Virchows Arch (1997) 431:11–15

ORIGINAL ARTICLE

**Alexander Meining · Manfred Stolte · Rudolf Hatz
Norbert Lehn · Stephan Miehlke · Andrea Morgner
Ekkehard Bayerdörffer**

Differing degree and distribution of gastritis in *Helicobacter pylori*-associated diseases

Received: 18 October 1996 / Accepted: 24 February 1997

Abstract Infection with *Helicobacter pylori* (*H. pylori*) causes gastritis, and may be associated with gastric and duodenal ulcers and also with such malignant diseases as MALT lymphoma and gastric carcinoma. In order to determine whether there are differences in the degree and distribution of gastritis, each patient with *H. pylori* gastritis only (n = 50) was matched for sex and age with four patients, one each with *H. pylori*-associated duodenal ulcer, gastric ulcer, gastric carcinoma or MALT lymphoma. From each patient, two biopsies were taken from the antrum and two from the corpus for histopathological examination of *H. pylori* gastritis. The median summed gastritis score decreases in the following order: antrum: gastric ulcer > duodenal ulcer > gastritis alone > carcinoma > MALT lymphoma, and corpus: gastric ulcer > carcinoma > MALT lymphoma > gastritis alone and duodenal ulcer. We conclude that the degree and distribution of *H. pylori* gastritis differs significantly among *H. pylori*-associated diseases. These differences may explain some of the underlying pathomechanisms associated with *H. pylori* infection.

A. Meining
Medical Department II, Klinikum Grosshadern,
University of Munich, Munich, Germany

M. Stolte (✉)
Institute of Pathology, Klinikum Bayreuth,
Preuschwitzerstrasse 101, D-95445 Bayreuth, Germany
Tel.: (49) 921-400 1790, Fax: (49) 921-400 1799

R. Hatz
Surgical Department, Klinikum Grosshadern,
University of Munich, Munich, Germany

N. Lehn
Department of Microbiology, Klinikum Rechts der Isar,
Technical University of Munich, Munich, Germany

S. Miehlke
Baylor College of Medicine, VA Medical Center, Houston Texas, USA

A. Morgner · E. Bayerdörffer
Department of Gastroenterology,
Hepatology & Infectious Diseases, University of Magdeburg, Germany

Key words Gastritis · *Helicobacter pylori* · Peptic ulcer · Gastric cancer · MALT lymphoma

Introduction

Following the rediscovery of *Helicobacter pylori* (*H. pylori*) by Warren and Marshall [29], it soon became evident that this bacterium is the leading cause of gastritis throughout the world. Numerous studies have shown that *H. pylori* is a causal factor in peptic ulcer disease, since when *H. pylori* infection is cured this cures both duodenal [10, 13, 19] and gastric ulcer disease [3, 13]. Epidemiological studies have shown that persons infected with *H. pylori* carry an increased risk of developing gastric carcinoma [11, 23], whereas other studies, which have shown regression of low-grade gastric MALT lymphoma following eradication of *H. pylori* [2, 30], have suggested that *H. pylori* infection also has a causal role in the development of gastric lymphomas.

It has been postulated that differences in the characteristics of *H. pylori* strains, as well as different environmental and genetic factors in the infected hosts are involved in the variable outcome of the infection [4, 5, 18]. However, there appear to be no studies investigating the association between the degree and distribution of *H. pylori* gastritis and the development of these five different diseases associated with *H. pylori* infection in populations matched by age and gender.

To clarify this point, we investigated the extent to which the direct consequence of *H. pylori* infection (*H. pylori* gastritis) differs between patients with gastritis only and those with duodenal ulcer, gastric ulcer, gastric carcinoma, or MALT lymphoma.

Patients and methods

To keep sex- and age-related influences to a minimum, each of the 50 patients (25 males, 25 females, mean age: 60.14 years, 95% CI: 56.27–64.01) with *H. pylori* gastritis only was matched with 4 other *H. pylori*-infected patients, 1 each with duodenal ulcer, gastric

ulcer proximal from the pylorus, gastric carcinoma or MALT lymphoma for sex and age (± 2 years).

