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Gastrointestinal Tract

Distribution of gastric carcinoma in an area with a high prevalence of *Helicobacter pylori*

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ABSTRACT

Background/Aims: South Asia is an enigma for gastric cancer (GC) because it is a low risk region with a high prevalence of *Helicobacter pylori (H. pylori)* infections. We evaluated the trend of GC clinical presentation and risk factors in patients with dyspeptic symptoms.

Materials and Methods: The medical records of patients, coded by the international classification of diseases (ICD-10-CM, 2015, Diagnosis Code C16.9) for malignancies of stomach diagnosed by esophagogastroduodenoscopy (EGD) and histopathology, were studied.

Results: 394 GC cases with a mean age of 54±15 years, range of 18 to 88, were analyzed. 256 (65%) were male. Distal non-cardiac and cardiac tumors were 302 (77%) and 92 (23%) cases, respectively. The WHO classification of GC defined 222 (56%) cases as intestinal type adenocarcinoma, 68 (17%) cases as signet ring cell carcinoma (SRC), 62 (16%) cases as diffuse type and 42 (11%) cases as B cell non-Hodgkin lymphoma. The co-morbid conditions associated with GC were *H. pylori* infection (positive in 246 (62%) cases), diabetes mellitus type 2 (in 90 (23%) cases), and cigarette smoking (in 94 (24%) cases). Of the male patients, 88 (34%) ($p<0.001$) were smokers. Body mass index was abnormal in all age groups and in both sexes. Cardiac regions for GC were more common in the 46- to 60-year old age range and in males. Diffuse GC was seen in all age groups but there were significantly more common in the 18- to 45-year old age range. Gastric non-Hodgkin's lymphoma was seen at an early age of 18-45 years in 14(12%) and a later of 61-88 years in 20 (15%).

Conclusion: Intestinal type GC is common at all ages but SRC and diffuse GC are more common in patients less than 50 years old. SRC and diffuse GC were not specific to the elderly in our study population.

Keywords: Gastric carcinoma, male, age, *H. pylori*, noncardiac, intestinal type carcinoma, signet cell carcinoma

Original Article

INTRODUCTION

Gastric carcinoma (GC) is one of the major causes of mortality and morbidity worldwide (1) and it is also one of the leading causes of death worldwide (2). GC prognosis remains poor as it is rarely detected early, and the majority of cases show distant metastasis at the time of diagnosis (3,4). Developing countries account for two-thirds of the reported incidences of GC worldwide (5). The incidence of GC in both men and women is concentrated primarily in Asia, and the highest incidence has been reported in Asian countries e.g. Japan, China and Korea (6,7).

Helicobacter pylori (*H. pylori*) is a major cause of gastroduodenal ulcer and risk factor for GC and lymphoma. In developing countries located in Asia e.g., Pakistan and India, *H. pylori* infection is frequent in the general population and occurs at an early age. In our country, *H. pylori* is acquired at an early age and *H.pylori* seropositivity in children (11-15 years old) is 53.5% (8). In contrast, in developed Asian countries like Japan and Singapore, the frequency of *H. pylori* infection is reported to be somewhat lower (9,10). In the United States, the prevalence of *H. pylori* has decreased to approximately 10% in the white middle and upper class populations

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younger than 50 years old (11). *H. pylori* is transmitted by the feco-oral route. It is associated with areas of overcrowding, poor sanitation, lower socioeconomic status, and poor water supply because these are risk factors for *H. pylori* infection. As a result, there is a higher frequency and lower age of acquisition for *H. pylori* in less developed Asian countries (12,13). In Pakistan, there is a high prevalence of *H. pylori*, but the prevalence of GC is low. This study determined the distribution of GC in our patients with upper gastrointestinal symptoms and risk factors associated with GC.

