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Original Contribution

Hit or a miss: Concordance between histopathologic-endoscopic findings in gastric mucosal biopsies☆,☆☆

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ABSTRACT

Background: Current literature shows a variable degree of concordance between endoscopic and histopathologic findings in gastric mucosal biopsies. Most prior studies have focused on specific gastric entities such as gastritis in patients with high prevalence of *Helicobacter pylori* (*H. pylori*). In this study, we assess concordance between histologic and endoscopic findings in a wide spectrum of targeted as well as non-targeted gastric endoscopic biopsies.

Methods: We retrospectively reviewed pathology database and slides at Hershey Medical Center to identify 630 gastric mucosal biopsies obtained from 525 consecutive patients. The corresponding clinical and endoscopic findings were retrieved from the electronic medical record.

Results: The rate of abnormal endoscopic and histologic findings was 72.9% and 74.4%, respectively, with Cohen's κ coefficient of 0.24. There were 444 (70.5%) concordant cases and 186 (29.5%) discordant cases (88 cases with abnormal endoscopy but normal histology, and 98 cases with normal endoscopy but abnormal histology). Some endoscopic findings, in particular, mass, polyp, ulcer, and nodule/papule were highly concordant with abnormal histopathologic findings; while other endoscopic findings such as inflammatory changes, normal and prominent folds were associated with normal and a variety of abnormal histopathology. Multivariate analysis showed no significant association between intestinal metaplasia and *H. pylori* in this study.

Conclusions: Histopathologic-endoscopic correlation in gastric biopsies varies depending on endoscopic mucosal patterns. Intestinal metaplasia may not have a significant association with *H. pylori* infection in populations with low prevalence of *H. pylori*.

1. Introduction

Upper gastrointestinal tract (GI) endoscopy is a commonly performed procedure for the diagnostic evaluation of signs and symptoms of a wide variety of GI complaints. A gastric biopsy is frequently obtained when mucosal abnormalities, such as inflammatory changes, atrophy, polyp, nodule, ulcer or mass, are identified. In many cases, biopsies are also obtained from normal-appearing mucosa in patients with dyspepsia for the detection of possible *Helicobacter pylori* (*H. pylori*) infection [1,2].

Pathologic-endoscopic correlation in gastric specimens is not always concordant. In daily practice, histopathologic diagnosis of gastric mucosal biopsies has generally been considered a “gold standard” and often dictates the subsequent patient management after endoscopic examination. It may be helpful to know the concordance between the histopathologic diagnoses and the various endoscopic appearances of gastric mucosa as some endoscopic patterns probably are more concordant with the histopathologic examination than others. It would be particularly helpful for the endoscopist to know which mucosal abnormalities most often have discordant histopathology in order to avoid premature characterization of these findings on their reports and discussions with their patients. Also, which biopsy sites within the

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stomach are more prone to discordant histopathology may improve the targeting of biopsies and interpretation of histopathology results.

Published studies on histopathologic-endoscopic correlation in gastric mucosal biopsies show that endoscopic findings have a variable degree of concordance with histopathologic diagnosis [3,4], and most studies have demonstrated a poor correlation in "gastritis" with average concordance rates between 54% and 66% [5-7]. However, the majority of the previous studies have largely used discrete analyses, focusing on specific gastric entities (e.g. gastritis, *H. pylori*, atrophy or intestinal metaplasia (IM)) [6-10]. There are rather limited data on correlation analysis of histologic assessment of a wide spectrum of targeted as well as non-targeted endoscopic biopsies including endoscopically normal appearing mucosa or inflammatory changes, ulcer, polyp, nodules/papules, mass, atrophy, and other miscellaneous findings. Additionally, many of the studies investigating risk factors of gastric precancerous lesions such as the relationship between *H. pylori* infection and IM have been done in Western Europe [9,11], Eastern Asia [12,13] and Africa [14], where the prevalence of *H. pylori* is higher than that in North America[15].

To this end, the aims of our study are to 1) evaluate a comprehensive spectrum of histologic findings seen in gastric mucosal biopsies and their concordance with various endoscopic findings; 2) compare the histopathologic findings among different biopsy sites including antrum, body, cardia, fundus and unspecified sites; and 3) identify the potential clinico-pathologic risk factors for precancerous lesions including IM and *H. pylori* infection in United States.

2. Methods

2.1. Study design

This Institutional Review Board approved retrospective cohort study was performed at Penn State Milton S. Hershey Medical Center. We reviewed our pathology database to identify all gastric mucosal biopsies performed in adult patients (ages 18 to 99-years-old) from 01/01/2016 to 08/31/2016. There were no selective criteria for presenting symptoms. The endoscopic reports were available in all patients whose endoscopy was done at HMC or any center affiliated with HMC. Exclusion criteria included: 1) no endoscopy reports available (in some cases of extramural consultation or transfer cases from outside hospitals); 2) Endoscopic examination suggested excessive gastric secretions, food, or blood in the entire stomach; so that the endoscopic evaluation of gastric mucosa was limited. The corresponding clinical information (age, gender, indication for upper GI endoscopy), endoscopic findings and pathology reports were retrieved from electronic medical record and pathology database. All the available H&E slides and available ancillary stains were re-reviewed by a GI fellowship trained pathologist (DK).

2.2. Endoscopic findings

The biopsy site in the stomach (if specified) and the endoscopic appearances were tabulated from the endoscopy reports.

2.3. Histopathologic features

The histological changes were classified as

(a) Normal
(b) Gastritis- This included chronic active gastritis, chronic inactive gastritis, and other patterns of gastritis (such as acute gastritis, focally-enhanced gastritis, and autoimmune atrophic gastritis). Chronic gastritis was diagnosed when there was either an expansion of lamina propria by plasma cells or even when few clusters of plasma cells were identified in the lamina propria. Active/acute gastritis was diagnosed when there was evidence of neutrophil-mediated epithelial injury with or without associated reactive epithelial changes. Autoimmune atrophic gastritis was diagnosed when there was chronic gastritis associated with metaplasia (intestinal metaplasia along with pyloric gland metaplasia with or without Paneth cell metaplasia), along with destruction of oxyntic mucosa and in the appropriate clinical context.
(c) Reactive gastropathy (including drug-induced reactive changes) - The histopathologic features include foveolar hyperplasia, foci of mucin loss, vascular ectasia, stranding of muscularis mucosae, and lamina propria edema. Typically, there was minimal active and chronic inflammation.
(d) Intestinal metaplasia (IM) (IM only, IM with other histologic findings such as IM with chronic gastritis, IM with reactive gastropathy, and IM seen with hyperplastic polyp).
(e) Proton pump inhibitor (PPI) therapy effects-The parietal cells typically show apocrine-like cytoplasmic blebbing/swelling along with variable foci of vacuolization of parietal cells.
(f) Polyps (including fundic gland polyp, hyperplastic polyp, tubular adenoma and inflammatory fibroid polyp).
(g) Neoplasms (including adenocarcinoma, lymphoma, and neuroendocrine tumors).
(h) Others (such as granulation tissue and xanthoma).

