Histology of Gastroesophageal Junction in Fetal and Pediatric Autopsy

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Context.—There is much debate over whether the gastric cardia exists from birth as a normal structure or is a metaplastic structure that develops as the result of gastroesophageal reflux disease. This question has become a matter of concern since the incidence of adenocarcinoma at the gastroesophageal junction has been increasing rapidly in the Western world for more than 2 decades. Various groups of investigators have tried to clarify this matter by examining the histology of the gastroesophageal junction in autopsy cases, and there have been striking discrepancies in their findings. In one group, it was observed that cardiac mucosa was present in all pediatric autopsies. On the contrary, another group concluded that pure cardiac mucosa was absent in 56% of their autopsy cases.

Objective.—Without regard to the definition of the cardiac mucosa, we focused on the distance between the squamocolumnar junction and the most proximal parietal cells to elucidate the histologic features of the gastroesophageal junction on the gastric side.

During the past 2 decades, several authors have reported that the incidence of adenocarcinoma of the gastroesophageal junction (GEJ) is increasing rapidly in the Western world, while distal gastric adenocarcinoma arising in the antral region is occurring less frequently.1-3 These junctional cancers appear to arise from the foci of intestinal metaplasia that develop either in the distal esophagus or in the proximal stomach.4,5 One of the major problems in evaluating cancers in this area lies in the definition of the gastric cardia as an established anatomic entity. It is not even clear whether the definitions are based on gross observation or microscopy. In one well-known textbook of gastrointestinal pathology, the cardia is defined grossly as “the narrow, approximately 1 cm long portion of the stomach immediately distal to the GEJ.”6 However, in another reference, it is defined histologically as follows: “the cardia is the zone . . . where the gastric glands are mucus secreting.”7

Besides the problem of defining the gastric cardia, there also have been conflicting views regarding the origin and histologic nature of this region. Separate groups of authors have reported strikingly different interpretations of the histology of the GEJ. In a study conducted by the Cleveland Clinic group, investigators observed that cardiac mucosa was present in all autopsy specimens, always on the gastric side of the GEJ.8 On the contrary, a group from the University of Southern California argued that pure cardiac mucosa was completely absent in 56% of their autopsy cases.9 This group also concluded that the presence and extent of this cardiac mucosa were mostly related to gastroesophageal reflux disease.8,9 The fact that there is no universally accepted definition of the cardiac mucosa may have contributed to this discrepancy. The Cleveland Clinic group defined the cardiac mucosa as “the mucosa composed of unequivocal PAS-positive mucous gland arranged in lobular configuration,”8 whereas the University of Southern California group defined it as “the mucosa composed of glands with mucous cells only.”9

Recently, another group of authors tried to describe this area in a different way. They defined the transitional zone as “the mucosa immediately distal to the SCJ—that is, between the squamous esophageal mucosa and the oxyntic mucosa (fundic gland).”10 They concluded that a transitional zone with the microscopic characteristics of cardiac mucosa was universally present at the squamocolumnar junction (SCJ) and the microscopic characteristics of this zone varied with age.11

The goal of this study was to evaluate the histology of GEJ in the early developmental stage by measuring the distance from the SCJ to the most proximal parietal cells...
and identifying the transitional zone. To do so, we evaluated the GEJ by mapping the distal esophagus and proximal stomach obtained from the autopsies of fetuses, infants, and children.

MATERIALS AND METHODS

Forty-five fetal (prenatal) and pediatric (postnatal) autopsies from Seoul National University Children's Hospital were evaluated both retrospectively and prospectively. The retrospective cases consisted of 17 cases, which were mostly postnatal autopsies performed in 1998 and 1999. The prospective cases consisted of 28 cases, all performed in 2001. Autopsy cases performed more than 48 hours postmortem were excluded. Cases with congenital malformations that could involve the gastrointestinal tract were also excluded from this study.

About 1 cm of the distal esophagus and the whole stomach was resected, opened along the greater curvature, and fixed in 10% buffered formalin for histologic evaluation. The distal half of the stomach was trimmed away, and 2 different colors of ink were applied on the serosal surface and proximal end of the specimen separately for mapping. The specimen was sectioned longitudinally in parallel in widths of 2 mm, and 10 to 16 sections were prepared for each case (Figure 1, A). Sections were routinely processed and embedded in paraffin. Ten 5-μm-thick serial sections were obtained from each paraffin block, and the sections were stained with either hematoxylin-eosin (Figure 1, B) or periodic acid–Schiff.

All microscopic slides were evaluated by measuring the distance from the SCJ to the most proximal parietal cell identified. The presence or absence of inflammation in this area was also noted. An additional attempt was made to evaluate the extent of the transitional zone into 3 groups (no glands, mixed, and mucous) and with parietal cells scattered at the bottom of foveolar pits or in mucous glands. Twenty-three cases were evaluated eventually (Table); 22 cases were excluded because of autolyzed or denuded gastric epithelium.

RESULTS

Autopsy Cases Examined

The fetuses ranged from 18 to 34 weeks' gestational age, and the postnatal autopsy cases ranged in age from 9 days to 15 years. Thirteen cases involved males and 10 involved females. The majority of fetal autopsies were therapeutic terminations for various fetal or maternal conditions, and the others were fetuses that were spontaneously aborted due to preterm labor. None of the postnatal cases had a history of gastroesophageal reflux disease.

