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Helicobacter pylori and gastric cancer

Marica OTAŠEVIĆ[1]
Aleksandar NAGORNI[2]
Dobrila STANKOVIĆ-ĐORĐEVIĆ[1]
Marina DINIĆ[1]
Ljiljana OTAŠEVIĆ[3]

BACKGROUND: *Helicobacter pylori (H.pylori) is classified as a Group 1 carcinogen, because H.pylori infection considerably increases the risk of gastric cancer development.*

METHODS: *The study involved a total of 191 patients divided into two groups. The first group comprised 117 patients who underwent endoscopy. A total of 203 biopsy specimens of the gastric mucosa were taken and analyzed using microbiological and histopathological methods. The second group comprised 74 patients with gastric cancer, who were examined for the gastric cancer type, the presence of H.pylori infection and the cancer localization. The presence of H.pylori infection in the tissue was confirmed by staining pathohistological sections according to the method of Warthin-Starry. The microbilogical diagnosis involved the staining of direct tissue smears according to the method of Gram, as well as the cultivation of the specimens. To test the hypothesis for possible differences in H.pylori positive findings between the treatment groups, χ^2 test with Yates correction or Fisher exact test were used.*

RESULTS: *The first treatment group comprised 117 patients with various clinical diagnoses. Gastric cancer was diagnosed in 8 patients, and of these 87.50% were found to have H.pylori. No statistically significant difference in H.pylori positive tests was detected between the patients with gastric ulcer and the patients with gastric cancer (Fisher exact test: $p=1.00$; $p>0.05$) nor was it established between the patients with duodenal ulcer and those with gastric cancer (Fisher exact test: $p=1.00$; $p>0.05$). The second treatment group comprised 74 patients, of whom 52 (70.27%) had intestinal-type gastric cancer and 22 (29.72%) had diffuse-type gastric cancer. No statistically significant difference in the positive tests for H.pylori was registered between the patients with intestinal-type and those with diffuse-type gastric cancer ($\chi^2=0.07$; $p=0.798$; $p>0.05$). The most frequent localization of the cancer was the antrum.*

CONCLUSION: *The results are supportive of the hypothesis on a correlation between H.pylori infection and gastric adenocarcinoma development, but no differences between the intestinal and diffuse type of adenocarcinoma have been revealed with respect to the malignant process.*

KEY WORDS: *Helicobacter pylori; Stomach Neoplasms; Helicobacter Infections, Gastric Mucosa; Adenocarcinoma*

[1]INSTITUTE FOR PUBLIC HEALTH, NIŠ, SERBIA AND MONTENEGRO
[2]CLINIC FOR GASTROENTEROLOGY, NIš CLINICAL CENTER, NIŠ, SERBIA AND MONTENEGRO
[3]FACULTY OF MEDICINE, UNIVERSITY OF NIš, NIŠ, SERBIA AND MONTENEGRO

INTRODUCTION

Although *Helicobacter pylori* (*H. pylori*) infection is widespread in the human population, the majority of infected subjects remain asymptomatic, whilst only a low percentage develop peptic ulcerous disease, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma.

Numerous studies have suggested a positive correlation between positive serological tests for *H. pylori* and gastric cancer. In 1996, the International Agency for Research on Cancer classified *H. pylori* as a Group 1 carcinogen, because *H. pylori* infection substantially increases the risk of gastric cancer development (1). Given that cancer is a several-phase process, long-term exposure to a potential mutation-inducing process considerably increases the risk of cancer development. Cell proliferation on a prolonged inflammation-affected site allows for the development of continu-

Address correspondence to:
Prof. Dr. Marica Otašević, Tome Roksandića 3a/7, 18000 Niš, Serbia and Montenegro

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ous mutation. As gastric cancer takes several years to develop, subjects with *H. pylori* infection acquired in early childhood are at higher risk of developing the cancer.

