Original Article

Association of helicobacter pylori with carcinoma of stomach
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Abstract

Objective: To note the association of Helicobacter pylori in patients having carcinoma of stomach.

Methods: A descriptive study was carried out at the Department of Histopathology, Ziauddin Medical University, Karachi from April 1992 to May 1998. Histological evaluation of 50 cases of carcinoma of stomach was compared with 50 cases each of chronic gastritis and histological normal gastric mucosa. Only those cases of carcinoma of stomach were included that contained sufficient non-neoplastic mucosa in addition to tumour tissue. Three glass slides with serial sections of each case of carcinoma of stomach, chronic gastritis and normal gastric mucosa were freshly cut and stained with H&E, PAS and Giemsa stains. All slides were examined by light microscopy.

Results: Helicobacter pylori were identified in 35 cases (70%) of carcinoma of stomach, in 42 cases (84%) of chronic gastritis, and in 12 cases (24%) of normal gastric mucosa. The presence of H. pylori in cases of carcinoma of stomach and chronic gastritis was highly significant (P<0.001) as compared to normal gastric mucosa. Chronic gastritis was observed in the non-neoplastic mucosa in 48 cases (96%) with carcinoma of stomach. Of 50 cases with carcinoma of the stomach, intestinal type of carcinoma was found in 30 cases (70%), and diffuse type in 15 cases (30%). No significant difference was noted in the prevalence of H. pylori between intestinal type (69%) and diffuse type (71%) gastric carcinoma. Significant Helicobacter pylori associated chronic gastritis was observed in intestinal type (94%) and diffuse type (100%) of gastric carcinoma. The prevalence of H. pylori was insignificant in the presence or absence of mucosal atrophy and intestinal metaplasia in both types of gastric carcinoma.

Conclusion: A significant number of H. pylori were found in patients of carcinoma of stomach. Both intestinal and diffuse types of gastric carcinoma showed strong association with H. pylori. Chronic gastritis appears to be the background lesion while atrophy and intestinal metaplasia indicate long term infection (JPMA 57:337:2007).
**Introduction**

Helicobacter pylori is a gastric pathogen.1 This bacterium is the commonest causative agent of chronic gastritis and peptic ulcer. Long term infection with this organism is considered a risk factor in the development of carcinoma of stomach.2,3

Carcinoma of stomach is the second commonest cancer in the world and carries a bad prognosis.4 Various environmental and dietary factors have been investigated as agents in the pathogenesis of carcinoma of stomach. But with the discovery of H. pylori in human stomach, an inflammation-related carcinogenesis has emerged in which this bacterium is implicated in the causation of gastric carcinoma.5 The epidemiological features of H. pylori and carcinoma of stomach are parallel in different populations of the world. Several studies have suggested that H. pylori is a risk factor in the development of carcinoma of stomach.2-5 This study was conducted to investigate the association of H. pylori with carcinoma of stomach.

**Patients and Methods**

The study included 50 consecutive cases of carcinoma of stomach diagnosed at the department of histopathology, Ziauddin Medical University Karachi from April 1992 to May 1998. For comparison 50 cases of chronic gastritis and 50 cases of histologically normal gastric mucosa were taken as controls. The controls were selected from the same period as the cases.

The inclusion criterion of carcinoma of stomach cases was the biopsies which in addition to tumour contained area of non-neoplastic tissue, while biopsies or tissues of gastric cardiac region were excluded. Similarly those biopsies of control cases of chronic gastritis and histologically gastric mucosa were included that contained well oriented sufficient amount of lamina propria. Fresh sections were cut from each paraffin tissue block of the cases included in the study. For each case of carcinoma of stomach, chronic gastritis and histologically normal gastric mucosa, three glass slides with serial tissue sections were prepared for 03 different stains. The stains used were Haematoxylin & Eosin, Periodic Acid-Schiff and Giemsa.

All the stained tissue slides of carcinoma of stomach, chronic gastritis and histological normal gastric mucosa were examined by light microscopy. Carcinoma of stomach was typed into intestinal and diffuse varieties according to Lauren’s classification;6 in intestinal carcinoma cohesive malignant cell clusters form glands with distinct lumina, whereas diffuse type carcinoma shows dissociate neoplastic cells which lack glandular lumina. In chronic gastritis, grading of density of chronic inflammation, active inflammation (neutrophils), atrophy, intestinal metaplasia and H. pylori was done into normal, mild, moderate, and marked in the guidelines of updated Sydney System aided by the provision of visual analogue scale.7 The histological parameters were assessed at a time in a particular or combination of stains. The histological finding of cases of carcinoma of stomach, chronic gastritis and histological normal gastric mucosa were entered in performa I, II and III respectively.