Between October 1993 and April 1995, patients were recruited for the study from those undergoing routine endoscopy at centres in Munich and Berlin, or in the offices of several gastroenterologists in private practice (see "Acknowledgements"). From each patient, two biopsy specimens from the antrum (2 cm away from the pyloric channel) and two from the corpus (middle third, greater curvature) were obtained. The biopsy specimens of MALT lymphoma and carcinoma patients had to be taken at least 2 cm distant from the tumour, and biopsies infiltrated with malignant cells were not evaluated in the study. We excluded from evaluation all those patients who had been taking any medication, such as acid-suppressing drugs, antibiotics, and bismuth that might possibly have influenced the extent of gastritis and *H. pylori* colonization at the time of examination.

In the gastric carcinoma group, 21 patients had intestinal, 27 had diffuse and 2 patients had an undifferentiated type of carcinoma according to the classification of Lauren [14]. In the MALT lymphoma group, 1 patient had a high-grade lymphoma while 49 patients had low-grade lymphomas. All tumours and gastric ulcers were located in the distal two-thirds of the stomach.

All sections were stained with H&E to grade gastritis, and with Warthin-Starry stain to detect and grade colonization with *H. pylori*. Grading of the variables in gastritis was done using the Sydney system [24], with slight modifications characterized by use of a scoring system ranging from 0=none to 4=severe, and including the degree of replacement of foveolae by regenerative epithelium as an additional variable [28]. All histological evaluations were done by one of the authors (M.S.). Studies of the pathologist intra-observer variation in the grading of the various observations have previously shown a high degree of reproducibility (unpublished findings) with kappa coefficients of 0.86 (*H. pylori* colonization), 0.78 (grade of gastritis), 0.82 (activity of gastritis), 0.63 (replacement of foveolae by regenerative epithelium), 0.74 (intestinal metaplasia), 0.72 (lymphoid follicles), and 0.66 (focal atrophy).

For every patient a gastritis score was calculated for the antrum and corpus comprising the summed values of *H. pylori* colonization, grade of gastritis, activity of gastritis, and replacement of foveolar epithelium by regenerative epithelium. Intestinal metaplasia, lymphoid follicles and focal atrophy were noted as present or absent.

Statistical calculations were done using the Mann-Whitney-test or χ^2-test for comparison of the indicators of gastritis investigated.

Results

There were no significant differences in the frequency of the variables observed in gastritis ($P > 0.05$) in terms of the site of gastric ulcers, carcinomas, MALT lymphomas (lower third/middle third of the stomach) or the type of carcinomas (intestinal/diffuse/undifferentiated).

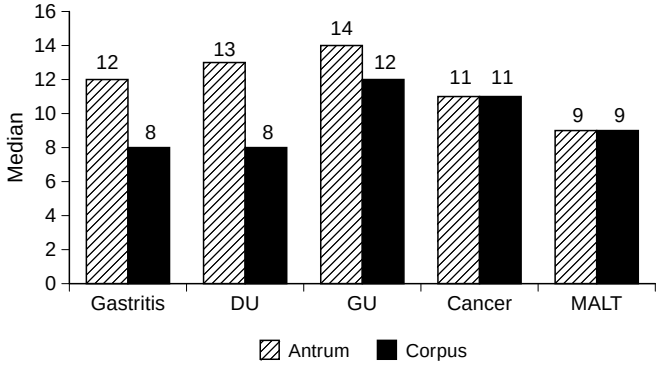

Fig. 1 Medians of the summed gastritis scores in antrum and corpus, formed by adding together the respective values of grade and activity of gastritis, replacement of foveolae by regenerative epithelium, and density of *H. pylori* colonization

Expressed as a summed gastritis score, gastritis associated with *H. pylori* infection is ranked in the following descending order of severity: gastric ulcer>duodenal ulcer>gastritis alone>gastric carcinoma>MALT lymphoma in the antrum, and gastric ulcer>gastric carcinoma>MALT lymphoma>gastritis alone and duodenal ulcer in the corpus (Fig. 1).

