

# Gastric MALT lymphoma: clinical characteristics and prevalence of *H. pylori* infection in a series of 37 cases

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## ABSTRACT

**Objective:** to perform a retrospective review of the clinical characteristics and prevalence of *H. pylori* infection in patients with gastric MALT lymphoma diagnosed in our hospital during the last 15 years.

**Methods:** patients with gastric MALT lymphoma diagnosed in our hospital during the last 15 years were retrospectively included. Demographic, clinic, analytic, endoscopic, and histological variables were reviewed. The extension study, the staging classification, and the presence of *H. pylori* infection were assessed.

**Results:** thirty-seven patients with gastric MALT lymphoma were identified. Mean age was 61 years, with 62% of males. The most common presentation symptom was dyspepsia (76%), followed by digestive bleeding (11%) and constitutional syndrome (8%). At endoscopy, erosive lesions were identified in 41%, and proliferative or exophytic lesions in 43%. Most lymphomas were classified as low-grade (68%). The stage distribution was EI for 56%, EII for 13%, EIII for 3%, and EIV for 28%. The prevalence of *H. pylori* infection (histology in all cases, rapid urease test in 19%, and <sup>13</sup>C-urea breath test in 24%) was 46%. When only low-grade lymphomas in stage EI were considered, *H. pylori* prevalence increased to 55%. When *H. pylori* infection was evaluated by <sup>13</sup>C-urea breath testing (in addition to histology), the prevalence of *H. pylori* infection increased to 78%.

**Conclusions:** it is probable that the reduced *H. pylori* prevalence found in some studies, as in ours, could be explained by false-negative results obtained when only one diagnostic method was used. Therefore, at least two (invasive) diagnostic methods should be performed. Furthermore, the performance of a non-invasive diagnostic method (such as a <sup>13</sup>C-urea breath test) before the exclusion of *H. pylori* infection should be considered.

**Key words:** MALT. Mucosa-associated lymphoid tissue. Gastric lymphoma. *Helicobacter pylori*.

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## INTRODUCTION

Non-Hodgkin's gastric lymphoma is a rare tumor accounting for less than 10% of lymphomas, and 3% of gastric neoplasms (1-5). However, primary gastric lymphoma is the most common extranodal lymphoma (1-5). Histological features of gastric low-grade lymphomas closely resemble mucosa-associated lymphoid tissue (MALT) (1-5). Nevertheless, most MALT lymphoma locations do not contain lymphoid tissue. For example, under normal conditions there is no evidence of organized lymphoid tissue in the gastric mucosa, where only the presence of a few lymphocytes has been described. However, as previously mentioned, this is the most common site for extranodal lymphomas. The clue to correctly explain this paradox is MALT development after *H. pylori* colonization (6).

Several lines of evidence establish a causal association between *H. pylori* infection and gastric MALT lymphoma, such as the high prevalence of the microorganism in this type of lymphoma and, particularly, the demonstration of tumor regression after *H. pylori* eradication. Therefore, the question of MALT lymphoma as an infectious disease has been recently proposed, and the answer was "partly yes" (6,7).

However, nowadays the real prevalence of *H. pylori* in MALT lymphomas is unknown, as it varies between the various epidemiologic studies performed. Some studies showed that the prevalence of infection depends on the lymphoma's histological grade or the diagnostic method

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used, among others (8). A knowledge of the true prevalence of *H. pylori* in patients with MALT lymphoma is clinically relevant, as the detection of this organism will be followed by adequate eradication treatment, with consequent tumor regression in a high number of cases (1-5).

Our objective was to perform a retrospective review of the clinical characteristics and the prevalence of *H. pylori* infection in patients with gastric MALT lymphoma diagnosed in our hospital during the last 15 years.

## METHODS

To carry out the present retrospective study all patients diagnosed with gastric MALT lymphoma in our center during the last 15 years (from January 1991 to December 2005) were initially identified. To this end, a triple search was carried out in the files of the Digestive, Hematology and Pathology units.