2.4. Ancillary testing for H. pylori identification

The preferred ancillary method of testing for *H. pylori* in our institution is the use of immunohistochemistry. The Rodger C. Haggitt Gastrointestinal Pathology Society (GIPS) recommendations are mostly used for ordering immunohistochemical stain on gastric biopsies for detection of *H. pylori* [16]. We found that the immunostain was usually ordered when the gastric biopsy showed chronic active gastritis or chronic inactive gastritis and the organisms were not visualized on the H&E stain. It was also performed on biopsies with intestinal metaplasia and in biopsies obtained from patients with history of *H. pylori* treatment. The immunostain was typically not performed in cases with no pathologic alteration or in biopsies with reactive gastropathy, up until specifically requested by the clinician to order this immunostain.

2.5. Statistical analysis

Categorical variables were summarized by frequencies and percentages. The correlation between endoscopic and histological findings was assessed using Cohen's κ coefficient. Positive predictive value (PPV, the probability that patients with abnormal endoscopic finding truly have abnormal histologic findings), negative predictive value (NPV, the probability that patients with normal endoscopic finding truly don't have abnormal histologic findings), sensitivity (true positive rate), specificity (true negative rate) and false negative rate (1- sensitivity, cases with normal endoscopy but abnormal histology) were calculated for each biopsy location in the stomach. Univariate and multivariate logistic regression analysis was performed in SPSS version 25.0 software (SPSS Inc., Chicago, IL, USA) for calculating odds ratio (OR) and 95% confidence interval (CI). Both univariate and multivariate analyses showed similar results, so only data from multivariate analysis is tabulated in this study. A p value < 0.05 was regarded as statistically significant.

3. Results

3.1. Patient characteristics

The study included 630 gastric mucosal biopsies taken from 525 consecutive patients, comprised of 312 females (mean age 52.5 ± 16.7 years, range 18 to 89 years) and 213 males (mean age 55.2 ± 17.2 years, range 18 to 91 years).

3.2. Endoscopic findings

The biopsy site was categorized as antrum (60.2%), body (18.6%), cardia (4.1%), fundus (4.0%), or unspecified (13.2%), based on the available endoscopy reports.

Endoscopic findings were broadly classified into these categories:

(a) Normal (171/630; 27.1%),
(b) Inflammatory changes including erythema, granularity, and edema (311/630; 49.4%),
(c) Ulcer (36/630; 5.7%),
(d) Polyp (58/630; 9.2%),
(e) Nodules/papules (23/630; 3.7%),
(f) Mass (10/630; 1.6%),
(g) Atrophy (13/630; 2.1%)
(h) Large folds (8/630; 1.3%).

3.3. Endoscopic-histopathologic concordance

Overall comparison of endoscopic findings with histologic findings showed 186 discordant cases (29.5%) and 444 concordant cases (70.5%). The discordant cases included 88 cases with abnormal endoscopy but normal histology, and 98 cases with normal endoscopy but abnormal histology (Table 1). Cohen's κ coefficient used to assess the level of concordance was 0.24, suggesting a fair agreement between gastric endoscopic and histopathologic findings. The overall PPV, NPV, sensitivity, specificity and false negative rates were 80.8%, 42.7%, 79.1%, 45.3%, and 20.9%, respectively.

For the specific endoscopic findings, the highest PPV was associated with mass (100%), followed by polyp (98.3%), ulcer (91.7%), nodules/papules (91.3%), and atrophy (84.6%). The lowest PPV was identified with inflammatory changes (75.6%) and large folds (50%).

3.4. Histopathologic findings seen in association with normal endoscopic appearance

Less than half (42.7%, n = 73/171) biopsies with normal endoscopy showed no pathologic alteration on histologic examination and were concordant, while the remaining 57.3% (n = 98/171) showed positive findings including 2.9% (n = 5/171) biopsies with H. pylori associated chronic gastritis (Fig. 1a, b) and 7% (n = 12/171) biopsies with intestinal metaplasia (Fig. 1c, d) (Tables 1, 2). Patients with *H. pylori*-associated chronic gastritis and normal endoscopic appearance presented with epigastric pain (3/5), intractable dyspepsia (1/5), and recurrent *H. pylori* with resistance to treatment (1/5). Patients with intestinal metaplasia had clinical history of well-documented Barret's esophagus (BE) (4/12), gastroesophageal reflux disease (GERD) (2/12), follow-up of prior history of IM (1/12), epigastric pain (2/12), functional dyspepsia (2/12) and melena (1/12). Three of the four biopsies taken in patients from a well-documented clinical history of BE had the specimen designated as "cardia" on the requisition slip and the forth patient with BE had the biopsy taken from the gastric body which showed IM. The remaining biopsies with IM in this category of normal endoscopic examination were taken from antrum. Additionally, coexistence of *H. pylori* infection and IM was not observed in this category of normal endoscopic finding. The varying histopathologic findings seen with normal endoscopic appearance is summarized in Tables 1 and 2.

3.5. Histopathologic findings seen in association with abnormal endoscopic appearance

With regard to inflammatory-type endoscopic appearance, which included erythema, edema, and granularity, 24.4% (n = 76/311) of the biopsies showed no significant pathologic alteration and were discordant (Fig. 2a, b). The spectra of histopathologic findings seen with various abnormal endoscopic appearances is summarized in Tables 1 and 2 (Fig. 2, 3). Remarkably, three cases with endoscopically visible ulcer (8.3%, n = 3/36) also showed normal histology. Further investigation of these cases demonstrated ulcers shared some common endoscopic features including small size of < 5 mm in the greatest dimension, and a clean ulcer base. Additionally, of the 10 biopsies diagnosed endoscopically as masses, 6 (60%) showed a neoplastic process (4 adenocarcinoma and 2 lymphoma) and 4 showed inflammatory/hyperplastic/reactive changes with or without granulation tissue, suggesting proximity to a mass lesion and possibly sampling issues.