In detail, the differences in single variables between patients with *H. pylori* gastritis only and patients with the various *H. pylori*-associated diseases are shown in Tables 1 and 2.

In the patients with gastric ulcers, the grade and activity of gastritis, as well as the replacement of foveolae by a regenerative type of epithelium, were significantly more frequently expressed than in the patients with *H. pylori* gastritis only. This was found both in the antrum and in the corpus. In the corpus, as in the gastric ulcer group, patients with gastric carcinomas had an increased expression of gastritis markers such as grade, activity and replacement by regenerative epithelium (Table 2). In parallel, lymphoid follicles and intestinal and focal atro-

Table 1 Differences in the antrum in the density of *H. pylori* colonization, grade and activity of gastritis, replacement of foveolar epithelium by regenerative epithelium, intestinal metaplasia, lymphoid follicles and focal atrophy in relation to the matched groups. Figures for HP (*H. pylori* colonization), grade, activity, and replacement by regenerative epithelium are medians/means±SD. In the case of intestinal metaplasia, lymphoid follicles and focal atrophy the percentages in the respective groups are given

	Gastritis (*n*=50)	Duodenal ulcer (*n*=50)	Gastric ulcer (*n*=50)	Gastric carcinoma (*n*=50)	MALT lymphoma (*n*=50)
HP	4/3.19±1.45	4/3.10±1.38	4/3.55±0.95	3/2.40±1.76*	3/2.35±1.56
Grade	3/3.09±0.81	3/3.31±0.63	4/3.59±0.54***	3/3.21±0.77	3/2.85±0.89
Activity	3/2.37±1.45	3/2.89±0.93	3/3.25±0.72***	3/2.53±1.32	3/2.35±1.33
Regenerative epithelium	2/2.14±1.28	3/2.62±0.89*	3/2.98±0.82***	3/2.21±1.26	1/1.46±1.42
Intestinal metaplasia[#]	28%	32%	50%*	58%**	16%
Lymphoid follicles[#]	70%	74%	60%	62%	50%
Focal atrophy[#]	6%	2%	8%	42%***	6%

* $P<0.05$; ** $P<0.01$; *** $P<0.001$ (Mann-Whitney test/[#] Chi-square test) compared with patients with *H. pylori* gastritis only

Table 2 Differences in the corpus in the density of *H. pylori* colonization, grade and activity of gastritis, replacement of foveolar epithelium by regenerative epithelium, intestinal metaplasia, lymphoid follicles and focal atrophy in relation to the matched groups. Figures for HP (*H. pylori* colonization), grade, activity, and replacement by regenerative epithelium are medians/means±SD. In the case of intestinal metaplasia, lymphoid follicles and focal atrophy the percentage in the respective group is given

	Gastritis (*n*=50)	Duodenal ulcer (*n*=50)	Gastric ulcer (*n*=50)	Gastric carcinoma (*n*=50)	MALT lymphoma (*n*=50)
HP	4/3.37±0.93	3/2.89±1.13*	4/3.64±0.78	3/3.12±0.93	3/2.54±1.41**
Grade	2/2.23±0.78	2/2.07±0.75	3/2.82±0.58***	3/2.91±0.87***	3/2.85±0.78***
Activity	2/1.74±1.31	1/1.36±0.91	3/2.55±0.87**	3/2.77±1.19***	3/2.33±1.32*
Regenerative epithelium	1/1.30±1.17	1/1.34±0.81	2/2.20±0.88***	3/2.40±1.29***	1/1.31±1.34
Intestinal metaplasia[#]	4%	0%	0%	8%	2%
Lymphoid follicles[#]	26%	34%	26%	74%***	32%
Focal atrophy[#]	0%	0%	0%	18%***	4%

* $P<0.05$; ** $P<0.01$; *** $P<0.001$ (Mann-Whitney test/[#] Chi-square test) compared with patients with *H. pylori* gastritis only

