Original Article

Topography of Gastritis and its Severity in 864 First Degree Relatives of Gastric Cancer Patients

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Abstract

Objectives: Studies on gastric mucosal histological findings among first degree relatives (FDR) of gastric cancer (GC) patients are scarce. The aim is to evaluate the topography and the severity of gastritis among FDR of GC patients.

Design: A total of 989 subjects who were FDR of GC patients, ages 40 – 65 years underwent gastroscopies. When no gross lesion was found, five specimens were evaluated according to the Sydney Classification and one for urease testing in order to determine the type of gastritis and its severity.

Results: Of the 989 subjects, 107 had significant lesions, including two with GC and one with esophageal cancer. The 864 subjects who had complete morphological data taken from five gastric areas (two from the antrum and three from the corpus) comprised 419 males (mean age 48.5±7 years) and 445 females (mean age 47±6.4 years). The *H. pylori* rate was 76.6%. Normal mucosa was seen in 6.9%, antrum-restricted gastritis in 7.4%, antrum-predominant gastritis in 63.5% and corpus-predominant gastritis in 20% (both had >80% *H. pylori* infection) and corpus-restricted gastritis in 2%. More atrophy was seen in the antrum and corpus of FDR females than males. The severity did not differ between those with one or more GC patients' relatives. Forty-nine percent of FDR had atrophy and 9.4% intestinal metaplasia (IM) in the corpus. After the age of 40, there was progression of intestinal metaplasia from 12.2 to 27.3% in the antrum and from 6.7% to 26.2% in the corpus during two decades. No high grade dysplasia was found in this mid-age population.

Conclusion: Only one-fifth of FDR have *H. pylori*-induced corpus-predominant gastritis who are at risk for cancer and suitable for eradication. Corpus-restricted gastritis is a rare disease in this area.

Key words: familial, gastric cancer, gastritis, *H. pylori*

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Accepted for publication: 19 May 2010

Introduction

Gastric cancer (GC) is the leading cause of cancer deaths among males in some Latin American, Asian countries, and in Iran.[1,2] The detection of early GC by routine endoscopic screening of those at risk can improve the survival of patients.[2,3] As *H. pylori*-induced atrophic gastritis is a precursor of distal GC, its eradication provides the best way for prevention of GC. Among

those with *H. pylori* infection, first degree relatives (FDR) of GC patients are more prone to GC than the general population.[4–8] Morphological changes, such as atrophy and intestinal metaplasia involving the corpus of the stomach are precancerous conditions for the development of GC.[9,10] There are few studies concerning the morphological findings of the stomach in FDR of GC.[11–15] This study has aimed to determine the topography, severity and extent of the gastritis and other precancerous conditions in FDR of GC with advancing age, and when one or two family members have been diagnosed with GC.

Materials and Methods

The residential addresses of subjects who underwent surgery for GC in Tehran hospitals during 2002 – 2005 were obtained from various hospital databases and from the Tehran Cancer Institute. Contact was made with the patients' FDR, including brothers, sisters, children, or parents of GC patients. All relatives between the ages of 40 to 65 years were invited to undergo a screening upper GI endoscopy in the hospital. Before the endoscopy, the patients' characteristics and number of additional FDR diagnosed with GC were obtained. Participants with had no macroscopic findings such as cancer or peptic ulcer in the duodenal bulb or stomach had biopsy specimens taken from five areas of the stomach for histological examination; two from the antrum (one just below the incisura angularis from the lesser and one from the greater curvature), three from the corpus (one from the lesser curvature in the mid-area between the cardia and incisura, one from the opposite side and one from the fornix, the superior most part of the stomach). One specimen was additionally taken from the incisura angularis for a rapid urease test (RUT).

All specimens were fixed in formalin, stained by Hematoxylin and Eosin (H&E) and/or giemsa and evaluated according to the updated Sydney Classification. In the initial part of the study, two pathologists who were blinded to all clinical and endoscopic data evaluated all biopsies and the rate of agreement was calculated. The severity of neutrophil or mononuclear cell infiltration, atrophy, and intestinal metaplasia (IM) was categorized according to four grades (none=0, slight=1, moderate=2, and severe=3). The mean scores of mononuclear and neutrophil cell infiltration were calculated separately for two areas of the antrum and three areas of the corpus.