MATERIALS AND METHODS

In this cross-sectional study, the medical records of patients aged 18 years and over who attended the hospital were reviewed. These patients presented with pain, nausea or vomiting, weight loss, hematemesis, melena, and had an esophagogastroduodenoscopy (EGD) between January 2000 and January 2016. The "gastric carcinoma cases" were defined as patients who fulfill the 2015 ICD-10-CM Diagnosis Code C16.9 for malignancies of the stomach. Three hundred and ninety-four patients fulfilled these criteria. The demographic characteristics that were taken into account included: mean age, sex, address of permanent residence, body weight (kg), height (cm), symptoms, use of medications [analgesics, proton pump inhibitors (PPIs), etc.], diagnosis, blood glucose levels, lipid profile, hemoglobin levels, hemoglobinA1c levels, liver function test, complete blood count, *H. pylori* serology, (14) carbon labeled-urea breath test (^{14}C-UBT) or stool antigen test (HpSA), and tumor markers [protein CA 125 (cancer antigen 125) and carcinoma embryonic antigen (CEA)] were recorded. Cigarette smoking, alcohol intake, and occupational history were also noted.

Study Design

This was a cross sectional study.

Setting

Retrospective data collection from patient medical records was performed after obtaining approval by the institutional ethics review committee.

Inclusion Criteria

All patients, irrespective of sex, age, and ethnic background, that presented with upper gastrointestinal symptoms and diagnosed as having GC between January 2000 and January 2016 were included.

Exclusion Criteria

Individuals with a history of gastrectomy for GC, aplastic anemia, scleroderma, gastric lymphoma, and gastrointestinal stromal tumor (GIST) were excluded.

Endoscopy

The morphology of GC was described as exophytic, ulcerated, infiltrative, or combined. Bormann's classification described the appearance of GC as type I for polypoid growth, type II for fungating growth, type III for ulcerating growth, and type IV for diffusely infiltrating growth (linitis plastica in SRC).

Esophageal carcinoma anatomic classification was if its epicenter was in the lower thoracic esophagus or gastroesophageal junction (GEJ) or within the proximal 5 cm of stomach (i.e., cardia) with the tumor mass extending into GEJ or distal esophagus. If the origin was >5 cm distal to the GEJ, or within 5 cm of GEJ but did not extend into GEJ or esophagus, it was grouped as GC (14).

Histopathology

At the time of endoscopy, at least 2 or more biopsies were obtained from gastric abnormalities with standard biopsy forceps and tissues were submitted for histopathological examination. Specimens were fixed overnight in 10% buffered formalin and gross examination performed the next day was followed by paraffin embedding. Slides were stained with hematoxylin and eosin. The reporting (according to the TNM staging system) incorporated gross examination, tumor location, type and grade, depth of invasion, surgical resection margins, and lymph node status. Histological classification of GC was based on Lauren's criteria (15).

Statistical Analysis

Results were expressed as mean±standard deviation. Univariate analysis was performed using an independent sample t-test, Pearson Chi-square test or Fisher Exact test where applicable. A p value <0.05 was considered significant. Statistical interpretation of data was performed using IBM Statistical Package for the Social Sciences Statistics (IMB SPSS Statistics; Armonk, NY, USA) version 19.0.

Technique

The technique used was non-probability consecutive sampling.

Data Collection Procedure

Exemption from the institutional ethics review committee (ERC) was obtained. All pathologically documented gastric cancer records during a 16-year period (from 2000 to 2016) were recorded. Cases of GC presenting for the first time during the 16- year period were identified. All demographic, clinical, and endoscopic data from each patient were gathered and analyzed.

RESULTS

There were 394 cases. The mean age was 53±15 (range: 18-88) years of age. Male patients constituted 256 (65%) cases and 138 (35%) cases were female patients.

