A SPECIAL ARTICLE

Gastric Adenocarcinoma: Part One


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INTRODUCTION

Despite an overall decrease in incidence, gastric cancer remains a leading cause of cancer-related mortality worldwide. Adenocarcinoma, which is divided into an intestinal-type and a diffuse-type, accounts for more than 90% of gastric malignancies. The intestinal-type is more common and accounts for most cases of sporadic gastric adenocarcinoma. The diffuse type is more commonly associated with a family history or underlying genetic predisposition. Lymphoma is the second most common type of gastric malignancy. The incidence of gastric cancer has decreased in the past several decades within the United States and reflects a disproportionate decline in the intestinal-type adenocarcinoma. Further, this decrease appears to parallel a decrease in the incidence of *Helicobacter pylori* (*H. pylori*) infection in the United States. Infection with *H. pylori* is an important risk factor for gastric cancer. Recent work examining the role of bacterial factors and host factors in disease progression has shown that the host immune response to infection is crucial in predicting disease outcome. Various animal models, including the Japanese monkey and the Mongolian gerbil, have been used to study the association between *H. pylori* and gastric cancer. Recent work using a mouse model of *Helicobacter*-associated gastric cancer has led to a paradigm shift regarding the cell-origin of gastric cancer. This review will be divided into two sections. The first section will include the epidemiology and etiology of gastric adenocarcinoma, with particular focus on *H. pylori*. The second section will include discussions of diagnosis, staging, and current treatment options for gastric adenocarcinoma.

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EPIDEMIOLOGY

There has been an overall decrease in the incidence of gastric cancer worldwide. Gastric cancer is currently the seventh leading cause of cancer-related mortality in the United States. Within the United States, it is estimated that 13,510 men and 8,350 women will be diagnosed with gastric cancer in 2005. Of these, 11,550 people will die as a result of their disease (1).

There is geographic, ethnic, and age variation in the epidemiology of gastric cancer; the association

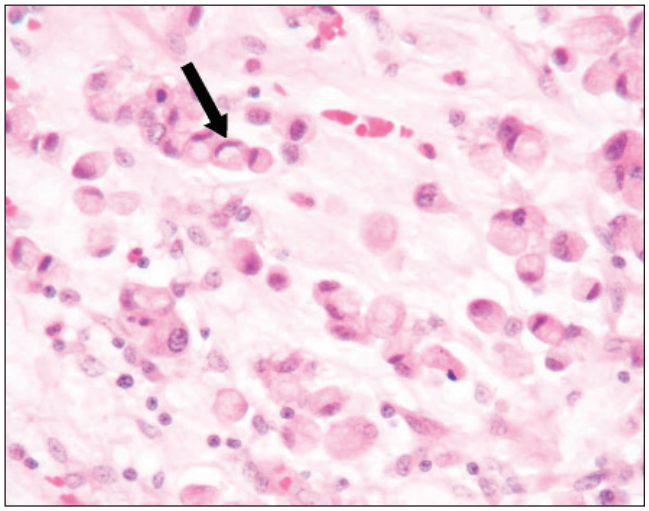

Figure 1A. Photomicrograph showing a sheet of signet ring cells, without any glandular formation or cellular cohesiveness. One signet ring cell is marked by an arrow.

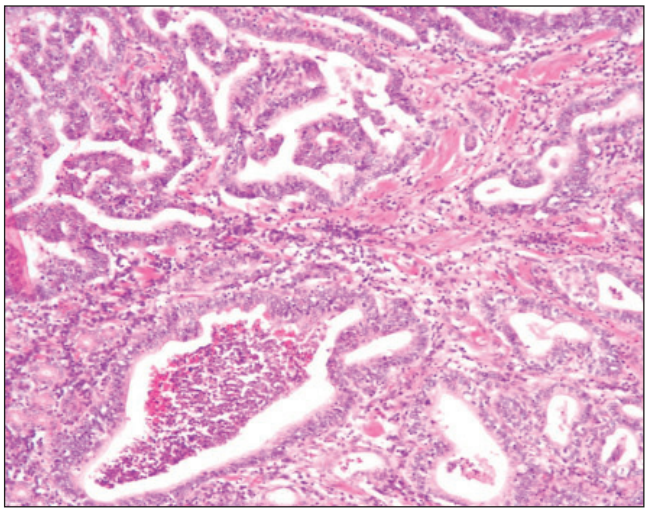

Figure 1B. Photomicrograph showing intestinal-type gastric adenocarcinoma. Glandular differentiation is evident.

with socioeconomic status is less clear. Previous studies have shown an inverse correlation between socioeconomic status and gastric cancer, but a recent prospective study of over 50,000 men did not support this conclusion (2). Rates are highest in Japan and lowest in North America and Australia (3,4). In the United States, the median age of gastric cancer in men is 70, and in women 74. The median age in high-risk countries is approximately ten years younger, but this may reflect lead-time bias due to aggressive screening programs (5). Previously, gastric cancer was seen mainly in industrialized nations, whereas today 60% of the incidence is within developing countries (4).