Subsequently, all medical records were recovered and a specifically designed questionnaire was completed, where the following variables were included:

1. *Demographic variables*: age, sex, smoking habit, alcohol intake, and history of neoplasm.

2. *Clinical variables*: most common reason for consultation (presentation symptom), and presence of B symptoms (fever, night sweats, and weight loss –more than 10% of body mass in the previous 6 months).

3. *Physical exploration*: presence of adenopathies (and their localization), oropharyngeal exploration, presence of hepatomegaly or splenomegaly.

4. *Laboratory variables*: human immunodeficiency virus (HIV) serology, Epstein-Barr virus serology, hepatitis B and C virus serology.

5. *Endoscopic variables*: type of macroscopic lesion (erosive, exophytic, hypertrophic), localization (antrum, body, diffuse), and characteristics of gastric biopsies obtained by the initial endoscopic exploration (number and localization).

6. *Histological variables*: low-grade and high-grade lymphoma classification.

7. *Extension study*: ORL exploration, chest X-rays, abdominal ultrasounds, gastrointestinal follow-through, cervical and thoraco-abdominal computerized tomography (CT) scans, and bone marrow cytology/biopsy.

8. *Staging*: according to the Ann Arbor classification as modified by Musshoff, where stage EI indicates disease is confined to the stomach, EII implies the involvement of subdiaphragmatic lymph nodes, EIII means the involvement of lymph nodes on both sides of the diaphragm, and EIV refers to the involvement of distant organs. A differentiation between stages EI<sub>1</sub> (confined to the mucosa and submucosa) and EI<sub>2</sub> (extended over the submucosa) was only performed in those few cases where an endoscopic ultrasonogram was performed.

9. *H. pylori infection*: prevalence and diagnostic methods used in its evaluation.

*Statistical analysis*: for qualitative variables, the percentage was calculated (with its corresponding 95% confidence interval or 95% CI). For quantitative variables, the arithmetic mean (and standard deviation) was provided. Although a comparison of the various variables was initially planned, only a descriptive analysis of variables could be done due to the limited number of patients included (37), resulting in reduced statistical power (that is, an elevated risk for beta errors).

## RESULTS

From 1991 to 2005, 37 patients with gastric MALT lymphoma were identified and included in our study.

1. *Demographic variables*: the mean age of patients was 61 ± 14 years; 62% were males, 30% were smokers, and 16% had a history of alcohol abuse. In 11% a previous history of neoplasm existed.

2. *Clinic variables*: the most common reason for consultation (presentation symptom) was dyspepsia (76%), followed by digestive bleeding (hematemesis or melena, 11%) and constitutional syndrome (8%); 11% had B symptoms, fever (5%), night sweats (5%), and weight loss (8%).

3. *Physical exploration*: adenopathies were identified in 22% of cases; of these, the distribution was: submaxillary (0%), cervical (14%), supraclavicular (5%), axillary (14%), and inguinal (8%). The oropharyngeal exploration was normal in 88% of patients, whereas the pharynx was hyperemic in 6%, and a hyperplasia of sublingual salivary glands was observed in 6% of patients. Hepatomegaly and splenomegaly were present in 11% and 5% of patients, respectively.

4. *Laboratory variables*: Epstein-Barr virus and HIV serology were negative in all cases, while the serology for hepatitis B and C virus was positive in 5 and 3% of cases, respectively.

5. *Endoscopic variables*: gastroscopy was normal in 16% of cases, whereas erosive lesions were identified in 41%, and proliferative or exophytic lesions in 43%. Endoscopic lesions were most commonly localized in the antrum (60%), were observed in the body in only 35% of cases, and were diffuse in 5%. The site for gastric biopsies obtained during the initial endoscopy was: antrum (89%), body (57%), incisura (16%), and fundus (11%). The mean number of biopsies obtained by endoscopy was 8 ± 3, with a range from 2 to 23.

