Human Pathology (2017) **61**, 19–25

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Human PATHOLOGY

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In this issue

Clinicopathological characteristics of invasive gastric *Helicobacter pylori*☆

Jonathan Dudley MD[a,*], Tad Wieczorek MD[b], Martin Selig BA[c], Hoiwan Cheung BA[a], Jeanne Shen MD[b], Robert Odze MD[b], Vikram Deshpande MBBS[c], Lawrence Zukerberg MD[c]

[a]*Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA*
[b]*Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA*
[c]*Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*

Received 24 July 2016; revised 14 September 2016; accepted 28 September 2016

Keywords:
Helicobacter pylori;
Gastritis;
Gastric ulcers;
Triple therapy;
Proton pump inhibitor

Summary *Helicobacter pylori* organisms have been observed deep within the stomach mucosa with an "intracellular" appearance, although the clinicopathological characteristics of such cases remain poorly understood. We analyzed 18 cases of deep mucosal *H pylori* and associated clinical (sex, age, history of *H pylori* infection, or proton pump inhibitor [PPI] use, medications, smoking, alcohol use, comorbidities, treatment response) and pathological (presence of lymphoid aggregates, intestinal metaplasia, PPI effect, active and/or chronic inflammation, quantity of invasive versus surface *H pylori*) characteristics. Electron microscopy was performed on 6 cases with the highest burden of invasive *H pylori*. Within our sample, 3 of 16 had a history of *H pylori* infection, 10 of 15 were receiving PPIs at the time of biopsy, and 12 of 13 had a negative posttreatment follow-up. Histology revealed that invasive *H pylori* were more commonly associated with chronic inflammation, in both the antrum (15/15 chronic, 8/15 acute) and fundus (17/18 chronic, 8/18 acute). Electron microscopy showed organisms within intercellular and luminal spaces, but no intracellular organisms. Deep mucosal *H pylori* often have an intracellular appearance but are contained within intercellular and luminal spaces and are responsive to standard therapy.
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1. Introduction

More than half the world's population is estimated to have gastric colonization by *Helicobacter pylori* [1]. The gram-negative bacterium is usually identified on the mucosal surface, where it stimulates a chronic and active inflammatory response. It is a major risk factor for peptic ulcer disease and increases the risk of developing gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma by three to six fold [2,3]. Despite these strong associations, only 15% to 20% of colonized individuals will ever develop gastric disease [4]. In addition, although the organism is usually eradicated by a combination of antibiotics and inhibitors of acid secretion, a subset of patients fails to respond or experience recurrence [5,6]. In light of the worldwide burden of gastric *H pylori*, these facts raise interest in identifying predictors of treatment resistance and future pathology.

Several mechanisms have been proposed to explain which patients are likely to suffer recurrence or future disease.

☆ Disclosures: None declared.

* Corresponding author: Department of Pathology, Stanford University School of Medicine, 300 Pasteur Dr, Lane 235, Stanford, CA 94305.
E-mail address: jonathan.dudley@stanford.edu (J. Dudley).

http://dx.doi.org/10.1016/j.humpath.2016.09.029
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H pylori is a genetically diverse species, and strains carrying the 31-gene *cag* locus, the *babA2* gene, and certain alleles of the *vacA* gene have all been associated with increased risk of gastric cancer [7]. Human polymorphisms also increase risk of disease; certain variants of the allele coding interleukin-1β, for example, result in increased expression of the protein and associated inflammation [8]. Additional host polymorphisms and dietary habits no doubt contribute in determining the baseline predisposition to gastric disease.

The location of *H pylori* in the stomach has also been postulated to determine its pathogenicity. Although the organism is usually confined to the mucosal surface, in a subset of patients, it can be observed deep within gastric pits, in intercellular spaces and the lamina propria, and even inside vacuoles within epithelial and inflammatory cells [4,9-12]. Some investigators have argued that such organisms, herein designated "invasive *H pylori*," are more resistant to treatment and significantly increase the likelihood of future disease [13]. Intracellular organisms, in particular, have been postulated to serve as a reservoir that can recolonize the stomach after antibiotic treatment eliminates extracellular bacteria [9,13]. As a result, some investigators have argued that antibiotics with intracellular activity should be used to ensure all organisms are eradicated [14,15].

