Features of chronic inflammation at the gastric cardia and the relationship with *Helicobacter pylori* infection and oesophagitis

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Abstract

Background : **The etiopathogenesis of chronic inflammation at the gastric cardia is still debated. It is suggested that carditis may be a finding of gastro-oesophageal reflux disease (GORD) or it may occur as a result of the gastritis caused by *Helicobacter pylori* (*H. pylori*) infection.**

Aim : **To examine morphological features of carditis, as well as the associations of carditis with *Helicobacter pylori* gastritis and oesophagitis as a marker of gastro-oesophageal reflux disease.**

Patients and methods : **Endoscopic biopsy specimens obtained systematically from oesophagus, cardia, corpus and antrum of 135 dyspeptic patients were retrospectively evaluated. In biopsies, we have searched for any correlations between clinical, endoscopic, and histological features.**

Results : **Carditis was detected in 123 (91.1%) of the cases. The mean age of the carditis group was 47.9 years and the male-to-female ratio was 1.08:1. The relation of carditis with age and sex was not significant ($p = 0.19$ and $p = 0.24$, respectively). All cases of the carditis group had concomitant chronic gastritis. In these cases, chronic inflammation, degree of neutrophil-mediated activity and *H. pylori* colonisation were significantly correlated in cardia, corpus and antrum ($p < 0.001$). Intestinal metaplasia was observed in 14 cases (11.3%) and, was associated with *H. pylori* colonisation ($p < 0.001$). Microscopic oesophagitis detected in 37.7% cases also showed correlation with reflux symptoms and endoscopic oesophagitis but not carditis. When all cases with carditis were evaluated for *H. pylori* infection and oesophagitis, which are presumed risk factors for carditis, *H. pylori* infection appeared to be an independent risk factor for carditis ($p = 0.012$), while oesophagitis did not.**

Conclusions : **This study suggests that carditis is commonly found in patients presenting with dyspepsia and the histological features of carditis were similar to those seen in *H. pylori* gastritis in antrum and corpus. In addition, our data have also shown that carditis was significantly associated with *H. pylori* infection but not with symptoms or signs of GORD.** (Acta gastroenterol. belg., **2003**, 66, **144-149**).

Key words : carditis, *Helicobacter pylori*, oesophagitis, intestinal metaplasia.

Introduction

The pathogenesis and clinical significance of chronic inflammation at the gastro-oesophageal junction is controversial (1). The gastric cardia can be defined as the proximal region of the stomach 1-2 cm below the gastro-oesophageal junction. It is lined by a mucus secreting columnar epithelium. This epithelium also covers the coiled and tubular glands dispersed in lamina propria. Parietal cells are usually absent in this region, but when they are present, they are observed either as individual cells or as small groups. Inflammatory cells in lamina propria are usually not found (2).

Chronic inflammatory infiltration observed on biopsy specimens taken from cardia is called carditis (3-5). In previous studies, some investigators have suggested that carditis is an inflammatory change that occurs as a consequence of gastro-oesophageal reflux disease (GORD), whereas others assumed that carditis represents an extension of *Helicobacter pylori* (*H. pylori*) related pangastritis (4-7). These studies are conflicting and it is unclear whether *H. pylori* infection or GORD is the cause of the inflammatory infiltration in cardia.

The aims of the present study were to determine the incidence of carditis in patients complaining of dyspepsia and to describe salient morphologic features of carditis and to search for any possible association with *H. pylori* gastritis or with oesophagitis caused by GORD.

Material & methods

One-hundred and thirty-five patients presenting with dyspepsia, which were admitted to Celal Bayar University Hospital during a two-year period were studied. Patients included in the study had one of the following presenting symptoms : epigastric pain, heartburn, regurgitation, belching, bloating, discomfort in the upper abdomen, nausea and vomiting. The presence of heartburn and/or regurgitation at least twice weekly for at least 6 months was considered as GORD (8). Patients who had previously received *H. pylori* eradication, those who had used antibiotics, bismuth or proton pump inhibitors (PPI) within 30 days before endoscopy, those who had undergone gastric surgery and those with malignancy were not studied. Patients with Barrett's oesophagus also were not studied due to the fact that presence of metaplastic epithelium in the gastro-oesophageal junction might lead to a confusion about the precise location of the cardia.

