Long segments of columnar-lined lower esophagus are not always metaplastic

António Dias Pereira, Tito Correia, Pedro Amaro, Carlos Sofia, Paula Chaves

DOI: 10.17235/reed.2015.3660/2014
Link: PDF


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Long segments of columnar-lined lower esophagus are not always metaplastic

Antonio Dias Pereira\textsuperscript{1,2}, Tito Correia\textsuperscript{3}, Pedro Amaro\textsuperscript{3}, Carlos Sofia\textsuperscript{3} and Paula Chaves\textsuperscript{2,4}

\textsuperscript{1}Serviço de Gastrenterologia., Instituto Português de Oncologia de Lisboa de Francisco Gentil. EPE. Lisboa, Portugal. \textsuperscript{2}Faculdade de Ciências da Saúde. Universidade da Beira Interior. Covilhã, Portugal. \textsuperscript{3}Serviço de Gastrenterologia. Centro Hospitalar e Universitário de Coimbra. Coimbra, Portugal. \textsuperscript{4}Serviço de Anatomia Patológica. Instituto Português de Oncologia de Lisboa de Francisco Gentil. EPE. Lisboa, Portugal

Received: 28/12/2014
Accepted: 11/01/2015
Correspondence: Antonio Dias Pereira. Serviço de Gastrenterologia. Instituto Português de Oncologia de Lisboa de Francisco Gentil, EPE. Rua Professor Lima Basto. 1099-023 Lisboa, Portugal

e-mail: adiaspereira1@gmail.com

ABSTRACT
The presence of columnar epithelium in the esophagus is associated with two conditions: Barrett’s esophagus and heterotopic gastric mucosa. The former results from the metaplastic replacement of the normal distal squamous esophageal lining, is associated with gastroesophageal reflux and is a pre-neoplastic condition. The second is thought as a congenital condition, resulting from the incomplete squamous epithelialization of the esophagus during embryologic development. It is found mainly in the cervical esophagus. Histologically, Barrett’s esophagus is composed of an admixture of cardiac mucosa, oxintocardic mucosa and intestinal metaplasia. Most of heterotopic gastric mucosa consists of oxyntic mucosa where the mucosal glands are straight and composed of parietal and chief cells.
There are few reports of heterotopic gastric mucosa in the lower esophagus, generally presenting as small islands.

In the present report, a series of four cases of large lower esophageal heterotopic gastric mucosa is described. All patients were initially misdiagnosed with Barrett’s esophagus and referred for surveillance. The correct diagnosis was based in endoscopic and histological features. In all, a circular tiny strip of squamous mucosa was observed at endoscopy between the lower end of the columnar-lined esophagus and the esophagogastric junction, defined as the proximal end of the gastric folds. Biopsy samples taken from the columnar-lined segments of the four patients showed pure oxyntic mucosa.

When columnar-lined esophagus is observed in the distal esophagus not in continuity with gastric mucosa, the diagnosis of heterotopic gastric mucosa must be thought and confirmed histologically by the presence of pure oxyntic mucosa.

Key words: Columnar-lined esophagus. Heterotopic gastric mucosa. Barrett’s esophagus.

INTRODUCTION

The presence of columnar epithelium in the esophagus, which is normally lined with squamous mucosa, is associated with two conditions. The first condition is the metaplastic replacement of the squamous epithelium of the lower esophagus associated with gastroesophageal reflux. It occurs mainly in men, is endoscopically characterized by the proximal displacement of the Z-line, and is histologically characterized by an admixture of three columnar epithelia (cardiac, oxyntocardiac, and intestinal metaplasia). This condition is known by the eponym Barrett’s esophagus (1) and has a well-known association with esophageal adenocarcinoma, the malignancy with the highest rising incidence in the last four decades in Western countries (2).

The second condition is heterotopic gastric mucosa (HGM) more frequently associated with the cervical esophagus (3). Its appearance varies from tiny microscopic foci to
large areas of red or salmon-red mucosa. HGM that presents as large patches is also called inlet patch. The most common location of HGM is the uppermost portion of the esophagus just below the upper esophageal sphincter. HGM is thought to have a congenital origin resulting from the incomplete squamous epithelialization of the esophagus during embryologic development (4,5). Histologically, most HGM cases consist of oxyntic mucosa with mucus-secreting columnar cells, chief cells, and parietal cells (4,6). Although a recent published review found 44 cases of adenocarcinoma arising in HGM (7), it is not considered a pre-malignant condition.