Despite the potential significance of invasive *H pylori*, their clinicopathological associations remain poorly understood. This article surveys 18 cases of invasive *H pylori* identified during routine histologic examination of gastric biopsies and resections within the Partners HealthCare system. We characterize the clinical characteristics of affected patients and the histologic features of each specimen using the updated Sydney System for the classification and grading of gastritis [16]. Six cases with the highest quantity of invasive organisms were additionally subjected to electron microscopic evaluation. The goal of this article is to evaluate the spectrum of clinical and pathological associations of invasive *H pylori* to clarify the significance of discovering these intracellular or invasive organisms in gastric specimens.

2. Materials and methods

2.1. Study cohort

The study cohort consisted of 18 patients who had either endoscopic gastric biopsies (n = 16) or resections (n = 2) within the Partners HealthCare system between September 2010 and February 2014. Invasive organisms were generally discovered after ordering an *H pylori* immunostain to evaluate for the presence of organisms. Patient records were reviewed to document age, sex, date of biopsy, history of *H pylori* infection or proton pump inhibitor (PPI) use before biopsy, other medical and medication history, history of tobacco or alcohol use, and *H pylori* status after treatment. The average follow-up time was 38 months. Most of the cases (n = 12) were identified by 2 of the authors (V. D. and T. W.) at an institution that routinely performs a *H pylori* immunostain on gastric biopsies.

2.2. Histologic analysis

All hematoxylin and eosin (H&E)–stained slides had an immunostain ordered for *H pylori*. Both the H&E and immunostain were evaluated and graded by 2 pathologists (J. D. and L. Z.), one of whom has subspecialty training in gastrointestinal pathology (L. Z.). The updated Sydney System for the classification and grading of gastritis was applied separately to the antrum and fundus to describe as "normal," "mild," "moderate," or "marked" the following characteristics: quantity of *H pylori*, atrophy, neutrophilic infiltrate, mononuclear cell infiltrate, and intestinal metaplasia [16]. Additional parameters assessed included the presence or absence of PPI effect, lymphoid aggregates, lymphoepithelial lesions, and the relative proportion of surface versus invasive organisms. One case of invasive *Helicobacter heilmannii* was also evaluated by the same criteria as well as by a Steiner stain.

2.3. Electron microscopic analysis

The 6 cases with the highest quantity of invasive organisms, as assessed by the *H pylori* immunostain (rabbit monoclonal primary antibody, clone SP48; Ventana, Tuscon, AZ), were microdissected from formalin-fixed, paraffin-embedded tissue blocks, soaked in 100% xylene overnight, rehydrated in a series of ethanol solutions, rinsed in sodium cacodylate buffer, and fixed for 1.5 hours with 2.5% glutaraldehyde, 2.0% paraformaldehyde, and 0.025% calcium chloride, in a 0.1 M sodium cacodylate buffer with a pH of 7.4. Tissues were further processed in a Leica, Hatfield, PA Lynx automatic tissue processor. Briefly, tissues were postfixed with osmium tetroxide, dehydrated in a series of ethanol solutions, en bloc stained during the 70% ethanol dehydration step for 1 hour, infiltrated with propylene oxide epoxy mixtures, embedded in pure epoxy, and polymerized overnight at 60.1°C. Thin sections were stained with lead citrate and examined with an FEI Morgagni transmission electron microscope (FEI, Hillsboro, OR). Images were captured with an Advanced Microscopy Techniques digital CCD camera (Woburn, MA). All cases were evaluated for the presence and location of *H pylori* and exhaustively searched for potential intracellular organisms. The case of *H heilmannii* was also evaluated using the above protocol.

The study protocols were approved by the institutional review board of Partners HealthCare.

3. Results

The average age of patients in the cohort was 58 years, with a range of 19 to 91 years and an equal distribution of sexes (Table 1). The average follow-up time was 38 months. Of

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