

***H. PYLORI*-NEGATIVE GASTRITIS**
WHAT TO DO WHEN *HELICOBACTERS* AREN'T THERE

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INTRODUCTION

H. pylori infection was recognized as the main cause of chronic active gastritis and peptic ulcer disease just over two decades ago ¹, and shortly thereafter the first effective treatments were introduced ^{2,3}. Since then, and likely even before its discovery, the prevalence of *H. pylori* infection has been steadily declining, particularly in industrialized and emerging economy countries; this is probably a reflection of improved sanitary conditions, widespread treatment of infected patients, and the pervasive use of antibiotics ⁴. In parallel with this decline, an increased proportion of *H. pylori*-negative ulcers has been reported, both in the United States ^{5,6} and elsewhere ⁷⁻⁹. Furthermore, although no studies documenting this phenomenon have been published to date, there is a common perception amongst pathologists practicing in the Western world that chronic active gastritis with no detectable *H. pylori* organisms ("*H. pylori* – negative chronic active gastritis") is on the rise ^{10 11}. The often cited 1990s axiom that even a small number of polymorphonuclear neutrophils in a gastric biopsy is an almost certain indication of current *H. pylori* infection is no longer applicable. While no formal hypothesis has been put forward and tested, commonly offered explanations include antibiotic therapy administered to treat other infections, the masking effect of proton-pump inhibitors (PPIs), and failure to detect organisms because of inadequate sampling or sub-optimal staining techniques.

The purpose of this presentation is to help the practicing pathologist confronted with a gastric biopsy that "looks like *H. pylori* should be there, but is not."

WHEN AND HOW TO SEARCH FOR *H. PYLORI*

Just as we used to say that active gastritis means *H. pylori* infection, we also said that there is no *H. pylori* infection without active gastritis. As it turns out, we were wrong on both accounts. As any experienced gastrointestinal pathologist will know, when an anti-*H. pylori* immunohistochemical stain (HP/IHC) is used in all gastric biopsies, one will occasionally find organisms in unexpected backgrounds, such as a virtually normal mucosa, an antral mucosa with reactive gastropathy and no active inflammation, or a fundic mucosa with a minimal sub-epithelial rim of lymphocytes and plasma cells and no neutrophils. Having been fooled by a few such cases, I advocate the preemptive use of HP/IHC in all gastric biopsies.

Those who cannot or choose not to routinely use the HP/IHC or other appropriate special stains for the detection of *H. pylori* must decide when to request such stains. When *H. pylori* are not detected by whatever means one uses routinely, a more sensitive stain (ideally the HP/IHC) should be used in the following circumstances:

- 1 - Chronic active gastritis (CAG)
- 2 - Focal active gastritis ("focally enhanced")¹²
- 3 - Chronic inactive gastritis with lymphoid follicles¹³
- 4 - Atrophic corpus gastritis, to exclude *H. pylori* before suggesting autoimmune gastritis
- 5 - When a duodenal or gastric ulcer is described in the endoscopy report, irrespective of the appearance of the gastric mucosa in the biopsy
- 6 - When the biopsies are obtained to confirm the success of eradication therapy
- 7 - Whenever suspicious speckles that could be *H. pylori* are seen
- 8 - If a MALT lymphoma is either seen or reported to have been treated in the past^{14, 15}

In circumstances 2 through 7 the expected (and desirable) finding is the absence of *H. pylori*, as in the case of a treated MALT lymphoma. *H. pylori*-negative MALT lymphomas do exist, but they are a distinct minority (<10%); therefore, a diligent search for the organisms is necessary. If they are not found, a suggestion for more representative sampling is usually well received by clinicians, who also need to determine the extent of the lymphoma. The true dilemma occurs in the case of *H. pylori*-negative CAG.

THE 3R APPROACH TO *H. PYLORI*-NEGATIVE CAG

Reconsider. When *H. pylori* is not found by HP/IHC one should first reconsider the initial diagnosis of CAG.¹⁶ After critically reviewing ~400 gastric biopsy specimens that had been diagnosed as "CAG - No *H. pylori* detected by the *H. pylori* Blue stain" we found that only approximately 120 cases represented true CAG; most of the other cases were reactive gastropathy with small erosions (where neutrophils are usually abundant)¹⁷; chronic inactive gastritis (neutrophils may have been present in the lamina propria, but were not found in the epithelium); and specimens from the cardia (where active inflammation is usually associated with reflux and not with *H. pylori* infection)^{18, 19}. Of the real CAG cases, the HP/IHC yielded a little over another 25% new positives. If going back to one's own dubious diagnoses seems futile or painful, it may be helpful to consider that each previously undetected case is a patient who will be treated and will not develop peptic ulcers, and whose risk of gastric cancer will be reduced by more than 70%. Table 1 shows possible sources of inaccurate diagnoses of CAG.