The major role of *H. pylori* in cancerogenesis might be its stimulation of cell proliferation. The proliferation of the gastric epithelial cells is more rapid in subjects with *H. pylori* infection than is in uninfected subjects. The proliferation can be a consequence of direct damage to the cells or a result of hypergastrinemia. The accelerated proliferation of the cells maximizes the potential for DNA damage due to response to other mutation-inducing factors (N-nitroso compounds). The elevated production of oxygen metabolites can also lead to increased DNA damage and molecular mutations. Taking into account all the above, and considering the association between gastric cancer and *H. pylori* infection, the Eurogast Study Group (2) determined that the presence of H. pylori confers an approximately six-fold risk of gastric cancer, accounting for about half of all those suffering from this malignancy.

Correa (3) has pointed out that patients with multifocal, chronic atrophic gastritis (MAG) belong to the group at high risk of developing gastric cancer. He has also found that *H. pylori* is present in all patients with dysplasia, however, being always located in the gastric epithelium beyond this precancerous lesion. Although *H. pylori* plays a dominant role in the development of diffuse atrophic gastritis, Correa (3) concludes : "*H. pylori* is not a sufficient cause for the development of gastric cancer". In his view, *H. pylori* is a relevant cofactor in the genesis of gastric cancer, which, however, requires the presence of MAG in order to exert its effect. Subsequent studies emphasize increasingly a causal relation between *H. pylori* infection and chronic atrophic gastritis (4).

It is considered that some of the factors of *H. pylori* virulence play a significant role in the development of severe diseases. The most important factors of virulence include the vacuolating cytotoxin A, that is, the *vacA* gene that encodes the synthesis of this exotoxin and typically contains one of the two signal sequence types (s1 and s2) and one of the two middle-region types (m1 and m2). Specific *vacA* s and m genotypes differ between one another with respect to cytotoxin production and, thereby, the degree of gastric epithelium damage.

H. pylori exerts a high level of genetic variability (5). However, differences in the phenotypic properties amongst *H. pylori* strains are small, the most remarkable ones being related to the production of the vacuolating cytotoxin A (VacA) and the cytotoxin-associated protein A (CagA), a potent immunogene protein (6). It has been noticed that the strains containing the *cagA* gene and the CagA protein also produce the vacuolating cytotoxin A. Although experimental data and clinical research suggest the effect of specific vacA genotypes upon the infection outcome, contradictory results may be also found that compromise the attempt to accurately define the role of this virulence factor in the development of severe gastrointestinal diseases in *H. pylori*-infected subjects. In addition to a good insight into the other factors of *H. pylori* virulence, it is necessary that the host immune response, that is, the microorganism-host interaction, be taken into consideration if this infection is to be understood properly.

The aim of the study was to determine the presence of *H. pylori* infection in the gastric mucosa of cancer patients relative to patients with other clinical diagnoses (gastric ulcer, duodenal ulcer). In addition, we wanted to examine a possible correlation between *H. pylori* infection and gastric cancerogenesis in both intestinal-type and diffuse-type adenocarcinoma.

PATIENTS AND METHODS

The study involved two treatment groups with a total of 191 patients. The first group comprised patients with various clinical diagnoses who underwent endoscopy due to disorders in their upper epigastrium. Following the pathologist's assessment, a total of 203 biopsy specimens of the gastric mucosa were taken and analyzed using microbiological and histopathological methods in order to identify pathological processes in the mucosa, as well as the presence of *H. pylori* infection. The second treatment group comprised 74 patients with gastric cancer, who were examined for the gastric cancer type, *H. pylori* infection, and the cancer localization in the antrum, corpus, and fornix. All the patients underwent an endoscopic examination of their stomach, such that biopsies, as least two per patient, were taken with standard biopsy pliers. Biopsy specimens were obtained from the antrum and corpus of bulb ulcer patients, from the antrum and ulceration border of gastric ulcer patients, and from the infiltration-adjacent region, i.e., the endoscopy-presented unaffected mucosa of cancer patients.