The pattern of stomach involvement with gastric cancer has also changed. The decrease in intestinal-type adenocarcinoma is reflected mainly in a decrease in distal cancers. The current anatomical distribution of gastric cancer within the United States is as follows: 39% in the proximal third, 17% in the middle third, 32% in the distal third, and 12% involving the entire stomach (6).

ETIOLOGY

Gastric adenocarcinoma is divided by the Lauren classification into a diffuse type and an intestinal type. (7) As the name implies, the diffuse form infiltrates the stomach wall without cellular cohesiveness and without glandular differentiation (Figure 1A). This form of gastric cancer occurs at an equal frequency throughout the world, tends to occur at a younger age, is less clearly associated with environmental factors, and carries a worse prognosis (8). The intestinal-type is characterized histologically by gland formation (Figure 1B). This subtype of gastric adenocarcinoma has been decreasing in incidence and is more clearly associated with *Helicobacter pylori* infection and other environmental exposures.

Analogous to the adenoma-to-carcinoma sequence that has been characterized for colon cancer, there appears to be a phenotypically similar multi-step process in the formation of gastric cancer. The initial step in the process is chronic inflammation, usually caused by *H. pylori*, which can be exacerbated by bile salt exposure or bacterial overgrowth as a result of achlorhydria. In the majority of cases, disease remains limited to chronic active gastritis. However, approximately 20% of patients will progress to atrophic gastritis where the mucosa is depleted of specialized glandular cells. Atrophic gastritis may be complicated by intestinal metaplasia, which is associated with dysplasia and progression to carcinoma (9). While adenocarcinoma is the most devastating outcome of *Helicobac-*

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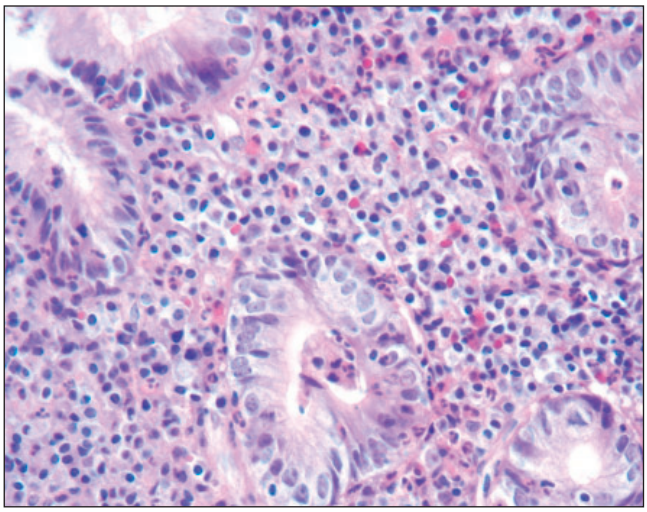

Figure 2A. Photomicrograph showing abundant chronic inflammation and glandular atrophy.

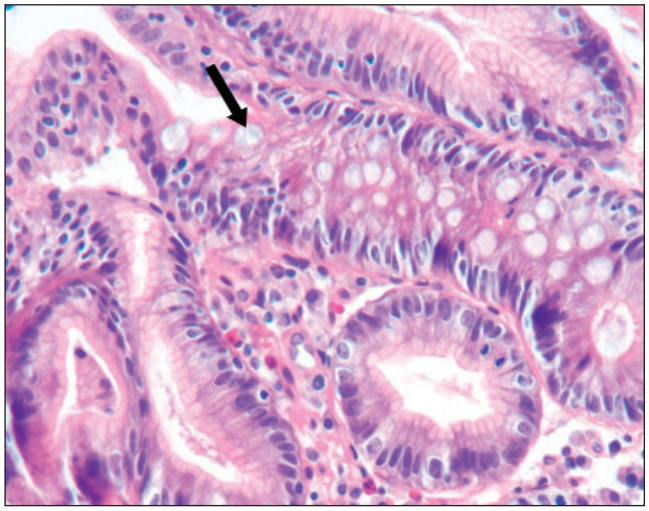

Figure 2B. Photomicrograph showing intestinal metaplasia. Several goblet cells are evident. One goblet cell is marked by an arrow.

ter pylori infection, it occurs in less than 1% of infected patients (10). In one study from Japan, the specific annual incidence was 0.37% (11), and in a separate South Korean study the annual incidence was 0.46% (12).