Frequency and percentage were computed for qualitative and categorical variables (gender, densities of H. pylori, morphological types of carcinoma of stomach), and mean and standard deviation for quantitative variable (age). Test of proportion was used for comparison of qualitative variable in three groups (Carcinoma of stomach, chronic gastritis and normal gastric mucosa). Analysis of variance (ANOVA) was applied for comparison of age (Mean ± S.D.) in three groups (Carcinoma of stomach, chronic gastritis and normal gastric mucosa). In all statistical analysis only P value <0.05 was considered significant.

**Results**

The age of patients ranged from 20 to 75 years with a mean age of 49 ± 15.5 years which was similar to both types of controls (chronic gastritis and normal gastric mucosa). However, the patients of gastric carcinoma were older than chronic gastritis and normal gastric mucosa. The age and gender distribution of all 3 groups is shown in Table 1. In all three groups gastric antrum was the predominant anatomical site.

H. pylori was identified in 35 cases (70%) of carcinoma of stomach, in 42 cases (84%) of chronic gastritis, and in 12 cases (24%) of normal gastric mucosa. The prevalence of H. pylori in carcinoma of stomach and chronic gastritis was highly significant (p<0.001) as compared to normal gastric mucosa. Chronic gastritis was seen in the non-neoplastic mucosa in 48 cases (96%) of carcinoma; and thirty (69%) of these had moderate chronic inflammation. Mucosal atrophic changes were seen in 41 cases (82%) of normal, mild, moderate, and marked in the guidelines of updated Sydney System aided by the provision of visual analogue scale.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Carcinoma of stomach (n=50)</th>
<th>Chronic Gastritis (n=50)</th>
<th>Normal Gastric Mucosa (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE (Years)</strong> Range</td>
<td>20-75</td>
<td>10-70</td>
<td>19-75</td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>49 ± 15.5</td>
<td>39 ± 15.3</td>
<td>44 ± 15.0</td>
</tr>
<tr>
<td><strong>SEX : Males</strong></td>
<td>30 (60%)</td>
<td>27 (54%)</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Females</td>
<td>20 (40%)</td>
<td>23 (46%)</td>
<td>25 (50%)</td>
</tr>
</tbody>
</table>

**Table 1. Age and sex distribution in Carcinoma of stomach, Chronic Gastritis and Normal Gastric Mucosa cases.**
In this study the association of *H. pylori* with carcinoma of stomach was investigated. Gastric carcinogenesis is a multi step and mutli factorial process. A study suggested that the prevalence of *H. pylori* in carcinoma of stomach was 89.2% compared with 31.8% in United States, the frequency of *H. pylori* in intestinal type gastric carcinoma was 89.2% compared with 31.8% in diffuse type gastric carcinoma. In the present study, the *H. pylori* prevalence in intestinal type carcinoma was 70% with no significance difference in the prevalence of organisms between intestinal (69%) and diffuse (71%) type carcinoma. Our results concur with the histological studies from Europe and Saudi Arabia which reported bacterial prevalence of 59% and 79.8% respectively; and in both studies no significant difference in the occurrence of *H. pylori* was found in both types of gastric carcinoma. Whereas in a similar retrospective study from United States, the frequency of *H. pylori* in intestinal type gastric carcinoma was 89.2% compared with 31.8% in diffuse type gastric carcinoma.

In the present study, the *H. pylori* prevalence in intestinal and diffuse type carcinoma was significantly higher as compared to 24% in controls with normal gastric mucosa (P<0.001). This high yield was due to high prevalence of bacteria in patients with chronic gastritis and peptic ulcer disease in our population. Helicobacter pylori was seen in 24 of 34 cases (69%) of intestinal type, and 11 of 15 cases (71%) of diffuse type carcinoma. No significant difference was noted in the prevalence of *H. pylori* between intestinal and diffuse type of carcinoma. The mean age in intestinal type was 50 years, and 44 years in diffuse type. Young age of diffuse type carcinoma was significant (P<0.01). Males were predominant in both types of gastric carcinoma. Chronic inflammation was noted in the non-neoplastic mucosa in 33 of 35 cases (94%) of intestinal type and 100% of diffuse type carcinoma. Atrophic mucosal changes were present in 26 of 35 cases (74%) of intestinal and all 15 cases of diffuse type. Mild to moderate degree of intestinal metaplasia was seen in 11 of 13 cases (85%) with intestinal type and 05 of 06 cases (83%) with diffuse type carcinoma. There was no significant difference in the prevalence of *H. pylori* in the morphologic variables of gastritis (Table 3). Mucosal atrophy and intestinal metaplasia in intestinal type was mostly observed in the antrum. Same morphology showed almost equal distribution in diffuse type carcinoma. Anatomical site had no influence of *H. pylori* in atrophy and metaplasia in both type of gastric carcinoma (Table 4).