The specimens for the histopatathological analysis were fixed in 10% formalin and stained with hematoxylin-eosin (to determine the gastritis type) and according to the method of Warthin-Starry (7) (to determine the presence of *H. pylori* in the tissue). Gastritis was classified according to Whotehead. The specimens for the microbiological analysis were transported to the laboratory in a 20% glycolic solution and processed within 2 hours from the moment of sampling. The microbiological analysis included: preparation of direct microscopic smears stained according to Gram and *H. pylori* cultivation. For the latter, we used a solid selective medium according to Skirrow (8), cerebral-cardiac infusion agar with sheep blood, and the medium that was made in our laboratory (9) for lack of cerebral-cardiac infusion agar. *H. pylori* was identified on the basis of morphologic appearance of the cells, morphology of the colonies, and urease, catalase, and oxidase tests.

To test the hypothesis for possible differences in *H. pylori* findings between the treatment groups, χ^2 test with Yates correction or Fisher exact test were used.

RESULTS

The paper presents the results of a study carried out on 191 patients hospitalized at the Clinic for Gastroenterology, Niš Clinical Center. The first treatment group comprised 117 patients with various clinical diagnoses, who underwent endoscopy due to disorders in their upper epigastrium.

In order to determine the presence of *H. pylori* infection and to verify gastritis, 203 biopsy specimens of the gastric mucosa (one or more per patient) were taken and analyzed histopathologically. Distribution of *H. pylori* positive tests by clinical diagnoses is given in Table 1. The presence of *H. pylori* was confirmed at a high rate for the patients with various clinical diagnoses. The rate was also high for the patients who declined endoscopy (84.61%).

Table 1. *Helicobacter pylori* in clinical gastric disease

Diagnosis	No. of patients	Helicobacter pylori test			
		Positive		Negative	
		No.	%	No.	%
Gastric ulcer	32	27	84.37	5	15.62
Duodenal ulcer	31	27	87.09	4	12.90
Gastric cancer	8	7	87.50	1	12.50
Pernicious anemia	6	5	83.33	1	16.66
Resected stomach	19	14	73.68	5	26.31
Benign epithelial tumors	8	6	75.00	2	25.00
Negative endoscopic finding	13	11	84.61	2	15.38
Total	117	97	82.90	20	17.09

There are no statistically significant differences in the prevalence of *H. pylori* positive tests between the patients with gastric ulcer and those with gastric cancer. (Fisher exact test: $p=1.00$; $p>0.05$). No statistically significant difference in the prevalence of positive tests for *H. pylori* was established between the patients with duodenal ulcer and those with gastric cancer (Fisher exact test: $p=1.00$; $p>0.05$).

Table 2. *Helicobacter pylori* in microscopic gastric lesions

Microscopic diagnosis	No. of samples	Presence of Helicobacter pylori	
		No.	%
Normal mucosa	26	16	61.53
Type I gastritis	33	24	72.72
Type II gastritis	69	53	76.81
Type III gastritis	13	9	69.23
Other lesions	48	31	64.58
Jejunitis	14	4	28.57
Total	203	137	67.48

H. pylori incidence according to histopathological diagnoses is given in Table 2. By the analysis of 203 samples of the gastric mucosa, *H. pylori* was detected at a 67.48% rate. *H. pylori* was found in 16 (61.53%) patients presented with unaffected gastric mucosa on microscopic examination. In the type 1 gastritis patients, positive *H. pylori* findings were revealed in 24 (72.72%) cases. This difference, however, is not statistically significant ($\chi^2=0.40$; $p=0.527$; $p>0.05$). No statistically significant difference in the incidence of positive *H. pylori* findings was found between the patients with type II gastritis and the subjects with healthy gastric mucosa ($\chi^2=1.51$; $p=0.218$; $p>0.05$). The incidence of positive tests for *H. pylori* in patients with type III gastritis is by almost 8% higher compared to the subjects with unaffected gastric mucosa, but this difference is not statistically significant (Fisher exact test: $p=0.733$; $p>0.05$). Positive tests for *H. pylori* were also analyzed relative to the colonization site in the stomach. The bacterium was found in the antrum of 78.35% patients and in the corpus of 61.95% patients.

