Prevalence and topography of intestinal metaplasia in columnar lined esophagus

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SUMMARY

Objectives — Barrett's mucosa is considered as a mosaic of three epithelial types but little is known about the topography of intestinal metaplasia in columnar lined esophagus. The aims of the study were to determine the prevalence of intestinal metaplasia within long and short segments of columnar lined esophagus and to analyze the distribution of the intestinal metaplasia within long segments of Barrett's esophagus.

Patients and methods — The study was performed on the initial endoscopy carried out among 112 patients enrolled in an endoscopic surveillance program. Seventy-two patients with columnar mucosa extending more than 3 cm into the esophagus (group I) and 40 patients with a short segment of columnar mucosa (group II) had multiple biopsies according to a standardized protocol. 1163 biopsies were analyzed on the whole: 949 biopsies in group I and 214 biopsies in group II.

Results — Intestinal metaplasia was identified among 650 (68.5%) and 50 (23.4%) biopsies in groups I and II respectively (P<10^-7). The proportion of biopsies with foci of intestinal metaplasia increased significantly with the length of the columnar mucosa. The diagnosis of Barrett's esophagus was confirmed in 100% of the patients in group I and in 45% of the patients in group II. In long segments of Barrett's esophagus, intestinal metaplasia was more frequently observed in the 2 upper thirds of the columnar mucosa that in the lower third (P<10^-7). Detailed mapping of the distribution of epithelial types within the columnar lined esophagus identified three patterns of distribution of intestinal metaplasia within long segments of Barrett's esophagus: unifocal, multifocal and diffuse, in 5%, 56% and 39% of the patients respectively. Dysplasia was present in 15% of patients with long segments of Barrett's esophagus and 11% of patients with short segments (NS).

Conclusion — The distribution of intestinal metaplasia within columnar lined esophagus is heterogeneous and three distinct patterns can be identified: unifocal, multifocal and diffuse. Considering the risk of sampling error, the current recommendations concerning the biopsy protocols are mandatory until the validation of new techniques such as chromoendoscopy or magnifying endoscopy.

RÉSUMÉ

Étude de la prévalence et de la topographie de la métaplasie intestinale au sein des endobrachyœsophages

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Objectifs — L’endobrachyœsophage (EBO) est classiquement considéré comme une mosaïque de trois types d’ épithélium mais les connaissances sur la topographie de ces types et de la métaplasie intestinale sont peu nombreuses. Les buts de l’étude étaient de déterminer la prévalence de la métaplasie intestinale au sein des EBO longs et des courts segments de muqueuse glandulaire de l’oesophage et d’analyser la topographie de la métaplasie intestinale au sein des EBO longs.

Méthodes — L’étude a porté sur l’endoscopie initiale réalisée chez 112 malades inscrits dans un programme de surveillance endoscopique. Soixante-douze malades ayant un segment de muqueuse glandulaire de 3 cm et plus (groupe I) et 40 malades ayant un court segment (groupe II) ont eu des biopsies multiples selon un protocole standardisé. 1163 biopsies ont été analysées au total : 949 biopsies dans le groupe I et 214 biopsies dans le groupe II.

Résultats — Une métaplasie intestinale a été identifiée au niveau de 650 (68,5 %) et de 50 biopsies (23,4 %) dans les groupes I et II respectivement (P<10^-7). La proportion des biopsies présentant des foyers de métaplasie intestinale augmentait significativement avec la hauteur de la muqueuse glandulaire. Le diagnostic d’EBO a été confirmé en histologie chez la totalité des malades du groupe I et chez 45 % des malades du groupe II. Au niveau des EBO longs, la métaplasie intestinale était plus fréquemment observée au niveau des 2/3 proximaux de l’EBO que au niveau du 1/3 distal (P<10^-7). Il existait 3 types de répartition de la métaplasie intestinale au sein des EBO longs : répartition unifocale, multifocale et diffuse observée chez respectivement 5 %, 56 % et 39 % des malades. La prévalence de la dysplasie était de 15 % chez les malades avec un EBO long et de 11 % chez les malades avec un EBO court (NS).

