Proliferative Epithelial Changes in Ectopic Gastric Mucosa of Meckel’s Diverticula

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Twenty-one Meckel’s diverticula containing an adequate amount of assessable heterotopic gastric mucosa were investigated for epithelial changes. Marked or moderate foveolar hyperplasia was present in 52% and 29% of the cases, respectively. Four cases displayed an excessive epithelial proliferation indefinite for dysplasia. It is pointed out that reflux type gastritis or gastropathy, which is the most common lesion in the ectopic gastric mucosa of Meckel’s diverticulum, can be associated with the same confusing epithelial proliferation as reflux gastritis in the stomach, but these lesions are best regarded as representing atypia of repair. Distinguishing features from dysplasia are maturation towards the surface, lack of hyperchromatism and absence of atypical mitoses. Negative p53 immunostaining and localization of the Ki-67 positivity to the expanded neck region could be additive clues that can help to classify lesions indefinite for dysplasia as negative for dysplasia. On the basis of the similarities of the ectopic and ortotopic gastric mucosa, it is suggested that these additive clues previously used in other parts of the digestive tract could also apply for the stomach. (Pathology Oncology Research Vol 4, No 2, 130–134, 1998)

Keywords: Meckel’s diverticulum, ectopic gastric mucosa, reflux gastritis, dysplasia, hyperplasia, p53, Ki-67

Introduction

Reflux gastritis is the pattern of a mucosal lesion associated with the reflux of bile containing duodenal secretion and hypochlorhydria. It is characterized by foveolar hyperplasia (the most pregnant change associated with the reflux of bile), edema, smooth muscle bundles radiating through the lamina propria, dilated capillaries and the absence of an increase in chronic or acute inflammatory cells. Chemical or reactive gastritis has been the name given to this type of tissue reaction, because it was recognized that reflux of bile was not the only noxious agent to evoke it. The histological pattern can be seen in the intact stomach too in association with reflux of pancreatic juice, alcohol abuse, NSAIDs, but it is not specific for these agents. The term gastropathy is preferred by some authors. Differentiation of reactive epithelial changes involving some degree of atypia from dysplasia, the premalignant lesion of the stomach was stressed in one of the first descriptions of reflux gastritis. "Reflux type gastritis/gastropathy" has been recently identified as the predominant form of histopathologic lesion in the heterotopic gastric mucosa of Meckel’s diverticulum. In a retrospective study, 4 cases of Meckel’s diverticulum were found to involve extensive epithelial changes that could be confused with dysplastic lesions. In this study we have tried to identify features that could help categorize these lesions indefinite for dysplasia better. As an adjunct to the differential diagnosis we have used immunohistochemistry for p53 and Ki-67 that were shown to have some value in identifying overtly malignant and dysplastic lesions elsewhere in the digestive tract.

Material and Methods

166 Meckel’s diverticula and other vitellointestinal duct remnants (2 fistulas and 1 cyst) resected between 1956 and 1995 were screened and revised for the presence of heterotopic gastric mucosa, as described elsewhere. Of the 28 specimens containing ectopic gastric mucosa, only 21 (20 diverticula and 1 cyst) contained assessable foveolar epithelium, and 4 demonstrated epithelial proliferation...
Table 1. Distinctive clinicopathological findings on individual patients.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Length of diverticulum (cm)</th>
<th>Chronic inflammatory cells</th>
<th>Neutrophils</th>
<th>Foveolar hyperplasia</th>
<th>Edema</th>
<th>Vasculature</th>
<th>Combined reflux score</th>
</tr>
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<tr>
<td>1</td>
<td>30</td>
<td>2</td>
<td>0</td>
<td>1</td>
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<td>0</td>
<td>2</td>
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<tr>
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<td>3</td>
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<td>3</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>1.5</td>
<td>2</td>
<td>0</td>
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<td>3</td>
<td>11</td>
</tr>
<tr>
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<td>10</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>17</td>
</tr>
</tbody>
</table>

The ectopic mucosa of patient 3 displayed typical „reflux type gastritis”, while that of patient 2 was interpreted as possibly representing „reflux type gastritis” shadowed by features of ulceration. (0: absent, 1: mild, 2: moderate, 3: severe.)

considered to be abnormal. The present report focuses principally on these 4 cases.

Foveolar hyperplasia was defined by an increase in the foveolar to glandular epithelium ratio in the mucosa, and tortuosity of the foveolar epithelium, giving it a corkscrew appearance. Neither cytological alterations nor an increased mitotic rate comprised part of the definition. Inflammatory changes and foveolar hyperplasia were scored (graded) by using the Sydney system\textsuperscript{10} and the criteria given by Dixon et al,\textsuperscript{6} respectively, and a „combined reflux gastritis score” was also determined.\textsuperscript{5}

Figure 2. High-power view of the same mucosa as seen in Figure 1. Note the nuclei reaching the upper half of the epithelium, the numerous mitotic figures, and the relatively large nuclei with multiple nuclei, but lacking hyperchromatism (HE; objective ×40, original magnification ×130).

Standard indirect p53 and Ki-67 immunostaining with microwave antigen retrieval was carried out on three formalin fixed and paraffin embedded specimens using the following primary antibodies: Ki-67 (polyclonal, DAKO, Copenhagen, Cat.# A0047) and anti-p53 (clone DO1, Immunotech, Marseille, France, Cat.# 1407).

Results

Of the 21 assessed specimens grade 3 or grade 2 foveolar hyperplasia was present in 11 (52%) and 6 (29%) specimens, respectively. The epithelial cells were judged to be normal in all cases except four. Distinctive clinicopathologic data of the patients are listed in Table 1. All the patients were male, and they were all operated on for symptoms of acute appendicitis. All had complete gastric heterotopia in their diverticulum, containing both foveolar and glandular epithelium. All but one patient displayed mucosa of both antral and fundic types; only mucosa of fundic type was present in the specimen from patient 3.