Risk Factors

There was no difference in the distribution of *H. pylori* infection in patients in relation to age, sex, and site of malignancy (Table 1, 2). The co-morbid conditions associated with GC were diabetes mellitus type 2 in 90 (23%) case, essential hypertension in

Table 1. Clinical details of the patients with gastric carcinoma (n=394)

Age (year) mean±SD	54±15
Range	18-88
Sex	
Male/Female	256/138
Symptoms	**n (%)**
Weight loss	290 (74)
Nausea	232 (59)
Loss of appetite	216 (55)
Epigastric pain	184 (53)
Dysphagia	114 (29)
Melena	66 (17)
Constipation	68 (17)
Gastric outlet obstruction	54 (14)
Hematemesis	48 (12)
Endoscopy features	
Diffuse	224 (59)
Fungoid	76 (19)
Ulceration	66 (17)
Polypoid	18 (5)
Site of tumor	
Cardiac	92 (23)
Non-cardiac	302 (77)
Histology	
Intestinal type	222 (56)
Signet cell carcinoma	68 (17)
Diffuse	62 (16)
Lymphoma	42 (11)
Histology	
Well differentiated	74 (19)
Moderately differentiated	194 (49)
Poorly differentiated	126 (32)
Risk factors	
Helicobacter pylori	246 (62)
Cigarette smoker	94 (24)
Alcohol	12 (3)
Metastases	
Lymph nodes	228 (60)
Peritoneum	64 (16)
Liver	48 (13)
Pulmonary	38 (11)
Bone	8 (2)
Small intestine	4 (1)
Pancreas	4 (1)

68 (23%) cases, and cigarette smoking in 94 (24%) cases. The distribution of GC was not related to the history of smoking. However, male patients [88 (34%) cases (p<0.001)] were more commonly smokers than female patients [6 (4%) cases] (Table 2). Body mass index was noted to be abnormal in all the age groups and in both sexes (Table 2).

Gastric Tumors

Gastric carcinoma arising from the non-cardiac region of the stomach was equally common in all age groups (Table 2). However, cardiac region tumors were more common in 46- to 60-year old patients and in males (Table 2). GC arising in the antrum were common in the 18 to 45-year old age group [68 (60%) cases (p=0.196)], but they were equally common in the two other age groups (Table 2). GC arising from the gastric lesser curve were more common in male patients compared to female patients and in the 46- to 60-year old age group [38 (25%) cases (p=0.006)] compared to the other age groups (Table 2). Diffuse GC was seen in all three age groups, but they were significantly more common in the younger age group (18- to 45-year old) and did not show any sex-related distribution (Table 2). Intestinal type GC was found equally in all age groups and also did not show any sex-related distribution (Table 2). GC, fungoid in shape in 36 (28%) cases, was significantly more common in the 61- to 88-year old age group than in the younger age groups (Table 2). SRCs were found frequently in the 18 to 45-year old and 46- to 60-year old age groups (Table 2). Gastric non-Hodgkin's lymphoma was not associated with sex and demonstrated two peaks in our patients: 14 (12%) cases in the 18- to 45-year old group and 20 (15%) cases in the 61- to 88-year old group (Table 2).

Gastric Metastases

Lymph node metastases were equally common in all age groups and marginally more common in female patients than male 98 (71%) vs. 156 (61%) (p=0.046), respectively (Table 2). Liver metastases were common in the older age group and occurred equally in both sexes (Table 2). Pulmonary metastases were also significantly more common in the older age group and in female patients [32 (23%) cases (p<0.001)] compared to male patients (26 (10%) cases) (Table 2). Peritoneal metastases were common in the 18- to 45-year old age group compared to the older age groups, and also significantly more common in females [32 (23%) cases (p<0.001)] compared to males [26 (10%) cases] (Table 2).

DISCUSSION

Gastric carcinomas were twice more common in males than in females. Only 32% of the GC cases were seen in elderly patients (61- to 88-year old age group). The study did not show a significant distribution in the elderly population as our patients with GC had a median age of 55 years. This is different from GC prevalence in other populations where GC is usually observed in patients 70 and older (16). Among the risk factors for GC, the *H. pylori* infection factor did not vary in the different age groups nor demonstrated a sex distribution (Table 2). *H. pylori* infection diagnoses involved in these cases was biopsy obtained at endoscopy for histology and did not include usage of a ^{14}C-UBT or HpSA test, which are better diagnostic tests (17). In practice, the *H. pylori* treatment prescribed is not based on local *H. pylori* antibiotic sensitivities. Post-treatment of *H. pylori* infection, there was an absence of documentation regarding eradication of the infection.