Conclusion — La répartition des foyers de métaplasie intestinale au sein des EBO est hétérogène et trois types de distribution peuvent être identifiés : distribution unifocale, multifocale et diffuse. Devant le risque d’erreur d’échantillonnage, les recommandations actuelles concernant les prélèvements biopsiques restent d’actualité dans l’attente de la validation d’une technique permettant d’orienter les biopsies telles que la chromoendoscopie ou l’endoscopie grossissante.
Introduction

Barrett’s esophagus is an acquired condition which develops as a consequence of long-lasting and severe gastro-esophageal reflux disease (GERD). The current definition of Barrett’s esophagus is based on a combination of endoscopic and histologic criteria. Barrett’s esophagus presence is usually suspected during endoscopic inspection of the esophagus when the squamocolumnar junction is displaced towards the gastro-esophageal junction. The diagnosis is then confirmed by histological analysis of biopsies taken from this glandular mucosa when intestinal metaplasia is detected.

In 1976, Paull et al. [1] described for the first time the existence of 3 types of epithelia in the columnar lined esophagus above the lower esophageal sphincter: a fundic-type epithelium with parietal and chief cells, a cardiac- or junctional-type epithelium with cardiac mucous glands, and a distinctive specialized columnar epithelium with a villiform surface, mucous glands and mucin-containing goblet cells (intestinal metaplasia). However, routine endoscopy without biopsy and histologic evaluation cannot distinguish intestinal metaplasia from fundic or cardiac epithelium.

Patients with Barrett’s esophagus are at risk of progressing to esophageal dysplasia and adenocarcinoma. Dysplasia arising in cardiac-type or fundic-type mucosa in the absence of coexisting intestinal metaplasia appears to be uncommon. However, intestinal metaplasia and dysplasia both adjacent to and remote from adenocarcinoma have been consistently evidenced in esophagogastrectomy specimens from patients with Barrett’s esophagus [2, 3]. Taken together, these observations suggest that intestinal metaplasia is the primary tissue predisposed to neoplastic progression.

The distribution of intestinal metaplasia in columnar lined esophagus remains incompletely understood and current guidelines suggest obtaining systematic 4-quadrant biopsy specimens at 2-cm intervals along the entire length of the Barrett’s segment.

The aims of the study were to determine the prevalence of intestinal metaplasia within long and short segments of columnar lined esophagus and to analyze the distribution of epithelial types within the long segments of Barrett’s esophagus

Patients and methods

Patients characteristics

The study was performed on the initial endoscopy carried out among 112 patients (91 men and 21 women) enrolled in an endoscopic surveillance program. Seventy-two patients with columnar mucosa extending more than 3 cm into the esophagus (group I) and 40 patients with shorter segment of columnar mucosa (group II) had multiple biopsies according to a standardized protocol.

Group I consisted of 60 males and 12 females. The mean age at the time of the diagnosis was 66 years (age range: 29-76 years). 62% of the patients were symptomatic with a mean duration of GERD symptoms of 9 years (range: 6 months-17 years). Thirty percent of the patients were treated by a PPI at the time of the diagnosis. A hiatal hernia was detected in 63 patients (87.5%). The mean length of the columnar segment was 8 cm (range: 4-16 cm).

Group II was composed of 31 males and 9 females. The mean age at the time of the diagnosis was 58 years (age range: 25-86 years). A hiatal hernia was noted in 29 patients (72.5%). The distribution of the patients in both groups according to the length of the columnar lining is presented in the figure 1.

Biopsy protocol

The protocol was set to obtain four-quadrant biopsy specimens using a standard biopsy forceps at 2 cm intervals along the entire length of the columnar mucosa, beginning at the end of the tubular esophagus just above the proximal margin of the gastric folds, and continuing to the squamocolumnar junction. If the length of the columnar mucosa was 3 cm or less, the biopsy specimens were taken at 1 cm intervals as recommended by the French Society of Digestive Endoscopy [4]. Each biopsy specimen was collected and fixed in a separate tube and was indexed according to the level and the quadrant of the biopsy site.

