Pancreatic Acinar Cell Metaplasia in Autoimmune Gastritis

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Objective—To determine the frequency and significance of pancreatic acinar cells in the gastric oxyntic mucosa.

Design—One hundred gastric oxyntic mucosal biopsy specimens from patients with chronic active gastritis (n = 30), multifocal atrophic gastritis (n = 15), autoimmune gastritis (n = 18), and normal gastric oxyntic mucosa (n = 37) were evaluated for the presence of pancreatic acinar cells. Formalin-fixed, paraffin-embedded tissues were stained with hematoxylin-eosin, and those positive for pancreatic acinar cells were immunostained with antibodies against trypsin and pancreatic amylase.

Results—Eleven (11%) of 100 oxyntic mucosal tissue samples contained pancreatic acinar cells. These samples came from 9 of the 18 (50%) specimens of autoimmune gastritis, 1 of the 15 (6.6%) specimens of multifocal atrophic gastritis, and 1 of the 37 (2.7%) specimens of normal oxyntic mucosa. None of the samples with chronic active gastritis contained pancreatic acinar cells.

Conclusions—Pancreatic acinar cells were found in the oxyntic mucosa of patients with autoimmune gastritis significantly more frequently (P < .001) than in individuals with multifocal atrophic gastritis, normal oxyntic mucosa, or chronic active gastritis. Our study supports a metaplastic origin for pancreatic acinar cells in the oxyntic mucosa. Furthermore, detection of pancreatic acinar cells in the oxyntic mucosa of patients with gastritis strongly suggests an autoimmune pathogenesis.

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METHODS AND DESIGN

Samples of gastric oxyntic mucosa were collected, through either endoscopic biopsy or gastrectomy, from 100 individuals. These samples included 30 cases of chronic active gastritis, 15 cases of multifocal atrophic gastritis, 18 cases of autoimmune gastritis, and 37 cases of unremarkable gastric oxyntic mucosa, based on the diagnosis contained in the corresponding surgical pathology report. Twenty-eight samples of oxyntic mucosa obtained from gastrectomy and 72 from multiple (range, 3–10 biopsies) gastric oxyntic mucosal biopsies were evaluated.

The clinical diagnosis of autoimmune gastritis was established based on a combination of features that included history of an autoimmune disease (5/18 patients), elevated serum gastrin levels (range, >500–6202 pg/mL) in 12 of 18 patients, history of anemia (5/18 patients), vitamin B12 deficiency (2/18 patients), and endoscopic evidence of gastric atrophy and/or nodular stomach (6/18 patients). Serum gastrin levels were not available for 3 patients.

Tissues fixed in 10% buffered formalin and embedded in paraffin were retrieved from the histology files of the departments of pathology. All tissue sections were sectioned and stained with hematoxylin-eosin. Each sample was evaluated for presence and type of gastritis. The histopathologic parameters used to identify the different categories of chronic gastritis are those listed in a previous publication. Enterochromaffin-like cells in the gastric body were identified using the Grimelius silver stain. Proliferation of enterochromaffin cells was classified based on the previous categorization.

In all samples demonstrating the presence of pancreatic acinar cells after hematoxylin-eosin staining, the finding was corroborated by immunostaining adjacent sections with antibodies against trypsin (Biodesign Inc, Kennebuth, Me; diluted 1:2000) and pancreatic amylase (BioGenex Inc, Carpinteria, Calif). The immunoreaction was visualized with the standard avidin-biotin complex immunoperoxidase technique. The frequency of pancreatic acinar cells in the gastric oxyntic mucosa of normal populations, a congenital origin has been proposed for these ectopic pancreatic acinar cells.
A, Gastric oxyntic mucosa with atrophic changes with pancreatic acini noted in the mucosa (hematoxylin-eosin, original magnification ×20). B, Pancreatic acinar cells with biocromasia with basal basophilia and apical eosinophilia (hematoxylin-eosin, original magnification ×40). C, Pancreatic acinar cells show brown cytoplasmic staining with α-amylase (immunoperoxidase stain, original magnification ×40). D, Pancreatic acinar cells show brown cytoplasmic staining with trypsin (immunoperoxidase stain, original magnification ×40).

