Infections in Oncology: Gastric Cancer: An Infectious Disease?

Melissa K. Conrad, MD, John T. Sinnott, IV, MD, FACP, and Michael Albrink, MD, FACS, and Pamela Sakalosky, BS

University of South Florida College of Medicine

“The ulcerous place...mining all within, Infects unseen...”

(Shakespeare W. Hamlet. Act III; scene 4; line 147.)

Introduction

It is tempting to speculate that Hamlet recognized the infectious etiology of peptic ulcer disease, thus presaging recent developments in modern medicine. As old microbes are resurfacing and new pathogens are emerging, the study of infectious causes of disease is again in the forefront of medicine. Helicobacter pylori, the elusive, acid-tolerant bacteria first associated with gastritis, peptic ulcer disease, nonulcer dyspepsia and, finally, gastric cancer, serve as a paradigm for the evolution of infectious disease in modern medicine. Until recently, the pathogenesis of ulcer disease was attributed to overproduction of acid and mucosal barrier destruction as a result of stress, smoking, or dietary factors. The dogma that environmental and genetic factors predisposed individuals to the development of gastric cancer was universally accepted, and H pylori was considered to be a possible cause of gastritis.[1] Now, a few years later, H pylori is a prominent topic at conferences and in medical journals and is notorious as a cause of a multitude of gastric diseases. The search for a causal role and for further understanding of the pathogenetic properties of H pylori has spawned numerous investigations. Its role in gastric cancer has raised questions regarding the association of the bacteria with carcinogenic processes, as well as its potential role for eradication of these bacteria in cancer prevention. This revolution in medical thought: the concept of a unified infectious cause of gastritis, ulcer disease, and cancer has led to a new path of progress that exemplifies the change in how human disease is approached.

History

In 1983, Barry J. Marshall, an internal medicine resident in Perth, Australia, and pathologist J. Robin Warren discovered the bacteria now known as H pylori. Marshall had been studying the spiral-shaped bacterium in tissue biopsies of ulcer patients but had been unable to culture the organism using routine techniques. In April 1982, the lab was burdened with an outbreak of antibiotic-resistant Staphylococcus aureus, and the cultures were left in the incubator longer than usual. The serendipitously ignored cultures grew the first isolates of the bacterium that Marshall and Warren named Campylobacter pyloritis.[2]

Marshall spent the next two years trying to prove that he had isolated the “ulcer bugs,” the infectious cause of peptic ulcer disease. Repeated animal testing failed to confirm his theory. In July 1984, in an attempt to prove his point, he drank a mixture containing the bacteria in question. Eight days later, he awoke with nausea and vomiting and developed headaches, weakness and malaise without fever. He had several headaches over the next week and felt weak and tired, but he had no fever. Two weeks later, Marshall underwent endoscopy and biopsy to compare with an examination performed before his self inoculation. Endoscopy revealed an inflamed mucosa, and biopsy exposed multitudes of bacteria infesting the inflamed gastric tissue. Four days later, Marshall clinical condition improved, and a third biopsy four days later revealed resolution of the infection, presumably a successful attack on the bacteria by Marshall’s immune system[3].

The first histologic description of spiral organisms in the stomachs of humans, which were found in the gastric contents of patients with ulcerative carcinoma, were reported in the early twentieth century. Subsequent reports noted the absence of these organisms in healthy patients and their presence in patients with peptic ulcer disease. In 1938, for spiral organisms in the human stomach but did not describe a relationship between the presence of the organism and gastric disease. To explain the presence of these organisms on gastric biopsy specimens, investigators hypothesized that the bacteria represented contamination that was introduced orally.[4]

Microbiology and Pathophysiology

H pylori is a curved or spiral, microaerophilic, Gram-negative rod that occupies a unique ecological niche beneath the mucous layer in any location where gastric mucosa may exist, including the stomach, metaplastic esophagus, duodenum, and even Meckel diverticula (Figure). Originally named Campylobacter pyloritis because of its morphologic similarity to other Campylobacter species, the organism was renamed H pylori in 1989. The new genus, Helicobacter, also includes mustelae, muridarum, and nemestrinae, which are urease-positive but appear to be limited to stomachs of other mammals.[5]

The presence of four to six sheathed flagella allows the bacteria to dwell beneath the mucous layer by burrowing through the mucosa. Its ability to survive the extremes of gastric pH can be attributed to a high molecularweight urease. This enzyme catalyzes the transformation of urea to ammonium and bicarbonate, which alkalizes the environment and protects the bacteria from gastric acid. The organism’s production of proteases, lipases, phospholipases, and cytotoxins, combined with its ability to attach to epithelial cells via adherence proteins, contributes to the pathogenicity of the organism.6