Histological evaluation

All biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin wax, and stained with haematoxylin and eosin in combination with alcian blue at pH 2.5. Two pathologists (AV and LD) reviewed all the biopsy specimens. Cardiac mucosa was characterized by glands composed entirely of mucous cells without any parietal or chief cells. Intestinal metaplasia was identified by the presence of well-defined goblet cells within columnar epithelium and was confirmed by Alcian blue staining at pH 2.5.

Dysplasia in the biopsy specimens was recognized by the presence of cytological and architectural abnormalities and was classified as no dysplasia, indefinite/lower grade dysplasia (LGD), and high grade dysplasia (HGD) based on the criteria defined by Riddell et al. [5].

For each patient a detailed mapping of the distribution of epithelial types and dysplastic changes within the columnar lined esophagus was established.

Statistical analysis

Biopsy confirmed intestinal metaplasia and dysplasia were used as the outcome measures. The Fisher exact test was used to compare proportions between 2 groups and Chi-square analysis was used to compare proportions between more than 2 groups. Spearman correlation coefficient was used to examine the relationship between the proportion of biopsies presenting the foci of intestinal metaplasia and the length of the Barrett’s esophagus. A P value below 0.05 was considered as statistically significant.

Results

A total of 1163 biopsies was analyzed: 949 biopsies in group I and 214 biopsies in group II. Intestinal metaplasia was identified in 700 biopsy specimens (60.2%). The percentage of biopsy specimens with intestinal metaplasia was significantly higher in the group I (650/949: 68.5%) than in the group II (50/214: 23.4%) (P<10⁻⁷).

The ratio of biopsies with intestinal metaplasia increased significantly with the length of the Barrett’s esophagus (figure 2).

All patients in group I and 18 patients out of 40 from group II had at least 1 biopsy in which intestinal metaplasia was detected. The diagnosis of Barrett’s esophagus was thus confirmed in 100% of the patients in group I and in 45% of the patients in group II.

Dysplasia was identified in 64 biopsies (5%). Among patients of group I, dysplasia was observed in 7% of the biopsy specimens (64/949): 43 were graded as LGD and 21 as HGD. These dysplastic biopsies accounted for eleven patients (1.5%). In group II, dysplasia was detected in only 2 biopsy specimens (1 LGD and 1 HGD) taken from two separate patients.

The proportion of biopsy specimens with dysplasia was statistically higher in group I than in group II (P<0.004); however, the prevalence of dysplasia was not statistically significant between the patients with long segments of Barrett’s esophagus (11/72: 15%) and those with short segments (2/18: 11%).

To analyze the distribution of each type of epithelium in group I, segments of Barrett’s esophagus were divided into 3 equal parts according to the length of the columnar mucosa: lower third, middle third and upper third. For each part, the proportion of biopsy specimens with the 3 types of epithelium was determined. The repartition of the various types of epithelium throughout the Barrett’s esophagus is presented in table I. The cardiac epithelium was equally distributed throughout the columnar lined esophagus. Intestinal metaplasia was more prevalent in the two upper thirds than in the lower third of the columnar lined esophagus, whereas the fundic mucosa was almost exclusively

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The analysis revealed a statistically significant difference in the distribution of the intestinal metaplasia between the two upper thirds of the Barrett’s esophagus and the lower third (P<10^{-7}). When present, intestinal metaplasia was always associated with cardiac epithelium, but was never associated with fundic epithelium.

Furthermore, dysplasia was always observed in conjunction with intestinal metaplasia. There was no preferential location of the dysplastic changes throughout the esophagus (data not shown).

Analysis of intestinal metaplasia distribution in each individual case enabled us to shed light on three distribution patterns: unifocal, multifocal and diffuse. The distribution pattern was called unifocal if intestinal metaplasia was found in a single biopsy specimen (we also considered that the distribution was unifocal when the percentage of biopsies presenting intestinal metaplasia was lower than 20% and the intestinal metaplasia was found in two adjacent biopsy sites). The presence of intestinal metaplasia in several distinct biopsy sites and a percentage of biopsies with intestinal metaplasia ranging between 20 and 80% corresponded to the multifocal distribution pattern. A percentage of biopsies with intestinal metaplasia higher than 80% corresponded to a diffuse distribution.