Table 1. Histologic Findings in Various Groups*

<table>
<thead>
<tr>
<th>Group</th>
<th>Acute Inflammation</th>
<th>Chronic Inflammation</th>
<th>Helicobacter pylori</th>
<th>ECL Hyperplasia</th>
<th>Intestinal Metaplasia</th>
<th>Pyloric Metaplasia</th>
<th>Pancreatic Metaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIG (n = 18)</td>
<td>3</td>
<td>14</td>
<td>3</td>
<td>18†</td>
<td>13</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>MAG (n = 15)</td>
<td>6</td>
<td>15</td>
<td>5</td>
<td>0</td>
<td>15</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>CAG (n = 30)</td>
<td>27</td>
<td>30</td>
<td>25</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unremarkable (n = 37)</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

* AIG indicates autoimmune gastritis; MAG, multifocal atrophic gastritis; CAG, chronic active gastritis; and ECL, enterochromaffin-like cells.
† Includes 8 patients with micronodular hyperplasia and 2 patients with carcinoid tumor.

Pancreatic acinar cell presence was determined for each patient category, and the results were compared with the χ² test for significance using SAS statistical software (SAS Institute Inc, Cary, NC). All tests of significance were 2-sided with α = .05.

RESULTS

Pancreatic acinar cells were identified in 11 (11%) of the tissue samples overall from both endoscopic biopsy specimens (8/11, 73%) and gastrectomy specimens (3/11, 27%). They were characterized by their pyramidal profile, basal basophilia, apical granular eosinophilia, and rounded nuclei with stippled chromatin. These cells were arranged in single or multiple acini and, less frequently, were encountered singly within the oxyntic glands (Figure, A and B). Immunoreactivity with antibodies against both trypsin (Figure, C) and pancreatic amylase (Figure, D) corroborated the findings.

In addition, biopsy specimens from patients with autoimmune gastritis demonstrated acute inflammation (4/18), chronic inflammation (14/18), Helicobacter pylori (3/18), enterochromaffin cell-like hyperplasia (18/18), intestinal metaplasia (13/18), and pyloric metaplasia (16/18) (Table 1). Pancreatic acinar cell metaplasia was also noted in 2 samples that demonstrated autoimmune gastritis with associated carcinoid tumor.

Pancreatic acinar cells were significantly (P < .001) more common in oxyntic mucosal samples from patients...
with atrophy than in those without atrophy (Table 2). Furthermore, pancreatic acinar cells were significantly more common in autoimmune gastritis (9/18, 50%) than in those of patients with multifocal atrophic gastritis (1/15, 6.6%) ($P = .007$) or patients with normal oxyntic mucosa (1/37, 2.7%) ($P < .001$) (Table 1). In this study, pancreatic acinar cells were absent from the oxyntic mucosa of patients with chronic active gastritis. The differences in frequency of pancreatic acinar cell metaplasia between autoimmune gastritis (9/18, 50%) and the other groups taken together (2/82, 2.4%) were also statistically significant ($P < .001$) (Table 3).

### COMMENT

The results of our study demonstrate that pancreatic acinar cells are present in a large proportion of gastric oxyntic mucosal samples from patients with autoimmune gastritis (50%) as opposed to being rare (2.4%) or absent altogether in the same mucosa from normal or other types of gastritic stomachs. Only a few studies have focused on pancreatic metaplasia in the gastric and lower esophageal mucosa. The initial observations by Doglioni and coworkers demonstrated that of all examined tissues pancreatic acinar cells were noted with higher frequency in cardiac (9.1%) and antral mucosa (0.8%) than in the oxyntic (0.16%) gastric mucosa. These authors, however, did not study the frequency distribution of pancreatic acinar cells in normal oxyntic mucosa and various gastritides in the oxyntic mucosa. Krishnamurthy et al demonstrated that only 10 (4%) of 239 of antral biopsy specimens and none of the 40 unremarkable oxyntic mucosal biopsy specimens demonstrated pancreatic acinar cells in pediatric patients. Frequency of pancreatic acinar cells in oxyntic mucosa has not been investigated in adult patients. The present study demonstrates a frequency of 11% (11/100) in the gastric oxyntic biopsy specimens in adult patients. Most of these cases represented pancreatic acinar cells in autoimmune gastritis (9 patients), whereas only 1 case each was from multifocal atrophic gastritis and normal gastric mucosa. The 1 case from normal gastric mucosa was noted in a patient who had undergone a partial gastrectomy.