There are two types of atrophic gastritis. Multifocal atrophic gastritis occurs secondary to *H. pylori* infection, is the most common type, and is most likely to be associated with metaplasia and the ultimate development of cancer (Figure 2A) (13). Diffuse corporal atrophic gastritis is associated with anti-parietal cell and intrinsic factor antibodies and as such, is confined to the body and fundus where parietal cells are located. This form of atrophic gastritis is also associated with the development of gastric cancer, but the risk is less (14).

Intestinal metaplasia is defined as the replacement of the normal gastric glandular or foveolar epithelium with intestinal-type epithelium (Figure 2B). Intestinal metaplasia can be divided into three types, as defined by Filipe and Jass (15). Type I is the complete form of intestinal metaplasia, containing goblet cells, Paneth cells, and absorptive epithelium. Type II is incomplete metaplasia, containing few absorptive cells, goblet cells, columnar cells of varying differentiation, and fewer Paneth cells. Type III, or colonic metaplasia, is intermediate between the two (16,17). Type II or III intestinal metaplasia occurs in 80% of intestinal-type cancers, but it remains controversial whether or not the specific type of metaplasia can be used to predict the development of gastric adenocarcinoma (16,17).

Helicobacter pylori was rediscovered by Marshall and Warren in 1984 (18), and has been designated class I carcinogen by the WHO (19). *H. pylori* is the causative agent for up to 80% of all cases of gastric adenocarcinoma and 90%–95% of gastric MALT lymphomas. It is not surprising then that the decrease in incidence of gastric cancer in the United States parallels a decrease in *H. pylori* infection. The incidence of infection has dropped from 60%–75% in the early 1900's when gastric cancer rates were greater than 50/100,000 persons to an infection rate of approximately 25% at present when gastric cancer rates have decreased to 7/100,000 persons (20).

The interaction between *H. pylori* and the host immune response determines the degree of inflammation, the type of cytokine pattern produced, and the likelihood of progression to cancer. Bacterial factors associated with a more severe disease status likely act through induction of a stronger immune reaction from the host rather than functioning as direct carcinogens. The bacterium contains a number of different viru-

lence factors, including adhesion proteins, urease, and the products of the Cag A pathogenicity island. Indeed, CagA+ strains are associated with more severe inflammation and a greater chance of progressing to adenocarcinoma (21).

HOST IMMUNE RESPONSE

H. pylori is a gram negative spiral microaerophilic organism that only colonizes gastric mucosa. Its preferred niche is within the mucous layer overlying gastric epithelial cells, where a neutral pH is maintained and the organism is protected from both gastric contents and the sweeping motility of the gut. *H. pylori* is not invasive though it infrequently attaches to the cell surface. It is not clear how an immune response is initiated. Regardless of the initiating event, an early innate immune response is quickly followed by a vigorous but ineffective adaptive response. The pattern of the adaptive response appears critical in determining disease outcomes.

Within the adaptive response, the Th1 cytokine profile is most closely linked with disease. Mouse models of disease have shown that strains which develop a strong Th1 response to infection develop more atrophy and metaplasia compared with strains which develop a predominantly Th2 response, which are resistant to disease. Studies evaluating Th1 and Th2 responses compare different strains of mice that have genetic differences in addition to those governing cytokine responses, and these genetic differences may independently contribute to gastric cancer risks. Therefore, experiments were carried out to switch the immune response to *Helicobacter* infection within a given strain and determine effects on disease. Indeed, converting a Th1 to a Th2 response in a susceptible mouse strain protects against the development of atrophy and metaplasia (22), whereas converting a protective Th2 response to a Th1 response in a strain that was previously resistant to *Helicobacter* induced disease allows the progression of mucosal alterations from atrophy to metaplasia and dysplasia, thus converting a resistant host to a susceptible one (23).

Human observations that support this theory include the so-called "African enigma." The incidence of gastric cancer in sub-Saharan Africa is low despite a high incidence of *H. pylori* infection. As the incidence of coinfection with parasites is high in this region, the immune response may be switched primarily in favor of Th2 cytokines, protecting against chronic active gastritis and its consequences (24). Specific cytokine profiles have been examined in humans for their role in gastric carcinogenesis in response to *H. pylori* infection. IL-1β is a pro-inflammatory cytokine shown to promote gastrin release, inhibit acid secretion, and promote apoptosis. Analysis of patients carrying IL-1β polymorphisms that increase IL-1β expression have been associated with an increased risk of atrophic gastritis and cancer secondary to *H. pylori* infection. Various other cytokine profiles have been examined as well and a profile resulting in the combination of elevated IL-1β, elevated TNF- , and decreased IL-10 levels confers a 50-fold risk of gastric cancer (25) further supporting the role of the Th1 response to infection.