Epidemiology

Identified risk factors for infection with H pylori include lower socioeconomic status and infection of family members. Thus, lack of hot water in the home, overcrowding, and sharing of beds are major predictive factors for H pylori infection.[7] Prevalence rates are significantly higher in developing areas such as Africa, where up to 80% of children under 20 years of age are infected, compared with 20% of children in developed countries.[8] Studies of incidence rates show a very low rate of acquisition in developed
The reservoir of the organism appears to be limited to human gastric mucosa and may be transmitted through the fecal oral route, although this path of infection has not been established.[7] Epidemiologic data also suggest that the prevalence of H. pylori infection is decreasing in developing countries, which may reflect changes in hygiene, socioeconomic status, and increasing use of antibiotics.[8] A decreasing prevalence rate of infection would suggest that the prevalence of such diseases as peptic ulcer, gastritis, and gastric cancer, if H. pylori is causally related, would be decreasing.

**Helicobacter Pylori and Gastric Cancer**

H. pylori infection has been linked to several types of gastric cancer, including gastric adenocarcinoma and gastric lymphoma. H. pylori is associated with adenocarcinomas distal to the cardia, including both intestinal and diffuse types.[8] In addition, non-Hodgkin’s lymphomas of the stomach, especially gastric mucosa associated lymphoid tissue lymphomas, have been associated with H. pylori infection.[9] Three sources of evidence support the association of H. pylori infection and gastric cancer: epidemiologic studies comparing gastric cancer and H. pylori infection prevalence rates, cross-sectional studies evaluating H. pylori infection in cancer patients, and prospective studies associating H. pylori with gastric cancer.[10]

Epidemiologically, rates of both H. pylori infection and gastric cancer follow similar geographic and temporal trends.[10] Because incidence rates of gastric cancer differ dramatically among countries, environmental factors were previously believed to play a more important role than genetic factors. Furthermore, these factors were believed to exert their influence during childhood, as demonstrated by studies of migrants.[8] In areas with a high gastric cancer prevalence, e.g., Peru, Mexico, and Colombia, virtually all adults are infected with H. pylori. Also, infection in these locations occurs at an earlier age than in countries with low rates of gastric cancer, where infection in children is rare.[10,11] This association suggests that H. pylori infection is an integral piece in the environmental puzzle posed by the geographic differences in gastric cancer rates. In addition, gastric cancer rates, like H. pylori infection rates, have decreased over time, which may reflect changes in socioeconomic development.[12]

Cross-sectional studies investigating evidence of H. pylori infection in gastric cancer patients reveal that H. pylori is more likely to infect populations of gastric cancer patients than normal populations, with rates of infection ranging from 50% to 100% in patients with gastric adenocarcinoma.[10,13] Paradoxically, histologic association of the bacteria with tumor can be difficult to determine because H. pylori has an affinity for normal gastric mucosa but not metaplastic, dysplastic, or malignant tissue.[14] Thus, tumor-associated infection must be determined either by examination of biopsy specimens of surrounding normal gastric tissue or by use of indirect diagnostic methods. Rates of prevalence of H. pylori infection in patients with gastric cancer have been compared to rates in cancer-free controls and to patients with other types of cancer, and these comparisons showed increased rates of infection in nongastric cancer patients as well.[15] Patients with gastric non-Hodgkin’s lymphoma also were more likely than matched controls to have evidence of prior infection with H. pylori. The finding that infection with H. pylori is more likely in gastric lymphoma patients than in nongastric lymphoma patients suggests a local basis for the carcinogenic events.[9] Although significantly higher rates of infection are apparent in gastric cancer patients, this association has not yet been proven to be causal in nature.

Prospective studies of H. pylori and cancer reveal that H. pylori infection increases the risk of developing gastric cancer in later life, although most people infected with H. pylori do not develop gastric carcinoma.[8,16,17] An increased risk was linked to adenocarcinomas of the antrum, body, and fundus of the stomach but was not associated with tumors of the cardia and gastroesophageal junction. H. pylori infection was a more significant risk factor for adenocarcinoma in women and in blacks.[8] One study suggested that 35% to 55% of all gastric cancer may be attributable to H. pylori infection.[17] If so, almost half of gastric cancers may be preventable with programs employing early eradication of the organism.