H. pylori infection was considered absent when both the RUT and histology of *H. pylori* in at least four out of five specimens were negative. *H. pylori* was confirmed by positive RUT and histological detection in at least one of the five specimens. The type of gastritis was characterized as antral gastritis only or antrum-predominant gastritis when the mean score of neutrophil and mononuclear cell infiltrations in both antral biopsies was higher than the mean score of the three corpus samples. Corpus-restricted gastritis was considered when the mean score of neutrophil and mononuclear cell infiltration from all three areas of the corpus mucosa was greater than the mean score from both areas of the antrum. Corpus gastritis was only considered when neither neutrophil nor mononuclear cells were seen in either areas of the antrum. The biomarkers pepsinogen I, II, and gastrin 17 by ELISA (Biohit, Oslow, and Finland) were measured in the sera of those with corpus-restricted gastritis. Parietal cell antibody was measured in these sera by immunofluorescence.[16]

Statistical analysis was done by SPSS (independent *t*-test and Chi-square *t*-test). The difference was considered significant with a value $P<0.05$. The study was approved by Institutional Review Board of the "Digestive Diseases Research Center of Tehran University of Medical Sciences" in accordance with the Declaration of Helsinki. Informed consent was obtained for all participants according to the guidelines of the Institute.

Results

During a period of 4 years (2001 – 2004) a total of 989 FDR from 551 families with GC were recruited to participate in this study. Of these, 357 FDR were from one GC family and the remaining 632 from 194 families with more than one GC were enrolled. The number of GC patients who underwent surgery in Tehran hospitals during the inclusion period was unknown. However, during 1998 – 2001, 1991 pa-

Table 1. Types of gastritis, mean age and *H. pylori* infection rate among FDR of GC patients (*n*=808)

Gastritis types	*n*(%)	Mean age (years)±SD	*H. pylori* infection, *n*(%)
Normal mucosa	56 (6.3)	46.4±6.1	3 (5.4)
Isolated antral gastritis	60 (7.2)	46.8±6.7	27 (45)
Antrum predominant gastritis	513 (63.5)	47.4±6.7	457 (89.1)
Corpus predominant gastritis	162 (20)	48.7±6.9	135 (83.3)
Isolated corpus gastritis	17 (2)	51±6.2	4 (23.5)

FDR=first degree relatives; GC=gastric cancer

tients with GC were registered in Tehran.[17] Taking the same number of GC patients observed during the same time length for the inclusion period in Tehran, the rate of families from which we recruited the subjects would have been about 27.6% of the total families with GC.

All invited FDR consented for endoscopy and study protocol. Ninety-two subjects had significant gastric lesions (32 with gastric ulcer, 58 had duodenal ulcer or deformity due to ulcer disease, two had symptomatic ulcerated gastric cancer, 11 had severe erosive duodenal erosions, four had combined gastric and duodenal ulcers and one subject had an esophageal tumor). These patients were treated accordingly and no protocol biopsies were obtained. In 17 subjects, histological classification was not possible due to the lack of data from all areas. Biopsy specimens were evaluated in 864 subjects [419 males with a mean age of 48.5±7.1 and 445 females with a mean age of 47±6.4 years. (range: 39 to 67 years)]. Ten patients had low grade dysplasia, localized along the lesser curvature in the corpus and mostly associated with intestinal metaplasia (IM). High grade dysplasia was not detected in the areas where biopsy specimens were routinely obtained. The positivity rate of *H. pylori* infection was 76.6%, with a significant difference in the age groups that were under and over 50 years (79% vs. 71.1%, $P<0.05$) but was not significant difference between men and women (78.7% vs.74.6%).

The measure of agreement (Kappa value) between the two pathologists in the evaluation of five areas of gastric mucosa in 147 subjects was 0.49 for normal mucosa, 0.55 for antral predominant gastritis, 0.51 for corpus predominant gastritis , 0.37 for any atrophy in the corpus and 0.47 for any intestinal metaplasia in the corpus (over all $P<0.001$).

There were 36 subjects in whom the mean score of cell infiltration of three areas of the corpus was the same as the mean score from two areas of the antrum. Thus, these cases were classified as having a corpus-predominant gastritis. The type of gastritis could not be verified in 56 individuals due to lack of optimal specimens for evaluation of inflammatory cell infiltration in one or more areas. The type of gastritis and *H. pylori* infection rate are given in Table 1.

Normal mucosa in all areas was seen in 6.9% of subjects. Antrum-restricted gastritis was found in 7.4%, while 63.5% had antrum-predominant gastritis and 20% corpus-predominant gastritis. Corpus-restricted gastritis was found in 2%. The mean age of subjects with all types of gastritis was approximately the same within each type. Subjects with corpus-predominant gastritis and antrum-predominant gastritis had high *H. pylori* infection rates of more than 80%, while the *H. pylori* infection rate in corpus-restricted gastritis was low at 23.5%.

The prevalence of precancerous conditions, atrophy and intestinal metaplasia as well as their severity are given in Table 2.

Forty percent of subjects had atrophy of both the antrum and corpus, 9.4% only in the corpus, 4% had IM both in the antrum and corpus, and 5.1% in the corpus only. Therefore, half of the FDR subjects had precancerous lesions in upper part of stomach. Less than 6% of them had advanced precancerous conditions (4.1% severe atrophy in corpus and 1.3% severe IM in corpus). In table 3 we have shown the progression of precancerous conditions and their severity with advancing age.