Table 3. Localization of intestinal-type and diffuse-type gastric cancer and *H. pylori* findings

Localization	Intestinal-type gastric cancer		Diffuse-type gastric cancer	
	No.	%	No.	%
The number of cancer patients	52	70.27	22	29.72
H. pylori positive finding	37	71.15	15	68.18
Localization in the antrum	20	38.46	10	45.45
Localization in the corpus	19	36.53	8	36.36
Localization in the fornix	13	25.0	4	18.18

The second group comprised 74 patients with gastric cancer (Table 3), 27-75 years of age (mean age, 51.10 years). Of a total number of the patients examined for adenocarcinoma, 46 cases (62.16%) were registered in males, whilst 28 cases (37.82%) were registered in females. Intestinal-type adenocarcinoma was diagnosed in 52 patients, of whom 37 (71.15%) were *H. pylori*-positive. Diffuse-type adenocarcinoma was diagnosed in 22 patients who showed a lower rate (68.18%) of *H. pylori* incidence. No statistically significant difference was revealed in the frequency of *H. pylori* positive findings between the patients with intestinal-type and those with diffuse-type gastric cancer ($\chi^2=0.07$; $p=0.798$; $p>0.05$).

Cancer localization is given in Table 3. Intestinal-type adenocarcinoma was confirmed in the antrum of 20 patients, in the corpus of 19 patients and in the fornix of 13 patients. Of 22 patients with diffuse-type adenocarcinoma, the malignant process was confirmed in the antrum of 10 patients, in the corpus of 8 patients, and in the fornix of 4 patients.

DISCUSSION

Numerous studies have demonstrated that *H. pylori* infection is the most important factor in the development of chronic atrophic gastritis that is closely associated with gastric cancer (10). It is well known that *H. pylori* exerts its effect directly through the

inflammation caused by the infection, but also through the reactivity of the very host (11-13). It forms ammonia, phospholipases, and cytokines that are released in the gastric lumen, thus leading to epithelial damage (14). This damage induces permanent proliferation and regeneration, providing conditions for a malignant alteration in the stem cells of the neck region of the gastric glands (15,16). *H. pylori* is, thus, considered a likely link in the chain of oncogenesis, but many aspects of this complex process are as yet to be unraveled (17,18). In addition to *H. pylori*, various other factors play a most important role in cancerogenesis, including both external (N-nitroso compounds, in particular) and internal factors (mutation of oncogenes and growth factors).

Correa (3) points out that patients with multifocal, chronic atrophic gastritis belong to the group at high risk of developing gastric cancer. This author concludes that *H. pylori* is a significant factor in the genesis of gastric cancer.

We examined the presence of *H. pylori* in the gastric mucosa of 117 patients who underwent endoscopy due to disorders in their upper epigastrium. We confirmed the presence of *H. pylori* in 84.37% patients with gastric ulcer, and 87.09% patients with duodenal bulb ulcer. These patients served as controls to *H. pylori*-positive patients with gastric cancer. Out of 117 examined patients who underwent gastroscopy, 8 were found to have gastric cancer. In 87.50% of them *H. pylori* was detected in the mucosa surrounding gastric cancer. It is well known that this microorganism does not colonize the cells of the cancer, but when accompanied with gastric cancer it helps maintain the colonization of the non-neoplastic gastric epithelium. A study carried out in California (19) confirms that *H. pylori* infection is present at an 89% rate in the mucosa surrounding intestinal-type gastric cancer, compared to a 32% rate in the mucosa adjacent to diffuse-type cancer.

H. pylori positive tests in 84.10% patients who declined endoscopy can be explained by gastritis that the majority of these patients present on histological examination. These findings can be in part compared with the results obtained by Langerberg (20), who confirmed gastritis histopathologically in 31 out of 32 *H. pylori*-positive patients. The positive tests we obtained for *H. pylori* in patients with type I, type II, and type III gastritis are consistent with the results by the abovementioned authors. Although individual, there are reports on a 62% rate of *H. pylori* incidence in healthy mucosa as well(21). Burnett (22) et al. has demonstrated the presence of *H. pylori* in the histologically normal mucosa, thus denying the results of Marshall et al.(23).

