Definition of Histopathologic Changes in Gastroesophageal Reflux Disease

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A series of 71 patients with multiple measured biopsies of the gastroesophageal junctional region permitting assessment of the presence and length of different glandular epithelial types is presented. All but nine of 53 patients in whom a 24-hour pH study was performed had abnormal reflux, suggesting that endoscopic recognition of an abnormal columnar mucosa at the gastroesophageal junction sufficient to precipitate multiple-level biopsies indicates a high probability of abnormal reflux. All patients had cardiac mucosa (CM) or oxyntocardiac mucosa (OCM). CM was present in 68 of 71 patients. The prevalence of intestinal metaplasia increased with increasing CM+OCM length, and was present in all 22 patients with a CM+OCM length >2 cm and in 20 of 49 patients with a CM+OCM length <2 cm. Patients with a CM+OCM length >2 cm had a markedly higher acid exposure than patients with a CM+OCM length <2 cm. The findings suggest that the presence of CM and OCM in the junctional region are predictive of abnormal acid exposure, and that increasing OCM+CM length correlates strongly with the amount of acid exposure. The histologic finding of CM and OCM represents a sensitive histologic criterion for gastroesophageal reflux rather than normal epithelia. These diagnostic criteria represent the first useful histologic definitions for assessing the presence and severity of reflux.

Key Words: Gastroesophageal reflux disease—Barrett’s esophagus—Cardiac mucosa—Carditis—Histopathology.


The occurrence of glandular mucosa in the lower esophagus has been recognized since the early 20th century.1,2,7,13,19,25 After some controversy about whether this was a tubular stomach secondary to a congenitally short esophagus,2,7 Barrett,3 in 1957, designated this as the “columnar lined esophagus,” which bears his name. During the next several years, evidence was produced that Barrett’s esophagus was an acquired condition resulting from gastroesophageal reflux disease, a concept that is now accepted universally.6,20

In 1976, Paull et al.22 described three types of glandular epithelium and established a histologic classification of Barrett’s esophagus into junctional, fundic, and specialized types (Table 1). When it was later recognized that Barrett’s adenocarcinoma arose only in the specialized columnar epithelium,11,23 the definition of Barrett’s esophagus was restricted to those cases that showed intestinal metaplasia.

The diagnosis of Barrett’s esophagus is problematic because of the existing belief that columnar epithelium distinct from gastric oxyntic mucosa is normally present in the junctional region. This mucosa, called junctional and cardiac, consists of gastric-type surface epithelium and glands composed entirely of mucous cells. The normal extent of this cardiac mucosa (CM) has never been defined. The most influential of the definitions of the extent of normal CM is that of Hayward,12 who asserted, without supporting data, that this mucosa normally lined the lower 2 cm of the tubular esophagus and extended into the proximal stomach.

Glandular mucosa in the lower esophagus is therefore considered abnormal only when it exceeds 2 cm. When >2 cm of glandular mucosa in the lower esophagus is shown to contain intestinal metaplasia, the diagnosis of long-segment Barrett’s esophagus is made. This is the only definition of Barrett’s esophagus that is accepted universally. The term “columnar lined esophagus of uncertain significance” has been suggested when there is no intestinal metaplasia in a glandular mucosa >2 cm.24

Intestinal metaplasia has also been shown to occur frequently in patients who have glandular mucosa that is within Hayward’s definition of normalcy.12 When this occurs in the lower 2 cm of the tubular esophagus, the term “short-segment Barrett’s esophagus” is used. When it occurs in the proximal stomach adjacent to the esoph-
ageal opening, the term “intestinal metaplasia of the gastric cardia” is used. The finding of glandular mucosa without intestinal metaplasia in the distal 2 cm of the tubular esophagus is currently regarded as normal.

These definitions are greatly dependent on endoscopic findings that make measurements from the gastroesophageal junction. It has been shown that endoscopic determination of the gastroesophageal junction is associated with considerable error when compared with manometry, compromising further the veracity of these definitions.

Growing epidemiologic evidence suggests that adenocarcinoma arising in the junctional region and gastric cardia are identical to Barrett’s adenocarcinoma of the lower esophagus. A recent study also found an association between reflux and all these types of carcinomas. The fact that proximal gastric cancer is associated with gastroesophageal reflux appears to confound all logic.

This study was undertaken to evaluate the relationship between the various histologic types of mucosae found in the junctional region and reflux, and to develop a hypothesis relating to the sequence of pathologic changes in reflux.