Atrophy in antrum and corpus persists after age 44, while IM progress in antrum from 12.2% to 19% in the first and from 19 to 27.3% in the second decade and in corpus from 6.7% to 12.3% in the first and from 12.3% to 26.2% in the second age decade. In

Table 2. Precancerous conditions in FDR of patients with GC (*n*=808)

Precancerous conditions	*n* (%)
Atrophy in antrum	495 (61.2)
Moderate to severe	134 (16.5)
Atrophy in corpus	408 (50.4)
Moderate to severe	169 (20.9)
Atrophy in corpus only	76 (9.4)
IM in antrum	124 (15.3)
Moderate to severe	65 (8)
IM in corpus	76 (9.4)
Moderate to severe	38 (4.7)
IM in corpus only	41 (5.1)
Atrophy in antrum and corpus	323 (40)
Moderate to severe	59 (7.3)
IM in antrum and corpus	32 (4)
Moderate to severe	14 (1.7)

FDR=first degree relatives; GC=gastric cancer

Table 3. The percentage of precancerous conditions in FDR subjects by age

	Age (yr) and number of FDR subjects		
Age group	38–50	51–60	>60
Mean age	44	54	63.6
Number	668	152	53
Precancerous conditions in FDR subjects (%)			
Atrophy			
In antrum	57.7	59.7	55.6
Moderate to severe	14.7	19.6	11.4
In corpus	49.1	46.6	54.8
Moderate to severe	19.4	20.8	31
IM			
In antrum	12.2	19**	27.3*
Moderate to severe	6.6	8.4	20.5*
In corpus	6.7	12.3**	26.2#
Moderate to severe	3.2	6.1	14.3#*

FDR=first degree relatives; IM= intestinal metaplasia *Compared to 38 – 50 years. $P<0.01$; **Compared to 38 – 50 years. $P<0.05$; #compared to 51 – 60 years. $P<0.05$

Table 4. Precancerous conditions in FDR of patients according to numbers of GC in families and gender of the GC patients

Precancerous conditions	FDR of one GC *n*=830(%)	FDR of more than one GC *n*=45 (%)	FDR of a male with GC *n*=555 (%)	FDR of a female with GC *n*=285 (%)
Atrophy in antrum	471 (56.7)	24 (54.5)	303 (54.5)	171 (60)*
Atrophy in corpus	387 (46.6)	21 (46.7)	245 (44.1)	146 (51.2)*
IM in antrum	117 (14.1)	7 (15.5)	76 (13.6)	42 (14.7)
IM in corpus	69 (8.3)	7 (15.5)	49 (8.8)	21 (7.3)
Corpus predominant gastritis	154 (18.5)	8 (17.7)	97 (17.4)	60 (21)

* $P<0.05$; GC=gastric cancer; FDR=first degree relatives

Table 4 we have shown precancerous lesion of FDR subjects according to the number of gastric cancer in family.

The FDR subject with two GC members in their families had the same percentage and severity of precancerous conditions as those with only one affected member. FDR of female GC patients had more atrophy in the antrum and corpus than FDR of male GC patients ($P<0.05$).

Parietal cell antibody was positive in 3 out of 17 subjects with corpus-restricted gastritis (titer>1:10). The mean level of pepsinogen I, pepsinogen II and

gastrin 17 were 108±47.3 (µg/L), 11.7±10.8 µg/L and 7.6±15 pmol/L, respectively. The mean Values of ratio of pepsinogen I to pepsinogen II was 13±7.

Discussion

Once gastritis develops in the antrum, it may progress under certain environmental, socioeconomic and genetic conditions with advancing age, from the antrum upward along the lesser curvature to the corpus and may finally lead to atrophic gastritis.[18] Biopsy specimens taken during endoscopic from different areas of the gastric mucosa have revealed three topographic types of gastritis (antrum-predominant, corpus-predominant and autoimmune gastritis) aside from normal mucosa. The first two types of gastritis are induced by *H. pylori* infection and the latter one is associated with multiple autoimmune reactions and the occurrence of various antibodies in sera.[19]

In 1938, the German surgeon Konjetzny, morphologically examined all resected stomachs in GC patients and described atrophic gastritis with metaplastic changes (Becherzellen Metaplasie as goblet cells) in all areas of the stomachs, while gastritis of the peptic ulcer type was almost entirely restricted to the antral area.[20] These metaplastic changes, known as IM, were confirmed with time by numerous other authors[21–24], particularly when seen to occur in the upper part of stomach. Gastritis with atrophy and IM, occurring in each area or in upper part of the stomach, was therefore considered to be a precancerous condition.[25]