Each patient had undergone an endoscopic procedure using the Olympus GIF E or GIF1-T30 video endoscope. Biopsy specimens were systematically taken from oesophagus, cardia, corpus and antrum. Biopsies were obtained with separate forceps to avoid possible contamination. The pinch at the end of the tubular oesophagus

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coinciding with the proximal margins of the gastric folds was taken as a landmark of the normal gastro-oesophageal junction. Oesophageal biopsy specimens were obtained 2 cm above the squamocolumnar junction which was defined as the mucosal demarcation located at the level of the gastro-oesophageal junction (9). The presence of oesophagitis was identified and graded according to Savary-Miller classification (10). Gastric cardia biopsy specimens were taken with the endoscope in a retroflexed position from areas within 1 to 2 cm below the squamocolumnar junction. Confirmation of the precise location of the cardia biopsy was performed by direct endoscopic visualization of the biopsy site with respect to the anatomic gastro-oesophageal junction. Hiatal hernia was defined by a number of endoscopic features such as nontubular pouchlike appearance, the presence of gastric rugae and a distance greater than 2 cm between the squamocolumnar junction and the diaphragmatic hiatus. In patients with hiatal hernia, oesophagus and cardia biopsies were obtained according to these features. In all cases, the cardia was verified by histological presence of mucosal glands containing mucous cells only. Corpus biopsy specimens were taken from mid-region of the greater curvature and antral biopsies about 2 cm proximal from the pylorus.

For the enzymatic detection of *H. pylori* in biopsy specimens, rapid urease test was performed. On the other hand, for histologic examination biopsy specimens were fixed in Hollande's fixative and sections were stained with hematoxylin and eosin. The presence of *H. pylori* was revealed with toluidine blue and intestinal metaplasic changes were demonstrated by periodic acid–Schiff/Alcian blue (pH = 2,5) stain. *H. pylori* infection was only diagnosed by the presence of the organism in biopsy specimens using histology as the "gold standard". Gastric cardia, corpus and antrum biopsies were evaluated according to the updated Sydney system (11). Oesophageal biopsies were evaluated for chronic oesophagitis, defined as the presence of intraepithelial eosinophiles in conjunction with basal cell hyperplasia and papillae extending upwards two-thirds or more of the thickness of the squamous epithelium (3).

Statistically, Mann-Whitney U test was used in revealing the relation of the incidence of carditis with age. Relation between sex and carditis was searched by Fischer's exact test. Comparisons among histologic, clinical and endoscopic parameters of carditis and oesophagitis were made by kappa and Kendall's tau-b tests. The roles of *H. pylori* and oesophagitis on the pathogenesis of carditis were evaluated by backward-Wald logistic regression model. The presence or absence of the independent variables included in the logistic regression model was defined as dummy variables.

Results

Demographic, clinical and endoscopic features of the one-hundred and thirty-five patients studied are given in Table I. Chronic inflammatory infiltration at the cardia was observed in 123 cases (91.1%). The mucosa of the cardia was found to be normal in 12 cases only. The male to female ratio was 1.08 :1 in the presence of carditis and 1:2 without carditis. Mean age was 47.9 ± 13.7 (range, 21-90 years) and 43.4 ± 9.6 (range, 30-64 years) in patients with inflammation and those without, respectively. These differences in age and sex ratio did not show statistical significance ($p = 0.19$ and $p = 0.24$, respectively).

Table I. — **Demographic, clinical and endoscopic features of patients**

Age (y) (mean ± SD)	47.54 ± 13.42
Sex ratio (M/F)	68/67
Reflux symptoms	60
Endoscopic findings	
Hiatal hernia	14
Endoscopic oesophagitis	49
Antral gastritis	112
Gastric ulcer	12
Duodenal ulcer	35

In all 123 cases with carditis, findings of chronic gastritis involving corpus and antrum were demonstrated except in 3 cases in which antral biopsies were not available. Gradings of the inflammatory infiltration, neutrophilic activity, *H. pylori* colonisation and intestinal metaplasia in gastric cardia, corpus and antrum biopsy specimens are presented in Table II. With respect to intensity of chronic inflammatory cell infiltration, all regions from a given case (gastric cardia, corpus and antrum) exhibited a significant paralellism ($p < 0.001$) and similar concordance was also found in terms of neutrophilic activity ($p < 0.001$). *H. pylori* colonisation was found in 72 (58.5%) of all 123 cases having carditis, with a high consistency between cardia, corpus and antrum ($p < 0.001$). In addition, for a given patient neutrophilic activity and *H. pylori* colonisation correlated exceptionally well ($p < 0.001$) in all regions.

On the other hand, rapid urease test performed for the detection of *H. pylori* status showed a sensitivity rate of 90.7 percent, with relatively low specificity rate of 74.2 percent (positive predictive value, negative predictive value and accuracy rates were 76.6%, 85.2% and 80%, respectively).