**MATERIALS AND METHODS**

Seventy-one patients presenting to the University of Southern California Foregut Surgery Service who had endoscopic biopsies that sampled a minimum of 4 cm of the gastroesophageal junctional region were selected. The biopsy levels were defined by distance from the incisor teeth. Each level had three or four biopsies. Sixty-four patients had an additional unmeasured retroflex biopsy around the tops of the gastric rugal folds. Sixty-four patients also had biopsies of the distal stomach including antrum and body, which was stained with Giemsa stain in addition to hematoxylin–eosin stain. These selection criteria were independent of symptoms or pH study results.

Patients with prior esophageal surgery, invasive adenocarcinoma, and *Helicobacter pylori* infection in the retroflex and junctional region biopsies were excluded. Patient selection and histopathologic study were blind to results of the pH monitoring study. Gastroesophageal reflux and *H. pylori* infection are recognized as possible causes of inflammation of CM. By excluding patients with *H. pylori* infection, this study permits a more restricted evaluation of the association between reflux and histologic changes in the junctional region.

All slides from these 71 patients were examined, and data regarding epithelial types and pathologic changes at each level were noted. The epithelial types found were defined after Paull et al. with modifications (Table 1) into the following five types:

1. Stratified squamous epithelium
2. Pure oxyntic mucosa (OM) in which the glands were straight and composed entirely of parietal cells without mucous cells below the foveolar region (Fig. 1).
3. Pure CM in which the glands were composed of mucous cells only, without parietal cells (Fig. 2). This is equivalent to the junctional epithelium of Paull et al. We prefer the term OCM because it is descriptive and because this epithelium differs from the epithelium that normally lines the gastric fundus, which is purely oxyntic.
4. Oxyntocardiac mucosa (OCM) in which the glands contained a mixture of mucous and parietal cells in varying numbers (Figs. 3 and 4). This is equivalent to the fundic epithelium of Paull et al. We prefer the term OCM because it is descriptive and because this epithelium differs from the epithelium that normally lines the gastric fundus, which is purely oxyntic.
5. Intestinal metaplastic mucosa (IM) characterized by the presence of definitive goblet cells in the surface epithelium, foveolar region, or glands (Fig. 5). This is equivalent to the specialized columnar epithelium of Paull et al.

The length of CM and OCM present was calculated by their presence at the measured biopsy levels. The CM+OCM length was deemed to be >2 cm when biopsies at a minimum of three levels ≥3 cm apart showed CM or OCM. The CM+OCM length was deemed to be ≤2 cm when biopsies showed CM or OCM in either two levels ≤2 cm apart or only in one level.

**TABLE 1. Criteria for classifying epithelial types at the gastroesophageal junctional region**

<table>
<thead>
<tr>
<th>Mucosal type</th>
<th>Paull et al. term</th>
<th>Normally seen in</th>
<th>Mucous cells*</th>
<th>Parietal cells*</th>
<th>Goblet cells*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td>Squamous</td>
<td>Esophagus and LES</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oxyntic</td>
<td>N/A</td>
<td>Stomach</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Junctional</td>
<td>?†</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oxyntocardiac</td>
<td>Fundic</td>
<td>?†</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Intestinal</td>
<td>Specialized</td>
<td>Abnormal</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

LES, lower esophageal sphincter; N/A, not applicable.
* Cell types present in the mucosal glands beneath the foveolar region.
† Cardiac and oxyntocardiac mucosae were reported as abnormal glandular epithelial types seen in Barrett’s esophagus by Paull et al. They are also regarded as normal epithelial types seen in the junctional region.
Ambulatory 24-hour pH monitoring was performed in 53 patients by a technique that has been reported previously. We used the percent time during the 24 hours in which the pH was less than 4 (pH value) to quantitate acid exposure of the lower esophagus. In studies of normal volunteers, the upper limit of normal of this pH value has been established as 4.5%.

The Ansari–Bradley rank test, Wilcoxon’s two-sample test, and the Kruskal–Wallis chi-square test were used in the comparison of variability and medians of pH values.

RESULTS

The most proximal level sampled contained squamous epithelium in all patients. The squamous epithelium showed intraepithelial eosinophils in 53 patients (75%). The distal gastric biopsies were negative for marked inflammation and H. pylori in 63 of 64 patients in whom a distal gastric biopsy was available.