3.6. Histopathologic and endoscopic correlation among various biopsy sites

Subsequently, endoscopic findings were compared with histologic findings among specific biopsy sites (Table 3). Tissue samples submitted without topographic identifiers had the highest Cohen's κ coefficient (0.301), followed by antrum (0.276), body (0.209), and fundus (0.172). Cardia had the lowest Cohen's κ coefficient (−0.076) for concordance between any endoscopic and histologic findings, suggesting that there is no agreement between these two findings. Almost half biopsy specimens designated on the requisition slip as "cardia" (n = 12/25) with normal endoscopic impressions were shown to have abnormal histologic findings. The false negative rate in the biopsies labeled as cardia (48%) was significantly higher than those in all other biopsy sites including antrum (21.1%), unspecified (20.3%), body (15.2%) and fundus (9.5%), giving an impression that the specimens labeled as cardia had the poorest concordance with endoscopic diagnosis. However, we did a case-by-case review of the twelve discordant cardia cases with an endoscopically normal-appearing cardia with abnormal histopathology. We found that while the pathology specimens were labeled "cardia" and the endoscopic appearance of the stomach (including

Table 1
Concordance between endoscopic and histopathologic findings in gastric mucosal biopsies.

Endoscopic findings	Histologic findings								
	Normal	Gastritis	Reactive gastropathy	PPI	IM	Polyp	Neoplasm	Other	Total
Normal	73 (42.7%)	65 (38%)	16 (9.4%)	5 (2.9%)	12 (7%)	0 (0%)	0 (0%)	0 (0%)	171 (100%)
Abnormal	88 (19.2%)	179 (39%)	78 (17%)	7 (1.5%)	37 (8.1%)	54 (12%)	10 (2.2%)	6 (1.3%)	459 (100%)
Inflammatory	76 (24.4%)	142 (45.7%)	61 (19.6%)	6 (1.9%)	21 (6.8%)	2 (0.6%)	1 (0.3%)	2 (0.6%)	311 (100%)
Ulcer	3 (8.3%)	19 (52.8%)	6 (16.7%)	0 (0%)	6 (16.7%)	0 (0%)	1 (2.8%)	1 (2.8%)	36 (100%)
Polyp	1 (1.7%)	4 (6.8%)	2 (3.4%)	0 (0%)	1 (1.7%)	50 (84.7%)	1 (1.7%)	2 (3.4%)	58 (100%)
Nodules/papules	2 (8.7%)	9 (39.1%)	4 (17.4%)	0 (0%)	4 (17.4%)	2 (8.7%)	1 (4.3%)	1 (4.3%)	23 (100%)
Mass	0 (0%)	1 (10%)	2 (20%)	0 (0%)	0 (0%)	0 (0%)	6 (60%)	1 (10%)	10 (100%)
Atrophy	2 (15.4%)	4 (30.8%)	3 (23.1%)	0 (0%)	4 (30.8%)	0 (0%)	0 (0%)	0 (0%)	13 (100%)
Large folds	4 (50%)	1 (12.5%)	0 (0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	0 (0%)	0 (0%)	8 (100%)
Total	161 (25.6%)	250 (39.7%)	94 (14.9%)	12 (1.9%)	43 (6.8%)	54 (8.6%)	10 (1.6%)	6 (1.0%)	630 (100%)

Cohen's κ = 0.24.
Abbreviation: PPI: proton pump inhibitor therapy effect; IM: intestinal metaplasia.

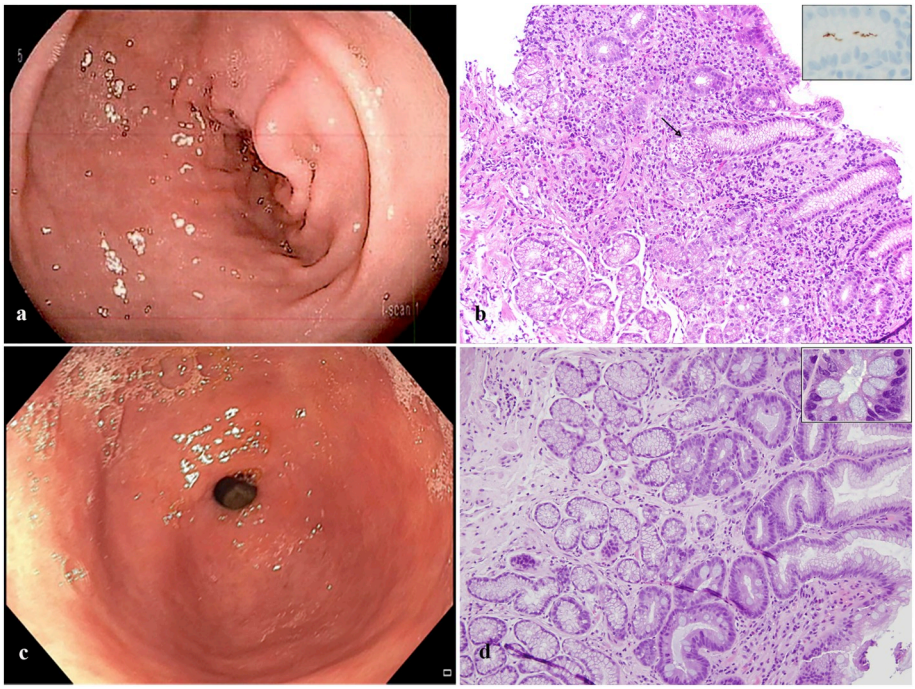

Fig. 1. Discordant cases with normal endoscopy and abnormal histopathology (a, b) Endoscopically normal appearing gastric antrum in a 30-year-old male with epigastric pain. Corresponding biopsy shows chronic active gastritis with the arrow highlighting neutrophil mediated epithelial injury (H&E × 100). The inset shows immunostain highlighting *H. pylori* organisms (Inset *H. pylori* immunostain × 400). (c, d) Endoscopically normal appearing gastric antrum in a 70-year-old male with a history of gastroesophageal reflux disease (d) Corresponding biopsy shows intestinal metaplasia (H&E × 200). Inset highlights the goblet cells (intestinal metaplasia) (inset H&E × 400).

cardia) was "normal" in the endoscopy reports, in only one case was a truly normal-appearing cardia exclusively targeted for biopsy. In all other cases, an abnormality in the gastroesophageal junction (GE) junction (commonly esophagitis, BE, and irregular z-line) was identified and targeted for biopsy along with non-targeted biopsy from "cardia" in the same container and the biopsy was labeled as "cardia", so the above high false negative rates in the cardia may not be entirely representative. Further, four of the patients were documented as having a small hiatal hernia which may have complicated the determination of the true GE junction.

