to Langner et al.

Interestingly, we identified cardiac-type glands in the esophageal wall in 76.7% of cases, and the length of the esophageal cardiac glands was increased in those aged ≥ 63 years and with circumferential cardiac mucosa. Nakanishi et al. (2007) found that 95% (125/131) of resected cases of middle and upper esophageal carcinoma had esophageal cardiac-type glands and suggested that esophageal cardiac-type glands may play an important role in the development of short segment BE. To our knowledge, in the western datasets, no direct demonstrations of esophageal cardiac-type glands are available in the literature. We presumed that a presence of esophageal cardiac-type glands represents evidence of injury to the GEJ.

For the histopathologic diagnosis of GERD and BE, Chandrasoma et al. (2010) suggested that a squamo-

oxyntic gap was equivalent to the columnar-lined esophagus and is a specific and sensitive indicator of reflux and GERD. They reported that the presence of intestinal metaplasia within the squamo-oxyntic gap is defined as BE (Chandrasoma et al., 2010). Our datasets revealed that 26 of 30 cases showed various intestinal metaplasia in the cardiac mucosa (none = 4, mild = 11, moderate = 13, marked = 2). Therefore, a considerable number of cases in our datasets (26/30, 86.7%) belong to the ultrashort segment BE category. Generally, the prevalences of GERD and GEJ adenocarcinoma in Asia are relatively lower than that in western countries; however, recent data suggest that the prevalence is rising in Asia (Kusano et al., 2008; Cho et al., 2010). If Chandrasoma's (2010) criteria for diagnosing GERD and BE are correct, our data indicate that a considerable proportion of Asian patients have GERD and BE. These findings may explain the rising prevalence of GEJ cancer in Asia. Although there is a possibility that *Helicobacter pylori* infections impact on an extension of cardiac mucosa, our cohort size is too small to define a relationship between *Helicobacter pylori* infection and status of the GEJ mucosa. Recently, there have been several reports showing that obesity and increased intra-abdominal pressure are associated with cardiac mucosa lengthening (Robertson et al, 2013; Lee and McColl, 2014). Furthermore, Lee et al reported that partial hiatus hernia was associated with short segment reflux (Lee et al, 2013).

In conclusion, we demonstrated that the length of the cardiac mucosa was increased in those aged 63 years and older, but not circumferentially evident in all cases of GEJ in a Korean adult population. These data may suggest that cardiac mucosa originates from the distal esophagus, and the presence of cardiac mucosa may be evidence of GERD, similar to the findings from Western datasets. More nationwide and multi-institutional studies are needed to confirm these findings.

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