Re-stain. If one is convinced that the histologic appearance is unequivocally that of CAG, a more sensitive stain should be examined. Thus, if only H&E-stained slides were prepared, a Giemsa (modified to Blue or Yellow) or a silver stain should be done; if still negative, the HP/IHC (which ought to be done in first place) should then be ordered. If the HP/IHC is negative and the impression of *H. pylori* gastritis is overwhelming, a second HP/IHC may be appropriate, particularly if the control was not perfect.

This sequential strategy will eventually yield cases of unequivocal CAG with no *H. pylori*. This is the time to

Retreat. After reviewing the slides, restaining, and perhaps staining once more, those who adhere to the precept "You are not obliged to finish the task, but neither are you free to neglect it" will be probably satisfied that they have not neglected the task and will feel free to desist from further action. They will issue a well-worded report stating that, in spite of the characteristic histologic appearance, no *H. pylori* was found after a meticulous search (and a long list of CPT codes). Such reports, however, are unlikely to gratify an inquisitive clinician, who will be left wondering what should be done. Therefore, striving to finish the task is a better alternative.

AFTER A DIAGNOSIS OF *H. PYLORI*-NEGATIVE CAG

Calling the clinician and explaining the circumstances that lead to an equivocal diagnosis is probably the best way to avoid being perceived as a timid pathologist. Before discussing a case, however, it is necessary to be maximally informed.

Two common clinical circumstances may decrease the gastric *H. pylori* load: recent use of antibiotics and proton-pump inhibitors. Other causes for the failure to detect organisms in a gastric biopsy are listed in table 2.

Antibiotic regimens not specifically prescribed for the treatment of *H. pylori* can temporarily attenuate or eradicate the infection in a proportion of patients, depending on the type of antibiotic used, the length of the treatment, and whether or not the patient was coincidentally using PPIs. In most patients intentional or unintentional eradication causes the disappearance of polymorphonuclear neutrophils from the gastric mucosa within days of the start of the therapy^{20,21}, leaving the histopathologic impression of a chronic inactive gastritis. Incomplete and unsuccessful eradication, however, may greatly reduce the bacterial load (thus making them undetectable in certain parts of the stomach) with little or no decrease of active inflammation. If one can elicit a history of recent antibiotic treatment, a significant step is made in finding an explanation for *H. pylori* CAG. Furthermore, the pathologist can predict that the infection, inadequately treated, will soon reemerge, and a new set of biopsies in a few weeks will likely show organisms.

A much more common reason for the apparent disappearance of *H. pylori* from some compartments of the stomach (particularly the antrum) is the use of proton pump inhibitors (PPIs).¹⁰ Now available in more than ten different preparations, some of which can be obtained over the counter, PPIs alter the gastric acid environment and induce shifts in the *H. pylori* populations within the stomach, usually reducing the bacterial burden in the antrum²² while increasing the inflammation in the corpus^{23-25 26-28}. Not only do these changes cause false negative urea breath tests²⁹⁻³¹, but they have also been shown to hinder the histopathologic detection of *H. pylori* in gastric biopsies²⁸. Thus, many diagnoses of *H. pylori*-negative CAG in antral biopsies could be avoided if samples from the gastric corpus were also available.

These explanations may convince the clinician to perform a non-invasive test (serology, urea breath test, fecal antigen detection) or to repeat the endoscopy and take more representative biopsies. Nothing could be worse than leaving the impression that *H. pylori*-negative CAG is a final diagnosis and the patient does not need further workup.

Table 1 - Causes of <i>Helicobacter pylori</i>-negative chronic active gastritis
• Crohn's Disease
• Focally enhanced gastritis
• Lymphocytic gastritis with a strong active component
• Autoimmune gastritis with a strong active component
• Reflux carditis (activity limited to the cardia)
• Drug-related (e.g NSAIDs)
• Biopsy near an erosion or ulcer
• Granulomatous gastritis
• Infectious (CMV, staphylococcus, syphilis)

Table 2 - Possible reasons for failure to detect <i>H. pylori</i>
Diagnostic error Bacteria were missed Condition is not chronic active gastritis
Sampling error Proton pump inhibitors shift bacteria from antrum into body
Factors causing an unfavorable local environment for bacteria Intestinal metaplasia Ulcer
Suppression resulting from incidental antibiotic or proton pump inhibitors use

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