Our findings of *H. pylori* in the histologically unaffected mucosa at a rate of 61.53% are consistent with the findings by Burnett (22) and are, thus, supportive of the few authors' claim that *H. pylori* is not an exclusive privilege of gastritis. The 64.57% incidence of H. pylori in gastritis-unrelated histological diagnoses (which we put under "other lesions" category) also supports the above claims. According to literature data, *H. pylori* is primarily antrum-dominant. Our findings are consistent with this claim (78.35%) but are also indicative of the presence of this microorganism in the corpus (61.95%).

The most widespread attitude nowadays is that one of the reasons for various clinical outcomes of *H. pylori* infection is a difference in its strain virulence. *H. pylori* strains can be divided into two types, type I being considered more virulent. Type I *H. pylori* produces CagA, an immunogene protein, which in the human organism induces the formation of various specific anti-CagA IgG antibodies. As this protein is considered a marker of virulence, detection of anti-CagA antibodies can help detection of type I *H. pylori* infected subjects, that is, the subjects at higher risk of developing ulcer disease and cancer. Numerous authors have confirmed that CagA antibodies are more prevalent in patients with duodenal ulcer and gastric cancer, although studies presenting results from various countries indicate that the association between the CagA status and more severe gastric diseases is not an absolute one (24). A definite attitude on the correlation between the prevalence of anti-CagA antibodies and gastric cancer development could be made only after extensive research that would involve the asymptomatic population in developed and developing countries.

A Japanese study on *H. pylori* infection as a risk factor for gastric cancer has confirmed a remarkable association between *H. pylori* seroprevalence and an increased risk of developing gastric cancer and precancerous conditions (25). The IgG *H. pylori* status was examined in 55 patients with gastric cancer, 57 patients at high risk of developing gastric cancer (precancerous conditions), and 75 control subjects. The seroprevalence of *H. pylori* was demonstrated at an 82% rate for patients with gastric cancer, an 89% rate for patients in precancerous condition, and a 60% rate for controls(25).

A seven-year long study carried out on 1,603 patients has showed that intestinal- and diffuse-type gastric cancer developed in 2.90% of *H. pylori*-infected patients, as well as in one person with no *H. pylori* infection. The infected were at higher risk of the cancer, due to severe gastric atrophy, corpus-dominant gastritis, and intestinal metaplasia. The results of this study suggest that the development of both cancer types was a result of *H. pylori*-associated gastritis, and that the risk of developing gastric cancer in *H. pylori*-negative subjects was rather low (10).

We also examined the presence of H. pylori in the mucosa adjacent to gastric cancer. Of 52 (70.27%) patients with intestinal-type cancer, *H. pylori* was identified in 71.15% cases. Of 22 (29.72%) patients with diffuse-type cancer, *H. pylori* was found in

68.18% cases. The role of *H. pylori* infection in cancerogenesis has been so far investigated for intestinal-type cancer, as the association of the infection with the development of this cancer type was earlier documented (active chronic *H. pylori*-associated gastritis, mucosal atrophy, intestinal metaplasia, mucosal dysplasia, early intestinal-type cancer, advanced adenocarcinoma). Further studies revealed the correlation of *H. pylori* infection with the process of cancerogenesis and the development of diffuse-type cancer: active chronic *H. pylori* gastritis, atypical hyperplasia of the gastric glands, loss of basal membrane, early diffuse-type adenocarcinoma, advanced diffuse-type adenocarcinoma (26). Our results demonstrate that no statistically significant difference in the incidence of *H. pylori* exists between patients with intestinal-type and those with diffuse-type gastric cancer ($p>0.05$). These results are consistent with the findings by Talley et al. (27). In addition to analyzing the *H. pylori* status in patients with gastric cancer, we examined the cancer localization. There is no statistically significant difference in the localization of intestinal-type gastric cancer, whereas diffuse-type cancer was in the majority of cases localized in the antrum.

CONCLUSION

H. pylori infection has a significant role in the development of gastric adenocarcinoma. No statistically significant difference in the incidence of *H. pylori* positive tests exists between the patients with intestinal-type adenocarcinoma and those with diffuse-type gastric cancer.

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