Patients diagnosed with HGM, as opposed to Barrett’s esophagus, are not considered to have an increased risk of esophageal cancer and have no indication for endoscopic surveillance. The correct diagnosis of HGM allows to exclude them from unnecessary endoscopic surveillance and to diminish the psychological stress known to be associated with the diagnosis of Barrett’s esophagus (8).

HGM has been seldom described in the middle portion of the esophagus. Reports of its occurrence in the lower esophagus are uncommon and always describe HGM as small islands (6). Chandrasoma (9) recently stated that it is hard to find in the literature any significant reference to “islets of gastric mucosa in the lower esophagus” after 1950 Barrett’s paper on *Chronic ulcer of the esophagus and “esophagitis”* (10). In this paper, we report four cases of large segments ($\geq 5$ cm long) of columnar-lined mucosa in the lower esophagus referred for surveillance with the diagnosis of Barrett’s esophagus but with an endoscopic appearance suggestive of HGM that was confirmed histologically, identified in the endoscopic datafiles of two tertiary Gastroenterology Departments (Instituto Português de Oncologia de Lisboa de Francisco Gentil and Centro Hospitalar e Universitário de Coimbra).

This study was approved by the Instituto Português de Oncologia de Lisboa review board.

**CASE REPORT**
The features of the four patients are summarized in table I. Three were referred to a Barrett’s esophagus surveillance program after diagnosis of Barrett’s esophagus by upper gastrointestinal endoscopies that were performed for complaints of long-standing heartburn; the other patient was referred to a tertiary hospital when she returned from abroad with the diagnosis of Barrett’s esophagus. Cases 1 and 2 were referred shortly after diagnosis, and HGM was suspected at the initial endoscopy performed at our institution. Case 3 was diagnosed with Barrett’s esophagus without intestinal metaplasia since 2004 to 2012 and submitted to several surveillance endoscopies. During these eight years she took regularly PPI. In 2012 she was referred to our program, and the diagnosis of HGM was thought in the first endoscopy. Case 4 was diagnosed abroad with Barrett’s esophagus and was subjected to an antireflux surgical procedure in 2006 shortly after diagnosis with no regression of heartburn. Shortly after surgery, the patient required the reintroduction of proton pump inhibitors. When she returned to Portugal, she was referred to a tertiary hospital where HGM was suspected at endoscopy and then confirmed by histology.

All four patients required proton pump inhibitors daily for heartburn control. All attempts to stop medication were shortly followed by heartburn complaints.

The endoscopic diagnosis of HGM of the lower esophagus was based on two features. First, a segment of grayish white mucosa was observed in all patients between the lowest limit of the columnar-lined mucosa and the esophagogastric junction defined as the proximal end of the gastric folds. Two Z-lines resulting from the more proximal transition from squamous to columnar esophageal mucosa and from a second, more distal transition, from squamous esophageal to columnar gastric mucosa were clearly observed in all cases. Second, the transition between the two mucosa was clearly demarcated, as the squamous edge was slightly elevated compared to the columnar edge. No change in HGM morphology was observed since the correct diagnosis was established.

Endoscopic images of cases 1, 2, 3, and 4 are reproduced in figure 1.

Multiple biopsies (ranging from eight to twelve) were performed in the four patients. Biopsies were taken along the columnar-lined segment including their most proximal
and distal ends. The histological features of all the biopsy samples that showed pure oxyntic mucosa confirmed HGM. In case 1, the pathologist also identified oxyntocardiac areas. The histological features of HGM are documented in figure 2 (corresponding to case 3). Biopsies taken from de grayish mucosa interposed between esophageal and gastric columnar mucosa showed squamous epithelium in all cases.

DISCUSSION

First recognized in the 19\textsuperscript{th} century, HGM occurs mainly in the esophagus but has been described in other locations such as the small intestine, rectum, and gallbladder. In the esophagus, it is mainly located in the cervical segment just below the upper esophageal sphincter, an area not easily accessed by endoscopy. In a recently published series, HGM was located 15-23 cm from the incisors in 96.8% of the 126 cases (11). This may influence its highly variable prevalence reported in endoscopic papers (0.1-10%), and evidence suggests that this entity is underestimated in the clinical setting (12). There is no difference in the prevalence of HGM between sexes. HGM diameter may range from a few millimeters to > 3 cm. There are reports of cases in which the HGM encircled the entire esophageal lumen (13). Virtual pan-esophageal involvement was reported in 1 case with HGM involving one-third to one-half of the esophageal circumference and extending to > 50% of the esophageal length starting 2 cm below the upper esophageal sphincter (14).

