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Original contribution

Prospective identification of *Helicobacter pylori* in routine gastric biopsies without reflex ancillary stains is cost-efficient for our health care system☆,☆☆

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Summary Despite the recommendation of expert gastrointestinal pathologists, private and academic centers (including our own) have continued to use ancillary stains for identification of *Helicobacter pylori*. For a 1-month period, gastric biopsies were prospectively evaluated for *H pylori* using routine hematoxylin and eosin (H&E) and a reflex Diff-Quik stain. During this time, 379 gastric biopsies were collected on 326 patients. *H pylori* organisms were prospectively identified in 23 (7%) patients, all of whom had superficial dense lymphoplasmacytic inflammation expanding the lamina propria. An additional 2 patients with neutrophilic inflammation were found to have *H pylori* by immunohistochemical staining. One patient diagnosed as having normal gastric mucosa was retrospectively found to have inflammation with rare *H pylori* organisms originally overlooked on both H&E and Diff-Quik but later identified on immunostain (0.5%). No patients with chemical gastritis (16%) or chronic inflammation (27%) were found to have *H pylori*. During the study month, 9 immunostains for *H pylori* were performed in addition to the 379 Diff-Quik. After discontinuation of reflex Diff-Quik, approximately 20 immunostains are performed for *H pylori* each month, which decreases technical time spent for processing gastric biopsies and reduces cost to the health care system. In our population with a low prevalence of *H pylori,* reflex staining for organisms is not cost-effective. The organisms can be seen on routine H&E; when suspicious superficial or active inflammation is present without visible organisms, immunohistochemical stains will confirm presence or absence within a day. Discontinuation of up-front ancillary studies is cost-effective without compromising patient care.

1. Introduction

Helicobacter pylori is a gram-negative bacterium that colonizes the human stomach. The ability to adhere to gastric epithelium and to produce urease allows *H pylori* to survive in the acidic gastric environment [1]. Described by Warren and Marshall [2] in 1983 as a bacterium associated with gastritis, *H pylori* is now known to be a causative agent in peptic ulcer disease,

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gastric adenocarcinoma, and extranodal marginal cell lymphoma of the stomach ("mucosa-associated lymphoid tissue" lymphoma). Although a minority of patients whose stomachs are colonized by the organism experience these adverse outcomes, it is both safe and cost-effective to eradicate the organism [1-4].

H pylori is frequently associated with the symptom of dyspepsia, one of the most common upper gastrointestinal complaints. In some centers, up to 40% of referrals to a gastrointestinal specialist are for this indication [5,6]. Not all dyspepsias are *H pylori* related, but the intractability of symptoms and risk of aforementioned unfavorable outcomes when the organism is present has led to decades of study to determine optimum clinical screening protocols. The cost-effectiveness of each strategy varies with patient population and reimbursement rates for services rendered [3,5,7,8].

Once endoscopic biopsy has been chosen as the modality for patient assessment, it is the responsibility of the pathologist to evaluate the gastric mucosa for the presence of *H pylori*. Because of the potentially serious sequelae of *H pylori* infection, many pathology centers have used reflex (up-front) ancillary stains on all gastric biopsies to ensure that no cases of *Helicobacter* are missed. The newest recommendations from the Gastrointestinal Pathology Society advise against ancillary staining [9], and yet our institution continued to perform a Diff-Quik (Siemens, Location Switzerland) stain on all gastric biopsies, in part because of laboratory routine and in part because many of our clinicians had come to expect a comment on staining for *H pylori* in gastric biopsies. The purpose of our study was to prospectively investigate if any cases of *H pylori* would be missed with the removal of an up-front Diff-Quik stain and to determine the impact of discontinuing this special stain on health care costs.

2. Materials and methods

Gastric biopsies were prospectively reviewed as part of the daily sign-out at the Johns Hopkins Hospital for a period of 1 month. During this time, the standard operating procedure for the laboratory dictated that all gastric biopsies were stained with routine hematoxylin and eosin (H&E; 2 levels) and with Diff-Quik (1 level). Diagnoses were rendered on each gastric biopsy, and the type of mucosa, antral or oxyntic, was recorded. The diagnostic categories included in this study are as follows (Fig. 1):

- Nondiagnostic findings (NDF): normal gastric mucosa
- Chemical gastropathy: decreased cytoplasmic mucin in foveolar epithelium, elongation and tortuosity of gastric pits, regenerative/reactive nuclei, and smooth muscle fibers in lamina propria
- Chronic inflammation: increased inflammation, predominantly plasma cells, within the lamina propria in a patchy, loose distribution; no destruction or involvement of epithelium; ×10 needed to identify clusters
- Inactive chronic gastritis (ICG): dense lymphoplasmacytic infiltrate of the lamina propria easily identifiable on ×4; includes infiltration and destruction of epithelium
- Active chronic gastritis (ACG): neutrophilic infiltrate of the epithelium in addition to lymphoplasmacytic infiltrate of the lamina propria
- Active or inactive *H pylori* gastritis: the presence of *H pylori* with or without neutrophils

If *H pylori* was identified, it was noted whether the organisms were visible on the H&E, the Diff-Quik, or both. Immunohistochemical (IHC) stains for *H pylori* were performed retrospectively in any case of ACG not previously stained, on at least 10 randomly selected cases from each additional diagnostic category, and on any biopsy for which an ancillary laboratory test for *H pylori* had been positive within 6 months of the biopsy date. Gastric biopsies (n = 12) were excluded from this study if the diagnosis was iron pill gastritis, graft-versus-host disease, eosinophilic gastritis, or autoimmune metaplastic atrophic gastritis [10]. Patient information was obtained from the electronic medical record and correlated with histologic findings. This study was performed in accordance with the ethics policies of the Johns Hopkins Institutional Review Board.

A Leica Bond automated stainer was used to perform IHC stains for *H pylori* (Dako, Denmark B0471 polyclonal rabbit anti-HBP at 1:200 dilution). Four-micrometer sections were cut, and heat-induced epitope retrieval using epitope retrieval solution 2 buffer was used before incubation. External controls were appropriately performed.

3. Results

From May 5, 2015, through June 4, 2015, 326 patients had gastric biopsies, resulting in 379 samples submitted to pathology. The median age of the cohort was 44 years (range, 1-89 years), and 56% of patients were women. Roughly two-thirds (67.5%) of the patients were white, whereas almost one-fifth (19.3%) were African American. The remaining patients were Asian (4.9%), Hispanic (2.2%), Middle Eastern (1.8%), and unknown (4.3%). The most common clinical complaints preceding endoscopy were abdominal pain (33.4%) and gastroesophageal reflux (24.8%). More than one-third (37.7%) of the patients had documented proton pump inhibitor use at the time of biopsy.

Of the 379 biopsies submitted, 23 (6.1%) biopsy specimens were prospectively diagnosed as active *H pylori* gastritis, 4 (1.1%) as inactive *H pylori* gastritis, 12 (3.2%) as ACG, 53 (14%) as chemical gastropathy, 73 (19.2%) as chronic inflammation, 23 (6.1%) as ICG, and 191 (50.3%) as histologically unremarkable ("NDF"). These categories are described in the Materials and methods section, and histologic examples are shown in Fig. 1.