6. *Histological variables*: most lymphomas were classified as low-grade (25 patients, that is 68%), whereas the remaining 12 patients (32%) had a high-grade lymphoma. Patient characteristics by histological grade are summarized in table I.

7. *Staging*: stage distribution was: EI in 56%, EII in 13%, EIII in 3%, and EIV in 28%. Differentiation between stages EI<sub>1</sub> and EI<sub>2</sub> was only possible in 2 patients (both were EI<sub>1</sub>).

**Table I. Characteristics of gastric MALT lymphoma patients based on histological grade**

	Low grade (n = 25)	High grade (n = 12)
Age (mean ± SD)	60 ± 15	65 ± 13
Sex (% males)	60	67
Smoking (% smokers)	36	17
Alcohol intake (% drinkers)	16	17
Diagnostic symptoms		
Dyspepsia (%)	80	67
Digestive bleeding (%)	8	17
Constitutional syndrome (%)	8	8
B symptoms (%)	8	17
Fever (%)	4	8
Night sweats (%)	4	8
Weight loss (%)	4	17
Hepatomegaly	5	22
Splenomegaly	2	10
HIV+ (%)	0	0
HBV+ (%)	4	8
HCV+ (%)	4	0
Endoscopic features		
Normal	16	17
Erosive pattern	40	42
Proliferative pattern	44	41
Localization		
Antrum (%)	58	67
Body (%)	38	33
Diffuse (%)	4	0
Stage		
EI (%)	49	70
EII (%)	14	10
EIII (%)	5	0
EIV (%)	32	20
<i>H. pylori</i> positive (%)	40	58

SD: standard deviation. HIV: human immunodeficiency virus. HBV: hepatitis B virus. HCV: hepatitis C virus.

8. *H. pylori* infection: the microorganism was initially detected in only 15 of 37 patients; therefore, all histological paraffin sections of *H. pylori*-negative patients were reviewed, and infection was identified in 2 further patients. Thus, *H. pylori* prevalence finally was 46% (31-62, 95% CI). *H. pylori* prevalence in high-grade lymphomas was 58% (28-85, 95% CI), but in low-grade lymphomas it was 40% (23-59, 95% CI). When only low-grade lymphomas in stage EI were considered (11 patients), *H. pylori* prevalence was 55% (23-83, 95% CI). The diagnosis of *H. pylori* infection was determined by histology (hematoxylin-eosin stain) in all cases. In 19 and 24% a rapid urease test and a <sup>13</sup>C-urea breath test, respectively, were performed besides histology. When *H. pylori* infection was detected both by histology and <sup>13</sup>C-urea breath testing (9 patients), the prevalence increased to 78%.

## DISCUSSION

In the present retrospective study, 37 patients with gastric MALT lymphoma were included for the last 15 years.

Gastric MALT lymphoma is an uncommon neoplasm, with an incidence of 0.4-0.9 cases per 100,000 persons (9). This tumor has been more frequently diagnosed during the last 50 years, with a mean age of 60-65 years, and is 2-3 times more common in males (10,11), as our results show (mean age 61 years, 62% males).

Gastric MALT lymphomas are often asymptomatic, and when symptoms are present, they are generally non-specific, predominantly dyspeptic (1-5,12,13). Therefore, the diagnosis of early gastric MALT lymphoma is difficult. In our patients the most common presentation symptom was dyspepsia (76%). In patients with advanced-stage lymphoma, anemia or a constitutional syndrome was present in 88% of our patients, these symptoms raising the possible diagnosis of gastric carcinoma (1-5,12,13). Finally, gastric MALT lymphoma may present with upper gastrointestinal bleeding in 20-30% of cases (1-5,12-14). In our experience, the presentation symptom was hematemesis or melena in 11% of patients.