All patients (12/12) with autoimmune gastritis in the study by Doglioni and coworkers demonstrated pancreatic acinar cells, whereas we saw pancreatic acinar cells in only 50% of our autoimmune population. This difference in frequency may in part be related to the indication for biopsy, prevalence of autoimmune gastritis, and stage of gastritis. Wang and colleagues have demonstrated a relationship between number of samples examined and incidence of pancreatic acinar cells; likewise, Doglioni and coworkers also recorded a higher frequency of pancreatic acinar cells in gastrectomy specimens than in endoscopic biopsy samples. In the present series, pancreatic acinar cells were detected in 3 (10.7%) of 28 cases (1 case each with autoimmune gastritis, multifocal atrophic gastritis, and normal oxyntic mucosa) from the gastrectomy specimens, whereas 8 (11%) of 72 cases were detected from multiple endoscopic biopsy sections examined. All 8 of these samples with pancreatic acinar cells were from patients with autoimmune gastritis.

The pathogenesis of pancreatic acinar cells in the gastric mucosa has been the subject of considerable speculation. In their original article, Doglioni and coworkers proposed an acquired, metaplastic origin based on the association of pancreatic acinar cells with inflamed gastric mucosa, metaplasia, and atrophy. However, more recent publications reported lack of such an association in adult patients at the gastroesophageal junction, gastric cardia, and gastric antrum. Likewise, pancreatic acinar cells have been reported in the gastric mucosa of pediatric subjects, where some of them have shown a dual differentiation characterized by the presence of endocrine and exocrine markers in the heterotopic cells. These observations in pediatric and adult patients have led some workers to conclude that pancreatic acinar cells have a congenital origin. However, in the pediatric patients studied by Krishnamurthy and colleagues, pancreatic acinar cells were observed only in the gastric antrum (10/239; 4.3%) and not in the corpus mucosa (0/44). On the contrary, the presence of such pancreatic heterotopia has almost invariably been associated with mucosal inflammation and, particularly, atrophy in gastric oxyntic mucosa by both Doglioni et al and our study. Coupled with the fact that autoimmune gastritis evolves rather late in life (fourth to fifth decade), this suggests that, at least when present in the gastric oxyntic mucosa, pancreatic acinar cell heterotopia reflects an acquired, metaplastic origin. Our findings, on the other hand, probably have little bearing on the origin of pancreatic acinar heterotopia in other locations, such as cardia or antrum, or in pediatric patients.

Based on the current observations, pancreatic acinar metaplasia can be regarded as a marker for autoimmune gastritis when found in the gastric oxyntic mucosa of adult patients. The diagnosis of autoimmune, or type A, gastritis is relatively easy in patients with the full-blown syndrome and in association with pernicious anemia, a late but frequent complication. However, in a prospective analysis of 729 elderly patients, it was noted that autoimmune gastritis was unrecognized in 14 (1.9%) of 729 patients who did not receive adequate treatment. It was also estimated in the same study that there are potentially 800 000 elderly patients with unrecognized autoimmune gastritis. It has been our observation that clinically unsuspected autoimmune gastritis or early-stage autoimmune gastritis often goes unrecognized by an unsuspecting pathologist. In such a scenario, a combination of pancreatic acinar metaplasia with other types of metaplasia, chronic inflammation, and/or atrophy of the oxyntic glands in the adult gastric mucosa should raise the suspicion of autoimmune

### Table 2. Association of Atrophy to Pancreatic Metaplasia

<table>
<thead>
<tr>
<th>Pancreatic Acinar Cell Metaplasia</th>
<th>Pancreatic Acinar Cell Metaplasia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>Not Observed</td>
<td></td>
</tr>
<tr>
<td>Atrophy noted</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>No atrophy noted</td>
<td>1</td>
<td>66</td>
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### Table 3. Association of Autoimmune Gastritis to Pancreatic Metaplasia

<table>
<thead>
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<th>Pancreatic Acinar Cell Metaplasia</th>
<th>Pancreatic Acinar Cell Metaplasia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Autoimmune gastritis</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Nonautoimmune gastritis</td>
<td>2</td>
<td>80</td>
</tr>
</tbody>
</table>
gastritis and trigger the appropriate testing to rule out or confirm this.

In conclusion, pancreatic acinar cells were found in the oxyntic mucosa of patients with autoimmune gastritis significantly more frequently ($P < .001$) than in individuals with multifocal atrophic gastritis or normal oxyntic mucosa. Our study supports a metaplastic origin for pancreatic acinar cells in the oxyntic mucosa. Finally, detection of pancreatic metaplasia in the oxyntic mucosa of patients with gastritis should inject a strong suspicion for an autoimmune pathogenesis.

References