All patients had CM or OCM in their junctional region. Pure CM was present in 68 of 71 patients, and was associated with IM in 42 patients. OCM was present in 46 of 71 patients and was found without CM in three patients.

Twenty-two patients had a CM+OCM length of >2 cm. The other 49 patients had CM and/or OCM at two

FIG. 1. Pure oxyntic mucosa from the gastric fundus showing a short foveolar pit and straight tubular glands comprised only of parietal and chief cells. No mucous cells are seen below the foveolar region.

FIG. 2. Cardiac mucosa showing an elongated foveolar region, mild inflammation, and slightly disorganized glands containing a mixture of mucous cells and parietal cells. Note the presence of marked inflammation in the lamina propria.

FIG. 3. Oxyntocardiac mucosa showing an elongated foveolar region, mild inflammation, and slightly disorganized glands containing a mixture of mucous cells and parietal cells.
measured levels 2 cm apart (n = 13), at two measured levels 1 cm apart (n = 2), at one measured level and in the retroflex biopsy (n = 17 cases), in the retroflex biopsy only (n = 8), and at one measured level only (n = 9). These 49 patients were categorized as having a CM+OCM length <2 cm.

All biopsies with CM showed histologic abnormalities indicative of inflammation including eosinophils, lymphocytes, and plasma cells (Figs. 2, 6, and 7). Neutrophils were rarely present in the absence of surface erosion. In addition, CM showed reactive changes that included foveolar elongation and serration, and smooth muscle proliferation in the lamina propria (Figs. 6 and 7).

IM was present in 42 of 71 patients and always occurred in CM (Fig. 5). There were no patients in whom IM occurred in OCM. IM was present in all 22 patients in whom the CM+OCM length was >2 cm and in 20 of 49 patients in whom the CM+OCM length was <2 cm. Thirteen of the patients with IM had dysplasia, eight low grade and five high grade.

Squamous-lined ducts were present in the lamina propria of CM or OCM in 10 patients (14%). Squamous-lined ducts are found normally only in the esophagus, and their presence indicates that CM and OCM lined the esophagus in these patients.

A 24-hour pH study was available in 53 patients. They had a median pH value (defined as percent time pH <4) of 10.4% with a range of 1.1% to 54.3% (Fig. 8). Only nine patients had a pH value in the normal range (upper limit of normal, 4.5%). This indicates that the selection criteria used for this study selected a group of patients with a high incidence of abnormal reflux. These 53 patients were classified into three groups: group A, 15 patients with CM+OCM >2 cm, and all were positive for IM; group B, 15 patients with CM+OCM <2 cm and positive for IM; and group C, 23 patients with CM+OCM <2 cm and negative for IM. The data and statistical analysis of the pH values of these groups is shown in Figure 8 and Tables 2 and 3. It is useful to recognize that there is no overlap in the interquartile range pH values between the patients with a CM+OCM length >2 cm (range, 16.1–41.1 cm; group A) and those with a CM+OCM length <2 cm (range, 5.2–12.1 cm; groups B and C; Table 2).
Highly significant differences (p < 0.001) were present between the following groups: Patients with CM+OCM >2 cm had higher pH values than those with CM+OCM <2 cm, and patients with IM had higher pH values than those without IM.

The three patients who had only OCM without CM had pH values of 1.1%, 1.7%, and 5.4% (Fig. 8). Of the 53 patients, nine had pH values in the normal (<4.5%) range. Eight of these patients had the criteria of reflux esophagitis in the squamous epithelium and the other patient had IM.

**DISCUSSION**

This study provides evidence that the combined lengths of CM and OCM in carefully measured biopsies of the lower esophagus predicts accurately the level of acid exposure in the lower esophagus as assessed in a 24-hour pH study. The presence of a >2-cm length of CM+OCM indicates a much more severe acid exposure of the lower esophagus than a CM+OCM length <2 cm.

The data in this study should be compared with the study of 334 patients reported by Oberg et al., for which the pathologic assessment was made by one of the authors (P.T.C.). These 334 patients had no endoscopically recognizable columnar lined esophagus at the junction, and they underwent thorough sampling of the squamocolumnar junctional region by retroflex and antegrade biopsies. Eighty-eight patients (26%) had neither CM nor OCM. These 88 patients had a mean percent time pH <4 of 1.1%, which was within the normal range and substantially less than the 246 patients (74%) in whom CM or OCM was present in the biopsies, who had a mean percent time pH <4 of 6.0%. The presence of CM or OCM in patients without a visible endoscopic abnormality very likely equates to a CM+OCM length that is less than the <2-cm group in the current series. When data from Oberg et al. are combined with the current study, it appears that the presence of CM and/or OCM is predictive of abnormal acid exposure of the lower esophagus by a 24-hour pH test, and that the CM+OCM length predicts accurately the severity of reflux. There is a sequentially higher probability of finding an abnormal

**FIG. 6.** Cardiac mucosa showing chronic inflammation in the lamina propria with numerous eosinophils and plasma cells. Also seen are smooth muscle fibers in the lamina propria.