The topography of intestinal metaplasia was extremely variable from one patient to another; it was unifocal in 4 patients (5.5%), multifocal in 40 patients (55.5%) and diffuse in 28 patients (39%). Figure 3 illustrates various types of intestinal metaplasia distribution patterns.

Discussion

The current definition of the Barrett’s esophagus is based on a combination of endoscopic and histological criteria: an abnormal appearing distal esophageal lining must be evidenced with...
Table I. – Repartition of the three types of epithelium throughout the Barrett’s esophagus (the segments of Barrett’s esophagus were divided into 3 equal parts according to the length of the columnar mucosa. For each third, the proportion of biopsy specimens with the 3 epithelial types was determined).

Répartition des 3 types d’épithélium au sein des EBO (la métaplasie glandulaire a été divisée en 3 segments égaux en fonction de sa hauteur ; pour chaque tiers, la proportion des 3 types d’épithélium a été calculée).

<table>
<thead>
<tr>
<th></th>
<th>Lower third (N=315)</th>
<th>Middle third (N=305)</th>
<th>Upper third (N=329)</th>
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<tbody>
<tr>
<td>Fundic epithelium</td>
<td>48 (15%)</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Junctional epithelium</td>
<td>267 (85%)</td>
<td>302 (99%)</td>
<td>329 (100%)</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>170 (54%)</td>
<td>227 (74%)</td>
<td>253 (77%)</td>
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N=total number of biopsy specimens.

histological confirmation of esophageal intestinal metaplasia. Endoscopic criteria for the recognition of a columnar lined distal esophagus include the proximal displacement of the squamocolumnar junction (Z-line) relative to the gastro-esophageal junction. The histological requirement for the definition of Barrett’s esophagus is the presence of intestinal metaplasia. The diagnosis of esophageal intestinal metaplasia requires multiple biopsies of the esophageal columnar mucosa since intestinal metaplasia is not visible during routine endoscopy and it is not uniformly distributed. As recommended by recent guidelines, we performed a biopsy protocol consisting in 4-quadrant biopsies spaced by 2 cm. Such a protocol allowed us to detect intestinal metaplasia in 60% of 1163 biopsy specimens taken during index endoscopy performed in 112 patients included in an endoscopic surveillance program. The proportion of biopsies with intestinal metaplasia was significantly higher in patients with long segments of columnar lined esophagus (>3 cm) (68.5%) than in patients with shorter segments (23.4%). Therefore, diagnosis of Barrett’s esophagus was confirmed by histology in all patients with a long segment of columnar lined esophagus and in 45% of the patients with a shorter segment.

These results are consistent with previous studies which found that intestinal metaplasia is more often found when endoscopy shows a long rather than a short segment of columnar lining [6]. In patients with endoscopic features suggestive of short-segment Barrett’s esophagus in whom biopsy specimens are obtained randomly, intestinal metaplasia is confirmed in approximately half of the cases [7, 8]. Even though we observed a great interindividual variability (figure 2), we found a positive correlation between the prevalence of intestinal metaplasia and the length of the columnar lined esophagus. These observations are consistent with the study of Csendes et al. [9] in which the prevalence of intestinal metaplasia was 35% among patients with short-segment columnar epithelium and increased progressively according to the length of columnar lining, being 100% in patients with a columnar segment of more than 10 cm in length. Furthermore, in the study of Chandrasoma et al. [10] the prevalence of intestinal metaplasia was 70.4% when the abnormal columnar epithelium lining the distal esophagus was 1-2 cm in length, 89.5% when it was 3-4 cm and 100% when it extended to 5 cm or more.

Detection of intestinal metaplasia is a critical process due to biopsy sampling errors. Even among patients with long segments of esophageal columnar mucosa, over 20% of patients may not be detected for intestinal metaplasia on a single set of biopsies. This observation is supported by the study of Öberg et al. [6] where the prevalence of intestinal metaplasia increased markedly with increasing number of surveillance endoscopies. The fact that both intestinal metaplasia types tended to be detected early during the follow-up of patients with long segments of columnar lined esophagus and that the cumulative prevalence of 100% was quickly reached suggests that intestinal metaplasia was already present at the time of the initial endoscopy but had not been detected. Kim et al. compared the results of histological assessment for patients with Barrett’s esophagus in two closely spaced endoscopies [11]. Among 116 patients who met the criteria for Barrett’s esophagus on at least one of the two examinations, 20% had intestinal metaplasia found on only one of the two endoscopies. The time laps between 2 examinations making implausible a progression or regression of the intestinal metaplasia, thus sampling error seemed responsible for this discrepancy.