3.7. Clinico-pathologic variables associated with IM

Univariate and multivariate analysis were performed on several clinico-pathologic variables to analyze factors affecting occurrence of intestinal metaplasia. The results demonstrated age older than 55 years ($p = 0.01$), biopsy specimen labeled as cardia ($p < 0.001$), the presence of endoscopic atrophy ($p = 0.005$), and the histologic presence of chronic active gastritis ($p = 0.004$) were associated with increased risk of IM. The presence of IM in gastric mucosal biopsy was significantly associated with the presence of low grade and/or high grade dysplasia ($p = 0.001$). A re-analysis was done, excluding biopsies labeled as "cardia", owing to the above reason and the re-analysis showed somewhat similar findings, as in the presence of IM was significantly associated with age older than 55 years ($p = 0.03$), the presence of endoscopic impression of atrophy ($p = 0.02$), histologic finding of chronic active gastritis ($p < 0.01$) and the presence of dysplasia ($p < 0.01$). (Table 4).

3.8. Clinico-pathologic variables associated with H. pylori

H. pylori associated gastritis can present with variable appearance on endoscopic examination. Although *H. pylori* was significantly associated with endoscopic finding of ulcer ($p < 0.05$), it was also found to present on endoscopy as inflammatory changes, nodules/papules, prominent folds and even as normal endoscopic appearance (in patients with dyspepsia or prior history of *H. pylori*) (Tables 2 and 5). *H. pylori* immunostain was performed in 58% of the biopsies in our study. Compared with chronic inactive gastritis (odds ratio: 0.97, $p = 0.97$), chronic active gastritis was more likely associated with the presence of *H. pylori* organisms on the mucosal biopsy specimen (odds ratio: 34.5, $p < 0.001$) (Table 5). Our studies also demonstrated that *H. pylori* infection was not seen in patients with other patterns of gastritis (including acute gastritis, focally enhancing gastritis, autoimmune atrophic gastritis) and in the histologic absence of gastritis. Additionally, in our series, *H. pylori* appeared to have no statistically significant association with intestinal metaplasia (OR: 1.31, $p = 0.67$) (Table 4).

4. Discussion

In this study, we examine the endoscopic-histopathologic correlation in targeted as well as random gastric biopsies. Our results showed that the rate of abnormal endoscopic and histologic findings was 72.9%, and 74.4%, respectively, with Cohen's κ coefficient of 0.24. There were 444 (70.5%) concordant cases and 186 (29.5%) discordant cases (88 cases with abnormal endoscopy but normal histology, and 98 cases with normal endoscopy but abnormal histology). The concordance rate of inflammatory-type endoscopic appearance with abnormal histology was 75.6%, which was somewhat higher than previously reported concordance rates. One possible explanation for this higher percentage may be the use of higher-definition endoscopy. Also, different pathologists have varying thresholds for histopathologic diagnosis of chronic gastritis, especially the pathologic diagnosis of mild chronic gastritis. As also emphasized in the literature [17], a precise definition of chronic gastritis is limited by lack of a universal standard for the number of mononuclear inflammatory cells in the normal mucosa. The expected number of mononuclear leukocytes in the lamina propria of gastric mucosa is reported as a maximum of 2 to 5 lymphocytes, plasma cells and macrophages per high power microscopic field (×40 objective) [17]. However, many pathologists agree that plasma cells should be sparse or absent from the stomach of healthy persons; and the presence of plasma cells in the gastric mucosal biopsies is an important indicator of a chronic inflammatory response, and should be reported as chronic gastritis [17]. Given the variability in the literature and differing thresholds among different pathologists with no gold standard, some would make the call when they see few interspersed plasma cells, while others need to see at least few clusters of

Table 2
Spectra of histopathologic findings seen with various endoscopic appearances in gastric mucosal biopsies.