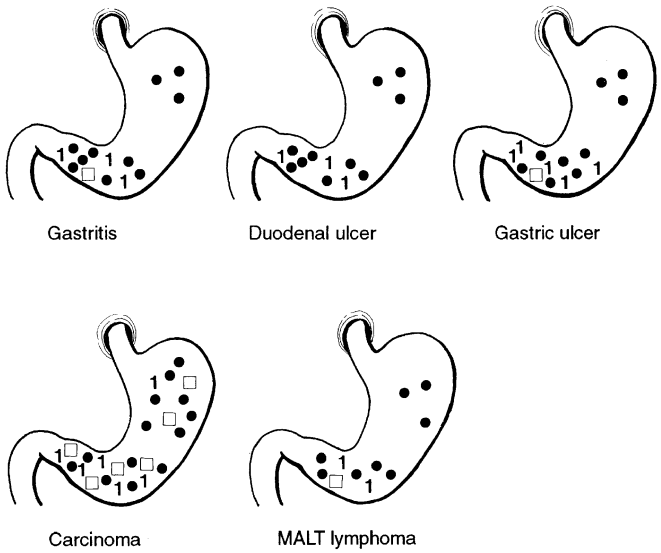

Fig. 2 Frequency of lymphoid follicles, intestinal metaplasia and focal atrophy in antrum and corpus; ● lymphoid follicles (≈10%), **1** intestinal metaplasia (≈10%), ■ focal atrophy (≈10%)

phy were frequently found in these patients (Fig. 2). However, comparison with patients having *H. pylori* gastritis alone revealed a significant difference only for intestinal metaplasia and focal atrophy in the antrum (Table 1) and for lymphoid follicles and focal atrophy in the corpus (Table 2).

The *H. pylori* gastritis in duodenal ulcer patients differed significantly from that in patients with *H. pylori* gastritis alone in that there was a higher grade of regenerative epithelium in the antrum and a lower density of *H. pylori* colonization in the corpus.

Gastritis variables evaluated from antral biopsies obtained from MALT lymphoma patients did not differ significantly from those obtained from the control group (Table 1). In the corpus, however, MALT lymphoma patients had a significantly lower expression of *H. pylori* colonization, but a significantly higher expression of grade and activity of gastritis (Table 2).

Discussion

A number of authors have claimed that different strains of *H. pylori* are associated with different diseases. Go et al. reported that *H. pylori* strains obtained from duodenal ulcer patients showed specific genetic fragments not found in strains obtained from patients with simple gastritis [12]. It has also been stated that *H. pylori* strains found in ulcer and gastric carcinoma patients show an increased production of the cytotoxin-associated CagA protein [7, 8, 21]. Recently, Atherton et al. reported that specific *H. pylori vacA* genotypes might influence the outcome of the infection [1], because there are differences in *vacA* expression between *H. pylori* strains found in patients with merely gastritis and those with duodenal or gastric ulcer.

Since no microbiological investigations were done in the present study, we do not know whether different genotypes of *H. pylori* are responsible for the differing degree and distribution of gastritis in the five groups we evaluated. However, we do not believe that strain factors alone suffice to explain why patients with duodenal ulcer, for example, have a rather mild corpus gastritis, whereas in gastric carcinoma patients it is quite severe. Hence, there must be other – namely host related – factors that influence the outcome of *H. pylori* infection.

It has been reported that patients with duodenal ulcer disease appear to have a higher gastric acid output than patients with gastritis only or those with gastric ulcer disease [27]. We speculate that this corresponds to the location of gastritis is located mainly in the antrum in duodenal ulcer patients, with only mild gastritis in the corpus, which might thus be able to remain its capacity to produce acid. A highly inflamed corpus, as found in gastric carcinoma patients, however, may be associated with a reduced acid output [22] and focal atrophy/intestinal metaplasia [9]. We found that intestinal metaplasia was mostly associated with carcinoma, and atrophic changes appeared almost exclusively in these patients (Fig. 2). Hence, as Lee et al. suggested [15], local acid output might determine the outcome of *H. pylori* infection. However, the question now arises as to what determines local acid production. Acid production is thought