Physical exploration in patients with gastric MALT lymphoma does not usually reveal any alterations (1-5,15), as was the case in most of our patients. Nonetheless, in high-grade lymphomas, clinical manifestations may be more evident. Thus, in advanced-stage lymphoma, hepatomegaly and splenomegaly can be detected (in 11 and 5% of our cases, respectively), or peripheral adenopathies can be found (in 22% of our patients).

A higher incidence of gastric MALT lymphoma in patients with hepatitis B virus has been described (16), as well as in patients with HIV (17,18). All our patients were HIV-negative, whereas 3% were infected by hepatitis B virus. Although this figure is higher than that reported for the general population, the small-size sample does not permit reliable conclusions to be drawn.

Endoscopic exploration may show a completely normal mucosa (this happened in 16% of our patients) or several endoscopic lesions. Three endoscopic patterns of gastric lymphoma have been described (ulcerative, exophytic and hypertrophic) (19). No hypertrophic pattern was found in our patients. Endoscopic lesions were more often localized in the antrum, as described in previous studies (1-5).

Gastric MALT lymphomas are divided up into high- and low-grade lymphomas according to the percentage of blast cells in gastric biopsy samples. At the time of diagnosis, 75-80% of lymphomas are classified as low grade (1-5) (as happened in 75% of our patients). It is very common to find both types of lymphoma in the same lesion, and it has been reported that up to one third of low-grade lymphomas progress to high-grade lymphomas (20), suggesting that both lesions represent the same tumoral process.

The Ann Arbor classification as modified by Musshoff is probably the most widely used staging method (1-5) -56% of our patients had stage EI. MALT lymphomas may invade not only other MALT tissues, but also lymph nodes and the bone marrow. In one Spanish study, 12% of low-

**Table II. Prevalence of *H. pylori* infection in patients with MALT lymphoma**

Author	Year of publication	n	<i>H. pylori</i> prevalence (%)	Diagnostic method
Nakamura et al. (24)	2005	96	93	H, S, C, RUT, C <sup>13</sup>
Lee et al. (25)	2004	53	90	H, RUT
Yeh et al. (26)	2003	20	85	H, C, RUT, C <sup>13</sup>
Lehours et al. (27)	2003	56	71	H, S, C
Ruskone et al. (28)	2001	44	77	H, S, C
Delchier et al. (29)	2001	53	85	S
Hiyama et al. (30)	2001	53	92	H
Cuttner et al. (31)	2001	12	67	S
Ben Rejeb et al. (32)	2000	65	63	H
Arista-Nasr et al. (33)	2000	54	57	H
Fischbach et al. (34)	2000	35	100	S
Konturek et al. (35)	2000	20	90	S, C <sup>13</sup>
Ohashi et al. (36)	2000	23	61	H, C, RUT
Steinbach et al. (37)	1999	34	82	H, S, RUT
Eck et al. (38)	1999	60	98	H, S
Yi et al. (39)	1997	39	87	H
Dogusoy et al. (40)	1999	32	72	H
Bouzourene et al. (41)	1999	31	58	H
Chang et al. (42)	1999	53	75	H
Vallina et al. (43)	1999	16	69	H
Jonkers et al. (44)	1997	52	69	H
Oberhuber et al. (45)	1997	89	84	H
Pavlick et al. (46)	1997	16	69	H
Eck et al. (47)	1997	68	99	S
Xu et al. (48)	1997	53	55	H
Gisbertz et al. (49)	1997	52	62	H
Nakamura et al. (50)	1997	198	63	H
Chiang et al. (51)	1996	19	92	H, S
Herrera et al. (52)	1996	27	85	H
Cammarota et al. (53)	1995	39	87	H, C, RUT
Miettinen et al. (54)	1995	22	59	H
Karat et al. (55)	1995	12	50	H, S, RUT
Calvert et al. (56)	1995	12	42	H
Muller et al. (57)	1995	45	80	H
Parsonnet et al. (58)	1994	33	85	S
Eidt et al. (59)	1994	121	100	H
Fagioli et al. (60)	1994	27	74	H
Wotherspoon et al. (61)	1991	110	92	H

n: number of patients; H: histology; S: serology; C: culture; RUT: rapid urease test; C<sup>13</sup>: urea breath test.

grade MALT lymphomas were diagnosed in stages III-IV, and there was bone marrow infiltration in 15% of patients (21). This conclusion was confirmed by other authors (22). In our experience, 31% of patients were in stages III-IV.