Endoscopic findings	Histologic findings	NO. of biopsies	*HP*
Normal	Abnormal	98 (57.3%)	
	Gastritis	65 (38%)	
	Chronic inactive gastritis	51 (29.8%)	2
	Chronic active gastritis	11 (6.4%)	3
	Other patterns of gastritis[a]	3 (1.8%)	
	Reactive gastropathy	16 (9.4%)	
	PPI	5 (2.9%)	
	IM	12 (7%)	
	IM with chronic gastritis	8 (4.7%)	
	IM only	4 (2.3%)	
	Normal	73 (42.7%)	
	Subtotal	171 (100%)	5
Inflammatory changes	Abnormal	235 (75.6%)	
	Gastritis	142 (45.7%)	
	Chronic inactive gastritis	99 (31.8%)	6
	Chronic active gastritis	27 (8.7%)	15
	Other patterns of gastritis[b]	16 (5.1%)	
	Reactive gastropathy	61 (19.6%)	
	PPI	6 (1.9%)	
	IM	21 (6.8%)	
	IM with chronic gastritis	16 (5.1%)	2
	IM only	5 (1.6%)	
	Other	5 (1.6%)	
	Fundic gland polyp	2 (0.6%)	
	Granuloma	2 (0.6%)	
	Residual lymphoma	1 (0.3%)	
	Normal	76 (24.4%)	
	Subtotal	311 (100%)	23
Ulcer	Abnormal	33 (91.7%)	
	Gastritis	19 (52.8%)	
	Chronic inactive gastritis	12 (33.3%)	2
	Chronic active gastritis	7 (19.4%)	3
	Reactive gastropathy	7 (19.4%)	
	IM	5 (13.9%)	
	IM with chronic gastritis	1 (2.8%)	
	IM with reactive gastropathy	4 (11.1%)	
	Other	2 (5.6%)	
	Adenocarcinoma	1 (2.8%)	
	Granulation tissue	1 (2.8%)	
	Normal	3 (8.3%)	
	Subtotal	36 (100%)	5
Polyp	Abnormal	58 (98.3%)	
	Polyp/adenoma	50 (84.7%)	
	Fundic gland polyp	38 (64.4%)	
	Hyperplastic polyp	10 (16.9%)	
	Adenoma	2 (3.4%)	
	Gastritis	4 (6.8%)	
	Chronic inactive gastritis	1 (1.7%)	
	Chronic active gastritis	3 (5.1%)	
	Chronic active gastritis	3 (5.1%)	
	IM with hyperplastic polyp	1 (1.7%)	
	Other	3 (5.1%)	
	Neuroendocrine tumor	1 (1.7%)	
	Reactive gastropathy	2 (3.4%)	
	Normal	1 (1.7%)	
	Subtotal	59 (100%)	0
Nodules/papules	Abnormal	21 (91.3%)	
	Gastritis	9 (39.1%)	
	Autoimmune atrophic gastritis	1 (4.3%)	
	Chronic inactive gastritis	4 (17.4)	1
	Chronic active gastritis	4 (17.4%)	2
	Reactive gastropathy	4 (17.4%)	
	IM	4 (17.4%)	
	IM with chronic inactive gastritis	1 (4.3%)	
	IM with reactive gastropathy	2 (8.7%)	
	IM only	1 (4.3%)	
	Other	4 (17.4%)	
	Fundic gland polyp	1 (4.3%)	
	Inflammatory fibroid polyp	1 (4.3%)	
	Neuroendocrine tumor	1 (4.3%)	
	Xanthoma	1 (4.3%)	
	Normal	2 (8.7%)	
	Subtotal	23 (100%)	3
Mass	Abnormal	10 (100%)	
	Neoplastic	6 (60%)	
	Carcinoma	4 (40%)	
	Lymphoma	2 (20%)	
	Non-neoplastic	4 (40%)	
	Chronic active gastritis	1 (10%)	
	Granulation tissue	1 (10%)	
	Reactive gastrophy	2 (20%)	
	Normal	0 (0%)	
	Subtotal	10 (100%)	0
Atrophy	Abnormal	11 (84.6%)	
	Gastritis	4 (30.8%)	
	Autoimmune atrophic gastritis	1 (7.7%)	
	Chronic active gastritis	1 (7.7%)	
	Chronic inactive gastritis	2 (15.4%)	
	Reactive gastropathy	3 (23.1%)	
	IM with chronic gastritis	4 (30.8%)	
	Normal	2 (15.4%)	
	Subtotal	13 (100%)	0
Large folds	Abnormal	4 (50%)	
	Chronic active gastritis	1 (12.5%)	1
	IM with high grade dysplasia	1 (12.5%)	
	Other	2 (25%)	
	Fundic gland polyp	1 (12.5%)	
	PPI effect	1 (12.5%)	
	Normal	4 (50%)	
	Subtotal	8 (100%)	1

Abbreviation: PPI: proton pump inhibitor therapy effect; IM: intestinal metaplasia, *HP*: *Helicobacter pylori* positive biopsies.
[a] Include 1 case of acute gastritis and 2 cases of focally enhanced gastritis.
[b] Include 12 cases of acute gastritis and 4 cases of focally enhanced gastritis.

plasma cells and yet others need to see a definite expansion of lamina propria by plasma cells. The latter category of pathologists' could argue that mild chronic inflammation in a gastric mucosal biopsy has no clinical significance and should be included in the normal group [18], especially given that the diagnosis of "mild chronic inactive gastritis of no specific etiology" is not an actionable finding and most gastroenterologists would not do anything specific when rendered with this diagnosis. All these factors may further contribute to varying concordance rates reported in the literature. The authors in this study believe that since clusters of plasma cells should not be identified in a normal stomach; hence, any clusters of plasma cells merit a diagnosis of chronic gastritis solely on histopathologic grounds, although we agree that there may not be any "action" from the clinician based upon this non-specific finding.

There are standardized systems available such as the updated Sydney system [17] which provide pathologists with guidelines to generate uniform and consistent gastric biopsy pathology reports. However, this system requires at least five biopsy specimens to be evaluated before synthesis of the report. Unfortunately, many a times, in routine clinical practice, the gastroenterologists may not adhere to these labeling and/or sampling protocols, and the pathologists are asked to generate a report based on merely one or two biopsy specimens. This is not addressed by the Sydney system, and hence this system cannot be used in these cases and limits its use in routine clinical practice.

Carr et al. compared the endoscopic diagnosis and pathologic diagnosis of gastritis in 400 patients, and concluded that endoscopy is a poor predictor of gastric inflammation and biopsy is the gold standard for accurate diagnosis of gastritis [5]. Khakoo et al. reported that endoscopic inflammatory findings including erythema, granularity and edema should be employed as descriptive, not diagnostic terms because no histopathological correlates were found [6]. On the contrary, others