Little is known about the natural history of intestinal metaplasia. In their study, Öberg et al. [6] have detected intestinal metaplasia late in the course of endoscopic surveillance in some cases of short segments of columnar lined esophagus. Jones et al. [12] evaluated the yield of intestinal metaplasia on repeated upper endoscopy in patients with suspected short Barrett’s esophagus. They found intestinal metaplasia in 23% of patients without

Fig. 3 – Examples of the three types of distribution of intestinal metaplasia within Barrett’s esophagus (each open circle symbolizes a biopsy site, red dots correspond to biopsy specimens with intestinal metaplasia).

Exemples des 3 types de répartition de la métaplasie intestinale au sein des EBO (chaque cercle représente un site de prélèvement ; les ronds rouges correspondent aux biopsies avec métaplasie intestinale).
evidence of intestinal metaplasia on first endoscopy. Thus on contrary to the traditional recommendations, repeated endoscopy with systemic biopsies is warranted in patients with substantial lengths of columnar lining in the distal esophagus without confirmed intestinal metaplasia on initial biopsies.

The accurate recognition of intestinal metaplasia in a biopsy sample is crucial for establishing the diagnosis of Barrett’s esophagus. Intestinal metaplasia is characterized by crypts and villi lined by mucus secreting columnar cells and goblet cells. The diagnosis is facilitated by identification of goblet cells that contain acidic mucins which is intensively stained with Alcian blue at pH 2.5 [13]. In most cases of Barrett’s esophagus, intestinal metaplasia can be identified easily on standard stained sections; however, in selected cases, alcian blue staining can help to confirm the diagnosis. Nandurkar et al. observed 36% of intestinal metaplasia in short segments of columnar lined esophagus using alcian blue staining [14]. They estimated that 50% cases of intestinal metaplasia would have been overlooked if haematoxylin-eosin had been the sole staining method used. In this study, there were no cases of intestinal metaplasia identified by eosin-eosin but missed by alcian blue staining.

We observed a preferential distribution of the epithelial types in the columnar lined esophagus. Intestinal metaplasia was more prevalent in the two upper thirds of the columnar lined esophagus than in the lower third, whereas the cardiac mucosa was equally distributed throughout the columnar lined esophagus. In contrast, the fundic mucosa was confined to the distal edge of the columnar lined esophagus. The histology of columnar lined esophagus was defined in 1976 by Paull et al. [1]. Intestinal metaplasia was the most frequently observed type of epithelium. When present, intestinal metaplasia was always the most proximal, and fundic type mucosa the most distal epithelium. Cardiac type mucosa was interposed between fundic type mucosa and intestinal metaplasia or squamous epithelium. More recently, Chandrasoma et al. [15] have also reported a distinct zonation of epithelial types by mapping the columnar lined esophagus in 32 patients. Consistent with our results, cardiac mucosa was present throughout the columnar lined esophagus, whereas fundic mucosa and intestinal metaplasia tended to occur in the distal and proximal part of the columnar lined esophagus, respectively. The density of goblet cells was highest in the most proximal level. The differences in prevalence and density of goblet cells between most proximal and most distal level biopsies were highly significant. These authors suggested that glandular transformation of squamous epithelium results in cardiac type mucosa, which evolves into fundic type and intestinal metaplasia by development of specialized parietal cells and goblet cells, respectively.