Mononuclear cell inflammation localized more in the corpus rather than the antrum (corpus-predominant gastritis) with IM found in the antrum and corpus of stomach of patients with early GC.[9] On follow-up examinations of patients with *H. pylori* infection, GC was observed mainly in those with corpus-predominant gastritis.[10] This type of gastritis and its advanced form is frequent in FDR of GC patients compared with controls.[11–15] The severity of atrophy and IM with advanced stage gastritis in FDR of GC patients in different studies is illustrated in Table 5. In these studies, FDR had more frequent atrophy and IM in the corpus or in the whole stomach when compared with controls. In two studies, the gastric acid output of subjects was measured and found to be reduced in FDR when compared with controls as a sign of earlier progression of advanced gastritis in this group.[11,13]

In our population, due to the high rate of *H. pylori* infection, only a small number of subjects had normal mucosa. Antral-restricted gastritis was seen in only 7.4% of the subjects. The majority of subjects had antrum-predominant gastritis, mostly *H. pylori* infected. Corpus-predominant gastritis was found in 20% of the subjects. Among this group only a small number had atrophy and IM as precancerous conditions for developing GC. As with our population, corpus-predominant gastritis was found in 22% of Scandinavian FDR of GC patients, which was more than in controls (10%) of the same age (about 47 years).[11]

The prevalence of corpus-restricted gastritis is 2% and only a few had parietal cell antibodies. The normal mean of pepsinogen I, ratio of pepsinogen I to II and gastrin-17 without *H. pylori* infection is indicative of the presence of an early type of non-infectious autoimmune gastritis, which is quite rare in our population in comparison with the higher rate in European studies. One study conducted in Germany had 7% fundic gastritis among 513 dyspeptic subjects.[26] In a study among the Estonian rural population, isolated fundic gastritis was found in 10% of patients[27] and in a Swedish population with a mean age of 60 years isolated fundic gastritis was seen in 5.6% of cases.[28]

The severity of morphological changes and percentage of corpus-predominant gastritis in FDR of GC patients was unrelated to family members with one or more GC patients. However, the FDR of female GC patients had more atrophy in the antrum and corpus than FDR of male GC patients, which was similar to a study from Scandinavia.[11] It was remarkable we had not find any high grade dysplasia in the biopsies were obtained.

While no progression of atrophy was documented after the fourth decade of life with increasing age, IM increased in the antrum as well as in the corpus. In the corpus the increase was less than 1% per year in the first decade and increased to greater than 1% per year during the second decade (Table 5).

A shortcoming of this study is the lack of a control group with no familial history of GC. Inclusion of healthy subjects for endoscopy purposes is ethically

Table 5. The percentage of precancerous conditions (atrophy or intestinal metaplasia) in FDR of GC patients and controls

Authors	FDR (*n*) Mean age (yr)	Controls (*n*) Mean age (yr)	Atrophy (%) Cases (controls)	Intestinal metaplasia (%) Cases (controls)
Ihamaeki (1979)	301 (47)	358 (46)	9 (3)	12 (7)
Chang (2002)	300 (46)	426 (45.8)	23 (11.4)	15 (2)
El-Omar (2002)	100 (43.7)	60 (44)	25 (3.3) in body	6 (1.6) in body
Sepulveda (2002)	111 (39.1)	77 (49.6)	—	—
Meining (1998)	237 (52.6)	237 (53.6)	—	7.7 (3) in body
Our study	881 (47.7)	—	49 in body	9.4 in body

FDR=first degree relatives; GC=gastric cancer

not justifiable and practically not possible in such a large sample size. In the three studies mentioned in Table 5, dyspeptic subjects or those at risk for organic diseases without a history of GC in their families were selected as controls.[12,14,15] In one study, the number of subjects was too small to determine the localization type of gastritis.[13] In a study from Finland that had a large sample size of FDR and healthy controls, the case group whose mean age was similar to our population had the same rate of corpus-predominant gastritis as our study (22% in cases and 10% in controls).[11] In all these studies, the possibility of decline in prevalence of gastritis and IM during the last decades of life must be taken into consideration.[29]

In conclusion, endoscopic screening in FDR of GC patients with a mean age of 48 years and a high *H. pylori* infection rate in endemic areas for GC is not justified. Only a fifth of this population have predominant corpus gastritis, mostly *H. pylori* infected, who are at risk for the development of GC and available for its eradication. Screening subjects with serum biomarkers in this high risk group may spare the number of endoscopies in those with no morphological changes.[30] The autoimmune type of gastritis is a rare disease in this geographic area.

Acknowledgment

I am sincerely indebted to Dr. M. Stolte (Professor, Institute of Pathology, Bayreuth, Germany) for his advice and evaluation of some of the histological findings and to Dr. F. Djavadi (Liver Unit, University of Southern California, Los Angeles, CA) for correction of this manuscript.

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