There is also evidence that HGM is an inherited condition that develops during fetal development (15). By gestation week 10, a single layer of columnar cells lines the esophagus. From gestation month 5, it is gradually replaced by squamous epithelium starting from the middle third of the esophagus and extending proximally and distally. The last esophageal segment re-epithelialized is the most proximal. HGM develops on incomplete re-epithelialization and persisting columnar cells at birth, usually proximally over the upper third of the esophagus or, much less frequently, distally over the esophagogastric junction. The preferential localization of HGM in the cervical esophagus is explained by the temporal difference in the stratified re-epithelialization of both ends of the esophagus (15).
A recent PubMed search combining the terms “heterotopic gastric mucosa,” “inlet patch,” “gastric heterotopy,” or “gastric heterotopia” with “lower esophagus” or “distal esophagus” failed to return any articles. When the same terms were combined with “esophagus,” the search returned 130 articles, only two of which referred to HGM occurrence in the lower esophagus (4,16). Borhan-Manesh et al reported on 64 cases of HGM in the upper esophagus in which occasional patches of HGM were found in the lower esophageal area 1-3 cm above the gastroesophageal junction with a histology similar to that of HGM in the cervical esophagus (4). Terada (16) reported a clinicopathological study of 910 consecutive esophageal biopsies with 98 gastric heterotopias occurring in all esophageal segments and described two types of gastric heterotopias: One with foveolar epithelium and oxyntic glands that he considered a congenital anomaly, and another consisting only of foveolar epithelium he considered a congenital anomaly or an acquired lesion.

In a literature review, von Rahden et al. (6) verified that most of the mucosa of HGM is uniformly the oxyntic type and is characterized by glands with chief and parietal cells. Less frequently, HGM shows a “transitional” cell type characterized by mucous glands without chief cells and with only a few parietal cells, called oxyntocardiac (17). There are scarce references of the presence of pure cardiac epithelium (18), and references of the presence of intestinal metaplasia are extremely rare (6).

The four cases reported in this paper presented with endoscopic features that strongly argued against the diagnosis of Barrett’s esophagus. At endoscopy, a proximal displacement of the squamous-columnar junction or Z-line is observed in Barrett’s esophagus in relation to the gastroesophageal junction. As such, columnar gastric mucosa is in continuity with metaplastic esophageal columnar epithelium. In all four cases in our series, there was a clear strip of circular grayish white (squamous) mucosa between the columnar-lined esophagus and the stomach that proved to be squamous histologically. The possibility that the observed endoscopic features were related to Barrett’s regression secondary to PPI use must be discussed. There is published evidence that Barrett’s esophagus can regress, even completely, under PPI use. However the complete circular distal squamous reepithelization of long segments of
Barrett’s esophagus has not been described in any of the published trials on the subject (19,20).

The endoscopic diagnosis of HGM was confirmed histologically in these four cases. Pure oxyntic mucosa, characterized by glands only with chief and parietal cells and devoid of mucous cells below the foveolar region, as shown here, is never observed in Barrett’s esophagus. On the other hand, cardiac epithelium, which is composed of glands with mucous cells without parietal or chief cells and can be considered the hallmark of metaplastic columnar-lined esophagus (17), was not present in any biopsy sample taken from these four patients.

Most cases of HGM are found incidentally during endoscopy. However, in some patients, HGM is associated with symptoms such as heartburn and a globus sensation probably related to acid secretion by the heterotopic mucosa (6). Proton pump inhibitors are widely used to control the symptoms associated with HGM. All four patients reported in this paper had heartburn and endoscopic esophagitis in the squamous mucosa close to the proximal squamous-columnar transition. It is not possible to rule out the presence of gastroesophageal reflux, but the very proximal location of the inflammatory changes strongly suggest they could be secondary to HGM-induced acid secretion. The persistence of reflux symptoms in one patient submitted to antireflux surgery, with the need of proton pump inhibitors reintroduction, also supports this hypothesis.