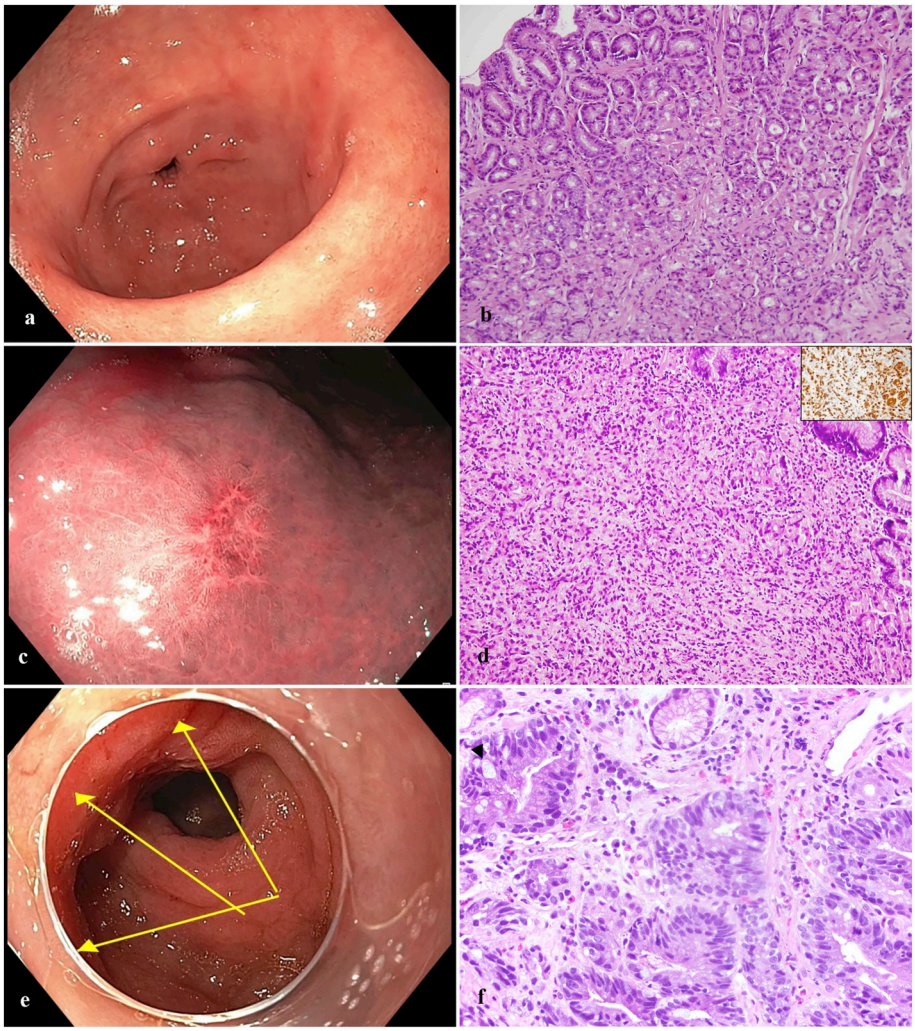

Fig. 2. Abnormal endoscopic appearance with corresponding histopathologic findings (a, b) Endoscopically visible erythematous changes in gastric antrum of an 82-year-old female with dysphagia. The corresponding biopsy shows no pathologic alteration (H&E × 100). (c, d) Endoscopically visible gastric body ulcer in a 77-year-old male with the history of iron deficiency anemia. Corresponding biopsy shows adenocarcinoma. Inset highlights the neoplastic cells positive for CK AE1/3 (H&E × 100; inset CK AE1/3 immunostain × 100). (e, f) Endoscopically visible enlarged gastric folds (depicted by arrows) in a 91-year-old male with a history of T1a gastric adenocarcinoma status post endoscopic submucosal resection. Corresponding biopsy shows at least high-grade dysplasia in a background of intestinal metaplasia (arrow head) (H&E × 200).

reported a high concordance, suggesting that endoscopy provides a reliable assessment for histologically severe gastritis and biopsy may not be necessary in each case of gastritis [19,20].

Notably, our study also found some endoscopic findings (e.g. mass, polyp, ulcer or nodule/papule) were highly concordant with positive histopathologic findings, while prominent folds and normal appearance on endoscopy were mostly associated with a varied spectrum of both normal and abnormal histologic findings. Interestingly, endoscopic ulcers with a small size of < 0.5 cm were likely to have normal histology and show discordance, though this may be due to sampling issues.

With regard to the site of the biopsy, we observed a significant discrepancy between endoscopic and histologic findings in the biopsy specimens which were received labeled as gastric “cardia” from the endoscopy suite. Roughly half of these cases had abnormal findings on histopathologic examination, including four biopsies with intestinal metaplasia and eight biopsies with expansion of lamina propria by lymphoplasmacytic inflammation (chronic gastritis). Per endoscopy report, the visualized stomach was normal in these cases. We found this to be quite surprising, particularly because the endoscopists often do not go out of their way to biopsy “normal appearing” cardia when there are other areas of the gastric mucosa from which random biopsies are more easily attained. Thus, we embarked on a case-by-case review of the twelve discordant cases with an endoscopically normal-appearing cardia with abnormal histopathology. We found that while the pathology specimens were labeled “cardia” and the endoscopic appearance of the stomach (including cardia) was “normal” in the endoscopy reports, in only one case was a truly normal-appearing cardia exclusively targeted for biopsy. In all other cases, an abnormality in GE junction (most commonly esophagitis, BE, and irregular z-line) was also identified and targeted for biopsy along with non-targeted biopsy from “cardia” in the same container. Further, four of the patients were documented as having a small hiatal hernia which may have complicated the determination of the true GE junction and added to this confusion. This great deal of discrepancy is probably multifactorial. One of the factors is related to the known high interobserver variability among gastroenterologists for identification of the GE junction [21,22]. Additionally, other factors such as hiatal hernia may further make this distinction difficult. Another reason in some cases may be the lack of precision on the part of the clinical team in regards to the information provided with the specimen. Given these findings, we are hoping that moving in future, the gaps in the information could be filled in by more precise endoscopy reports/site of the biopsy and perhaps this could help pathologists when looking at specimens labeled as “cardia”.

Several groups have studied the correlation of endoscopy with histology in premalignant GI lesions such as *H. pylori* infection, atrophy, or IM. A study from South Korea found that the sensitivity and specificity of endoscopic diagnosis of IM based on histopathologic evaluation is approximately 24% and 90% in gastric mucosa. The presence of IM in this study from South Korea was determined by whitish color change on the gastric mucosa, and the endoscopic IM grade was divided into: Grade I (metaplastic mucosa with fine or granular plaques); Grade II (coarse plaques or patches) and Grade III (cases with coarser and larger plaques or patches). The authors concluded that since the endoscopic IM diagnosis has a low sensitivity, a high index of suspicion for IM is