Intestinal metaplasia at the cardia was observed in 14 cases (11.3%) (Fig. 1). In these cases antrum and corpus regions also showed intestinal metaplasic areas and *H. pylori* colonisation was found in eight cases, with significant correlation with intestinal metaplasia ($p < 0.001$). Among all antral biopsies intestinal metaplasia was seen in 17 cases (14.1%). Atrophic changes, which were never seen in gastric cardia, were found in antral mucosa of only 16 cases.

Histologically, features of chronic oesophagitis were found in 51 (37.7%) cases of which 43 also had inflammation at the cardia (Fig. 2). The presence of microscopic oesophagitis was significantly associated with the reflux symptoms and endoscopic oesophagitis.

Table II. — **In carditis group, histological features seen in gastric cardia, corpus and antral biopsies**

Histological Findings	Cardia		Antrum		Corpus	
	%	n = 123	%	n = 120	%	n = 123
Chronic inflammation						
Mild	35.0	(43)	14.2	(17)	30.1	(37)
Moderate	42.3	(52)	53.3	(64)	40.6	(50)
Severe	22.8	(28)	32.5	(39)	29.3	(36)
Neutrophil-mediated activity						
None	36.6	(45)	34.2	(41)	45.5	(56)
Mild	30.1	(37)	30.8	(37)	26.9	(33)
Moderate	24.4	(30)	29.2	(35)	19.5	(24)
Severe	8.9	(11)	5.8	(7)	8.1	(10)
H. pylori colonisation						
None	41.5	(51)	41.7	(50)	43.9	(54)
Mild	27.6	(34)	26.7	(32)	27.6	(34)
Moderate	17.9	(22)	18.3	(22)	17.1	(21)
Severe	13.0	(16)	13.3	(16)	11.4	(14)
Intestinal metaplasia						
None	88.6	(109)	85.8	(103)	87	(107)
Mild	5.7	(7)	10.9	(13)	9	(11)
Moderate	2.4	(3)	3.3	(4)	2.4	(3)
Severe	3.3	(4)	–		1.6	(2)

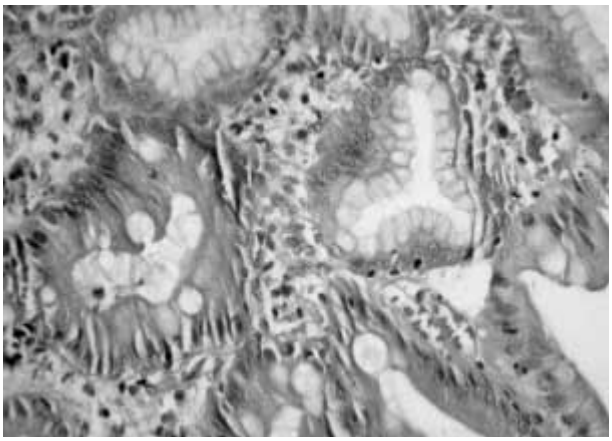

Fig. 1. — Intestinal metaplasia of the cardia in a background of carditis. The surrounding lamina propria is expanded by mononuclear inflammatory cells, indicative of carditis (H&E, ×200).

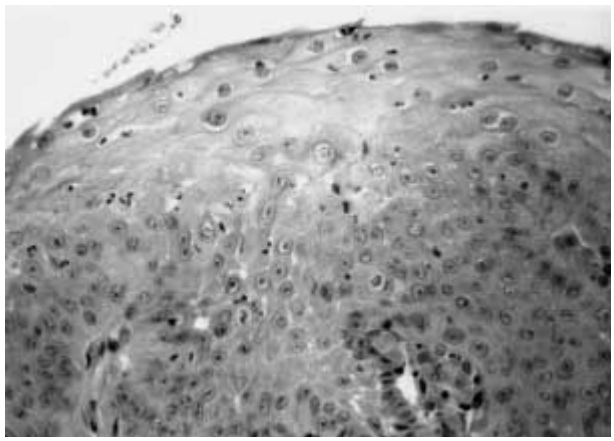

Fig. 2. — Intraepithelial neutrophils and predominantly intraepithelial eosinophils are present between the epithelial cells, as an indicative of reflux oesophagitis, in oesophageal mucosa (H&E, ×400).

Clinicopathologic characteristics of cases with oesophagitis in relation to associated carditis are seen in Table III.