**Recent Classifications of Most of the Common Chronic Gastritides**

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**Theories of Carcinogenesis**

The putative carcinogenic effects of H. pylori may be related to the chronic inflammation caused by its exuberant elaboration of many extracellular enzymes. Probably the predominant cause of type B antral (or environmental) gastritis, H. pylori most likely predisposes to gastric cancer through this consequence of infection.[18] A concrete classification scheme for gastritis has not yet been developed, and various methods for classification have been published (Table).

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A large body of data supports the hypothesis that H. pylori causes gastritis. Volunteers who swallowed the organisms subsequently developed acute inflammatory gastritis,[8] and accidental inoculation during a study of gastric secretory function resulted in an epidemic of gastritis with hypochlorhydria.[19] Animal models also developed chronic inflammation and a human like, chronic, active gastritis after introduction of H. pylori.[8] Also, the majority of gastritis resolves after treatment and eradication of H. pylori.[20] Thus, H. pylori is believed to be a primary cause of nonerosive, nonspecific gastritis, particularly antral gland (or type B) gastritis with histologic findings of mononuclear cells in an atrophic bed.

Chronic inflammation has been causally linked to a variety of cancer types, including colon cancer in ulcerative colitis patients and bladder cancer in patients with vesicular schistosomiasis.[8] Previously established models for gastric adenocarcinoma pathogenesis proposed that an environmental agent, possibly salt, caused irritation of the gastric mucosa that led to the development of chronic atrophic gastritis. The resultant hypochlorhydria and bacterial overgrowth, with the subsequent conversion of nitrates to the mutagenic N-nitrosamines, were postulated to be the instigating events that led to metaplasia, dysplasia, and cancer. Through their antinitrosation and antioxidant effects, betacarotene and ascorbic acid were believed to halt this progression to cancer and thus act as protective factors.[10] However, this dogma has been supplanted by the hypothesis that H. pylori infection in early life leads to the formation of chronic atrophic gastritis, and the resultant transformation to metaplasia, dysplasia and, ultimately, malignancy.

The role of H. pylori infection in causation of gastric cancer remains unclear, although the association has been firmly established.[8,16,17] Several new hypotheses for gastric carcinogenesis have examined the possible pathogenic mechanisms of H. pylori infection. The adverse effects of H. pylori infection on the gastric mucosa, which alter the properties of the mucous layer, may decrease its protective properties, thereby making the mucosa more susceptible to other carcinogenic factors. H. pylori has also been
reported to decrease gastric secretion of the naturally protective ascorbic acid, which may permit cellular damage as a result of the unopposed oxidant effects of gastric N-nitrosamines.[24] Alternatively, metabolic products of the bacteria may directly transform the mucosa.

However, the most convincing hypothesis supports the previous finding that chronic inflammation, with the resultant inflammation-related mutagenesis, may lead to genetic mutations culminating in malignant transformation. In addition, the resulting cellular proliferation may increase the likelihood of mitotic error and invoke a role for genotoxicity. This model also acknowledges the role of dietary factors in gastric carcinogenesis. While dietary mutagens may increase the risk of mutation, dietary antioxidants may act as protective factors. Because some DNA damage can be self-corrected, H pylori-related mutations only rarely may lead to malignant transformation. Thus, longer duration of infection, especially infection acquired during childhood and continuing until old age, increases the risk of significant DNA damage with subsequent malignant transformation.[10]

An association of H pylori with another neoplasm, gastric lymphoma, has also been described. Studies suggest that mucosa-associated lymphoid tissue (MALT) not present in the normal stomach develops in response to H pylori infection and then provides the setting for future evolution of lymphoma.[9,25] With 60% of gastric non-Hodgkin's lymphomas arising in the setting of chronic gastritis, H pylori infection, with its chronic inflammation and proliferation of lymphoid tissue, may be a carcinogenic factor for gastric lymphoma development.[9]

H pylori infection has been shown to be an independent risk factor for gastric adenocarcinoma in studies that factored out confounding variables, eg, dietary and H pylori economic factors.[24] An epidemiologic study showed a sixfold increase in the risk of gastric cancer in populations with 100% H pylori infection compared to populations without infection.[26] Because of the possible role of H pylori infection in identifying patients with an increased risk of gastric cancer, H pylori screening and treatment of asymptomatic infection have become areas of great concern for clinicians. Universal screening with subsequent preventive treatment is a tempting concept, but a causal association between H pylori infection and gastric cancer first must be proven. Without confirmation of carcinogenesis, the costs of largescale screening and treatment, as well as the risks of adverse drug effects and the increased incidence of drug resistance, are prohibitive at this time. If populations at high risk could be identified, then screening and treatment might be beneficial.[8,10] These high-risk populations probably include highincidence ethnic groups, patients with strong family histories, and patients with preexisting ulcer disease. However, until high-risk groups are more accurately defined, screening and treatment are more thoroughly studied, and the causal relationship between H pylori infection and gastric cancer is proven, indiscriminate screening and treatment are not recommended.[10,24]