How does a Th1 cytokine response lead to disease? IFN-γ, TNF-α and IL1-β have been shown to increase Fas-mediated apoptosis, leading to cell loss and tissue remodeling. There is evidence that Fas signaling may have a role in proliferation, and in some cases function as an oncogene (26). A new model of gastric cancer formation, one that may also explain other inflammation-associated epithelial cancers, has recently been proposed. Using the *Helicobacter felis* gastric cancer model, it was recently reported that the cell of origin of gastric cancer is not a native epithelial cell or native tissue stem cell but rather a bone marrow derived stem cell (BMDC). These cells are recruited into the tissue in response to injury, and once within their new niche exposed to the inflammatory environment, they develop as cancer (27). The inflammatory environment associated with gastric cancer may initiate gastric mucosal cell injury required for engraftment of BMDC, may contribute to homing and engraftment signals and/or may direct differentiation and growth of these cells.

GENETICS

The specific mutations that occur at each step within the multi-step process from gastritis to cancer have not been clearly elucidated as they have in the adenoma-

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to-carcinoma sequence in colon cancer. However, a number of discoveries have been made. Mutations in the p53 tumor suppression gene have been found in gastric cancer, intestinal metaplasia, and gastric dysplasia, indicating that p53 mutations may be a necessary early step in the pathway (28). Mutations in the APC gene have been associated with gastric cancer formation, but not with gastric dysplasia, indicating that a mutation in this gene may be a later event in the sequence (29).

A number of familial syndromes pose an increased risk of gastric cancer. As already mentioned, mutations in the APC gene have been discovered in a significant number of gastric cancers. Patients with familial adenomatous polyposis (FAP) have an approximately tenfold risk of gastric cancer compared to the general population (30). Patients with hereditary nonpolyposis colorectal cancer (HNPCC) have an 11% incidence of gastric cancer (31). Microsatellite instability, the key defect in HNPCC, is seen in 15%–50% of sporadic gastric cancer cases (32). Juvenile polyposis may carry an increased risk of gastric cancer, but the number of cases reported in the literature is small (33).

There is also data supporting a genetic predisposition in certain cases of diffuse-type gastric cancer. One third of patients with hereditary diffuse gastric cancer have germline mutations in the E-cadherin (CDH-1) gene. The interaction of E-cadherin with the catenins is important for cell-cell adhesion (34).

ENVIRONMENTAL TRIGGERS

Although *H. pylori* infection is the most commonly associated environmental trigger for gastric cancer, there are other exposures thought to increase the risk of gastric cancer. High salt intake is associated with a higher incidence of atrophic gastritis in humans and animals in the presence of *H. pylori* infection (35). Smoking has been shown in multiple case-control studies to be a risk factor for gastric cancer (36,37). The data for nitrate intake is less conclusive. A recent prospective cohort study of 120,852 men followed for over six years did not demonstrate an increased risk of gastric cancer with increased nitrate intake (38). Other risk factors studied include a history of partial gastrectomy, Menetrier's disease, and gastric adenomas (39).

OTHER CANCER TYPES

Adenocarcinoma accounts for greater than 90% of gastric malignancies. However, there are a number of other tumors that can arise within the stomach, which are important to recognize as therapy differs for each. Gastric lymphoma is the second most common malignancy to affect the stomach and is also associated with *H. pylori* infection. Disease ranges from low-grade mucosa associated lymphoid tissue (MALT) lymphoma to high-grade lymphoma. The normal stomach does not contain lymphoid tissue. With *H. pylori* infection however, lymphocytes enter the lamina propria and invade up through the layers of the mucosa. It is from this group of cells that an *H. pylori* specific-clonal B-cell population may arise (40,41). Between 72% and 98% of patients with MALT lymphomas have evidence of *H. pylori* infection (42,43). Elimination of *Helicobacter* infection removes the antigenic stimulation of the malignant B-cell clone and may be sufficient for cure in early stage disease. Other less common forms of gastric cancer include leiomyosarcoma, gastrointestinal stromal tumor (GIST) and other more rare cancers including carcinoid tumors, rhabdomyosarcomas, choriocarcinomas, and hemangiopericytomas (3).

CONCLUSION

In summary, the epidemiology of gastric adenocarcinoma in the United States is changing, particularly in regard to the intestinal-type cancer. This parallels the changing incidence of *H. pylori* infection. There are certain genetic predispositions and there appear to be other environmental factors involved, but *H. pylori* remains the single most important factor in the pathogenesis of gastric adenocarcinoma. ■

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