Clinical and histological features of cases with or without findings of carditis are presented in Table IV. It is noteworthy that *H. pylori* colonisation at the cardia was detected only in one case in which gastric cardia showed no inflammatory infiltration. No association was found between the presence of carditis and other parameters such as reflux symptoms, hiatal hernia and endoscopic or microscopic oesophagitis.

When all cases with carditis (n = 123) were evaluated for *H. pylori* colonisation and oesophagitis, which are presumed risk factors for carditis, 48 cases had *H. pylori* positivity only and 19 cases showed oesophagitis only, whereas 24 cases had both features (Fig. 3). By applying logistic regression model, *H. pylori* colonisation appeared to be an independent risk factor for carditis (p = 0.012), while oesophagitis did not (Table V).

Discussion

Since the initial description of chronic inflammatory infiltration of the mucosa at the cardia, known as "carditis", it has been the subject of many investigations. Moreover, rapidly rising incidence of cancer at this location has also increased the current interest. The conflicting results have been reported about the incidence of

Table III. — **Clinicopathologic characteristics of cases with oesophagitis in relation to associated carditis**

	Oesophagitis with associated carditis n = 43	Oesophagitis without associated carditis n = 8	p
Age (average)	46.42	45.14	NS*
Male/Female	25/17	3/5	NS
Reflux symptoms	43/43	8/8	NA**
Endoscopic oesophagitis	42/43	7/8	NS
H. pylori colonisation	24/43	0/8	0.003

*NS = Not significant.
**NA = Nonapplicable.

Table IV. — **Clinicopathologic characteristics of cases with their relative significance in carditis and non-carditis groups**

	Carditis Group n = 123	Noncarditis Group n = 12	p
Age (average)	47.91	43.45	NS*
Male/Female	64/59	4/8	NS
H. pylori colonisation	72/123	1/12	0.012
Oesophagitis	43/123	8/12	0.031
Antral gastritis	123/123	12/12	–
Intestinal metaplasia	14/123	0/12	NS

NS = Not significant.

Table V. — Backward-Wald logistic regression model analysis as carditis is dependent variable, while *H. pylori* and oesophagitis are independent variables

Independent variable	B	SE	Wald	p	Exp (B)
Helicobacter pylori	2.67	1.07	6.27	0.012	14.4
Oesophagitis	-1.19	0.67	3.17	0.075	0.31
Constant	2.16	0.54	16.19	0.000	

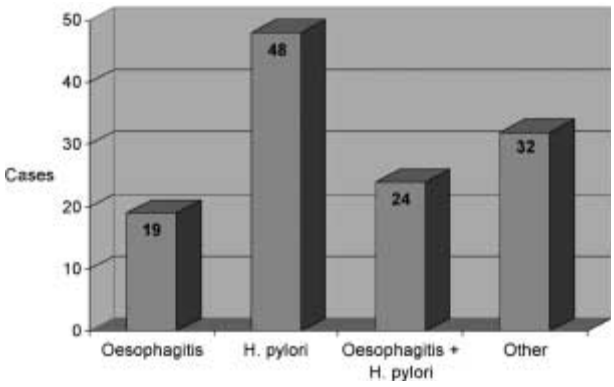

Fig. 3. — Distribution of cases based on the risk factors in carditis group.

carditis and its etiopathogenesis. Some authors have found association with GORD, whereas others have suggested a relationship with *H. pylori*, but recent studies have focused more on possible role of *H. pylori* infection (6,7,12-18).

Although high incidence of carditis has been reported, rates varied greatly (from 41% to 92%) among different studies (3-7,12-17). In a recent study, Der *et al.* reported a series of 141 cases that they could not find any case without inflammation at the cardia and they further suggested that cardiac mucosa always showed inflammation histologically (19). In our study, however, mucosa of the cardia was found to be normal in 12 cases (8.9%), and majority of cases (91.1%) showed findings of carditis. Marked variability of these rates can partly be attributed to the fact that some authors have been dealing with the cases of isolated carditis only, categorizing the cases with accompanying gastritis in a different group. In addition, incidence of *H. pylori* infection differs greatly among populations.

