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.

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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.

DESIGN

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-
Pancreatic Acinar Metaplasia and NSAID Use

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor.

RESULTS

Four hundred forty-four consecutive patients were identified and the related pathology material was retrieved. Because many of the biopsies were designated “distal esophagus/GE junction” by the gastroenterologists, it was not possible to get a reliable separation by exact location. None of the lesions (PAM) were visible endoscopically. The lesion size varied on microscopic examination (M.Y., unpublished data, July 2017), but this information was not recorded/recorded. The male to female ratio was 1:1.15 and the age range was 10 to 88 years (mean, 55.4 years; median, 58 years). An example of PAM is shown in the Figure. Seventy-one patients (15.9%) were found to have PAM. The presence of PAM on histopathologic examination was correlated with several clinical and pathologic findings.

There was no significant association between PAM and patient gender (24 male, 47 female versus 166 male, 207 female; P = .12), the mean number of biopsy pieces taken at endoscopy (3.5 versus 3.6; P = .75), the presence of active inflammation (9 of 70 versus 66 of 377, P = .39), Barrett metaplasia (21 of 71 versus 103 of 373, P = .58), the presence of pseudogoblet cells (9 of 71 versus 57 of 373, P = .72), or multilayered epithelium (6 of 71 versus 20 of 373, P = .28). In patients for whom the appropriate clinical information was documented, we found no significant association between PAM and clinical diagnosis of reflux esophagitis (30 of 70 versus 160 of 354, P = .79), current or previous Helicobacter pylori gastritis (12 of 71 versus 50 of 362, P = .46), history of bariatric surgery (1 of 68 versus 11 of 358, P = .70), or history of cholecystectomy (12 of 68 versus 61 of 359, P = .86).

Pancreatic acinar metaplasia was significantly associated with chronic carditis (66 of 70 versus 309 of 373, P = .01), patient age younger than 51 years (35 of 71 versus 105 of 373, P < .001), chronic PPI use (40 of 71 versus 137 of 352, P = .008), and chronic NSAID use (19 of 69 versus 34 of 347, P < .001). To determine whether the factors significantly associated with PAM were independent variables, the data were reviewed and 30 cases that did not have complete information on either or both PPI and NSAID use were removed. The remaining 414 cases, 68 of which had PAM, were used in the subsequent analysis. The results of univariate and multivariate analyses show that chronic carditis, patient age younger than 51 years, chronic PPI use, and chronic NSAID use are independently associated with PAM (Table).

DISCUSSION

In the present study, PAM was found in 15.9% of biopsies from the EJG. This prevalence rate is slightly lower than that reported by Wang et al2 but higher than that originally reported by Doglioni and colleagues.1 Data in the literature regarding PAM prevalence are considerably variable. Whereas Polkowski et al10 noted pancreatic acinar cells in 14% of cases, Sarbia et al11 found pancreatic acinar cells in 61% of specimens. It has been suggested that the prevalence rates of pancreatic acinar cells at the EJG are highly dependent on the methodology applied for their detection, and that the prevalence rate will be lower if only one section of the biopsy is examined. In one study, it was suggested that PAM can be found in the cardiac region of all subjects if the area is exhaustively sampled.4

In a study that included 155 patients, Wang et al12 found significant association of PAM with young age and proposed that PAM is congenital in nature. In our study, although we found significant association with younger age, PAM was also significantly and independently associated with chronic inflammation at the gastric cardia and chronic use of PPIs and NSAIDs, all of which have to occur after birth. Whether a subset of PAM may be congenital needs to be confirmed by studying neonatal autopsies.

| Variable                  | Univariate Analysis | Multivariate Analysis |
|---------------------------|---------------------|-----------------------|
|                          | OR (95% CI)         | P                     | OR (95% CI)          | P                     |
| Age  $<$ 51 y             | 2.64 (1.554–4.492)  | .001                  | 3.127 (1.761–5.551)  | .001                  |
| Chronic carditis          | 3.289 (1.153–9.383) | .03                   | 3.019 (1.012–9.003)  | .047                  |
| Chronic PPI use           | 2.029 (1.2–3.343)   | .008                  | 1.865 (1.074–3.238)  | .03                   |
| Chronic NSAID use         | 3.678 (1.94–6.973)  | <.001                 | 4.684 (2.35–9.333)   | <.001                 |

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,1,11 we found that PAM is significantly associated with chronic carditis. Faller and Kirchner2 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.12

Recently, experimental in vivo studies in rat models4,8,13 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.14–16 NSAID use and PAM, which has not been reported to our knowledge, association between NSAIDs and PAM has not been 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.

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