Smoking was common in all age groups, particularly in male patients (Table 2). This is in keeping with our National Health Survey, which described 46% men and 5.7% women as smoking tobacco (contributing to 80,000 deaths annually) (18). A cross sectional survey in a tertiary care center revealed that 39% of patients aged 18 years or older had either hypertension

Table 2. Association of gastric carcinoma with age and sex

	Age				Sex		
	Group I (18- to 45-year olds) n=114	**Group II (46- to 60-year olds) n=152**	**Group II (61- to 88- year olds) n=128**	**p**	**Male n=256**	**Female n=138**	**p**
Site							
Cardia							
Yes	18 (16)	48 (32)	26 (22)	0.007	70 (27)	22 (16)	0.011*
No	96 (84)	104 (68)	102 (78)		186 (73)	116 (84)	
Fundus							
Yes	20 (18)	36 (24)	40 (31)	0.045	68 (27)	28 (20)	.166
No	94 (82)	116 (76)	88 (69)		188 (73)	110 (80)	
Corpus							
Yes	38 (33)	52 (34)	46 (36)	0.909	80 (31)	56 (41)	0.063
No	76 (67)	100 (66)	82 (64)		176 (69)	82 (59)	
Antrum							
Yes	68 (60)	74 (49)	66 (52)	0.196	128 (50)	80 (58)	0.131
No	46 (40)	78 (51)	62 (48)		128 (50)	58 (42)	
Lesser curve							
Yes	14 (12)	38 (25)	16 (12)	0.006	56 (22)	12 (9)	0.001
No	100 (88)	114 (75)	112 (88)		200 (78)	126 (91)	
Greater curve							
Yes	8 (7)	14 (9)	16 (13)	0.344	28 (11)	10 (7)	0.236
No	106 (93)	138 (91)	112 (87)		228 (89)	128 (93)	
Boremann classification							
Polypoid	4 (3)	6 (4)	8 (6)	0.001	16 (6)	2 (1)	0.070
Fungoid	12 (10)	28 (18)	36 (28)		46 (18)	30 (22)	
Ulcerating	18 (16)	20 (13)	28 (22)		46 (18)	20 (15)	
Diffuse	110 (72)	98 (65)	56 (44)		148 (58)	86 (62)	
WHO GCa Classification							
Adenocarcinoma							
Intestinal type	34 (30)	54 (37)	48 (38)		96 (38)	40 (29)	
Papillary	0 (0)	0 (0)	2 (2)		2 (1)	0 (0)	
Mucinous	0 (0)	6 (4)	4 (3)		10 (4)	0 (0)	
Signet ring cell	26 (23)	32 (21)	10 (8)		38 (15)	30 (22)	
Adenoosquamous	4 (3)	4 (2)	0 (0)	<0.001	4 (2)	4 (3)	0.022
Diffuse	36 (32)	42 (27)	34 (26)		70 (27)	42 (30)	
GI stromal tumor	0 (0)	2 (1)	4 (3)		4 (2)	2 (1)	
Lymphoma	14 (12)	8 (5)	20 (15)		24 (9)	18 (13)	
Metastatic carcinoma	0 (0)	4 (3)	6 (5)		8 (3)	2 (1%)	
Metastases							
Lymph nodes							
Yes	84 (74)	98 (64)	72 (56)	0.018	156 (61)	98 (71)	0.046
No	30 (26)	54 (36)	56 (44)		100 (39)	40 (29)	
Liver							
Yes	4 (4)	20 (13)	18 (14)	0.005	32 (12)	10 (7)	0.107
No	110 (96)	132 (87)	110 (86)		224 (88)	128 (93)	
Pulmonary							
Yes	4 (4)	20 (13)	20 (16)	0.003	26 (10)	32 (23)	<0.001
No	110 (96)	132 (87)	108 (84)		230 (90)	106 (77)	
Peritoneal							
Yes	24 (21)	20 (13)	14 (11)	0.067	26 (10)	32 (23)	<0.001
No	90 (79)	132 (87)	114 (89)		230 (90)	106 (77)	
Risk factors							
Cigarette smoker							
Yes	24 (21)	36 (24)	34 (27)	0.603	88 (34)	6 (4)	<0.001
No	90 (79)	116 (76)	94 (73)		168 (66)	132 (96)	
Body mass index (BMI)							
Healthy<23	8 (7)	2 (1)	4 (3)	0.047	2 (1)	12 (8)	<0.001
Over weight>23	106 (93)	150 (99)	124 (97)		254 (99)	126 (91)	
Helicobacter pylori							
Positive	68 (60)	92 (60)	86 (67)	0.397	160 (63)	86 (62)	0.972
Negative	46 (40)	60 (40)	42 (33)		96 (37)	52 (38)	
Diabetes mellitus							
Positive	18 (16)	30 (20)	42 (33)	0.004	56 (22)	34 (25)	0.533
Negative	96 (84)	122 (80)	86 (67)		200 (78)	104 (75)	

