Pancreatic Acinar Metaplasia in Distal Esophageal Biopsies Is Associated With Chronic Nonsteroidal Anti-inflammatory Drug Use

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• Context.—The cause of pancreatic acinar metaplasia (PAM) at the distal esophagus/esophagogastric junction is still controversial. Whereas some authors believe it is congenital, others believe it is acquired because of inflammation of the gastric cardia, and more recently it was proposed to be due to chronic proton pump inhibitor use based on a study in rats.

Objective.—To determine whether there is correlation between chronic proton pump inhibitor use and PAM in humans. We also investigated the correlation between several clinical and pathologic factors and PAM.

Design.—Four hundred forty-four consecutive biopsies from the distal esophagus/esophagogastric junction were reviewed for the presence of PAM, which was then correlated with several clinical and pathologic findings.

Results.—Pancreatic acinar metaplasia was found in 71 patients (16%). Pancreatic acinar metaplasia was significantly associated with patient age younger than 51 years ($P < .001$), chronic carditis ($P = .01$), and chronic proton pump inhibitor use ($P = .008$). Surprisingly, we also found significant association between PAM and chronic nonsteroidal anti-inflammatory drug use ($P < .001$). These associations, including that with chronic nonsteroidal anti-inflammatory drug use, remained significant in multivariate analysis.

Conclusions.—Our findings confirm the previous reports of significant association between PAM and chronic carditis and the findings from animal studies of association with chronic proton pump inhibitor use. The strong association with chronic nonsteroidal anti-inflammatory drug use has not been previously reported and warrants further studies.


Pancreatic acinar metaplasia (PAM), also called pancreatic acinar cell metaplasia, is defined as the presence of islands of glandular tissue forming acini composed of cells with coarse apical eosinophilic granules, with or without mucous cells closely resembling exocrine pancreatic tissue. It has been reported in gastric mucosa, at the esophagogastric junction (EGJ), at the distal esophagus, and in Barrett esophagus; however, the pathogenesis of this entity is still unclear. Whereas some authors have suggested that PAM is an acquired process representing a metaplastic change in association with chronic gastritis and autoimmune gastritis, others have raised the possibility of PAM being congenital in nature. More recently, experimental in vivo studies in rats suggested that PAM may be caused by chronic use of proton pump inhibitors (PPIs). The aim of this study was to determine whether there is a correlation between chronic PPI use and PAM in humans. We also investigated the correlation between several clinical and pathologic factors and PAM.

The study was approved by the Institutional Review Board for the University of Texas Health Science Center at Houston McGovern Medical School.

We searched the computerized pathology database at our hospital for a 1-year period (May 1, 2016–April 30, 2017) for all patients who underwent upper gastrointestinal endoscopy with EGJ and/or distal esophageal biopsy. Four hundred forty-four consecutive patients were identified and included in this study. Copies of the pathology reports and the pathology glass slides (sections of formalin-fixed, paraffin-embedded tissue, stained with hematoxylin-eosin) were obtained, and the computerized medical records were searched for relevant information. Pancreatic acinar metaplasia was defined as previously described by Wang et al. The histopathologic examination was performed by a single experienced gastrointestinal pathologist. Chronic nonste-
Univariate and Multivariate Analysis of Factors Associated With Pancreatic Acinar Metaplasia at the Esophagogastric Junction/Distal Esophagus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age &lt;51 y</td>
<td>2.64 (1.554–4.492)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chronic carditis</td>
<td>3.289 (1.153–9.383)</td>
<td>.03</td>
</tr>
<tr>
<td>Chronic PPI use</td>
<td>2.029 (1.2–3.343)</td>
<td>.008</td>
</tr>
<tr>
<td>Chronic NSAID use</td>
<td>3.678 (1.94–6.973)</td>
<td>&lt;.001</td>
</tr>
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Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor.

*P < .05 is significant.
Similar to what has been reported by others,\textsuperscript{1,11} we found that PAM is significantly associated with chronic carditis. Faller and Kirchner\textsuperscript{12} postulated that pancreatic metaplasia can be regarded as the result of altered morphogenesis within the gastric mucosa. Impaired expression of the gastric morphogenetic factor sonic hedgehog by parietal cells and increased expression of the pancreatic morphogenetic factor PDX1 seem to be crucial for the development of pancreatic transdifferentiation. Altered expression of the morphogenetic factors is partly caused by changes in the gastric milieu.\textsuperscript{12}

Recently, experimental in vivo studies in rat models\textsuperscript{8,13} have shown a link between long-term treatments with PPIs and risk of PAM development, and our results from this study support those reported in the rat models. In biopsies that contained oxyntic gastric mucosa, changes suggestive of PPI use, such as parietal cell hyperplasia and dilated fundic glands, were seen on microscopic examination. Proton pump inhibitors are a class of very efficient acid suppressors that are highly successful in controlling gastroesophageal reflux disease symptoms and prevent its complications, mainly esophageal inflammation and strictures. It is difficult to speculate on the mechanism by which chronic PPI use leads to PAM, especially because chronic inflammation at the cardia, which is supposed to be prevented by PPIs, is also significantly associated with PAM.

Probably the most important finding in this study is the significant and independent association between chronic NSAID use and PAM, which has not been reported to our knowledge in the English literature. Nonsteroidal anti-inflammatory drugs are a broad family of compounds primarily used to treat pain, control inflammation, and prevent heart attacks. Studies have also shown that NSAIDs are effective in the prevention of a few common cancers.\textsuperscript{14–16}

Bombardo et al\textsuperscript{17} investigated the effect of NSAIDs in the course of acute pancreatitis in terms of progression of inflammation and regeneration of the organ, using a murine model. They found that NSAIDs are able to directly inhibit mitogen-induced proliferation of pancreatic acinar cells. The findings from that study do not explain the link between chronic NSAID use and PAM in humans. To our knowledge, association between NSAIDs and PAM has not been reported in animal models.

The clinical significance of PAM at the EGJ/distal esophagus, if any, is still largely unknown. If PAM is functional and pancreatic enzymes are secreted within the local tissue of the distal esophagus or cardia, then perhaps PAM could be the cause of chronic inflammation (carditis) in that location, rather than being caused by it, which could explain why chronic PPI use has seemingly the opposite effect. It is still not known, for example, if larger PAM is associated with more significant inflammation, fibrosis, or other pathology in that location. Although no significant association is found between PAM and Barrett metaplasia in our study, we still don’t know what role, if any, PAM plays in the malignant progression of Barrett metaplasia. Finally, given the divergent molecular pathways of NSAID and PPI action, it would be interesting to know if PAM associated with either drug has a different clinical implication.

In conclusion, our results confirm the significant association between PAM and chronic inflammation of the gastric cardia (chronic carditis) and the association with chronic PPI use previously proposed from a rat model. The strong association with chronic NSAID use has not been previously reported, and we believe it warrants further studies.

\textbf{References}