Significant evidence suggests that the development of Barrett’s esophagus is a two-step process. The metaplastic process likely begins in the distal esophagus by conversion of the squamous mucosa to cardiac-type epithelium; hiatal hernia size and duration of esophageal acid exposure determine the length of the columnar lined esophagus [16]. The second step consists of the “intestinalisation” of this epithelium. Our data are consistent with this scheme: a) the cardiac type epithelium was equally distributed throughout the columnar lined esophagus; b) when present, intestinal metaplasia was always associated with cardiac epithelium. Factors predisposing to the development of intestinal metaplasia in a columnar-lined segment include time spent with GORD and the presence of duodenal content in the refluxed material. A number of experimental and human studies have emphasized the synergistic role of duodeno-gastro-esophageal reflux in the development of Barrett’s esophagus. Several studies have demonstrated significantly greater esophageal bilirubin exposure in patients with Barrett’s esophagus compared with those having reflux esophagitis or nonerosive reflux disease and healthy controls [17-19]. However, the exact components of the duodenal and gastric refluxate that promote esophageal mucosal injury and the events that transform cardiac mucosa to intestinal metaplasia remain unknown. Ambulatory monitoring data from patients with short segments of esophageal columnar mucosa suggest that those with intestinal metaplasia have significantly greater bilirubin exposure than those with cardiac-type epithelium [20]. Ex vivo studies have demonstrated that the pattern of acid exposure alters columnar cell proliferation and differentiation, which may partly explain the structural heterogeneity observed within Barrett’s esophagus [21].

While both the duration and the level of esophageal acid exposure are essential factors for determining the specific length of Barrett’s esophagus [22, 23] their implication and the interaction between gastric and duodenal contents in the genesis of epithelial changes need to be investigated. A previous study by Fitzgerald et al. [24] demonstrated that there is an inflammatory gradient within Barrett’s esophagus. Inflammation is maximal in the proximal Barrett’s esophagus and is characterized by increased expression of the proinflammatory cytokines IL-1ß and IL-8. In contrast, the distal segment is characterized by a relatively non-inflamed columnar epithelium associated with high levels of IL-10 expression. These authors found that this inflammatory gradient was independent of the metaplastic subtypes. However, and in contrast to our study, the authors showed no difference in the prevalence of the various epithelia throughout the columnar lined esophagus.

Mapping the esophagus allowed us to individualize three different distribution patterns of intestinal metaplasia throughout the columnar lined esophagus. Unifocal distribution was much less frequent than multifocal or diffuse distribution. In our series, patients were not evaluated by 24-hr ambulatory pH and bile reflux monitoring so we could not establish a relation between these distribution patterns and the severity and the nature of the gastro-esophageal reflux. We did not find any significant relation between history of the reflux symptoms and intestinal metaplasia distribution pattern. The prospective follow-up of our patients will allow us to establish a temporal link between these patterns. In particular it will be of interest to know if there is a progression with time from unifocal to multifocal and finally to a diffuse pattern. Furthermore, it will also allow us to assess the specific neoplastic risk of each profile.

Patients with Barrett’s esophagus are at risk of progressing to esophageal dysplasia and adenocarcinoma. Prospective studies and retrospective case-control studies have shown a trend for increasing cancer risk with longer segments of Barrett’s esophagus [25-28]. However, there is no evidence that a risk gradient may be defined above any particular length. In our study the proportion of biopsy specimens with dysplasia was higher in patients with segments of columnar lined esophagus extending more than 3 cm than in patients with shorter segments. However the prevalence of dysplasia was not statistically different between the patients with short segments and those with long segments of Barrett’s esophagus. Most authors now agree that the distinction between short and long segments of Barrett’s esophagus seems artificial and that endoscopic surveillance should be proposed without regard to segment length.

In conclusion, mapping the esophagus by a standardized protocol with four-quadrant biopsies made possible the diagnosis of Barrett’s esophagus in all patients with a long segment of columnar lined esophagus (>3 cm) and in 45% of the cases when the endoscopy revealed the presence of a shorter segment of columnar mucosa in the distal esophagus. Intestinal metaplasia was more prevalent in the two upper thirds of the columnar mucosa than in the lower third; however the distribution of intestinal metaplasia was heterogeneous and variable from one individual to another. We identified three patterns of distribution of intestinal metaplasia within columnar lined esophagus: unifocal, multifocal and diffuse. Considering the risk of sampling error, the
current recommendations concerning the biopsy protocols are mandatory until the validation of new techniques such as chro-
moendoscopy or magnifying endoscopy.

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