to be lower in older patients [27]. However, since the groups evaluated in this study were age-matched, it would not appear likely that age alone influences the distribution of gastritis. Another factor that might determine intragastric acid production is the number of parietal cells, which is determined by the size of the corpus. More than 40 years ago, Cox found that the relative size of the antrum and corpus varies from one person to another [6]. In a report by Oi it is noted that the fundic-pyloric border determines acid secretion and, thus, the type and extent of gastritis [22]. If a person with a small antrum and a rather large corpus becomes infected with *H. pylori*, the resulting high acid secretion will cause the gastritis to predominate in the antrum, while remaining quite mild in the corpus. Consequently, a person infected with *H. pylori* will then be predisposed to develop duodenal ulcers. In contrast, a person with a comparatively low number of parietal cells might be at an increased risk of developing gastric carcinoma. That the distribution of gastritis is related to intragastric acid output agrees with a report by Logan et al. noting that once acid production is suppressed, *H. pylori* gastritis decreases in the antrum [17], and increases in the corpus.

We speculate that the capability of producing acid – possibly responsible for the different outcomes in *H. pylori* infection – may be inherited in the same manner as such other characteristics as height. It is reported, for example, that in Yemeni patients the prevalence of *H. pylori* is high, but the frequency of intestinal metaplasia and the incidence of gastric carcinoma are quite low, compared with British patients [26]. Nevertheless, Scott et al. noted that there are families in whom gastric carcinoma appears disproportionately often, even in very young family members [25]. These reports also agree with a recent finding of ours that *H. pylori* gastritis is significantly more frequent in the corpus in relatives of gastric carcinoma patients than in matched controls with similar complaints but without such a family history [20].

Surprisingly, in the other group of malignant diseases investigated (the MALT lymphoma group), the extent of gastritis expressed by the summed gastritis score was no higher in the antrum than in the corpus, a phenomenon also found in gastric carcinoma patients (Fig. 1). Thus, both malignant diseases differ from the other three, benign, *H. pylori*-associated diseases in terms of the antrum/corpus ratio of gastritis. However, focal atrophy and intestinal metaplasia were uncommon in our MALT lymphoma patients (Fig. 2), and the overall extent of gastritis was not as severe as in patients who had a carcinoma. An interesting finding regarding the observed differences between MALT lymphoma and gastric carcinoma might be that the production of vacuolizing cytotoxin in strains obtained from MALT lymphoma patients is sparse compared with strains from gastric carcinoma patients [16]. Hence, as mentioned earlier, *H. pylori* strain factors might be responsible for the different degree and distribution of *H. pylori* gastritis, at least to some extent.

In conclusion, in the diseases associated with *H. pylori* infection, the expression of *H. pylori* gastritis differs – independently of sex and age. However, the reasons for the differences in the degree and distribution of gastritis in different *H. pylori*-associated diseases have not yet been fully understood and require further investigation, including the examination of both *H. pylori* strain and host factors.

Acknowledgements The authors would like to thank Ms Christine Otahal for her valuable help in preparing this study. We are indebted to the following colleagues who helped in recruiting patients: W. Höchter and J. Weingart (Munich), A. Sommer (Cologne), H. Klann (Passau), T. Simon (Munich), W. Krämer (Pirmasens) and E. Bästlein (Munich). S. Miehlke is supported by an educational grant from the Deutsche Forschungsgemeinschaft.