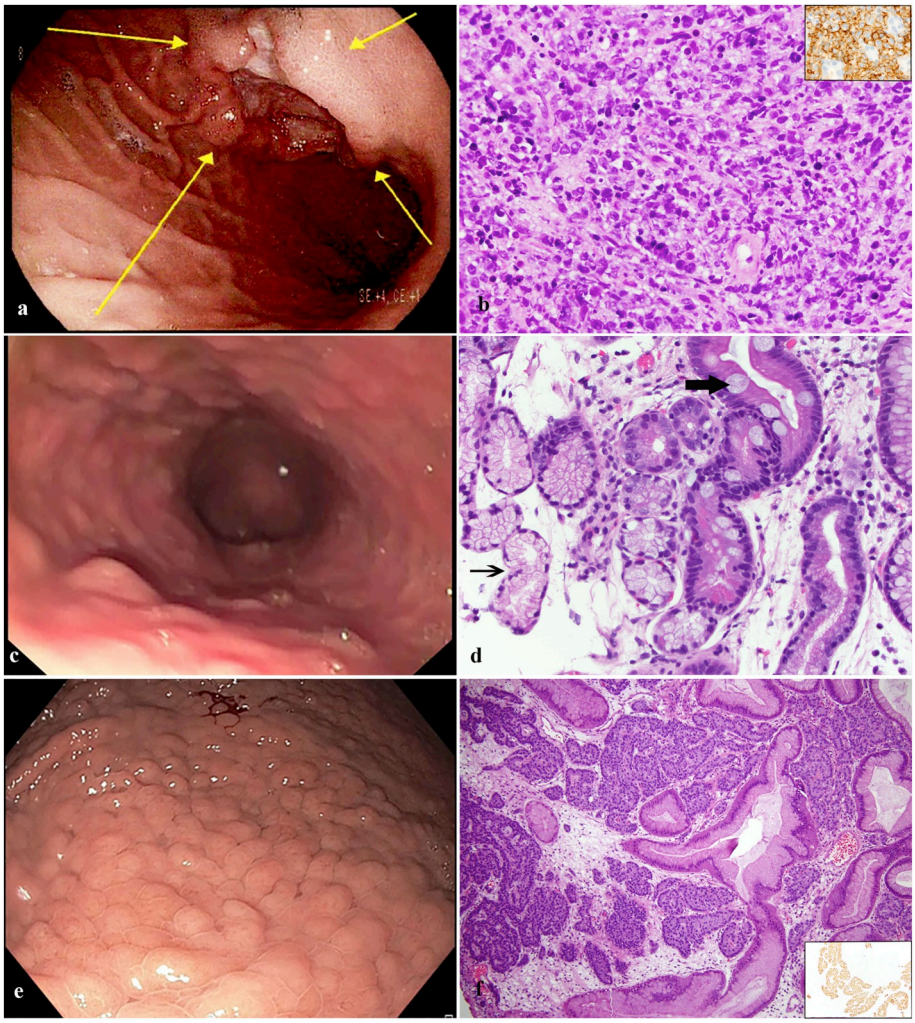

Fig. 3. Abnormal endoscopic appearance with corresponding histopathologic findings. (a, b) Endoscopically visible multiple ulcerated masses in the greater curvature of a 78-year-old female with abnormal abdominal CT. Corresponding biopsy shows diffuse large B cell lymphoma with the inset highlighting the neoplastic cells to be positive for CD20 (H&E X200, inset CD20 immunostain X 200). (c, d) Nodular, atrophic appearing gastric body mucosa in a 65-year-old female. Corresponding biopsy shows autoimmune atrophic gastritis including the pseudopyloric metaplasia (thin black arrow), and intestinal metaplasia (thick black arrow) (H&E X200). (e, f) Endoscopically visible nodular gastric body in a 57-year-old male with dyspepsia. Corresponding biopsy shows neuroendocrine tumor, grade 2 (H&E X200). Inset highlights that the neoplastic cells are positive for chromogranin (inset chromogranin immunostain ×200).

crucial in the presence of atrophy and requires confirmation by histology[8]. Another study showed endoscopic diagnosis of atrophy may not be accurate, especially for age < 50-year-old and the mild degree of histological atrophy [10]. According to Correa's model of the gastric carcinogenesis, the precancerous cascade involves nonatrophic chronic gastritis, multifocal atrophic gastritis, intestinal metaplasia, dysplasia (first low grade and then high grade) and ultimately, gastric cancer [23]. A large cohort study by Song et al further qualified the increased incidence of gastric cancer among patients with gastric precancerous lesions, indicating that approximately 1 in 256 with normal mucosa, 1 in 85 with gastritis, 1 in 50 with atrophic gastritis, 1 in 39 with intestinal metaplasia, and 1 in 19 with dysplasia will develop gastric

Table 3
Endoscopic and histologic findings in relation to the gastric biopsy sites.

Biopsy site	Endoscopic finding	Histologic finding			% any endoscopic finding	% any histologic finding	Cohen's k	PPV %	NPV %	Sens %	Spec %	False negative rate
		Abnormal	Normal	Total								
Antrum	Abnormal	221	50	271	71.5	73.9	0.276	81.6	45.4	78.9	49.5	21.1
	Normal	59	49	108								
	Total	280	99	379								
Body	Abnormal	67	25	92	78.6	67.5	0.209	72.8	52.0	84.8	34.2	15.2
	Normal	12	13	25								
	Total	79	38	117								
Cardia[a]	Abnormal	13	1	14	53.8	96.2	−0.076	92.9	0.0	52.0	0.0	48.0
	Normal	12	0	12								
	Total	25	1	26								
Fundus	Abnormal	19	3	22	88.0	84.0	0.172	86.4	33.3	90.5	25.0	9.5
	Normal	2	1	3								
	Total	21	4	25								
Nonspecified	Abnormal	51	9	60	72.3	77.1	0.301	85.0	43.5	79.7	52.6	20.3
	Normal	13	10	23								
	Total	64	19	83								

Abbreviation: PPV: positive predictive value; NPV: negative predictive value; Sens: Sensitivity; Spec: Specificity.
[a] See Results for further details on histologic findings from biopsies labeled as cardia.

Table 4
Multivariate analysis of clinical, endoscopic and histologic features in gastric biopsies with and without intestinal metaplasia (biopsies labeled as "cardia" were excluded, see Results).

	IM		Odds ratio	95% CI	*P*
	Positive	Negative			
	n = 40	n = 565			
Age, yr					
≥55	27	278	2.14	1.08–4.24	0.03[a]
< 55	13	287			
Gender					
Female	24	336	1.02	0.53–1.97	0.95
Male	16	229			
Biopsy sites					
Antrum	30	349	1.83	0.88–3.82	0.11
Body	6	112	0.71	0.29–1.74	0.46
Fundus	0	25	0.26	0.02–4.38	0.35
Nonspecified	4	79	0.68	0.24–1.97	0.48
Endoscopic findings					
Normal	8	151	0.69	0.31–1.52	0.35
Inflammatory	20	284	0.99	0.52–1.88	0.97
Ulcer	5	31	2.46	0.90–6.72	0.08
Polyp	0	56	0.11	0.01–1.84	0.12
Nodule/papules	3	17	2.61	0.73–9.32	0.14
Mass	0	10	0.65	0.04–11.35	0.77
Atrophy	3	9	5.01	1.30–19.3	0.02[a]
Large folds	1	7	2.04	0.25–17.0	0.51
Histologic chronic gastritis					
Absent	12	359	0.25	0.12–0.49	< 0.01[a]
Chronic inactive gastritis	18	160	1.56	0.81–2.99	0.18
Chronic active gastritis	10	55	3.09	1.43–6.66	< 0.01[a]
H. pylori					
Present	3	33	1.31	0.38–4.46	0.67
Absent	37	532			
Dysplasia					
Present	2[#]	2[$]	14.8	2.03–108.1	< 0.01[a]
Absent	38	563			

Abbreviation: IM: intestinal metaplasia; CI: confidence interval.
[a] $p < 0.05$; # associated with high grade dysplasia; $ include 1 gastric adenoma (low grade dysplasia) and 1 fundic gland polyp with focal low grade dysplasia.