**FIG. 7.** Cardiac mucosa adjacent to squamous epithelium showing marked, active chronic inflammation and foveolar hyperplasia—features that define reflux carditis.
pH study and a sequentially higher quantitative acid exposure as the CM+OCM length increases from 0 to >2 cm.

The literature provides corroboration for these findings. Csendes et al.\(^8\) reported a proximal migration of the squamocolumnar junction with increasing reflux. Jain et al.\(^14\) reported the absence of CM (defined, as in the current study, as a mucosa with glands composed of mucous cells devoid of parietal cells) in 65% of patients with a normal endoscopic junction after extensive biopsy sampling.

Kilgore et al.,\(^16\) in a meticulous autopsy study of the entire circumference of the squamocolumnar junction in a series of patients younger than 18 years who had no evidence of reflux, found a CM length between 1 and 4 mm, with a median of 1.8 mm. Their definition of CM (mucosa that contains glands in which mucous cells are present without reference to the absence of parietal cells) includes CM and OCM, as defined in the current study. The finding of a length of 0.18 cm of CM+OCM contrasts greatly with the current series of patients with a high incidence of reflux disease in whom the CM+OCM length was >2 cm in 22 of 71 patients. A total of 32 of 49 patients classified as having a CM+OCM length <2 cm had CM or OCM at two biopsy levels, almost certainly indicative of a CM+OCM length >0.4 cm, which was the maximum found by Kilgore et al.\(^16\) in normal patients.

These data raise serious doubts regarding the normalcy of CM and OCM at the gastroesophageal junction. The absence of CM and OCM in some patients,\(^14\) their very short length in a population of young people,\(^16\) the fact that their presence correlates with abnormal acid exposure, and the sequentially higher quantitative acid exposure as the CM+OCM length increases from 0 to >2 cm.

TABLE 2. Summary of pH data expressed as percent time pH <4 in 53 patients who had 24-hour pH monitoring

<table>
<thead>
<tr>
<th>Group</th>
<th>Defining characteristics</th>
<th>No. of patients</th>
<th>Median</th>
<th>Range (QL, QU)</th>
<th>IQR (QL, QU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>CM + OCM &gt;2 cm; IM+</td>
<td>15</td>
<td>10.4</td>
<td>1.1–54.3</td>
<td>5.7, 20.5</td>
</tr>
<tr>
<td>B</td>
<td>CM + OCM &lt;2 cm; IM+</td>
<td>15</td>
<td>10.5</td>
<td>1.8–39.7</td>
<td>6.6, 20.5</td>
</tr>
<tr>
<td>C</td>
<td>CM + OCM &lt;2 cm; IM−</td>
<td>23</td>
<td>6.1</td>
<td>1.1–18.2</td>
<td>4.2, 9.8</td>
</tr>
<tr>
<td>A + B</td>
<td>IM+</td>
<td>30</td>
<td>16.5</td>
<td>1.8–54.3</td>
<td>8.5, 33.7</td>
</tr>
<tr>
<td>B + C</td>
<td>CM + OCM &lt;2 cm</td>
<td>38</td>
<td>7.1</td>
<td>1.1–39.7</td>
<td>5.2, 12.1</td>
</tr>
</tbody>
</table>

IQR, interquartile range; (QL, QU), (25%, 75%) quartiles; CM, cardiac mucosa; OCM, oxyntocardiac mucosa; IM, intestinal metaplasia.
exposure, the proximal migration of the squamous epithelium with increasing reflux, and the findings in the current study that the CM+OCM length increases with increasing lower esophageal acid exposure all make it highly likely that CM and OCM are abnormal epithelia caused by reflux. The very common presence of short lengths of CM and/or OCM in the population can be explained by the fact that reflux episodes occur in almost all persons when 24-hour pH tracings from normal volunteers are examined.