References

1. Atherton JC, et al (1995) Specific *Helicobacter pylori vacA* genotypes are associated with presence of duodenal and gastric ulceration, and degree of gastric inflammation. J Biol Chem 270:1–7
2. Bayerdörffer E, et al (1995) Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue after cure of *Helicobacter pylori* infection. Lancet 345:1591–1594
3. Bayerdörffer E, et al (1996) Cure of gastric ulcer disease after cure of *Helicobacter pylori* infection – German gastric ulcer study. Eur J Gastroenterol Hepatol 8:343–349
4. Blaser MJ (1994) *Helicobacter pylori* phenotypes associated with peptic ulceration. Scand J Gastroenterol 29:1–5
5. Correa P (1988) A human model of gastric carcinogenesis. Cancer Res 48:3554–3560
6. Cox AJ (1952) Stomach size and its relation to chronic peptic ulcer. Arch Pathol 54:407–422
7. Crabtree JE, et al (1991) Mucosal IgA recognition of *Helicobacter pylori* 120 kDa protein, peptic ulceration, and gastric pathology. Lancet 338:332–335
8. Crabtree JE, et al (1993) Systemic and mucosal humoral responses to *Helicobacter pylori* in gastric cancer. Gut 34:1339–1343
9. Eidt S, Stolte M (1993) *Helicobacter pylori* and gastric malignancy. Zentralbl Bakteriol 280:137–143
10. Forbes GM, et al (1994) Duodenal ulcer treated with *Helicobacter pylori* eradication: seven year follow-up. Lancet 343: 258–260
11. Forman D, et al (1991) Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. BMJ 302:1302–1305
12. Go MF, et al (1995) Cluster analysis of *Helicobacter pylori* genomic fingerprints suggests gastroduodenal disease-specific associations. Scand J Gastroenterol 30:640–646
13. Graham DY, et al (1992) Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. Ann Intern Med 116:705–708
14. Lauren P (1965) The two histological main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. An attempt at a histoclinical classification. Acta Pathol Microbiol Scand 64: 31–49
15. Lee A, et al (1995) Local acid production and *Helicobacter pylori*: a unifying hypothesis of gastroduodenal disease. Eur J Gastroenterol Hepatol 7:461–465
16. Lehn N, et al (1994) Serologic response to *Helicobacter pylori* (HP) and significance of vacuolizing cytotoxic activity of HP in gastric cancer and MALT lymphoma (A438). Am J Gastroenterol 89:1394
17. Logan RPH, et al (1995) Changes in the intragastric distribution of *Helicobacter pylori* during treatment with omeprazole. Gut 36:12–16

18. Malaty HM, et al (1994) *Helicobacter pylori* infection: genetic and environmental influences. Ann Intern Med 120:982–986
19. Marshall BJ, et al (1988) Prospective double-blind trial of doudenal ulcer relapse after eradication of *Campylobacter pylori*. Lancet III:1437–1442
20. Meining A, Stolte M (1996) Different expression of *H. pylori*-gastritis in relatives of gastric cancer patients. Gut 39 [Suppl 2]:A17–A18
21. Oderda G, et al (1993) Serological IgG recognition of *Helicobacter pylori* cytotoxin-associated protein, peptic ulcer and gastroduodenal pathology in childhood. Eur J Gastroenterol Hepatol 5:695–699
22. Oi M (1995) Peptic ulcer and gastric acidity: a new look at an old aphorism, 'the higher the ulcer, the lower the acidity'. J Gastroenterol 30:122–127
23. Parsonnet J, et al (1991) *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 325:1127–1131
24. Price AB (1991) The Sydney system: histological division. J Gastroenterol Hepatol 6:209–222
25. Scott N, et al (1990) *Helicobacter* gastritis and intestinal metaplasia in a gastric cancer family. Lancet 335:728
26. Shousha S, et al (1993) *Helicobacter pylori* and intestinal metaplasia: comparison between British and Yemeni patients. Am J Gastroenterol 88:1373–1376
27. Stadelmann O, et al (1971) The peptic gastric ulcer – histotopographic and functional investigations. Scand J Gastroenterol 6:613–623
28. Stolte M, et al (1995) Relationship between the degree of *Helicobacter pylori* colonization and the degree and activity of gastritis, surface epithelial degeneration and mucus secretion. Z Gastroenterol 33:89–93
29. Warren JR, Marshall B (1983) Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet I:1273–1275
30. Wotherspoon AC, et al (1993) Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. Lancet 342:575–577