Extent of the Transitional Zone

The transitional zone did not exist in 5 cases (22%) (2 [25%] of 8 postnatal cases and 3 [20%] of 15 fetal cases). These cases showed direct transition from the squamous epithelium to the mucosa with fundic glands (Figure 2, A). In the remaining cases, the transitional zone measured less than 0.4 mm in greatest dimension (Figure 2, B), and the parietal cells were always identifiable at the transitional zone (Figure 3). The transitional zone in fetal stomach was usually composed of several pits of foveolar epithelium without glandular portions (Figure 2, B), whereas in the postnatal cases, especially in infants and children older than 4 months, the transitional zone contained glandular structures composed of both parietal cells and mucosal cells (Figure 3).

The extent of this region did not seem to have much correlation with gestational age. Although the average length of the transitional zone in fetal stomach (average, 226 μm) was slightly longer than that of the postnatal stomach (average, 167 μm), the difference was not statistically significant (P = .17, Student t test; Figure 5).

Direct Transition From Squamous Epithelium to Parietal Cells

Examination of the SCJ revealed that the parietal cells were consistently in direct transition from the esophageal squamous epithelium (Figure 4). Although there were cases in which the parietal cells were not identified directly adjacent to the squamous epithelium in one plane of section, serial sections of the same case always revealed parietal cells in direct contact with SCJ. None of the fetal cases showed inflammation in this region. Two cases (cases 20 and 21) showed inflammatory cell infiltration in the lamina propria, but this presence was probably due to the systemic infections in these patients, because none of the patients had a history of gastroesophageal reflux disease.

COMMENT

The gastric cardia has long been defined conceptually as the region of the stomach that joins the esophagus. Endoscopists have defined the GEJ somewhat arbitrarily, as the level of the most proximal extent of the gastric folds. Pathologists, on the other hand, often define the gastric cardia by its histologic features rather than by its gross anatomic appearance. Traditional teaching holds that the most proximal portion of the stomach normally is lined by a columnar epithelium (called cardiac or junctional-type epithelium) characterized by foveolae with subjacent mucous glands that are composed almost exclusively of mucus-secreting cells, and that are devoid of acid-secreting parietal cells. However, even pathologists are not consistent in their histologic criteria for cardiac epithelium. Some pathologists believe that the presence of any parietal cells in the gastric glands precludes a histologic diagnosis of cardiac epithelium, whereas others contend that cardiac epithelium can contain occasional parietal cells, provided that other morphologic and architectural features of the glands are typical of cardiac mucosa.

We observed that the transitional zone was present in 78% of our cases. Zhou et al subclassified the transitional zone into 3 groups (no glands, mixed, and mucous) and advocated that the transitional zone composed of pure mucous gland existed in both prenatal (6%) and postnatal (47%) groups. However, in the present study, the transitional zone always harbored some scattered parietal cells at the bottom of foveolar pits or in mucous glands. This finding is generally consistent with the results of Chandrasoma et al, who observed oxyntocardiac mucosa in 74% of their autopsy specimens.

The glandular portions of the well-formed fundic mucosa (mucosa composed entirely of fundic-type glands) gradually decreased toward the SCJ, especially early in the fetal period. Therefore, it was very difficult to define the transitional zone in the fetal period, but delineation of transitional zone from the fundic mucosa became easier as the age increased. We also observed that the transitional zone in the early developmental stage was usually composed of several pits of foveolar epithelium without any glandular portions and with parietal cells scattered at the bottom. In later development, this region contained glandular portions with mucous and parietal cells, which made it easier to discriminate it from the fundic-type mucosa. These findings imply that the lower portions of the
transitional zone with the parietal cells at the early developmental stage later turn into glandular structures. The average length of the transitional zone in the fetal autopsy group and that of the postnatal group did not show a statistical difference, even though the average length of the stomach increased. Although there were not enough cases accumulated, these cases support the idea that the transitional zone is a transient structure, not only structurally, but also chronologically.

In this study, regardless of the definition of the cardiac...
### Autopsy Cases Examined

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Autopsy No.</th>
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<th>Cause of Death†</th>
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<td>CA01-29</td>
<td>F/34 wk</td>
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</table>

**Prenatal Cases**

**Postnatal Cases**

* Age designated as weeks gestational age for prenatal cases.
† PPROM indicates preterm premature rupture of membrane; FDIU, fetal death in utero; IIOC, incompetent internal os of cervix; TAPVR, total anomalous pulmonary venous return; and TOF, tetralogy of Fallot.

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**Figure 5.** The extent of the transitional zone. There is no correlation between the length of the transitional zone and age. Asterisks indicate the cases in which fundic mucosa is in direct transition from the squamous epithelium. The cases are arranged in order as listed in the Table.

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mucosa, we focused on the distance from the SCJ to the most proximal parietal cells identified. We observed that the parietal cells were directly opposed to the squamous epithelium in all fetal and early pediatric autopsy specimens. This finding implies that the mucosa composed exclusively of mucus cells does not exist in early development and thus is not a normal developmental structure.

The results of our study indicate that the cardiac mucosa composed exclusively of mucous-secreting cells does not exist in the fetal and early postnatal period. However, it is undeniable that such an area exists in the adult population. In studies of populations without symptoms of gastroesophageal reflux, the cardiac mucosa was absent in 29% of patients at autopsy and in 26% of patients during endoscopy. When the cardiac mucosa was identified, its extent correlated strongly with the severity of reflux. From these findings, we believe that cardiac mucosa is an acquired and metaplastic structure, and the main cause for the histogenesis of this area is gastroesophageal reflux.

Our study demonstrates that the region from the SCJ to the mucosa with parietal cells is in direct transition in early developmental stomach. Cardiac mucosa composed exclusively of mucous-secreting cells is not a normal developmental structure.

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### References

3. Pera M, Cameron AJ, Trastek VF, Carpenter HA, Zinsmeister AR. Increasing...
incidence of adenocarcinoma of the esophagus and esophagogastric junction.