In these four cases the appearance of the foveolar epithelium suggested marked proliferation, with certain pseudostratification. The cells had relatively large, mostly oval nuclei. The nuclei exhibited some degree of pleomorphism, one to several nucleoli and a loose, vesicular chromatin pattern. Several typical mitoses were observed in the neck region of the glands, some of them displaced towards the lumen. Overall, the epithelial changes were most prominent in the neck region, but a number of mitoses were also seen towards the surface epithelium, which displayed minor pseudostratification at some areas, but the cells were otherwise normal (Figs 1, 2).
The p53 immunostaining was negative in the investigated cases. The Ki-67 immunostaining was localized at the expanded neck region of the heterotopic gastric glands, and the base of the crypts of orthotopic intestinal mucosa. No diffuse staining pattern characteristic of neoplastic lesions (malignant or dysplastic) was seen (Figs 3, 4).

The lesions initially found indefinite for dysplasia were classified as reactive.

Discussion

The confusing epithelial changes in heterotopic gastric mucosa of Meckel’s diverticulum described here were seen in connection with „reflux type gastritis or gastropathy” in only two cases (patients #3 and probably #2), but the remaining two patients also demonstrated foveolar hyperplasia of grade 3.

Hyperplasia and regenerative changes may mimic dysplasia, and regenerative atypia may sometimes be indistinguishable from dysplasia. Maturation towards the surface epithelium may be a clue to the exclusion of dysplasia, while some cases will inevitably fall in an unclassified group. This has led to the introduction of a five-tiered classification for dysplasia instead of the earlier ones. The new classification includes categories negative, indefinite and positive for dysplasia, subdividing this later into low and high grade dysplasia and also adding intramucosal carcinoma at the end of the spectrum. These categories seem to work well in case of colorectal and gastric lesions and lesions of the Barrett’s esophagus. This is a reproducible system.

Goldstein et al. agree that despite attempts providing photographic and written histological criteria, there will always be cases in which a pathologist will be unsure if the gastric epithelial lesion is dysplastic or reactive, and these will form the indefinite category. We feel that the lesions studied belong to this category.

The epithelial changes were more common in the expanded neck region of the gastric glands and this, coupled with the absence of atypical mitoses and the lack of hyperchromatism, could be regarded as a key feature for the exclusion of dysplasia, although this latter is probably of limited value, since some cases of dysplasia are not hyperchromatic. Dixon et al. stress the importance of distinguishing true dysplastic changes from reactive, regener-
ative atypia in reflux gastritis. Reflux type gastritis or gastropathy in Meckel’s diverticulum requires the same distinction. Weinsein et al. reported changes in the stomach similar to those seen in Meckel’s diverticulum, and also dissociated them from dysplasia. 

Although gastric dysplasia is considered to be a premalignant lesion, its natural history remains to be elucidated. It should be stressed that, although dysplasia is defined as a precancerous lesion, it does not suggest an obligatory downhill course in any part of the body. The risk for progression to carcinoma is high in the case of high-grade dysplasias, while it seems low for moderate or mild dysplasias. It is likely that dysplasia develops in an area of extensive proliferation (the neck region) as in the cases of many other sites in the body (e.g., the squamocolumnar junction of the uterine cervix), but there is no evidence linking regenerative atypia with subsequent progression to dysplasia. These entities are distinguished from each other on the basis of their different potentials for malignant change. This explains the increased need to differentiate between them.

p53 gene or function alterations are reported to be the most common molecular changes in multistep human carcinogenesis. Although not all, several premalignant changes display p53 immunopositivity. Reports on p53 immunostaining of gastric dysplasias are somewhat contradictory. Several investigators found no immunopositivity in low grade gastric dysplasias, while others reported an increasing positivity in staining with increasing grade of dysplasia. It is well accepted that these contradictory findings may reflect a difference in interpretation of degrees of dysplasia. However cases of regenerative atypia were consistently negative for p53 immunostaining in a recent study. p53 immunonegativity could possibly be an additive clue for the exclusion of dysplasia in case of epithelial changes that cause difficulties in interpretation, and this could be applied for heterotopic mucosa too.

Ki-67 immunostaining has been recently shown to be of help in differentiating dysplastic and reactive proliferations in Barrett’s esophagus and the colon. This may also be true for gastric epithelium, either ortoptotic or heterotopic. Although gastric epithelial dysplasia and reactive hyperplasia still need a comparative Ki-67 study, we have seen an immunostaining pattern compatible with regenerative/hyperplastic changes.

Malignant neoplasms of Meckel’s diverticulum are on the whole rare and epithelial ones are only the third most frequent. It seems reasonable to suppose that adenocarcinomas of the intestinal type arising in the ectopic mucosa are also preceded by dysplastic changes. The gastric glands may have a higher oncogenic potential than previously believed, but this potential could not be ascertained by the presence of true dysplasia (whatever its natural history) in this relatively small series, since all the reported changes were finally categorized as negative for dysplasia.

In conclusion the present study focuses on atypical/excessive proliferative epithelial changes seen in the ectopic gastric mucosa of Meckel’s diverticulum displaying reflux type gastritis/gastropathy or foveolar hyperplasia. These hyperplastic proliferations should be differentiated from dysplasia on the basis of their accentuation towards the surface, the lack of hyperchromatism and the presence of ovoid nuclei with loose chromatin pattern, while the lack of p53 immunopositivity and the localization of Ki-67 positivity to the expanded neck region could be additive clues in their evaluation. These latter findings could also help limiting the category indefinite for dysplasia in both the stomach and ectopic gastric mucosa.

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References