If CM and OCM are abnormal epithelia, the only normal epithelia in this region are squamous epithelium and pure OM. OM is designed to resist gastric acid. Squamous epithelium is damaged by gastric acid. It therefore must follow that CM and OCM represent glandular transformation of the squamous epithelium as a result of reflux. The fact that 14% of patients with CM or OCM in the current study had squamous-lined ducts in the lamina propria lends support to the concept that CM and OCM line the esophagus and not the stomach. Squamous-lined ducts in the mucosa are histologic structures that are unique to the esophagus in the entire foregut.

These data suggest that the finding of CM and OCM in biopsies of the junctional region represents the earliest morphologic evidence of abnormal acid exposure. Their presence is a highly sensitive marker of squamous epithelial damage by acid and can therefore be used as a histologic definition of abnormal acid exposure. Nine of the 71 patients with CM and/or OCM had a normal 24-hour pH test, suggesting that the presence of CM and/or OCM is a more sensitive marker of abnormal acid exposure than the 24-hour pH test, which is the current gold standard for reflux.

The analysis of the data relating IM to pH abnormality is complex. Although there is a highly significant difference in pH values between those with and without IM, it is possible that this reflects the dominant relationship between CM+OCM length and pH value, rather than being a primary difference. The incidence of IM increases with increasing length of CM, and is 100% in those with a CM+OCM length >2 cm and is 39% in those with a CM+OCM length <2 cm in the current series. When patients with a CM+OCM length <2 cm with and without IM are compared, the level of statistical significance is less (Table 3). It is possible that the differences between these two groups can be explained by the fact that the <2-cm measurement is relatively crude, and that patients with IM more likely include those with longer CM+OCM lengths within this group than those without IM.

Also remarkable is the fact that IM occurs only in CM and does not occur in OCM. This observation was made originally by Paull et al., who stated that goblet cells were not seen in fundic epithelium (OCM as defined here). This fact permits the development of a rational histologic definition of reflux disease. Although the presence of either CM or OCM is predictive of abnormal acid exposure, only those patients with CM in their junctional region are at risk for developing IM. Because IM defines Barrett’s esophagus and is the only epithelial type that progresses to adenocarcinoma, only those persons with CM at their junction are at risk. The presence of CM in biopsies can therefore be used to define reflux disease if one uses Barrett’s adenocarcinoma as the end point indicator of reflux disease. Patients who have OCM without CM at the junction have no risk of having IM and adenocarcinoma at the time of the biopsy, and can be classified appropriately as having compensated reflux rather than reflux disease. However, it is possible that continued acid exposure in patients with OCM only may result in future transformation into CM and IM, with the attendant risk of adenocarcinoma.

This concept of histologic changes establishes cardiac transformation of squamous epithelium as the early stage of the pathologic sequence by which gastroesophageal reflux results in adenocarcinoma. It also establishes a histologic parameter by which treatment of reflux disease can be measured. Any treatment modality that converts IM or CM to squamous mucosa, OCM, and pure OM removes the patient from the reflux–adenocarcinoma sequence, and can be regarded as a histologic cure of reflux disease.

### REFERENCES


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**TABLE 3.** *p* values for comparing groups in terms of variability (scale)/median of percent time pH <4

<table>
<thead>
<tr>
<th>Group</th>
<th>Characteristics</th>
<th>(A) CM + OCM &gt;2 cm; IM+</th>
<th>(B) CM + OCM &lt;2 cm; IM+</th>
<th>(C) CM + OCM &lt;2 cm; IM−</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td>CM + OCM &gt;2 cm; IM+</td>
<td>0.067*0.026†</td>
<td>0.001*&lt;0.001†</td>
<td>0.012*0.052†</td>
</tr>
<tr>
<td>(B)</td>
<td>CM + OCM &lt;2 cm; IM+</td>
<td>0.001*&lt;0.001†</td>
<td>0.012*0.052†</td>
<td>0.001*&lt;0.001†</td>
</tr>
<tr>
<td>(A+B)</td>
<td>CM + OCM &gt;2 cm; IM+</td>
<td>0.001*&lt;0.001†</td>
<td>0.012*0.052†</td>
<td>0.001*&lt;0.001†</td>
</tr>
<tr>
<td>(A+B+C)</td>
<td>CM + OCM &lt;2 cm</td>
<td>0.001*&lt;0.001†</td>
<td>0.012*0.052†</td>
<td>0.001*&lt;0.001†</td>
</tr>
</tbody>
</table>

* Ansari–Bradely rank test.
† Wilcoxon two-sample test.
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