or dyslipidemias with a history of active smoking (19). Based on the data of the National Health Survey, the overall prevalence of smoking among 15-year olds or older was 15.2% and the prevalence of smoking was 28.6% in men compared to 3.4% in women (20). The incidence of GC in male patients was in keeping with the prevalence of smoking in the male population. Increased salt intake has been described as an independent risk factor of GC. In a population based study, an increased dietary salt intake was documented among different communities in Karachi (21). Furthermore, according to the National Health Survey, 25.0% of the population was overweight or obese (22). The majority of patients with GC had a BMI that was deemed "overweight" in the majority of our GC patients, regardless of age or sex (Table 2). This is in agreement with the high BMI that was associated with the distribution of GC. Diabetes mellitus type 2 was significantly associated with GC in all age groups with a marked distribution in the 61- to 88-year old group [33% (p=0.004)] (Table 2). This is in keeping with the high prevalence of diabetes mellitus in this age group (equal sex distribution). According to the 2011 figure of the World Health Organization, the prevalence of diabetes mellitus in our population was the 7th highest in the world at 12.9%, which is the 10% of our population (23).

The gastric rich lymphatic and vascular supply explained extensive lymph node and liver metastases in GC at presentation. Lymph nodes metastases were equally common in all age groups regardless of sex. However, they were more common in the early age group of 18- to 45-year olds (84 (74%) cases) compared the older age group of 61- to 88-year olds (72 (56%) cases) (Table 2). At presentation, liver metastases were common in the two older age groups (Table 2). Pulmonary metastases [32 (23%) cases (p<0.001)] were more common in female compared to male (26 (10%) cases) patients. In previous studies, diffuse GC was found commonly in young female patients (24,25) while intestinal GC (associated with intestinal metaplasia) and *H. pylori* infection was found equally in all age groups (25,26). In an earlier local study, 53% of GC cases were located in the gastric antrum and 35% in the proximal part (27). However in the present study, distal gastric tumors and cardiac tumors were 77% and 23%, respectively (Table 1).

The implications of this study is that the education of the population at large and effective treatment of the risk factors of GC should be offered to the patients. In the absence of effective screening for early diagnosis of GC, we will continue to see patients with extensive disease progression at presentation.

Gastric carcinoma incidence has decreased in industrialized countries. GC is still a cause of mortality and morbidity in developing countries. A non-cardiac predominant disease was shown here to be associated with *H. pylori* infection and will require more effective management and eradication. In conclusion, GC is not an elderly disease in our population, which is different from developed countries.

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