To carry out a correct classification of gastric MALT lymphoma the following is required: a minute physical exploration, paying special attention to: presence of adenopathies, splenomegaly, oropharyngeal lesions; laboratory studies, with hemogram and biochemical tests including proteinogram, immunoglobulins, and lactate dehydrogenase; chest X-rays; cervical and thoracoabdominal computerized tomography (CT) scans; and bone marrow cytology/biopsy.

Finally, endoscopic ultrasounds constitute a fundamental exploration to accurately evaluate not only the le-

sion's extent (infiltration of gastric wall) but also the presence of perigastric adenopathies (1-5). Furthermore, response to *H. pylori* eradication treatment can be predicted with this technique (23).

The prevalence of *H. pylori* infection in our patients was only 46%, a figure lower than that generally described in the literature. In this respect, we recently carried out a systematic review of all 38 studies (including a total of 1,844 patients) that evaluate *H. pylori* prevalence in patients with gastric MALT lymphoma (24-61), and the overall prevalence was 79% (8) (although the results varied between 100% (34,38,59) and less than 50% (55,56). Explanations for this diversity may be multiple and seem to depend, at least partly, on the number and type of techniques used to detect the infection, the histological grade of lymphoma, and the depth of tumor invasion. Thus, if appropriate diagnostic methods (in number and characteristics) are used, and if only low-grade lymphomas are considered, the prevalence of *H. pylori* infection increases to nearly 90%, which reinforces the causal role of these bacteria in gastric MALT lymphoma (8). Nevertheless, in our study, when only low-grade lymphomas in stage EI were considered, *H. pylori* prevalence was still low (55%).

The number of diagnostic methods used in our study was probably insufficient, as most patients were only evaluated by histology. A higher *H. pylori* prevalence has been described when serologic rather than histological methods were used (8). This probably could be explained by a decrease in bacterial colonization due to gastric atrophy and hypochlorhydria; however, antibodies against bacteria can be detected even years after mucosal clearance (38,54). On the other hand, *H. pylori* gastric mucosa colonization is not uniform; thus, even in the presence of infection, microorganisms may not be detected if the biopsy is taken from a non-colonized mucosal area. Therefore, *H. pylori* detection by histology is highly dependent on the number of gastric biopsies (38,51).

From the aforementioned results, we can deduce that in the presence of a negative result obtained by histology, a non-invasive diagnostic method such as the <sup>13</sup>C-urea breath test or serology should be performed after definitely excluding *H. pylori* infection (27,38). In this respect, when *H. pylori* infection was evaluated by <sup>13</sup>C-urea breath testing as well as by histology (this happened in the last 9 patients), the prevalence of infection increased to 78%. Thus, in our daily practice we usually use two biopsy-based methods (histology and a rapid urease test), and always perform a <sup>13</sup>C-urea breath test to confirm negative cases.

To summarize, the accurate identification of *H. pylori* infection in patients with gastric MALT lymphoma is very relevant, as lymphoma regression has been demonstrated after *H. pylori* eradication. It is probable that the reduced *H. pylori* prevalence found in some studies, as in ours, could be explained by false-negative results ob-



tained when only one diagnostic method was used. Therefore, one negative result obtained by histology (or rapid urease testing) should be followed by the use of a non-invasive diagnostic method before the exclusion of *H. pylori* infection.

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