The present study included patients irrespective of the presence antral gastritis to evaluate importance of *H. pylori* infection and/or GORD symptoms in the pathogenesis of carditis. In one of the initial reports on the subject, Oberg *et al.* suggested a positive and strong association between the presence of carditis and GORD, as determined by symptoms and 24-hour pH values (5). In this and some other studies, the possibility that *H. pylori* infection might cause inflammation at the cardia has not been investigated (3,4). In the study by Bowrey *et al.*, it was assumed that GORD induced the inflammation by similar mechanisms found in *H. pylori* infection and they concluded that inflammatory reactions caused by these two etiologic factors could not be

discriminated on morphological grounds (14). In other studies, however, *H. pylori* colonisation was reported to accompany carditis with varying rates ranging from 77 to 95 percent (6,7,12,15-17). These studies emphasized that *H. pylori* was the most significant risk factor in the development of carditis and GORD did not seem to play an important role in developing carditis. Similarly, our data have shown that the incidence of *H. pylori* infection at the cardia is high (58.5%) in patients with carditis. In our study, a number of features such as intensity of inflammation, neutrophilic activity and *H. pylori* colonisation in cardia, corpus and antrum were in concordance with each other. In addition, *H. pylori* infection has also a striking correlation with neutrophilic activity in gastric cardia. It is therefore reasonable to think that the inflammation in gastric cardia is associated with *H. pylori* infection. Moreover, Sharma *et al.* reported that eradication of *H. pylori* led to improvement in the inflammation of the gastric cardia (18).

Morphologically, reflux oesophagitis, especially the presence of intraepithelial eosinophils, is almost always associated with acid exposure of the lower oesophageal mucosa (20). Therefore, histologic features of reflux oesophagitis might be considered as an indicator of GORD, although it is not diagnostic. The abnormal acid exposure measured by a 24-hour pH test seems to be more reliable for the diagnosis of GORD, but it has relatively low sensitivity (19). In the current study, we have assumed that histological reflux oesophagitis could be an appropriate criterion for GORD. In our series, microscopic oesophagitis was found in 37.7% of cases of which 15.7% had no inflammatory infiltration in gastric cardia. As expected, microscopic oesophagitis was associated with reflux symptoms and endoscopic oesophagitis, but not with carditis. In 19 cases which had microscopic oesophagitis along with carditis *H. pylori* infection could not be detected. We have therefore speculated that GORD might be involved in the development of carditis in these cases. Our data have shown that carditis is significantly correlated with *H. pylori* colonisation while it was not correlated with reflux symptoms, endoscopic and microscopic oesophagitis. The other interesting finding of our study is that, in one-fourth of the cases with carditis we have also observed inflammation in antral and corpus mucosa (pangastritis) without any findings of oesophagitis or *H. pylori* colonisation even though these two features are considered to be risk factors. The significance of carditis in this group remains unclear. Based on our observations, we think that carditis in these cases may due to *H. pylori*, but that we failed to identify the organism by both histology and rapid urease test. We speculate that it might be necessary to enroll patients with history of antibiotherapy or PPI therapy longer than 30 days after cessation. Furthermore, other additional tests for the diagnosis of *H. pylori* would have been done.

Currently, there are increasing number of reports pointing at the role of intestinal metaplasia in carcinogenesis at the gastric cardia (21-25). It has been reported that frequency of intestinal metaplastic changes found at the cardia in routine endoscopy practice varies between 10 to 20 percent (7,13,15,26,27,28). In two studies done by Spechler *et al.* and Johnston *et al.*, the rate of intestinal metaplasia was found to be 18 and 9 percent respectively, and it is noteworthy that those investigators did not find any possible relation between erosive oesophagitis and intestinal metaplasia (29,30). In our study, intestinal metaplasia has been found in 11.3% of cases all of which also showed findings of carditis. Some authors have demonstrated a link between *H. pylori* colonisation and intestinal metaplastic changes (7,15,29). Also in our study, we have noted significant relationship between these two features, suggesting that chronic inflammation and subsequent reactive changes caused by *H. pylori* might lead to the development of intestinal metaplasia. In this study, possible interrelationships between intestinal metaplasia at the gastric cardia, Barrett's oesophagus and carcinoma of the gastric cardia have not been studied. We think that studies with long term follow-up are needed to assess the significance of intestinal metaplasia and *H. pylori* infection in the development of cancer at the cardia.

In conclusion, inflammatory cell infiltration is a feature commonly seen in biopsies taken from gastric cardia, and chronic gastritis in antrum and corpus frequently accompanies it, which is then called pangastritis. In these cases intensity of chronic inflammation and neutrophilic activity in the gastric cardia shows marked concordance with those seen in antrum and corpus. In addition, our data suggest that neutrophilic activity and intestinal metaplasia found in the gastric cardia are highly related to *H. pylori* colonisation. Our study also showed that microscopic oesophagitis is significantly correlated with the reflux symptoms and endoscopic oesophagitis. However, carditis is not correlated with reflux symptoms, endoscopic or microscopic oesophagitis. In the view of these findings, we suggest that *H. pylori* infection seems to be an independent risk factor in the etiopathogenesis of carditis.

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