Table 5
Multivariate analysis of clinical, endoscopic and histologic features in *H. pylori*-positive and *H. pylori*-negative gastric mucosal biopsies.

	H. pylori		Odds ratio	95% CI	*P*
	Positive	Negative			
	n = 37	n = 593			
Age, yr					
≥55	17	306	0.80	0.41–1.55	0.67
< 55	20	287			
Gender					
Female	21	352	0.90	0.46–1.76	0.75
Male	16	241			
Biopsy sites					
Antrum	25	354	1.41	0.69–2.85	0.34
Body	5	113	0.66	0.25–1.74	0.40
Cardia	1	24	0.66	0.09–5.01	0.69
Fundus	0	25	0.29	0.02–4.84	0.39
Nonspecified	6	77	1.25	0.51–3.10	0.62
Endoscopic findings					
Normal	5	166	0.40	0.15–1.05	0.06
Inflammatory	23	288	1.62	0.83–3.16	0.16
Ulcer	5	31	2.74	1.01–7.51	0.049*
Polyp	0	59	0.12	0.01–1.92	0.13
Nodule/papules	3	20	2.45	0.69–8.65	0.16
Mass	0	10	0.72	0.04–12.53	0.82
Atrophy	0	13	0.56	0.03–9.56	0.69
Large folds	1	7	2.26	0.27–18.85	0.45
Histologic chronic gastritis					
Absent	0	377	0.01	0.00–0.13	< 0.001*
Chronic inactive gastritis	11	178	0.97	0.48–2.04	0.97
Chronic active gastritis	26	38	34.5	15.9–75.1	< 0.001*

* $p < 0.05$.

cancer within 20 years in a low- risk Western population [24]. Our findings showed that intestinal metaplasia is more frequently seen with histopathologic presence of chronic active gastritis, endoscopically atrophic lesion and microscopic evidence of dysplasia, which was consistent with the above-mentioned theory.

H. pylori is a well-known bacterial carcinogen and an important risk factor for various gastrointestinal diseases, ranging from chronic active gastritis to peptic ulceration, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma (MALT). Previous reports emphasized infection only with *cag*-positive *vacA* s1 m1 strains of *H. pylori* were associated with precancerous lesions and the development of gastric cancer [25]. Our results showed *H. pylori* is significantly associated with endoscopic evidence of ulcer and histologic evidence of chronic active gastritis. However, surprisingly, *H. pylori* infection didn't seem to have a statistically significant association with IM in our study, and is not in keeping with previous studies, which show that IM was found more often in *H. pylori* positive patients compared with *H. pylori* negative patients [9]. There are some possible explanations for these findings. Our patients were exclusively from central Pennsylvania, which is a predominantly Caucasian population with low *H. pylori* prevalence. We found a prevalence of 5.7%, which is much lower than Africa (70%), Western Asia (66.6%), Western Europe (34.3) and even other parts of Northern America (37.1%), where IM was more commonly associated with *H. pylori* positivity [15]. Therefore, it is possible that *H. pylori* may not show a significant association with IM in the areas with low prevalence of *H. pylori*. However, a definite assumption is not possible as treatment of *H. pylori* infection often eradicates *H. pylori* organisms, but may not significantly improve IM, leading to lack of finding organisms in some of these biopsy specimens. Interestingly, some reports have demonstrated that intestinal metaplasia can still persist after *H. pylori*-eradiated therapy [26,27], while others have shown IM can be slightly improved in *H. pylori*-eradicated patients [28,29]. Lastly, while *H. pylori* immunochemical stain is known as a gold standard to detect *H. pylori* organism with reported sensitivities of 82%–98% [30-32], negative immunoreactivity does not completely exclude *H. pylori* infection. The uneven distribution and lower density of *H. pylori* at different sites of the stomach with IM could possibly lead to sampling error, thus underestimating *H. pylori* prevalence in these biopsies. It is worth mentioning that several other risk factors for IM have been identified, including family history, high salt intake, smoking, alcohol, chronic bile influx, and atrophic gastritis [33], which may be additional factors leading to development of IM in areas with a low *H. pylori* prevalence.

Lastly, we do recognize that our study has some limitations. Firstly, this was a single-institution study with a relatively limited case cohort and with a short study time period. Secondly, the study was conducted in a predominantly Caucasian population with lower prevalence of *H. pylori*. Therefore, our findings may not be representative of the entire United States population, given the increasing diversity. Unfortunately, selection biases were unavoidable due to the nature of the study.

5. Conclusion

The present study shows that while some endoscopic findings are highly concordant with abnormal histologic diagnosis; in particular

mass (100%), polyp (98.3%), ulcer (91.7%) or nodule/papule (91.3%), other endoscopic findings are associated with a varied spectrum of both normal and abnormal histopathologic findings, in particular inflammatory changes (75.6%), normal (57.3%) and large folds (50%). We found that *H. pylori* can be seen in endoscopically normal appearing gastric mucosa, especially in patients with complaints of abdominal pain and/or dyspepsia, reinforcing the need to biopsy normal-appearing gastric mucosa in patients with significant GI complaints. The presence of IM was significantly associated with age older than 55 years, the endoscopic impression of atrophy, histologic finding of chronic active gastritis and the presence of dysplasia; however it appears that IM in our study was not significantly associated with *H. pylori* infection. This is probably due to the fact that our study examined a predominantly Caucasian population with lower prevalence of *H. pylori*, as compared to other parts of the world; although sampling issues and uneven distribution of *H. pylori* in these biopsies may be other contributing factors. More multi-institutional studies from larger patient cohorts over a longer time duration would be helpful.

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