Diagnosis

A number of diagnostic studies, both direct and indirect, are available for detecting H pylori infection. Direct methods include histologic or microbiologic evidence of the presence of the helical bacteria, while indirect methods detect an immunologic host response or a characteristic metabolic byproduct of the bacteria. Endoscopy with biopsy, though expensive and invasive, often is performed on asymptomatic patients who are refractory to traditional therapy and frequently is part of the evaluation for gastric cancer. Diagnostic methods that require endoscopy with biopsy include histologic examination, culture, and the urease test, which requires a biopsy specimen, a pellet of agar, and a pH indicator that produces a color change in the presence of urease. Noninvasive methods include serologic tests and urease breath tests.

Histologic examination is the traditional method for detecting the presence of the unusual gastric bacterium and can be performed on gastric biopsy specimens to diagnose H pylori infection. Because the bacteria may colonize different sites in the stomach, two antral biopsy specimens are recommended. The sensitivity and specificity depend on the experience of the observer, the choice of sampling, and the stains used. Although histologic examination has the benefit of contributing additional information about the extent of inflammation of the gastric mucosa, the cost of histopathologic evaluation and the need for ancillary techniques to obtain tissue disadvantages of this standard approach to diagnosis.

Also expensive and invasive, culture of gastric biopsies can prove bacterial presence and may be used in determining antibiotic susceptibility for treatment resistant organisms. H pylori is difficult to grow in culture, and growth can be further decreased by recent antibiotic use, ingestion of topical anesthetic or simethicone during endoscopy, and contamination of the biopsy forceps with other organisms.[27]

The urease test, which is the current diagnostic procedure of choice for detecting H pylori on gastric biopsy specimens, detects the conversion of urea to ammonia and bicarbonate and alters the pH of the medium, thus causing a color change. The urease test is frequently and effectively used to detect H pylori in biopsy specimens because it is less expensive than histologic examination and culture, its sensitivity and specificity are comparable, and test results can be rapidly determined.

Other indirect methods that do not require endoscopy offer the advantage of being less invasive. H pylori serologic antibody titers, which are relatively inexpensive and noninvasive, are useful in detecting infection, especially in epidemiologic studies. Serologic tests are easily used in the outpatient setting, provide high sensitivity and specificity, and are often the diagnostic procedure chosen by clinicians to document infection. However, their usefulness in monitoring response to antimicrobial treatment is limited by the slow decrease in titers after eradication of the bacteria. At this time, serologic tests are useful in determining current infection but cannot be used for shortterm followup.

The labelled carbon (14C or 13C) urease breath test is another noninvasive indirect method that reliably indicates response to antimicrobial therapy and can be used to determine eradication of the organism. The breath test, which relies on H pylori's efficient hydrolysis of urea, can be easily performed but is expensive and not widely available. 14C breath tests are used most frequently due to the relative ease of testing. However, the nonradioactive 13C breath tests, which require the use of a gas isotope ratio mass spectrometer, should be used for children and pregnant women and in situations in which multiple tests are required. Currently, most authorities would recommend evaluation of suspected ulcer disease with endoscopy and urease testing.[28]

Treatment

Because studies of various antimicrobial regimens are still in progress, recommendations for treatment of H pylori are constantly changing. Tripletherapy regimens were used initially because they have the advantage of both luminal and systemic activity and are less likely than single agents to allow resistance development. However, doubletherapy regimens are equally effective. The original combination included bismuth, tetracycline or amoxicillin, and metronidazole for two weeks, but this has been replaced by omeprazole with clarithromycin or amoxicillin. Although this indication is not approved by the Food and Drug Administration, H pylori infection is a method of treatment for MALT lymphomas. Determining who should be treated remains controversial, but most would include patients with refractory peptic ulcer disease for a two to fourweek course.

Conclusions

The common H pylori infection is in all likelihood a significant predisposition to the development of gastric cancer. Some gastric malignancies may be preventable by alterations in diet and hygiene, while gastric cancer may be preventable by treating a premalignant condition, H pylori gastritis. The astute clinician will be aware of the role of H pylori as a predisposing factor to gastric malignancy, will approach the diagnosis aggressively, and will appropriately manage patients at high risk for infection.

References
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