A recent multicenter sham controlled trial showed that the ablation of HGM in the cervical esophagus using argon plasma coagulation was associated with a significant and sustained control of the globus sensation (21). However, the mean and maximum diameters (7 and 30 mm, respectively) of the treated lesions in these cases of HGM were smaller than those of our cases and noncircular. The efficacy and potential adverse effects, namely stricture formation, of this procedure in these large heterotopias are not known.

There are reports of esophageal strictures, esophagorespiratory fistulas, and adenocarcinomas complicating HGM (6). Esophageal adenocarcinoma associated with HGM is very rare, with 44 cases being described to date (7).
*Helicobacter pylori* colonization of cervical inlet patches is common and was reported in 73% of the patients with simultaneous gastric colonization and in none of those who tested negative for gastric infection (22). It was closely related to *Helicobacter pylori* density in the stomach (22). In our series, *Helicobacter pylori* infection was observed in only one patient with HGM, but its status in the stomach was not systematically searched.

An association between the presence of HGM (inlet patch) and Barrett’s esophagus has been proposed, but remains debatable. In a recent revision of the literature (15), the authors found five reports describing an association between HGM in the proximal esophagus and Barrett’s esophagus. However, five other studies failed to find such an association. A pathogenic association between the two entities was suggested by similar mucin staining patterns, but others studies found differences that argued against this association (15).

In summary, although HGM frequently occurs in the upper esophagus, there are only scarce references of its location in the lower esophagus, and those that are available all described it as small islands above the esophagogastric junction. From this first report of a series of patients with long HGM of the lower esophagus that was initially labeled as Barrett’s esophagus, we stress the importance of the anatomic landmarks and histological features that support the differential diagnosis of these entities.

**REFERENCES**

Legends

Fig. 1. Endoscopic images of HGM of the distal esophagus. A. An almost circular HGM with columnar mucosa clearly separated from the esophagogastric junction by a strip of squamous mucosa with 2-3 centimeters (case 1); B. A circular HGM separated from the esophagogastric junction by a thin circular strip of squamous mucosa (case 2). C. The slight elevated proximal and distal (right low corner) columnar-squamous transition of the HGM (case 3). D. Linear erosion is visible at 3 o’clock in the squamous mucosa above the proximal limit of the HGM (case 4).

Fig. 2. Histology of HGM shows pure oxyntic mucosa characterized by the presence of glands with chief and parietal cells (slide from case 3).
<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis of CLE</td>
<td>23</td>
<td>30</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Complaints</td>
<td>Heartburn</td>
<td>Heartburn</td>
<td>Heartburn</td>
<td>Heartburn</td>
</tr>
<tr>
<td><strong>Endoscopic data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of complaints until CLE diagnosis (months)</td>
<td>6</td>
<td>6</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>Proximal limit of CLE (cm from incisors)</td>
<td>30</td>
<td>28</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Distal limit of CLE (cm from incisors)</td>
<td>35</td>
<td>35</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>Esophagogastric junction (cm from incisors)*</td>
<td>38</td>
<td>37</td>
<td>37</td>
<td>39</td>
</tr>
<tr>
<td><strong>Histological data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopic esophagitis** (LA classification)</td>
<td>Grade A</td>
<td>Grade B</td>
<td>Grade A</td>
<td>Grade B</td>
</tr>
<tr>
<td>CLE morphology</td>
<td>Almost circular</td>
<td>Circular</td>
<td>Non-circular (3/4 of the circumference)</td>
<td>Circular</td>
</tr>
<tr>
<td>Histology of CLE</td>
<td>Oxyntic mucosa</td>
<td>Oxyntic mucosa</td>
<td>Oxyntic mucosa</td>
<td>Oxyntic mucosa</td>
</tr>
<tr>
<td>Histology of mucosa below</td>
<td>Squamous</td>
<td>Squamous</td>
<td>Squamous</td>
<td>Squamous</td>
</tr>
<tr>
<td>CLE</td>
<td>Helicobacter pylori</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Time elapsed since diagnosis of CLE (years)</td>
<td>15</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

CLE, columnar-lined esophagus; LA, Los Angeles

*Defined as the proximal limit of the gastric folds

**Maximum grade observed