**Discussion**

In this study the association of *H. pylori* with carcinoma of stomach was investigated. Gastric carcinogenesis is a multi step and multi factorial process. A study suggested that the prevalence of *H. pylori* in carcinoma of stomach was 89.2% compared with 31.8% in United States, the frequency of *H. pylori* in intestinal type gastric carcinoma was 89.2% compared with 31.8% in diffuse type gastric carcinoma. In the present study, the *H. pylori* prevalence in intestinal and diffuse type carcinoma was significantly higher as compared to 24% in controls with normal gastric mucosa (P<0.001). This high yield was due to high prevalence of bacteria in patients with chronic gastritis and peptic ulcer disease in our population. Various other important studies have used specific serum antibodies against *H. pylori*, and two prospective case-control serological studies from Britain and Hawaii showed significant bacterial prevalence of 69% and 94% respectively in patients of gastric carcinoma. The overall prevalence of 70% in patients with gastric carcinoma in this

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**Table 2. Densities of *H. pylori* in Carcinoma of stomach, Chronic Gastritis and Normal Gastric Mucosa cases.**

<table>
<thead>
<tr>
<th>Densities of <em>H. pylori</em></th>
<th>Carcinoma of stomach (n=50)</th>
<th>Chronic Gastritis (n=50)</th>
<th>Normal Gastric Mucosa (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>15 (30%)</td>
<td>8 (16%)</td>
<td>38 (76%)</td>
</tr>
<tr>
<td>Mild</td>
<td>20 (40%)</td>
<td>14 (28%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (24%)</td>
<td>13 (26%)</td>
<td>00 (0)</td>
</tr>
<tr>
<td>Marked</td>
<td>3 (6%)</td>
<td>15 (30%)</td>
<td>00 (0)</td>
</tr>
</tbody>
</table>

No significant difference.

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**Table 3. Prevalence of *H. pylori* according to morphological variables of Gastritis in Carcinoma of stomach cases according to type of cancer.**

<table>
<thead>
<tr>
<th>Morphological variables</th>
<th>Intestinal (n=35)</th>
<th>Diffuse (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number +ve (%)</td>
<td>Number +ve (%)</td>
<td></td>
</tr>
<tr>
<td>Chronic gastritis</td>
<td>33 22 (67)</td>
<td>15 11 (73)</td>
</tr>
<tr>
<td>Active inflammation</td>
<td>12 9 (75)</td>
<td>4 4 (100)</td>
</tr>
<tr>
<td>Atrophy</td>
<td>26 17 (65)</td>
<td>15 11 (73)</td>
</tr>
<tr>
<td>Intestinal Metaplasia</td>
<td>13 8 (62)</td>
<td>6 5 (83)</td>
</tr>
</tbody>
</table>

No significant difference.

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**Table 4. Topographical distribution of atrophy and intestinal metaplasia with prevalence of *H. pylori* in Carcinoma of stomach cases according to type of Cancer.**

<table>
<thead>
<tr>
<th>Morphological variables</th>
<th>Intestinal (n=35)</th>
<th>Diffuse (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number +ve (%)</td>
<td>Number +ve (%)</td>
<td></td>
</tr>
<tr>
<td>Atrophy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body / Fundus</td>
<td>4 3 (75)</td>
<td>7 5 (71)</td>
</tr>
<tr>
<td>Antrum</td>
<td>22 14 (64)</td>
<td>8 6 (75)</td>
</tr>
<tr>
<td>Intestinal Metaplasia</td>
<td>1 1 (100)</td>
<td>2 2 (100)</td>
</tr>
</tbody>
</table>

No significant difference.
The association between H. pylori and chronic gastritis is well known. Helicobacter pylori associated chronic gastritis was the background lesion in majority of the intestinal and diffuse type of gastric carcinoma in this study. The bacteria act directly via the release of enzymes or toxins, or by the inflammatory response, which it provokes, and is thought to cause epithelial damage. Several studies have suggested the role of H. pylori in gastric carcinogenesis through stages of chronic gastritis to mucosal atrophy to intestinal metaplasia more so with intestinal type carcinoma. However, a recent research indicates that H. pylori infection is associated with DNA damage in gastric epithelial cells, which could be a risk for gastric cancer in humans. Although mucosal atrophic changes were present in significant number of intestinal and diffuse type of gastric cancer but there was no obvious correlation of mucosal atrophy and intestinal metaplasia with H. pylori in gastric carcinoma cases in the present study. In a report from Japan, no precursor lesions were found in the margins of microcarcinoma. Hence, it was postulated that gastric atrophy and intestinal metaplasia appear to be an indicator of long-standing proliferation, but are not necessarily specific precancerous lesions. Strain variation has impact on gastroduodenal diseases and it is shown that patients infected with H. pylori CagA strains had increased rate of gastric epithelial cell proliferation.

References

21. Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in


